Traceless Solid-Phase Syntheses for Heterocycles Based on Cyclization-Cleavage Approaches

February 2010

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(環化–切断法に基づく複素環のトレースレス固相合成)

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Contents

Abbreviation

Following abbreviations have been used throughout.

Ac	acetyl
ATR	attenuated total reflection
Bop	(benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate
br	broad (in spectra)
Bu	butyl
Cbz	benzyloxycarbonyl
d	doublet (in spectra)
δ	scale (NMR), dimensionless
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DHP	3,4-dihydro-2H-pyran
DIC	diisopropylcarbodiimide
DIEA	diisopropylethylamine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
e.g.	for example
equiv	equivalent
Et	ethyl
EP	prostaglandin E

et al.	and others (*et all*)
FKBP	FK506 binding protein
g	gram
h	hour
Het	heterocycle
HIV	human immunodeficiency virus
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
5-HT	5-hydroxytryptamine
HTS	high-throughput screening
Hz	hertz (s^{-1})
i	iso
i.e.	that is (*id est*)
IKK2	IκB kinase 2
IR	infrared
LRMS	low resolution mass spectrum
m	multiplet (in spectra)
m	meta
M	mol/dm^3
Me	methyl
min	minute
MS	mass spectrum
m/*z*	mass-to-charge ratio

n	normal
NMM	*N*-methylmorpholine
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Ns	2-nitrobenzenesulfonyl
o	ortho
ODS	octadecyl silica
p	para
Ph	phenyl
PNMT	phenylethanolamine *N*-methyltransferase
Pr	propyl
PyBop	benzotriazol-1-yl-oxytripyrro-lidinophosphonium hexafluorophosphate
PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	quartet (in spectra)
ref	reference
RyR	ryanodine receptor
s	singlet (in spectra)
S_N2	bimolecular nucleophilic substitution
t	tripret (in spectra)
TACE	TNF-α converting enzyme
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
tert	tertiary
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TMAD	*N,N,N′,N′*-tetramethylazodicarboxamide
Tr	triphenylmethyl (trityl)
VLA-4	very late antigen-4
17β-HSD II	type II 17β-hydroxysteroid dehydrogenase

Chapter 1

General Introduction

1. Chemical libraries including heterocycles

Heterocycles, *e.g.*, piperazine, pyrimidine, are virtually present in every class of known drugs (Figure 1).[1] These cyclic structures mostly serve as scaffolds for the correct spatial positioning of pharmacophoric substituents and/or are parts of the pharmacophore itself.

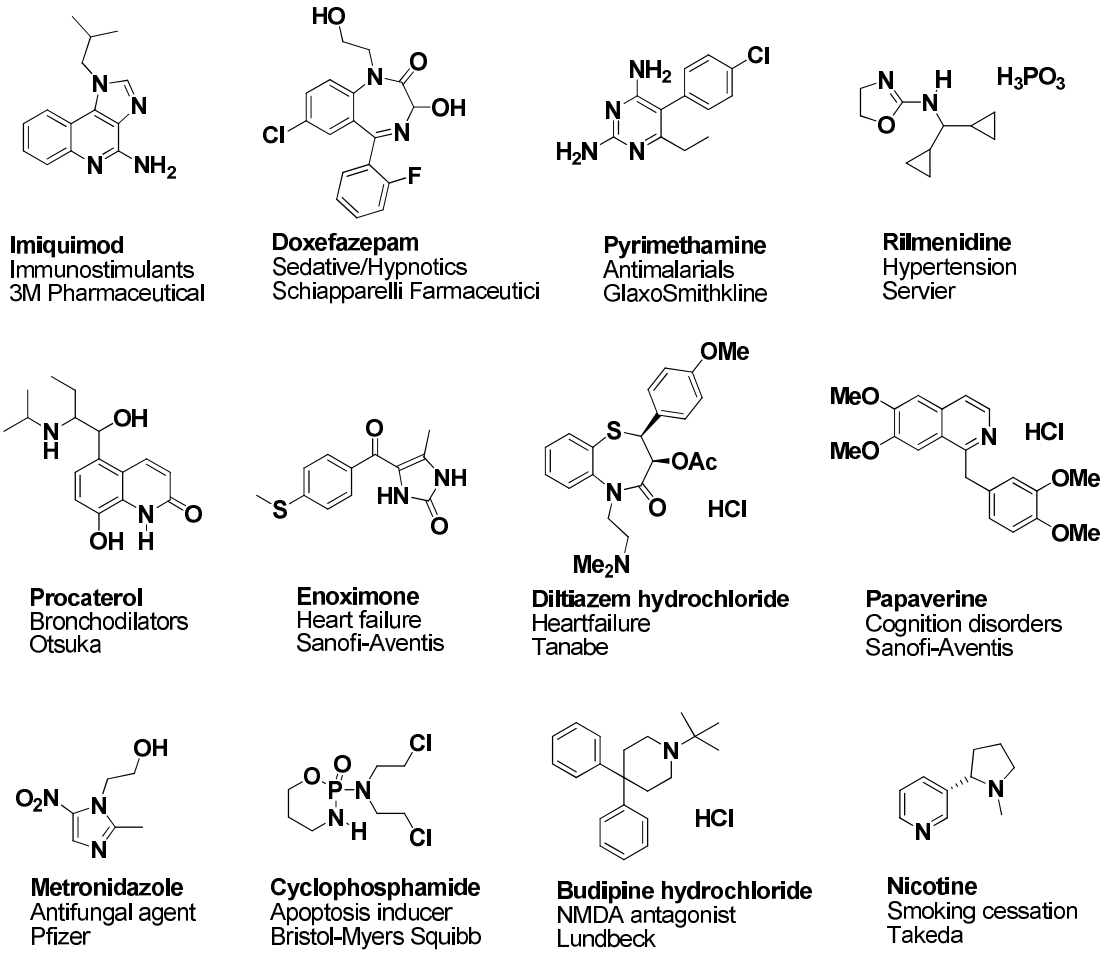


Figure 1-1. Structures of several known drugs.

Therefore, chemical libraries, which have the structures as scaffolds, are expected to play important roles on finding novel compounds with pharmacological activities.

Chemical libraries including heterocyclic structures are generally constructed according to a flow diagram described in Figure 1-2. Heterocyclic structures extracted from the existing biologically active compounds are used as scaffolds of chemical libraries.

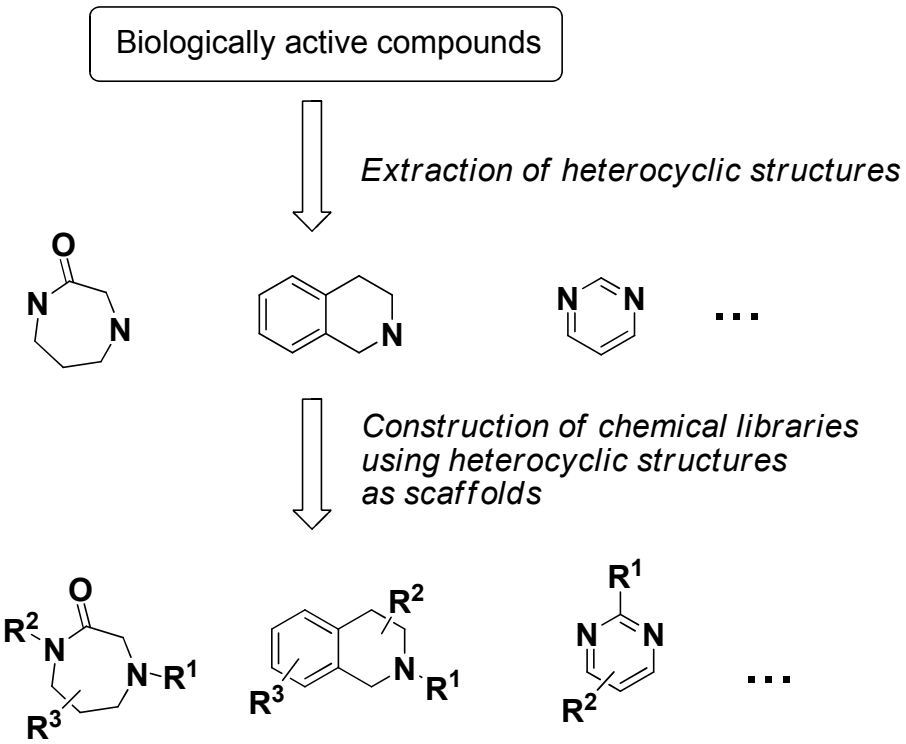


Figure 1-2. Construction of chemical libraries based on heterocyclic structures.

So far, many reports have reported the construction of chemical libraries based on the strategy described above (Figure 1-3). For example, Yu and co-workers reported libraries of 3,5,6-substituted 2-pyridone derivatives,[2] which are contained in the chemical structures of specific non-nucleoside reverse transcriptase inhibitors of human immunodeficiency virus-1 (HIV-1) and cardiotonic agents for the treatment of heart failure.[3, 4] In addition,

synthetic examples of libraries based on 1,4-benzodiazepine[5, 6] and imidazole[7, 8] were also reported.

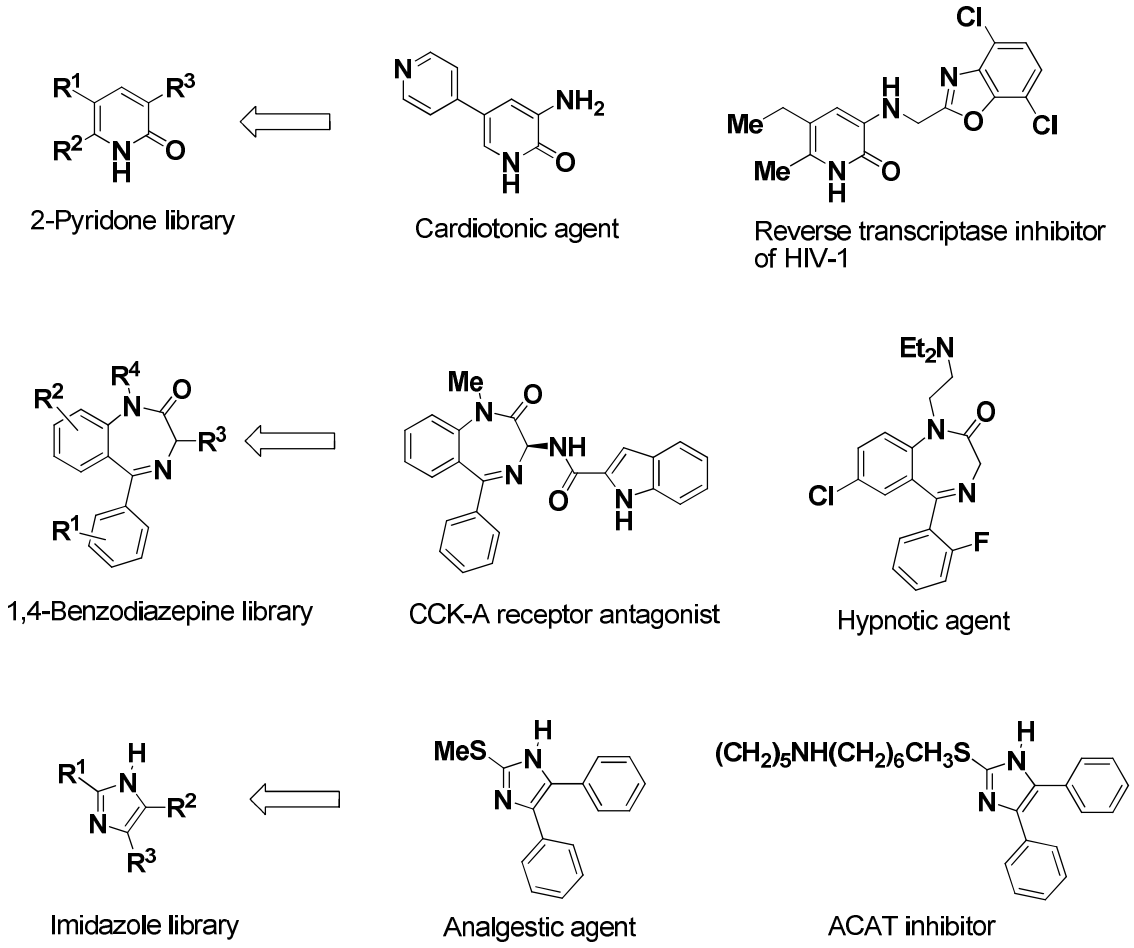
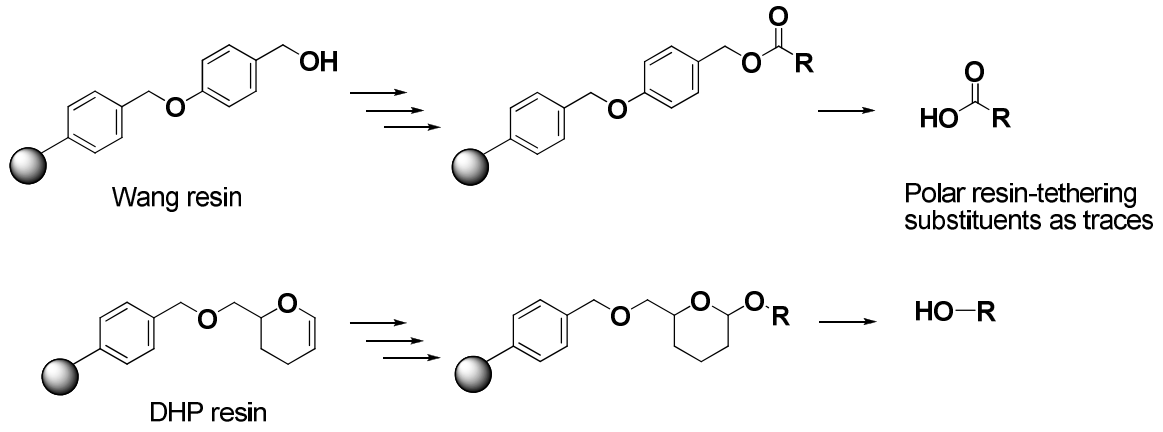


Figure 1-3. Existing libraries based on heterocyclic structures.

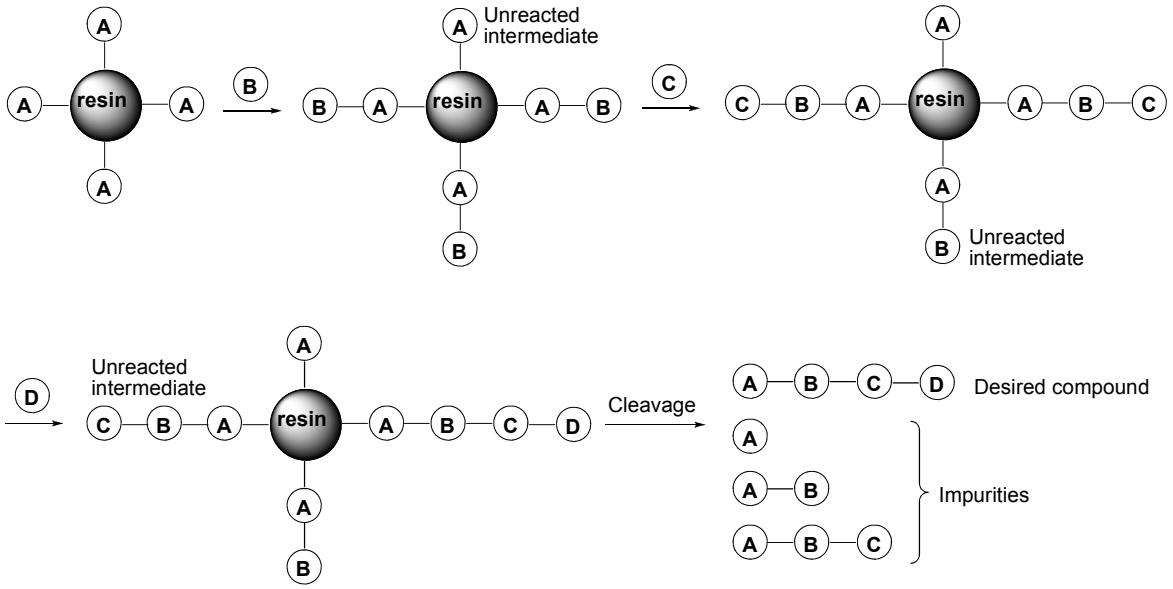
2. Synthetic strategy of chemical libraries including heterocycles

Two synthetic methods, namely conventional solution-phase method and solid-phase method, are used for synthesizing chemical libraries, although both methods have inevitable drawbacks, respectively. Solution-phase methods are inappropriate for the multi-step syntheses of the libraries due to tedious purification required in each step. On the other hand, solid-phase methods can omit the purification of synthetic intermediates but generate the final products with polar resin-tethering substituents. For example, compounds synthesized by using well-known Wang resin and DHP resin have carboxyl and hydroxyl groups as traces, respectively (Scheme 1-1). Such polar and metabolically labile functional groups often compromise bioavailability and reduce structural diversity of the chemical libraries.



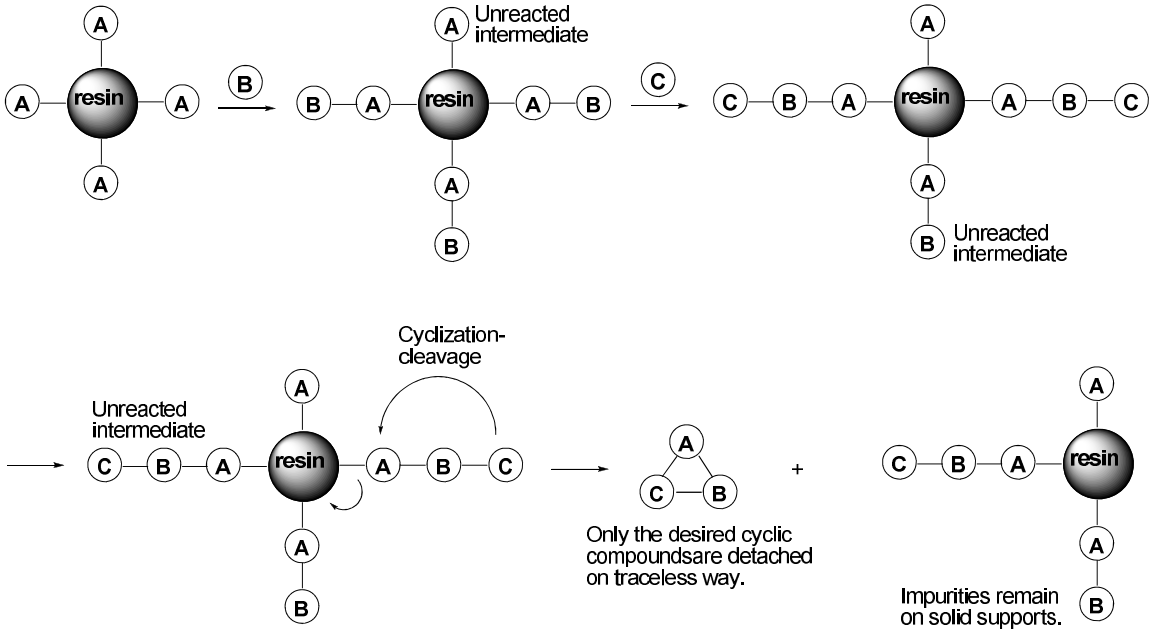
Scheme 1-1.

