Journal of Organometallic Chemistry, 375 (1989) 45–49
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 20118

α,β-Unsaturated esters from the tri-n-butylarsine-promoted reaction of bromomalonic esters with aldehydes

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(Received April 18th, 1989)

Abstract

A convenient synthesis of α,β-unsaturated esters (in 68–96% yields) from the reaction of a bromomalonic ester with aldehydes promoted by tri-n-butylarsine is described. A mechanism involving halophilic attack of tri-n-butylarsine leading to the formation of a salt followed by reaction with carbonyl compounds is proposed. This methodology provides a convenient route to α,β-unsaturated esters and represents an alternative to the Knoevenagel reaction.

Introduction

Hoffmann and Froster reported the halophilic reaction of triphenylphosphine with diphenylsulfonylbromomethane [1], and the carbanion that is formed can then be treated with formaldehyde to give an alkene [2]. Trialkylstibines can also mediate in the reaction of haloacetic esters with carbonyl compounds, in Barbier-type reactions, and in the synthesis of cyclopropanes [3]. In our previous paper we reported a novel double acylation by a halophilic reaction of tri-n-butylarsine and it was found to be applicable to the synthesis of tetrasubstituted methanes having four electron-withdrawing groups [4]. In our continuing investigation of halophilic reactions of tri-n-butylarsine in organic synthesis, we report here that the bromomalonic ester can condense with aldehydes in a reaction promoted by tri-n-butylarsine under neutral conditions to give α,β-unsaturated esters in high yields.

Results and discussion

The condensation of aldehydes or ketones with malonic esters is usually called the Knoevenagel reaction [5]. Most aldehydes give alkylidene- or arylidene-malonic esters. Under the usual conditions of the reaction, a secondary amine is used as the catalyst and the water formed must be removed by azeotropic distillation; the

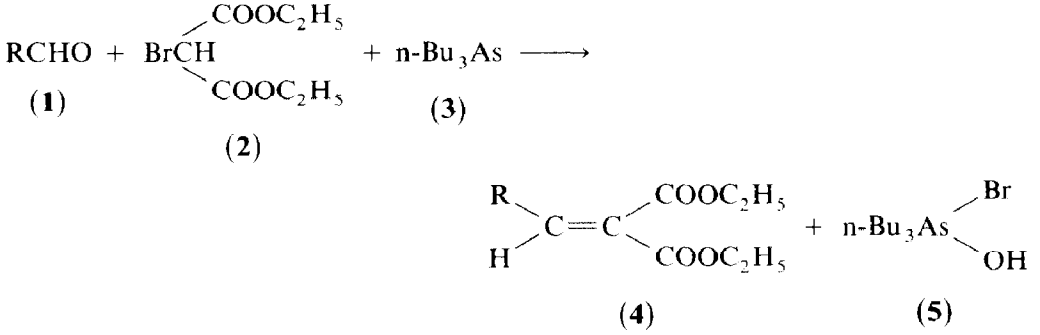
Table 1

Preparation of α,β-unsaturated esters $RCH{=}C(CO_2C_2H_5)_2$ (**4**).

Compound	R	Reaction conditions		Yield (%)
		Temp (°C)	Time (h)	
4a	C_6H_5	80	4	90
4b	4-ClC_6H_4	80	12	93
4c	4-BrC_6H_4	80	10	95
4d	4-FC_6H_4	80	12	92
4e	4-$NO_2C_6H_4$	80	5	92
4f	4-$CH_3OC_6H_4$	80	12	68
4g	2-pyridyl	80	1.5	95
4h	2-furyl	80	11	81
4i	$C_6H_5CH{=}CH$	80	7	96
4j	n-C_3F_7	18	7	90

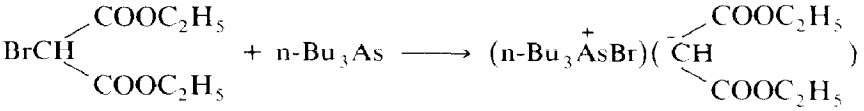
procedure is troublesome [6]. In addition, the condensation gives rise to unexpected products which result from secondary reactions [6].

The tri-n-butylarsine-promoted reaction of a bromomalonic ester with aldehydes under neutral conditions, however, conveniently gives α,β-unsaturated esters in 68–96% yields.



