Electrophilic Amination: Preparation and Use of *N*-Boc-3-(4-cyanophenyl)oxaziridine, a New Reagent That Transfers a *N*-Boc Group to N- and C-Nucleophiles

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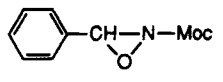
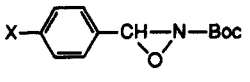
Summary: We describe the preparation of the title compound **2b** via aza-Wittig reaction of *N*-Boc-triphenyliminophosphorane (**6**) with 4-cyanobenzaldehyde followed by Oxone oxidation of the resulting imine **5b**. Oxaziridine **2b** is a stable, crystalline solid, which transfers under mild conditions its *N*-Boc fragment to primary and secondary amines (to give N_β-Boc-hydrazines) and enolates (to give *N*-Boc-amino derivatives).

Electrophilic amination is an important synthetic process,[1] and from a practical point of view, the development of reagents that would allow the direct transfer of a N-protected group to nucleophilic centers may be of great interest. In this context, inspired by the oxaziridine methodology of Schmitz,[2] we have recently described the synthesis of oxaziridine **1**[3] and shown that this easy-to-use reagent transferred under very mild conditions its *N*-(methoxycarbonyl) (*N*-Moc) fragment to most primary and secondary amines to give the corresponding N_β-Moc hydrazines >NNHMoc. As the cleavage of the N_β-Moc group to the free amine may require too harsh of conditions for certain applications, particularly in amino acid chemistry, we found it desirable to modify this reagent by replacing its transferable Moc fragment by a more conventional N-protecting group, such as the Boc, Fmoc, or Z groups commonly used in peptide synthesis. Along these lines, we now report the preparation of the new oxaziridine **2b**, which, like its congener **1**, proved capable of transferring its *N*-Boc fragment to various N- and C-nucleophiles. For instance, as shown below, **2b** allowed the conversion of (*S*)-2-(methoxymethyl)pyrrolidine to Boc-SAMP (**10**) in 30 min at rt (78% yield), thus providing a simple access to this chiral hydrazine.[4]



1

(Moc = CO_2Me)

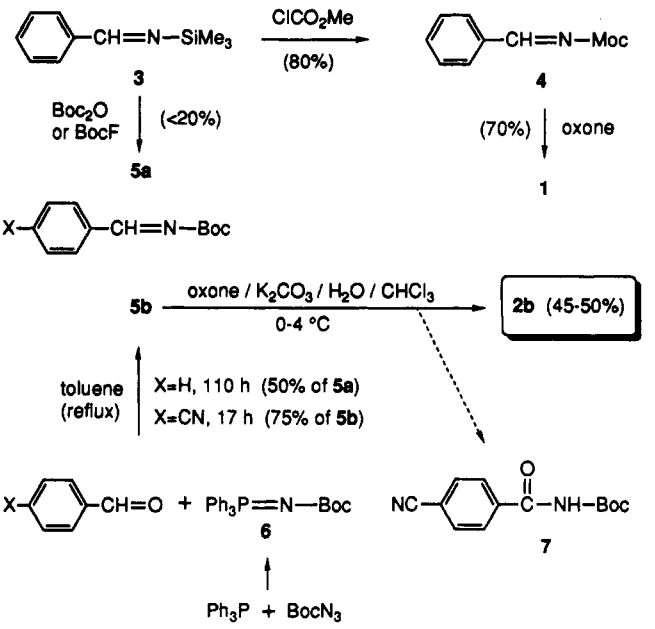


2a: X=H
2b: X=CN

(Boc = CO_2t-Bu)

For the synthesis of **1**, we had used the sequence of reaction depicted in Scheme I, which rests on the acylation of the silylimine **3** with methyl chloroformate, giving **4** in excellent yield, followed by the Oxone oxidation of **4** to **1**.[3]

Scheme I



This sequence proved in fact unsuitable for the preparation of *N*-Boc-oxaziridine **2a** because at the first step the acylation of **3** with di-*tert*-butyl dicarbonate (Boc_2O) or *tert*-butyl fluoroformate (BocF)[5] did not afford the desired N-Boc-imine **5a** in acceptable yield.

