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PREPARATION OF α-BROMOESTERS VIA THE HALF ESTERS OF MALONIC ACIDS A NOVEL METHOD FOR RAPID DECARBOXYLATION UNDER MILD CONDITIONS

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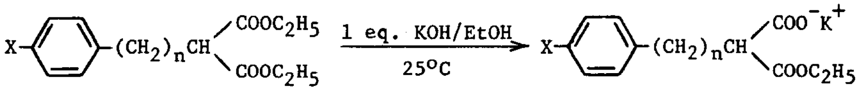
Abstract: α-Bromomalonic acid half esters were prepared in high yield and found to be rapidly decarboxylated to α-bromoesters under mild conditions using lithium carbonate in refluxing tetrahydrofuran.

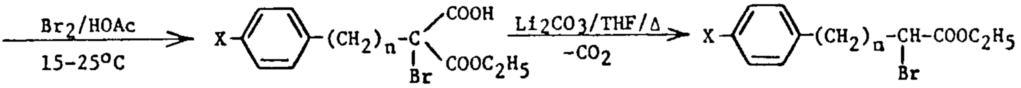
α-Bromoesters are very useful intermediates in such well-known organic reactions as the Wittig, Reformatsky, and in substitution reactions with various nucleophiles.[1] The classical preparation of these was achieved by the bromination of monoalkylated malonic acids followed by thermal decarboxylation and esterification.[2,3] This method is still the primary source of α-bromoesters. Another primary route is the method of Stotter and Hill[4] which involves the bromination of sodium enolates derived from monoalkylated acetoacetic esters by reaction with sodium hydride and then deacetylation. While this method affords good overall yields of α-bromoesters, the use of sodium hydride on large scale poses significant hazard. The α-bromination of carboxylic acids and acid chlorides accomplished by the Hell-Volhard-Zelinsky reaction and its variation[2,5] requires the availability of the parent acid. Moreover, the application of these methods to our requirements of α-bromoesters containing a benzyl group gave complex mixtures which were of little preparative value. These considerations also apply to the Rathke and Lindert method[6] on the direct halogenation of lithium ester enolates.

We wish to report novel modifications in the malonic ester synthesis of α-bromoesters which substantially enhance its preparative usefulness on a large scale. This is shown in the following scheme.



I

II



III IV

X=H, Cl; n=1,2,3

This method offers the advantage of eliminating the esterification step, no HBr evolution, excellent yields, and mild reaction conditions throughout. The α-bromoesters were obtained as pale to colorless oils in 94-99% purity without distillation or chromatography. While it is well established[7] that the malonic esters may be hydrolyzed to the half esters, the direct bromination of the potassium salts of half esters to α-bromomalonic acid half esters does not appear to have been reported. Bromination at the α-position proceeds in high yield in glacial acetic acid medium at room temperature (See Reference 8 for X = OCH_3, n=2). The α-bromomalonic acid half esters are easily decarboxylated to α-bromoesters in the presence of a mildly basic catalyst. Especially, lithium carbonate in refluxing tetrahydrofuran cleanly catalyzes the rapid decarboxylation with no concomitant dehydrobromination. Decarboxylation is catalyzed at a faster rate by triethylamine in THF but some dehydrohalogenation also takes place especially when elimination leads to conjugation (n=1). In the absence of a catalyst, decarboxylation occurred at 150-160°C to yield dark red oils containing 60-70% of the desired product. The results are summarized in the following tables.

Table 1 Compounds II and III in the Synthetic Scheme

Entry	Malonic Ester Ia	Yield of II[b,c]	M.P.	Yield of III[e]	M.P.[e]
1	n=1, x=H	91	120-123	89	90-92
2	n=2, x=H	94	149-153	90	101-103
3	n=3, x=H	81	waxy solid	86	oil
4	n=1, x=Cl	98[d]	147-150	83	57-61
5	n=2, x=Cl	92	42-48	80	98-100

a. monoalkylated malonic esters I have been reported previously;[3,9]

b. satisfactory microanalysis and nmr spectra were obtained; c. yields are of recrystallized materials from THF or EtOH with n-hexane as diluent. d. not recrystallized. e. yields and M.P. are of unrecrystallized materials which gave satisfactorily elemental analyses and nmr spectra.

