Article

Et₃B, an Efficient Mediator for Xanthate Transfer Based Radical Processes

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Abstract. The triethylborane mediated intermolecular addition of diverse carbon radicals, derived from the corresponding xanthates, to allyl acetate (**10b**) and 4-allyl-1,2-dimethoxybenzene (**10a**) was studied in various solvents. In most cases, the product yields in water at room temperature were as good as, or better than, those obtained using 1,2-dichloroethane as the solvent. In contrast, ethanol in most cases was not a useful solvent in which to conduct these reactions.
Key words. Xanthate, triethylborane, radical addition, olefins.

Resumen. El trietilborano fue utilizado como iniciador de la reacción de adición intermolecular de diversos radicales alquilo derivados de los correspondientes xantatos al acetato de alilo (**10b**) y al 4-alil-1,2-dimetoxibenceno (**10a**). La reacción fue estudiada en diversos disolventes; en la mayoría de los casos, los rendimientos obtenidos en agua a temperatura ambiente fueron mejores que cuando se utilizó 1,2-dicloroetano como disolvente. En contraste, el etanol no fue un disolvente útil para llevar a cabo estas reacciones.
**Palabras clave:** Xantato, trietilborano, adiciones radicalarias, olefinas.

Introduction

The interest in free radical reactions in organic synthesis has been increasing in recent years [1]. The use of triethylborane (Et₃B) as a radical initiator was reported first by Oshima in 1987 [2]. The main advantage of this reagent is its effectiveness at low temperature (-78 ºC), which is especially important in the case of stereoselective radical reactions [3,4] or for thermally unstable reaction products. Zard *et al*. have demonstrated the efficiency of xanthate chemistry for the formation of C-C bonds in both the intra and intermolecular modes [1,5]. Because of the difficulty in removing the lauroyl peroxide derived decomposition products in these reactions, triethylborane has been examined as an alternative radical initiator [6-8]. Previous work has shown that the use of triethylborane often results in an increase in the diastereoselectivity of the free-radical addition to substituted allylsilanes [6d]. Recently, Miranda [7] reported an efficient intermolecular oxidative radical alkylation of various heterocyclic aromatic systems including pyrroles and indoles using xanthate based radical chemistry in the presence of iron (II) sulfate and triethylborane as the initiator in dichloromethane at room temperature. However, the use of water as the solvent in these types of reactions has not been reported for such processes using Et₃B. Water is a desirable reaction solvent for reasons of cost, safety, and environmental concerns, and the study of organic reactions in aqueous solvents has considerable precedent. [8] Most notably, certain pericyclic reactions such as Diels-Alder cycloadditions [9] and Claisen rearrangements [10] of hydrophobic compounds have been found to be accelerated in dilute aqueous solution.

In order to widen the scope of the xanthate based radical methodology it was of interest to study the reaction at room temperature using triethylborane as an initiator, and water as the reaction solvent. This article describes the results of our work in this area using allyl acetate (**10b**) and 4-allyl-1,2-dimethoxybenzene (**10a**) as radical acceptors .

Results and Discussion

The xanthates (**1-4**) used in this study were synthesized from the corresponding halo compounds using the method reported by Zard [5]. We first examined the reaction of the xanthate **1** with allyl acetate **10b** (Scheme 1) using a stoichiometric amount (0.30 equiv) of Et₃B in 1,2-dichloroethane as a solvent at room temperature. Adduct **13b** was obtained in 62 % yield (Table 1, entry 2). When this reaction was effected in water as the solvent at room temperature, **13b** was produced almost as efficiently (57 % yield). In contrast, when the reaction was conducted in ethanol solution, the yield of **13b** was greatly diminished (26 %). The triethylborane promoted addition of the radicals derived from xanthates **1-4** to **10a** and **10b** was examined in all three solvents. The results in Table 1 clearly show that the product yields in water at room temperature are as good or better, in all cases but one (**14b**, entry 4) than those obtained in 1,2-dichloroethane (room temperature), and both are significantly better than the reactions which were effected in alcohol solution. The formation of the ketonic products **16a** and **16b** (entries 7 and 8) was inefficient in all three solvents, because of the unexpected reduction of xanthate **4** to acetone. Nevertheless, **16a** and **16b** were obtained most efficiently in the reactions carried out in water. An analogous reduction of iodides has been reported by Oshima and co-workers [11], and by Danishefsky [12] in the total synthesis of UCS1025A and has very recently been exploited by Zard and co-workers [6d] in the radical additions of xanthates to vinyl epoxide.
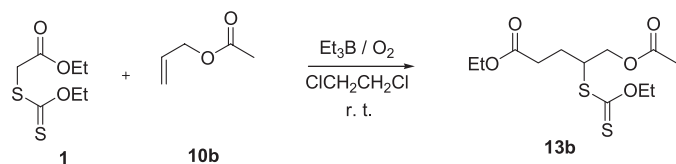
Scheme 1