In addition, the cleavage reactions from the resin in the final step often give mixtures of desired compounds with many kinds of impurities generated by incomplete reactions on the polymer support in the previous steps. Therefore, purification after cleavage can not always provide the desired compounds in high purity (Scheme 1-2).



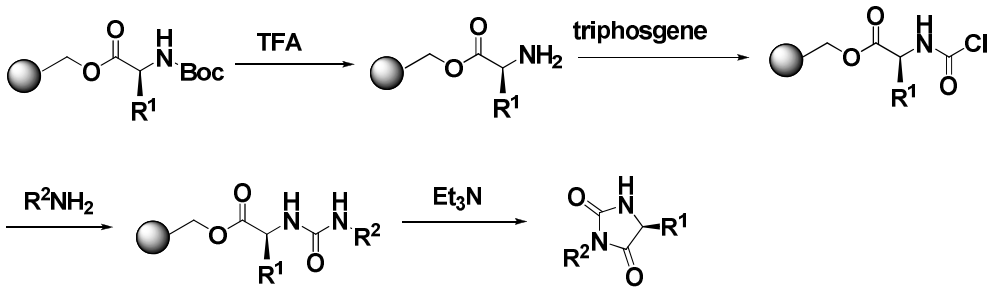
Scheme 1-2.

To overcome such disadvantage of conventional solid-phase synthesis and construct chemical libraries of heterocycles efficiently, cyclization-cleavage approaches are recognized highly valuable methods of solid-phase synthesis. One of advantages of the approach is that only the desired cyclic compounds are detached from solid supports (Scheme 1-3). The byproducts generated from incomplete and/or undesired reactions remain on solid supports. Consequently, these methods can provide the desired heterocycles in high purity without time-consuming purification steps like column chromatography. This preferable property regarding purification is quite suitable to construct chemical libraries consisting of large number of compounds. Another advantage is that desired compounds can be obtained on “traceless way” which leaves no evidence of resin attachment in the final products. This property is very important because polar functional groups as traces often have a dramatically negative outcome on the medicinal efficacy of the final products.



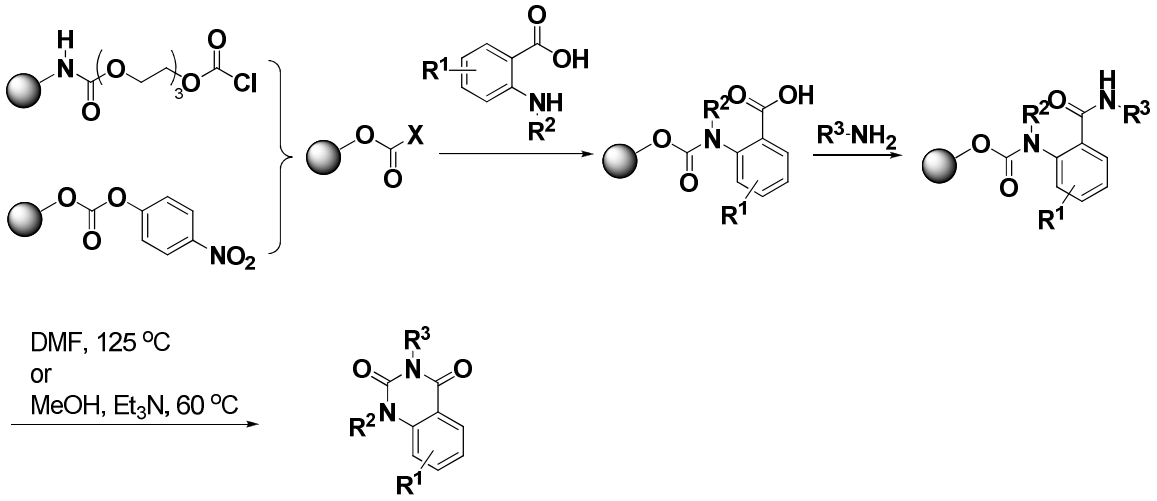
Scheme 1-3.

Recently several cyclization-cleavage approaches have been reported. The groups of Matthews and Kim elaborated strategies towards 1,3,5-trisubstituted hydantoins by employing mild base catalysis in the final step (Scheme 1-4).[9] The primary amine of amino acids loaded on Wang resin was treated with triphosgene and a broad range of aliphatic and aromatic primary amines to obtain ureas as hydantoin precursors. Addition of mild bases such as Et_3N liberated the 1,3,5-trisubstituted hydantoins in 48-100% yield, generally as a single peak on HPLC.



Scheme 1-4.

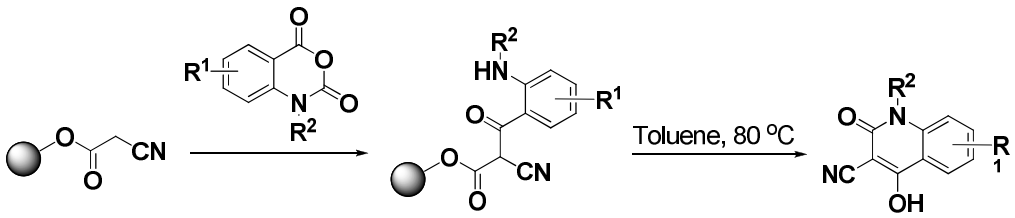
Concurrently, the groups of Smith and Martinez reported a similar cyclization-cleavage approach towards quinazoline-2,4-diones (Scheme 1-5).[10] In order to improve solvation properties, Smith, *et al.*, introduced a triethyleneglycol spacer unit between the polystyrene matrix and the starting activated carbonate (*i.e.* chloroformate), while Martinez *et al.* started with the mixed carbonate resin from *p*-nitrophenol and hydroxymethyl polystyrene. Anthranilic acids were reacted with activated resin-bound mixed carbonates, followed by PyBOP or BOP mediated amidation of the benzoic acid moieties with several aliphatic or aromatic primary amines. Cyclization-cleavage was accomplished under high temperatures (DMF, 125 ^{o}C) or by using base catalysis at elevated temperatures (Et_3N, MeOH, 125 ^{o}C,) to give the 1,3-disubstituted- (Smith) or 3-substituted-quinazoline-2,4-diones (Martinez). The yields were 22-72% with purities generally exceeding 95%.



Scheme 1-5.

Ganesan *et al.* showed that isatoic anhydrides can be transformed into 4-hydroxyquinolin-2(*1H*)ones in a two step procedure via Wang resin bound cyanoacetate (Scheme 1-6).[11] Reaction of the resin-bound activated methylene compound with isatoic

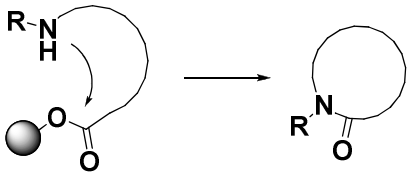
anhydrides employing Et_3N as a base proceeded smoothly at room temperature. After washing away the excess reagents, cyclization was effected by heating the resins in toluene at 80 ^{o}C to give the 4-hydroxyquinolin-2(*1H*)ones in yields of 22-65% with purities ranging from 72-99%.



Scheme 1-6.

3. Development of new solid-phase methods for heterecycles based on cyclization-cleavage approaches

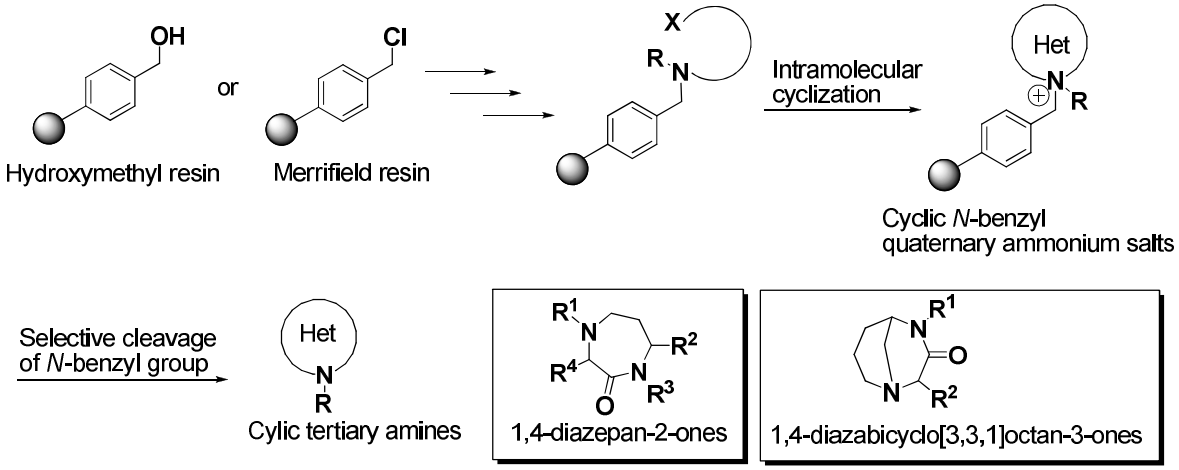
Besides examples described above, several heterocycles were reported to be successfully synthesized via cyclization-cleavage approaches, while most of them utilized intramolecular aminolysis of the resin-bound ester by the terminal amine as ring-closing reactions (Scheme 1-7).



Scheme 1-7.

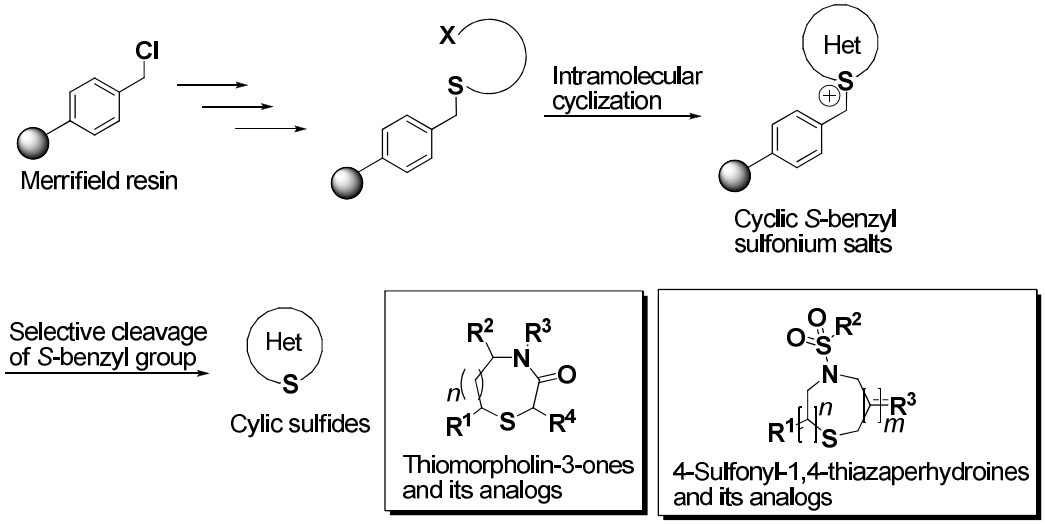
To construct more various heterocycles and expand diversity of chemical libraries for a purpose of raising hit rates of HTS, the author has embarked upon development of new solid-phase methods for heterecycles based on cyclization-cleavage approaches.

In chapter 2 and 3 is described traceless solid-phase syntheses of 1,4-diazepan-2-ones and 1,4-diazabicyclo[3.3.1]octan-3-ones via 'intramolecular cyclization to form cyclic *N*-benzyl quaternary ammonium salts' followed by 'selective cleavage of their *N*-benzyl group to release cyclic tertiary amines from solid supports' (Scheme 1-8).



Scheme 1-8.

Chapter 4 and 5 deals with thiomorpholin-3-ones and 4-sulfonyl-1,4-thiazaperhydroines as cyclic sulfides, which are provided by similar synthetic approach described above (Scheme 1-9).



Scheme 1-9.

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Chapter 2

Traceless Solid-Phase Synthesis of 1,4-Diazepan-2-ones

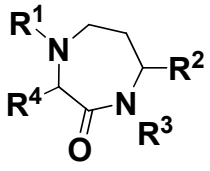
Abstract: A novel synthesis of 1,4-diazepan-2-ones using a traceless solid phase approach is described, in which many kinds of 1,4-diazepan-2-one have been efficiently obtained in high purity. The strategy is based on an intramolecular alkylation of tertiary amines, followed by elimination of the desired tertiary amines from the generated quaternary ammonium salts.

1. Introduction

Compounds having a 1,4-diazepan-2-one (Figure 2-1) skeleton have been known to show intriguing biological activities, e.g., antagonism on muscarinic receptors, inhibition of platelet aggregation, inhibition of HIV protease, inhibition of bacterial translocase (Figure 2-2).[1] Therefore this skeleton is very attractive as a template of chemical libraries to generate new bioactive compounds in high-throughput screenings. Compounds **2-1** have been synthesized using conventional solution-phase methods (Scheme 2-1),[2] although these methods are not applicable for multi-step syntheses of libraries, due to the purification required in each step.

On the other hand, efficient traceless syntheses of tertiary amines on polymer supports suitable for library syntheses have been reported.[3] However, no library synthesis of tertiary amines having the 1,4-diazepan-2-one skeleton has been reported.

In relation to the research to find new drug candidates from chemical libraries, the author developed an efficient traceless solid-phase synthesis of 1,4-diazepan-2-one derivatives via elimination of tertiary amines from quaternary ammonium salts on a polymer support.



2-1

Figure 2-1. 1,4-Diazepan-2-ones.

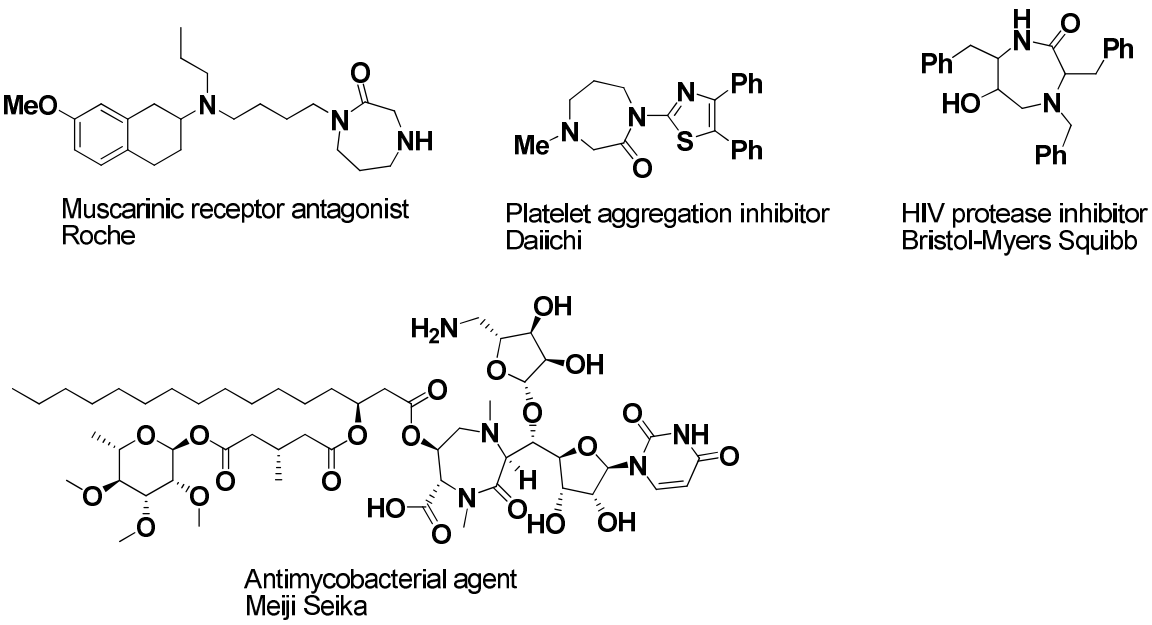
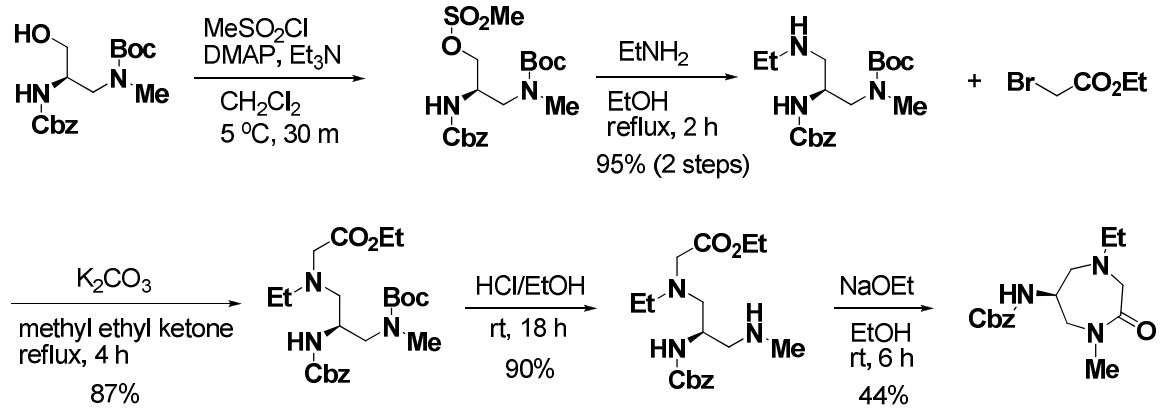


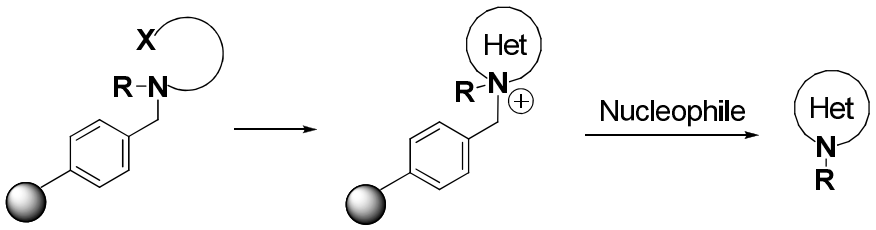
Figure 2-2. Bioactive 1,4-diazepan-2-ones.



