Formation of Furan Derivatives from Phenacyl Bromides and Sodium Telluride; Attempted Extension to Coumarin Synthesis

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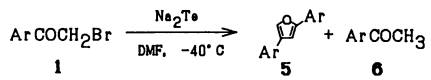
Synopsis. The enolates, generated from phenacyl bromides by sodium telluride, yield 2,4-diarylfurans in addition to the expected dehalogenation products. No 1,4-dicarbonyl compounds could be isolated even in the presence of excess oxidizing agent, copper(II) chloride. Condensation of 2-(methoxymethoxy)arenecarbaldehydes with ethyl bromoacetate in the presence of sodium telluride gave the expected α,β-unsaturated esters which resisted cyclization to yield the desired coumarin derivatives. Attempted intramolecular Reformatsky-type reaction of 2-(bromoacetoxy)-benzaldehyde gave only 6,12-epoxy-6*H*,12*H*-dibenzo[*b*,*f*]-[1,5]dioxocin as the major product.

Sodium telluride, as a reagent for effecting many functional group transformations, has been studied in our laboratory for quite some time. Many heterocyclic compounds containing tellurium as the heteroatom have been synthesized using sodium telluride,[1] while there have been no reports concerning the formation of non-tellurium heterocyclic compounds using sodium telluride. Herein we wish to report the formation of 2,4-diarylfurans (**5**) from the ketone enolates generated from phenacyl bromides (**1**) and the results of our efforts to synthesize coumarins using sodium telluride.

2,4-Diarylfurans. Ketone enolates and ester enolates have been oxidatively coupled to give synthetically important 1,4-diketones employing $CuCl_2$,[2] $FeCl_3$,[3] and $Cu(OTf)_2$.[4] Ketene silyl acetals have also been subjected to similar reaction.[5] Recently, Belletire reported the occurrence of symmetrical dimerizations of carboxylic dianions and β-keto ester dianions using molecular iodine as oxidant.[6] He also reported the C-C coupling at γ-position of the dianions from β-keto sulfones. These results prompted us to investigate whether a coupling at the active methylene of halo ketones could be achieved from the enolate generated by sodium telluride taking advantage of the affinity of telluride anion for the halogens. Such a study would enable us to see the fate of enolates generated by sodium telluride under oxidative coupling conditions.



As a model compound we studied the enolate derived from phenacyl bromide **1** in the presence of iodine. Addition of a solution of **1a** in *N*,*N*-dimethylformamide (DMF) to a suspension of sodium telluride in the same solvent at −40 °C followed by the addition of iodine in DMF resulted in a dark reaction mixture which gave two fractions after chromatography. The first, hexane fraction, showed ^{1}H NMR spectrum which was completely devoid of aliphatic protons. The second one was easily identified as acetophenone (**6a**; 29%). From the elemental analysis and spectral data in combination with comparison of reported melting points of diphenylfuran derivatives, the product isolated from the hexane fraction was identified as 2,4-diphenylfuran (**5a**; 14%). When anhydrous copper(II) chloride was employed in place of iodine the furan was obtained in a slightly better yield (17%). To our surprise no oxidatively coupled product could be isolated from the reaction mixture. Isolation of furan derivative was also possible using iron(III) chloride. Similarly from other substituted phenacyl bromides were obtained 2,4-diarylfurans (**5b—5d**) in varying yields (Table 1).

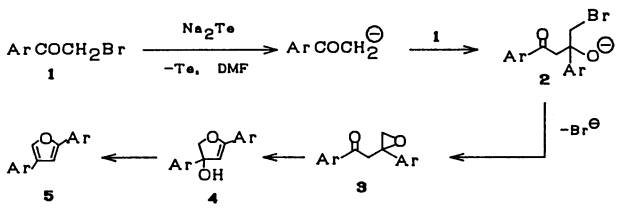
The formation of furan **5** could be attributed to an intermolecular condensation between the enolate generated and the bromo ketone **1** followed by presumably a formation of an epoxide ring which underwent further cyclization (Scheme 1). Synthesis of 2,4-diarylfurans from phenacyl bromides by electrochemical reduction[7] and formation of 2,4-diarylfurans from reactions of phenacyl bromides with nickel carbonyl in DMF[8] and with copper(I) chloride in DMSO[9] have been reported. Formation of furan derivatives during the dehalogenation of halo ketones by magnesium in tetrahydrofuran (THF)[10] has also been observed. Condensation of imino ketones from 1-amino-4,6-diaryl-2-pyridone with phenacyl bromides followed by acid treatment afforded 2,4-diarylfurans having different substituents.[11]

