Tetrahedron Letters 49 (2008) 7383–7385

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Electrophilic amination of diorganozinc reagents by oxaziridines

Mohammed Ghoraf, Joëlle Vidal *

*Université de Rennes 1, CNRS UMR 6510, Laboratoire de Chimie et Photonique Moléculaires, Bâtiment 10A, Campus de Beaulieu, 35042 Rennes Cedex, France*

ARTICLE INFO

*Article history:*
Received 19 September 2008
Revised 8 October 2008
Accepted 10 October 2008
Available online 17 October 2008

*Keywords:*
Electrophilic amination
Oxaziridine
Diorganozinc reagent

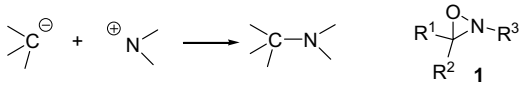
ABSTRACT

Electrophilic amination of organozinc reagents by oxaziridines has been studied. Diorganozinc reagents $R_2Zn$ (R = alkyl or aryl) react with *N*-Boc oxaziridine to afford *N*-Boc protected primary amines BocNHR in moderate to good yields. No additives are needed in this reaction, which proceeds at 0 °C. We suggest that the presence of two heteroatoms in oxaziridine allows Lewis base activation of the diorganozinc reagent.

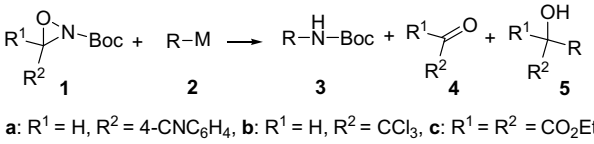
© 2008 Elsevier Ltd. All rights reserved.

Numerous amination methods have been developed for the synthesis of amines, which are of fundamental interest in many fields of chemistry.[1] Electrophilic amination is an attractive method for the C–N bond construction since organometallic reagents (carbanionic reagents) are widely used and thus, several [$NH_2^+$] synthons have been developed (Scheme 1).[2]

Among them, correctly N-substituted oxaziridines **1** ($R^3$ = H, COR, $CO_2R$, CONRR') behave as useful aminating reagents,[3] and we previously reported that *N*-alkoxycarbonyl oxaziridines **1** ($R^3 = CO_2R$) transferred their *N*-alkoxycarbonyl group to amines very efficiently in order to synthesize N-protected hydrazines in high yields and mild conditions.[4] Only a few examples of oxaziridine-mediated organometallic amination have been reported. Stabilized alkali enolates have been aminated by *N*–H oxaziridines **1** ($R^3$ = H) to give, depending on the nature of the $R^1$ and $R^2$ substituents, either the free amine or the corresponding $R^1COR^2$ imine.[3b,5] Moreover, nitrile or ester substituents in the substrate were hydrolyzed and sometimes, in the case of ester, further decarboxylation occurred. *N*-Alkoxycarbonyl oxaziridines were also used to aminate alkali enolates or carbanions.[4a,b,6] Although useful stable N-protected α-amino ketones were obtained in one step within a few minutes at −78 °C, yields were low (16–39%) due to competing aldol reaction producing **5** from the co-product **4** and the starting enolate (Scheme 2). Extensive studies of the reaction conditions and modifications of the oxaziridine structure resulted in slight improvement of the yields.[6b–d]



**Scheme 1.** C–N bond formation by an electrophilic amination reaction and oxaziridine general formula.



**a**: $R^1$ = H, $R^2$ = 4-$CNC_6H_4$, **b**: $R^1$ = H, $R^2 = CCl_3$, **c**: $R^1 = R^2 = CO_2Et$

**Scheme 2.** Electrophilic amination of organometallic reagents **2** with *N*-Boc oxaziridines **1**.

We reasoned that the use of organozinc reagents **2**, known for their low reactivity towards aldehydes or ketones,[7] would avoid the formation of by-product **5**. Herein we report that *N*-Boc oxaziridine **1a** reacts with diorganozinc reagents **2** (M = ½Zn) to afford *N*-Boc protected primary amines **3** in moderate to good yields (Scheme 2). No catalyst is needed in this reaction, which proceeds at 0 °C.

At first, we studied amination of three classes of organozinc reagents **2**: organozinc halides (M = ZnX), diorganozincs (M = ½Zn) and lithium triorganozincates (M = 1/3ZnLi).[7b,7c] Only a few electrophilic aminating reagents have been reacted so far with these organozinc reagents. A former publication described sluggish amination of diethylzinc with chloramines in 46% yield.[8] No catalyst was needed to react di-*tert*-butyl azodicarboxylate (BocN=NBoc) with organozinc halides or functionalized arylazotosylates (ArN=$NSO_2$Ar) with organozinc halides and diorganozincs to give the corresponding hydrazines.[9,10] A further in situ cleavage of the N–$NSO_2$Ar bond led to secondary amines in 45–79% overall

