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Radical-Chain Desulfurisation of α-(Alkylthiomethyl)acrylates with Triphenylphosphine: a New Route to α-Alkylacrylates

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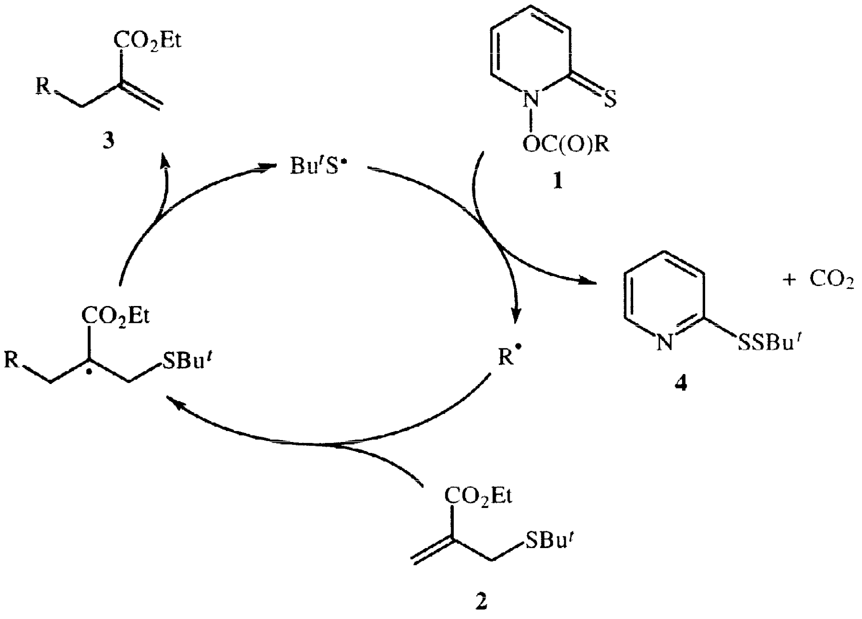
Abstract: *2-Methylene-3-alkylthiopropanoate esters $H_2C=C(CO_2Et)CH_2SR$ react with triphenylphosphine in refluxing octane, in the presence of a peroxide initiator, to give 2-methylenealkanoates $H_2C=C(CO_2Et)CH_2R$ in moderate yields, together with triphenylphosphine sulfide.* © 1997 Elsevier Science Ltd. All rights reserved.

The development of new methods for the construction of carbon-carbon bonds is a subject of perenial interest. In recent years, synthetic approaches that involve free-radical intermediates have become well established among the many options available to the organic chemist.[1] In the present work, we have brought together two previously known radical reactions and combined them to provide a simple new method for C-C bond formation.

Barton and Crich[2] have reported that esters of *N*-hydroxy-2-thiopyridone ("Barton"[3] or "PTOC"[4] esters) **1** react with ethyl 2-methylene-3-*tert*-butylthiopropanoate **2** in refluxing chlorobenzene to give the 2-methylenealkanoate **3** in reasonably good yields. This allylation reaction follows the radical-chain mechanism shown in Scheme 1 and the key C-C



