An unusual reaction of ethyl 4-bromomethylbenzoate with the carbanion of substituted ethyl acetate

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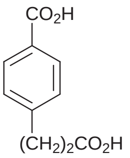
Reaction of ethyl 4-bromomethylbenzoate with the carbanion of substituted ethyl acetate affords nucleophilic aromatic substitution of the bromomethyl group instead of the expected alkylation of the benzylic bromide.

In connection with a project on the synthesis of a natural product, we needed 2-(4-carboxyphenyl)propanoic acid **1** as one of the intermediates. A straightforward procedure was employed to prepare this compound by alkylation of ethyl 4-bromomethylbenzoate **2** with the carbanion of diethyl malonate (generated by NaH in C_6H_6) followed by decarboxylation[1] of the resulting alkylated diethyl malonate **3** in aqueous DMSO containing NaCl. The crude product on purification by column chromatography afforded a white crystalline compound as the only product. The ^{1}H NMR and ^{13}C NMR spectra[†] did not support the expected structure of the diethyl ester of **1**, suggesting the structure to be **5**. In order to further corroborate the structure **5** of the product, it was synthesized by the literature[2] method and was found to be identical with the isolated product **5** of the present reaction (IR, ^{1}H NMR, ^{13}C NMR, mp and TLC). It is likely that an S_NAr mechanism[3] in this case is being preferred over the usual S_N reaction in spite of using a benzylic bromide. Such an S_NAr reaction with *ipso* attack on an aromatic ring having only one ethoxycarbonyl group resulting in the elimination of the bromomethyl group is quite unprecedented under the reaction conditions. Probably the nucleophile is attacking the aromatic carbon carrying the bromomethyl substituent to provide an intermediate **6** (Scheme 1), which in turn may eliminate either $CH_2(CO_2Et)_2$ to give starting compound **2**, or MeBr which may escape as a gas shifting the equilibrium to furnish the product **4**.



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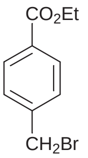

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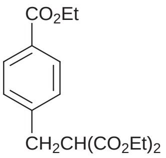

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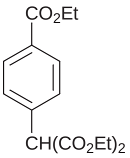

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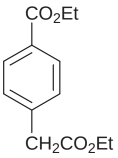

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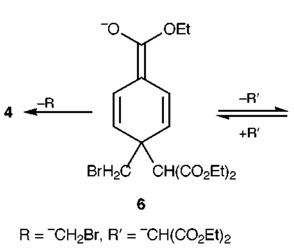
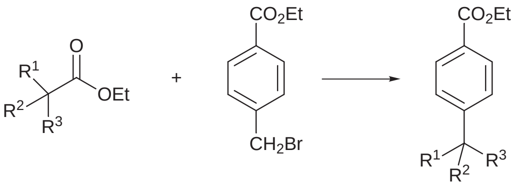


Scheme 1

This type of reaction has also been exhibited by the substituted ethyl acetate carbanions shown in Table 1 (studied so far). A detailed investigation of this reaction is in progress.

Table 1 Results of reactions with various substituted acetates



Reactant			Product				Yield[a] (%)
R¹	R²	R³	No.	R¹	R²	R³	
CO_2Et	H	H	**5**[b]	CO_2Et	H	H	63
H	CN	H	**7**[b]	H	CN	H	68
CO_2Et	Me	H	**8**	CO_2Et	Me	CO_2Et	75
Me	CN	H	**9**	Me	CN	CO_2Et	73

[a] The yield of the product is an average of the yields obtained in repeated experiments. The other product obtained from the chromatographic column was the unreacted starting compounds. [b] Isolated product after decarboxylation with NaCl in aq. DMSO (ref. 1).

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Notes and references

[†] *Selected data* for **5**: δ_H 1.17 (3H, t, *J* 7.2), 1.38 (3H, t, *J* 7.2), 3.27 (2H, s), 4.12 (2H, q, *J* 7.2), 4.37 (2H, q, *J* 7.2), 7.22 (2H, d, *J* 8.4), 7.92 (2H, d, *J* 8.4); δ_C 13.88, 14.34, 38.22, 60.59, 60.93, 127.43, 128.93, 129.50, 141.51, 166.42, 170.46. For **7**: δ_H 1.40 (3H, t, *J* 7.2), 3.12 (2H, s), 4.38 (2H, q, *J* 7.2), 7.31 (2H, d, *J* 8.1), 8.03 (2H, d, *J* 8.1); δ_C 14.22, 35.06, 37.76, 60.91, 120.41, 128.96, 129.71, 129.99, 141.41, 166.11. For **8**: δ_H 1.25 (6H, t, *J* 7.2), 1.36 (6H, m), 4.19 (4H, q, *J* 7.2), 4.36 (2H, q, *J* 7.2), 7.21 (2H, d, *J* 8.1), 7.94 (2H, d, *J* 8.1); δ_C 13.90, 14.21, 19.69, 54.63, 60.74, 61.32, 129.29, 129.88, 130.14, 141.55, 166.32, 171.51. For **9**: δ_H 1.28 (3H, t, *J* 7.2) 1.41 (6H, m), 4.21 (2H, q, *J* 7.2), 4.38 (2H, q, *J* 7.2), 7.24 (2H, d, *J* 8.1), 7.96 (2H, d, *J* 8.1); δ_C 14.11, 14.26, 19.71, 54.73, 60.74, 61.31, 129.62, 129.91, 130.21, 131.33, 141.62, 166.38, 171.54.

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2 J. F. Codington and E. J. Mosettig, *J. Org. Chem.*, 1952, **17**, 1035.
3 J. March, *Advanced Organic Chemistry*, 4th edn., Wiley, New York, 1992, p. 641.

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