Scheme 2-1. Conventional solution-phase synthesis of a 1,4-diazepan-2-one derivative.[2d]

2. Results and Discussion

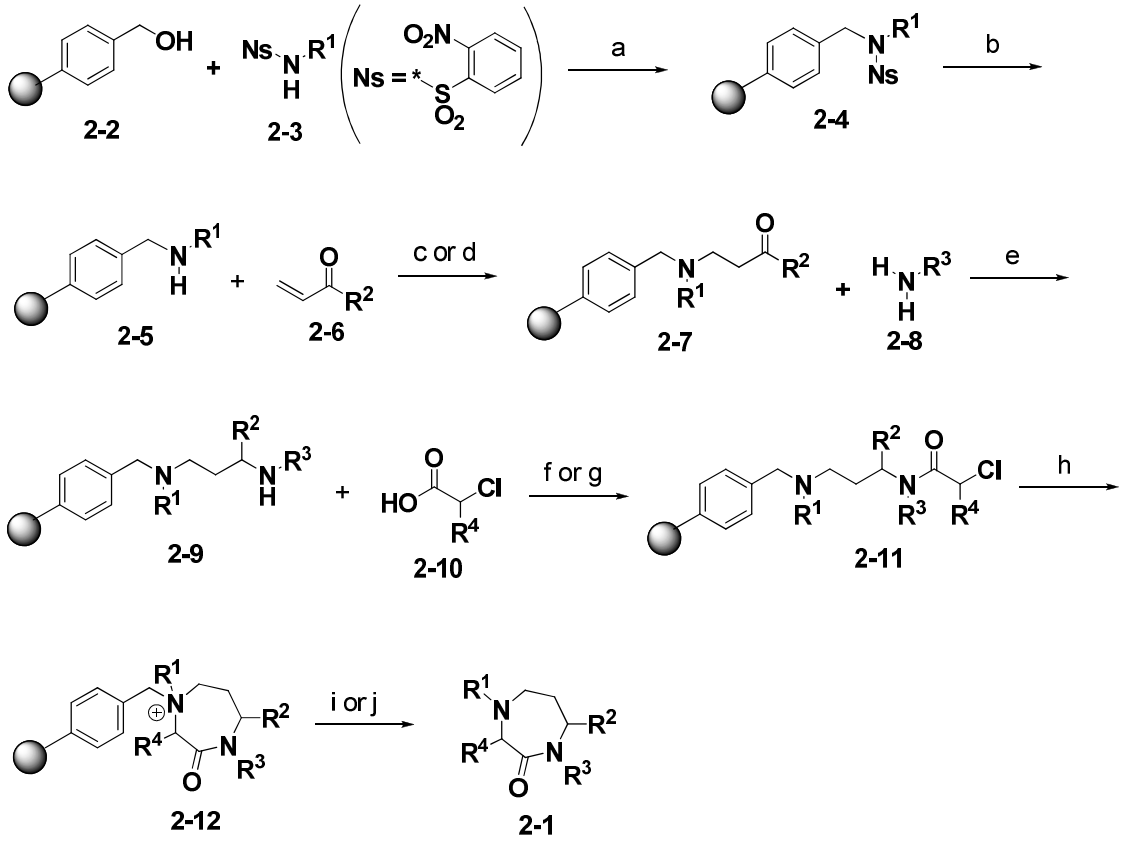
In many cases of multi-step solid-phase syntheses, products obtained by cleavage of the resin in the final step are often mixtures of the desired compounds, along with many impurities generated by incomplete reactions on the polymer support in the previous steps. In our strategy depicted in Scheme 2-2, the author expected that the debenzylation of quaternary ammonium salts by an S_N2 reaction could afford products in high purity without time-consuming purification steps such as column chromatography. By-products generated from incomplete and/or undesired reactions would remain on the solid support.[4] For instance, while the last debenzylation step might be accompanied by an S_N2 reaction at the α-position of the carbonyl group, the by-products generated from such an undesirable reaction would remain bound to the solid support and not reduce the purity of the products. In addition, all of the assumed unreacted intermediates would not be detached from the solid support at the end of the reaction scheme.



Scheme 2-2.

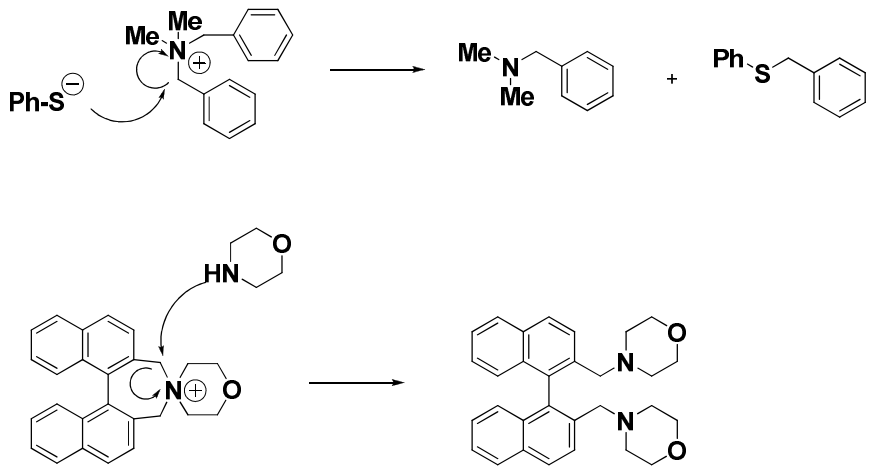
The synthesis began with Mitsunobu reaction on 4-hydroxymethyl polystyrene **2-2** with *N*-monosubstituted 2-nitrobenzenesulfonamides **2-3** (Scheme 2-3).[5,6] Next, *N, N*-disubstituted 2-nitrobenzenesulfonamides **2-4** provided the secondary amines **2-5** by deprotection of the 2-nitrobenzenesulfonyl (Ns) group. Next, by Michael addition, **2-5** were transformed into *β*-amino ketones **2-7**, which were then converted to the

corresponding diamines **2-9** by reductive amination. Diamines **2-9** were transformed into the key intermediates **2-11** by acylation with α-haloacetic acids **2-10**. Intramolecular cyclization and the quaternarization of the resin-bound tertiary nitrogen were carried out in the presence of CsI in dioxane-H_2O at 95 ºC. The products **2-12** were treated with thiols under conditions reported in the literature[7a] to provide the desired compound **2-1** in high purity without column chromatography purification.



Scheme 2-3. (a) **2-3**, PPh_3, DEAD, THF, rt, 16 h; (b) $HOCH_2CH_2SH$, DBU, DMF, rt, 1 h; (c) **2-6**, $ClCH_2CH_2Cl$, 40 ºC, 72 h; (d) **2-6**, $ClCH_2CH_2Cl$, 80 ºC, 96 h; (e) $NaBH(OAc)_3$, **2-8**, CH_2Cl_2, rt, 48 h; (f) DIC, **2-10**, DMF, rt, 20 h; (g) PyBrop, **2-10**, *i*-Pr_2NEt, rt, 20 h; (h) CsI, dioxane, water, 95 ºC, 3 h; (i) $HOCH_2CH_2SH$, 2 N NaOH aq, EtOH, 70 ºC, 3 h; (j) $HSCH_2CO_2H$, 2 N NaOH aq, EtOH, 70 ºC, 3 h.

There have been some reports that *N*-benzyl groups of quaternary ammonium salts were cleaved by several nucleophiles (Scheme 2-4).[7] Among them, the author chose thiolates because they have high nucleophilicity and can cleave *N*-benzyl groups of quaternary ammonium salts in relatively mild conditions and keep *N*-benzyl groups of primary, secondary and tertiary amines intact to afford products in high purity.



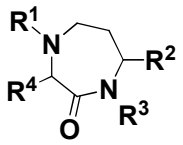
Scheme 2-4.

To demonstrate the usefulness of this approach, several 1,4-diazepan-2-one derivatives were synthesized and characterized. Representative results of these syntheses are shown in Table 2-1. Alkyl and aryl groups could be introduced at R^1–R^4 with high purities and moderate total yields, while compounds with functional groups such as basic nitrogen could also be obtained (Entry 9). It is worth noting that introduction of the benzyl groups at R^1 (Entries 2–4) was also possible, but the yields were relatively low (Entries 3 and 4) under these conditions because nucleophilic attack during the last step might have occurred at R^1 instead of the resin-bound benzyl group. Although 2-hydroxyethyl benzyl sulfides might be detached from solid supports under this cleavage condition, such

impurities can be removed by simple solid-phase-extraction based on cation exchange. Introduction of substituents at R^4 gave mixtures of diastereomers. Unexpectedly, the major/minor diastereomer ratio exceeded 90:10 because epimerization might have occurred at the final cleavage step under the basic conditions at 70 ºC. Compound **2-1g** having no substituents at R^2 could not be prepared, probably due to the instability of the intermediate (Entry 7). Compound **2-1j** lacking substituents at R^3 was obtained by this route, though the yield was low (Entry 10). In this case, reductive amination of ketone **2-7** with ammonia was needed. While many studies of reductive amination of ketones with primary and secondary amines on solid supports have been published, only one example using ammonia has been reported (Scheme 2-5).[8] At first, the conditions shown in Scheme 2-5 was applied to prepare diamine **2-9,** but the reaction did not proceed at all. In fact, MeOH used as a solvent to dissolve NH_4OAc was not suitable for solid-phase synthesis because of its low swelling property. The reductive amination was then successfully achieved by bubbling ammonia gas through the CH_2Cl_2 solution. This method could be widely applied to reductive amination on solid-phase synthesis.

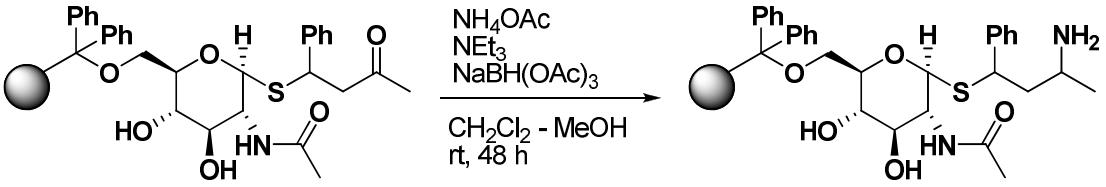
In conclusion, the author has demonstrated that 1,4-diazepan-2-one derivatives can be obtained in good yields and high purity based on the novel traceless solid-phase synthesis. This approach should be applicable to construct novel and diverse chemical libraries for high-throughput screenings to find the new compounds showing biological activities.

Table 2-1. Syntheses of 1,4-diazepan-2-one derivatives **2-1**



Entry	**2-1**	R^1	R^2	R^3	R^4	**2-5→ 2-7**	**2-9→ 2-11**	**2-12→ 2-1**	Yield[a] (purity[b])	dr[c]
1	**2-1a**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	44% (97%)	-
2	**2-1b**	(4-Br)$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	45% (98%)	-
3	**2-1c**	$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	33% (97%)	-
4	**2-1d**	(4-MeO)$PhCH_2$	Et	(4-F)$PhCH_2CH_2$	H	c	f	i	18% (95%)	-
5	**2-1e**	Ph	Et	(4-F)$PhCH_2CH_2$	H	d	f	i	25% (98%)	-
6	**2-1f**	(4-Br)$PhCH_2CH_2$	Me	(4-F)$PhCH_2CH_2$	H	c	f	i	48% (91%)	-
7	**2-1g**	(4-Br)$PhCH_2CH_2$	H	(4-F)$PhCH_2CH_2$	H	c	f	i	0%	-
8	**2-1h**	(4-Br)$PhCH_2CH_2$	Et	(4-CF_3O)Ph	H	c	g	i	27% (97%)	-
9	**2-1i**	(4-Br)$PhCH_2CH_2$	Et	(4-NMe_2)$PhCH_2$	H	c	f	i	51% (95%)	-
10	**2-1j**	(4-Br)$PhCH_2CH_2$	Et	H	H	c	f	j[d]	16% (92%)	-
11	**2-1k**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	Me	c	f	i	32% (97%)	99:1
12	**2-1l**	(4-Br)$PhCH_2CH_2$	Et	(4-F)$PhCH_2CH_2$	Ph	c	f	i	23% (93%)	95:5

[a] Isolated overall yields (7 steps) based on **2-2**. [b] HPLC was carried out using a reverse phase column [ODS, eluent: CH_3CN/20 mM phosphate buffer (pH 6.5)]. Purity was determined by summation of integrated HPLC peak areas at 210 nm. [c] HPLC was carried out using a column with a chiral stationary phase (Chiralpak IA, eluent: hexane/2-PrOH) because a reverse phase column (ODS) could not achieve separation of diastereomers. Ratio of the diastereomers was determined by summation of integrated HPLC peak areas at 210 nm. [d] Condition j gave a slightly higher purity of 92% than condition i (purity of 89%).



Scheme 2-5.

Experimental Section

Typical experimental procedure is as follows:

To a mixture of alkoxy resin **2-2** (18.0 g, 36 mmol, Polymer Laboratories; 2.0 mmol/g), *N*-[2-(4-bromophenyl)ethyl]-2-nitrobenzenesulfonamide **2-3** (27.7 g, 72 mmol) and PPh_3 (18.9 g, 72 mmol) in THF (300 ml) was added a 40% toluene solution of DEAD (33.3 ml, 72 mmol) at 0 ºC. After stirring for 5 min, the whole was allowed to stir at room temperature for 20 h. The resin was washed with CH_2Cl_2 (x5), THF (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) to give **2-4**. To the resin **2-4** in DMF (500 ml) was added DBU (53.8 ml, 360 mmol) and sulfanylethanol (25.2 ml, 360 mmol) at 0 ºC. After stirring for 2 min, the whole was allowed to stir at room temperature for 1 h. The resin was washed with Et_3N-water (1:9, x3), DMF (x3), water (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) and was dried *in vacuo* (**2-5**: 24.8 g; equivalent to 1.45 mmol/g). To the resin **2-5** (413 mg, 0.6 mmol) in $ClCH_2CH_2Cl$ (20 ml) was added but-1-en-3-one (0.95 ml, 12 mmol). The whole was allowed to stir at 40 ^oC for 72 h. The resin was washed with CH_2Cl_2 (x5), THF (x5), Et_2O (x5) and MeOH (x5). The resin **2-7** was suspended in a mixture of sodium triacetoxyborohydride (636 mg; 3 mmol), 2-(4-fluoropheny)ethylamine (334 mg; 2.4 mmol) and CH_2Cl_2 (10 ml) and stirred at room temperature for 48 h, then diluted with Et_3N (2 ml) and water (10 ml). The resin washed with Et_3N-water (1:9, x3), water (x3), MeOH (x3), CH_2Cl_2 (x5), Et_2O (x5) and MeOH (x5) to give **2-9**. Obtained resin **2-9** was swollen with a mixture of chloroacetic acid (680 mg; 7.2 mmol), diisopropylcarbodiimide (1.11 ml, 7.2 mmol), DMF (15 ml) and the mixture was agitated for 20 h at room temperature. Then the resin was washed with DMF (x5), Et_3N-water (1:9,

x5), THF (x5) and MeOH (x5) to give **2-11**. The resin **2-11** was swollen with a mixture of CsI (312 mg, 1.2 mmol), dioxane (16 ml) and water (4 ml) and stirred at 95 ºC for 3 h. Then to the mixture were added sulfanylethanol (540µl, 7.2 mmol), 2N NaOH (3 ml, 6 mmol), and EtOH (20 ml) and the whole was allowed to stir at 70 ºC for 3 h. The resin was washed with MeOH-$CHCl_3$ (1:4, x3) and EtOH (x5) and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with brine and dried with Na_2SO_4 and evaporated. The residue was diluted with MeOH and the impurities generated from sulfanylethanol was removed by solid phase extraction (500 mg, Polymer Laboratories; PL-SO_3H MP SPE) to provide product **2-1a** as a pale yellow oil (126 mg, 44%).

All products gave satisfactory 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR and MS spectra. The spectral data of **2-1** are given below:

4-[2-(4-Bromophenyl)ethyl]-7-ethyl-1-[2-(4-fluorophenyl)ethyl]-1,4-diazaperhydroepin-2-one (2-1a). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45 (2H, d, J = 8.19 Hz), 7.29-7.24 (2H, m), 7.17 (2H, d, J = 8.19 Hz), 7.10-7.06 (2H, m), 3.93-3.87 (1H, m), 3.49 (1H, d, J = 15.62 Hz), 3.30-3.22 (2H, m), 3.09-3.00 (1H, m), 2.92-2.58 (8H, m), 1.83-1.60 (4H, m), 0.84 (3H, t, J = 7.17 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 24.6, 28.0, 33.4, 33.5, 50.1, 51.4, 55.8, 59.7, 60.7, 115.2 (d, J = 21.1 Hz), 119.8, 130.2 (d, J = 7.7 Hz), 130.5, 131.4, 134.8 (d, J = 3.2 Hz), 139.1, 161.5 (d, J = 242.5 Hz), 172.3; IR (KBr) ν_{max}: 2938, 1627, 1509, 1222, 824, 511; MS: m/z 447/449 $[M+H]^+$.

4-[2-(4-Bromophenyl)methyl]-7-ethyl-1-[2-(4-fluorophenyl)ethyl]-1,4-diazaperhydr

oepin-2-one (2-1b). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51 (2H, d, J = 8.19 Hz), 7.33-7.30 (2H, m), 7.21 (2H, d, J = 8.19 Hz), 7.15-7.11 (2H, m), 4.02-3.92 (1H, m), 3.52-3.42 (3H, m), 3.21-3.06 (3H, m), 2.88-2.77 (3H, m), 2.64-2.57 (1H, m), 1.87-1.66 (4H, m), 0.85 (3H, t, J = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 24.8, 28.4, 33.5, 49.4, 51.3, 58.8, 60.3, 60.6, 115.2 (d, J = 21.1 Hz), 121.0, 130.3 (d, J = 7.9 Hz), 130.5, 131.5, 134.9 (d, J = 3.2 Hz), 137.3, 161.6 (d, J = 242.7 Hz), 172.2; IR (KBr) ν_{max}: 2937, 1627, 1509, 1487, 1221, 825; MS: m/z 433/435 $[M+H]^+$.

7-Ethyl-1-[2-(4-fluorophenyl)ethyl]-4-benzyl-1,4-diazaperhydroepin-2-one (2-1c). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33-7.22 (7H, m), 7.16-7.11 (2H, m), 3.99-3.90 (1H, m), 3.54 (1H, d, J = 13.313.31 Hz), 3.48 (1H, d, J = 13.313.31 Hz), 3.44 (1H, d, J = 15.62 Hz), 3.313.31-3.27 (1H, m), 3.21 (1H, d, J = 15.62 Hz), 3.11-3.04 (1H, m), 2.87-2.74 (3H, m), 2.62-2.56 (1H, m), 1.88-1.66 (4H, m), 0.85 (3H, t, J = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 24.7, 28.3, 33.5, 49.2, 51.4, 59.6, 60.5, 60.6, 115.2 (d, J = 21.1 Hz), 127.2, 128.3, 128.8, 130.3 (d, J = 7.8 Hz), 134.9 (d, J = 3.3 Hz), 138.3, 161.6 (d, J = 242.7 Hz), 172.4; IR (KBr) ν_{max}: 2968, 2938, 1628, 1510, 1221, 825, 700; MS: m/z 355 $[M+H]^+$.

7-Ethyl-1-[2-(4-fluorophenyl)ethyl]-4-[(4-methoxyphenyl)methyl]-1,4-diazaperhydroepin-2-one (2-1d). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.33-7.29 (2H, m), 7.17-7.10 (4H, m), 6.87 (2H, d, J = 8.45 Hz), 3.98-3.89 (1H, m), 3.74 (3H, s), 3.48-3.25 (4H, m), 3.19 (1H, d, J = 15.62 Hz), 3.10-3.04 (1H, m), 2.86-2.74 (3H, m), 2.61-2.53 (1H, m), 1.86-1.66 (4H, m), 0.85 (3H, t, J = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 24.7, 28.4, 33.5, 49.1, 51.4, 55.2, 59.0, 60.3, 60.7, 113.7, 115.2 (d, J = 21.1 Hz), 130.0, 130.3 (d, J = 8.3 Hz), 132.0, 135.0 (d, J = 3.1 Hz), 158.8, 161.6 (d, J = 242.6 Hz), 172.5; IR (KBr) ν_{max}: 2937,

1624, 1509, 1247, 1221, 826; MS: m/z 385 $[M+H]^+$.

