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# NOVEL CYCLOAROMATIZATION IN REFORMATSKY REACTION ON α-OXOKETENE DITHIOACETALS: A REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED ETHYL 2-HYDROXY-6-METHYLTHIOBENZOATES[1]

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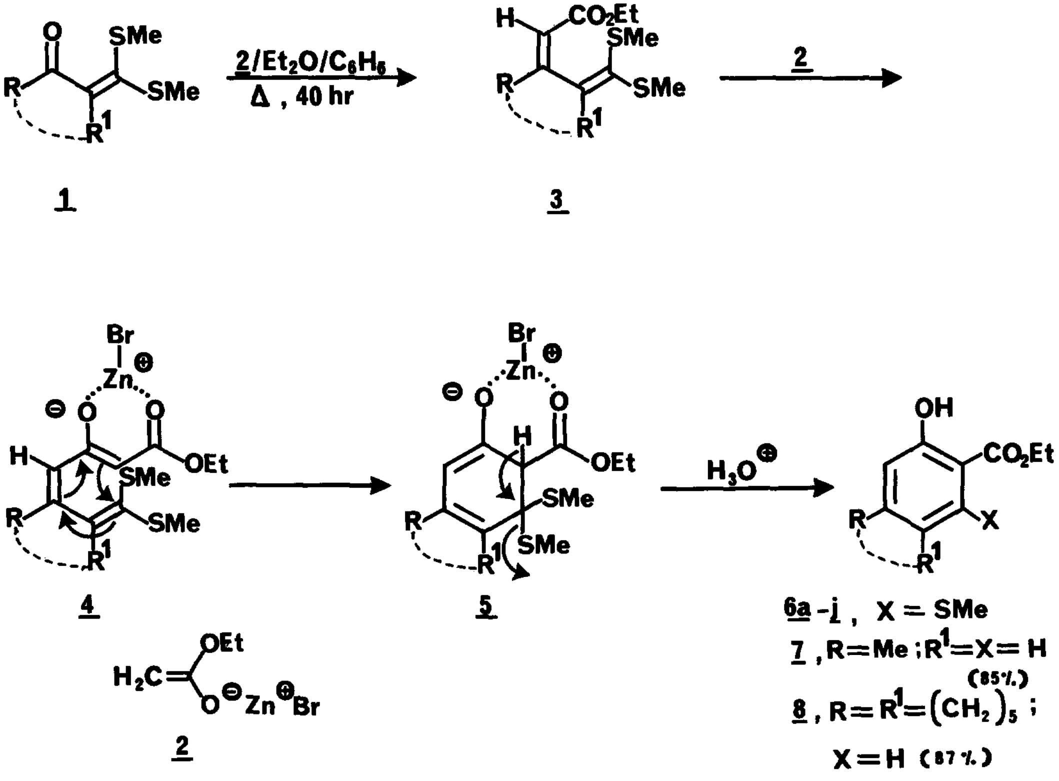
Summary: A novel cycloaromatization reaction leading to substituted ethyl 2-hydroxy-3-methylthiobenzoates 6 by condensation of α-oxoketene dithioacetals 1 with excess of Reformatsky reagent 2 from ethyl bromoacetate through intermediate dienes 3 has been reported.

In one of our recent reports, we had observed that ethyl bromoacetate under Reformatsky reaction conditions, adds to α-oxoketene dithioacetals in 1,2 fashion to yield the corresponding 1,1-bis(methylthio)-3-aryl/alkyl-4-ethoxycarbonyl-1,3-butadienes 3 in good yields[2]. We considered these dienes 3 of potential synthetic interest, if they undergo further condensation with the Reformatsky reagent 2 on ethoxycarbonyl group[3], since the resulting zinc enolates 4 should undergo facile electrocyclic ring closure followed by elimination of methylmercaptan to give the regiospecifically substituted 2-hydroxy-6-methylthiobenzoates 6 or the corresponding salicylates after desulphurization. We have realized this goal in one pot reaction and report our preliminary results in this communication.

