β-Tosylethylamine: A Useful Reagent for Preparation of N-Protected Amides, Carbamates, and Related Compounds. Application to Synthesis of β-Lactams

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Received July 22, 1994[⊗]

Summary: Readily prepared β-tosylethylamine (**3**) can be used to synthesize *N*-tosylethyl (TSE)-protected amido compounds and β-lactams, which can be deprotected under mild conditions with potassium *tert*-butoxide.

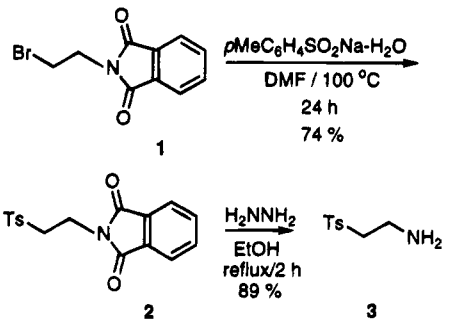
Relatively few generally useful nitrogen protecting groups are currently available for amides, carbamates, and related functionality.[1] In this paper we demonstrate the utility of β-tosylethylamine (**3**) in the synthesis of various *N*-protected β-tosylethyl (TSE) amido compounds which can be deprotected by treatment with base.

In the course of a recent alkaloid total synthesis we required a basic primary amine which could act as an ammonia synthon. The most commonly used reagent of this type, benzylamine, proved unsuitable for our purposes since dealkylation generally requires reductive conditions incompatible with our alkaloid substrate. We therefore considered using β-tosylethylamine (**3**) in this regard. This compound has been reported once,[2] but apparently has never found use in synthesis. This stable, crystalline amine can be easily prepared via an efficient modification of the reported route[2] as shown in Scheme 1. Thus, commercially available *N*-(2-bromoethyl)phthalimide (**1**) was combined with sodium *p*-toluenesulfinate to afford sulfone **2**. Hydrazinolysis of the phthalimido group of **2** provided β-tosylethylamine (**3**) in good overall yield.

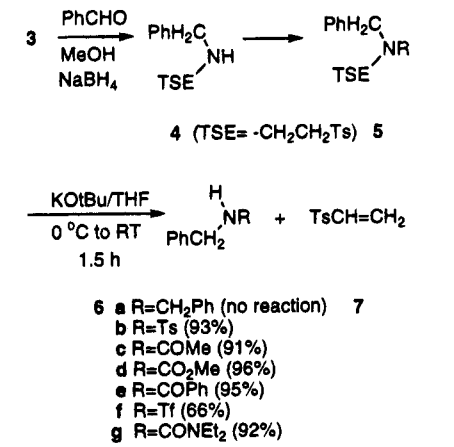
Compound **3** undergoes reductive amination with, for example, benzaldehyde to afford *N*-benzyl-β-tosylethylamine (**4**) (Scheme 2). A second reductive amination leads to dibenzylamine (**5a**) which is stable to a variety of acids and bases. However, if secondary amine **4** is *N*-acylated or *N*-sulfonylated, the resulting amido compounds **5b–g** are now susceptible to removal of the TSE group by β-elimination with potassium *tert*-butoxide to produce **6b–g**, along with vinyl sulfone **7**, which usually polymerizes.[3–5] Protected amido compounds **5b–g** are unaffected by weaker bases such as DBU in refluxing toluene and 10% NaOH at room temperature.

Amine **3** is also particularly useful in the synthesis of *N*-protected β-lactams. Imine **8** could be condensed with α-bromo esters **9** to yield TSE-protected β-lactams **10a–d** in yields similar to those reported for related imino systems (Scheme 3).[6] Compound **10b** was formed as a chromatographically separable 1.3/1 *trans*/*cis* mixture. Deprotection of these β-lactams to the known compounds[7] **11a–d** can be effected cleanly under very mild conditions with potassium *tert*-butoxide. Lactam ring opening by the base was not encountered in these cases. Moreover,

