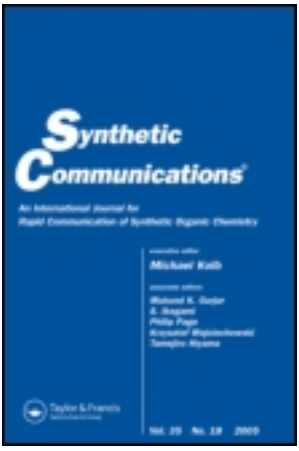



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# NEW PROTOCOL FOR CONVERTING ALCOHOLS INTO AMINES

Anna Klepacz [a] & Andrzej Zwierzak [b]
[a] Institute of Organic Chemistry, Technical University, (Politechnika), Żeromskiego 116, Lódź, PL-90924, Poland
[b] Institute of Organic Chemistry, Technical University, (Politechnika), Żeromskiego 116, Lódź, PL-90924, Poland
Published online: 09 Nov 2006.

To cite this article: Anna Klepacz & Andrzej Zwierzak (2001): NEW PROTOCOL FOR CONVERTING ALCOHOLS INTO AMINES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:11, 1683-1689

To link to this article: http://dx.doi.org/10.1081/SCC-100103987

SYNTHETIC COMMUNICATIONS, 31(11), 1683–1689 (2001)

# NEW PROTOCOL FOR CONVERTING ALCOHOLS INTO AMINES

**Anna Klepacz and Andrzej Zwierzak***

Institute of Organic Chemistry, Technical University
(Politechnika), Żeromskiego 116,
PL-90924 Łódź, Poland



## ABSTRACT

The reactions between diethyl N-(t-butoxycarbonyl)phosphoramidate **1**, diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP) and primary or secondary alcohols lead to the corresponding diethyl N-alkyl-N-(t-butoxycarbonyl)phosphoramidates **2a**–**o**. Deprotection of crude **2** by refluxing with p-toluenesulfonic acid monohydrate in ethanol affords ammonium tosylates **3a**–**o** in moderate to good overall yields. The N-alkylation of **1** proceeds stereoselectively with complete inversion of the configuration of the alkyl group.

Phthalimide was first subjected to N-alkylation with alcohols in Mitsunobu reaction.[1] This synthesis of primary amines directly from alcohols suffers from undesirably vigorous conditions necessary for cleavage of phthaloyl protection. A number of alternatives[2] to phthalimide such as iminodicarbonates,[3] acylcarbamates[4] and sulfonylcarbamates[5] have been

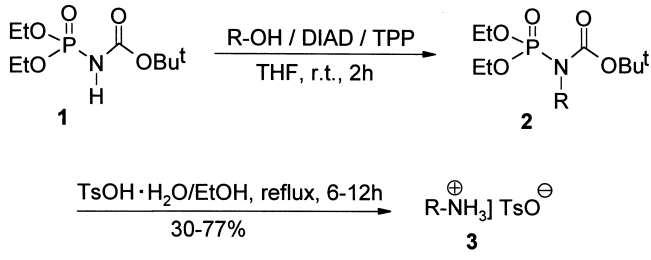
* Corresponding author.

also used for converting alcohols into amines but the procedures required reagents which are not conveniently accessible or needed rather drastic conditions of deprotection.

Judicious combination of the Staudinger and the Mitsunobu reactions was proposed by Golding et al[6] for transforming alcohols into amines. Some years ago we reported on possible application of diethyl N-(t-butoxycarbonyl)-phosphoramidate **1** for the synthesis of amines from alcohols under Mitsunobu conditions.[7] Despite its simplicity and satisfactory yields of amine hydrochlorides obtained this procedure suffered from some significant drawbacks: (a) – poor reproducibility of the reactions leading to sec-alkyl amine hydrochlorides; (b) – the use of toxic benzene as solvent and relatively expensive diethyl azodicarboxylate (DEAD) as hydroxyl group activating reagent; (c) – inconvenient deprotection procedure using gaseous hydrogen chloride in benzene. All these disadvantages, obviously diminishing the preparative value of the reported methodology, can be circumvented or at least partially avoided. It is the aim of this paper to present our attempts in this matter.

