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Alkylation of Diethyl Acetamidomalonate by Weak Electrophiles

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Abstract :

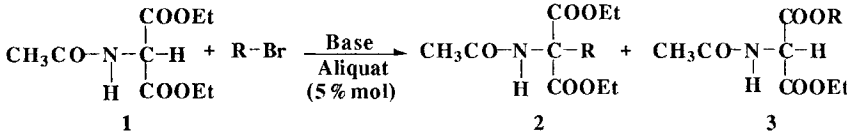
Diethyl acetamidomalonate was efficiently alkylated with electrophiles of low reactivity under modified phase transfer-catalysis conditions in the absence of organic solvent using potassium *tert*-butoxide as a base.

INTRODUCTION

Preparations of numerous amino-acids involve in the first step the alkylation of diethyl acetamidomalonate **1**[1]. Various enzymatic enantioselective hydrolyses have been described for the preparation of the amino-acids starting from **1**[2]. The achievement of this synthesis is however limited by the initial alkylation of **1** which proceeds only with sufficiently reactive electrophiles. Long chain alkyl halides do not react under classical alkylation conditions. Consequently, the synthesis of long chain alkyl substituted amino-acids avoids the acetamidomalonate pathway. For instance, 2-acetamidotetradecanoïc acid has been prepared by reacting, under pressure, acetamide, 1-dodecene, carbon monoxide and hydrogen in the presence of $Co(CO)_4$[3]. 2-Methylaminooctadecanoate resulted from the condensation of N,N-bis-trimethylsilylaminoglycinate with hexadecyl bromide[4] catalyzed by $[Me_2(MeO)Si]_2NK$. However, it can be noticed that octylacetamidomalonate **2a** has been previously described. It was obtained from **1** by a two steps procedure[5]: the condensation of **1** with buta-1,3-diene in the presence of triethylamine and $Pd(OAc)_2(CH_3CN)_2$ as a catalyst, yields diethyl octa-2,7-dienylacetamidomalonate which was further reduced to **2a**.

RESULTS AND DISCUSSION

We had previously used solid-liquid phase transfer catalysis in the absence of solvent to achieve the alkylation of **1** but the introduction of long chain alkyl halides could not be realized[6]. We now report that the title coupounds are easily obtained if potassium tert.butoxide is reacted in place of potassium hydroxide.
The reaction takes advantage of our conditions that allow a larger choice of bases than classical PTC methods [7]. When KOH was the base, only minor amounts of the alkylated product **2b** could be isolated. The main product of this reaction was dodecyl ethyl α-acetamido malonate **3b** which resulted from the transesterification of **1** with dodecanol.



1 2 3

a R = C_8H_{17}
b R = $C_{12}H_{25}$
c R = $C_{16}H_{33}$

RBr	Base	Temperature [°C]	Yield [%] 2	3
$C_8H_{17}Br$	KOtBu	20	12	0
$C_8H_{17}Br$	KOtBu	70	53	0
$C_{12}H_{25}Br$	KOtBu	20	75	0
$C_{12}H_{25}Br$	KOH	20	2	0
$C_{12}H_{25}Br$	KOH	70	8	68
$C_{16}H_{33}Br$	KOtBu	70	87	0

The better reactivity of **1** in the presence of KOtBu probably resulted from a rise in the concentration of the anion due to the greater basicity of terbutoxide compared to hydroxide. We believe that the solvation of the anion can also be of importance when KOH is used (solid KOH contains 15% H_2O). We previously observed a similar effect of KOtBu under solvent free solid-liquid PTC conditions when we alkylated N-hydroxyphtalimide [8], or during aromatic nucleophilic substitution [9, 10] and also in isomerization of allylic compounds [11].

EXPERIMENTAL

M.p. were determined on a Büchi apparatus and are uncorrected. The ^{1}H- NMR spectra were recorded in $CDCl_3$ and TMS as internal reference on a Brucker 270 spectrometer.

General Procedure for the Alkylation of Diethyl Acetamidomalonate : Diethylacetamidomalonate (2.17, 10mmol) alkylating agent (10mmol) base : KOtBu 10 mmol and Aliquat 336 (0.2g, 0.5mmol) was shaken for 3h at 20°C. The reaction mixture was extracted with diethyl ether (3x5ml). The extracts were washed with 1N hydrochloric acid (2x20ml) and evaporated under reduced pressure. The residual product cristallizes after trituration in n-hexane ; its structure is verified by ^{1}H NMR and the purity established by microanalysis.

Diethyl α-acetamido-α-octyl malonate (**2a**)

M. p. 46°C. (reported mp. 40-43°C)[3] NMR(δ). 0.88(t, 3H); 1.23(m, 12H); 1.31(t, 6H); 2.05(s, 3H); 2.30(m, 2H); 4.21(q, 4H); 6.77(s, 1H).
$C_{17}H_{31}NO_5$(329.3).
Calcd.: C 62.01 H 9.42 N 4.25
Found: C 61.85 H 9.56 N 4.38

Diethyl α-acetamido-α-dodecyl malonate (**2b**)

M.p. 61-63°C. NMR(δ). 0.86(t, 3H); 1.20(m, 20H); 1.29(t, 6H); 2.07(s, 3H); 2.31(m, 2H); 4.23(q, 4H); 6.71(s, 1H).
$C_{21}H_{39}NO_5$(385.3)
Calcd.: C 65.45 H 10.13 N 3.63
Found: C 65.36 H 10.02 N 3.75

Diethyl α-acetamido-α-hexadecyl malonate (**2c**)

M.p. 68°C. NMR(δ). 0.86(t, 3H); 1.20(m, 28H); 1.26(t, 6H); 2.01(s, 3H); 2.28(m, 2H); 4.21(q, 4H); 6.75(s, 1H).
$C_{25}H_{47}NO_5$(441.4)
Calcd.: C 68.03 H 10.65 N 3.17
Found: C 67.85 H 10.74 N 3.35

Dodecyl ethyl α-acetamido malonate (**3b**)
Was separated from **2b**, when KOH was the base, by column chromatography (silica gel-eluant : toluene-ethylacetate 9:1).

M.p. 76°C. NMR(δ). 0.88(t, 3H); 1.24(m, 18H); 1.28(t, 3H); 1.60(m, 2H); 2.07(s, 3H); 4.27(q, 2H); 645(d, 1H). Mass spectra (chemical ionization) : 358(M+1, 100%) ; 385(M+ 18).
$C_{19}H_{35}NO_5$(357.3)
Calcd.: C 63.86 H 9.80 N 3.92
Found: C 63.95 H 9.87 N 3.95

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