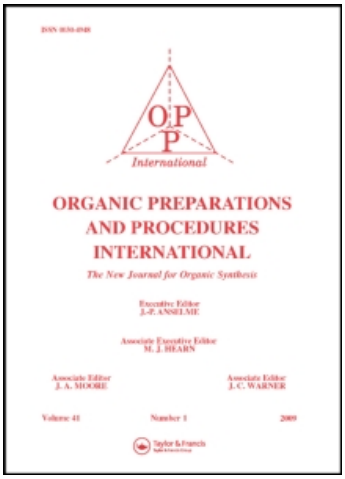

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IMPROVED ALKYLATION OF ETHYL ACETOACETATE AND DIETHYL MALONATE

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IMPROVED ALKYLATION OF ETHYL ACETOACETATE AND DIETHYL MALONATE

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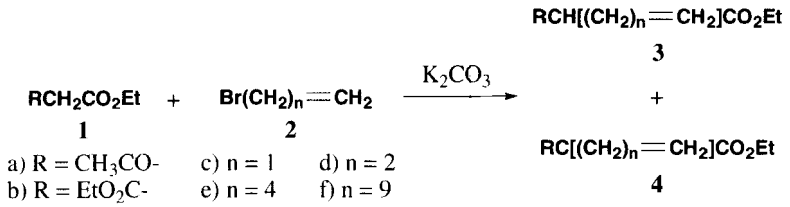
Alkylation of ethyl acetoacetate is a widely used reaction which can lead to a great variety of ketones, after subsequent hydrolysis and decarboxylation. This alkylation was often conducted in ethanol with sodium ethoxide,[1,2] which requires long times and the use of metallic sodium. Thus, we investigated more convenient preparation techniques.



We studied the reaction of ethyl acetoacetate with unsaturated alkyl halides (allyl bromide and less reactive derivatives) by phase-transfer catalysis.[3,4] This reaction generally leads to mono- and dialkylation. Various parameters (solvent, reaction time, phase transfer reagents and temperature) were studied and the optimum monoalkylation yields were reported. The results are summarized in the Table.

We first investigated the reaction of allyl bromide **2c** with ethyl acetoacetate **1a** at 80° in a biphasic system (toluene-water) with 3% of tetrabutylammonium chloride (TBA) added as a phase transfer reagent. The best yield of **3a,c** was obtained in one hour using 3.3 molar equivalents of potassium carbonate. Longer reaction times cause the degradation of the ketoester and enhance the yield of **4a,c**. Lower temperatures or base concentrations reduce the reactivity. The use of dichloromethane as the solvent with a stoichiometric amount of TBA minimizes but does not eliminate degradation of the products. Lower conversion was observed with the use of benzyltriethylammonium chloride (TEBA) but selectivity towards **3a,c** increases. The alkylation was also conducted with less reactive alkyl halides. The bromides ($n > 2$) give only the product of monoalkylation whereas chlorides afford lower yields. The reaction must be effected in dichloromethane with a stoichiometric amount of TBA.

The alkylation of diethyl malonate (**1b**) with allyl bromide was also investigated. The reaction proceeds best in dichloromethane with 100% TBA for 15 hours. Longer reaction times do not increase the yield. Reaction in toluene at 80° causes saponification and decarboxylation of the diester. The reaction with other halides ($n > 2$) gives very poor yields of alkylated products.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker AC 300 spectrometer in deuterochloroform.

General Procedure.- A mixture of 11.09 g of potassium carbonate (0.08 mol), 50 mL of water, 4.29 g of ethyl acetoacetate (0.033 mol), 4.00 g of alkyl halide (0.033 mol), 50 mL of toluene and 0.27 g of tetrabutylammonium chloride (0.001 mol, 3% molar equivalent of the ethyl acetoacetate) was stirred at 80° for 1 hr. After cooling, the aqueous layer was separated, acidified with 5N hydrochloric acid and extracted with ether. The organic layers were dried over magnesium sulfate and distilled.

TABLE. Alkylation of **1** with Alkyl Bromides and Phase-transfer Reagent

Starting Cmpds	Solvent	Catalyst	Time (hrs)	(%) Conv.	(%) **3**	(%) **4**
1a + 2c	toluene	3% TBA	1	100	58	10
1a + 2c	toluene	3% TBA	6	100	50	12
1a + 2c	toluene	3% TBA	15	100	40	13
1a + 2c	DCM	50% TBA	1	80	66	14
1a + 2c	DCM	100% TBA	1	88	66	12
1a + 2c	DCM	100% TEBA	1	70	74	7
1a + 2d	DCM	100% TBA	39	93	59	0
1a + 2e	DCM	100% TBA	39	100	50	0
1a + 2f	DCM	100% TBA	39	100	42	0
1b + 2c	toluene	3% TBA	1	34	100	0
1b + 2c	toluene	100% TBA	1	79	67	0
1b + 2c	DCM	100% TBA	1	47	80	0
1b + 2c	DCM	100% TBA	5	63	86	0
1b + 2c	DCM	100% TBA	15	74	91	0
1b + 2c	DCM	100% TBA	45	87	79	0
1b + 2d	DCM	100% TBA	40	64	37	0

