A Mild Exchange Reaction of Xanthates with Bromine

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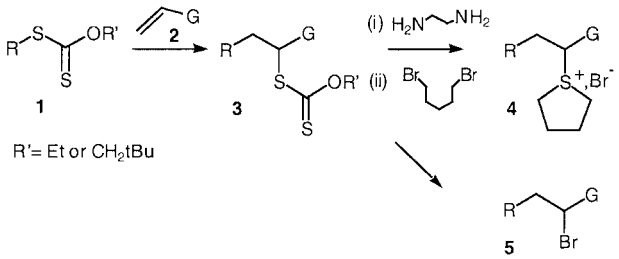
Abstract: Secondary *S*-alkyl-*O*-ethyl (or *O*-neopentyl) xanthates can be converted into the corresponding bromides by heating with ethyl 2-bromo-2-methylpropionate and cumyl peroxide in refluxing chlorobenzene; this transformation can be coupled to a xanthate transfer radical addition to an olefin.

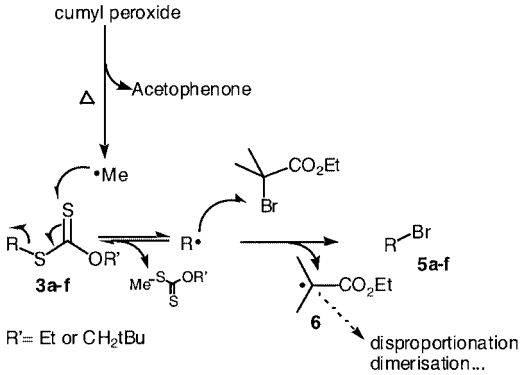
Key words: bromine atom transfer, xanthates, radical reactions, lactones

We have, over the past few years, shown that xanthates **1** and related dithiocarbonate derivatives undergo an efficient group transfer radical addition to a variety of olefins **2** (Scheme 1).[1] The adducts, **3**, are also xanthates and lend themselves to a number of subsequent radical and non-radical transformations. The xanthate group may thus be used in another C-C bond forming radical sequence[2] or reductively removed using tri-*n*-butyltinhydride, Raney nickel, nickel boride, or by the action of lauroyl peroxide in isopropanol.[3] Alternatively, the xanthate group can be ionically cleaved to the corresponding thiol with alkali or a primary or secondary amine.[4] Alkylation of the resulting thiol with 1,4-dibromobutane converts it to the sulfonium bromide **4**, which acts as a reasonably effective leaving group.[5] In the present Letter, we describe the direct transformation of a secondary xanthate into the corresponding bromide **5**, thus accessing an equally powerful nucleofuge (Scheme 1)



Scheme 1

Our concept is outlined in Scheme 2. Thermal decomposition of cumyl peroxide generates highly reactive methyl radicals which rapidly interact with the thiocarbonyl group of the xanthate leading, by an addition-fragmentation sequence, to the formation of radicals R˙. Although these radicals can exchange a xanthate group by reacting with the starting xanthate, this is a degenerate process that does not compete with the desired bromine atom abstraction from ethyl 2-bromo-2-methylpropionate leading to bromides **5a–f** and isobutyryl radicals **6**. In contrast to the initial methyl radicals, the isobutyryl radicals **6** are too stabilised to propagate the chain and presumably decay by the usual radical-radical interactions (dimerisation and disproportionation). Stoichiometric amounts of peroxide are therefore required to ensure complete transformation of the substrate.



Scheme 2

Indeed, gradual addition of cumyl peroxide (1.5 equiv) to a refluxing solution of xanthate **3a–f** (1.0 equiv) and ethyl 2-bromo-2-methylpropionate (ethyl bromoisobutyrate) (5.0 equiv) in chlorobenzene resulted in the effective formation of bromides **5a–f** (30–85%).[6] A fraction of the methyl radicals is consumed by direct reaction with the bromoisobutyrate; hence the need for over-stoichiometric amounts of cumyl peroxide and an excess of the bromine atom transfer agent. A number of examples is collected in the Figure. Except for xanthate **3c**, which gave only a poor yield of the corresponding bromide, the desired conversion occurred efficiently. The use of *O*-neopentyl xanthates in some cases was dictated by the need to facilitate chromatographic separation of the bromide from the other products of the reaction. We examined other peroxides such as *tert*-butylperoxide and lauroyl peroxide as mediators for the reaction but these turned out to be generally inferior to cumyl peroxide. Essentially all the precursors were made by the xanthate transfer radical addition to olefins containing various functional groups. Of special interest are lactones **3e**,**f** and **5e**,**f** because they represent sub-structures of many natural products.[7]

