Pergamon

Tetrahedron Letters 41 (2000) 1841–1844

TETRAHEDRON LETTERS

Intermolecular *N*-alkylation of amines under conditions of the Mitsunobu reaction: a new solid-phase synthesis of tertiary benzylamines

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Received 19 November 1999; accepted 23 December 1999

Abstract

Support-bound secondary aliphatic amines can be *N*-benzylated with benzyl alcohols under the standard conditions of the Mitsunobu reaction if the amine is converted into the corresponding ammonium iodide salt prior to Mitsunobu reaction.

Keywords: amino acids and derivatives; benzylation; Mitsunobu reactions; solid-phase synthesis.

The Mitsunobu reaction enables the conversion of aliphatic alcohols into alkylating agents in situ and under mild reaction conditions. However, alkylations under Mitsunobu conditions are generally limited to rather acidic nucleophiles, such as carboxylic acids, phenols, or strongly C–H acidic compounds.[1] Also, N–H acidic compounds, such as sulfonamides[2] or cyclic imides,[3] can be *N*-alkylated by alcohols in the presence of a phosphine and an oxidant. Aliphatic amines are, however, usually resistant towards *N*-alkylation under Mitsunobu conditions,[4] and only few examples of intramolecular *N*-alkylations (cyclization of aminoalcohols) have been reported.[5]

With the aim of expanding the scope of the Mitsunobu reaction to other types of nucleophile, we sought conditions for performing *intermolecular N*-alkylations of aliphatic amines. As expected, we found that treatment of polystyrene-bound secondary aliphatic amines with benzyl alcohol under the standard conditions as the Mitsunobu reaction (tributylphosphine, azodicarboxylic acid dipiperidide (ADDP), THF or *N*-methylpyrrolidinone (NMP), 20°C, 20 h) did not lead to any detectable *N*-alkylation. Because Mitsunobu reactions generally proceed best under acidic conditions,[6] we then investigated the reaction of various support-bound ammonium salts with benzyl alcohol/PBu_3/ADDP. We found that ammonium iodides underwent clean *N*-alkylation under Mitsunobu conditions if benzylic alcohols were used[7] (Scheme 1).

Further results, which illustrate the scope of this synthesis, are listed in Table 1. α-Amino acid derivatives and aliphatic secondary amines could be cleanly *N*-benzylated with various benzyl alcohols.

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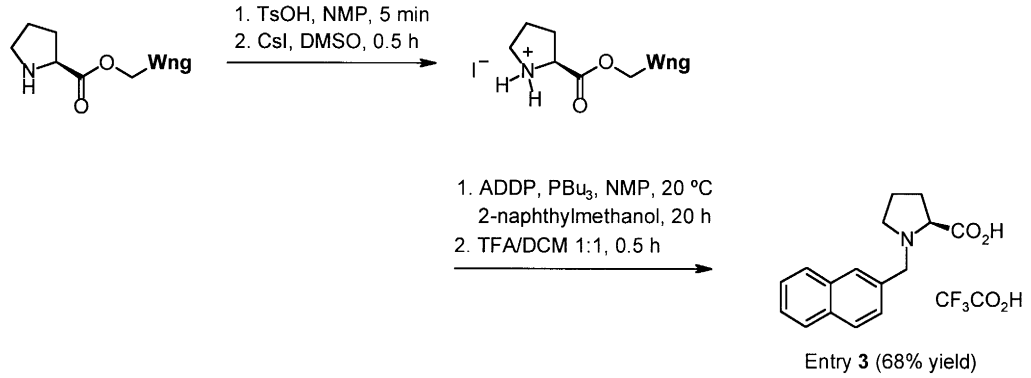
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00028-9



Scheme 1. **Wng**: 1% cross-linked polystyrene with Wang linker

No significant racemization of amino acid derivatives (e.g. Entry **3**) could be detected.[8] If primary amines (e.g. Wang resin bound phenylalanine) were subjected to the conditions given above, mixtures of non-, mono-, and bisbenzylated phenylalanine were obtained, monobenzylated phenylalanine being, however, the main product. The only other ammonium salts which underwent *N*-benzylation cleanly were tosylates. Other ammonium salts, such as ammonium chlorides, fluorides, sulfates, phosphates, triflates, or tetrafluoroborates were either only partly alkylated, or not alkylated at all. Best results were obtained if the ammonium iodides were prepared by first protonating the support-bound amine with toluene *p*-sulfonic acid, and then exchanging the tosylate anion by iodide (Scheme 1).