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The radical addition sequence is summarized in Fig. 1 for the case of allyl acetate (**10b**) with xanthate **1**. The process begins with air oxidation of triethylborane (**17**) to release an ethyl radical (**18**). This radical reacts with xanthate (**1**) to provide intermediate **19**, which rapidly decomposes to triethyl dithiocarbonate **20** and substrate-derived alkyl radical

21. This species reacts with allyl acetate (**10b**) and substrate-derived alkyl radical **22** then reacts with xanthate **20** to provide the observed product (**13b**) and a stoichiometric amount of ethyl radical capable of propagating the radical chain. This mechanism is consistent with the experimental results and they are in agreement with the mechanism proposed by Wood [13].

In summary, we have demonstrated the use of a simple and efficient method for the xanthate transfer radical addition to both allyl acetate and 4-allyl-1,2-dimethoxybenzene with a stoichiometric amount of triethylborane at room temperature in an open flask in water at room temperature. In most cases the product yields are as good or better than those obtained in 1,2-dichloroethane solution at reflux temperature.

Table 1. Radical additions of xanthates (**1-4**) to both olefins (**10a** and **10b**) with different solvents

Entry	Xanthates	Olefins	Product	Yields (%)[a]		
				DCE	H_2O	EtOH
1	1	10a	13a	62	72	39
2	1	10b	13b	62	57	26
3	2	10a	14a	40	32	41
4	2	10b	14b	60	29	34
5	3	10a	15a	63	80	60
6	3	10b	15b	42	67	44
7	4	10a	16a	17	30	27
8	4	10b	16b	19	30	13

Xn = SC(=S)OEt
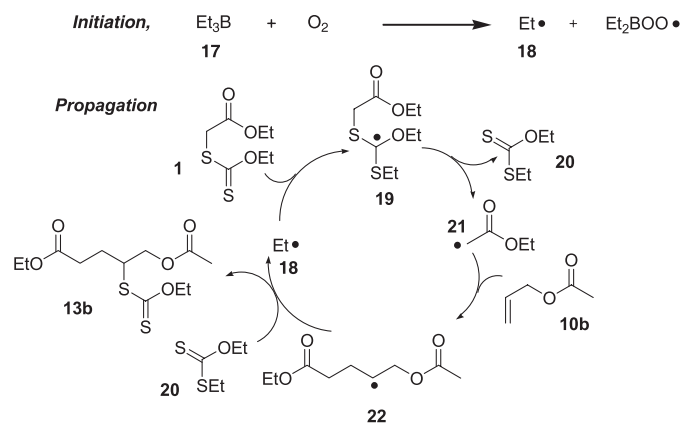[a] Isolated yields obtained after silica gel column chromatography.

Fig. 1. Proposed Mechanism for Xanthate transfer radical addition.

Experimental

Column chromatography was carried out on Silica gel, grade 60 (70-230 mesh ASTM) or (230-400 mesh ASTM). ¹H NMR spectra were recorded on a Jeol Eclipse+400 spectrometer (400 MHz), ¹³C NMR (100 MHz). The spectra were recorded in CDCl₃ solution, using TMS as internal reference. IR were carried out with a Perkin Elmer TF-IR System 2000 as KBr pellets or CsI cuvettes. Mass spectra were recorded at 70 eV on a Hewlett-Packard 5989-A spectrometer. Elemental analyses: Perkin–Elmer Series II CHNS/O Analyser.

General procedure for the radical addition to allyl acetate and 4-allyl-1,2-dimethoxybenzene 10b and 10a. (13a-b, 14a-b, 15a-b, 16a-16b) A solution of Xanthate **1-4** (1.0 mmol) was added to allyl acetate or 4-allyl-1,2-dimethoxy benzene (**10a** and **10b**) (2.0 mmol) in the corresponding solvent (1,2-dichloroethane, H₂O or ethanol) (*ca.* 1 mL), in small portions every 10 min was added trietylborane (1.0 M in hexane, 0.3 equiv/2h) until almost complete consumption of the xanthate. The solvent was removed under reduced pressure and the residue purified by chromatography on silica to give the corresponding product **13-16**.