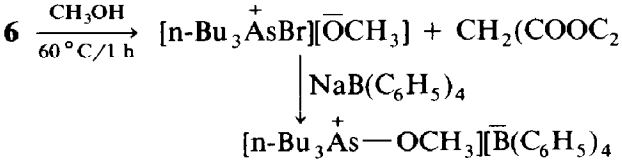
1a, R = C_6H_5 **1f**, R = 4-$CH_3OC_6H_4$
1b, R = 4-ClC_6H_4 **1g**, R = 2-pyridiyl
1c, R = 4-BrC_6H_4 **1h**, R = 2-furyl
1d, R = 4-FC_6H_4 **1i**, R = $C_6H_5CH{=}CH$
1e, R = 4-$NO_2C_6H_4$ **1j**, R = n-C_3F_7

The results are listed in Table 1. On treatment of tri-n-butylarsine with bromomalonic esters an exothermic reaction takes place. Thus we suggest that the reaction is initiated by the halophilic attack of tri-n-butylarsine on bromomalonic ester to an arsonium salt (**6**) which is similar to the halophilic reaction of triphenylphosphine [1].



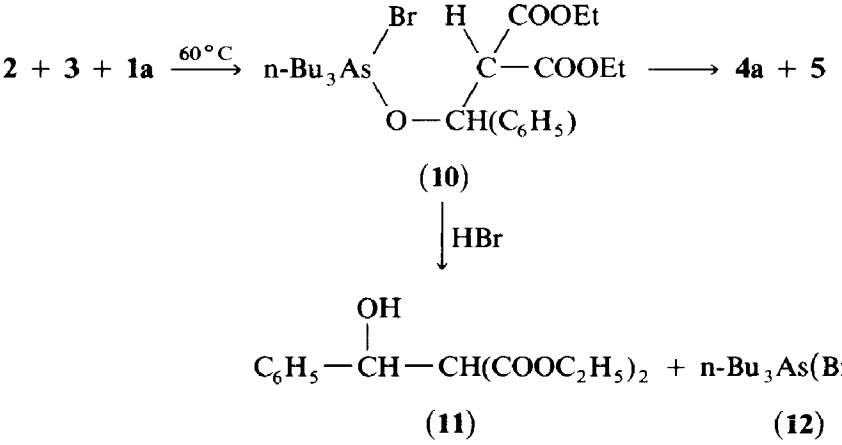
(**6**)

The formation of **6** is further supported by the following evidence:
(1) Attempts to isolate arsonium salt (**6**) are unsuccessful as reported in the literature [7], but heating of **6** with methanol followed by the addition of sodium tetraphenylborate gives a white precipitate $[n\text{-}Bu_3\overset{+}{A}s\text{–}OCH_3]\overline{B}(C_6H_5)_4$ (**7**), which has been characterised by IR and NMR spectroscopy and elemental analysis.



(**7**)

(2) Treatment of **6** with D_2O at 60 °C for 4 h gives the deuterated ethyl malonate (**8**) and tri-n-butyldeuteroxybromoarsorane (**9**), which have also been characterised by NMR spectroscopy.
(3) When the reaction is carried out at a lower temperature (60 °C), followed by passage of anhydrous HBr through the solution to cleave the adduct (**10**) formed, the β-hydroxy alkyl malonic ester (**11**) and tri-n-butyldibromoarsorane (precipitate) are obtained along with **4a** and **5**.



Experimental

All boiling and melting points are uncorrected. Infrared spectra of the solid products were obtained as KCl disks and those of the liquid products as films on a Shimadzu IR-440 spectrometer. ^1H NMR spectra (chemical shifts in ppm from TMS) were recorded on a Varian EM-360 spectrometer at 60 MHz. Mass spectra were obtained on a Finnigan GC-MC 4021 mass spectrometer.