We could eventually achieve a more practical preparation of **5a** by aza-Wittig reaction[6] between the iminophosphorane **6**[7] and benzaldehyde. This reaction was, however, very sluggish, only 50% of **5a**[8] being isolated after 4–5 days in refluxing toluene. This circumstance led us to turn to the use of the more electrophilic 4-cyanobenzaldehyde, which, as we expected, reacted well with **6** (17 h reflux) to give **5b** (mp 87 °C), isolated (75%) by flash filtration on a short silica gel column.[9]

Oxaziridine **2b** was obtained in 45–50% yield (10–15-g scale) by controlled oxidation of **5b** using buffered potassium peroxymonosulfate (Oxone), under biphasic conditions at 0–4 °C. The oxidation of **5b** to **2b** was slower than that of **4** to **1**, and it was necessary to recycle the

(1) Recent reviews on electrophilic amination: Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*; VCH Publishers: Weinheim, 1991; pp 45–53. Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980. See also: Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900–5902. Genêt, J.-P.; Mallart, S.; Greck, C.; Piveteau, E. *Tetrahedron Lett.* **1991**, *32*, 2359–2362.

(2) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327–341.

(3) Vidal, J.; Drouin, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1991**, 435–437.

(4) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173–182. Enders, D.; Kipphardt, H.; Fey, P. *Org. Synth.* **1987**, *65*, 183–301.

(5) We used BocF instead of BocCl, in view of the known instability of the latter. For the preparation of BocF, see: Dang, V. A.; Olofson, R. A.; Wolf, P. R.; Piteau, M. D.; Senet, J.-P. G. *J. Org. Chem.* **1990**, *55*, 1847–1851.

(6) Golobokov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.

(7) Iminophosphorane **6** was easily prepared by reaction of $BocN_3$ with triphenylphosphine (Et_2O, rt, 20 min, 93%, mp 148 °C). For the preparation of ether solutions of $BocN_3$, see: Bodansky, M.; Bodansky, A. *The practice of Peptide Synthesis*; Springer-Verlag: New York, 1984; p 242. *Caution*: to avoid explosion risks in large-scale preparations, it is not advised to concentrate the ether solution of $BocN_3$.

(8) Compound **5a** was a liquid: $Eb_{0.1}$ 90 °C; ^1H NMR ($CDCl_3$, δ of residual $CHCl_3$ set to 7.24) δ 1.57 (*t*-Bu), 7.44 (m) and 7.89 (d, arom H's), 8.85 (s, CH=N). The oxidation of **5a** to **2a** proved to be difficult and discouraged us to proceed further in this direction.

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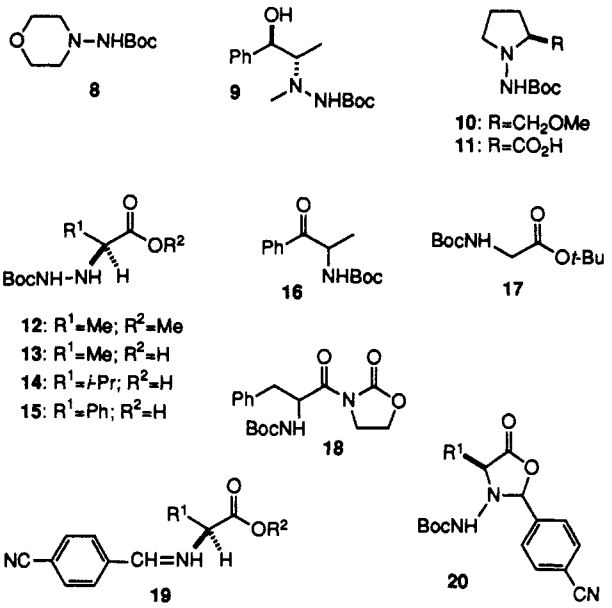
Table I. Amination of Amines and Enolates by Oxaziridine 2b[a]

