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Reaction of *N*-Chloroamines with Carbanions Derived from Ethyl Acetoacetate and Diethyl Malonate

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Abstract—Carbanions derived from ethyl 3-oxobutanoate and diethyl malonate reacted with an equimolar amount of *N*-chloro-*N*-ethylethanamine, *N*-chloromorpholine, or *N*-chloropiperidine to give diethyl 2,3-diacetylbutanedioate and tetraethyl ethane-1,1,2,2-tetracarboxylate in 68–83% yield. The possibility of heterocoupling of ethyl 3-oxobutanoate and diethyl malonate carbanions by the action of *N*-chloro-*N*-ethylethanamine and the effect of the molar reactant ratio on the selectivity of oxidative homo- and heterocoupling were studied.

Keywords: diethyl malonate, acetoacetic ether, α-carbanions, metallation, oxidative homo- and heterocoupling, *N*-chloroamines

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Reactions of α-carbanions derived from carboxylic acids and their esters with various aminating agents [*N*-haloamines, *O*- and *N*-substituted hydroxylamines, oxaziridines, *O*-(arenesulfonyl) ketone oximes, arenediazonium salts, azides, dialkyl azodicarboxylates, 1-chloro-1-nitrosocycloalkanes, *N*-(4-methylbenzenesulfonyl)iminophenyl-λ^3-iodane, etc.] provide a nontrivial and attractive synthetic approach to α-amino acids [1].

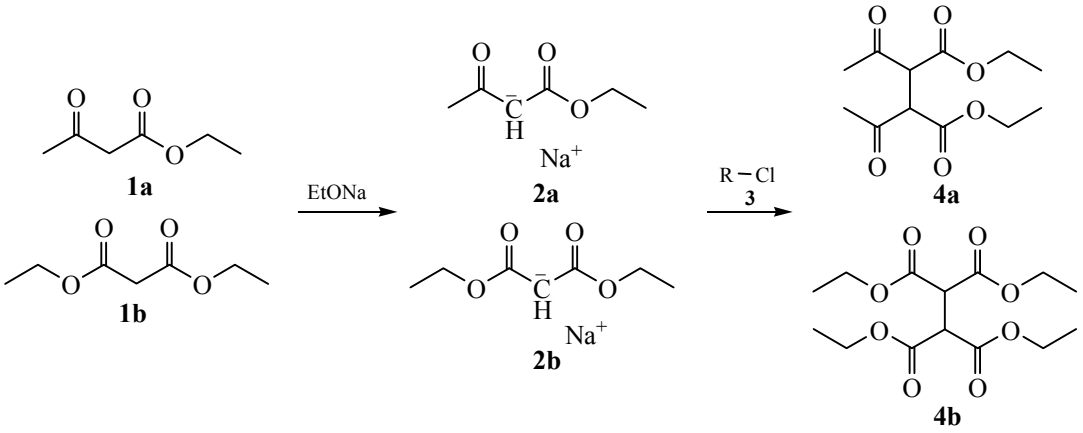
The reaction of chloramine (NH_2Cl) with metalated carboxylic acids in tetrahydrofuran at –50°C was reported to give the corresponding α-amino acids in a very low yield [2, 3]. However, carbanions generated by metalation of diethyl malonate and its substituted derivatives reacted with chloramine to produce 72–90% of diethyl 2-aminomalonates [4]. In view of the above stated, study of the synthetic potential of this reaction, in particular with participation of *N*-chlorodialkylamines attracts interest.

We have found that carbanions **2a** and **2b** generated from ethyl 3-oxobutanoate (**1a**) and diethyl malonate (**1b**) by the action of sodium ethoxide in diethyl ether under argon react with an equimolar amount of *N*-chloro-*N*-ethylethanamine (**3a**), *N*-chloroporpholine (**3b**), or *N*-chloropiperidine (**3c**) at room temperature (reaction time 2 h) to give the corresponding oxidative homocoupling products, diethyl 2,3-diacetylbutanedioate (**4a**) and tetraethyl ethane-1,1,2,2-tetracarboxylate (**4b**), respectively, in 68–83% yield (Scheme 1, Table 1).

