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

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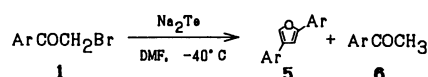
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Synopsis. The enolates, generated from phenacyl bromides by sodium telluride, yield 2,4-diarylfurans in addition to the expected dehalogenation products. No 1,4-dicarbonyl compounds could be isolated even in the presence of excess oxidizing agent, copper(II) chloride. Condensation of 2-(methoxymethoxy)arene-carbaldehydes 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 $\text{Cu}(\text{OTf})_2$.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 ^1H 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).

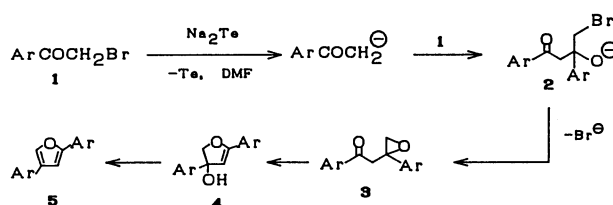
The formation of furan **5** could be attributed to an intermolecular condensation between the enolate generated and the bromo ketone **1** followed by presumably a formation of an epoxide ring which underwent further cyclization (Scheme 1). Synthesis of 2,4-diarylfurans from phenacyl bromides by electrochemical reduction⁷⁾ and formation of 2,4-diarylfurans from reactions of phenacyl bromides with nickel carbonyl in DMF⁸⁾ and with copper(I) chloride in DMSO⁹⁾ 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/ $^\circ\text{C}$ 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- $\text{C}_6\text{H}_5\text{C}_6\text{H}_4$	258–263 (267–268)	2	58

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



Scheme 1.

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 Brown¹⁸) 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 $132\text{--}134^{\circ}\text{C}$ (lit.¹¹ 130°C). IR: 1490, 1450, 1155, 1100, 1090, 1010, 930, 910, 835, 805, 770, 690 cm^{-1} ; $^1\text{H NMR}$: $\delta=6.79$ (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 $158\text{--}160^{\circ}\text{C}/2\text{ mmHg}$.^{††} IR: 1720, 1640, 1600, 1500, 1325, 1280, 1240, 1175, 1090, 1000 cm^{-1} ;

[†] 1 M=1 mol dm^{-3} .

^{††} 1 mmHg \approx 133.322 Pa.

$^1\text{H NMR}$: $\delta=1.25$ (t, 3H; $J=7\text{ Hz}$), 3.43 (s, 3H), 4.21 (q, 2H; $J=7\text{ Hz}$), 5.16 (s, 2H), 6.43 (d, 1H; $J=16\text{ Hz}$), 6.8–7.6 (m, 4H), 8.00 (d, 1H; $J=16\text{ Hz}$).

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

8c: Yield 60%. Bp $165\text{--}170^{\circ}\text{C}/2.5\text{ mmHg}$. IR: 1700, 1595, 1510, 1410, 1360, 1220, 1160, 1000 cm^{-1} ; $^1\text{H NMR}$: $\delta=1.13$ (t, 6H; $J=7\text{ Hz}$), 1.23 (t, 3H; $J=7\text{ Hz}$), 3.15–3.66 (q, 4H; $J=7\text{ Hz}$), 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; $J=9\text{ Hz}$), 7.83 (d, 1H; $J=16\text{ Hz}$).

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-6H,12H-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 $127\text{--}131^{\circ}\text{C}$ (lit.¹⁴ $127\text{--}130^{\circ}\text{C}$). 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} . $^1\text{H NMR}$: $\delta=6.22$ (s, 2H), 6.7–7.4 (m, 8H). Found: C, 73.84; H, 4.65%. Calcd for $\text{C}_{14}\text{H}_{10}\text{O}_3$: C, 74.33; H, 4.43%.

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