starting nucleophile	condns	product (%)	physical properties (mp (°C); $[\alpha]^{25}_D$)
amines			
morpholine	Et_2O, rt, 30 min	8 (90)	mp 128[b]
(−)-ephedrine	Et_2O, rt, 4 h	9 (70)	mp 144; −14.2 (c 1.3, $CHCl_3$)[b]
(*S*)-2-(methoxymethyl)pyrrolidine	Et_2O, rt, 30 min	10 (78)	mp 37; −45.2 (c 1, acetone)[b]
proline ($BnMe_3N^+$ salt)	$CHCl_3$, −15 °C, 1 h	11 (77)	mp 128; −41.2 (c 1, 95% EtOH)[c]
alanine methyl ester	Et_2O, rt, 3 1/2 h	12 (67)	oil; −44.7 (c 1, $CHCl_3$)[d]
alanine ($BnMe_3N^+$ salt)	$CHCl_3$, −30 °C, 1 h	13 (50)	mp 105; −20.4 (c 1, MeOH)[b]
valine ($BnMeN^+$ salt)	$CHCl_3$, −30 °C, 1 h	14 (17)	mp 78; −13.4 (c 0.7, CH_2Cl_2)[b]
phenylalanine ($BnMe_3N^+$ salt)	$CHCl_3$, −30 °C, 1 h	15 (41)	mp 184; +20 (c 1, DMF)[e]
enolates			
$PhCOCH(Li)CH_3$	THF, −78 °C, 30 min	16 (38)	mp 81[b,f]
$(Li)CH_2CO_2$-*t*-Bu	THF, −78 °C, 30 min	17 (35)	mp 48[g]
$PhCH_2CH(Li)CON(C_3H_4O_2)$	THF, −78 °C, 30 min	18 (33)	mp 139[b,h]

[a] A solution of **2b** (1.02–1.05 equiv) is added dropwise (amines) or all at once (enolates) to a solution of the nucleophile in the indicated solvent. The yields given correspond to isolated, fully characterized pure products; all mp's were recorded by dsc. [b] New compound. [c] Lit.[17] mp 124–126 °C. [d] Lit.[18] $[\alpha]^{25}_D$ −53.4 ($CHCl_3$, no c given). [e] Lit.[19] mp 185–186 °C, $[\alpha]^{25}_D$ +21 (c 1, DMF). [f] For optically pure Boc-cathinone see Wolf et al.[20] [g] Although Steglich et al.[21] report a different mp (64 °C) for **17**, the ^{1}H-NMR spectrum given is identical with that of our sample. [h] The amination of this enolate by a different method has been reported by Genêt et al.[1]

aqueous phase several times in order to regenerate the oxidizing agent.[10] The main side product (ca. 25%) was the amide **7**. This amide became the major product when the oxone oxidation was carried out at rt, or in the presence of a phase-transfer reagent (Bu_4NCl), and was even the sole product when other oxidizing agents, such as peracids, were employed.[11]

Oxaziridine **2b** was isolated as a crystalline solid (mp 61 °C), thermally stable up to 110–115 °C (as shown by dsc) and existing in solution as a 88:12 mixture of *trans* and *cis* isomers arising from a relatively slow inversion of the pyramidal nitrogen ($\Delta G^{\ddagger}_{cis \rightarrow trans}$ ca. 17 kcal mol^{-1} at 300 K). In order to assess the scope and limitations of the use of **2b** in electrophilic amination, we examined its reaction with various amines and enolates to give the corresponding N_β-Boc-hydrazines **8**–**15** and -amines **16**–**18** (Table I).



