

METHYLENE DIESTERS OF CARBOXYLIC ACIDS FROM DICHLOROMETHANE

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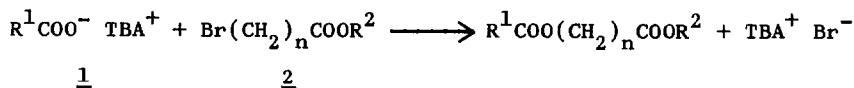
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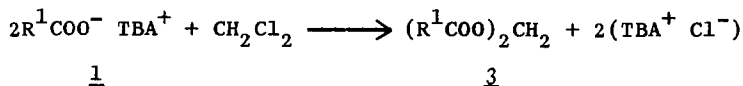
The reaction of a tetrabutylammonium (TBA) salt with an alkyl halide in dichloromethane is a convenient method for the preparation of esters of most carboxylic acids.¹



We have esterified a number of carboxylates (1, R¹ = alkyl or aryl) with alkyl bromides of type 2 (R² = alkyl, n = 1 or 3). The reactions were performed by extracting the quarternary ammonium carboxylate into dichloromethane, adding the alkyl bromide to the dried extract, and refluxing the solution overnight.² The yields were generally good with unreacted starting materials being obtained as the main side components.



In all reactions, however, a by-product was noticed as a spot on TLC with R_f = 0.65 - 0.70 on silica gel plates developed with toluene/EtOAc 2:1. During the course of the reaction the spot increased in intensity. From one reaction mixture the by-product was collected, and its spectroscopic data showed it to be a methylene diester (3), obviously formed by the reaction of the ion pair 1 with dichloromethane.



The formation of diester 3 was unexpected since dichloromethane is considered to be a relatively inert compound. Under these conditions, however, dichloromethane seems to be an electrophile strong enough to react with the carboxylate ion even in the presence of unconsumed bromide (2).

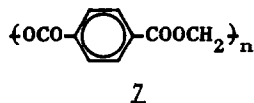
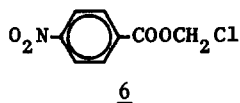
A search of the literature showed that only a few methylene diesters are

known. These esters have generally been prepared from formaldehyde vapour and acid anhydrides with H_2SO_4 as catalyst³ or from paraformaldehyde and acid halides in the presence of $ZnCl_2$.⁴ The formation of an aromatic methylene diester by heating a mixture of a carboxylic acid, methylene chloride, and triethylamine has also been reported;⁵ this reaction can be considered to proceed via an ammonium salt analogous to 1.

Since the reaction between TBA salts of carboxylic acids and dichloromethane described above seemed to be a general and simple method for the preparation of methylene diesters, we decided to evaluate this reaction. The procedure consists of extraction of the TBA salt of the acid from an aqueous solution by dichloromethane and, after drying, refluxing the organic phase. After four days the esters are formed in good yields (see the table). The work-up requires only washing with aqueous solutions and removal of the dichloromethane to give fairly pure products.

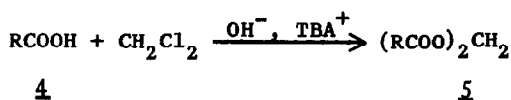
The nucleophilicity of a carboxylate anion decreases with increasing strength of the acid, and consequently, ions of stronger acids would be expected to react more slowly than ions of weaker ones. In fact, while the carboxylates of acids 4b-4g ($pK_a \geq 4.0$ at $25^\circ C$ in H_2O) reacted in boiling dichloromethane, the anion of *p*-nitrobenzoic acid (4a, $pK_a = 3.4$ at $25^\circ C$ in H_2O) did not. However, by refluxing 4a in a mixture of dichloromethane/toluene 1:4 the diester 5a was obtained.

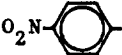


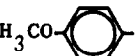
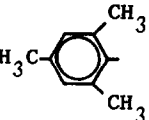
In addition to 5a, a considerable amount of the monoester (6) of *p*-nitrobenzoic acid was isolated. As expected, the ratio diester/monoester increased with longer reaction time. This was the only case when substantial amounts of a chloromethyl ester was observed.



As can be seen from the table, sterically hindered acids like 4e and 4g presented no problem. This is in accordance with earlier results of extractive alkylations of 2,6-disubstituted benzoic acids.¹

The reactivity of some bis-TBA salts of dicarboxylic acids was also examined. Terephthalic acid gave a polymer (7) which precipitated during the course of the reaction. Surprisingly, succinic acid and phthalic acid gave no esters, neither chloromethyl esters nor cyclic methylene diesters. It is possible that the cyclic esters are difficult to prepare as they have not been mentioned in the literature.

Table. Reaction of carboxylic acids with dichloromethane.

	R	Reaction temp., °C	Product			
			Yield, %	M.p., °C	Found, %	Calc., %
a		72	60	179-80	C: 51.9 H: 3.01	C: 52.0 H: 2.91
b		40	88	96-7*)	not analyzed	
c		40	84	99-100	C: 55.3 H: 3.15	C: 55.4 H: 3.10
d		40	85	112-3	C: 64.4 H: 5.10	C: 64.5 H: 5.10
e		40	87	71-2	C: 73.9 H: 7.19	C: 74.1 H: 7.11
f	$\text{CH}_3(\text{CH}_2)_2^-$	40	79	b.p. 26°C (0.2 mm)**)	not analyzed	
g	$(\text{CH}_3)_3\text{C}^-$	40	80	b.p. 34°C (0.1 mm)	C: 60.8 H: 9.28	C: 61.1 H: 9.32

*) Lit.,⁴ 99°C.

***) Lit.,⁶ 220°C (760 mm).

Preparation of diesters 5b-5g. 0.1 mol of the carboxylic acid and 0.1 mol of TBA hydrogen sulphate were dissolved in 100 ml 2 M NaOH. The solution was extracted with three 250 ml portions of dichloromethane, and the extract was dried over MgSO_4 and refluxed for 4 days. The dichloromethane solution was washed with 2.5 M H_2SO_4 (2 x 300 ml), H_2O (300 ml), aqueous NaHCO_3 (2 x 300 ml), and H_2O (300 ml). The solution was dried over MgSO_4 , and the residue obtained after evaporation of the solvent was purified by recrystallization from ethanol

(5b-5e) or by distillation (5f, 5g). The yields given in the table are isolated yields after purification.

Preparation of diester 5a and monoester 6. The dichloromethane extract (750 ml, see above) was concentrated to a volume of 200 ml, 800 ml of toluene was added, and the solution was refluxed for 4 days. The residue, obtained after the same work-up procedure as described above, was recrystallized from ethanol to give 5a. The filtrate from the recrystallization was evaporated to dryness, and the residue was recrystallized from diisopropyl ether. Compound 6 (m.p. 88-9°C) was obtained in a yield of 35%. (Found: C 45.0; H 2.93; Cl 15.6. Calc. for $C_8H_6NO_4Cl$: C 44.6; H 2.81; Cl 16.5.)

The aromatic diesters 5a-5e, as well as monoester 6 and polymer 7, exhibited strong IR absorption at 1750-1760 cm^{-1} (KBr) due to the conjugated ester CO groups. The aliphatic diesters 5f and 5g showed a corresponding peak around 1775 cm^{-1} .

The protons of the methylene group of the products gave a singlet in the NMR spectra (60 MHz) at the following positions (δ , ppm): 5a (dioxane): 6.40, 5b-5e ($CDCl_3$): 6.20-6.28, 5f ($CDCl_3$): 5.73, 5g ($CDCl_3$): 5.78, and 6 ($CDCl_3$): 6.02.

Acknowledgements

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References and notes

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