Scheme 1

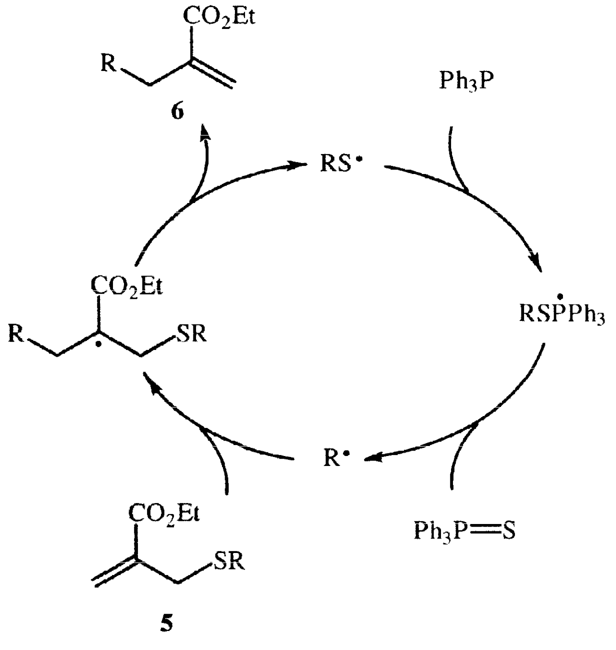
PII: S0040-4039(97)10587-1

bond-forming reaction involves addition of an alkyl radical to the acrylate **2** followed or (in our view, less likely) accompanied[2c] by elimination of the *tert*-butylthiyl radical. The alkyl radical is then regenerated by reaction of the thiyl radical with the PTOC ester to complete the chain and the thiyl radical ends up in the by-product **4**. Simple allylic sulfides, without the electron-withdrawing ester substituent, give poor yields, presumably because nucleophilic alkyl radicals add more rapidly to the electron-deficient double bond in **2**.[2,5,6]

Walling and his co-workers[7] showed many years ago that alkylthiyl radicals undergo desulfurisation reactions with phosphorus(III) compounds to give the corresponding alkyl radicals, *via* β-scission of an intermediate phosphoranyl radical adduct [eqn. (1)].[8] Therefore, we reasoned that acrylates of the type **5** should react with triphenylphosphine to undergo

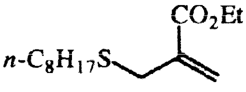
$$RS^{\bullet} + PX_3 \longrightarrow [RSPX_3]^{\bullet} \longrightarrow R^{\bullet} + S{=}PX_3 \qquad (1)$$

desulfurisation and allylic rearrangement (not detectable here) to give 2-methylenealkanoates of the type **6**, by the radical-chain mechanism shown in Scheme 2.



Scheme 2

The reactions of each of the four 2-methylene-3-alkylthiopropanoate esters[9] **7-10** with triphenylphosphine (1.1 molar equivalents) were carried out in refluxing octane or chlorobenzene (for **10**), in the presence of 1,1-bis(*tert*-butylperoxy)cyclohexane **15** as a thermal source of initiating alkoxyl radicals.[11] The initiator was added in three equal portions of *ca.* 3 mol% (based on starting acrylate), one present initially and the others added after 1 and 2 h; the total reaction time was 3 h. After removal the solvent, the acrylates **11-14** were isolated by flash chromatography on silica gel and the yields of the purified products are given beneath the structures.[13,14] Di-*tert*-butyl peroxide (20 mol%), added in a single portion at the start of the reaction, could also be used as initiator, although the reaction time had to be extended to 6 h and the yields of **11-14** were somewhat lower than those obtained using the peroxyketal **15**.



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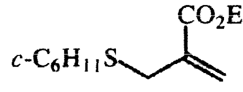

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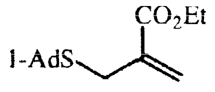

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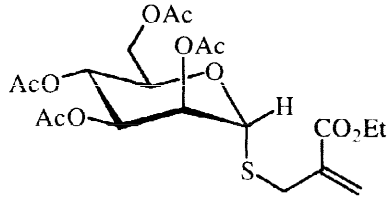

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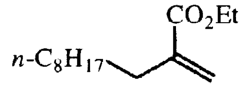
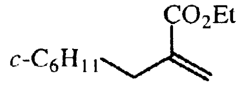
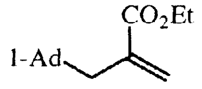


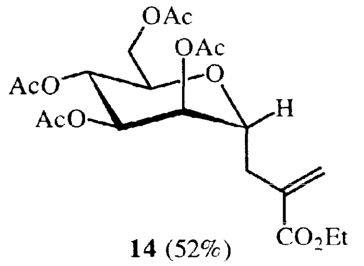
11 (51%)