N-Alkylation could not be achieved with primary or secondary, *non-benzylic* alcohols (1-pentanol, cyclohexanol), despite numerous experiments, in which the solvent (THF, NMP, DMPU, 1,2-dichloropropane) and the counter-ion (e.g. chloride, fluoride, sulfate, phosphate, triflate, tetrafluoroborate, tetraphenylborate) were varied.

The mechanism of this reaction is not yet fully understood. Two possible paths are sketched in Scheme 2. It remains unclear if the benzyloxyphosphonium salt **A** or the benzyl iodide **B** is the alkylating agent. The fact that the outcome of the reaction depends on the counter-ion strongly suggests that benzyl iodides are formed as intermediates and are the main alkylating agents.

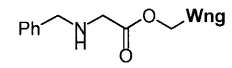
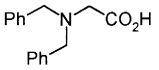
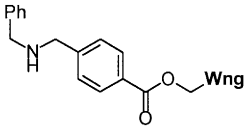
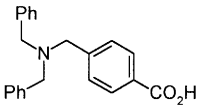
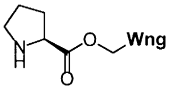
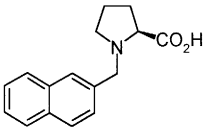
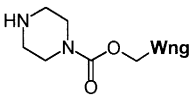
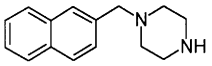
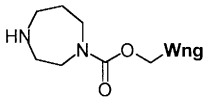
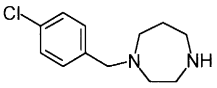
Acknowledgements

We thank Hanne Bultoft and Annemarie R. Varming for analyzing product **3** (*N*-(2-naphthylmethyl)proline) by chiral HPLC. Thanks are also due to Vibeke Rode for LC-MS analyses of all products and Flemming Gundertofte for the elemental analyses.

References

1. Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127–164; Hughes, D. L. *Org. React.* **1992**, *42*, 335–656; Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1999**, *71*, 1053–1057.
2. Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron* **1994**, *50*, 5579–5590.
3. Jia, Z. J. *Synlett* **1999**, 565–566; Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352–5355.
4. Nikam, S. S.; Kornberg, B. E.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62*, 3754–3757. Examples of intermolecular *N*-alkylations of amines with other phosphorus-derived reagents have been reported: Kubota, T.; Miyashita, S.; Kitazume, T.; Ishikawa, N. *J. Org. Chem.* **1980**, *45*, 5052–5057; Tanigawa, Y.; Murahashi, S.; Moritani, I. *Tetrahedron Lett.* **1975**, 471–472; Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1971**, 4368–4373.

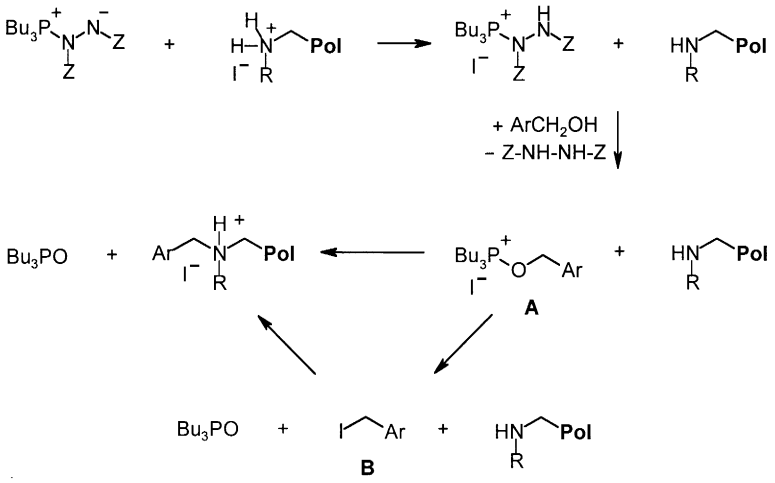
Table 1
Yields and purities of crude benzylamines prepared according to Scheme 1