It has been well established now that the present version of the previously reported procedure offers the most effective way of transforming alcohols into corresponding ammonium tosylates **3a**–**o**. (Scheme) Diethyl N-(t-butoxycarbonyl)-phosphoramidate **1** is relatively strong NH-acid ($pKa = 9.32$)[8] and can be easily subjected to N-alkylation under Mitsunobu conditions. The Mitsunobu reaction between **1** and primary or secondary alcohols can be most effectively carried out in tetrahydrofuran in the presence of 10% excess of triphenylphosphine (TTP) and diisopropyl azodicarboxylate (DIAD). It was found that twice less expensive DIAD can be used as a substitute of more often recommended diethyl azodicarboxylate (DEAD) without affecting the yields of amines.

N-Alkylation of **1** is completed after 2 hours at room temperature. Crude diethyl N-alkyl-N-(t-butoxycarbonyl)phosphoramidates **2** can be easily separated from triphenylphosphine oxide and other by-products by evaporation of solvent followed by extraction of solidified residue with hexane. Cumbersome chromatographic purification can be thus avoided. Crude **2** are easily and conveniently deprotected to the corresponding ammonium tosylates **3a**–**o** by refluxing with p-toluenesulfonic acid monohydrate in ethanol. Compounds **2k**–**o** with secondary alkyl groups linked to nitrogen atom are completely deprotected after 12 hours in concentrated ethanolic solutions of p-toluenesulfonic acid monohydrate. For N-alkyl derivatives **2a**–**j**, derived from primary alcohols, refluxing for 6 hours in less concentrated solution is sufficient to achieve full deprotection. Ammonium tosylates **3a**–**o** can be easily isolated in spectroscopically pure state by evaporation of solvent followed by precipitation with diethyl ether.




DIAD = Pr$^i$O$_2$C-N=N-CO$_2$Pr$^i$

TPP = Ph$_3$P

| 2,3 | R | 2,3 | R |
|---|---|---|---|
| a | Bu | j | Ph-CH=CH-CH$_2$ |
| b | i-Bu | k | i-Pr |
| c | Me$_3$C-CH$_2$ | l | sec-Bu |
| d | C$_6$H$_{13}$ | m | c-C$_5$H$_9$ |
| e | CH$_2$=CH-CH$_2$ | n | CH(Me)C$_4$H$_9$ |
| f | HC≡C-CH$_2$ | o | CH(Me)C$_6$H$_{13}$ |
| g | -CH$_2$-C≡C-CH$_2$- | p | Me-CO-CH$_2$ |
| h | Bn | q | Ph-CO-CH$_2$ |
| i | Ph-CH$_2$CH$_2$CH$_2$ | | |

***Scheme.***

One recrystallization from the suitable solvent (see Table 1) affords analytically pure samples of **3a–o**. Overall yields, melting points, and reported melting points of ammonium tosylates **3a–o** are presented in Table 1. All new compounds prepared could be satisfactorily analyzed and gave IR, $^1$HN MR and MS spectra fully compatible with the expected structures. For unknown reasons hydroxyacetone (acetol) and 2-hydroxyacetophenone did not react with **1** under Mitsunobu conditions. Stereochemical course of N-alkylation, proceeding with complete inversion of the configuration, was confirmed using both enantiomers of 2-octanol as model compounds. From S-(+)-2-octanol, $[\alpha]_D^{20} + 10.0$ (c 1, EtOH) R-(−)-1-methylheptylamine, $[\alpha]_D^{20} - 5.2$ (c 2, $C_6H_6$) was obtained and R-(−)-2-octanol, $[\alpha]_D^{20} - 10.0$ (c 1, EtOH) afforded S-(+)-1-methylheptylamine, $[\alpha]_D^{20} + 5.2$ (c 2, $C_6H_6$) respectively.

*Table 1.* Preparation of Ammonium Tosylates (**3**)

