



Reductive BOC-amination of aldehydes

Elżbieta Bernacka, Anna Klepacz and Andrzej Zwierzak*

Institute of Organic Chemistry, Technical University (Politechnika), Żeromskiego 116, 90-924 Lodz, Poland

Received 29 March 2001; accepted 24 May 2001

Abstract—Base-assisted elimination–reduction of α -amidoalkyl sulfones with sodium borohydride proceeds in tetrahydrofuran at room temperature leading to the corresponding BOC-amines in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

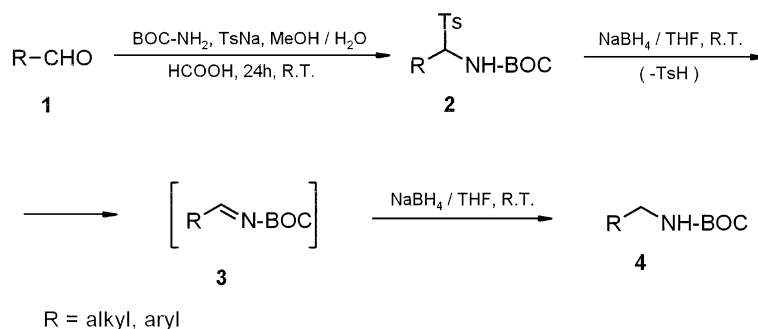
The *N*-protection of amino functions is essential in many synthetic transformations.¹ Among a wide variety of protecting groups the *t*-butoxycarbonyl group (BOC) is of fundamental importance due to its availability, useful protection and ready cleavage.² Although many reagents and methods are available to introduce BOC groups novel, operationally simple, and effective procedures are still in demand.

Incidental to our studies on potential synthetic applications of *N*-BOC imines **3** we tried to prepare these compounds by base-assisted elimination³ of *p*-toluenesulfonic acid from easily available α -amidoalkyl sulfones **2**.^{3,4} Unexpectedly it was found that in addition to the desired imine **3** considerable amounts of *N*-BOC amines **4** were formed when the elimination was performed with stoichiometric amounts of sodium borohydride in tetrahydrofuran at room temperature. This result suggests that sodium borohydride initially acts as a base inducing elimination and then immediately reduces the C=N bond of the *N*-BOC imine **3** to give the respective *N*-BOC amine **4** (Scheme 1).

The similar utilization of α -amidoalkyl sulfones **2** as *N*-acylimine equivalents has been described previously.^{5–8} The reaction of α -amidoalkyl sulfones **2** with an excess of sodium borohydride in tetrahydrofuran afforded *N*-BOC amines **4** in good yields and excellent purity (¹H NMR).

The following typical conditions were used. Finely powdered sodium borohydride (1.13 g, 30 mmol) was suspended in THF (40 ml). Solid crude α -amidoalkyl sulfone **2**⁹ was added portionwise with stirring for ca. 15 min. The resulting mixture was then stirred for 2 h at room temperature, cooled to 5°C, and quenched with satd aq. NH₄Cl (15 ml). Stirring was then continued for 0.5 h. The organic layer was separated and the aqueous phase extracted with CH₂Cl₂ (2×15 ml). The combined extracts and organic phase were dried over MgSO₄ and evaporated to give spectroscopically pure **4**. Yields, mps and literature mps of **2** and **4** are listed in Table 1.

In conclusion, we have disclosed a simple and convenient variant of the reductive amination of aldehydes leading directly to BOC-amines.



Scheme 1.

Keywords: α -amidoalkyl sulfones; *N*-BOC imines; reductive amination.

* Corresponding author. Fax: (48-42)636-55-30.

Table 1. α -Amidoalkyl sulfones **2** and BOC-amines **4**^a

Entry	R	2 Yield (%) ^b	2 Mp (°C)	4 Yield (%) ^b	4 Mp (°C) ^c
a	Ph	65	177–178 (–)	73	52–53 (52–53) ¹²
b	<i>p</i> -Cl-C ₆ H ₄	77	174–175 (–)	71	71–74 (75–76) ¹³
c	<i>p</i> -MeO-C ₆ H ₄	68	179–180 (–)	87	48–50 (50–50.5) ¹⁴
d	<i>p</i> -Me-C ₆ H ₄	77	183–185 (–)	91	65–68 (72.5–73) ¹³
e	2-Furyl	54	148–150 (–)	82	48–51 (–)
f	Me	76	88–90 (–)	77	^d (–)
g	Et	69	114–6 (114–115) ¹¹	87.5	^d (–)
h	<i>i</i> -Pr	76	109–111 (–)	82	^d (–)
i	<i>c</i> -C ₆ H ₁₁	80	151–154 (–)	73	41–44 (50–51) ¹⁵

^a All new compounds were fully characterized by MS, IR and ¹H NMR spectra.

^b Yields of crude products.

^c Mps of crude products. Literature mps are given in parentheses.

^d Low-melting solid.

References

- See for example: (a) Almeida, L. M. S.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1905–1911; (b) Beak, P.; Lee, W. K. *Tetrahedron Lett.* **1989**, *30*, 1197–1200.
- Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, 1999; pp. 518–525.
- Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238–1240.
- Engberts, J. B. F. N.; Strating, J. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 942–950.
- Morton, J.; Rahim, A.; Walker, E. R. H. *Tetrahedron Lett.* **1982**, *23*, 4123–4126.
- Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972.
- Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449–4452.
- Mecozzi, T.; Petrini, M. *Tetrahedron Lett.* **2000**, *41*, 2709–2712.
- Experimental conditions for the preparation of **2**: A mixture of aldehyde **1** (20 mmol), crude *t*-butyl carbamate¹⁰ (2.34 g, 20 mmol), anhydrous sodium *p*-toluenesulfonate (3.57 g, 20 mmol), water (40 ml), methanol (20 ml) and formic acid (5 ml) was stirred for ca. 15 min until it became homogeneous and then left for 24 h at room temperature. The crystalline sulfone **2** was filtered off with suction, washed successively with water (30 ml), and ether (30 ml) and dried over P₂O₅. Sulfones **2a–d** were washed only with water (30 ml) and then dried. Crude **2** were spectroscopically pure (¹H NMR). Analytically pure samples were obtained by crystallization from ethyl acetate (**2a–c**), ethyl acetate–hexane (**2d,e,h**), ethanol–hexane (**2i**), and ether–hexane (**2f,g**).
- Loev, B.; Kormendy, M. F. *J. Org. Chem.* **1963**, *28*, 3421–3426. Crude carbamate prepared in CH₂Cl₂ was ca. 90% pure and had mp 90–93°C.
- Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622–2636.
- Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715–721.
- Tanaka, K. I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1988**, *36*, 3125–3129.
- Afonso, C. A. M. *Synth. Commun.* **1998**, *28*, 261–276.
- Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554–3561.