7-Ethyl-1-[2-(4-fluorophenyl)ethyl]-4-phenyl-1,4-diazaperhydroepin-2-one (2-1e). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (2H, m), 6.88-6.78 (7H, m), 4.27 (1H, d, *J* = 16.64 Hz), 4.22-4.15 (1H, m), 4.02 (1H, d, *J* = 16.64 Hz), 3.72-3.69 (1H, m), 3.37-3.29 (1H, m), 3.00-2.93 (2H, m), 2.77-2.66 (2H, m), 1.80-1.54 (4H, m), 0.89 (3H, t, *J* = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 24.8, 28.2, 33.5, 44.6, 52.5, 56.5, 62.0, 113.3, 115.1 (d, *J* = 20.9 Hz), 117.8, 129.5, 130.3 (d, *J* = 7.8 Hz), 134.9 (d, *J* = 3.1 Hz), 147.6, 161.4 (d, *J* = 242.4 Hz), 172.7; IR (ATR) ν_{max}: 2965, 2935, 1623, 1598, 1506, 1218, 752; MS: m/z 341 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-1-[2-(4-fluorophenyl)ethyl]-7-methyl-1,4-diazaperhydroepin-2-one (2-1f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45 (2H, d, *J* = 8.45 Hz), 7.29-7.24 (2H, m), 7.17 (2H, d, *J* = 8.45 Hz), 7.11-7.07 (2H, m), 3.74-3.67 (1H, m), 3.58-3.52 (1H, m), 3.46 (1H, d, *J* = 15.62 Hz), 3.36 (1H, d, *J* = 15.62 Hz), 3.21-3.13 (1H, m), 2.95-2.88 (1H, m), 2.80-2.60 (7H, m), 1.90-1.80 (1H, m), 1.61-1.53 (1H, m), 1.21 (3H, t, *J* = 6.91 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4, 31.2, 33.4, 33.6, 50.1, 50.4, 56.4, 59.5, 115.2 (d, *J* = 21.1 Hz), 119.8, 130.3 (d, *J* = 7.8 Hz), 130.5, 131.8, 134.9 (d, *J* = 3.1 Hz), 139.1, 161.6 (d, *J* = 242.6 Hz), 172.4; IR (KBr) ν_{max}: 2936, 1627, 1509, 1489, 1221, 823; MS: m/z 433/435 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-7-ethyl-1-[4-(trifluoromethoxy)phenyl]-1,4-diazaperhydroepin-2-one (2-1h). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.46 (2H, d, *J* = 8.45 Hz), 7.37 (2H, d, *J* = 8.70 Hz), 7.28 (2H, d, *J* = 8.70 Hz), 7.20 (2H, d, *J* = 8.45 Hz), 3.67-3.60 (2H,

m), 3.55 (1H, d, *J* = 15.36 Hz), 3.08-2.99 (1H, m), 2.89-2.70 (5H, m), 2.19-2.13 (1H, m), 1.89-1.80 (1H, m), 1.72-1.61 (1H, m), 0.78 (3H, t, *J* = 7.17 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 25.0, 28.5, 33.4, 51.3, 59.6, 63.2, 119.2, 119.9, 121.7, 129.1, 130.6, 131.4, 139.0, 147.6, 173.0; IR (KBr) ν_{max}: 2939, 1648, 1508, 1262, 1163, 1262, 1163, 807; MS: m/z 485/487 $[M+H]^+$.

1-{[4-(Dimethylamino)phenyl]methyl}-4-[2-(4-bromophenyl)ethyl]-7-ethyl-1,4-diaza perhydroepin-2-one (2-1i). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45 (2H, d, *J* = 8.19 Hz), 7.17 (2H, d, *J* = 8.19 Hz), 7.09 (2H, d, *J* = 8.70 Hz), 6.63 (2H, d, *J* = 8.70 Hz), 4.94 (1H, d, *J* = 14.43 Hz), 3.84 (1H, d, *J* = 14.43 Hz), 3.54 (1H, d, *J* = 15.36 Hz), 3.41 (1H, d, *J* = 15.36 Hz), 3.24-3.16 (2H, m), 2.86 (6H, s), 2.73-2.60 (5H, m), 1.72-1.53 (4H, m), 0.81 (3H, t, *J* = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 24.2, 27.6, 33.4, 40.6, 50.3, 51.1, 55.6, 58.2, 59.7, 112.5, 119.7, 125.7, 129.6, 130.6, 131.3, 139.2, 149.9, 172.6; IR (KBr) ν_{max}: 2937, 1616, 1523, 1488, 1351, 1126, 808; MS: m/z 458/460 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-7-ethyl-1,4-diazaperhydroepin-2-one (2-1j). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (2H, d, *J* = 8.19 Hz), 7.08 (2H, d, *J* = 8.19 Hz), 5.61 (1H, s), 3.57 (1H, d, *J* = 15.11 Hz), 3.48 (1H, d, *J* = 15.11 Hz), 3.38-3.33 (1H, m), 3.16-3.11 (1H, m), 2.93-2.69 (5H, m), 1.79-1.70 (1H, m), 1.60-1.50 (3H, m), 0.98 (3H, t, *J* = 7.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.5, 28.9, 32.1, 33.4, 54.6, 55.2, 56.1, 58.9, 119.8, 130.5, 131.4, 139.0, 174.7; IR (ATR) ν_{max}: 2934, 1659, 1488, 1127, 810; MS: m/z 325/327 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-7-ethyl-1-[2-(4-fluorophenyl)ethyl]-3-methyl-1,4-diazap

erhydroepin-2-one (2-1k). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (2H, d, J = 8.19 Hz), 7.27-7.24 (2H, m), 7.16 (2H, d, J = 8.19 Hz), 7.12-7.08 (2H, m), 3.95-3.90 (1H, m), 3.80-3.71 (1H, m), 3.61-3.52 (1H, m), 3.27-3.20 (1H, m), 3.05-2.90 (2H, m), 2.82-2.55 (6H, m), 1.83-1.73 (1H, m), 1.65-1.47 (3H, m), 0.96-0.92 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 16.7, 26.4, 27.8, 35.2, 35.3, 44.9, 48.2, 50.9, 59.3, 59.4, 115.2 (d, J = 21.1 Hz), 119.8, 130.1 (d, J = 7.8 Hz), 130.6, 131.3, 135.0 (d, J = 3.2 Hz), 139.2, 161.6 (d, J = 242.7 Hz), 174.5; IR (KBr) ν_{max}: 2938, 1639, 1509, 1221, 825, 522; MS: m/z 461/463 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-7-ethyl-1-[2-(4-fluorophenyl)ethyl]-3-phenyl-1,4-diazap erhydroepin-2-one (2-1l). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.16 (9H, m), 7.01-6.91 (4H, m), 4.93 (1H, s), 3.97-3.87 (1H, m), 3.40-3.25 (2H, m), 3.14-3.06 (1H, m), 2.97-2.82 (5H, m), 2.72-2.69 (2H, m), 2.04-1.96 (1H, m), 1.49-1.25 (3H, m), 0.83 (3H, t, J = 7.30 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 16.7, 25.6, 27.9, 34.1, 34.2, 44.2, 49.3, 53.5, 59.7, 72.3, 115.2 (d, J = 21.0 Hz), 119.8, 127.1, 127.6, 128.1, 130.3 (d, J = 7.7 Hz), 130.5, 131.3, 134.9 (d, J = 3.2 Hz), 138.8, 139.1, 161.6 (d, J = 242.6 Hz), 173.3; IR (ATR) ν_{max}: 2937, 1649, 1612, 1509, 1488, 1219, 1156, 1072, 1011, 824, 719, 698, 516; MS: m/z 523/525 $[M+H]^+$.

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Chapter 3

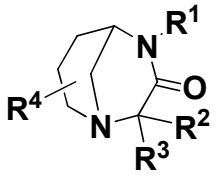
Traceless Solid-Phase Synthesis of 1,4-Diazabicyclo[3,.3.,1]octan-3-ones

Abstract: A novel synthesis of 1,4-diazabicyclo[3,.3,.1]octan-3-one derivatives using a traceless solid-phase approach is described, in which many kinds of 1,4-diazabicyclo[3,3,13.3.1]octan-3-one derivatives have been efficiently obtained in high purity, based on an intramolecular alkylation of tertiary amines followed by an elimination of desired tertiary amines from the generated quaternary ammonium salts.

1. Introduction

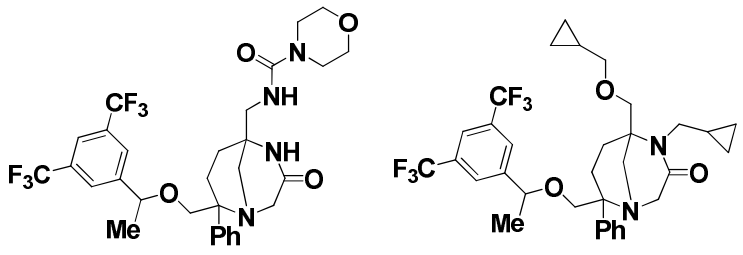
1,4-Diazabicyclo[3,3,13.3.1]octan-3-one (**3-1**) skeleton is very attractive as a template of a chemical library for drug discovery because the structure is unique and can be easily functionalized to provide a diverse library. Recently, compounds having this skeleton have been reported to show antagonism on the substance P receptor.[1] So far, 1,4-Diazabicyclo[3,3,13.3.1]octan-3-ones **(3-1)** have been synthesized using conventional solution-phase methods.[1,2]

Because of the high potency of this skeleton as a pharmacophore, the author intended to establish an efficient-traceless-solid-phase synthesis of 1,4-diazabicyclo[3,3,13.3.1]nonane derivatives via an elimination of cyclic tertiary amines from quaternary ammonium salts on polymer support in a similar way described in chapter 2.



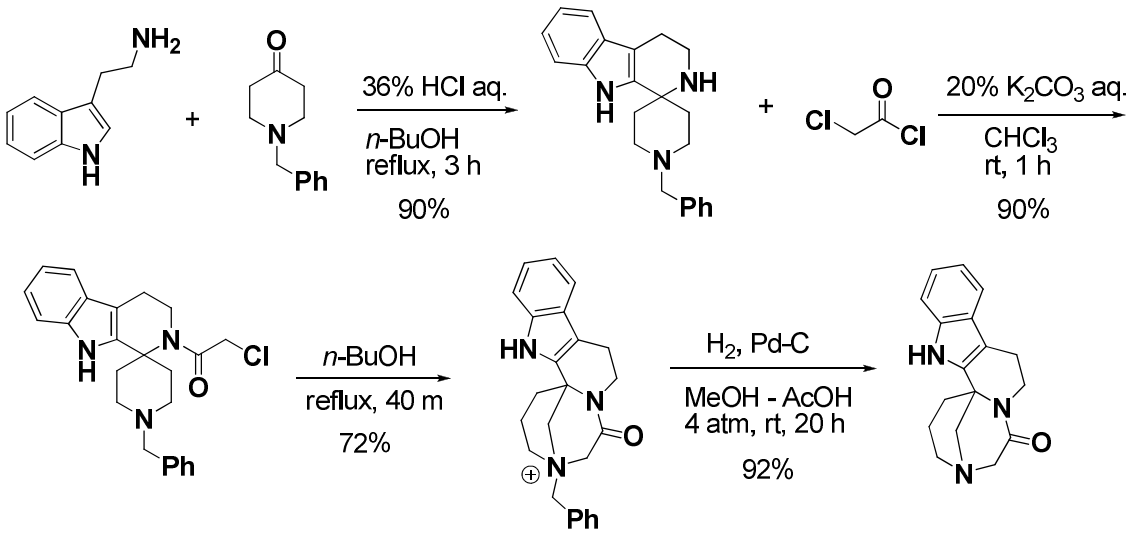
3-1

Figure 3-1. 1,4-Diazabicyclo[3,3,13.3.1]octan-3-ones.



NK1 antagonist
Schering-Plough

Figure 3-2. Bioactive 1,4-diazabicyclo[3,3,13.3.1]octan-3-ones.

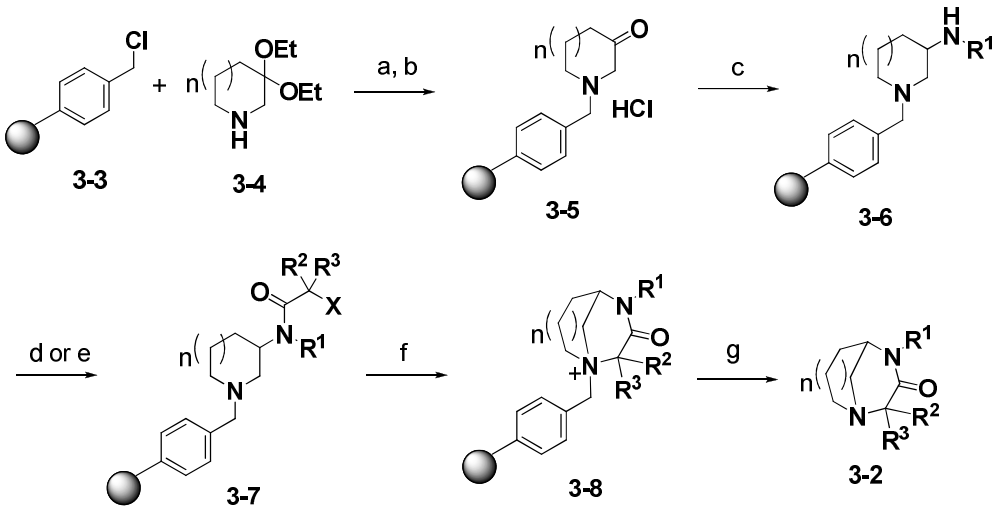

NH2
O
N
H
N
Ph
36% HCl aq.
n-BuOH
reflux, 3 h
90%
NH
N
H
N
Ph
Cl
O
Cl
20% K2CO3 aq.
CHCl3
rt, 1 h
90%
N
H
N
O
Cl
N
Ph
n-BuOH
reflux, 40 m
72%
HN
N
O
N
Ph
H2, Pd-C
MeOH - AcOH
4 atm, rt, 20 h
92%
HN
N
O
N

Scheme 3-1.[2b]

2. Results and Discussion

In our strategy depicted in Scheme 2-2 on chapter 2, the author expected that only desired heterocycles were detached from the polymer support by debenzylation of cyclic quaternary ammonium salts via S_N2 reaction and the byproducts generated from incomplete and/or undesired reactions remained on the polymer support. In this chapter, 1,4-diazabicyclo[3,3,13.3.1]nonane derivatives were efficiently synthesized via similar way.

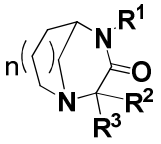
The synthesis began with the amination of Merrifield resin **3-3** with the cyclic amines **3-4** (Scheme 3-2). Next, the polymer-supported products were converted to the corresponding ketones **3-5**, which provided the diamine **3-6** by reductive amination. Then **3-6** were transformed into the key intermediates **3-7** by acylation with α-halo-acetic acids. The intramolecular cyclization, quaternarization of the tertiary nitrogen of the piperidine ring was carried out in the presence of *n*-Bu_4NI in DMF at 120 ºC, which was higher temperature than that of 1,4-diazepan-2-ones described on chapter 2 due to the strain of a 1,4-diazabicyclo[3,3,13.3.1]nonane structure. The products **3-8** were treated with mercaptoethanol under reported conditions to provide the desired compounds **3-2** in high purity without time-consuming purification steps like column chromatography.

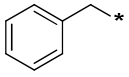
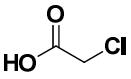
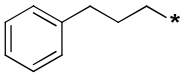
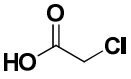
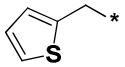
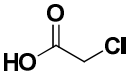
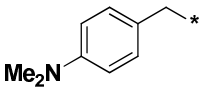
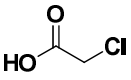
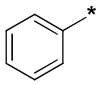
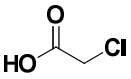
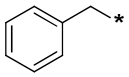
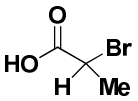
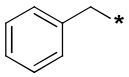
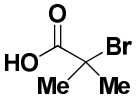
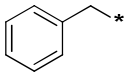
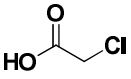


Scheme 3-2. (a) **3-4**, Et_3N, *n*-Bu_4I, DMF, 60 ºC, 24 h; (b) 6 N HCl aq., dioxane, rt, 2.5 h; (c) $NaBH(OAc)_3$, R^1NH_2, CH_2Cl_2, rt, 48 h; (d) DIC, $XCR^2R^3CO_2H$, DMF, rt, 20 h; (e) PyBrop, $XCR^2R^3CO_2H$, *i*-Pr_2NEt, rt, 20 h; (f) *n*-Bu_4NI, DMF, 120 ºC, 5.5 h; (g) $HOCH_2CH_2SH$, 2 N NaOH aq., EtOH, 70 ºC, 3 h.

To demonstrate the usefulness of this approach, several 1,4-diazabicyclo[3,3,13.3.1]octan-3-one derivatives were synthesized and characterized by ^{1}HNMR and MS. The representative results are shown in Table 1. Alkyl and aryl groups can be introduced in R^1 with high purities (>95%) and moderate or low total yields (5–51%) (Entries 1, 2, 3, 5), while a compound with basic nitrogen could be obtained (Entry 4). Effect of bulkiness of the substituents on α-position (R^2, R^3) of the carbonyl group on the yield was clearly observed (Entries 6 and 7), where monosubstitution is only successful, although disubstituted halide did not give the product. Construction of 1,4-diazabicyclo[3,2,1]octan-3-one skeleton (Entry 8) was also possible and this result would expand the diversity of the libraries based on this synthetic route.

Table 3-1. Syntheses of 1,4-diazabicyclo[3,3,13.3.1]octan-3-one derivatives **3-2**



Entry	3-2	n	R^1	R^2	R^3	Amide formation	Yield[a] (purity[b])
1	**3-2a**	1		H	H	d, 	51% (99.3%)
2	**3-2b**	1		H	H	d, 	46% (97.7%)
3	**3-2c**	1		H	H	d, 	47% (99.7%)
4	**3-2d**	1		H	H	d, 	26% (92.3%)
5	**3-2e**	1		H	H	e, 	5% (97.0%)
6	**3-2f**	1		H	Me	e, 	41% (97.0%)
7	**3-2g**	1		Me	Me	e, 	0%
8	**3-2h**	0		H	H	d, 	6% (95.2%)

[a]Isolated overall yields (6 steps) based on Merrifield resin (**3-3**).

[b]Reverse-phase HPLC was carried out using CH_3CN/20 mM phosphate buffer (pH 6.5). Flow rate: 1 mL/min. Column: ODS. HPLC purities were determined by summation of integrated HPLC peak areas at 220 or 210 nm.

In conclusion, the author has demonstrated that 1,4-diazabicyclo[3,3,13.3.1]octan-3-one derivatives can be obtained in good yields and high purity based on the novel traceless solid-phase synthesis. This approach should be applicable to construct novel and diverse chemical libraries for high-throughput screenings to find the new compounds showing

biological activities.