Compounds **4a** and **4b** were identified by ^1H and ^{13}C NMR and mass spectra. Their spectral parameters satisfactorily coincided with those given in [5, 6]. Diethyl 2,3-diacetylbutanedioate (**4a**) was isolated as a mixture of *meso* and *rac* diastereoisomers at a ratio of ~1 : 5 (according to the ^1H and ^{13}C NMR and mass spectral data). Signals in the ^{13}C NMR spectra were assigned to *meso* and *rac* diastereoisomers with account taken of published data [7, 8]. As follows from the data in Table 1, the reaction of *N*-chloro amines **3a**–**3c** with diethyl malonate carbanion **2b** was more efficient. The best yield of tetraethyl ethane-1,1,2,2-tetracarboxylate (**4b**) was attained with the use of *N*-chloromorpholine (**3b**). Analysis of our results and published data [5, 9, 10] suggests that oxidative homocoupling of metalated ethyl acetoacetate or diethyl malonate by the action of *N*-chloro amines **3a**–**3c** is analogous to the reactions of the same substrates with iodine or alkyl hypochlorites.

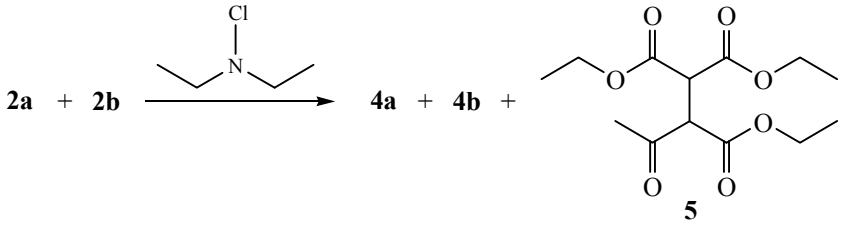
We presumed that both homo- and hereocoupling products could be formed simultaneously in the reaction of a mixture of ethyl 3-oxobutanoate and diethyl malonate carbanions with *N*-chloro amines. The possibility of heterocoupling was studied using

Scheme 1.



R = Et_2N (**a**), morpholin-4-yl (**b**), piperidin-1-yl (**c**).

Scheme 2.



N-chloro-*N*-ethylethanamine; we also examined the effect of the molar reactant ratio on the selectivity for homo- and heterocoupling products.

The reaction of an equimolar mixture of carbanions **2a** and **2b** with *N*-chloro amine **3a** (molar ratio **1a**:**1b**:**3a** = 1:1:2) at 20–25°C in 2 h afforded a mixture of homo- and heterocoupling products **4a**, **4b**, and **5** in an overall yield of 79% (Scheme 2). The product ratio depended on the molar ratio **2a**/**2b**, so that the selectivity for heterocupling product **5** can be varied (Table 2).

Similar results were obtained previously in the oxidative coupling of lithium derivatives of carboxylic acids by the action of *tert*-butyl hypoiodite [11], iodine [12], 1,2-dibromoethane [13], tetrachloro- [14] and tetrabromomethanes [15], and *N*-chloro- and *N*-bromo-*N*-ethylethanamines [16].

Thus, no amination products are formed in the reactions of carbanions **2a** and **2b** with *N*-chlorodialkylamines, but oxidative coupling of **2a** and **2b** occurs instead.

Table 1. Oxidative homocoupling of ethyl 3-oxobutanoate and diethyl malonate carbanions **2a** and **2b** with *N*-chloroamines **3a**–**3c**[a]

N-Chloroamine	Yield, %	
	4a	**4b**
3a	68	75
3b	74	83
3c	72	80

[a] Ratio **2**:**3** = 1:1, diethyl ether, 20–25°C, inert atmosphere (argon), reaction time 2 h.

Table 2. Ratios of homo- and heterocoupling products in the reaction of mixtures of ethyl 3-oxobutanoate and diethyl malonate carbanions **2a** and **2b** with *N*-chloro-*N*-ethylethanamine (**3a**)[a]

2a : **2b**	Product ratio, %		
	4a	**4b**	**5**
1 : 1	17	67	16
2 : 1	52	21	27
4 : 1	69	21	10

[a] Diethyl ether, 20–25°C, inert atmosphere (argon), reaction time 2 h.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 75.47 MHz using tetramethylsilane as internal standard. The products were analyzed by gas chromatography on a Khromatek-Kristal 5000.2 instrument equipped with a flame ionization detector (carrier gas helium, flow rate 1.1 mL/min; Restek RTX-5 capillary column, 30 m × 0.25 mm, film thickness 0.25 μm; oven temperature programming from 50 to 270°C at a rate of 10 deg/min). GC/MS analysis was performed with a Shimadzu GCMS-QP2010S instrument (electron impact, 70 eV; a.m.u. range 33–350; HP-1MS capillary column, 30 m × 0.25 mm, film thickness 0.25 μm; injector temperature 300°C, ion source temperature 250°C; oven temperature programming from 50 to 300°C at a rate of 20 deg/min; carrier gas helium, flow rate 1.1 mL/min).