When the dithioacetal 1a was refluxed with excess of 2 (4 eqv) in ether/benzene, work-up of the reaction mixture yielded a crystalline solid, which was characterized as ethyl 2-hydroxy-4-methyl-6-methylthiobenzoate (6a) (60%); $\nu_{max}$ (KBr): 3250(br,OH); 1700(CO) cm$^{-1}$; $^1$H n.m.r. (90 MHz) (CDCl$_3$) $\delta$ 1.33(t,3H,CH$_3$CH$_2$); 2.13(s,3H,SCH$_3$); 2.24(s,3H,CH$_3$); 4.29(q,2H,OCH$_2$CH$_3$); 6.30(brs,1H,H-5); 6.40(brs,1H,H-3); 11.31(brs,OH,exchangeable with D$_2$O); m/z 226(M$^+$,69%); 180(100). The structure of 6a was further confirmed by its desulphurization with Raney Nickel, which afforded the corresponding ethyl m-cresotate(7)[4,5]. The other substituted 2-hydroxy-6-methylthiobenzoates 6b-e and the corresponding 4,5-annelated derivatives 6f-j were similarly obtained from the respective dithioacetals 1b-j under identical conditions in 52-63% overall yields (Table)[6]. One of the cyclic benzoates 6h[7] was also desulphurized under similar conditions to give 8. The $^1$H n.m.r. spectral data[7] of 8 further confirmed the regiochemistry of the products 6.

The probable mechanism for the formation of 6 from 1 and 2 is depicted in the Scheme. The intermediacy of the diene 3 was established by reacting 3b with 2 (1.5 eqv) in a separate experiment, which afforded the corresponding 6b in 72% yield. The dienes 3 could also be trapped in few reactions (1a and 1b) along with 6 by curtailing the reaction time (8 hr) under identical conditions. The reaction proceeds as expected, thus the acylation of 2 with 3 results in the formation of intermediate zinc enolate 4 which on electrocyclization followed by elimination of methylmercaptan during acid work-up affords 6 through the intermediate 5. The overall transformation represents a novel cycloaromatization[8] involving sequential condensation of 2 with α-oxoketene dithioacetals 1 to give dienes 3 as five carbon fragments and then cyclic six carbon aromatic systems 6 in one pot reaction (a 3C + 2C + 1C approach),thus providing acetoacetate dianion equivalency[8,9] to the Reformatsky reagent 2. The reaction is therefore a facile entry to substituted 2-hydroxy-6-methylthio benzoates 6 and ultimately to the corresponding salicylates[10] from easily accessible α -oxoketene dithioacetals. Further work to study the scope and the mechanism of the reaction is in progress.

In a typical experiment, a suspension of activated zinc (5.2g, 0.08g atom), few crystals of iodine and ethyl bromoacetate (4.8 ml, 0.04 mol) in dry ether (50 ml) is refluxed with

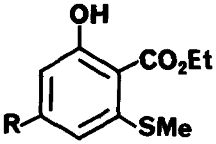
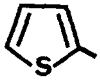
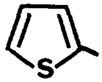
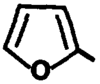
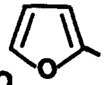
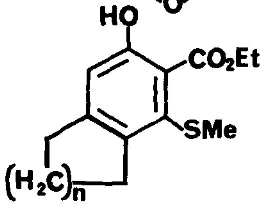
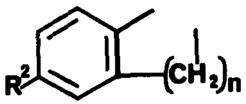
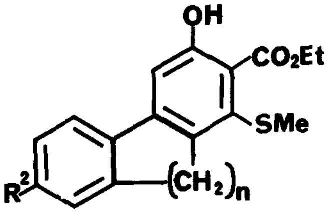


6a-i , X = SMe

7 , R=Me ; $R^1$=X= H (85%)

8 , R= $R^1$=$(CH_2)_5$ ; X=H (87%)