Experimental Section

Typical experimental procedure is as follows:

Merrifield resin **3-3** (51.9 g; 97.5 mmol, Polymer Laboratories; 1.88 mmol/g) was swollen with a mixture of DMF (600ml), 3,3-diethoxypiperidine **3-4** (n=1, 33.7 g, 195 mmol), *n*-Bu_4NI (2.4 g, 19.5 mmol) and the mixture was heated with slow stirring at 60 ºC for 24 h. The resin was washed with DMF (x5), DMF-water-Et_3N-EtOH (2:2:2:1, x5), water (x5), and MeOH (x5) and was dried *in vacuo* (**3-10**: 65.4 g; 100%; equivalent to 1.49 mmol/g). The resin **3-10** (805 mg; 1.2 mmol) was treated with 6 N HCl-dioxane (1:1, 10 ml) at room temperature for 2.5 h. Then the resin was washed with water (x5), MeOH (x5), CH_2Cl_2 (x5), and Et_2O (x5) to give **3-5**. The resin **3-5** was suspended in a mixture of sodium triacetoxyborohydride (1.27 g; 6 mmol), 3-phenyl-1-propylamine (649 mg; 4.8 mmol) and CH_2Cl_2 (20 ml) and stirred at room temperature for 48 h, then diluted with Et_3N (2 ml) and water (10 ml). The resin washed with Et_3N-water (1:9, x3), water (x3), MeOH (x3), CH_2Cl_2 (x5), and Et_2O (x5) to give **3-6**. Obtained resin **3-6** was swollen with a mixture of chloroacetic acid (1.36 g; 14.4 mmol), diisopropylcarbodiimide (2.23 ml, 14.4 mmol), DMF (15 ml) and the mixture was agitated for 20 h at room temperature. Then the resin was washed with DMF (x5), Et_3N-water (1:9, x5), CH_2Cl_2 (x5), MeOH (x5), and *N*-methylpyrrolidone (x5) to give **3-7**. The resin **3-7** was swollen with a mixture of *n*-Bu_4NI (456 mg; 3.6 mmol), *N*-methylpyrrolidone (10 ml) and stirred slowly at 120 ºC for 5.5 h. Then the resin was washed with DMF (x5), CH_2Cl_2 (x5), MeOH (x5), and EtOH (x5) to give **3-8**. The resin was swallen with a mixture of mercaptoethanol (540 μl, 7.2 mmol), 2 N NaOH (3 ml, 6 mmol), and EtOH (20 ml) and stirred at 70 ºC for 3 h. The

resin was washed with MeOH-$CHCl_3$ (1:4, x3) and EtOH (x5) and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was removed. The aqueous layer was saturated with NaCl and washed with AcOEt. The combined organic washings were dried with Na_2SO_4 and evaporated. The residue was diluted with MeOH and the residual mercaptoethanol was removed by solid phase extraction (Varian Bond Elut, 1 g) to provide product **3-2b** as a pale yellow oil (142 mg, 46%).

All products gave satisfactory 400 MHz ^{1}H NMR and MS spectra. The spectral data of **3-2** are given below:

1,4-Diaza-4-benzylbicyclo[3.3.13.3.1]nonan-3-one (3-2a). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35-7.24 (5H, m), 4.97 (1H, d, J = 15.11 Hz), 4.09 (1H, d, J = 15.11 Hz), 3.62 (1H, d, J = 18.18 Hz), 3.23-3.13-3.16 (2H, m), 2.98-2.84 (4H, m), 1.81-1.76 (1H, m), 1.63-1.51 (2H, m), 1.32-1.23 (1H, m); MS: m/z 231 $[M+H]^+$.

1,4-Diaza-4-(3-phenylpropyl)bicyclo[3.3.13.3.1]nonan-3-one (3-2b). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29-7.15 (5H, m), 3.75-3.68 (1H, m), 3.46 (1H, d, J = 17.92 Hz), 3.40-3.30 (1H, m), 3.05 (1H, d, J = 17.92 Hz), 2.92-2.78 (5H, m), 2.56 (2H, t, J = 7.94 Hz), 1.89-1.70 (3H, m), 1.63-1.45 (2H, m), 1.30-1.26 (1H, m); MS: m/z 259 $[M+H]^+$.

1,4-Diaza-4-(2-thienylmethyl)bicyclo[3.3.13.3.1]nonan-3-one (3-2c). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.42 (1H, dd, J = 5.12, 1.28 Hz), 7.04 (1H, dd, J = 3.58, 1.28 Hz), 6.95 (1H, dd, J = 3.58, 5.12 Hz), 4.93 (1H, d, J = 14.89 Hz), 4.41 (1H, d, J = 14.89 Hz),

3.54 (1H, d, *J* = 18.18 Hz), 3.16 (1H, d, *J* = 18.18 Hz), 2.93-2.79 (4H, m), 1.84-1.74 (1H, m), 1.61-1.45 (2H, m), 1.29-1.23 (1H, m); MS: m/z 237 $[M+H]^+$.

1,4-Diaza-4-{[4-(dimethylamino)phenyl]methyl}bicyclo[3.3.13.3.1]nonan-3-one (3-2d). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (1H, d, *J* = 8.45 Hz), 6.67 (1H, d, *J* = 8.45 Hz), 4.84 (1H, d, *J* = 14.59 Hz), 3.96 (1H, d, *J* = 14.59 Hz), 3.58 (1H, d, *J* = 17.92 Hz), 3.22 (1H, m), 3.18 (1H, d, *J* = 17.92 Hz), 2.89 (4H, m), 2.86 (6H, s), 1.81-1.76 (1H, m), 1.56-1.48 (2H, m), 1.29-1.25 (1H, m); MS: m/z 274 $[M+H]^+$.

1,4-Diaza-4-phenylbicyclo[3.3.13.3.1]nonan-3-one (3-2e). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.45-7.38 (2H, m), 7.31-7.25 (3H, m), 3.73 (1H, m), 3.64 (1H, d, *J* = 18.18 Hz), 3.64 (1H, d, *J* = 18.18 Hz), 3.313.31-3.26 (2H, m), 3.07-3.03 (1H, m), 2.96-2.93 (2H, m), 1.91-1.77 (1H, m), 1.69-1.54 (2H, m), 1.42-1.35 (1H, m); MS: m/z 217 $[M+H]^+$.

1,4-Diaza-2-methyl-4-benzylbicyclo[3.3.13.3.1]nonan-3-on (3-2f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34-7.23 (5H, m), 4.97 (1H, d, *J* = 14.85 Hz), 4.02 (1H, d, *J* = 14.85 Hz), 3.72-3.65 (1H, m), 3.63 (1H, q, *J* = 7.42 Hz), 3.23 (1H, m), 3.11-2.99 (3H, m), 2.76-2.68 (1H, m), 1.87-1.79 (1H, m), 1.60-1.53 (1H, m), 1.48-1.32 (1H, m), 1.27 (3H, d, *J* = 7.42 Hz), 1.23 (1H, m); MS: m/z 245 $[M+H]^+$.

1,4-Diaza-4-benzylbicyclo[3.2.1]octan-3-one (3-2h). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.29-7.15 (5H, m), 4.81 (1H, d, *J* = 14.85 Hz), 4.08 (1H, d, *J* = 14.85 Hz), 3.70 (1H, m), 3.50 (1H, d, *J* = 17.67 Hz), 3.08 (1H, m), 3.07 (1H, d, *J* = 17.67 Hz), 2.97-2.84 (2H, m), 2,48-2,42 (1H, m), 1.89-1.85 (1H, m), 1.78-1.70 (1H, m); MS: m/z 217 $[M+H]^+$.

References and Notes

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Chapter 4

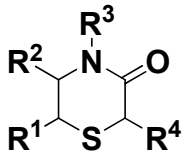
Traceless Solid-Phase Synthesis of Thiomorpholin-3-ones

Abstract: A novel synthesis of thiomorpholin-3-ones using a traceless solid-phase approach is described, in which many kinds of thiomorpholin-3-ones were efficiently obtained in high purity based on an intramolecular alkylation of sulfides followed by an elimination of desired thiomorpholin-3-ones from the generated sulfonium salts.

1. Introduction

Compounds having thiomorpholin-3-one skeletons (Figure 4-1) have been known to show intriguing biological activities, *e.g.,* enhancement of brain noradrenaline and dopamine turnover (cognition enhancement),[1] hypnotic activity,[2] antagonism on 5-HT1b receptor,[3] EP4 receptor,[4] integrin α4β1,[5] inhibition on nitric oxide synthase,[6] calcium channel blockade,[7] acne therapy,[8] *etc* (Figure 4-2). Therefore, this skeleton is very attractive as a template for chemical libraries to generate newly-bioactive compounds on high-throughput screenings.

Compounds **4-1** have been synthesized using conventional solution-phase methods (Scheme 4-1)[2, 9, 10] and solid-phase methods (Scheme 4-2),[11-13] although both methods have the drawbacks for synthesizing chemical libraries, which were described on chapter 1. In relation to the research to find new drugs from the chemical library, the author developed an efficient traceless solid-phase synthesis of thiomorpholin-3-ones.



4-1

Figure 4-1. Thiomorpholin-3-ones.

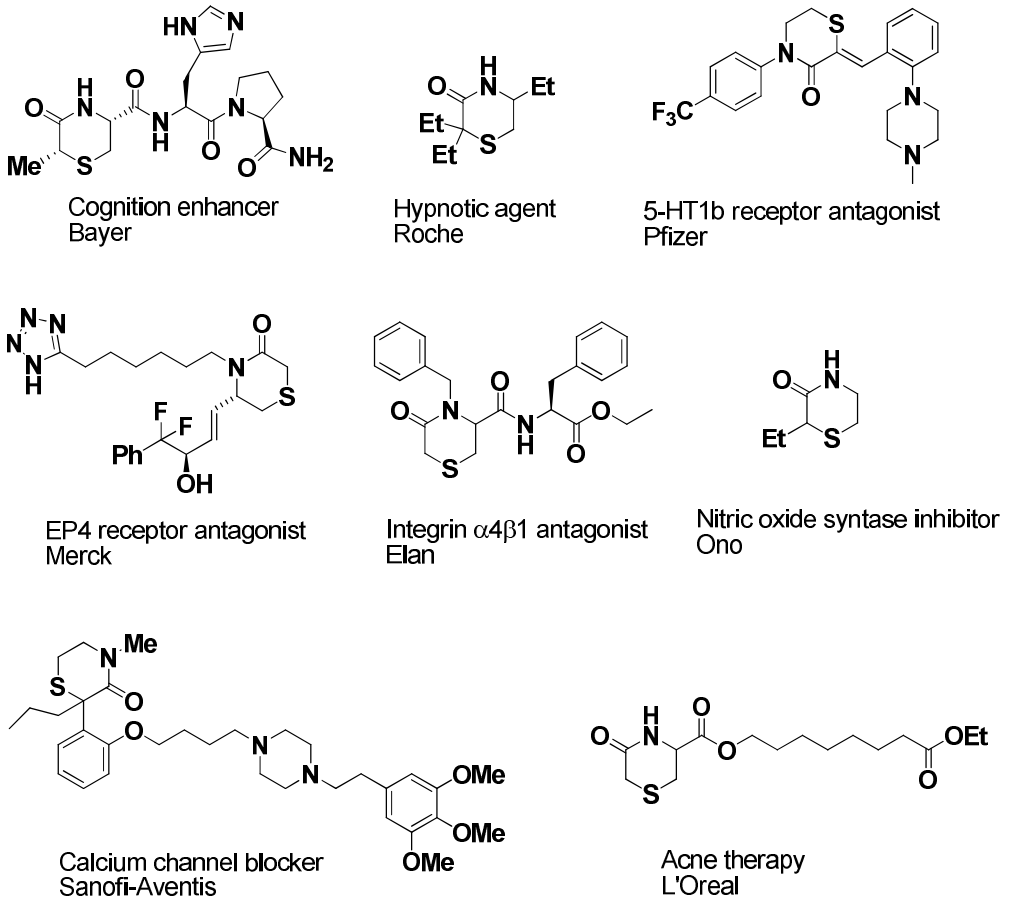
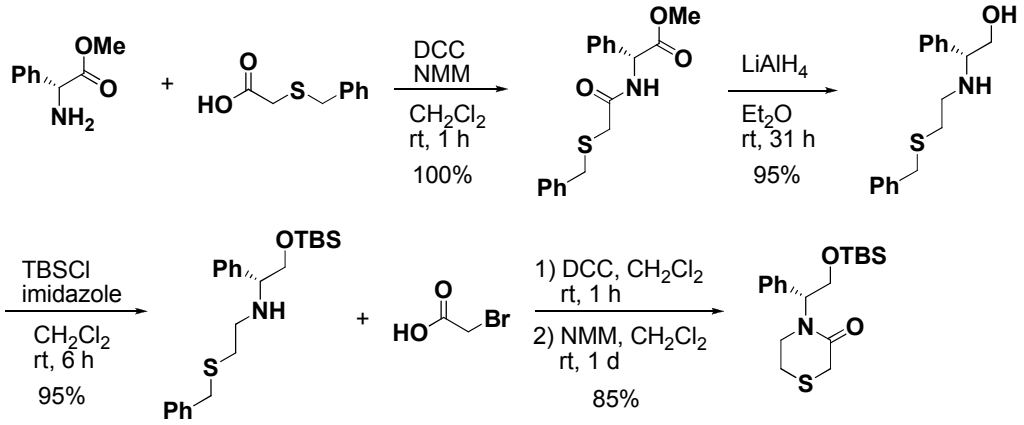
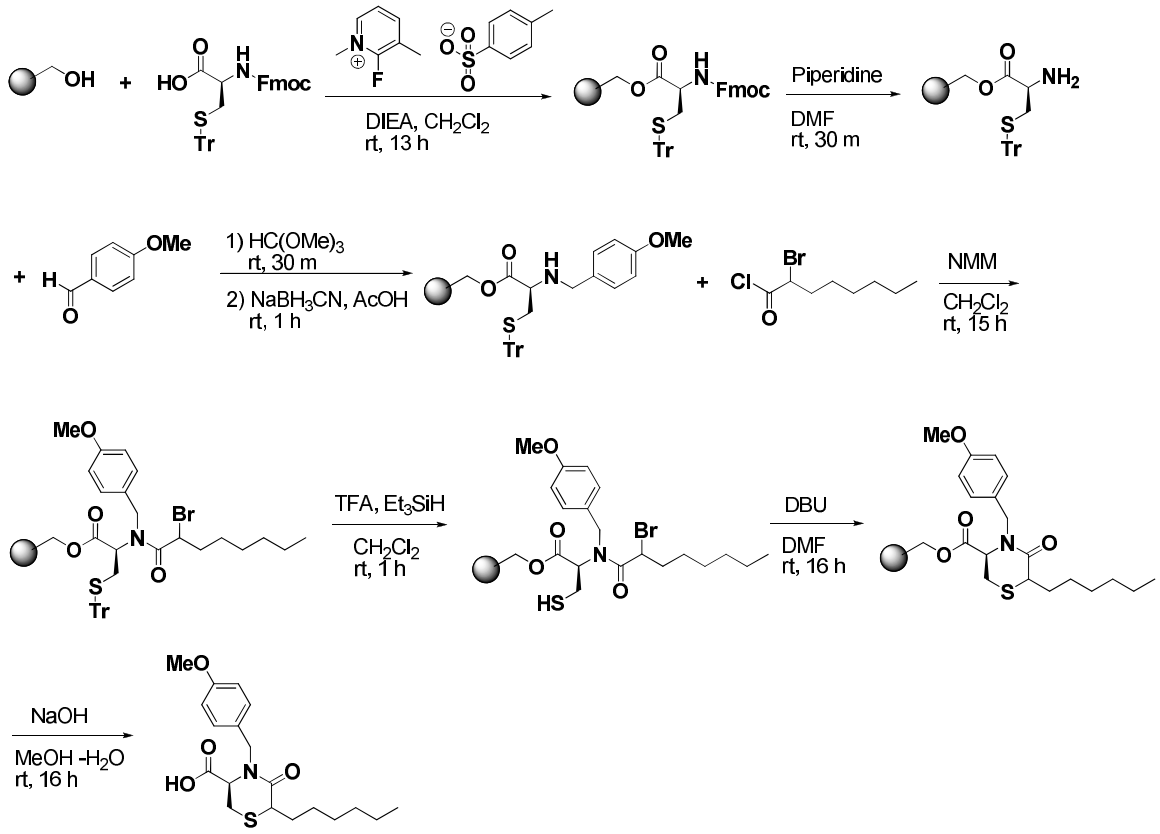


Figure 4-2. Bioactive thiomorpholin-3-ones.



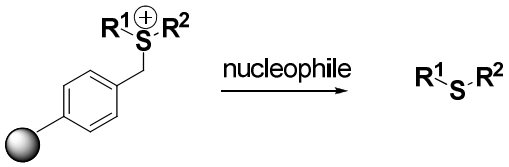
Scheme 4-1. Conventional solution-phase synthesis of a thiomorpholin-3-one derivative.[9]



Scheme 4-2. Conventional solid-phase synthesis of a thiomorpholin-3-one derivative.[12]

2. Results and Discussion

The traceless solid-phase syntheses of cyclic tertiary amines were effected based on the selective debenzylation of *N*-benzyl quaternary ammonium salts as described in former chapters. This methodology was then successfully applied to construction of cyclic sulfide structures via *S*-benzyl sulfonium salts (Scheme 4-3). The results are shown below.

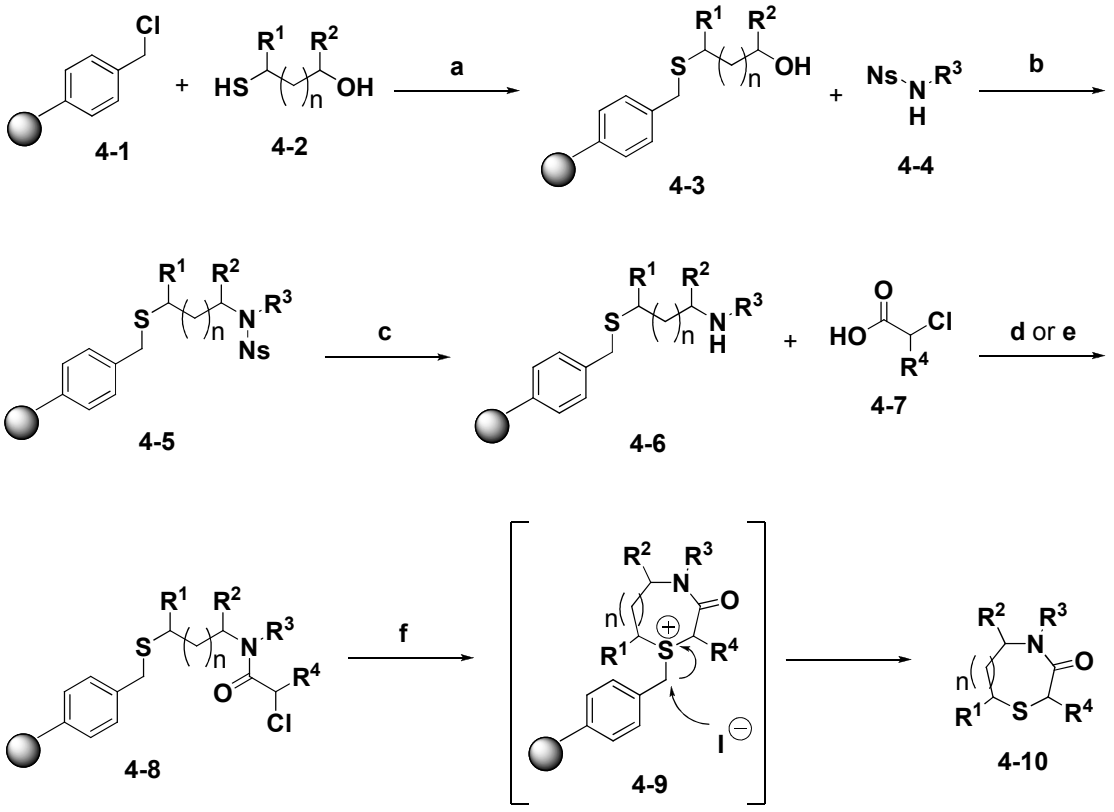


Scheme 4-3.