A support for the proposed mechanism was provided by reacting excess of the enolate generated from

Table 1. 2,4-Diarylfuran Derivatives Isolated

	Ar **1**	Mp/ °C **5** (lit,[7] Mp)	Yield/%[a] **5**	 **6**
a	C_6H_5	108—110 (109—110)	17	47
b	4-BrC_6H_4	157—160 (159—160)	36	43
c	4-ClC_6H_4	127—129 (127—128)	19	47
d	4-$C_6H_5C_6H_4$	258—263 (267—268)	2	58

a) Yields refer to the products isolated using an equimolar amount of copper(II) chloride.



Scheme 1.

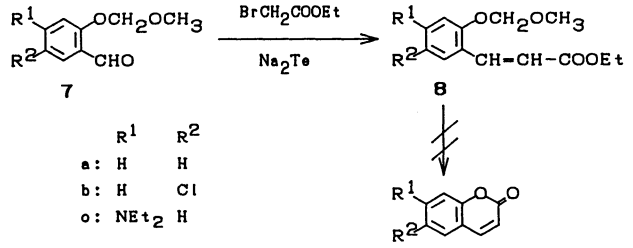
acetophenone by potassium hydride[12] with 4-chlorophenacyl bromide (**1c**) in the presence of copper(II) chloride under the similar conditions. From the reaction mixture the expected 2-phenyl-4-(4-chlorophenyl)furan was obtained in 36% yield. It was found that when the reaction was carried out in the absence of copper(II) chloride or if the formation of enolate was carried out in a short time the yield of furan derivative was considerably low. Attempts to develop an efficient method for synthesizing mixed 2,4-diarylfurans based on the above route did not give encouraging results.

To find the role of the oxidizing agent the reaction was carried out in the absence of copper(II) chloride and also in the presence of potassium iodide. Even in these cases furan derivative **5** was isolated in about 10% yield. This rules out the possibility of additives actually taking part in the reaction, but it is worth mentioning that the presence of copper(II) chloride or iron(III) chloride led to a very clean reaction mixture. In the absence of tellurium species, i.e., only in the presence of sodium hydride, 4-bromophenacyl bromide was recovered intact under similar conditions. With the view to obtain the furans in better yields the reaction was carried out deliberately using a less amount of sodium telluride. Such an attempt was, however, unsuccessful.

Finally in an attempt to isolate the oxidatively coupled product from the ketone enolate, generated from α-bromo ketone by sodium telluride, experiment was carried out using a large excess of copper(II) chloride. No oxidatively coupled product could be isolated from the reaction mixture (Table 2).

It is interesting to note the difference in behavior of both the ester enolate from ethyl bromoacetate and ketone enolates from phenacyl bromide derivatives generated by sodium telluride. In contrast to the ester enolate which has been found to be unreactive towards ketones,[13] the ketone enolates in the present study underwent intermolecular condensation and further cyclization leading to furan derivatives.

Coumarins. Recently we developed a novel route to α,β-unsaturated esters from aldehydes and ethyl bromoacetate using sodium telluride.[13] It was anticipated that extension of this reaction to salicylaldehyde derivatives would lead to coumarin derivatives. Attempted condensation of salicylaldehyde with ethyl bromoacetate resulted only in the recovery of the aldehyde. However, the desired α,β-unsaturated esters (**8a—c**) were obtained from 2-(methoxymethoxy)-benzaldehydes (**7a—c**) and ethyl bromoacetate in moderate yields. Attempted cyclization of these unsaturated esters in acetic acid under reflux for 6 h resulted only in the hydrolysis of methoxymethoxy group. Cyclization using sulfuric acid or polyphosphoric acid gave a dark polymeric reaction mixture. Reluctance for cyclization could probably be attributed to the demand of sterically less favorable cis configuration of unsaturated esters for cyclization to occur.