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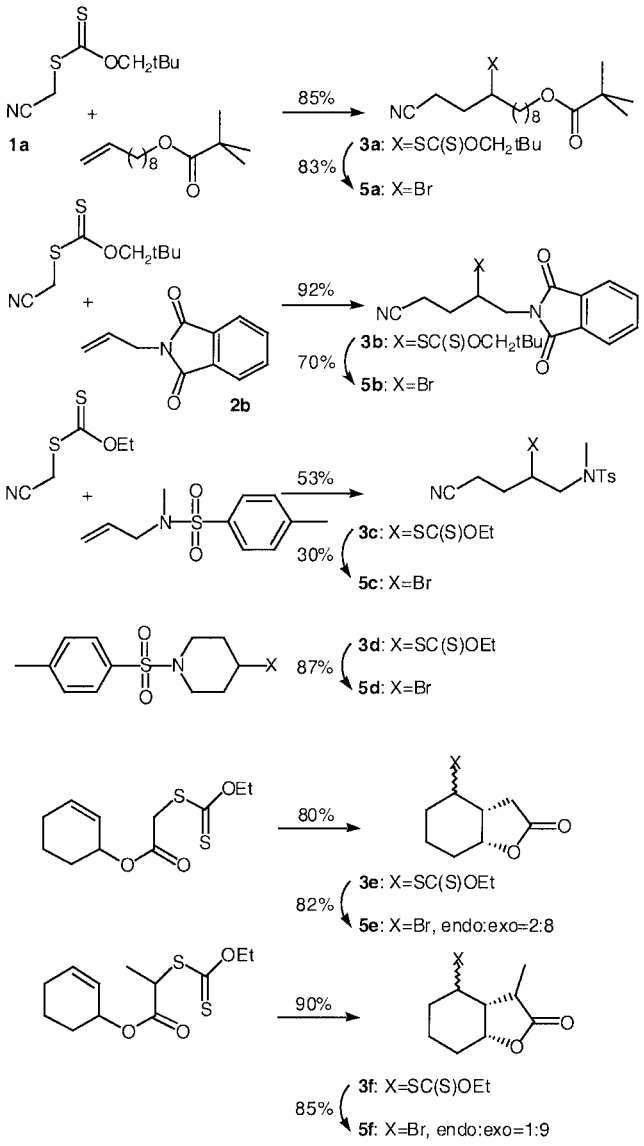
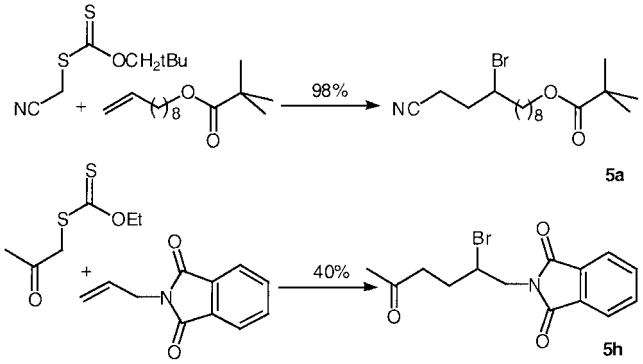


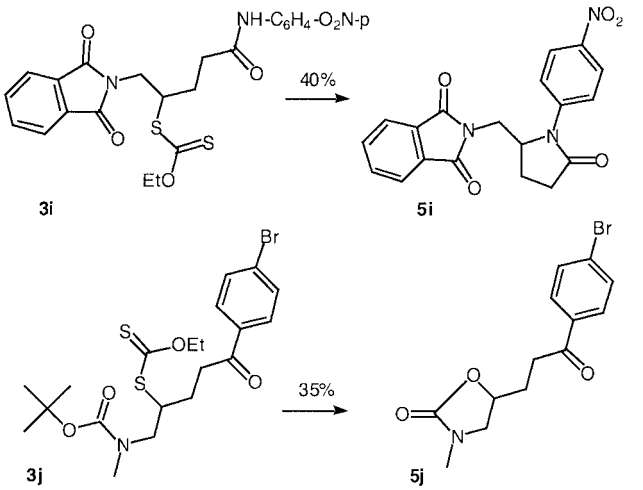
Figure

We found in some cases that the intermolecular radical addition to the olefin and the xanthate exchange with bromine could be done in one pot, as illustrated by two examples pictured in Scheme 3. The yield in the second example refers to the material obtained after one recrystallisation of the concentrated reaction mixture. The actual yield is obviously higher.