The synthesis began with the nucleophilic displacement of benzyl chloride on Merrifield resin **4-1** with the sulfanylethanols **4-2** (Scheme 4-4). Next, under the Mitsunobu conditions with *N*-monosubstituted 2-nitrobenzenesulfonamides **4-4**,[14] the polymer-supported alcohols **4-3** were converted to the *N*,*N*-disubstituted 2-nitrobenzenesulfonamides **4-5**, which provided the secondary amines **4-6** by the deprotection of the 2-nitrobenzenesulfonyl (Ns) group. Then **4-6** were transformed into the key intermediates **4-8** by acylation with chloroacetic acids **4-7**. The intramolecular cyclization of **4-8** and the debenzylation of the sulfonium salts **4-9** were carried out in the presence of CsI, providing the product **4-10** in high purity without purification by column chromatography.

If the polymer-supported alcohols **4-3** did not react with *N*-monosubstituted 2-nitrobenzenesulfonamides **4-4** completely, the esters composed of the residual **4-3** and chloroacetic acids **4-7** might be formed in the amide formation steps (step d or e). The

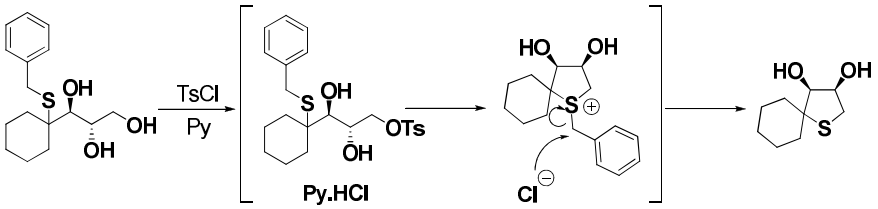
esters then might lead to the formation of the lactones as impurities at the cleavage steps. Fortunately, such by-products have not been identified so far and the desired products were obtained with high purities, because the Mitsunobu reactions proceeded completely. The progress of these reactions were checked with the elemental analysis of the *N*,*N*-disubstituted 2-nitrobenzenesulfonamides **4-5** (data not shown).



Scheme 4-4. (a) **4-2**, DBU, DMF, rt, 24 h; (b) **4-4**, PPh_3, DEAD, THF, rt, 16 h; (c) $HOCH_2CH_2SH$, DBU, DMF, rt, 1 h; (d) DIC, **4-7**, DMF, rt, 20 h; (e) PyBrop, **4-7**, *i*-Pr_2NEt, rt, 20 h; (f) CsI, dioxane, water, 95 ºC, 1-2 h.

While it was described in the chapter 2 and 3 that the cleavage of *N*-benzyl groups of quaternary ammonium salts needed the relatively strong nucleophiles like thiolates, there have been some reports that *S*-benzyl groups of sulfonium salts were cleaved by weak

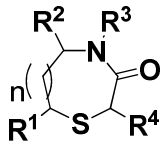
nucleophiles like halogenide anions (Scheme 4-5).[15] The author also found that *S*-benzyl groups of cyclization precursors **4-8** were simultaneously cleaved by a chloride or an iodide anion as cyclization.



Scheme 4-5.

To demonstrate the usefulness of this approach, several thiomorpholin-3-one derivatives were synthesized. The representative results are shown in Table 4-1. The alkyl and aryl groups can be introduced in R^1 – R^4 with high purities and moderate total yields (entries 1-6), while compounds with functional groups such as ester and basic nitrogen could be obtained (entry 4, 5). Construction of a 7-membered and an 8-membered ring (entry 7, 8) was also possible, and this result would expand diversity of the libraries based on this synthetic route.

Table 4-1. Syntheses of thiomorpholin-3-one derivatives 4-10



Entry	**4-10**	R^1	R^2	R^3	R^4	n	Yield[a] (purity[b]) of **4-10**
1	**4-10a**	H	H	(4-Br)$PhCH_2CH_2$-	H	0	65% (99%)
2	**4-10b**	Me	Me	(4-Br)$PhCH_2CH_2$-	H	0	58% (100%)
3	**4-10c**	H	H	(4-Br)Ph-	H	0	72% (100%)
4	**4-10d**	H	H	(4-Me_2N)$PhCH_2$-	H	0	50% (97%)
5	**4-10e**	H	H	(4-MeOCO)$PhCH_2$-	H	0	47% (100%)
6	**4-10f**	H	H	(4-Br)$PhCH_2CH_2$-	Me	0	49% (96%)
7	**4-10g**	H	H	(4-Br)$PhCH_2CH_2$-	H	1	74% (99%)
8	**4-10h**	H	H	(4-Br)$PhCH_2CH_2$-	H	2	53% (95%)

[a] Isolated overall yields (6 steps) based on Merrifield resin **4-1**.

[b]Reverse-phase HPLC was carried out using CH_3CN/20 mM phosphate buffer (pH 6.5). Flow rate: 1 mL/min. Column: ODS. HPLC purities were determined by summation of integrated HPLC peak areas at 210 or 220 nm.

In conclusion, the author has demonstrated that thiomorpholin-3-one derivatives and its analogs can be obtained in good yields and high purity based on the novel traceless solid-phase synthesis. This approach should be applicable to construct novel and diverse chemical libraries for high-throughput screenings to find the new compounds showing biological activities.

Experimental Section

Typical experimental procedure is as follows:

To Merrifield resin **4-1** (20.0 g, 38.8 mmol, Polymer Laboratories; 1.94 mmol/g) in DMF (200 ml) was added DBU (23.2 ml, 155mmol) and sulfanylethanol **4-2** (8.17 ml, 117 mmol) at 0 ºC. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with DMF (x5), water (x5), MeOH (x5), THF (x5) and Et_2O (x5) and was dried *in vacuo* (**4-3**: 22.3 g; 100%; equivalent to 1.74 mmol/g). To a mixture of the resin **4-3** (3.45 g, 6 mmol), *N*-[2-(4-Bromophenyl)ethyl]-2-nitrobenzenesulfonamide **4-4** (925 mg, 2.4 mmol) and PPh_3 (3.15 g, 12 mmol) in THF (100 ml) was added a 40% toluene solution of DEAD (5.56 ml, 12 mmol) at 0 ºC. After stirring for 2 min, the whole was allowed to stir at room temperature for 16 h. The resin was washed with CH_2Cl_2 (x5), THF (x5), MeOH (x5), THF (x5) and Et_2O (x5) to give **4-5**. To the resin **4-5** (3.45 g, 6 mmol) in DMF (10 ml) was added DBU (1.79 ml, 12 mmol) and sulfanylethanol (842 μl, 12 mmol) at 0 ºC. After stirring for 2 min, the whole was allowed to stir at room temperature for 1 h. The resin was washed with Et_3N-water (1:9, x3), DMF (x3), water (x5), MeOH (x5), THF (x5) and Et_2O (x5) to give **4-6**. The obtained resin **4-6** was swollen with a mixture of chloroacetic acid (1.36 g; 14.4 mmol), diisopropylcarbodiimide (2.23 ml, 14.4 mmol), DMF (12 ml) and the mixture was agitated for 20 h at room temperature. The resin was then washed with DMF (x5), Et_3N-water (1:9, x5), THF (x5), MeOH (x5) to give **4-8**. The resin **4-8** was swollen with a mixture of CsI (624 mg, 2.4 mmol), dioxane (8 ml) and water (2 ml) and stirred at 95 ºC for 1 h. The resin was washed with MeOH-$CHCl_3$ (1:4, x3) and MeOH (x5) and the

filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine and dried with Na_2SO_4. The solvent was evaporated to provide a product **4-10a** as a pale yellow solid (235 mg, 65%).

All products gave satisfactory 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR and MS spectra. The spectral data of **4-10** are given below:

4-[2-(4-Bromophenyl)ethyl]-1,4-thiazaperhydroin-3-one (4-10a). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.80-2.74 (4H, m), 3.20 (2H, s), 3.54-3.50 (4H, m), 7.21 (2H, d, J = 8.45 Hz), 7.48 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 30.3, 3.33, 50.1, 50.2, 120.4, 130.6, 131.6, 137.8, 166.3; IR (KBr) ν_{max}: 2933, 1652, 1484, 1425, 1362, 809, 515; MS: m/z 300/302 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-5,6-dimethyl-1,4-thiazaperhydroin-3-one (4-10b). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (0.8H, d, J = 6.40 Hz), 1.20 (0.8H, d, J = 6.40 Hz), 1.27 (2.2H, d, J = 6.40 Hz), 1.33 (2.2H, d, J = 6.40 Hz), 2.91-2.71 (2H, m), 3.18-3.03 (2H, m), 3.32 (2H, s), 3.60-3.53 (1H, m), 3.85-3.75 (1H, m), 7.25-7.20 (2H, m), 7.52-7.47 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 17.3, 20.5, 20.8, 26.5, 30.2, 33.3, 33.4, 38.2, 39.1, 49.3, 49.9, 60.3, 61.4, 120.3, 130.6, 131.6, 131.7, 137.7, 138.0, 165.1, 165.2; IR (KBr) ν_{max}: 2975, 2930, 1628, 1488, 1428, 1404, 1072, 1012, 807, 510; MS: m/z 328/330 $[M+H]^+$.

4-(4-Bromophenyl)-1,4-thiazaperhydroin-3-one (4-10c). ^{1}H NMR (400 MHz,

DMSO-d_6): δ 3.03 (2H, t, J = 5.63 Hz), 3.42 (2H, s), 3.96 (2H, t, J = 5.63 Hz), 7.29-3.26 (2H, m), 7.60-7.56 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.7, 30.6, 52.1, 120.6, 127.8, 132.4, 141.6, 166.8; IR (KBr) ν_{max}: 3056, 2930, 1656, 1489, 1396, 1011, 825, 551; MS: m/z 272/274 $[M+H]^+$.

4-{[4-(Dimethylamino)pheny]methyl}-1,4-thiazaperhydroin-3-one (4-10d). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.75 (2H, t, J = 5.89 Hz), 2.86 (6H, s), 3.29 (2H, s), 3.48 (2H, t, J = 5.89 Hz), 4.42 (2H, s), 6.69-6.67 (2H, m), 7.10-7.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 30.4, 40.6, 48.0, 50.0, 112.6, 124.4, 129.3, 150.1, 166.4; IR (KBr) ν_{max}: 2932, 2812, 1648, 1533, 1442, 1365, 1189, 807, 586; MS: m/z 251 $[M+H]^+$.

Methyl 4-[(3-oxo-1,4-thiazaperhydroin-4-yl) methyl]benzoate (4-10e). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84 (2H, t, J = 5.63 Hz), 3.36 (2H, s), 3.57 (2H, t, J = 5.63 Hz), 3.85 (3H, s), 4.64 (2H, s), 7.40 (2H, d, J = 8.19 Hz), 7.94 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 30.5, 49.0, 50.6, 52.1, 127.8, 129.7, 130.1, 142.0, 166.6, 166.7; IR (KBr) ν_{max}: 2988, 2948, 1726, 1649, 1436, 1416, 1282, 1112, 744; MS: m/z 266 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-2-methyl-1,4-thiazaperhydroin-3-one (4-10f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (3H, t, J = 6.91 Hz), 2.79-2.70 (3H, m), 2.90-2.87 (1H, m), 3.68-3.47 (5H, m), 7.21 (2H, d, J = 8.19 Hz), 7.48 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 26.4, 33.7, 36.1, 49.5, 50.3, 120.3, 130.6, 131.6, 137.9, 170.3; IR (KBr) ν_{max}: 2977, 2933, 1655, 1488, 1451, 1425, 1072, 1011, 811, 508; MS: m/z 314/316 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-1,4-thiazaperhydroepin-3-one (4-10g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-1.75 (2H, m), 2.73 (2H, t, J = 7.94 Hz), 2.80 (2H, t, J = 5.63 Hz), 3.32 (2H, s), 3.46-3.44 (4H, m), 7.21 (2H, d, J = 8.45 Hz), 7.47 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.1, 32.9, 33.8, 34.9, 50.1, 50.5, 120.2, 130.6, 131.6, 137.9, 172.6; IR (KBr) ν_{max}: 2931, 1642, 1486, 1448, 1422, 1133, 1011, 803, 512; MS: m/z 314/316 $[M+H]^+$.

4-[2-(4-Bromophenyl)ethyl]-1,4-thiazaperhydroocin-3-one (4-10h). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.68-1.62 (2H, m), 1.87-1.81 (2H, m), 2.64 (2H, t, J = 5.12 Hz), 2.77 (2H, t, J = 7.94 Hz), 3.35 (2H, s), 3.47-3.39 (4H, m), 7.21 (2H, d, J = 8.45 Hz), 7.48 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.2, 29.8, 32.8, 33.3, 46.9, 47.2, 120.2, 130.6, 131.6, 138.1, 171.1; IR (KBr) ν_{max}: 2937, 1600, 1485, 1469, 1430, 1234, 1129, 1070, 1010, 806, 516; MS: m/z 328/330 $[M+H]^+$.

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Chapter 5

Traceless solid-phase synthesis of multiple sulfonamide-containing cyclic sulfides exploiting microwave irradiation

Abstract: In this chapter, a new synthetic method of sulfonamide-containing cyclic sulfides using a microwave-assisted traceless solid-phase approach is described. Using this new method, many highly pure cyclic sulfides were efficiently synthesized based on intramolecular alkylation of the sulfides followed by elimination of the desired products from the generated sulfonium salts.

1. Introduction

Compounds having sulfonamide-containing cyclic sulfide skeletons (**A-C**, Figure 5-1) are known to show a number of intriguing biological activities, such as antimalarial effect,[1] VLA-4 antagonistic effect,[2] RyR receptors modulatory effect,[3] antiobesity effect,[4] and inhibitory effect on matrix metalloproteinase,[5] TACE,[6] PNMT,[7] FKBP12,[8] carbonic anhydrase,[9] IKK2[10] and 17β-HSD II[11] (Figure 5-2). Therefore, it is believed that these skeletons and their analogs are very attractive templates for chemical libraries to generate novel bioactive compounds in high-throughput screenings (HTS).

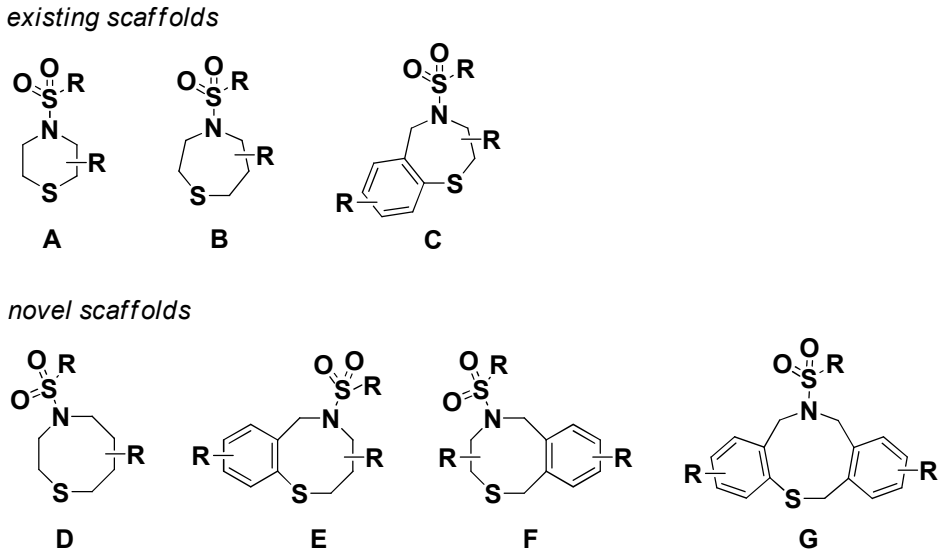


Figure 5-1. Sulfonamide-containing cyclic sulfides.

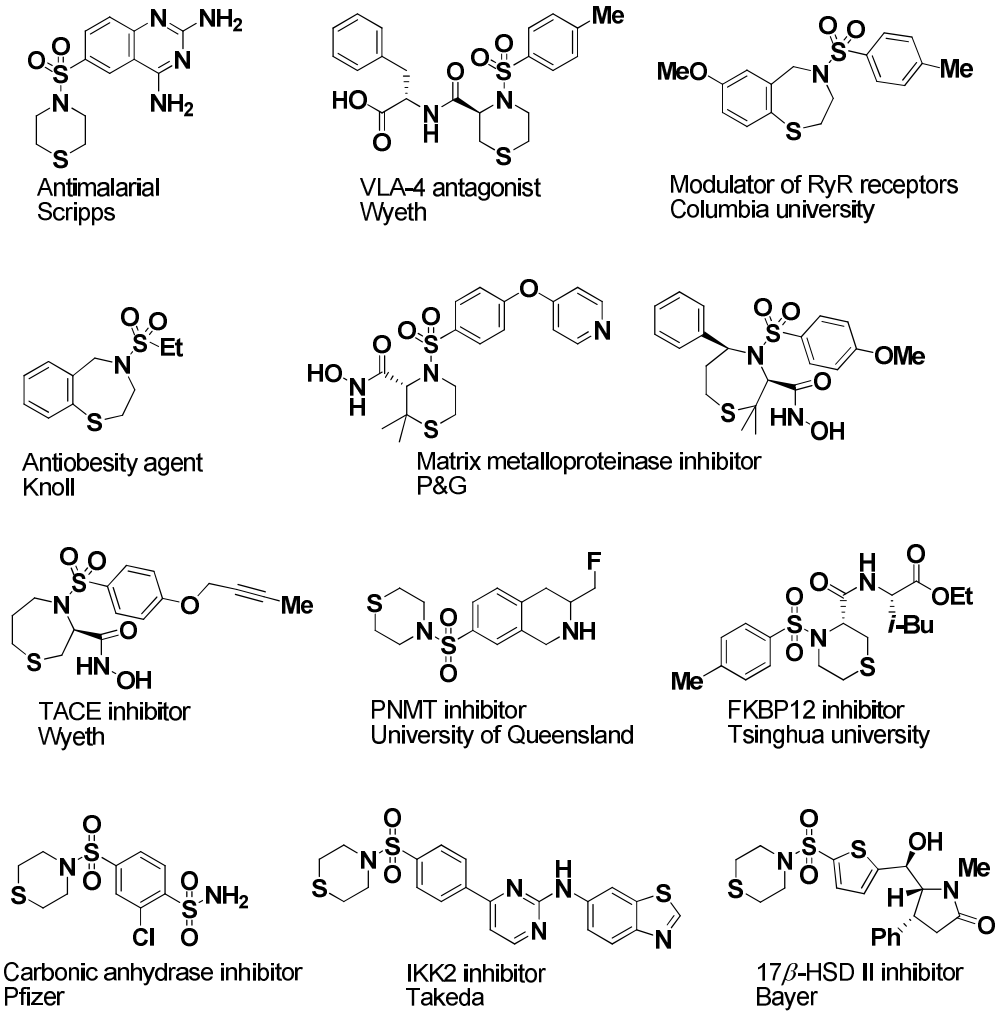
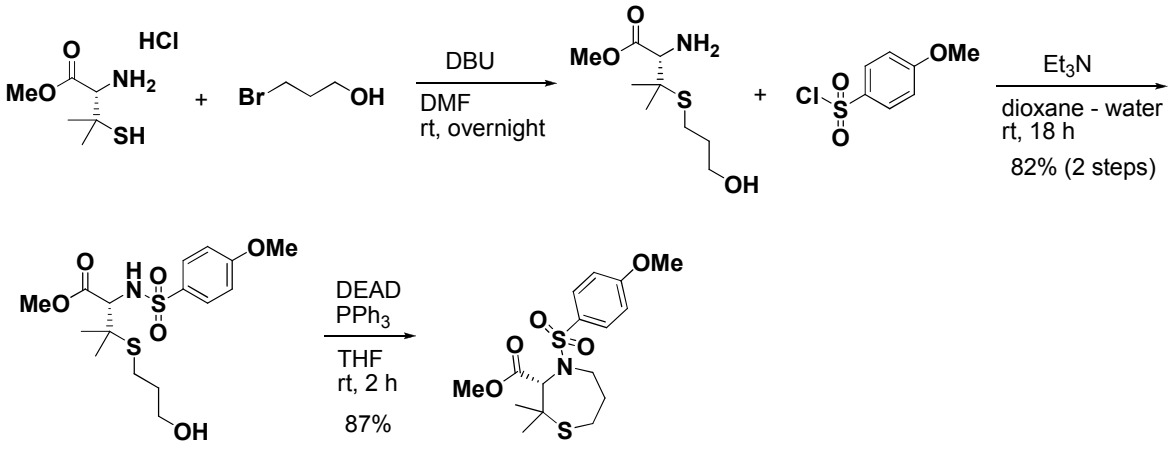


Figure 5-2. Bioactive sulfonamide-containing cyclic sulfides.

