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Stereospecific One-pot Synthesis of Enamides and Enimides by the Copper Iodide Promoted Vinylic Substitution

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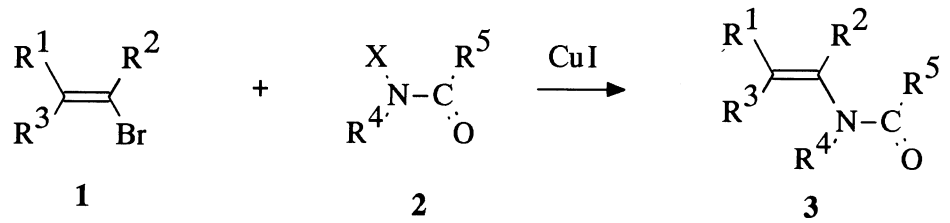
Enamides and enimides were prepared stereospecifically from vinyl bromides by direct vinylic substitution in the presence of copper salt in aprotic polar solvents.

Enamides are often found in nature as physiologically active compounds,[1] and also have been used as important intermediates for some natural product syntheses.[2] These type of compounds have been prepared by (a) addition of amides to epoxides followed by dehydration,[3] (b) direct addition of amides to alkynes,[4] (c) the Beckmann rearrangement of α,β-unsaturated ketone oximes,[5] (d) the Curtius reaction of α,β-unsaturated acyl azides,[1] (e) acylation of imines,[2] or (f) the amide Peterson olefination.[6] However, all of these known methods are not free from some drawbacks; although the methods (a) and (b) can produce E- and Z-enamides respectively, both suffer from low yields. The methods (c) and (d) lack the stereospecificity, while method (e) is subject to competitive C- and N-acylation.[2] The method (f) requires laborious access to the starting materials. Enimides are not accessible by any of these methods through a single step procedure.

We report herein that the well stereo-defined enamides and enimides of general type **3** can be obtained in moderate to good yields via the single step manner via the copper iodide promoted vinylic substitution of vinyl bromides[7] which are readily available by known stereocontrolled syntheses.[8]



1 **2** **3**

The reaction procedures are quite simple and straightforward: A mixture of vinyl bromide (1 mmol), potassium phthalimide (3 mmol), copper iodide (1 mmol), and a dry aprotic solvent (5 ml) was heated at 130 °C under a nitrogen atmosphere. When consumption of the starting bromide was confirmed by TLC (SiO_2, hexane/CH_2Cl_2), ca. 10% aq. HCl solution saturated with NaCl was added. The

product was extracted with benzene, dried with Na_2SO_4, and purified by passing through a silicagel column using hexane/CH_2Cl_2 as the solvent. For the vinylation of less acidic amides and imides, the potassium salts were better generated in situ by the action of potassium hydride on amides or imides (Runs **p–v**). Sodium hydride (Run **j**) and potassium t-butoxide (Run **k**) were unsatisfactory as a base. The results were listed in Table 1.[9]

Ordinary cyclic and acyclic amides produced the corresponding enamides in moderate yields (Runs **p–u**), while more acidic trifluoroacetamide (Run **v**) and cyclic imides (Runs **a–o**) afforded the corresponding enamides and enimides in good yields. From these results it might be understood that the more acidic amides (and imides) would give the higher yields of products. However, this was not the case. Acyclic imides such as N-acetylbenzamide or diacetamide, which are more acidic than monoamides, failed to furnish the expected enimides, and only complicated product mixtures were obtained. This would probably be attributed to the chelate formation between acyclic imides and copper species. Similar phenomena were also observed in the copper promoted reactions of 1,3-dicarbonyl compounds with vinyl bromides.[7] The substitution reaction readily occurred not only with conjugated alkenyl bromide (2-bromo-1-phenylethene) but also with non-conjugated alkenyl bromide (1-bromo-1-octene).

The reactions of 1-bromo-2-phenylethene with potassium phthalimide were compared in several solvent systems: In 1,3-dimethyl-2-imidazolidone (DMIZ), reaction time and yield were comparable with those of HMPA (Run **c**). In tetramethylurea (TMU), reaction time needed for completion was longer but the yield of enimide was better (Run **d**). In dimethylformamide (DMF), the yield was alike with that of HMPA but the reaction time was longer (Run **e**). Thus, considering potential carcinogenicity of HMPA, the use of DMIZ or TMU as the solvent is recommended.

