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Reformatsky Reaction on Thiocarbonyl Compounds : New C-C Bond Forming Reaction

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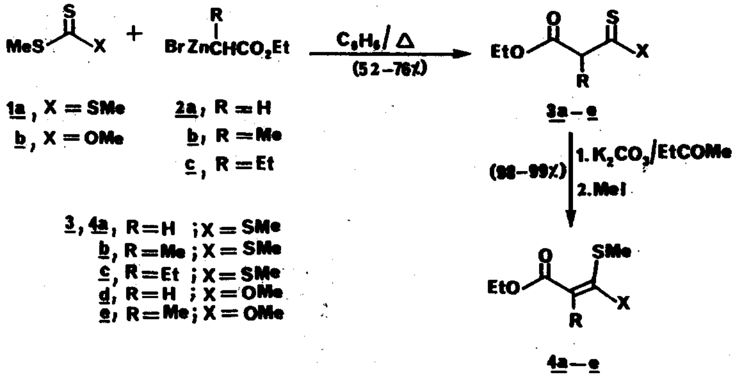
Abstract: Reformatsky reagents are shown to undergo facile C-C bond formation on trithiocarbonates, xanthates, thione and dithioesters through carbophilic addition yielding products formed by elimination of either sulphur or alkylthio group.

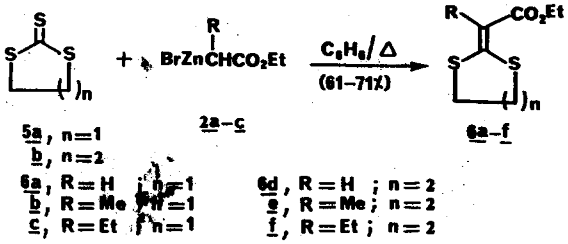
Remarkable developments have taken place in the chemistry of thiocarbonyl compounds producing exciting results in organic synthesis. Examples of particular importance are the C-C bond forming reactions involving stereospecific synthesis of olefins[1], preparation of tetrathiofulvalene [2], Eschenmoser sulfide contraction [3] reactions with trivalent phosphorous compounds [4] which have been the focus of interest in the past several years. The thiocarbonyl compounds can undergo addition with alkyl and allyl Grignard reagents in highly regioselective either carbophilic or thiophilic manner under appropriate experimental conditions[5], which has been usefully applied in many synthetic transformations [6]. The narrowing electronegativity difference between carbon and sulfur coupled with characteristic atomic volume of sulfur and its polarizability appear to make this difference in reactivity from those of carbonyl compounds. It is therefore interesting to examine the behaviour of these compounds towards various organometallics for dispelling the factors responsible about their reactivities. Our interest in organosulfur compounds prompted us to investigate the behaviour of Reformatsky reagents towards thiocarbonyl compounds. From the literature survey it is apparent that the Reformatsky reagents in the recent past have been successfully reacted with a variety of electrophiles including azomethines, nitriles, carboxylic acid chlorides, anhydrides, lactones, oxiranes, azirines, aminals and nitrones etc.[7]. However there is no report on the addition of these reagents to the thiocarbonyl compounds. We therefore became interested in these reactions and our results are presented herein.

The reaction of trithiocarbonate **1a** with ethyl bromozinc acetate was first examined due to our interest in the synthesis of ketene dithioacetals derived from alkyl alkanoates for which there are no satisfactory methods available in the literature [8]. In a typical experiment, ethyl bromozinc acetate was reacted with **1a** in refluxing benzene, when the corresponding ß-carboethoxydithioacetate **3a** was isolated in 52% yield along with some dithioacetal **4a** (21%). The dithioacetate **3a** was separated from the crude reaction mixture by column chromatography and subsequently alkylated with methyl iodide in the presence of potassium carbonate to afford **4a** in quantitative yield (72% overall yield). However when the crude reaction mixture (**3a** and **4a**) was directly alkylated as described above, **4a** was obtained in improved yield (84%) (Scheme 1). The Reformatsky reagents **2b-c** derived from ethyl α-bromopropanoate and ethyl α-bromobutyrate respectively reacted with **1a** to afford only the dithioacetates **3b-c** in high yields, while the corresponding dithioacetals **4b** and **4c** were not detected in the reaction mixture. Alkylation of **3b** and **3c** as described above afforded the respective **4b** and **4c** in almost quantitative yield. The cyclic trithiocarbonates **5a** and **5b** underwent facile sulfur extrusion on reaction with ethyl bromozinc acetate and its higher homologs to afford the corresponding cyclic ketene dithioacetals **6a-f** in overall high yields (Scheme 2). Under similar reaction conditions, **2a** and