To generate a high rate of hits in HTS, diversity of compounds is extremely important. However, most reported chemical libraries are designed based on a single scaffold,[12] the diversity of which is relatively low because all compounds in the library have the same structure as the scaffold. The most notable feature in this chapter is to construct highly diverse chemical libraries containing multiple scaffolds using the same synthetic approach. With respect to cyclic sulfide skeletons, our method can efficiently provide not only existing scaffolds[1-11] (**A**-**C**, Figure 5-1) but also novel scaffolds (**D**-**G**, Figure 5-1) the

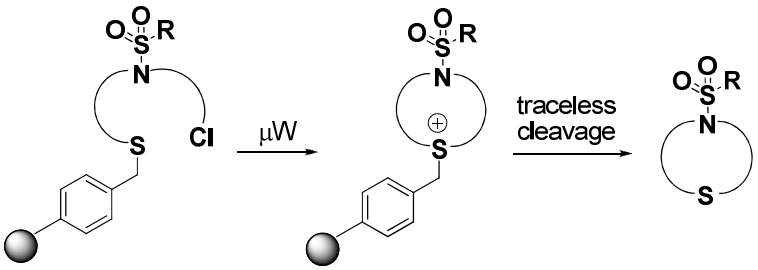
author first report herein, on the selection of appropriate building blocks.

The cyclization-cleavage approach was also employed for the synthesis of sulfonamide-containing cyclic sulfides. This method is superior to the solution-phase synthesis in Scheme 5-1 with regard to easiness of purification.[1-11]



Scheme 5-1. Conventional solution-phase synthesis of a sulfonamide-containing cyclic sulfide derivative.[5]

In the syntheses of thiomorpholin-3-ones as cyclic sulfides and two kinds of cyclic tertiary amines described in the former chapters,, intermediates possessing α-chloroacetamide moiety with strong alkylating activity were cyclized under mild conventional heating conditions. Because the cyclization precursors in Scheme 5-2 showed much weaker reactivity than those in chapter 4, microwave irradiation was used to promote the ring-forming reaction under higher temperature. Interestingly, conventional heating was not as effective as microwave irradiation as described below. A polymer-supported base was used as hydrogen chloride scavenger.

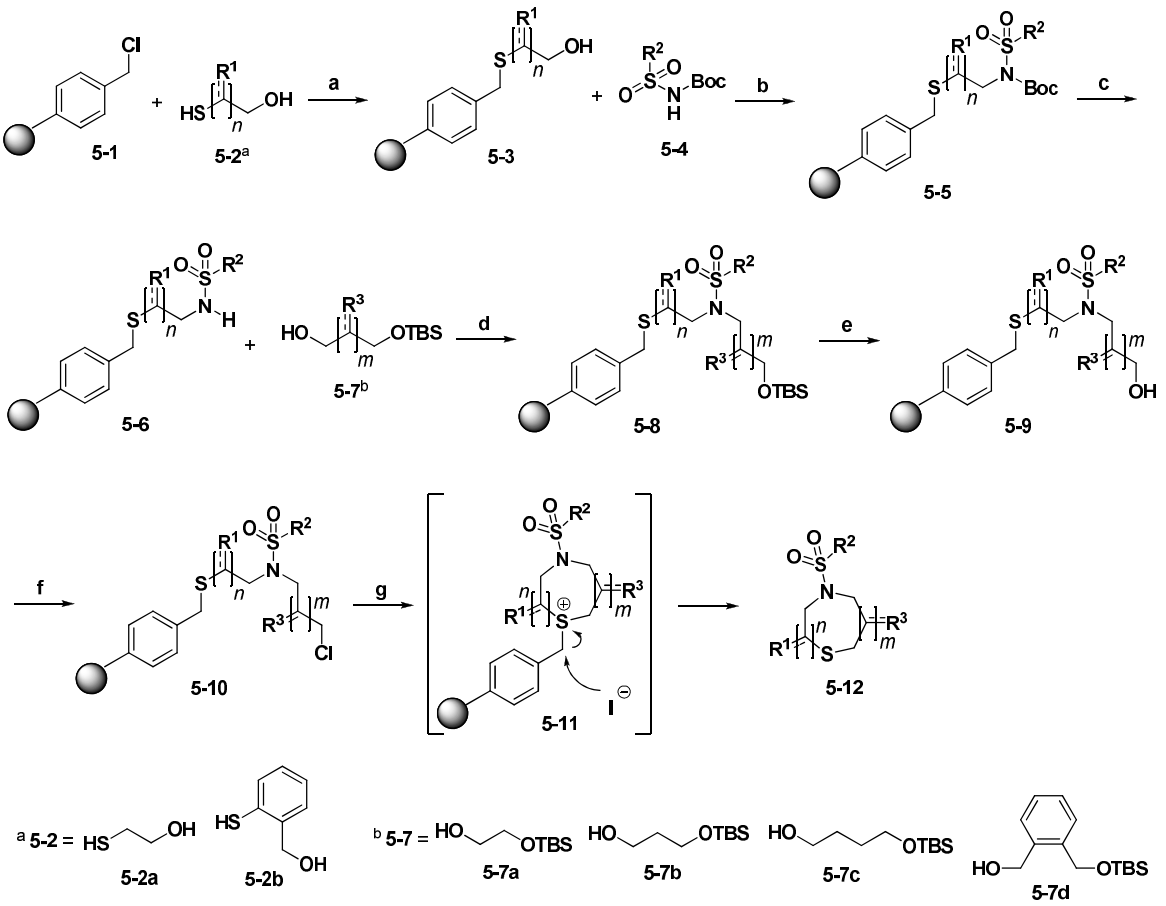


Scheme 5-2.

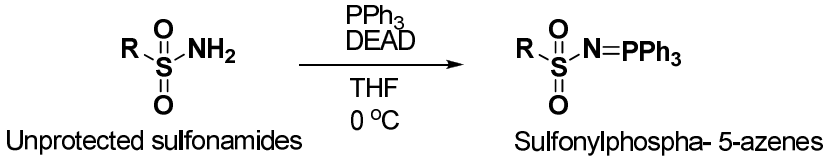
2. Results and Discussion

The synthesis began with nucleophilic displacement of the benzyl chloride on Merrifield resin **5-1** with the sulfanylalchohols **5-2** (Scheme 5-3). Next, under the traditional Mitsunobu conditions with the *N*-Boc-protected sulfonamides **5-4**, the polymer-supported alcohols **5-3** were converted to the *N*-alkyl-*N*-Boc-proctected sulfonamides **5-5**. It was known that the Mitsunobu reaction with the unprotected primary sulfonamides using PPh_3 and DEAD gave the sulfonylphospha-λ^5-azenes in high yields (Scheme 5-4). Therefore *N*-Boc-protected sulfonamides **5-4** was applied for the Mitsunobu reaction[13] to give **5-5.** Treatment of **5-5** with *n*-$BuNH_2$ then gave the deprotected sulfonamides **5-6**.[14] *N*-Boc groups are generally cleaved by TFA or other strong acids, which may cause decrease in yield and purity and restrict the number of avilable building blocks, thereby lowering diversity of the chemical library. To avoid these disadvantages, *n*-$BuNH_2$ was adopted as a mild reagent for deprotection. **5-6** were then alkylated by the mono-TBS-protected diols **5-7** under the improved Mitsunobu conditions with *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) and *n*-Bu_3P.[15] The resulting **5-9** were transformed into the alkyl halides **5-10**. Intramolecular cyclization of **5-10** and debenzylation of the sulfonium salts **5-11** were carried out under microwave irradiation to provide the product **5-12** in high purity without purification by column chromatography. Initially, the last cyclization-debenzylation step was run by refluxing the mixed solvent of dioxane and water for 24 h in the presence of only CsI under conventinal heating condition. However, the product **5-12a** was formed in only 25% yield, suggesting that more vigorous conditions were required to facilitate this reaction. The author then tried running the reaction in the microwave at 180 ^oC for 1 h and the yield increased to over 90%. Another

improvement of this reaction step was the addition of polymer-supported base, piperidinomethyl polystyrene, to scavenge the acids. Without the addition of the base, impurities generated by hydrolysis of resin-bound benzyl halides under the acidic conditions were detected by ^{1}H NMR. Addition of triethylamine also gave a similar result regarding yield and purity, but the use of the polymer-supported base was much more convenient.



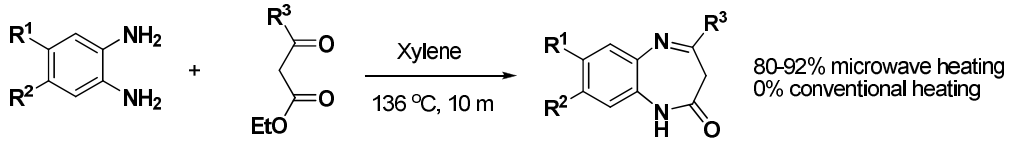
Scheme 5-3. (a) **5-2**, DBU, DMF, rt, 24 h; (b) **5-4**, PPh_3, DEAD, THF, rt, 24 h; (c) *n*-$BuNH_2$, rt, 24 h; (d) **5-7**, TMAD, *n*-Bu_3P, THF, rt, 24 h; (e) 1M TBAF/THF, rt, 24 h; (f) Cl_3CCCl_3, PPh_3, CH_2Cl_2, rt, 24 h; (g) CsI, piperidinomethyl polystyrene, dioxane, water, 180 ºC (μW), 1-2 h.



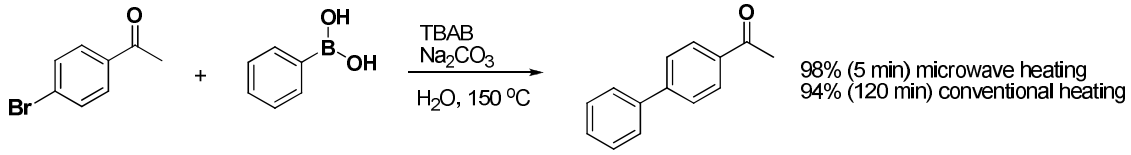
Scheme 5-4.

The cyclization reaction was also carried out under conventional heating conditions in a sealed tube at the same temperature (180 ºC) for the same reaction time (1 h) in order to assess the utility of microwave irradiation. Interestingly, microwave heating gave the much better yield of **5-12a** (88%, Table 5-1, entry 1) than conventional heating (27%). It implied that the specific effect of microwave promoted cyclization and/or cleavage. There have been some other reports that the microwave enhancement can be attributed to its specific effect.[16] Soufiaoui reported that the microwave acted the condensation of ethyl acetate or ethyl benzoylacetate with *o*-phenylenediamine by the specific effect, when microwave heating was compared with conventional heating under the same conditions of time and temperature (Scheme 5-5). Leadbeater found that microwave heating dramatically shortened the reaction time conventional heating needed under same temperature (Scheme 5-6). It has been reported that the specific effect of microwave would be due to "hot spots" in samples irradiated with microwave.[17] This is a thermal effect that arises as a consequence of the inhomogeneity of the applied field, resulting in the temperature in certain zones within the sample being much greater than the macroscopic temperature. These regions are not representative of the reaction conditions as a whole. While several authors have reported the specific effect of microwave described above, Kappe's kinetic experiments has showed that there was no appreciable difference in reaction rates and

yields between reactions carried out under microwave irradiation and thermal heating at identical temperatures.[18] It is understandable that all of reactions are not equally stimulated by microwave because hot spots may be created by the difference in dielectric properties of materials, which are unique to every reaction.



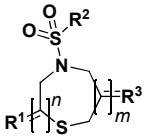
Scheme 5-5[16a].

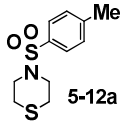
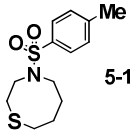
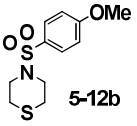
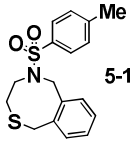
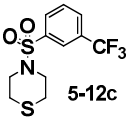
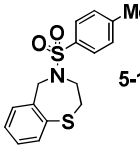
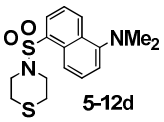
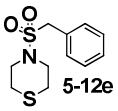
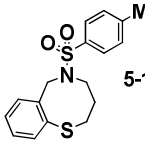
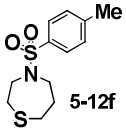
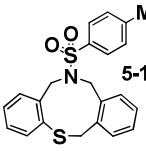


Scheme 5-6[16b].

To demonstrate the usefulness of this approach, several sulfonamide-containing cyclic sulfides were synthesized. The representative results are shown in Table 5-1. Various aryl and alkyl groups were introduced into R^2 giving compounds with high purity and good total yield (entries 1-5). A compound with a functional group such as a basic nitrogen could also be obtained (entry 4). Construction of 7- and 8-membered rings (entry 6, 7) and condensed rings (entry 8-11), both of which are regarded as novel scaffolds, was also possible by switching the building blocks. This finding indicates that this synthetic route can expand diversity of the libraries without any difficulties, making the discovery of new bioactive compounds in HTS more favorable.

Table 5-1. Syntheses of sulfonamide-containing cyclic sulfides **5-12**



Entry	5-2	5-7	Time of condition g (h)	Product	Yield[c] (%) (Purity[d] (%))	Entry	5-2	5-7	Time of condition g (h)	Product	Yield[c] (%) (Purity[d] (%))
1	5-2a	5-7a	1	 5-12a	88 (98)	7	5-2a	5-7c	1	 5-12g	71 (91)
2	5-2a	5-7a	1	 5-12b	91 (98)	8	5-2a	5-7d	1	 5-12h	93 (98)
3	5-2a	5-7a	1	 5-12c	89 (96)	9	5-2b	5-7a	2	 5-12i	62 (98)
4	5-2a	5-7a	1	 5-12d	62 (94)						
5	5-2a	5-7a	1	 5-12e	70 (98)	10	5-2b	5-7b	2	 5-12j	53 (98)
6	5-2a	5-7b	1	 5-12f	68 (97)	11	5-2b	5-7d	2	 5-12k	74 (99)

[a] Isolated overall yields (7 steps) based on Merrifield resin **5-1**.

[b]Reverse-phase HPLC was carried out using CH_3CN/20 mM phosphate buffer (pH 6.5). Flow rate: 1 mL/min. Column: ODS. HPLC purities were determined by summation of integrated HPLC peak areas at 210 nm.

It is generally known that solution-phase construction of medium-sized rings containing 8- and 9-membered rings is often attended with undesirable intermolecular reactions and therefore tends to result in low yields or failure. By contrast, the author's method afforded the 8- and 9-membered rings in yields comparable to those of the 6- and 7-membered rings (entry 1, 6 vs 7, 8, 11). The author hypothesized that the pseudo high-dilution effect on the

solid support probably favored the intramolecular cyclization over the intermolecular side reaction (Figure 5-3). Synthesis of 8-membered rings **5-12g** by the solution-phase method was then carried out to compare the yield with that on the solid-phase and to check whether dimerization took place or not. Unexpectedly, no detectable amount of the dimmer **5-15** could be identified and the yield of **5-12g** by the solution-phase method was comparable to that on the solid-phase (Scheme 5-7).

While the pseudo high-dilution effect on the solid support could not be confirmed in this case, Mazur had demonstrated earlier the interesting feature of the solid-phase synthesis (Scheme 5-8).[19] *o*-Benzyne was generated by oxidation of 1-aminobenzotriazole derivative covalently bound to a resin. When lead tetraacetate was employed as the oxidizing agent, *o*-benzyne was converted to a mixture of isomeric aryl acetates. This reaction was not observed for 1-aminobenzotriazole on solution-phase, where dimerization was the predominant pathway. The results were explained by a low frequency of encounter between the resin-bound intermediates which allow the relatively slow acetate formation.