| Compound | Overall Yield (%)[a] | M.p. (°C) (Solvent) | |
|---|---|---|---|
| | | Found | Reported |
| 3a | 76 | 120–121 ($EtOH/Et_2O$) | 119–119.5[10] |
| 3b | 65 | 115–116 ($EtOH/Et_2O$) | b |
| 3c | 30 | 163–165 ($EtOH/Et_2O$) | b |
| 3d | 76 | 123–124 ($EtOH/Et_2O$) | 124–125[10] |
| 3e | 73 | 94–95 (AcOEt) | 96–97[10] |
| 3f | 52 | 150–151 ($EtOH/Et_2O$) | 152–153[10] |
| 3g | 49 | 269–271 dec. (MeOH) | b |
| 3h | 76 | 175–176 (EtOH) | 186–188[11] |
| 3i | 71 | 173–174 (EtOH) | 172–174[11] |
| 3j | 66 | 209–210 (EtOH) | 203–204[10] |
| 3k | 77 | 122–124 ($EtOH/Et_2O$) | b |
| 3l | 62 | 76–78 ($EtOH/Et_2O$) | b |
| 3m | 70 | 129–131 (EtOH) | b |
| 3n | 71 | 112–114 ($EtOH/Et_2O$) | b |
| 3o (dl) | 70 | 127–129 ($EtOH/Et_2O$) | b |
| 3o (+) | 69 | 99–101 ($EtOH/Et_2O$) | b |
| 3o (−) | 65 | 99–101 ($EtOH/Et_2O$) | b |
| 3p | 0 | — | — |
| 3q | 0 | — | — |

[a] Overall yields of spectroscopically pure compounds.
[b] Satisfactory microanalysis obtained C ± 0.20, H ± 0.25, N ± 0.15.

This optimized procedure for converting alcohols into amines exemplifies a useful, attractive, and relatively inexpensive alternative to the previously reported methods.

## EXPERIMENTAL

All solvents and reagents were of reagent grade and were purchased from Fluka. Melting points (determined in open capillary tubes) are uncorrected. IR spectra (KBr discs) were measured using a Specord M 80 (C. Zeiss) instrument. $^1$H NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer operating at 250 MHz, using $D_2O$ solutions. FAB/MS were measured on an APO Electron (Ukraine) Model M1 12001 E mass spectrometer equipped with a FAB ion source (thioglycerol matrix).

Diethyl N-(t-butoxycarbonyl)phosphoramidate **1** was obtained as described previously.[9]

***Table 2.*** Spectroscopic Data for New Ammonium Tosylates (**3**)

| Compound | IR (KBr) ($cm^{-1}$) | $^1H$ NMR ($D_2O$/TMS) δ, J (Hz) | MS-FAB m/z $MH^+$ (%) |
|---|---|---|---|
| 3b | 3424, 3064, 1632, 1524, 1180, 1124, 1032, 1008, 816, 684, 568 | 0.96 (d, 6H, J = 6.75), 1.87–1.98 (m, 1H), 2.38 (s, 3H) 2.82 (d, 2H, J = 7.0), 7.34–7.70 (AA`, XX` system, 4H) | — |
| 3c | 2968, 1624, 1536, 1480, 1172, 1140, 1124, 1036, 1024, 1008, 816, 680, 568 | 1.00 (s, 9H), 2.39 (s, 3H), 2.81 (s, 2H), 7.35–7.70 (AA`, XX` system, 4H) | — |
| 3g | 2992, 1236, 1180, 1152, 1120, 1024, 1004, 688, 568 | 2.38(s, 6H), 3.88 (s, 4H), 7.34–7.70 (AA`, XX` system, 8H) | — |
| 3k | 3424, 3040, 2752, 1528, 1464, 1188, 1128, 1032, 1008, 816, 684, 568 | 1.28 (d, 6H, J = 6.5), 2.38 (s, 3H), 3.46 (7 lines, 1H, J = 6.5), 7.34–7.70 (AA`, XX` system, 4H) | 232 (25) 60 (100; $M_K^+$) |
| 3l | 3064, 1512, 1456, 1184, 1136, 1120, 1040, 1008, 820, 684, 568 | 0.95 (t, 3H, J = 7.5), 1.26 (d, 3H, J = 6.5), 1.51–1.72 (m, 2H), 2.39 (s, 3H), 3.26 (sextet, 1H, J = 6.5), 7.34–7.70 (AA`, XX` system, 4H) | 246 (16) 74 (100; $M_K^+$) |
| 3m | 3016, 1188, 1120, 1032, 1008, 680, 568 | 1.55–2.13 (m, 8H), 2.38 (s, 3H), 3.54–3.68 (m, 1H), 7.34–7.70 (AA`, XX` system, 4H) | 258 (15) 86 (100; $M_K^+$) |
| 3n | 3088, 1636, 1532, 1496, 1460, 1224, 1216, 1192, 1136, 1128, 1040, 1012, 816, 688, 576 | 0.86 (dist.t., 3H, J = 6.9), 1.22–1.63 (m, 9H), 2.38 (s, 3H), 3.30 (sextet, 1H, J = 6.7), 7.33–7.68 (AA`, XX` system, 4H) | 274 (11.5) 102 (100; $M_K^+$) |
| 3o | 3072, 1460, 1192, 1128, 1040, 1008, 816, 688, 568 | 0.84 (dist.t, 3H, J = 6.5), 1.24–1.63 (m, 13H), 2.38 (s, 3H), 3.31 (sextet, 1H, J = 6.7) 7.34–7.69 (AA`, XX` system, 4H) | 302 (6) 130 (100; $M_K^+$) |