3a,c, [4] bp 62° (1 mmHg); ^{1}H NMR: δ 1.20 (t, J = 6.7 Hz, 3H), 2.17 (s, 3H), 2.55 (t, 2H), 3.48 (t, J = 7.4 Hz, 1H), 4.15 (q, J = 6.7 Hz, 2H), 5-5.1 (m, 2H), 5.63-5.78 (ddt, J = 7.2, 10.2 and 17.1 Hz, 1H).

3a,d, bp 70° (1 mmHg); ^{1}H NMR: δ 1.25 (t, J = 6.7 Hz, 3H), 1.87-2.03 (m, 4H), 2.10 (s, 3H), 3.41 (t, J = 7 Hz, 1H), 4.15 (q, J = 6.7 Hz, 2H), 4.95-5.05 (m, 2H), 5.70-5.8 (ddt, J = 7.2, 10.2 and 17.1 Hz, 1H). *Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.28; H, 8.73.

3a,e, bp 93° (1.2 mmHg); ^{1}H NMR: δ 1.25 (m, 5H), 1.35-1.45 (m, 2H), 1.8-1.9 (m, 2H), 2.05 (m, 2H), 2.20 (s, 3H), 3.38 (t, J = 7 Hz, 1H), 4.15 (q, 2H), 4.9-5.0 (m, 2H), 5.7-5.85 (ddt, J = 7.2, 10.2 and 17,1 Hz, 1H). *Anal.* Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.49. Found: C, 67.52; H, 9.51.

3a,f, bp 134° (1 mmHg); ^{1}H NMR: δ 1.22-1.33 (m, 17H), 1.78 (m, 2H), 2.00 (m, 2H), 2.20 (s, 3H), 3.50 (t, J = 6.7 Hz, 1H), 4.15 (q, J = 6.7 Hz, 2H), 4.85-5.05 (m, 2H), 5.65-5.85 (ddt, J = 7.2, 10.2 and

17.1 Hz, 1H). *Anal.* Calcd. for $C_{17}H_{30}O_3$: C, 72.29; H, 10.70. Found: C, 72.59; H, 10.88.

3b,c,[5] bp 70° (0.45 mmHg); ^{1}H NMR: δ 1.15 (t, J = 7.3 Hz, 6H), 2.53 (t, 2H), 3.30 (t, J = 7.58 Hz, 1H), 4.10 (q, J = 7.3 Hz, 4H), 4.90-5.03 (m, 2H), 5.60-5.70 (ddt, J = 7.2, 10.2 and 17 Hz, 1H).

3b,d,[6] bp 78° (1 mmHg); ^{1}H NMR: δ 1.22 (t, J = 7.3 Hz, 6H), 1.92-2.0 (m, 2H), 2.0-2.13 (m, 2H), 3.35 (t, J = 7.2 Hz, 1H), 4.15 (q, J = 7.3 Hz, 4H), 5-5.1 (m, 2H), 5.70-5.80 (ddt, J = 7.2, 10.2 and 17 Hz, 1H).

4a,c,[5] bp 73° (1.5 mmHg); ^{1}H NMR: δ 1.20 (t, J = 7.3 Hz, 3H), 2.09 (s, 3H), 2.55 (d, J = 7.2 Hz, 4H), 4.15 (q, J = 7.3 Hz, 2H), 4.9-5.0 (m, 4H), 5.45-5.60 (ddt, J = 7.2, 10.2 and 17 Hz, 1H).

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IMPROVED PREPARATION OF 4-CHLOROMETHYLPHENYL ACETATE

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4-Chloromethylphenyl acetate (**1**) is used for the protection of thiols as base-labile 4-acetoxybenzylsulfides.[1] Recently it has been shown that the 4-acetoxybenzyl group is a very useful protective group in the synthesis of unsymmetrically substituted tetrathiafulvalenes.[2,3] Compound **1** is prepared by reaction of 4-hydroxymethylphenol with acetyl chloride,[1] but because a high cost of the starting material and a yield of only 40%, we developed the present synthesis, starting from inexpensive 4-hydroxybenzaldehyde. The aldehyde is reduced with $NaBH_4$ in ethanol to give 4-hydroxymethylphenol, which is treated with acetyl chloride to give **1** The use of a larger amount of acetyl chloride in the last step, increased the yield from 40%[1] to an overall yield of 59%.