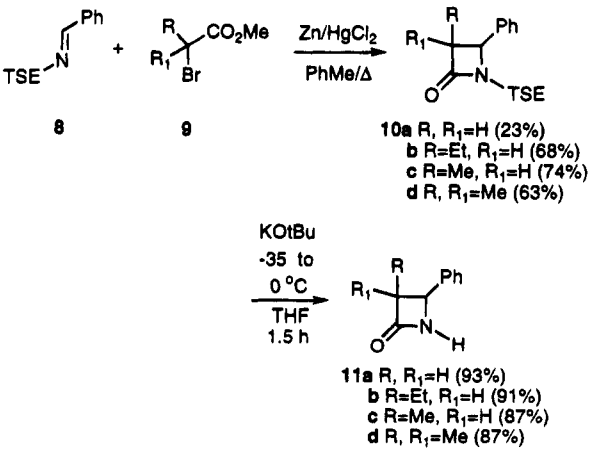
Scheme 1



Scheme 2



Scheme 3



[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed.; Wiley: New York, 1991; pp 397–405.

(2) Madinaveitia, J.; Martin, A. R.; Rose, F. L.; Swain, G. *Biochem. J.* **1945**, *39*, 85.

(3) For examples of various other protecting groups which are removed by a β-elimination process, see: Kader, A. T.; Stirling, C. J. M. *J. Chem. Soc.* **1964**, 258. Gaffney, B. L.; Jones, R. A. *Tetrahedron Lett.* **1982**, *23*, 2257. Katritzky, A. R.; Khan, G. R.; Marson, C. M. *J. Heterocycl. Chem.* **1987**, *24*, 641. Ohtsuka, Y.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 203. Tener, G. M. *J. Am. Chem. Soc.* **1961**, *83*, 159.

(4) *N*-Acylated derivatives of primary amine **3** are stable toward β-elimination with base.

(5) Attempts to directly introduce a TSE group into amido compounds like **6** using vinyl sulfone **7** and various bases have to date been unsuccessful. *Cf.* Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1543.

(6) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.

(7) Ha, D. C.; Hart, D. J.; Yang, T. K. *J. Am. Chem. Soc.* **1984**, *106*, 4819. Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T. K. *J. Org. Chem.* **1983**, *48*, 289.

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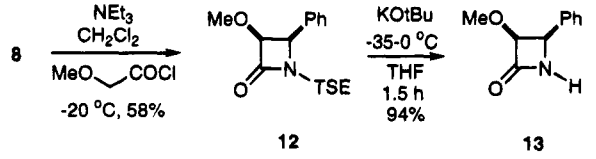
Scheme 4

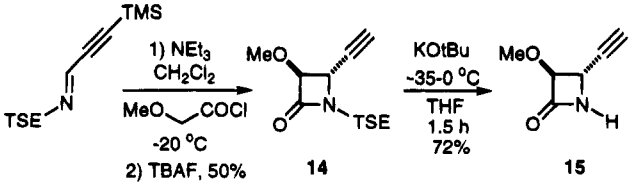


deprotection of the purified stereoisomers of **10b** gave no indication of any α-epimerization. A second group of methoxy-substituted β-lactams **12** and **14** was generated as shown in Schemes 4 and 5.[8] Once again, the TSE group could be cleaved with KOtBu leading to the deprotected β-lactams **13** and **15** with no evidence of ring opening or epimerization.

TSE protection of β-lactams should nicely complement the most commonly used groups for this purpose such as *N*-benzyl (cleaved reductively), *N*-(*p*-methoxyphenyl) (cleaved oxidatively), and *N*-(trialkylsilyl) (removed hydrolytically).[6] Amine **3** may also prove to be a useful ammonia equivalent and benzylamine substitute for other synthetic purposes.

(8) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.

Scheme 5



Acknowledgment. We are grateful to the National Institutes of Health for financial support through grant CA-34303.

Supplementary Material Available: Experimental procedures for β-tosylethylamine (**3**) and all new compounds. Copies of NMR spectra of all new compounds (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.