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# Electrophilic Amination Reagents : A New Method For The Preparation Of 3-Aryl-N-BOC (or N-FMOC) Oxaziridines

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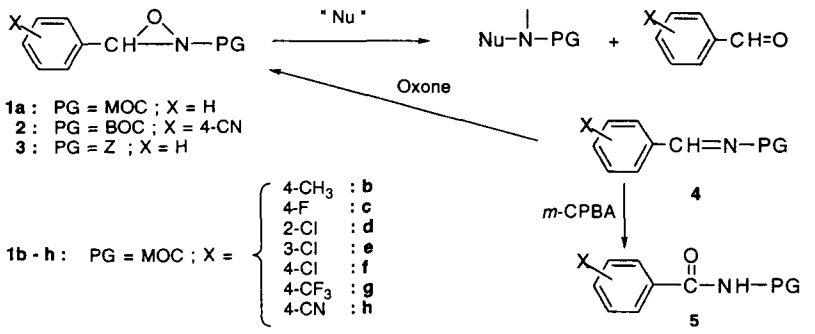
**Abstract :** N-BOC or N-FMOC benzaldimines are oxidized to the corresponding 3-Aryl-N-BOC or N-FMOC oxaziridines by reaction with Li m-chloroperoxybenzoate under aprotic conditions. The new oxaziridines can transfer their N-BOC or N-FMOC group to morpholine to give the corresponding $N_{\beta}$-protected hydrazines.

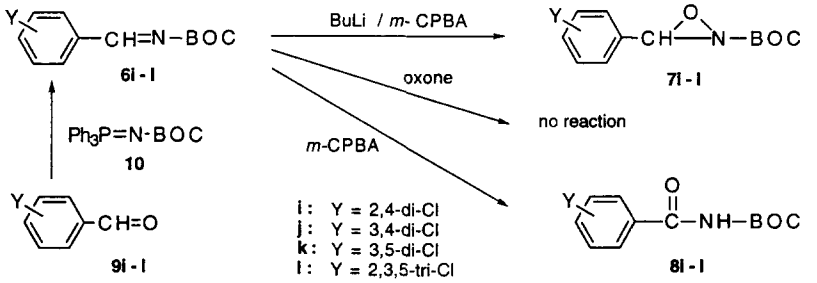
Electrophilic amination is an important synthetic process whereby an electron deficient nitrogen group « $N^+$ » is transferred to a suitable nucleophilic center « Nu » to create a new Nu-N bond.[1] We are currently interested in the development of reagents that would allow the direct transfer of a N-protected group (N-PG), rather than a free amino group, to nucleophiles.[2] Along these lines, we have recently described[3,4] the new oxaziridines **1a** and **2**, and shown that under particularly mild conditions these crystalline, stable, and easy-to-use reagents transferred their N-(methoxycarbonyl) (N-MOC) or N-(*t*-butoxycarbonyl) (N-BOC) fragments to amines (primary, secondary), amino acids, and to various enolates to give the desired N-protected amination products. Several applications of **1a** and **2** have since been reported,[5,6] and the analogous reagent **3**, bearing a transferable N-(benzyloxycarbonyl) group (N-Z), has been used by Vederas[7] in a short synthesis of hydrazinoserine.



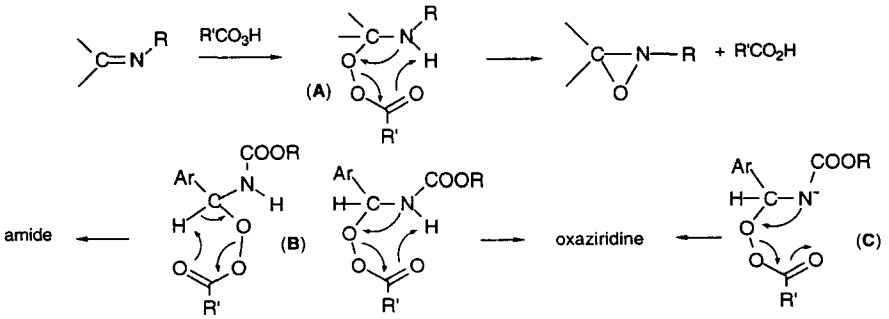

In order to explore the scope of application of these reagents and to gain a better understanding of the various aspects of their chemistry, we have synthesized a series of analogues of **1a** (**1b-h**), and found that these reagents exhibited electrophilic amination properties essentially similar to **1a**.[8] All reagents **1-3** could be prepared, in modest to good yields, by controlled oxidation of the corresponding benzaldimines **4** using buffered potassium peroxymonosulfate (oxone) under biphasic conditions at 0-4 °C. During these studies, we