Scheme

| Entry | Starting material | R | R$^1$ | Product | Yield[a] [%] | M.p. [°C] |
|---|---|---|---|---|---|---|
| | | | |  | | |
| 1 | <u>1a</u> | $CH_3$ | H | <u>6a</u>, R = $CH_3$ | 60 | 78 |
| 2 | <u>1b</u> | 4-$ClC_6H_4$ | H | <u>6b</u>, R = 4-$ClC_6H_4$ | 63 | 108 |
| 3 | <u>1c</u> | $C_6H_5$ | H | <u>6c</u>, R = $C_6H_5$ | 60 | 72 |
| 4 | <u>1d</u> |  | H | <u>6d</u>, R =  | 63 | 91 |
| 5 | <u>1e</u> |  | H | <u>6e</u>, R =  | 58 | 92 |
| | | | |  | | |
| 6 | <u>1f</u> | $-(CH_2)_3-$ | | <u>6f</u>, n = 1 | 52 | 68 |
| 7 | <u>1g</u> | $-(CH_2)_4-$ | | <u>6g</u>, n = 2 | 57 | 138 |
| 8 | <u>1h</u> | $-(CH_2)_5-$ | | <u>6h</u>, n = 3 | 60 | 128 |
| | |  | |  | | |
| 9 | <u>1i</u> | R$^2$ = H ; n = 1 | | <u>6i</u>, R$^2$ = H ; n = 1 | 55 | 117 |
| 10 | <u>1j</u> | R$^2$ = MeO ; n = 2 | | <u>6j</u>, R$^2$ = MeO; n = 2 | 58 | 148 |

[a] Yield of pure isolated product based on <u>1</u> .

stirring for 45 min. A solution of 1a (1.62g, 0.01 mol) in dry benzene (50 ml) is then added dropwise (30 min) and the reaction mixture is further refluxed for 40 hr. It is then cooled, poured over 5% $H_2SO_4$ (100 ml), the organic layer separated and the aqueous layer extracted with EtOAc (50 ml). The combined extracts are washed with water (2x100 ml), dried ($Na_2SO_4$) and evaporated to give crude 6a, which is purified by passing through silica gel column using EtOAc-hexane (1:20) as eluent; colourless crystals ($CHCl_3$-hexane),yield 1.30g (60%).

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## References and Notes

1. Part 69 of the series; Part 68: A. Thomas, J.N. Vishwakarma, S. Apparao, H. Ila and H. Junjappa, Tetrahedron (communicated).
2. S. Apparao, A. Datta, H. Ila and H. Junjappa, Synthesis, 169 (1985).
3. Reformatsky reagents are known to undergo condensation with $\alpha$-bromoesters to give $\beta$-ketoesters as the side products; H.O. House in 'Modern Synthetic Reactions', W.A. Benjamin, Inc., 1972, Chapt. 10, p. 673-675.
4. N.K. Kochetkov, L.J. Kudryashov and B.P. Gottich, Tetrahedron, 12, 63 (1961).
5. 7: Oil; $\nu_{max}$ (neat) 3240(OH); 1680(CO) $cm^{-1}$; $\delta_H(CCl_4)$: 1.38(t,3H,$CH_3CH_2$); 2.30(s,3H, $CH_3$); 4.32(q,2H,$OCH_2CH_3$); 6.56(brd,J=8Hz,1H,H-5); 6.68(brs,1H,H-3); 7.60(d,J=8Hz,1H,H-6); 10.60(s,1H,OH, exchangeable with $D_2O$). The chemical shift values for aromatic and methyl protons for 7 are very similar to those reported for methyl m-cresotate, ref. 10.
6. The structures of all the products were established with the help of spectral and analytical data.
7. 6h: $\nu_{max}$ (KBr): 3248(br,OH); 1695(CO) $cm^{-1}$; $\delta_H$ ($CDCl_3$): 1.43(t,3H,$CH_3CH_2$); 1.35-1.97 (m,6H,$CH_2$); 2.30(s,3H,$SCH_3$); 2.77-2.86(m,2H,$CH_2$); 3.10-3.32(m,2H,$CH_2$); 4.43(q,2H,$OCH_2CH_3$); 6.73(s,1H,ArH); 10.48(s,1H,OH,exchangeable with $D_2O$); 8: colourless crystals (hexane); m.p. 61°C; $\nu_{max}$ (KBr): 3210(br,OH); 1665(CO); $\delta_H(CDCl_3)$: 1.40(t,3H,$CH_3CH_2$); 1.30-2.0 (m,6H,$CH_2$); 2.53-2.86(m,4H,$CH_2$); 4.32(q,2H,$OCH_2CH_3$); 6.52(s,1H,ArH); 7.43(s,1H,ArH); 10.40(s,1H,OH,exchangeable with $D_2O$).
8. For a review, see: P. Bamfield, P.F. Gordon, Chem. Soc. Rev., 13, 441 (1984).
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10. T-H. Chan and P. Brownbridge, J. Am. Chem. Soc., 102, 3534 (1980).

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