For secondary amines, we observed that the transfer of the *N*-Boc fragment proceeded smoothly at rt, the protected hydrazines **8**–**10** being eventually isolated in excellent yields. It is interesting to note that the hydroxy group of ephedrine was inert in this reaction; incidentally, *N*-aminoephedrine is a new chiral hydrazine which, as SAMP and related reagents, may find applications in asymmetric synthesis or as resolving agent for carbonyl compounds. Proline, as its benzyl trimethylammonium salt (soluble in $CHCl_3$), could be converted quantitatively (77% isolated) at −15 °C to N_β-Boc-hydrazinoproline (**11**), thus providing a straightforward preparation of this hydrazino acid in a protected form, suitable for the preparation of hydrazinopeptides by the standard peptide synthesis methods.[12]

With primary amines such as alanine methyl ester, the N-amination was easy, but the actual yield of **12** was only 67%, due to a side reaction occurring between the released

(9) A mixture of 38.26 g of **6** and 13.28 g of 4-cyanobenzaldehyde in 50 mL of anhydrous toluene was refluxed under argon for 17 h. After cooling and addition of 50 mL of dry hexane, most of the Ph_3PO crystallized off and was separated by suction filtration. The concentrated filtrate was percolated *rapidly* (less than 15 min) through 350 g of silica gel (Et_2O/hexane (2:1)), affording 17.5 g (75%) of **5b** as a white solid (mp 87 °C by dsc), which was immediately oxidized to the oxaziridine **2b**: ^{1}H NMR (200 MHz, $CDCl_3$, δ of residual $CHCl_3$ set of 7.24) δ: 1.57 (s, *t*-Bu), 7.74 (d) and 7.99 (d, J = 8.2 Hz, arom. H's), 8.80 (s, CH=N); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9 (Me's of *t*-Bu), 83.1 (C of *t*-Bu), 116.4 and 117.9 ($C_{ar}CN$), 130.1 and 132.5 (arom. CH's), 137.8 ($C_{ar}CH$=N), 161.7 (NCO_2), 166.7 (CH=N).

(10) In a 2-L three-necked flask cooled in an ice–water bath and equipped with a very efficient stirrer was placed a solution of 17.49 g of **5b** in 245 mL of $CHCl_3$ (amylene stabilized) and a chilled solution of 54.38 g of K_2CO_3 in 420 mL of water. Then, to this vigorously stirred mixture was added in 10 min a cold solution of 83.96 g of freshly purchased Oxone in 860 mL of water. After 50 min (0–4 °C), the water phase was discarded, and the organic phase was submitted to the same treatment as described above using new solutions of K_2CO_3 and Oxone. A total of 6 such recycling were effected. Finally, the chloroform layer was washed with 5% aqueous $KHSO_4$ and 5% aqueous $KHCO_3$, dried over $MgSO_4$, and rotatory evaporated (bath temperture <30 °C), and the residue was chromatographed over 400 g of silica gel (Et_2O–pentane (1:3)), yielding 9.35 g (50%) of **2b** (mp 61 °C), followed by 4.67 g of **7** (mp 143 °C). Oxaziridine **2b** gave elemental analyses in agreement with $C_{13}H_{14}N_2O_3$: Anal. Calcd: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.6; H, 5.7; N, 11.4. Spectroscopic data: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, *t*-Bu, *cis* isomer, 12%), 1.53 (s, *t*-Bu, *trans* isomer, 88%), 5.04 (s, CH, *trans*), 5.33 (s, CH, *cis*), 7.57 and 7.70 (m, arom H's); ^{13}C NMR (50 MHz, CD_3OD) δ for the major trans isomer 27.9 (Me's of *t*-Bu), 77.3 (CH), 86.6 (C of *t*-Bu), 115.6 and 119.1 ($C_{ar}CN$), 129.9 and 132.5 (arom. CH's), 139.3 ($C_{ar}CH$), 161.5 (NCO_2).

(11) The photochemical, thermal, or acid-catalyzed rearrangement of oxaziridines to amides is a well-documented reaction; for examples of photochemical isomerizations see: Oliveros, E.; Rivière, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 739–753. Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499–508. Examples of thermal or acid-catalyzed rearrangements: Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccini-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929–3934. Plaquevent, J.-C.; Bénard, D.; Goument, B. *New. J. Chem.* **1991**, *15*, 579–585. We have no evidence, however, that such a rearrangement may occur during the preparation **2b**, and we suspect that the formation of **7** is actually due to a side reaction rather than to the isomerization of **2b**.