also noticed that oxidation of benzaldimines **4** (e.g., to give **1a**, **2** or **3**) with *m*-chloroperbenzoic acid (*m*-CPBA) only produced the corresponding amides **5** (also obtained as side products in the oxone oxidation of **4**), although this peracid has been commonly employed for the oxidation of imines to oxaziridines.[9]

In addition to the above mentioned compounds, we wished to synthesize polychlorinated oxaziridines such as **7i-l**. We found that the N-BOC benzaldimine **6i**,[10] obtained from aza-Wittig reaction of iminophosphorane **10** with 2,4-dichlorobenzaldehyde **9i**, was not converted to the desired oxaziridine **7i** upon oxone oxidation. Once again, the use of *m*-CPBA in a two-phase mixture of $K_2CO_3$-$H_2O$ and $CHCl_3$ gave the amide **8i** as the major product, together with a small quantity of oxaziridine **7i**.




It has been proposed[9] that the formation of oxaziridines from N-alkyl imines and peracids involves the addition of $R'CO_3H$ to the >C=NR bond to give intermediate (**A**) (see sketch below), followed by an intramolecular displacement of the $R'CO_2H$ group by the nucleophilic nitrogen. A similar mechanism may be postulated for the oxone oxidation of imines (the leaving group being $SO_4^{2-}$). In N-acyl imines such as **4** or **6i-l**, however, the acylated nitrogen of intermediate (**B**) is of less nucleophilic character than that of (**A**), and a different fragmentation can occur which leads to the formation of the amide. This path is likely to be favoured when percarboxylic acids rather than persulfate reagents (oxone) are employed, because carboxylate groups are not such good leaving groups as sulfate ions. On these grounds, we anticipated that the nucleophilic character of the acylated nitrogen should be restored if it could be generated in a non-protonated form, such as in intermediate (**C**) below.




We expected that this intermediate (**C**) could be obtained by reaction of a N-acyl benzaldimine with the conjugate base of a peracid under aprotic conditions. Relevant experiments for the reaction of imines **6i-l** with *m*-CPBA in the presence of various bases in anhydrous dichloromethane are assembled in Table 1.

**Table 1.** Reaction of N-BOC benzaldimine **6i-l** with *m*-CPBA and various bases.

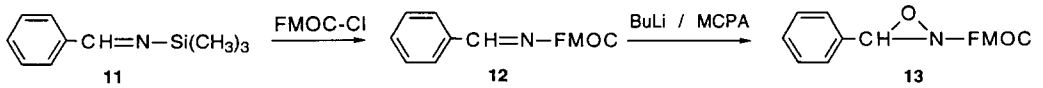
| Entry | **6i-l** | *m*-CPBA (eq.) | Base (eq.) | Reaction conditions | Crude product (NMR) **7i-l / 8i-l / 9i-l** |
|---|---|---|---|---|---|
| 1 | **6i** | (2.0) | KF (4.0)[a] | rt 25 min; then **6i** -78 °C 2 h and rt 30 min | 23 / 73 / 4 |
| 2 | **6i** | (1.1) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6i** -78 °C 2 h and rt 30 min | 74 / 26 / 0 |
| 3 | **6i** | (1.0) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6i** -78 °C 2 h and rt 30 min | 81 / 13 / 6 |
| 4 | **6i** | (1.05) | NaH (1.0)[c] | -78 °C 15 min; then **6i** -78 °C 2 h and rt 30 min | 0 / 95 / 5 |
| 5 | **6i** | (1.05) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6i** -78 °C 2 h and rt 30 min | 87 / 2 / 11 |
| 6 | **6j** | (1.05) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6j** -78 °C 2 h and rt 30 min | 71 / 8 / 21 |
| 7 | **6k** | (1.05) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6k** -78 °C 2 h and rt 30 min | 83 / 17 / 0 |
| 8 | **6l** | (1.05) | *n*-BuLi (1.0)[b] | -78 °C 15 min; then **6l** -78 °C 2 h and rt 30 min | 48 / 32 / 20 |

a) KF was activated at 110 °C/0.024 mbar for 1 h 30 min before use; b) 1.6 M solution of BuLi in hexane; c) NaH suspension (60%) in oil, washed with pentane.