Having met with no success in the above scheme we turned our attention to an intramolecular Reformatsky-type reaction of 2-(bromoacetoxy)benzaldehyde (**9**). Fuson and coworkers observed that the Reformatsky reaction of **9** occurs only in the presence of anhydrous zinc bromide in addition to zinc.[14] The products isolated include salicylaldehyde (65%), coumarin (26%), and *trans-o*-hydroxycinnamic acid (9%). Attempted intramolecular Reformatsky-type reaction of **9** using sodium telluride gave only 6,12-epoxy-6*H*,12*H*-dibenzo[*b*,*f*][1,5]dioxocin (**10**; disalicylaldehyde) (32%) in addition to salicylaldehyde (8%). Compound **10** would result from the self-acetalization of salicylaldehyde, generated from 2-(bromoacetoxy)-benzaldehyde by the elimination of ketene. Formation of this compound from reactions using salicylaldehyde has been observed earlier.[15] Thus our attempts to synthesize coumarin derivatives using sodium telluride was entirely unsuccessful.

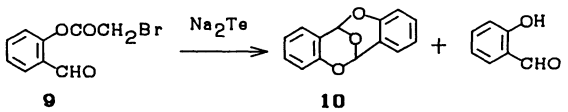


Table 2. Influence of Oxidizing Agents and the Relative Amounts of Halo Carbonyl Compounds, Na_2Te and Oxidant on the Yields of Furan Derivatives **5**

Phenacyl halide	Oxidant	Amounts employed (equiv)			Yield/%	
		Substrate **1**	Na_2Te	Oxidant	Furan **5**	Ketone **6**
4-$BrC_6H_4COCH_2Br$	—	1.0	1.0	0	10	40
	I_2	1.0	1.0	1.0	8	45
	$FeCl_3$	1.0	1.0	1.0	22	44
	$CuCl_2$	1.0	1.0	1.0	36	43
	$CuCl_2$	1.0	0	1.0	—	—[a]
	$CuCl_2$	2.0	1.0	1.0	22	34
	$CuCl_2$	1.0	1.0	5.0	22	44
4-$BrC_6H_4COCH_2I$	$CuCl_2$	1.0	1.0	1.0	11	36

a) Starting material was recovered intact.

Experimental

2-(Methoxymethoxy)arene carbaldehydes (**7a—c**) were prepared following the procedure reported by La Forge for the preparation of **7a**.[16] 2-(Bromoacetoxy)benzaldehyde (**9**) was prepared from salicylaldehyde and bromoacetyl bromide following the method reported.[14]

2,4-Diarylfurans: General Procedure: To sodium telluride (prepared from tellurium (1.0 mmol) and sodium hydride (2.2 mmol; washed with hexane prior to use))[17] in dry DMF (3 ml) at −40 °C was slowly added a solution of halo ketone (**1**: 1.0 mmol) in dry THF (3 ml) followed by the addition of anhydrous copper(II) chloride (1.0 mmol) in DMF (3 ml). Initially the reaction mixture could be stirred, but near the end of complete addition of halo ketone the mixture became very thick. Reaction mixture was kept at that temperature for 2 h and then slowly raised to room temperature. After 1 h the reaction was quenched by adding saturated aqueous ammonium chloride (10 ml) and the organic phase was extracted into benzene. The mixture was freed from insoluble inorganic materials by filtration through a thin layer of Celite. The organic layer was separated and the aqueous layer was extracted with benzene. The combined extracts were washed with 0.5 M† sulfuric acid followed by brine and dried over sodium sulfate. The crude product, obtained after evaporation, was purified by column chromatography over silica gel. Furan derivatives **5** were eluted first using hexane as eluent and then dehalogenated ketone **6** using a mixture of hexane and dichloromethane.

2-Phenyl-4-(4-chlorophenyl)furan: Acetophenone (1.0 mmol) in THF (5 ml) was added to potassium hydride (1.2 mmol; after removal of oil matrix following the procedure and precautions reported by Brown[18]) in THF (35 ml) at 20 °C and after the evolution of hydrogen ceased the reaction mixture was stirred for 24 h. The reaction mixture was cooled to −40 °C and 4-chlorophenacyl bromide (0.6 mmol) in DMF (3 ml) was added followed by the addition of copper(II) chloride (0.6 mmol) in DMF (3 ml). The dark reaction mixture was stirred at this temperature for 30 min and the reaction went to completion during this period. Water (10 ml) was added, THF was removed under vacuum, and the reaction mixture was extracted into benzene. 2-Phenyl-4-(4-chlorophenyl)furan was isolated in 36% yield. Mp 132—134 °C (lit,[11] 130 °C). IR: 1490, 1450, 1155, 1100, 1090, 1010, 930, 910, 835, 805, 770, 690 cm^{-1}; ^1H NMR: δ= 6.79 (s, 1H), 7.0—7.7 (m, 10H).