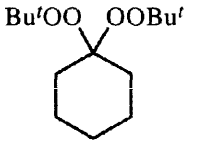
12 (57%)



13 (71%)



14 (52%)



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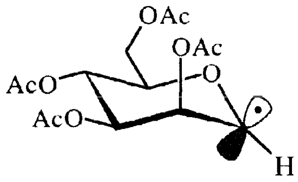

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The α-mannosyl derivative **10** gave only the α-*C*-glycoside **14** and none of the β-anomer was detected. The exclusive formation of **14**, as a consequence of attack of **10** at the axial face of the intermediate radical **16**, would be expected on both stereoelectronic and steric grounds.[1d,15] The structural assignment was confirmed by NOE experiments, in which strong enhancements of the absorptions from the axial protons attached to C-3 and C-5 were observed during irradiation of the less-shielded allylic proton (δ 2.77).[13]

Acknowledgements

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4. Johnson, C.C.; Horner, J.H.; Tronche, C.; Newcomb, M. *J. Am. Chem. Soc.*, 1995, **117**, 1684.
5. For similar reactions of PTOC esters with $CH_2{=}C(NO_2)CH_2SPh$, see Barton, D.H.R.; Togo, H.; Zard, S.Z. *Tetrahedron*, 1985,

41, 5507. For the related use of $CH_2=C(CO_2Et)CH_2SnBu_3$, see Baldwin, J.E.; Adlington, R.M.; Crawford, J.A.; Sweeney, J.B. *J. Chem. Soc., Chem. Commun.*, **1986**, 1339.