The present vinylic substitution is stereospecific; the reaction of 1-bromo-1-octene of isomeric composition E/Z=42/58 afforded the corresponding enamide of nearly equal E/Z ratio (43/57) in 94% yield (Run **n**). Starting from the bromide of isomeric purity E/Z < 1/99, the enamide of E/Z = 7/93 was obtained in 69% yield (Run **o**). In the reaction of 1-bromo-2-phenylethene, the stereoselectivity was also satisfactory (Run **f**).

Several mechanisms have been proposed for the copper salt promoted substitution reactions of nonactivated aromatic halides.[10–13] Seeing the high stereospecificity of the present reaction, the possibility of "the addition-elimination reaction" can be readily excluded. Electron transfer mechanism is not probable,[13] because no correlation was observed between $E_{1/2}$ of the potassium salts of imides and amides in HMPA with their apparent reactivity.[14] Possible formation of the copper imidate *in situ* during the course of the reaction was denied by the observation that a cyclic voltamogram of the mixture of CuI with potassium phthalimide in HMPA showed only the CuI peak and no peak attributable to other copper species were observed. The most likely tentative mechanism at present is the activation of vinyl bromides through the coordination of copper species to the bromine atom as has been proposed for the copper promoted nucleophilic aromatic substitutions.[10]

The present reaction provides a new method, by which enamides and enimides can be obtained stereospecifically in good to moderate yields from easily accessible starting materials in a simple and straightforward manner. We are now examining the application of our procedure to the syntheses of some physiologically active natural compounds.

Table 1. Synthesis of Enamides and Enimides from Vinyl Bromides

Run	Vinyl Bromide 1				Amide 2					Time	Enamide 3 Yield	
	R^1	R^2	R^3	E/Z[a]	X	R^4	R^5	Sol.[b]	Base	h[c]	%[d]	E/Z[a]
a.	Ph	H	H	>99/1	H	-C(=O)C_6H_4-[e]		HMPA	KH	4	85	>99/1
b.	Ph	H	H	>99/1	K	-C(=O)C_6H_4-[f]		HMPA	—	2	86	>99/1
c.	Ph	H	H	>99/1	K	-C(=O)C_6H_4-[f]		DMIZ	—	2	84	>99/1
d.	Ph	H	H	>99/1	K	-C(=O)C_6H_4-[f]		TMU	—	7	95	>99/1
e.	Ph	H	H	>99/1	K	-C(=O)C_6H_4-[f]		DMF	—	5	82	>99/1
f.	H	H	Ph	13/87	K	-C(=O)C_6H_4-[f]		HMPA	—	4	77	22/78
g.	H	H	4-ClC_6H_4	26/74	K	-C(=O)C_6H_4-[f]		HMPA	—	24	76	52/48
h.	H	H	4-MeOC_6H_4	52/48	K	-C(=O)C_6H_4-[f]		HMPA	—	21	57	57/43
i.	Ph	H	H	>99/1	H	-C(=O)$(CH_2)_2$-		HMPA	KH	5	68	>99/1
j.	Ph	H	H	>99/1	H	-C(=O)$(CH_2)_2$-		HMPA	NaH	5	0	———
k.	Ph	H	H	>99/1	H	-C(=O)$(CH_2)_2$-		HMPA	tBuOK	5	36	>99/1
l.	Ph	H	H	>99/1	K	-C(=O)$(CH_2)_2$-		HMPA	—	3	72	>99/1
m.	Ph	H	H	>99/1	H	-C(=O)$(CH_2)_3$-		HMPA	KH	1.5	44	>99/1
n.	H	H	$CH_3(CH_2)_5$	42/58	K	-C(=O)C_6H_4-[f]		HMPA	—	2	94	43/57
o.	H	H	$CH_3(CH_2)_5$	<1/99	K	-C(=O)C_6H_4-[f]		HMPA	—	3	69	7/93
p.	Ph	H	H	>99/1	H	H	CH_3	HMPA	KH	3	45	>99/1
q.	Ph	H	H	>99/1	H	H	Ph	HMPA	KH	1	38	>99/1
r.	Ph	H	H	>99/1	H	$-(CH_2)_3-$		HMPA	KH	22	43	>99/1
s.	Ph	H	H	>99/1	H	$-(CH_2)_4-$		HMPA	KH	5	31	>99/1
t.	Ph	H	H	>99/1	H	$-(CH_2)_5-$		HMPA	KH	5	38	>99/1
u.	Ph	H	H	>99/1	H	Ph	CH_3	HMPA	KH	3	38	>99/1
v.	Ph	H	H	>99/1	H	H	CF_3	HMPA	KH	2	83	>99/1
w.	(Ph)	Ph	(H)	———[g]	K	-C(=O)$(CH_2)_2$-		HMPA	—	23	28	———[g]

