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ALKYLATION OF ETHYL NITROACETATE IN THE ABSENCE OF SOLVENT.

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Abstract

Alkylation of ethyl nitroacetate by solid-liquid phase transfer catalysis (PTC) in solvent-free conditions has been performed. In regard to other chemical procedures the method provide a simplification of the experimental procedure; however, not in all cases, yield are improved.

Introduction

Nitroacetic esters are useful starting materials for the synthesis of a great variety of compounds.[1] For example, alkylation of nitroacetic esters provide useful intermediates to prepare α-aminoacids.[2] However reported procedures for alkylation are not satisfactory. Habitually, yields are poor and O-alkylation is an important side-reaction.[1] Only a recent paper[3] provide a good method for the

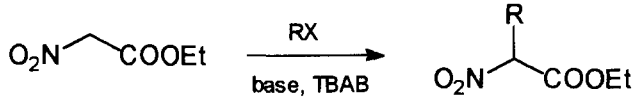
preparation of alkylated nitroacetic ethyl ester (**1**) by electrogeneration of their anion.

Previous work of our laboratory show that PTC in the absence of solvent[4] is a convenient method for the alkylation of relatively strong acids, as malononitrile[5]. Now we have tested the method in the alkylation of title compound.

Benzyl bromide, methyl iodide, allyl bromide and ethyl bromoacetate have been used as alkylating agents since they represent entries to several α-aminoacids. Allyl derivatives may be reduced yielding the corresponding propyl ones.

Results and Discussion

Influence of the nature of base ($KHCO_3$, KOH, $KOBu^t$) and reaction time have been tested to determine the best conditions for each halide. In all cases a 2:1:1 (**1**:halide:base) molar ratio have used to prevent the formation of dialkylated derivative.



Reaction with benzyl bromide (Table 1) has been used to test the effect of the other factors, as the temperature and the presence of phase transfer agent.

Obtained results show that the base has not a significative influence. However the presence of catalyst improves the yield, probing the efectiveness of the phase transfer catalysis (table 1, entry 6). Use of a 1:1:1 (**1**:halide:base) molar ratio (table 1, entry 1) yield some dibenzylated derivative. The increase in the temperature (table 1, entry 5) produces a low conversion in the alkylation because side-reactions and polymerization takes place.

$KHCO_3$ has been used as base for the other alkylating agents, except methyl iodide. In this case a strong base ($KOBu^t$) is neccesary

Table 1. Benzylation of nitroacetic ethyl ester (**1**)

entry	molar ratio	base	T	catalyst	t (h)	yield
1	1 : 1 : 1	$KHCO_3$	RT	yes	24	40[a]
2	2 : 1 : 1	$KHCO_3$	RT	yes	24	58
3	2 : 1 : 1	KOH	RT	yes	24	55
4	2 : 1 : 1	$KOBu^t$	RT	yes	16	48
5	2 : 1 : 1	$KHCO_3$	60°C	yes	24	17
6	2 : 1 : 1	$KHCO_3$	RT	no	24	7

a) 10% of the dibenzylated derivative has been detected.

Table 2. Selected conditions for alkylation of **1**.[a]

Halide	base	time (h)	yield [b]
$BrCH_2Ph$	$KHCO_3$	24	58
$BrCH_2CH{=}CH_2$	$KHCO_3$	36	40
$BrCH_2COOEt$	$KHCO_3$	72	44[c]
ICH_3	$KOBu^t$	120	32

a) **1**:halide:base molar ratio = 2:1:1. b) isolated. c) 3% of the dialkylated product has been detected.

to obtain moderate yields. Reaction time depends of the reactivity of the halide. Table 2 summarizes the best conditions for the reactions.

In conclusion solid-liquid phase transfer catalysis in the absence of solvent provide a simple method to prepare alkylated nitroacetic ethyl esters, starting material for α-aminoacids.