(12) Hydrazinopeptides are currently the object of many chemical and biological studies. See: Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891–894. Aubry, A.; Bayeul, D.; Mangeot, J.-P.; Vidal, J.; Stérin, S.; Collet, A.; Lecoq, A.; Marraud, M. *Biopolymers* **1991**, *31*, 793–801. Amour, A.; Collet, A.; Dubar, C.; Reboud, M. Submitted.

4-cyanobenzaldehyde and the starting amine, leading to ca. 20% of the Schiff base (see **19**, $R^1 = R^2 = Me$). In the case of alanine, valine, and phenylalanine ($BnMe_3N^+$ salts), the amination was fast at −30 °C and was similarly attended by the formation of variable amounts of the Schiff base (**19**, $R^2 = H$). During the isolation of the N_β-Boc-protected hydrazino acids, which required slightly acidic conditions, a fast reaction between the desired products (**13–15**) and the 4-cyanobenzaldehyde released from **19** upon hydrolysis gave rise to the formation of oxazolidinones **20**; this side reaction was particularly important with valine.[13] We are currently examining alternative workup procedures in order to avoid the formation of this oxazolidinone[14] and in turn increase the yield of the desired products.

In the reaction of **2b** with ketone, ester, and amide lithium enolates, we observed in all cases a fast transfer of the *N*-Boc group to the nucleophilic carbon at −78 °C. This interesting behavior, which we cannot presently explain, is in sharp contrast with that of *N*-sulfonyloxaziridines, which on reaction with enolates afford the C-hydroxylation products exclusively.[15] The reaction of **2b** with the enolate of propiophenone thus gave *N*-Boc-cathinone **16**, the pharmacologically active constituent of the leaves of Khat,[16] no α-hydroxypropiophenone being detected in the reaction mixture. Not unexpectedly, a substantial amount of the enolate was consumed by aldol condensation with 4-cyanobenzaldehyde, reducing the yields of the amines **16–18** (33–38% with respect to the enolate). Preliminary investigations led us to expect that this side reaction could be reduced or even suppressed by the use of ortho-substituted oxaziridines.

In spite of the present limitations, these results seem convincing enough to recommend the use of **2b** and of other oxaziridines of this kind for electrophilic amination of N- and C-nucleophiles. *We wish to emphasize that, in its present form, this methodology is particularly well suited for the preparation of chiral hydrazines derived from secondary amines and for the direct synthesis of N_β-Boc-protected* L- *or* D-*hydrazino acids from the corresponding amino acids.* Detailed reports on the preparation, structure, chemical reactivity, and use of these oxaziridines will be provided in due course.

Acknowledgment. We are grateful to Dr. René Grée (Rennes) for useful suggestions.

Supplementary Material Available: ^{1}H-NMR spectra of new compounds (13 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.

(13) About 35% of the Schiff base **19** was formed in this case.
(14) Oxazolidinones **20** may also be regarded as N_β,N_α,C-trisprotected hydrazino acids; their utilization in pseudopeptide synthesis is currently under study.
(15) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703–5742. Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919–934.
(16) Berrang, B. D.; Lewin, A. H.; Carroll, F. I. *J. Org. Chem.* **1982**, *47*, 2643–2647.
(17) Decorte, E.; Caplar, V.; Sega, A.; Sunjic', V. *Acta Pharm. Jugoslav.* **1980**, *30*, 183–187.
(18) Hoffmann, R. V.; Kim. H. O. *Tetrahedron Lett.* **1990**, *31*, 2953–2956.
(19) Niedrich, H. *Chem. Ber.* **1967**, *100*, 3283–3288.
(20) Wolf, J. P.; Pfander, H. *Helv. Chim. Acta* **1986**, *69*, 1498–1504.
(21) Münster, P.; Steglich, W. *Synthesis* **1987**, 223–225.