a) E/Z ratios were determined by ^{1}H NMR. b) HMPA = hexamethylphosphoric triamide, DMIZ = 1,3-dimethyl-2-imidazolidone, TMU = tetramethylurea, and DMF = dimethylformamide. c) Reaction time indicates when the starting bromide was consumed completely. d) Yields refer to the isolated products and were not optimized. e) Phthalimide. f) Potassium phthalimide. g) Not determined.

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9) Spectral and analytical data of some representative products are as follows: **(E)-N-(2-phenylethenyl)phthalimide (3a)**; mp 199.0–200.2 °C; ^{1}H NMR ($CDCl_3$) δ = 7.1–8.0 (m); IR (KBr) 3000, 2300, 1760, and 1700 cm^{-1}; MS (70 eV) m/z (rel intensity) 249 (M^+, 100). Anal. ($C_{16}H_{11}NO_2$) C, H, N. **(Z)-N-(2-phenylethenyl)phthalimide (3f)**; mp 127.5–129.0 °C; ^{1}H NMR ($CDCl_3$) δ = 6.30 (d, J=9.6 Hz, 1H), 6.61 (d, J=9.6 Hz, 1H), 7.20 (s, 5H), and 7.6–7.9 (m, 4H); IR (KBr) 3070, 2980, 1760, and 1710 cm^{-1}; MS (70 eV) m/z (rel intensity) 249 (M^+, 100). Anal. ($C_{16}H_{11}NO_2$) C, H, N. **(Z)-N-(1-octenyl)phthalimide (3o)**; oil; ^{1}H NMR ($CDCl_3$) δ = 0.82–0.87 (m, 4H), 1.26–1.46 (m, 7H), 2.03–2.12 (m, 2H), 5.77 (d, J=8.5 Hz, 1H), 6.08 (dt, J=8.5, 1.8 Hz, 1H), 7.72–7.90 (m, 4H); IR (NaCl) 2940, 2910, 1760, and 1720; MS (70 eV) m/z (rel intensity) 257 (M^+, 10) and 186 (100). Anal. ($C_{16}H_{19}NO_2$) C, H, N. **(E)-N-phenyl-N-(2-phenylethenyl)acetamide (3u)**; mp 102.0–103.5 °C; ^{1}H NMR ($CDCl_3$) δ = 1.80 (s, 3H), 5.15 (d, J=14.1 Hz, 1H), 7.1–7.5 (m, 10H), 8.16 (d, J=14.1 Hz, 1H); IR (KBr) 3050, 3000, 1750, and 1670 cm^{-1}; MS (70 eV) (rel intensity) 237 (M^+, 45) and 195 (100). Anal. ($C_{16}H_{15}NO$) C, H, N. **(E)-N-(2-phenylethenyl)trifluoroacetamide (3v)**; mp 159–162 °C; ^{1}H NMR ($CDCl_3$) δ = 6.46 (d, J=13.8 Hz, 1H), 7.1–7.6 (m, 6H); IR (KBr) 3250, 1700, 1680 and 1660 cm^{-1}; MS (70 eV) m/z (rel intensity) 215 (M^+, 100). Anal. ($C_{10}H_8F_3NO$) C, H, N.

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14) $E_{1/2}$ values were measured by cyclic voltammetry with 0.5 M tetrabutylammonium perchlorate as the supporting electrolyte.

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