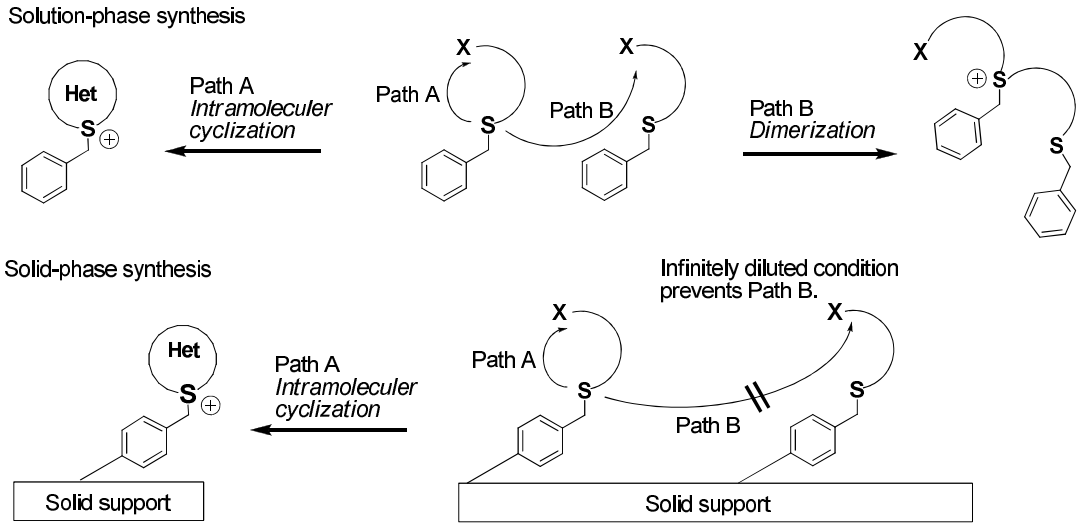
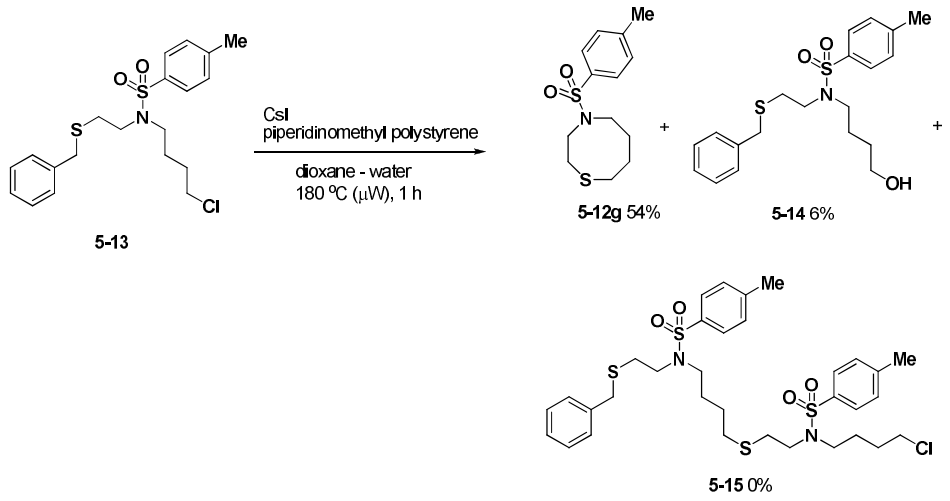
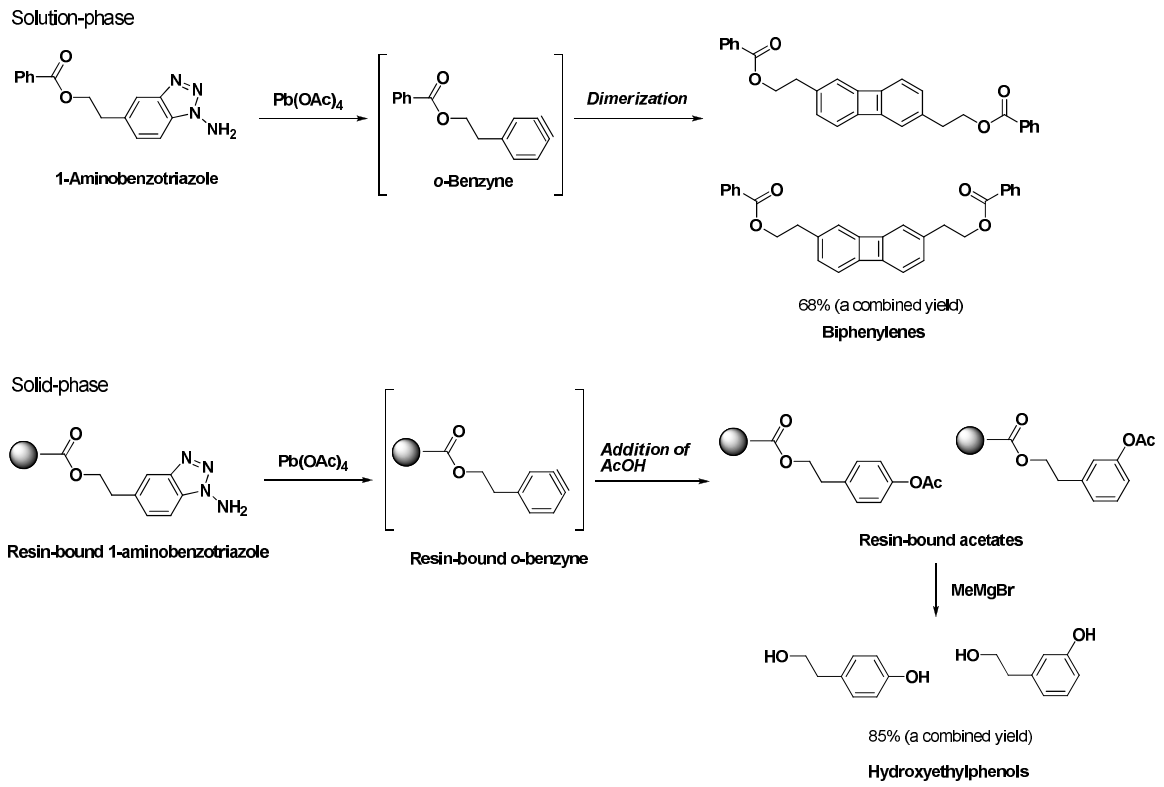


Figure 5-3. The pseudo high-dilution effect on the solid support.

In the present study, the author did not observe the apparent pseudo high-dilution effect on the solid support. The author thought the present cyclization-cleavage approaches are thus inherently advantageous for the monomer formation.



Scheme 5-7.



Scheme 5-8.

In conclusion, the author has demonstrated that sulfonamide-containing cyclic sulfides can be obtained in good yields and high purity based on the novel traceless solid-phase synthesis. This approach should be applicable to construct novel and diverse chemical libraries for high-throughput screenings to find the new compounds showing biological activities.

Experimental Section

Typical experimental procedure is as follows:

To Merrifield resin **5-1** (20.0 g, 38.8 mmol, Polymer Laboratories; 1.94 mmol/g) in DMF (200 ml) was added DBU (23.2 ml, 155mmol) and sulfanylethanol **5-2** (9.09 ml, 116 mmol) at 0 ºC. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with DMF (x5), water (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) and dried *in vacuo* (**5-3**: 21.4 g; equivalent to 1.81 mmol/g). To a mixture of the resin **5-3** (11.9 g, 21.6 mmol), *N*-(*tert*-Butoxycarbonyl)-*p*-toluenesuflonamide **5-4** (23.4 g, 86.4 mmol) and PPh_3 (22.7 g, 86.4 mmol) in THF (200 ml) was added dropwise 40% toluene solution of DEAD (40 ml, 86.4 mmol) at 0 ºC for 30 min. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with CH_2Cl_2 (x5), THF (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) and dried *in vacuo* (**5-5**: 21.4 g; equivalent to 1.17 mmol/g). To the resin **5-5** (3.08 g, 3.6 mmol) was added *n*-$BuNH_2$ (20 ml), and the whole was allowed to stir at room temperature for 24 h. The resin was washed with Et_3N-DMF (1:4, x5), DMF (x5), CH_2Cl_2 (x5), THF (x5), Et_2O (x5) and MeOH (x5) to give **5-6**. To a mixture of the obtained resin **5-6**, 2-(*tert*-Buthyldimethylsilanyloxy)ethanol **5-7** (2.54 g, 14.4 mmol) and *n*-Bu_3P (3.6 g, 14.4 mmol) in THF (200 ml) was added *N,N,N',N'*-tetramethylazodicarboxamide (2.48 g, 14.4 mmol) at 0 ºC. After stirring for 10 min, the whole was allowed to stir at room temperature for 24 h. The resin was washed with water (x3), DMF (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) to give **5-8**.

To the resin **5-8** was added 1 M THF solution of TBAF (25 ml), and the whole was allowed to stir at room temperature for 24 h. The resin was washed with THF (x5), MeOH (x5), THF (x5) and MeOH (x5) to give **5-9**. The obtained resin **5-9** was swollen with a mixture of PPh_3 (3.78 g, 14.4 mmol), hexachloroethane (3.41 g, 14.4 mmol) and CH_2Cl_2 (40 ml) and the mixture was stirred for 24 h at room temperature. The resin was then washed with CH_2Cl_2 (x5), MeOH (x5), THF (x5), Et_2O (x5) and MeOH (x5) to give **5-10**. To the resin **5-10** was added CsI (312 mg, 1.2 mmol), piperidinomethyl polystyrene (400 mg, 1,2 mmol, Polymer Laboratories; 3.0 mmol/g), dioxane (12 ml) and water (3 ml). The mixture was then heated in a microwave at 180 ºC for 1 h. The resin was washed with water (x3), MeOH-$CHCl_3$ (1:4, x3) and MeOH (x5) and the filtrate was evaporated. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ and brine and dried with Na_2SO_4. The solvent was evaporated to provide product **5-12a** as pale yellow solid (130 mg, 88%).

All products gave satisfactory 400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR and HRMS spectra. The spectral data of **5-12** are given below:

4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroine (5-12a). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s), 2.64-2.67 (4H, m), 3.16-3.18 (4H, m), 7.46 (2H, d, J = 8.19 Hz), 7.63 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 27.3, 47.9, 127.5, 129.8, 133.8, 143.8; IR (ATR) ν_{max}: 1336, 1160, 894, 715, 703, 584, 545; HRMS (ESI): calculated for $C_{11}H_{16}NO_2S_2$ $[M+H]^+$ 258.0616, found 258.0626.

4-[(4-Methoxyphenyl)sulfonyl]-1,4-thiazaperhydroine (5-12b). ^{1}H NMR (400 MHz,

DMSO-d_6): δ 2.65-2.67 (4H, m), 3.14-3.17 (4H, m), 3.86 (3H, s), 7.16 (2H, d, J = 8.70 Hz), 7.67 (2H, d, J = 8.70 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 47.9, 55.6, 114.4, 128.3, 129.5, 163.1; IR (ATR) ν_{max}: 1258, 1156, 1093, 899, 853, 705, 583, 555; HRMS (ESI): calculated for $C_{11}H_{16}NO_3S_2$ $[M+H]^+$ 274.0566, found 274.0578.

4-{[(3-(Trifluoromethyl)phenyl]sulfonyl}-1,4-thiazaperhydroine (5-12c). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67-2.69 (4H, m), 3.26-3.29 (4H, m), 7.93 (1H, t, J = 7.94 Hz), 7.99 (1H, s), 8.09 (1H, d, J = 7.94 Hz), 8.14 (1H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 47.9, 123 (q, J = 271 Hz), 124.3 (q, J = 3.80 Hz), 129.6 (q, J = 3.60 Hz), 130.1, 130.5, 132.0 (q, J = 33.5 Hz), 138.4; IR (ATR) ν_{max}: 1165, 1124, 1068, 693, 568; HRMS (ESI): calculated for $C_{11}H_{13}NO_2F_3S_2$ $[M+H]^+$ 312.0345, found 312.0334.

4-{[(5-(Dimethylamino)naphthyl]sulfonyl}-1,4-thiazaperhydroine (5-12d). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.59-2.62 (4H, m), 2.84 (6H, s), 3.43-3.45 (4H, m), 7.28 (1H, d, J = 7.68 Hz), 7.60-7.68 (2H, m), 7.12-7.13 (1H, m), 8.20 (1H, d, J = 8.70 Hz), 8.52 (1H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.3, 45.4, 47.3, 115.3, 119.4, 123.1, 128.1, 130.1, 130.3, 130.7, 133.5, 151.8; IR (ATR) ν_{max}: 1318, 1080, 913, 568; HRMS (ESI): calculated for $C_{16}H_{21}N_2O_2S_2$ $[M+H]^+$ 337.1038, found 337.1030.

4-(Benzylsulfonyl)-1,4-thiazaperhydroine (5-12e). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.55-2.57 (4H, m), 3.313.31-3.32 (4H, m), 4.43 (2H, s), 7.35-7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7, 48.0, 57.6, 128.7, 128.9, 130.4, 130.7; IR (ATR) ν_{max}: 1149, 899, 699, 528; HRMS (ESI): calculated for $C_{11}H_{16}NO_2S_2$ $[M+H]^+$ 258.0616, found 258.0623.

4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroepine (5-12f). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-1.92 (2H, m), 2.39 (3H, s), 2.67-2.74 (4H, m), 3.32-3.41 (4H, m), 7.41 (2H, d, J = 8.19 Hz), 7.69 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 31.0, 31.9, 35.5, 48.8, 53.8, 126.8, 129.7, 136.8, 143.2; IR (ATR) ν_{max}: 1329, 1156, 714, 546; HRMS (ESI): calculated for $C_{12}H_{18}NO_2S_2$ $[M+H]^+$ 272.0773, found 272.0787.

4-[(4-Methylphenyl)sulfonyl]-1,4-thiazaperhydroocine (5-12g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.71-1.77 (2H, m), 1.85-1.91 (2H, m), 2.39 (3H, s), 2.71-2.73 (2H, m), 2.90-2.93 (2H, m), 3.09-3.11 (2H, m), 3.29-3.32 (2H, m), 7.42 (2H, d, J = 7.94 Hz), 7.66 (2H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 23.6, 27.0, 31.6, 33.5, 49.6, 51.0, 127.2, 129.7, 134.9, 143.3; IR (ATR) ν_{max}: 1324, 1155, 693, 647, 591, 546; HRMS (ESI): calculated for $C_{13}H_{20}NO_2S_2$ $[M+H]^+$ 286.0929, found 286.0947.

5-[(4-Methylphenyl)sulfonyl]-1H,3H,4H,6H-benzo[f]1,4-thiazaperhydroocine (5-12h). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s), 2.46-2.52 (2H, m), 3.49-3.52 (2H, m), 4.03 (2H, s), 4.42 (2H, s), 7.21-7.31 (4H, m), 7.44 (2H, d, J = 8.19 Hz), 7.73 (2H, d, J = 8.19 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 29.3, 32.9, 50.4, 51.0, 127.1, 127.7, 129.1, 129.9, 130.5, 134.3, 136.0, 136.9, 143.6; IR (ATR) ν_{max}: 1330, 1156, 718, 651, 543; HRMS (ESI): calculated for $C_{17}H_{20}NO_2S_2$ $[M+H]^+$ 334.0929, found 334.0922.

4-[(4-Methylphenyl)sulfonyl]- 2H,3H,5H-benzo[f]1,4-thiazaperhydroepine (5-12i). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s), 2.77-2.79 (2H, m), 3.65-3.52 (2H, m), 4.51 (2H, s), 7.27-7.32 (2H, m), 7.35 (2H, d, J = 7.94 Hz), 7.41-7.47 (2H, m), 7.60 (2H, d, J = 7.94 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 33.8, 52.3, 54.0, 127.0, 128.1, 128.2,

129.7, 130.4, 132.9, 136.0, 137.0, 142.1, 143.3; IR (ATR) ν_{max}: 1327, 1149, 1090, 1071, 1054, 553, 543; HRMS (ESI): calculated for $C_{16}H_{18}NO_2S_2$ $[M+H]^+$ 320.0773, found 320.0786.

5-[(4-Methylphenyl)sulfonyl]-2H,3H,4H,6H-benzo[g]1,5-thiazaperhydroocine (5-12j). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.66-1.72 (2H, m), 2.41 (3H, s), 2.72-2.75 (2H, m), 3.30-3.36 (2H, m), 4.58 (2H, s), 7.32-7.45 (5H, m), 7.59 (1H, d, J = 7.68 Hz), 7.76 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 29.3, 36.5, 47.1, 51.9, 127.1, 129.1, 129.8, 131.5, 135.0, 136.6, 137.2, 141.7, 143.2; IR (ATR) ν_{max}: 1154, 1092, 749, 715, 653, 606; HRMS (ESI): calculated for $C_{17}H_{20}NO_2S_2$ $[M+H]^+$ 334.0929, found 334.0917.

12-[(4-Methylphenyl)sulfonyl]-6H,11H,13H-dibenzo[b,g]1,5-thiazaperhydroonine (5-12k). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.45 (3H, s), 4.14 (2H, s), 4.21 (2H, s), 4.47 (2H, s), 7.00-7.14 (5H, m), 7.21-7.29 (2H, m), 7.36-7.38 (1H, m), 7.48 (2H, d, J = 8.45 Hz), 7.84 (2H, d, J = 8.45 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 37.9, 47.4, 49.7, 127.3, 127.7, 128.3, 128.4, 128.6, 129.8, 130.3, 131.3, 131.4, 133.9, 134.8, 136.8, 137.4, 137.7, 141.1, 143.4; IR (ATR) ν_{max}: 1327, 1150, 909, 719, 614, 527; HRMS (ESI): calculated for $C_{22}H_{22}NO_2S_2$ $[M+H]^+$ 396.1086, found 396.1074.

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General Conclusion

The studies described in this thesis are directed to the traceless solid-phase syntheses for heterocycles based on cyclization-cleavage approaches, which can provide the desired heterocycles in high purity without time-consuming purification steps and are quite preferable for the construction of the chemical libraries.

While, on the basis of the approaches, the author developed the novel synthetic methods of two types of cyclic tertiary amines (1,4-diazepan-2-ones and 1,4-diazabicyclo[3,3,13.3.1]octan-3-ones) and two types of cyclic sulfides (thiomorpholin-3-ones and sulfonamide-containing cyclic sulfides), it is expected that the other N- and S-containing heterocycles which have the druglike properties could also be synthesized via the similar strategy. Furthermore, while the syntheses described in this thesis were conducted manually, the automated systems could expectedly be adopted to further accelerate the syntheses based on the cyclization-cleavage approaches. Combination of the approaches and pool-split methods are also possible to make the libraries composed of huge number of compounds.

Chemical libraries are important in the discovery of lead molecules which are active for various new targets validated from genomics and proteomics research. The strategy in this thesis contributes to constructing chemical libraries time- and cost-effectively and therefore, can stimulate the developments of the high-quality drug candidates.

Instrumentation and Method

The following details apply to all experimental parts of this thesis.

IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE (400 MHz) spectrometer. Chemical shifts are reported in ppm downfield from an internal standard of tetramethylsilane. LRMS spectra were obtained on a Thermo-Fisher LXQ spectrometer. HRMS spectra were obtained on an Applied Biosystems QSTAR® Elite spectrometer. Analytical HPLC of the products was performed on an Agilent 1100 using a CERI L-column ODS. Microwave heating was conducted by a Biotage Initiator^{TM} which is a single-mode microwave reactor. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merck silica gel 60 F_{254}.

Publication List

Chapter 2

A Traceless Solid Phase Synthesis of 1,4-Diazepan-2-ones

Saruta, K.; Ogiku, T. *Chem. Lett.* **2008**, *37*, 820-821.

Chapter 3

A Traceless Solid Phase Synthesis of 1,4-Diazabicyclo[3,3,13.3.1]octan-3-ones

Saruta, K.; Ogiku, T. *Chem. Lett.* **2007**, *36*, 1430-1431.

Chapter 4

A Traceless Solid Phase Synthesis of Thiomorpholin-3-ones

Saruta, K.; Ogiku, T. *Tetrahedron Lett.* **2008**, *49*, 424-427.

Chapter 5

Traceless solid-phase synthesis of multiple sulfonamide-containing cyclic sulfides exploiting microwave irradiation

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