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Efficient and Scalable Method for the Selective Alkylation and Acylation of Secondary Amines in the Presence of Primary Amines

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Abstract:

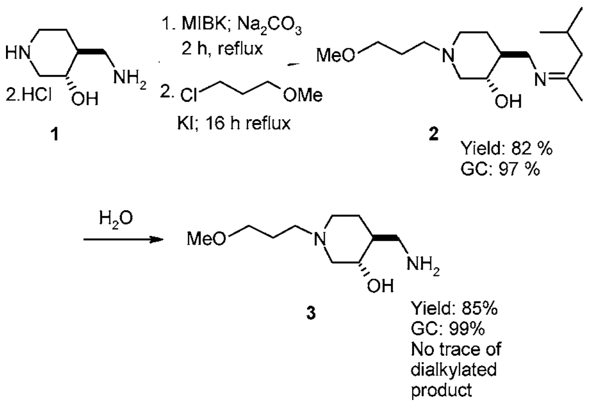
Selective substitution of secondary amines in the presence of primary amines is performed by using the reaction solvent, methyl isobutylketone (MIBK), as a temporary protecting group for the primary amine. After acylation or alkylation of the secondary amine, the resulting imine intermediate is smoothly hydrolysed, leading to the free primary amine in high yield and purity. This procedure represents a cheap and scalable alternative to multistep methods requiring several protections and deprotections.

Despite many amino protecting groups being available,[1] efficient and cost-effective differentiation between NH and NH_2 sites of diamino compounds is a major challenge in organic synthesis. Some methods allowing the selective protection of a primary amine in the presence of a secondary amine are described in the literature. However, they all require the use of an additional reagent such as ethyl trifluoroacetate,[2] trityl chloride,[3] or benzaldehyde[4] that have to be removed after deprotection, making the process more expensive. Procedures avoiding these drawbacks are therefore highly desired for large-scale synthesis.

During our work necessitating a selective alkylation of a secondary amine in the presence of a primary amine, we developed a short procedure in which 4-methyl-2-pentanone (MIBK), an inexpensive solvent, was used not only as the reaction medium but also as a temporary protecting group for the primary amine (Scheme 1). We found that heating **1** in MIBK with sodium carbonate in the presence of 1-chloro-3-methoxypropane led selectively to the alkylated imine **2**. Hydrolysis of **2** provided the free primary amine **3** in good yield and high purity. Alkylation of **1** carried out in other solvents gave **3** with large amounts of polyalkylated products.

It is known that imines of some closely related 1,3-amino alcohols exist as mixtures with the corresponding 1,3-oxazine;[5] however, this tautomer (possibly leading to bis-alkylation) was not observed in the case of **2**.

Scheme 1

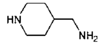
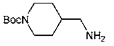
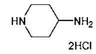
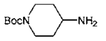
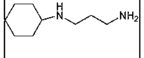
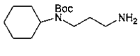
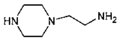
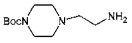
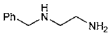
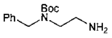


Basically, the diamino compound is condensed with MIBK to form an imine leaving the secondary amine available to react with an alkylating or acylating agent. The imine is finally hydrolyzed under neutral conditions providing the free primary amine.

This method was generalised to some representative commercially available diamino compounds and actually allowed the chemoselective acylation and alkylation of secondary amines.

4-Methyl-2-pentanone (MIBK) boils at 116 °C and provides an efficient azeotrope with water boiling at 88 °C. On the basis of this property, three different processes for the imine formation were developed. First, we found that high boiling free diamines could be quantitatively transformed to the imine by removal of water by azeotropic distillation (Table 1, Method A). Low boiling free diamines were converted to the Schiff base by heating them in the presence of a dehydrating agent such as magnesium or sodium sulphate (Table 1, Method B). Finally, hydrochloride

Table 1. **Selective Boc-protection of secondary *N* in the presence of primary *N***

	Diamines	Methods[a]	Products[b, 7]	Physical Yields	GC (% area) Product : diacyl
1		B		92 %	>99
2		C		99 %	96 : 4
3		A		99 %	92 : 7
4		A		99 %	97 : 3
5		A		99 %	93 : 4

[a] (1) (A) azeotropic distillation in MIBK; (B) reflux in MIBK with Na_2SO_4 or $MgSO_4$; (C) azeotropic distillation in MIBK with 2.5 equiv of Na_2CO_3. (2) $(Boc)_2O$, 0 °C, 30 min. (3) H_2O or IPA/H_2O. [b] All products and imine intermediates were characterised by GC−MS and/or NMR spectra.

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(1) (a) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339. (b) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(2) O'Sullivan, M. C.; Dalrymple, D. M. *Tetrahedron Lett.* **1995**, *36*, 3451

(3) (a) Krakowiak, K. E.; Bradshaw, J. S. *Synth. Commun.* **1998**, *28*, 3451. (b) Xu, D.; Mattner, P. G.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **1996**, *37*, 5301.