Entry	Starting resin	Alcohol	Product[a]	Yield[b]	Purity (HPLC) 214 nm	254 nm	ELS[c]
1		benzyl alcohol		91%	77%	75%	98%
2		benzyl alcohol		80%	62%	61%	77%
3		2-naphthyl-methanol		77%	91%	97%	98%
4		2-naphthyl-methanol		66%	79%	100%	74%
5		4-chlorobenzyl alcohol		97%	74%	60%	74%

[a] All products were ammonium trifluoroacetates.

[b] Determined by ^{1}H NMR using DMSO-d_5 as internal standard.

[c] Evaporative light scattering.



Scheme 2. Possible mechanisms of *N*-benzylation of ammonium iodides under Mitsunobu conditions. Z: 1-piperidinylcarbonyl

5. Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Itô, S. *Tetrahedron Lett.* **1996**, *37*, 2463–2466; Walker, M. A. *Tetrahedron Lett.* **1996**, *37*, 8133–8136; Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161–164.
6. Hughes, D. L.; Reamer, R. A. *J. Org. Chem.* **1996**, *61*, 2967–2971.
7. Typical procedure: *N*-(2-Naphthylmethyl)proline trifluoroacetate. Proline esterified with Wang resin (0.63 g, 0.47 mmol; prepared by deprotection of Wang resin bound Fmoc proline; Novabiochem) was washed (2×4 min) with 15 mL of a solution of $TsOH \cdot H_2O$ (0.84 g, 4.39 mmol) in a mixture of methanol (0.5 mL) and NMP (30 mL). The support was then washed once with NMP (15 mL, 10 s), and then (2×15 min) with 15 mL of a solution of CsI (2.61 g, 10.05 mmol) in DMSO (30 mL). After two additional washings with NMP (15 mL, 10 s), were added, in the order given, a solution of 2-naphthylmethanol (1.63 g, 10.27 mmol, 22 equiv.) in NMP (7.5 mL), a suspension of ADDP (2.23 g, 8.82 mmol, 19 equiv.) in NMP (7.5 mL), and finally PBu_3 (1.63 mL, 6.51 mmol, 14 equiv.). The mixture was shaken at 20°C for 23 h, filtered, and the support was extensively washed with NMP, methanol, and dichloromethane. Treatment of the support with a mixture of dichloromethane (7.5 mL) and TFA (7.5 mL) at 20°C for 0.5 h, followed by filtration and concentration of the filtrate, yielded 233 mg *N*-(2-naphthylmethyl)proline trifluoroacetate, which was analyzed by HPLC, LC-MS, and ^{1}H NMR (see Table 1). Recrystallization from ethyl acetate/heptane yielded colorless crystals (119 mg, 68%), mp 156–157°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82–1.95 (m, 1H), 1.98–2.14 (m, 2H), 2.40–2.50 (m, 1H), 3.32 (q, *J*=9 Hz, 1H), 3.46–3.53 (m, 1H), 4.39 (t, *J*=8 Hz, 1H), 4.49 (d, *J*=12 Hz, 1H), 4.64 (d, *J*=12 Hz, 1H), 7.56–7.68 (m, 3H), 7.93–8.02 (m, 3H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.56 (t), 27.49 (t), 53.89 (t), 57.10 (t), 64.97 (d), 126.20 (d), 126.55 (d), 127.16 (d), 127.53 (d), 127.91 (d+s), 129.94 (d), 131.99 (s), 132.54 (s), 169.42 (s). Anal. calcd for $C_{16}H_{17}NO_2 \cdot C_2HF_3O_2$ (369.34): C, 58.54; H, 4.91; N, 3.79. Found: C, 58.54; H, 4.91; N, 3.89.
8. Both enantiomers of proline were *N*-alkylated with 2-naphthylmethanol and analyzed by HPLC on a chiral stationary phase.