Preparation of the Unsaturated Esters (8a—c): General Procedure: To sodium telluride (4.0 mmol) in dry DMF (3 ml) at −20 °C was added, 2-(methoxymethoxy)benzaldehyde (**7a—c**) (1.0 mmol) in dry DMF (3 ml) followed by ethyl bromoacetate (4.0 mmol) in DMF (4 ml). Immediate separation of tellurium was observed and the reaction mixture was stirred at this temperature for 1 h and then at room temperature for 1 h. The reaction was quenched by the addition of 0.5 M sulfuric acid (5 ml) and the reaction mixture was extracted with benzene (10 ml). After stirring for 30 min the insolubles were removed by filtration through a bed of Celite and the aqueous layer was extracted with benzene (5 ml). The combined organic layer was washed with water and dried, and the solvent was removed under reduced pressure to give the crude unsaturated ester, which was purified by chromatography on silica gel using hexane as eluent.

8a: Yield 76%. Bp 158—160 °C/2 mmHg.†† IR: 1720, 1640, 1600, 1500, 1325, 1280, 1240, 1175, 1090, 1000 cm^{-1}; ^1H NMR: δ=1.25 (t, 3H; J=7 Hz), 3.43 (s, 3H), 4.21 (q, 2H; J=7 Hz), 5.16 (s, 2H), 6.43 (d, 1H; J=16 Hz), 6.8—7.6 (m, 4H), 8.00 (d, 1H; J=16 Hz).

8b: Yield 44%. Bp 160—165 °C/3 mmHg. IR: 1710, 1630, 1480, 1320, 1180, 1160, 1080, 990 cm^{-1}; ^1H NMR: δ=1.29 (t, 3H; J=7 Hz), 3.45 (s, 3H), 4.23 (q, 2H; J=7 Hz), 5.20 (s, 2H), 6.43 (d, 1H; J=16 Hz), 7.1—7.4 (m, 3H), 7.92 (d, 1H; J=16 Hz).

8c: Yield 60%. Bp 165—170 °C/2.5 mmHg. IR: 1700, 1595, 1510, 1410, 1360, 1220, 1160, 1000 cm^{-1}; ^1H NMR: δ=1.13 (t, 6H; J=7 Hz), 1.23 (t, 3H; J=7Hz), 3.15—3.66 (q, 4H; J=7 Hz), 3.45 (s, 3H), 4.18 (q, 2H), 5.16 (s, 2H), 6.0—6.5 (m, 2H), 6.36 (s, 1H), 7.32 (d, 1H; J=9 Hz), 7.83 (d, 1H; J=16 Hz).

Reaction of 2-(Bromoacetoxy)benzaldehyde (9) with Sodium Telluride. To a suspension of sodium telluride (1.0 mmol) in DMF (3 ml) at −40 °C was added a solution of 2-(bromoacetoxy)benzaldehyde (**9**) (1.0 mmol) in DMF (3 ml). The reaction was carried out as in the above case and the crude reaction mixture was purified by chromatography on silica gel. First, 6,12-epoxy-6*H*,12*H*-dibenzo[*b*,*f*][1,5]-dioxocin (**10**) was eluted followed by salicylaldehyde (8%) and only trace of coumarin, detectable on TLC, was eluted. Compound **10**, obtained in 32% yield, was crystallized from hexane. Mp 127—131 °C (lit,[14] 127—130 °C). MS: m/z (rel intensity) 226 (M^+, 100), 197 (24), 181 (22), 180 (10), 121 (12), 121 (67); IR: 1610, 1590, 1480, 1460, 1320, 1270, 1220, 1110, 1060, 1030, 970, 950, 760, 700 cm^{-1}. ^1H NMR: δ=6.22 (s, 2H), 6.7—7.4 (m, 8H). Found: C, 73.84; H, 4.65%. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.43%.

† 1 M=1 mol dm^{-3}.

†† 1 mmHg≈133.322 Pa.

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