(4) Prugh, J. D.; Birchenough, L. A.; Eghertson, M. S. *Synth. Commun.* **1992**, *22*, 2357.

(5) (a) Pedrosa, R.; Andrés, C.; Duque-Soladana, J. P.; Rosón, C. D. *Tetrahedron: Asymmetry* **2000**, *11*, 2809. (b) Fülöp, F.; Lázár, L.; Pelczer, I.; Bernáth, G. *Tetrahedron* **1988**, *44*, 2993.

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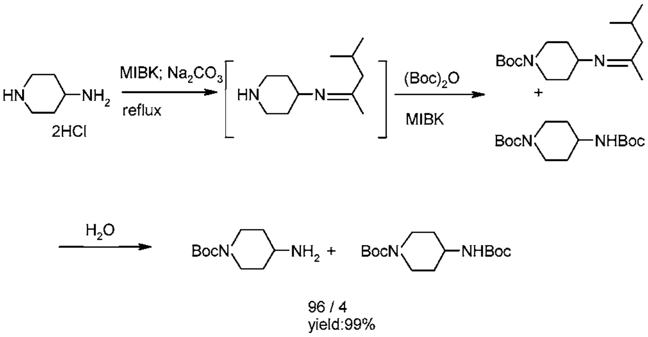
ammonium salts required sodium carbonate to liberate the free base while azeotropic distillation allowed the water removal (Table 1, Method C).

After complete imine formation (monitored by GC and further characterized by GC−MS), 1 equiv of the electrophile was added to the reaction mixture. We demonstrated that acylation with Boc anhydride (Scheme 2, Table 1), as well as alkylation with alkyl halides (Scheme 1, Table 2), took place smoothly. The Schiff bases are therefore stable to substitution conditions as long as water is excluded.

Scheme 2

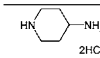
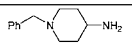
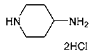
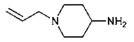


A short aqueous workup removed the salts, and the MIBK phase containing the alkylated or acylated imine was evaporated, and subsequently heated with water until complete hydrolysis. Evaporation of water (and eventual cosolvent) provided finally the free secondary amine in good yield and purity.

Reactions with Boc anhydride were carried out with cyclic and acyclic diamines and showed high selectivities (Table 1). The products were obtained in high yields and with high purities (GC > 92%). The only encountered byproduct was the diacylated product formed by substitution of the primary and the secondary amines with $(Boc)_2O$. Further purification (where necessary) lead to the pure compounds in very good yields.

Reactions with alkyl halides are outlined in Table 2. In this case, one additional equivalent of an inorganic base was required to trap the liberated acid. Benzylation gave a high yield of monobenzylated product containing 8% of the dibenzylated product. However, before hydrolysis of the imine, we observed that the reaction with benzyl chloride had yielded less than 0.5% of the dibenzylated product. This can be explained by the difference in the response factors in GC between the imine and the amine. The low yield obtained for the reaction with allyl bromide is presumably due to loss of product during workup. No optimization was performed.

Table 2. **Selective alkylation of secondary *N* in the presence of primary *N***

Diamines	Electrophile	Products[a, 7]	Physical Yields	GC (% area) Product : dialkyl
	Benzyl chloride		90 %	91 : 8
	Allyl bromide		50 %	98 : 1

[a] Method C: (1) azeotropic distillation in MIBK with 3.5 equiv of Na_2CO_3. (2) Electrophile, rt. (3) H_2O or IPA/H_2O.

Scheme 1 demonstrated that a less activated alkyl chloride gave also rise to the monoalkylated product in high yield and high purity.[7] This reaction was performed in the presence of a catalytic amount of potassium iodide. No trace of a dialkylated byproduct was detected.

In conclusion, we demonstrated the efficiency of a method allowing the selective substitution of secondary amine in the presence of a primary amine. The latter is temporarily protected by MIBK, the reaction solvent. The potential of