Table 2 Bromoesters IV

Entry	Catalyst and Amount	Reaction Time, hr	Yield[a,b]	Purity(glc)
1	Li_2CO_3, 0.1 mole/mole of III	2	84	95[c]
1	$(Et)_3N$, 0.1	1	92	90[d]
2	Li_2CO_3, 0.1 mole	3	89	99[e]
2	Li_2CO_3, 1.0 mole	1.5	92	99
2	$(Et)_3N$, 0.1 mole	0.5	88	98
2	$(Et)_3N$, 1.0 mole	0.2	89	99
3	Li_2CO_3, 0.1 mole	3	92	94
3	$(Et)_3N$, 0.1 mole	1	95	92
4	Li_2CO_3, 0.1 mole	1.0	88	98
5	Li_2CO_3, 0.1 mole	1.5	90	99

a. undistilled materials; b. satisfactory elemental analyses and/or nmr, i.r, spectra were obtained; c. no ethyl cinnamate was detected in the crude product; d. the product contained 9% ethyl cinnamate which was separated by prep HPLC and compared with an authentic sample; e. an authentic sample was prepared as described in Reference 3.

Experimental: To a solution of 22.2 g (88.6 m moles) benzylmalonic acid diethyl ester, I (entry 1) in 61 ml of absolute ethanol was added a filtered clear solution of 5.8 g (88.6 m moles) KOH (86% assay) in 71 ml of absolute ethanol at 25°C. After one hour of stirring the solvent was removed and the residual colorless syrup crystallized from THF and n-hexane to yield 21 g of II (entry 1)[10]; 1H NMR (D_2O) δ 1.16 (t, $\underline{J}$ = 9 Hz, 3H), 3.12 (d, 2H), 3.57 (q, $\underline{J}$ = 6 Hz, 1H), 4.05 (q, $\underline{J}$ = 9 Hz, 2H), 7.13 (s, 5H).

A solution of 19 g (73 m moles) of II from above in 190 ml of glacial acetic acid was cooled to 15°C and 11.7 g (73 m moles) of bromine added to the slush at 15°C over 1.5 hr. After stirring overnight at room temperature, KBr was filtered off and the filtrate diluted with equal volume of chlorobenzene. The acetic acid-chlorobenzene azeotrope was removed under vacuum. The residue was dissolved in ether, washed with water and dried over $MgSO_4$. The clear dry ether solution was stripped to dryness and triturated with n-hexane. The product crystallized slowly to yield 19.6 g of III (entry 1); ^1H NMR ($CDCl_3$) δ 1.23 (t, $\underline{J}$ = 6 Hz, 3H), 3.58 (AB q, $\underline{J}$ = 15 Hz, 2H), 4.2 (q, $\underline{J}$ = 6 Hz, 2H), 7.13 (s, 5H), 9.82 (s, 1H).

A mixture of 5.0 g (17 m moles) of III and 123 mg (1.7 m moles) of Li_2CO_3 powder in 42 ml of THF was refluxed for 2 hours when tlc indicated complete reaction (EM slica gel plate; developer: toluene:CH_3CN:HOAC 10:9:1). The mixture was filtered and evaporated to dryness. The residue was dissolved in n-hexane, washed with water, 0.1 N HCl, sat. brine and dried over anhydrous $MgSO_4$. The filtrate on evaporation gave 3.6 g of 2-bromo-3-phenylpropanoic acid, ethyl ester as a pale oil. I.R. (liquid film) 1740 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.19 (t,$\underline{J}$ = 7 Hz, 3H), 3.3 (m, 2H), 4.11 (q, $\underline{J}$ = 7 Hz, 2H), 4.35 (t, $\underline{J}$ = 7.5 Hz, 1H), 7.13 (s, 5H).

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References and Notes

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