6. A requirement for the success of the reactions reported by Barton and Crich[2] and, especially, of those described in this paper is that the 2-methylene-3-alkylthiopropanoate **5** must be more reactive towards addition of alkyl radicals than the product acrylate ester **6**. In contrast to the view expressed in ref. 2c, we believe that the nature of the substituent Y can still have a marked effect on the rate of the overall process $R^{\bullet} + H_2C{=}C(X)CH_2Y \longrightarrow RCH_2C(X){=}CH_2 + Y^{\bullet}$, even when this reaction proceeds in a stepwise manner by an addition-elimination mechanism (as shown in Schemes 1 and 2). Some polymerisation of the product acrylate takes place towards the end of the reaction when the concentration of **5** is low and this seems to be the main factor limiting the yield of **6** obtained from our reactions.
7. (a) Walling, C.; Rabinowitz, R. *J. Am. Chem. Soc.*, 1957, **79**, 5326, (b) Walling, C.; Basedow, O.H.; Savas, E.S. *J. Am. Chem. Soc.*, 1960, **82**, 2181. (c) Walling, C.; Pearson, M.S. *J. Am. Chem. Soc.*, 1964, **86**, 2262.
8. (a) Dockery, K.P.; Bentrude, W.G. *J. Am. Chem. Soc.*, 1997, **119**, 1388 and references cited therein. (b) Roberts, B.P. *Adv. Free-Radical Chem.*, 1980, **6**, 225.
9. The acrylates **7-10** were prepared from ethyl β,β-dibromoisobutyrate[10] [which contained some of the monodehydrobrominated ester, ethyl α-(bromomethyl)acrylate] and the corresponding thiol, using the method described for the preparation of **2**.[2c] Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
10. Ferris, A.F. *J. Org. Chem.*, 1955, **20**, 780.
11. The peroxide **15** was handled as a 50% w/w solution in mineral oil, obtained from Peroxid-Chemie Ltd.; it is also available from the Aldrich Chemical Company as an 80% w/w solution in benzyl butyl phthalate. The half-life of this peroxyketal at 130 °C is *ca.* 15 min.[12]
12. (a) Matsuyama, K.; Kumura, H. *J. Org. Chem.*, 1993, **58**, 1766. (b) *Half-lifetimes of Organic Peroxides*, Technical Information Bulletin P 3.2.1, Peroxid-Chemie Ltd., Pullach, 1996.
13. NMR data (Varian VXR-400, $CDCl_3$ solvent, coupling constants in Hz): **11**: δ_H: 0.88 (3H, t, *J* 6.8), 1.26-1.32 (15H, m), 1.45 (2H, m), 2.29 (2H, t, *J* 7.6), 4.20 (2H, q, *J* 7.2), 5.50 (1H, br.s), 6.10 (1H, d, *J* 1.4); δ_C: 14.2, 22.7, 28.4, 29.1, 29.2, 29.3, 29.4, 29.5, 31.8, 31.9, 60.5, 124.1, 141.1, 167.4. **12**: δ_H: 0.88 (2H, m), 1.20 (2H, m), 1.29 (3H, t, *J* 7.1), 1.43 (1H, m), 1.67 (6H, m), 2.18 (2H, d, *J* 7.0), 4.19 (2H, q, *J* 7.1), 5.46 (1H, br.s), 6.13 (1H, d, *J* 2.0); δ_C: 14.2, 26.2, 26.5, 33.0, 36.6, 39.9, 60.5, 125.4, 139.5, 167.5. **13**: δ_H: 1.30 (3H, t, *J* 7.8), 1.44 (6H, br.s), 1.63 (6H, m), 1.92 (3H, br.s), 2.15 (2H, s), 4.18 (2H, q, *J* 7.8), 5.40 (1H, m), 6.17 (1H, d, *J* 2.0); δ_C: 14.2, 28.7, 37.0, 42.1, 42.3, 45.5, 60.6, 126.9, 137.6, 168.3. **14**: δ_H: 1.29 (3H, t, *J* 7.1), 2.01 (3H, s), 2.05 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 2.63 (1H, dd, *J* 14.6 and 4.5, allylic-H^A), 2.77 (1H, dd, *J* 14.6 and 9.8, allylic-H^B), 3.95 (1H, m, H-5), 4.03 (1H, dd, *J* 12.1 and 2.8, H-6^A), 4.20 (2H, q, *J* 7.1), 4.21 (1H, m, H-1), 4.29 (1H, dd, *J* 12.1 and 6.1, H-6^B), 5.20 (2H, m, H-2,4), 5.27 (1H, dd, *J* 9.0 and 3.2, H-3), 5.71 (1H, d, *J* 1.0), 6.29 (1H, d, *J* 1.0) (the assignments were made on the basis of proton-proton decoupling experiments); δ_C: 14.2, 20.7(1), 20.7(2), 20.8, 20.9, 31.5, 61.0, 66.8, 68.7, 70.2, 70.4, 73.8, 121.8, 135.8, 166.3, 169.6, 170.0, 170.2, 170.6. Satisfactory microanalytical data were obtained for all new compounds.
14. *Representative procedure*: A solution of ethyl 2-methylene-3-(1-adamantylthio)propanoate **9** (0.70 g, 2.5 mmol), triphenylphosphine (0.72 g, 2.75 mmol) and the peroxide **15** (50% w/w in mineral oil, 43 μl, 0.08 mmol) in octane (5 cm^3) was heated under reflux under argon for 3 h. A further portion of peroxide (0.08 mmol) was added after 1 h, and another was added after 2 h. The mixture was allowed to cool and petroleum (b.pt. 40-60 °C; 5 cm^3) was added. Triphenylphosphine sulfide was removed by filtration, the filter cake was washed with petroleum and the solvent was removed from the filtrate by rotary evaporation. The residue was purified by flash chromatography on silica gel, eluting with petroleum-diethyl ether (10:1), to give the acrylate **13**[2c] as an oil (0.44 g, 71%).
15. (a) Giese, B.; Dupuis, J. *Tetrahedron Lett.*, 1984, **25**, 1349. (b) Giese, B.; Linker, T.; Muhn, R. *Tetrahedron*, 1989, **45**, 935. (c) Pontén, F.; Magnusson, G. *J. Org. Chem.*, 1996, **61**, 7463.