In preliminary experiments, freshly prepared anhydrous solutions of *m*-CPBA in dichloromethane (0.30-0.38 M) were first allowed to react with the base, then with **6i** as indicated in entries 1-4 of Table 1. The use of *m*-CPBA/KF in the preparation of N-phosphinoyl oxaziridines has already been described.[11] In the present work (entry 1), we found that when this reagent was employed the desired oxaziridine **7i** was present in the reaction mixture (23%), but the major product was still the amide **8i**. This result may seem consistent with the fact that since KF and *m*-CPBA are a weak base and a weak acid, both intermediates (**B**) and (**C**) can coexist in the reaction medium. The desired oxaziridine became the major product (74-81%) when the lithium salt of *m*-CPBA was used. This salt was conveniently formed *in situ* by reaction of *m*-CPBA with BuLi prior to the addition of **6i** (entries 2 and 3). By contrast, the reaction of **6i** with the sodium salt of *m*-CPBA (entry 4) gave the amide **8i** in almost quantitative yield, a result that we are presently unable to explain.

These experiments allowed us to set up the following procedure for the oxidation of **6i-l** to **7i-l** ; we found it preferable to use a slight excess of *m*-CPBA (1.05 eq.) with respect to the benzaldimine and to the base (entries 5-8). Typically, *m*-CPBA(Li) was generated at -78 °C by addition of BuLi (1.6 M in hexane, 3.13 mL, 5 mmol) to 15 mL of a 0.35 M (5.25 mmol) solution of *m*-CPBA in dichloromethane.[12] After 15 min, a dichloromethane solution of imine **6** (5 mmol) was added dropwise and the reaction was allowed to proceed for 2 h at -78 °C then 30 min at rt. After addition of water and usual workup, the oxaziridine **7** was isolated by flash chromatograpy (dichloromethane/hexane or pentane); **7i-l** were thus obtained[13] in 79, 63, 56 and 36% yield, respectively.

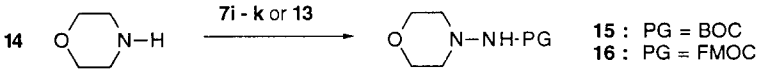
The same procedure was applied to the synthesis of the N-9-fluorenylmethoxycarbonyl (N-FMOC) oxaziridine **13**, from the corresponding N-FMOC benzaldimine **12**.[14] In this case, however, the major reaction product was the amide, and the desired oxaziridine **13** could only be secured in 8% yield.[15]




**11** **12** **13**

Preliminary amination studies showed that the oxaziridines **7i-l** and **13** were capable of transferring their N-BOC or N-FMOC group to morpholine **14** to give the corresponding carbazates **15** (mp 128-129 °C)

and **16** (mp 142 °C). For instance, **7i** on reaction with **14** gave **15** in 77% yield (diisopropyl ether, rt, 24 h), and **13** similarly yielded **16** in 53% yield ($CHCl_3$, rt, 1 h). This last result indicates that the transfer of the N-FMOC group to morpholine is faster than the base-induced cleavage of this group; for comparison, FMOC-amino acids can be deprotected in 1 min by a 50% solution of morpholine in DMF.[16] Moreover, competition experiments showed that the trichlorophenyl oxaziridine **7l** transferred its BOC group to morpholine twice as fast as did its 4-cyanophenyl analogue **2**. More details relating to the amination properties of these new oxaziridines will be reported in due course.[8]

