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AN OPTIMIZED VERSION OF GABRIEL-TYPE NUCLEOPHILIC AMINATION

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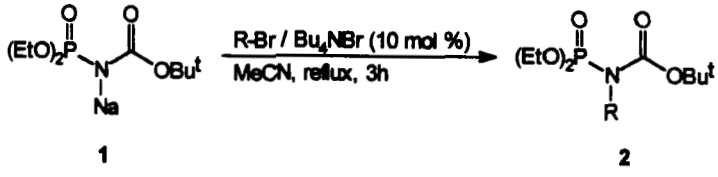
Abstract: N-Alkylation of primary alkyl bromides with diethyl N-sodio-N-(t-butoxycarbonyl)phosphoramidate **1** carried out in boiling acetonitrile in the presence of 10mol% of tetrabutylammonium bromide as catalyst leads to the corresponding N-alkyl derivatives **2a-l**. Deprotection of 2 by refluxing with p-toluenesulfonic acid in ethanol affords ammonium tosylates **3a-l** in reasonable yields.

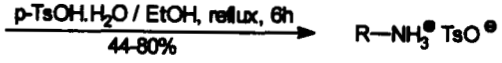
The Gabriel synthesis, involving alkylation of potassium phthalimide followed by cleavage of the phthaloyl group, is one of the classical methods for synthesis of primary amines. Serious preparative problems connected with deprotection limit, however, the applicability of this approach. During the last two decades several substitutes for phthalimide have been proposed.[1] Some years ago we reported[2] on possible replacement of this reagent by more versatile and preparatively more convenient diethyl N-sodio-N-(t-butoxycarbonyl) phosphoramidate **1**. Despite its simplicity and generally satisfactory overall yields of amine hydrochlorides our procedure was not free from some drawbacks and

inconveniances: (a) – the use of toxic benzene as solvent for nucleophilic amination was discouraging; (b) – deprotection procedure by means of gaseous hydrogen chloride in benzene was cumbersome and inconvenient; (c) – only moderate or low yields of some amine hydrochlorides were obtained. All these disadvantages can be circumvented and it is the purpose of this paper to disclose our attempts in this mater.

In the light of our findings the following procedure offers an optimized approach to the ammonium tosylates **3a-l** from the corresponding organic bromides:



1 **2**



3

2, 3	R	2, 3	R
a	Et	g	$PhCH_2CH_2CH_2$
b	Bu	h	$PhCH{=}CH{-}CH_2$
c	C_6H_{13}	i	$Me_2CHCH_2CH_2$
d	$CH_2{=}CH{-}CH_2$	j	$CH_2{=}CHCH_2CH_2$
e	$CH{\equiv}C{-}CH_2$	k	$Me{-}CO{-}CH_2$
f	Bn	l	$Ph{-}CO{-}CH_2$

Scheme

The solid-liquid PTC variant of nucleophilic amination by means of diethyl N-sodio-N-(t-butoxycarbonyl)phosphoramidate **1** in the presence of tetrabutylammonium bromide as catalyst can be most effectively carried out in acetonitrile. The use of tetrahydrofuran as solvent is also possible but the overall yields of ammonium tosylates **3** are somewhat lower. Crude diethyl N-alkyl-N-(t-butoxycarbonyl)phosphoramidates **2a-l** can be easily and conveniently deprotected to the corresponding ammonium tosylates **3a-l** by refluxing with p-toluenesulfonic acid monohydrate in ethanol. Ammonium tosylates **3a-l** are isolated in pure state by evaporation of solvent followed by precipitation with diethyl ether. Recrystallization from the suitable solvent (see Table 1) affords analytically pure samples of **3**. Overall yields and melting points of ammonium tosylates **3a-l** are compiled in Table 1. All new compounds reported give IR, ^{1}H NMR and MS spectra (Table 2) fully compatible with the expected structures. The scope of this nucleophilic amination is strictly limited to primary organic halides. Attempted N-alkylation of **1** with secondary alkyl bromides under the described conditions was totally unsuccessful leading to unreacted starting materials.

This optimized protocol for transforming organic bromides into amines constitutes an attractive alternative to the Gabriel synthesis.