Reactions of ethyl-3-oxobutanoate and diethyl malonate carbanions with *N*-chloro amines *(general procedure)*. Ethyl 3-oxobutanoate (**1a**) or diethyl malonate (**1b**), 0.005 mol, was added with stirring at 20–25°C to a solution of sodium ethoxide prepared from 0.0075 mol of sodium and 25 mL of anhydrous ethanol. Sodium derivative **2a** or **2b** separated from the solution. The mixture was evaporated to dryness, the residue was dissolved in 30 mL of anhydrous diethyl ether, the solution was cooled to 0–5°C, and a solution of 0.005 mol of *N*-chloro amine **3a**–**3c** in 15 mL of diethyl ether was added. The mixture was stirred for 2 h at 20–25°C and treated with 30 mL of distilled water, the organic phase was separated, the aqueous phase was extracted with diethyl ether (3 × 30 mL), and the extracts were combined with the organic phase, dried over Na_2SO_4, and evaporated to isolate crystalline product **4a** or **4b**.

The oxidative coupling of a mixture of ethyl-3-oxobutanoate and diethyl malonate carbanions by the action of *N*-chloro-*N*-ethylethanamine was carried out in a similar way. A mixture of esters **4a**, **4b**, and **5** was isolated.

Diethyl 2,3-diacetylbutanedioate (4a). mp 88°C.

***mezo*-4a.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (6H, CH_3, J = 7.2 Hz), 2.37 s (6H, CH_3CO), 4.14 q (4H, CH_2, J = 6.9 Hz), 4.45 s (2H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.92 (CH_3), 30.08 ($\underline{C}H_3C$=O), 58.55 (CH), 62.89 (CH_2), 167.05 (COO), 201.14 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 258 (0.2) $[M]^+$, 198 (14), 173 (28), 167 (16), 145 (15), 128 (9), 127 (50), 117 (12), 99 (31), 97 (9), 43 (100).

***rac*-4a.** ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (6H, CH_3, J = 7.2 Hz), 2.42 s (6H, CH_3CO), 4.15 q (4H, CH_2, J = 6.9 Hz), 4.48 s (2H, CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.73 (CH_3), 30.79 ($\underline{C}H_3CO$), 57.77 (CH), 62.10 (CH_2), 167.05 (COO), 201.56 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 258 (0.2) $[M]^+$, 198 (15), 173 (30), 167 (20), 145 (16), 128 (9), 127 (50), 117 (13), 99 (32), 97 (9), 43 (100).

Tetraethyl ethane-1,1,2,2-tetracarboxylate (4b). mp 75°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (12H, CH_3, J = 7.2 Hz), 4.13 s (2H, CH), 4.22 q (8H, CH_2, J = 6.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.91 (4C, CH_3), 51.42 (2C, CH), 62.02 (4C, CH_2), 167.08 (4C, C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 319 (0.2) $[M]^+$, 273 (17), 273 (18), 245 (26), 227 (30), 226 (16), 200 (19), 199 (47), 173 (33), 171 (33), 154 (19), 145 (16), 143 (47), 128 (12), 127 (100), 117 (17), 100 (10), 99 (93), 55 (12), 45 (10).

Triethyl 3-oxobutane-1,1,2-tricarboxylate (5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.76 (2C, CH_3), 13.95 (CH_3), 29.72 (CH_3), 51.07 (CH), 57.47 (CH), 61.56 (2C, CH_2), 61.62 (CH_2), 166.59 (3C, COO), 202.89 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 256 (6), 241 (9), 195 (6), 185 (7), 183 (8), 167 (24), 165 (11), 143 (9), 142 (11), 141 (7), 124 (14), 115 (9), 53 (9), 44 (6), 43 (100).

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