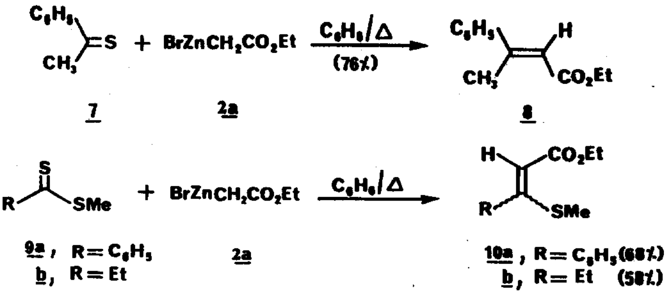
Scheme 1

2b reacted with dimethyl xanthate 1b to afford the respective β-carboethoxythioacetate 3d and 3e as major products. The corresponding O,S-dimethyl acetals 4d and 4e were subsequently obtained in high yields from 3d-e by the alkylation process (Scheme 1).

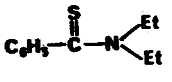


Scheme 2

The Reformatsky reagents thus add to these substrates (trithiocarbonates and xanthate) in carbophilic manner leading to C-C bond formation followed by extrusion of either alkylthio group or sulfur. The other thiocarbonyl compounds were also examined for their behaviour towards Reformatsky reagents. Thus thioacetophenone 7 on reaction with 2a afforded the corresponding β-methylcinnamate 8 in 76 % yield like its oxygen counterpart [7b] (Scheme 3). Similarly the dithiobenzoate 9a and dithiopropionate 9b underwent carbophilic addition with 2a accompanied with extrusion of sulfur to afford β-methylthio α,β-unsaturated esters 10a-b in good yields (Scheme 3). In none of these experiments, the products derived from thiophilic attack of the Reformatsky reagent were observed.



Scheme 3



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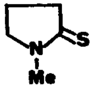

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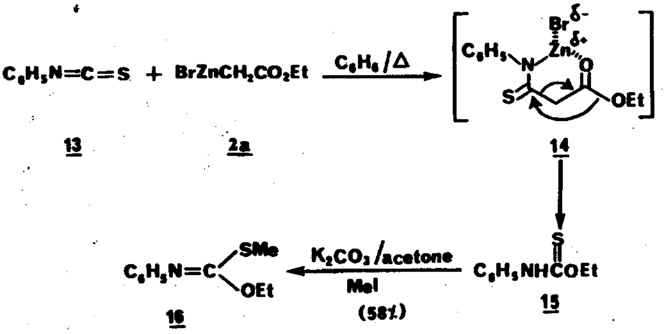
Attempted reaction of ethyl bromozinc acetate with either acyclic 11 or cyclic 12 thioamides did not afford any clear cut products. Interestingly when the phenyl isothiocyanate 13 was reacted with 2a under the identical conditions the product isolated was characterized as the thiocarbamate 15 which on methylation afforded N-phenyliminothiocarbamate 16 (Scheme 4) in good yield. The probable mechanism of this transformation which apparently involves ketene elimination is under investigation.



Scheme 4

In conclusion we have demonstrated that the Reformatsky reagents undergo facile carbophilic addition to various thiocarbonyl compounds involving C-C single or double bond formation. The reaction thus provides a facile route for the synthesis of α-carboethoxy S,S-, O,S-acetals and the corresponding ß-alkylthio α,ß-unsaturated esters. Further work to study the scope of these reactions is in progress.

General Experimental Procedure.

To a stirred suspension of Zinc metal (2.6g, 0.04 mol, preheated at 110°C for 1hr) and a few crystals of iodine in dry ether (20ml), ethyl bromoalkanoate (0.02 mol) in dry ether (10ml) was added (one lot) with stirring and the mixture refluxed for 45 min. A solution of respective thiocarbonyl compounds (0.01 mol) in dry benzene (50 ml) was then added dropwise (30min) and the refluxing continued for another 5-6 hr (monitored by TLC). The reaction mixture was then cooled to room temperature, poured over ice-cooled dilute H_2SO_4 (5%, 100ml), organic layer separated, aqueous layer extracted with benzene (1x50ml). The combined extract was washed twice (2x100ml) with water, dried (Na_2SO_4) and solvent evaporated to give crude product (or product mixture) which were purified by column chromatography over silica gel using hexane/EtOAc (99:1) as eluent.

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9. All the products were characterized with the help of spectral, analytical data and by comparing with the data of known compounds. The spectral data for few selected compounds :

   Methyl 2-carboethoxy dithioethanoate (3a). Yellow viscuos liquid ; 52% ; IR (neat) 1745, 1420, 1380 cm^{-1} ; ^1H NMR (CCl_4) 1.27 (3H, t, J=7Hz, OCH_2CH_3), 2.67 (3H, s, SCH_3), 4.04 (2H, s, CH_2), 4.22 (2H, q, J=7Hz, OCH_2CH_3).