### Conversion of Alcohols into Ammonium Tosylates 3a–o; General Procedure

A solution of diisopropylazodicarboxylate (DIAD, 2.22 g, 11 mmol) in THF (5 mL) was added dropwise with stirring and external cooling (ice-salt bath) to a mixture of **1** (2.53 g, 10 mmol), triphenylphosphine (2.88 g, 11 mmol), the respective alcohol (10 mmol), and THF (20 mL) at 0°–+5°C within ca. 15 min. After the addition was complete, the temperature of the mixture was raised to 20–25°C, and stirring was continued at this temperature for 2 h. In the case of isobutyl alcohol the mixture was refluxed for 2 h and in the case of neopentyl alcohol – for 12 h. Solvent was then evaporated and the residue was extracted with hexane ($3 \times 25$ mL). On evaporation the combined extracts *in vacuo*, crude diethyl N-alkyl-N-(t-butoxycarbonyl)-phosphoramidate **2a–o** was obtained as pale yellow oil. This was dissolved in ethanol (20 mL for R = 1° alkyl or 10 mL for R = 2° alkyl) and refluxed with $TsOH \cdot H_2O$ (1.91 g, 10 mmol) for 6 h (R = 1° alkyl) or 12 h (R = 2° alkyl). The resultant solution was concentrated, diluted with $Et_2O$ (40 mL), and refrigerated overnight. Crystalline ammonium tosylate **3a–o** was filtered off, washed thoroughly with dry $Et_2O$, dried over $P_2O_5$, and recrystallized from the suitable solvent. (Table 1) Yields, melting points, and spectroscopic data of ammonium tosylates **3a–o** are compiled in Tables 1 and 2. Optically active 1-methylheptylamines were liberated from the tosylates (prepared as described above) by the following procedure: the solution of crude tosylate **3o** in ethanol (5 mL) was made strongly alkaline with 20% NaOHaq and the free amine was extracted with $CH_2Cl_2$ ($3 \times 15$ mL). The extracts were dried over anhydrous $Na_2SO_4$, filtered, and evaporated *in vacuo*. Crude 1-methylheptylamines **3o** thus obtained were used for specific rotation determinations.

## REFERENCES

1. Mitsunobu, O.; Wada, M., and Sano, T. J. Am. Chem. Soc. **1972**, *94*, 679.
2. Ragnarsson, U. and Grehn, L. Acc. Chem. Res. **1991**, *24*, 285, and references cited therein.
3. (a) Koppel, I.; Koppel, J.; Degerbeck, F.; Grehn, L. and Ragnarsson, U. J. Org. Chem. **1991**, *56*, 7172; (b) Degerbeck, F.; Fransson, B.; Grehn, L. and Ragnarsson, U. J. Chem. Soc. Perkin Trans 1 **1992**, 245; (c) Chong, J.M. and Park, S.B. J. Org. Chem. **1993**, *58*, 7300.
4. Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Wallin, A.; Grehn, L. and Ragnarsson, U. J. Chem. Soc. Perkin Trans 1 **1993**, 655.

5. Campbell, J.A. and Hart, D.J. J. Org. Chem. **1993**, *58*, 2900.
6. Fabiano, E.; Golding, B.T. and Sadeghi, M.M. Synthesis **1987**, 190.
7. Ślusarska, E. and Zwierzak, A. Liebigs Ann. Chem. **1986**, 402.
8. Koppel, I.; Koppel, J.; Leito, I.; Pihl, V.; Grehn, L. and Ragnarsson, U. J. Chem. Res. (S) **1994**, 212.
9. Zwierzak, A. and Pilichowska, S. Synthesis **1982**, 922.
10. Koziara, A. and Zwierzak, A. Synthesis **1992**, 1063.
11. Zwierzak, A. Synth. Commun. **2000**, *30*, 2287.

Accepted in the Netherlands August 3, 2000