Ethyl 5-(3,4-dimethoxyphenyl)-4-(ethoxycarbonothioyl-thio) pentanoate (13a). ¹H NMR (400 MHz, CDCl₃) Δ: 6.78 (2H, d, *J* = 9.2 Hz), 6.77 (1H, s), 4.59 (2H, q, *J* = 7.0 Hz), 4.07 (2H, q, *J* = 7.3 Hz), 3.95 (1H, m), 3.86 (3H, s), 3.83 (3H, s), 3.04 (1H, dd, *J* = 6.2, 14.3 Hz), 2.78 (1H, dd, *J* = 8.4, 14.0 Hz), 2.46 (1H, m), 2.36 (1H, m), 2.07 (1H, m), 1.81 (1H, m), 1.38 (3H, t, *J* = 7.0 Hz), 1.20 (3H, t, *J* = 7.3 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 214.1, 172.9, 148.8, 147.9, 130.9, 121.4, 112.4, 111.2, 70.0, 60.5, 55.9, 52.0, 40.9, 31.8, 28.0, 14.3, 13.8 ppm;. IR (CsI): ν 2981 (C-H); 1732 (C=O); 1237 (OCO); 1049 (C=S) cm⁻¹; MS (70 eV): *m/z* 386 (M+); Anal. Calcd. for C₁₈H₂₆O₅S₂; C, 55.93; H, 6.78; Found C, 56.14 H, 6.82.

Ethyl 5-acetoxy-4-(ethoxycarbonothioylthio)pentanoate (13b). ¹H NMR (400 MHz, CDCl₃) Δ: 4.65 (2H, q, *J* = 7.0 Hz), 4.31 (1H, dd, *J* = 4.8, 11,4 Hz), 4.23 (1H, dd, *J* = 6.2, 11.4 Hz), 4.13 (2H, q, *J* = 7.3 Hz), 4.01 (1H, m), 2.49 (2H, m), 2.16 (1H, m), 2.08 (3H, s), 1.94 (1H, m), 1.43 (3H, t, *J* = 7.0 Hz), 1.26 (3H, t, *J* = 7.3 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 212.7, 172.5, 170.5, 70.3, 65.5, 60.6, 48.8, 31.5, 26.0, 20.7, 14.2, 13.7 ppm; IR (KBr): v̄ 2982 (C-H); 1740 (C=O); 1228 (OCO); 1049 (C=S) cm⁻¹; MS (70 eV): *m/z* 309 (M+); Anal. Calcd. for C₁₂H₂₀O₅S₂; C, 46.73; H, 6.54; Found C, 46.55; H, 6.68.

S-1-(3,4-dimethoxyphenyl)-5-oxo-5-(piperidin-1-yl)pentan-2-yl-O-ethyl carbonodithioate (14a). ¹H NMR (400 MHz, CDCl₃) Δ: 6.82 (2H, d, *J* = 12.8 Hz), 6.78 (1H, s), 4.58 (2H, q, *J* = 7.0 Hz), 3.94 (1H, m), 3.87 (3H, s), 3.84 (3H, s), 3,49 (2H, m), 3.30 (2H, m), 3.1 (1H, dd, *J* = 6.2, 14.0 Hz), 2.82 (1H, dd, *J* = 8.4, 14.0 Hz), 2.50 (1H, m), 2.34 (1H, m), 2.13 (1H, m), 1.82 (1H, m), 1.59 (2H, m), 1.47 (4H, m) 1.4 (3H, t, *J* = 7.0 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 214.4, 170.1, 148.8, 147.8, 131.1, 121.5, 112.5, 111.1, 70.0, 56.0, 52.5, 46.6, 42.7, 41.2, 30.9, 28.4, 26.5, 25.6, 24.6, 13.9 ppm; IR (CsI) v 2935 (C-H); 1635 (C=O); 1443 (C-N) 1261 (OCO); 1028 (C=S) cm⁻¹.

2-(ethoxycarbonothioylthio)-5-oxo-5-(piperidin-1-yl)pentylacetate (14b). ¹H NMR (400 MHz, CDCl₃) Δ 4.55 (2H, q, *J* = 7.0 Hz), 4.25 (1H, dd, *J* = 4.8, 11.4 Hz), 4.18 (1H, dd, *J* = 6.4, 11.0 Hz), 3.94 (1H, m), 3.47 (2H, dd, *J* = 5.0, 9.5 Hz), 3.30 (2H, t, *J* = 5.5 Hz), 2.41 (2H, m), 2.15 (1H, m), 2.0 (3H, s), 1.84 (1H, m), 1.55 (2H, m), 1.48 (4H, m), 1.35 (3H, t, *J* = 7.0 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 213.4, 170.7, 169.8, 70.3, 65.8, 49.3, 46.6, 42.8, 30.3, 26.6, 26.6, 25.5, 24.5, 20.8, 13.8 ppm; IR (CsI): v 2937 (C-H); 1740 (C=O); 1444 (C-N) 1235 (OCO); 1046 (C=S) cm⁻¹; MS (70 eV): *m/z* 298 (M+); Anal. Calcd. for C₁₅H₂₅O₄NS₂; C, 51.85; H, 7.25; Found C, 51.66; H,7.25.