Preparation of α,β-unsaturated esters (4); general procedure:

Tri-n-butylarsine (0.49g, 2.0 mmol) was injected into a solution of an aldehyde (2.0 mmol) and ethyl bromomalonate (0.48 g, 2.0 mmol) under nitrogen. The reaction mixture was stirred and heated for several hours. After the disappearance of the aldehyde, chromatography on silica gel with light petroleum (b.p. 60–90 °C)-

ethyl acetate (85 : 15) as eluent gave the product **4** and elution with acetone gave **5**.
4a: b.p. 136–138 °C/1 Torr (Lit. data [8], 178 °C/12 Torr). Selected IR data (film): 1720(s), 1630(s), 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.23 (t, 3H, *J* 8.0 Hz); 1.30(t, 3H, *J* 8.0 Hz); 4.22(q, 4H, *J* 8.0 Hz); 7.35 (m, 5H); 7.57(s, 1H).
4b: b.p. 115–118 °C/0.1 Torr (Lit. data [9], 156–158 °C/1.5 Torr). Selected IR data (film): 1720(s), 1630(s); 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.30(t, 3H, *J* 7.5 Hz); 1.33(t, 3H, *J* 7.5 Hz); 4.28(q, 4H, *J* 7.5 Hz); 7.06–7.48(m, 4H); 7.60(s, 1H).
4c: m.p. 42–43 °C (Lit. data [10], 42–43 °C). Selected IR data (KCl): 1720(s), 1630(s), 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.35(t, 3H, *J* 8.0 Hz); 1.40(t,3H, *J* 8.0 Hz); 4.30(q, 4H, *J* 8.0 Hz); 7.36(d, 2H, *J* 8.0 Hz); 7.56(s, 1H); 7.63(d, 2H, *J* 8.0 Hz).
4d: 120–122 °C/0.4 Torr (Lit. data [10], 140–142 °C/0.2 Torr). Selected IR data (film): 1720(s), 1640(s) 1230(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.28(t, 3H, *J* 7.0 Hz); 1.32(t, 3H, *J* 7.0 Hz); 4.24(q, 4H, *J* 7.0 Hz); 6.90–7.50(m, 4H); 7.55(s, 1H). ^{19}F NMR (CCl_4/TFA_{ext}): δ 31.3 (m, 1F).
4e: m.p. 91–92 °C (Lit. data [11], 94 °C). Selected IR data (KCl): 1730(s), 1610(s), 1220(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.28 (t, 3H, *J* 8.0 Hz); 1.35(t, 3H, *J* 8.0 Hz); 4.25(q, 4H, *J* 8.0 H); 7.58(d, 2H, *J* 8.5 Hz); 7.61(s, 1H); 8.19(d, 2H, *J* 8.5 Hz).
4f: b.p. 128–130 °C/0.1 Torr (Lit. data [9], 166–168 °C/1.2 Torr). Selected IR data (film): 1720(s), 1600(s), 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.28(t, 3H, *J* 7.0 Hz); 1.30(t, 3H, *J* 7.0 Hz); 3.78(S, 3H); 4.21(q, 4H, *J* 7.0 Hz); 6.78(d, 2H, *J* 8.8 Hz); 7.32 (d, 2H, *J* 8.8 Hz); 7.47(s, 1H).
4g: b.p. 148–150 °C/0.2 Torr (Lit. data [12], 157 °C/0.5 Torr. Selected IR data (film): 1730(s), 1640(s), 1250(s) cm^{-2}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.33(t, 3H, *J* 8.0 Hz); 1.35(t, 3H, *J* 8.0 Hz); 4.21(q, 4H, *J* 8.0 Hz); 7.01–7.62(m, 3H); 7.40(s, 1H); 8.50(dd, 1H, *J* 6, 1.8 Hz).
4e: b.p. 128–130 °C/2 Torr (Lit. data [13], 174–176 °C/15 Torr). Selected IR data (film): 1730(s), 1640(s), 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.30(t, 6H, *J* 7.5 Hz); 4.15(q, 2H, *J* 7.5 Hz); 4.22 (q, 2H, *J* 7.5 Hz); 6.26–6.48(m, 1H); 6.60–6.75(m, 1H); 7.30(s, 1H); 7.25–7.50(m, 1H).
4i: b.p. 140–142 °C/0.2 Torr (Lit. data [14], 36 °C). Selected IR data (film): 1740(s), 1640(s), 1260(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.25(t, 3H, *J* 7.0 Hz); 1.28(t, 3H, *J* 7.0 Hz); 4.20 (q, 4H, *J* 7.0 Hz); 7.02–7.55(m, 8H).
4j: b.p. 51–52 °C/0.6 Torr. Anal.: Found: C, 38.63; H, 3.29; $C_{11}H_{11}F_7O_4$ Calcd: C, 38.84; H, 3.26%. Selected IR data (film): 1750(s), 1680(s), 1240(s) cm^{-1}. ^1H NMR (CCl_4/TMS_{ext}): δ 1.32(t, 3H, *J* 7.5 Hz); 1.35(t, 3H, *J* 7.5 Hz); 4.30(q, 4H, *J* 7.5 Hz); 6.68(t, 1H, *J* 14.2 Hz). ^{19}F NMR (CCl_4/TFA_{ext}): 2.1(t, 3F, *J* 8.0 Hz); 33.2–34.7(m, 2F); 48.4(t, 2F, *J* 4 Hz). MS *m/i*: 341($M^+ + 1$), 295($M^+ - OC_2H_5$), 267($M^+ - COOC_2H_5$).
5: ^1H NMR (CCl_4/TMS_{ext}): δ 0.95–2.75(m, 27H); 5.80(br.s, 1H). MS *m/e*: 325(n-$Bu_3\overset{+}{A}sBr$), 263(n-Bu_3AsOH), 57.