   Mythyl 2-carboethoxy dithiobutanoate (3c). Yellow viscous liquid; 72%; IR (neat) 1750,1280,1190 cm^{-1}; ^1H NMR (CCl_4) 0.95 (3H, t, J=7Hz, CH_2CH_3), 1.23 (3H, t, J=7Hz, OCH_2CH_3), 1.84-2.30 (2H, m, CH_2CH_3), 2.63 (3H, s, SCH_3), 3.83-4.28 (3H, m, CH & OCH_2CH_3)

   Methyl 2-carboethoxy thionoethanoate (3d). Yellow viscous liquid ; 68% ;IR (neat) 1723, 1438, 1396 cm^1 ; ^1H NMR (CCl_4) 1.28 (3H, t, J=7Hz, OCH_2CH_3), 4.05 (3H, s, OCH_3), 4.06-4.33 (4H, m, CH_2).

   Ethyl 3,3-bismethylthio-2-propenoate(4a). Light yellow solid ($CHCl_3$/hex); 99% ; mp 42-43°C; IR (KBr) 1690, 1540, 1440, 131cm^{-1}; ^1H NMR ($CDCl_3$) 1.25(3H, t, J=7Hz, OCH_2CH_3), 2.40(3H, s, SCH_3), 2.43 (3H,s, SCH_3), 4.12 (2H, q, J=7Hz, OCH_2CH_3), 5.51(1H, s, =CH).

   Ethyl 2-bismethylthiomethylidine butanoate (4c). Yellow viscous liquid; 98%; IR (neat) 1735, 1460, 1380, 1300 cm^{-1}; ^1H NMR (CCl_4) 1.04 (3H, t, J=7Hz, CH_2CH_3), 1.31 (3H, t, J=7Hz, OCH_2CH_3), 2.26 (3H, s, SCH_3), 2.31 (3H, s, SCH_3), 2.57 (2H, q, J=7Hz, CH_2CH_3), 4,21 (2H, q, J=7Hz, OCH_2CH_3).

   Ethyl 3-methoxy-3- methylthio- 2-propenoate (4d). Light yellow viscous liquid; 99% ; IR(neat)1760, 1705, 1580, 1458, 1340 cm^{-1} ;^1H NMR(CCl_4) 1.22 (3H,t,J=7Hz,OCH_2CH_3), 2.23(3H,s,SCH_3), 3.85(3H,s, OCH_3), 4.12(2H,q,J=7Hz,OCH_2CH_3), 5.16(1H,s,=CH).

   Ethyl 2-(1,3-dithiolan-2-ylidine)ethanoate (6a). Yellow viscous liquid; 71% ;IR(neat) 1700, 1580, 1385, 1323 cm^1;^1H NMR(CCl_4)1.22 (3H,t, J=7Hz, OCH_2CH_3), 3.39 (4H,s, CH_2), 4.16 (2H,q, J=7Hz,OCH_2CH_3), 6.02(1H,s,=CH).

   Ethyl 2-(1,3-dithian-2-ylidine)ethanoate (6d). Yellow viscuos liquid : 70%; IR (neat) 1747, 1550, 1265 cm^1 ; ^1H NMR (CCl_4) 1.23 (3H, t, J=7Hz, OCH_2CH_3), 2.07-2.41 (2H, m, CH_2), 2.68-3.18 (4H, m, SCH_2), 4.11 (2H, q, J=7Hz, OCH_2CH_3), 6.05 (1H, s, =CH).

   Ethyl 3-methylthio-3-phenylpropenoate (10a). Yellow viscous liquid; 68% ; IR(neat) 1720, 1605, 1460, 1380, 1360 cm^{-1}; ^1H NMR (CCl_4)1.06(3H,t,J=7Hz,OCH_2CH_3), 2.30(3H,s,SCH_3), 3.93(2H,q,J=7Hz,OCH_2CH_3), 5.60(1H,s,=CH), 7.35(5H,brs,ArH).

   Ethyl 3-methylthio-2-pentenoate (10b) Light yellow viscous; 58% ; IR (neat) 1739, 1456, 1377 cm^1 ; ^1H NMR (CCl_4) 1.03 (6H, m, CH_3), 2.04 (3H, s, SCH_3), 2.62 (2H, q, J=7Hz, CH_2CH_3), 3.71 (2H, q, J=7Hz, OCH_2CH_3), 5.09 (1H, s, =CH).

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