Not surprisingly, when the bromine atom was introduced close to a nucleophilic site, a subsequent ionic cyclisation was observed, as shown by the modestly efficient transformations in Scheme 4. The formation of lactam **5i** and cyclic carbamate **5j** could not be avoided due to the proximity of the nucleophile in both cases. Such reactions are nevertheless synthetically useful since the C-S bond of the xanthate can be replaced by a C-N bond and a C-O bond respectively.



Scheme 3 Conditions: cumyl peroxide 1.5 equiv. ethyl bromoisobutyrate 3 equiv. olefin 3 equiv. chlorobenzene (0.1 M). Reflux 6–8 h.



Scheme 4

One further interesting point concerns the choice of bromoisobutyrate as the bromine transfer agent. Our initial experiments were in fact carried out with bromotrichlomethane, a more commonly used bromine atom source.[8] The results were disappointing: complex mixtures were invariably obtained. We ascribed these initial failures to the relatively high reactivity of the electrophilic trichloromethyl radical generated upon bromine atom abstraction from the bromotrichloromethane. Such radicals are known to abstract hydrogen atoms leading to the uncontrolled formation of unwanted side products. Cristol and Seapy,[9] who attempted to photochemically replace the C-O bond in xanhates using $BrCCl_3$, also obtained poor results.

In conclusion, we have described a simple, yet efficient and flexible method for replacing a xanthate group with a bromine atom under neutral conditions. A number of functional groups commonly encountered in organic synthesis are tolerated. This new functional group interchange process, in combination with the powerful C-C bond forming ability of the xanthate transfer radical addition, opens access to structures not easily available otherwise.

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(5) (a) Boivin, J.; Pothier, J.; Ramos, L.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 9239. (b) **Typical Procedure**: 1 g (4.9 mmol) of xanthate **1a** and 1.8 g (9.8 mmol) of olefin **2b** dissolved in 6 mL of 1,2-dichloroethane were refluxed for a few minutes under nitrogen before addition of 98 mg (0.24 mmol) of commercially available lauroyl peroxide. The reflux is maintained for another 2 h. The solvent was then removed under reduced pressure and the residue was purified by chromatography on silica gel (PE/EtOAc 9/1–7/3) to give 1.8 g of a white solid (mp 107 °C) **3b** (92%). ^{1}H NMR ($CDCl_3$, 200 MHz, ppm): δ = 7.92–7.83 (2 H, m), 7.80–7.70 (2 H, m), 4.30 (2 H, s), 4.29 (1 H, m), 4.03 (1 H, dd, *J* = 7–14 Hz), 3.97 (1 H, dd, *J* = 7–14 Hz), 2.74–2.48 (2H, m), 2.28–1.96 (2 H, m), 1.00 (9 H, s). ^{13}C NMR ($CDCl_3$, 50 MHz, ppm): δ = 212.0 (*C*=S), 168.0 (*C*=O), 134.4 (*C*HAr), 131.9 (*C*qAr), 123.7 (*C*HAr), 118.7 (*C*N), 84.0 (CH_2O), 48.8 (*C*HS), 40.4 (CH_2), 32.0 (CMe_3), 28.3 (CH_2), 26.6 (CMe_3), 15.0 (CH_2). IR (CCl_4, cm^{-1}) 2962, 2250, 1777, 1723, 1392, 1227, 1064. MS (CI): $[MH]^+$ = 391, $[MNH_4]^+$ = 408.

(6) 0.20 g (0.5 mmol) of xanthate **3b** and 0.49 g (2.5 mmol) of ethyl 2-bromo-2-methylpropionate dissolved in 7 mL of chlorobenzene were refluxed for a few minutes under nitrogen before addition of 68 mg of commercially available cumyl peroxide. While maintaining the reflux under nitrogen, the same amount of peroxide was added every 2 h until complete disappearence of the starting xanthate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel (PE/EtOAc 9/1–7/3) to give after recrystallisation from ethanol 105 mg of white crystals (mp 120 °C) **5b** (70%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ = 7.90–7.85 (2 H, m), 7.78–7.40 (2 H, m), 4.38 (1 H, m) 4.14 (1 H, dd, *J* = 7–14 Hz), 3.99 (1 H, dd, *J* = 7–14 Hz), 2.72 (1 H, ddd, *J* = 4.5–8–17 Hz), 2.59 (1 H, td, 8–17 Hz), 2.28 (1 H, m), 2.09 (1 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm): δ = 167.9 (*C*=O), 134.5 (*C*HAr), 131.6 (*C*qAr), 123.8 (*C*HAr), 118.4 (*C*N), 49.0 (*C*HBr), 43.8 (CH_2), 31.8 (CH_2), 15.9 (CH_2). IR (CCl_4, cm^{-1}): 2250, 1776, 1724, 1392. MS (CI): $[MNH_4]^+$ = 324 and 326.

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