S-4-cyano-1-(3,4-dimethoxyphenyl)butan-2-yl-O-ethyl carbonodithioate (15a) ¹H NMR (400 MHz, CDCl₃) Δ: 6.7 (1H, m), 6.7 (2H, m), 4.6 (2H, q, *J* = 7.1 Hz), 3.9 (1H, m), 3.8 (3H, s), 3.8 (3H, s), 3.0 (1H, dd, *J* = 6.2, 14.0 Hz), 2.7 (1H, dd, *J* = 8.4, 14.0 Hz), 2.4 (2H, m), 2.0 (1H, m), 1.8 (1H, m), 1.3 (3H, t, *J* = 7.1 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 212.9, 149.0, 148.1, 130.1, 121.3, 119.1, 112.2, 111.3, 70.4, 55.9, 51.1, 40.5, 28.9, 15.1, 13.8 ppm; IR (KBr): v 2981 (C-H), 2248 (CN), 1743 (C=O), 1230 (OCO), 1049 (C=S) cm⁻¹; MS (70 eV): *m/z* 339 (M+).

4-cyano-2-(ethoxycarbonothioylthio)butyl acetate (15b). ¹H NMR (400 MHz, CDCl₃) Δ; 4.6 (2H, q, *J* = 7.1 Hz), 4.3 (1H, dd, *J* = 4.6, 11,6 Hz), 4.2 (1H, dd, *J* = 6.2, 11.6 Hz), 4.0 (2H, m), 2.5 (2H, m), 2.1 (1H, m), 2.0 (3H, s), 1.9 (1H, m), 1.4 (3H, t, *J* = 7.1 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ; 211.6, 170.4, 118.7, 70.8, 65.1, 48.2, 27.2, 20.7, 15.1, 13.7 ppm; IR

(KBr): ν 2936 (C-H), 2247 (CN), 1750 (C=O), 1294 (OCO), 1043 (C=S) cm⁻¹; MS (70 eV): *m/z* 261 (M+)

S-1-(3,4-dimethoxyphenyl)-5-oxohexan-2-yl-O-ethyl carbonodithioate (16a). ¹H NMR (400 MHz, CDCl₃) Δ: 6.7 (1H, m), 6.7 (2H, m), 4.6 (2H, q, *J* = 7.1 Hz), 3.9 (1H, m), 3.8 (3H, s), 3.8 (3H, s), 3.0 (1H, dd, *J* = 6.2, 14.0 Hz), 2.7 (1H, dd, *J* = 8.4, 14.0 Hz), 2.4 (2H, m), 2.0 (1H, m), 1.8 (1H, m), 1.3 (3H, t, *J* = 7.1 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 212.9, 207.7, 149.0, 148.1, 130.1, 121.3, 119.1, 112.2, 111.3, 70.4, 55.9, 51.1, 40.5, 28.9, 15.1, 13.8 ppm; IR (KBr): ν 2981 (C-H), 2248 (CN), 1743 (C=O), 1230 (OCO), 1049 (C=S) cm⁻¹; MS (70 eV): *m/z* 356 (M+).

2-(ethoxycarbonothioylthio)-6-oxohexylacetate (16b). ¹H NMR (400 MHz, CDCl₃) Δ: 4.6 (2H, q, *J* = 7.1 Hz), 4.3 (1H, dd, *J* = 4.7, 11.2 Hz), 4.2 (1H, dd, *J* = 6.4, 11.2 Hz), 3.9 (1H, m), 2.6 (2H, m), 2.1 (3H, s), 2.0 (3H, s),1.8 (1H, m), 1.4 (3H, t, *J* = 7.1 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃) Δ: 213, 207.3, 170.7, 70.4, 65.7, 48.9, 40.5, 30, 24.5, 20.9, 13.7 ppm; IR (KBr): ν 2935 (C-H), 1715 (C=O), 1252 (OCO), 1049 (C=S) cm⁻¹; MS (70 eV): *m/z* 278 (M+).

Acknowledgements

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