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(6) (Experimental) **Method A**: In a flask equipped with a Dean−Stark trap and a condenser, a mixture of the diamine in 2 L/M of MIBK was heated to reflux under nitrogen. Reaction progress was monitored by recording the volume of water produced and/or by GC analysis of the reaction mixture. After no more water was produced, the mixture was cooled to 0 °C. Boc anhydride (1 equiv) dissolved in a minimum of MIBK was then added dropwise to the flask. After stirring for 0.5 h at room temperature, water (0.2 L/M) was added. The aqueous layer was split off, and MIBK was evaporated under reduced pressure leading to the imine intermediate. Water and 2-propanol were then added, and the mixture was heated to 50 °C until completion of the hydrolysis. Solvents were then distilled off providing the free primary amine. **Method B**: A mixture of 4-(aminomethyl)-piperidine (57 g, 0.5 mol) and anhydrous $MgSO_4$ (30 g, 0.25 mol) in MIBK (1000 mL, 2 L/M) was heated to reflux under nitrogen. After no more starting material was observed by GC, the reaction mixture was cooled to 0 °C. To this mixture, was added dropwise to a solution of BOC anhydride (109 g, 0.5 mol) dissolved in a minimum of MIBK. After stirring for 0.5 h at room temperature, water (100 mL, 0.2 L/M) was added to dissolve inorganic salts. The aqueous layer was split off, and MIBK was evaporated under reduced pressure leading to the imine intermediate. Water (50 mL) and 2-propanol (500 mL) were then added, and the mixture was heated to 50 °C until completion of the hydrolysis. Solvents were then distilled off providing *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (98.4 g, 92% yield). MS (CI) m/z 215 (MH^+). ^1H NMR (400 MHz, $CDCl_3$): 1.08 (2H, m), 1.45 (10H, m), 1.70 (2H, bd, $J = 13.3$ Hz), 1.81 (2H), 2.58 (2H, d, $J = 6.6$ Hz), 2.68 (2H, m), 4.10 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): 28.31, 29.63, 39.27, 43.68, 47.68, 79.09, 154.71. **Method C for Boc protection:** MIBK (2 L/M) was added to a flask containing the diamine hydrochloride salt (1 equiv) and sodium carbonate (2.5 equiv). The heterogeneous mixture was heated to reflux under nitrogen, and water was removed from the reaction mixture with a Dean−Stark trap. When the imine formation went to completion, the flask was cooled to 0 °C. Boc anhydride (1 equiv) dissolved in a minimum of MIBK was then added dropwise to the flask. After stirring for 0.5 h at room temperature, water (0.5 L/M) was added. The aqueous layer was split off, and MIBK was evaporated under reduced pressure leading to the imine intermediate. Water and 2-propanol were then added, and the mixture was heated to 50 °C until completion of the hydrolysis. Solvents were then distilled off providing the free primary amine. **Method C for alkylation:** MIBK (2 L/M) was added to a flask containing the diamine hydrochloride salt (1 equiv) and sodium carbonate (3.5 equiv). The heterogeneous mixture was heated to reflux under nitrogen, and water was removed from the reaction mixture with a Dean−Stark trap. When the imine formation went to completion, the flask was cooled to room temperature. Alkyl halide (1 equiv) was then added to the mixture. After the mixture stirred overnight at room temperature, water (0.5 L/M) was added. The aqueous layer was split off, and MIBK was evaporated under reduced pressure leading to the imine intermediate. Water and 2-propanol were then added, and the mixture was heated to 50 °C until completion of the hydrolysis. Solvents were then distilled off providing the free primary amine.

(7) (3*S*,4*S*)-4-(aminomethyl)-1-(3-methoxypropyl)piperidin-3-ol (**3**): MS (CI) m/z 203 (MH^+). ^1H NMR (360 MHz, $CDCl_3$): 1.14−1.27 (m, 1 H), 1.27−1.39 (m, 1 H), 1.55 (ddd, $J = 12.7$, 6.1, 2.7 Hz, 1 H), 1.72−1.83 (m, 3 H), 1.92 (td, $J = 11.5$, 2.5 Hz, 1 H), 2.35−2.50 (m, 2 H), 2.69 (dd, $J = 12.2$, 10.0 Hz, 1 H), 2.81−2.89 (m, 1 H), 3.02 (t, $J = 3.6$ Hz, 1 H), 3.03−3.08 (m, 1 H), 3.32 (s, 3 H), 3.38 (br, 3H), 3.41 (t, $J = 6.4$ Hz, 2 H), 3.63 (td, $J = 9.5$, 4.4 Hz, 1 H). Products identified by comparison with authentical samples made by literature methods: (*tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate) Yoneda, Y.; Kawajiri, S.; Hasegawa, A.; Kito, F.; Katano, S.; Takano, E.; Mimura, T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1261; (*tert*-butyl 4-aminopiperidine-1-carboxylate) Mach, R. H.; Luedtke, R. R.; Unsworth, C. D. et al. *J. Med. Chem.* **1993**, *36*, 3707; (*tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate) Yang, L.; Patchett, A. A.; Pasternak, A. et al. WO 9845285; (*tert*-butyl (2-aminoethyl)benzylcarbamate) Kruijtzer, J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997**, *38* (30), 5335; (1-benzylpiperidine-4-amine) Acros no. 18766. Identity of all products was also confirmed at the level of their crystalline derivatives which are pharmaceutical intermediates under patenting.

this protocol was illustrated by carrying out acylation reactions with BOC anhydride as well as alkylation reactions in MIBK under homogeneous or heterogeneous conditions.Moreover, those transformations could be easily performed in a “one-pot” fashion making this methodology very attractive for large-scale synthesis.

Acknowledgment

This contribution is dedicated to the memory of Vanessa Tamborowski.

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