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10. Iminophosphorane **10** (25 mmol) and aldehyde **9i-l** (25 mmol) were refluxed for 3 days in 17 mL of dry toluene; then, $Ph_3PO$ was precipitated by addition of 17 mL of dry hexane; the desired (water sentitive) benzaldimines **6i-l** were isolated (**6i**, **6j**) or used without further purification (**6k**, **6l**); **6i** : mp 56 °C, $^1H$ NMR ($CDCl_3$) δ 1.57s, 7.30dd, 7.44d, 8.12d, 9.18s and $^{13}C$ NMR ($CDCl_3$) 27.8, 82.7, 127.7, 129.8, 129.9, 130.0, 138.2, 140.0, 162.0, 164.4; **6j** : mp 84°C, $^1H$ NMR ($CDCl_3$) δ 1.56s, 7.52d, 7.68dd, 8.00d, 8.74s and $^{13}C$ NMR ($CDCl_3$) 27.9, 82.8, 129.0, 131.0, 131.2, 133.6, 133.9, 137.8, 161.9, 166.8; **6k** : $^1H$ NMR ($CDCl_3$) δ 1.59s, 7.50t, 7.77d, 8.70s ; **6l** : $^1H$ NMR ($CDCl_3$) δ 1.57s, 7.61d, 8.09d, 9.16s.
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12. The *m*-CPBA solutions were prepared immediately before use. Technical (50-60%) *m*-CPBA (1.5 g) was dissolved in 15 mL of dichloromethane and dried over $Mg_2SO_4$ for 15 min. After filtration, the solution was dried again in the presence of 4Å molecular sieves, then was titrated (KI/$Na_2S_2O_3$).
13. Oxaziridine **7i** : oil, $^1H$ NMR ($CDCl_3$, equilibrium mixture of *cis* (19%) and *trans* (81%) isomers) δ 1.13s (*cis*) and 1.53s (*trans*), 5.43s (*trans*) and 5.50s (*cis*), 7.18-7.50; $^{13}C$ ($CDCl_3$, *trans* isomer) 27.7, 74.4, 85.7, 127.8, 129.0, 129.2, 129.4, 135.5, 137.1, 161.0; **7j** : mp 51°C, $^1H$ NMR ($CDCl_3$, equilibrium mixture of *cis* (8%) and *trans* (92%) isomers) δ 1.20s (*cis*) and 1.52s (*trans*), 4.96s (*trans*) and 5.24s (*cis*), 7.30dd, 7.48d, 7.55d; $^{13}C$ ($CDCl_3$, *trans* isomer) 27.5, 76.1, 85.9, 127.1, 129.6, 130.6, 132.3, 132.9, 135.2, 159.6; **7k** : mp 67 °C, $^1H$ NMR ($CDCl_3$, equilibrium mixture of *cis* (13%) and *trans* (87%) isomers) δ 1.23s (*cis*) and 1.53s (*trans*), 4.94s (*trans*) and 5.22s (*cis*), 7.34d, 7.37d, 7.42t; $^{13}C$ ($CDCl_3$, *trans* isomer) 27.6, 76.0, 85.8, 126.4, 131.0, 135.4, 135.8, 159.7; **7l** : mp 39 °C, $^1H$ NMR ($CDCl_3$, equilibrium mixture of *cis* (20%) and *trans* (80%) isomers) δ 1.17s (*cis*) and 1.54s (*trans*), 5.45s (*trans*) and 5.52s (*cis*), 7.29d (*trans*), 7.38d (*cis*), 7.52d. Anal. calcd. C 44.40, H 3.73, N 4.32; found C 44.65, H 4.0, N 4.05.
14. Imine **12** was prepared by reaction of **11** (see for example ref. 3) with FMOC-Cl ($CHCl_3$, rt, 3 h); white solid, $^1H$ NMR ($CDCl_3$) δ 4.37t, 4.57d, 7.24-7.68m, 7.77d, 7.95d, 8.89s.
15. Oxaziridine **13** : white solid, $^1H$ NMR ($CDCl_3$) δ 4.29t, 4.58d, 4.91s, 7.24-7.49m, 7.61t, 7.74t; $^{13}C$ NMR 46.6, 69.7, 78.3, 120.1, 125.1, 127.3, 127.9, 128.0, 128.7, 131.2, 131.9, 141.3, 142.8, 162.2.
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