Study of the mechanism. (1) Tri-n-butylarsine (0.49 g, 2 mmol) and ethyl bromomalonate (0.48 g, 2 mmol) were stirred and heated (60 °C) for 10 min under nitrogen. Then the methanol (5 ml) was added and the mixture was further stirred and heated (60 °C) for 0.5 h. After the addition of sodium tetraphenylborate (0.68g, 2 mmol), the white precipitate formed was washed with methanol and dried.
7: Anal.: Found: C, 74.07; H, 8.65. $C_{37}H_{50}AsBO$ calcd.: C, 74.50; H, 8.45%.

Selected IR data (KCl): 1650(s), 1260(s) cm^{-1}. ^1H NMR ($CDCl_3/TMS_{int}$): δ 0.80–2.48(m, 27H); 3.25(s, 3H); 6.88–7.61(m, 20H).

(2) Tri-n-butylarsine (0.245 g, 1 mmol) and ethyl bromomalonate (0.24 g, 1 mmol) were stirred and heated (60 °C) for 0.5 h under nitrogen. D_2O was then added and the mixture was further stirred and heated (60 °C) for 4 h. The products **8** and **9** were separated by chromatography as mentioned above.

8: ^1H NMR (CCl_4/TMS_{ext}): δ 1.30(t, 6H, *J* 7.0 Hz); 4.20(q, 4H, *J* 7.0 Hz).

9: ^1H NMR ($CDCl_3/TMS_{int}$): δ 0.95–2.80(m, 27H).

(3) Tri-n-butylarsine (0.49g, 2 mmol), ethyl bromomalonate (0.48 g, 2 mmol) and benzaldehyde (0.21 g, 2 mm0l) were stirred and heated (60 °C) under nitrogen for 2 h. Then anhydrous HBr was passed through the mixture, and it was stirred and heated (80 °C) for a further 2 h. The solution was left to stand overnight and the resultant precipitate was filtered to give **12** (0.16g, 20%), and **11** (0.11g, 21%) and **4a** (0.37g, 75%) were obtained by chromatography.

11: ^1H NMR (CCl_4/TMS_{ext}): δ 1.26(t, 6H, *J* 3.0 Hz); 2.98(br.s, 1H); 3.18(d, 1H, *J* 7.5 Hz); 3.83(d, 1H, *J* 7.5 Hz); 4.20(q, 4H, *J* 7.0 Hz); 7.10–7.41(m, 5H).

12: Anal.: Found C, 35.56; H, 6.67. $C_{12}H_{27}AsBr_2$ calcd.: C, 35.49; H, 6.70%. ^1H NMR ($CDCl_3/TMS_{int}$): δ 1.01(t, 9H, *J* 7.0 Hz); 1.31–2.03(m, 12H); 2.66–3.41(m, 6H).

Acknowledgement

The authors thank the National Natural Science Foundation of China and Academia Sinica for financial support.

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