Experimental

All reagents were of commercial quality from freshly opened containers. Column chromatography was performed on silica gel 60 Merck (70-230 mesh or 230-400 mesh). ^{1}H-NMR spectra were

recorded in chloroform-d_1 (TMS) solution using a Varian Unity 300 MHz spectrometer.

In all experiments 2 mmol of ethyl nitroacetate and 40 mmol/mol of tetrabutylammonium bromide (TBAB) are used.

General procedure:

In a flask provided with a reflux condenser, ethyl nitroacetate, alkyl halide and TBAB were stirred for 30 min at desired temperature. Base was added and the stirring was continued for the appropriate time (Tables 1 and 2). The crude mixture was extracted with dichloromethane (30 ml). Removal of the solvent and column chromatography on the appropriate silica gel afforded the pure compounds.

Ethyl 3-phenyl-2-nitropropionate: Column chromatography on silica gel 60 Merck (70-230 mesh) using toluene as eluent.

^{1}H-NMR δ (ppm): 1.26 (t, *J*= 7, 3H, CH_3), 3.49 (ABX, *J*= 14.4, 6.0, 1H, CH_2-CH), 3.57 (ABX, *J*= 14.4, 9.4, 1H, CH_2-CH), 4.27 (q, *J*= 7, 2H, O-CH_2), 5.34 (ABX, *J*= 6.0, 9.4, 1H, CH-CH_2), 7.15-7.34 (m, 5H, arom.).

Ethyl 2-benzyl-3-phenyl-2-nitropropionate:

^{1}H-NMR δ (ppm): 1.13 (t, *J*= 7, 3H, CH_3), 3.49 (s, 4H, CH_2-Ph), 4.13 (q, *J*= 7, 2H, CH_2-O), 7.17-7.34 (m, 10H, arom.)

Ethyl 2-nitro-4-pentenoate: Column chromatography on silica gel 60 Merck (70-230 mesh) using carbon tetrachloride-dichloromethane (1:1) as eluent.

^{1}H-NMR δ (ppm): 1.31 (t, *J*= 7, 3H, CH_3), 2.88-3.06 (m, 2H, CH_2-CH=CH_2), 4.30 (q, *J*= 7, 2H, CH_2-O), 5.14-5.27 (m, 3H, CH_2=CH and CH-COOEt), 5.69-5.83 (m, 1H, CH=CH_2).

Diethyl nitrosuccinate: Column chromatography on silica gel 60 Merck (230-400 mesh) using dichloromethane as eluent.

^{1}H-NMR δ (ppm): 1.28 (t, *J*= 7, 3H, CH_3), 1.32 (t, 3H, *J*= 7, CH_3), 3.14 (dd, *J*= 17.8, 5, 1H, CH-CH_2), 3.36 (dd, *J*= 17.8, 9.3, CH-CH_2), 4.20 (q, *J*= 7, 2H, CH_2-O), 4.31 (q, *J*= 7, 2H, CH_2-O), 5.56 (dd, *J*= 9.3, 5, 1H, CH-CH_2).

Diethyl 3-carbetoxy-3-nitroglutarate:

^{1}H-NMR δ (ppm): 1.27 (t, *J*= 7, 6H, CH_3), 1.30 (t, 3H, *J*= 7, CH_3), 3.48 and 3.53 (AB, *J*= 17.2, 4H, CH_2-COOEt), 4.18 (q, *J*= 7, 4H, CH_2-O), 4.31 (q, *J*= 7, 2H, CH_2-O).

Ethyl 2-nitropropionate: Column chromatography on silica gel 60 Merck (70-230 mesh) using carbon tetrachloride-dichloromethane (2:1) as eluent.

^{1}H-NMR δ (ppm): 1.32 (t, *J*= 7, 3H, CH_3-CH_2), 1.80 (d, *J*= 7, 3H, CH_3-CH), 4.30 (q, *J*= 7, 2H, CH_2-O), 5.20 (q, *J*= 7, 1H, CH-CH_3).

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