EXPERIMENTAL

All solvents and reagents were of reagent grade and were purchased from Fluka. All mps (determined in open capillary tubes) are uncorrected. IR spectra (KBr discs) were measured using a Specord M80 (C.Zeiss) instrument. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer operating at

TABLE 1

Preparation of ammonium tosylates (**3**)

Product	Overall yield (%)[a]	m.p. (°C) (solvent)	
		found	reported
3a	68	116-118 ($EtOH/Et_2O$)	b
3b	72	119-121 ((EtOH)	119-119.5[3]
3c	65	123-125 ($EtOH/Et_2O$)	124-125[3]
3d	69	95-96 ((EtOAc)	96-97[3]
3e	69	156-157 ($EtOH/Et_2O$)	152-153[3]
3f	69	186-188 (EtOH)	b
3g	61	172-174 (EtOH)	169-170[3]
3h	74	210-212 (EtOH)	203-204[3]
3i	44	93-95 (Me_2CO)	99-101[4]
3j	52[c]	103-105 (Me_2CO)	103-104[4]
3k	80	138-139 (EtOH)	b
3l	62	179-181 (EtOH)	b

[a] Overall yields od spectroscopically pure compounds
[b] Satisfactory microanalysis obtained C ± 0.15, H ± 0.25, N ± 0.20
[c] Prepared from the corresponding chloride.

TABLE 2

Spectroscopic Data for New Ammonium Tosylates (**3**)

Product	IR (KBr) (cm^{-1})	^1H NMR (D_2O/TMS δ, J(Hz)	MS-FAB m/z MH^+ (%)
3a	3064,1496,1176, 1030,1016,816, 684,628,568	1.25 (t,3H,J=7.4,CH_3) 2.39 (s,3H,CH_3-Ar), 3.02 (q,2H,J=7.4,CH_2), 7.35-7.71 (4H,AA`XX` system, ArH)	218 (34) 46 (100; M_k^+)
3f	3432,3040,2928, 1488,1184,1124, 816,728,692	2.39 (s,3H,CH_3-Ar), 4.18 (s,2H,CH_2),7.35-7.70 (m,9H,ArH)	280 (8) 108 (100;M_k^+)
3k	3360,3032,2944, 1732,1480,1192, 1124,1036,824, 680,572	2.27 (s,3H,CH_3CO), 2.39 (s,3H,CH_3-Ar), 4.08 (s,2H,CH_2),7.35-7.70 (4H,AA`XX` system,ArH)	246 (18) 74 (100;M_k^+)
3l	3448,3288,3056, 1696,1176,1140, 1128,1036,1008, 816,688,628,568	2.39 (s,3H,CH_3-Ar), 4.85 (s,2H,CH_2),7.35-7.77 (m,9H,ArH)	307 (9) 136 (61;M_k^+)

250 MHz, using D_2O solutions. FAB/MS were measured on an APO Electron (Ukraine) Model MI 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix).

Diethyl N-sodio-N-(t-butoxycarbonyl)phosphoramidate **1** was obtained as described previously.[2]

Conversion of Organic Bromides into Ammonium Tosylates 3; General Procedure:

A mixture of organic bromide (10 mmol), diethyl N-sodio-N-(t-butoxycarbonyl)phosphoramidate (**1**; 2.75 g, 10 mmol), Bu_4NBr (0.32 g, 1 mmol), and acetonitrile (30 mL) was refluxed with efficient stirring for 3h. Solvent was then evaporated and the residue was treated with a mixture of hexane (15 mL) and toluene (15 mL). The solution was filtered and evaporated under reduced pressure. Crude **2** was dissolved in EtOH (20 mL) and refluxed with $TsOH \cdot H_2O$ (1.9 g, 10 mmol) for 6h. The resultant solution was concentrated, diluted with Et_2O (40 mL) and refrigerated overnight. Crystalline ammonium tosylate **3** was filtered off, washed with Et_2O and recrystallized from the suitable solvent. Yields, melting points, and spectroscopic data of ammonium tosylates **3** are compiled in Tables 1 and 2.

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