* Corresponding author. Tel.: +33 2 23 23 57 33; fax: +33 2 23 23 69 78.
*E-mail address:* joelle.vidal@univ-rennes1.fr (J. Vidal).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.10.049

**Table 1**
Reactivity of organometallic reagent **2** (R = *n*Bu, M = ZnI, ½Zn, 1/3ZnLi, Li) with oxaziridine **1a** ($R^3$ = Boc)

| Entry | Organometallic reagent **2** | Solvent | Conditions | Yield **3** (%) | Yield **5a** (%) |
|---|---|---|---|---|---|
| 1 | *n*BuZnI | $Et_2O$ | rt, 20 h | No reaction | |
| 2 | $nBu_2Zn$ | $Et_2O$/hexane 5:1 | 0 °C, 35 min | 57 | — |
| 3 | $nBu_3ZnLi$ | THF/ $Et_2O$/ hexane 6:1:2 | 0 °C, 30 min | 16 | 27 |
| 4 | *n*BuLi | THF/hexane 4:1 | −78 °C, 10 min | 15 | 35 |

yields.[10] With other electrophilic aminating agents, *O*-acyl-N-substituted hydroxylamines (RR′N–OCOR″) or acetone-*O*-arylsulfonyloxime ($Me_2C$=N–$OSO_2Ar$), copper catalysis was needed to allow for the preparation of, respectively, a wide range of secondary and tertiary amines from diorganozinc reagents (43–98% yields),[11] or aryl and benzyl primary amines from organozinc halides, diorganozincs and bromomagnesium triorganozincates (30–95% yields).[12] Our work began by studying the reactivity of organozinc reagents **2** (M = ZnI, ½Zn, 1/3ZnLi) with commercially available oxaziridine **1a**.[4a,b] Results are reported in Table 1.

Butylzinc iodide, pre-prepared from BuI and activated Zn,[7b,c] did not react at room temperature (entry 1). Dibutylzinc was preformed from *n*BuLi in hexanes and freshly fused anhydrous $ZnCl_2$ (0.5 equiv) in anhydrous ether (entry 2).[7b,c] We were pleased to find that reaction with oxaziridine **1a** (molar ratio 1:1) was complete within a few minutes (30 min) at 0 °C, without any additive. Moreover, alcohol **5a** was not detected by TLC. After acidic work-up and purification by chromatography, N-protected butylamine **3** was isolated in 57% yield. Reaction of $Bu_3ZnLi$, pre-prepared from BuLi in hexanes and anhydrous $ZnCl_2$ (0.33 equiv) in THF,[7b,c] with **1a** (molar ratio 1:1) occurred in a short time at 0 °C (entry 3). However, *N*-Boc butylamine was isolated in a low yield, along with alcohol **5a**. The use of *n*BuLi, which reacted with **1a** at −78 °C, gave yields of **3** and **5a** similar to those obtained with the lithium zincate reagent (entry 4).

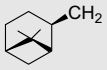
Having identified that dibutylzinc is the best reagent for electrophilic amination by oxaziridine **1a**, optimization of the reaction conditions was conducted using commercial diethylzinc in hexanes (Table 2). Diethylzinc and oxaziridine **1a** (1:1 ratio) in a 5:1 mixture of $Et_2O$ and hexane gave within 30 min at 0 °C *N*-Boc ethylamine in 67% isolated yield (entry 1). Other *N*-Boc oxaziridines, **1b**[4c] and **1c**,[13] were used since kinetics of their reaction with nitrogen nucleophiles is known to greatly depend on the $R^1$ and $R^2$ substitutents.[4a–c] As expected, reaction with oxaziridine **1b** took place at −50 °C overnight (entry 2). However, pure *N*-Boc ethylamine could not be obtained after chromatography on silica gel because of the presence of chloral **4b**. The use of oxaziridine **1c** did not improve the yield (entry 3). Nevertheless, its high aminating ability allowed reaction with BuZnI in ether (0 °C, 1 h) to give *N*-Boc butylamine in 38% yield (data not shown, see also Table 1, entry 1). An experiment using a 0.5:1 ratio of $Et_2Zn$ and **1a** showed that only one ethyl residue of diethyl zinc could be aminated at 0 °C (entry 4). Increasing hexane content of the solvent resulted in a better yield (entry 5).

**Table 2**
Amination of diethylzinc with oxaziridines **1a–c** ($R^3$ = Boc)

| Entry | Oxaziridine | Solvent $Et_2O$/ hexane | $Et_2Zn$: **1** ratio | T (°C) | Reaction time | Yield of EtNHBoc (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | 5:1 | 1:1 | 0 | 30 min | 67 |
| 2 | **1b** | 5:1 | 1:1 | −50 | 22 h | Impure |
| 3 | **1c** | 5:1 | 1:1 | 0 | 105 min | 34 |
| 4 | **1a** | 5:1 | 0.5:1 | 0 | 60 min | nd[a] |
| 5 | **1a** | 1:4 | 1:1 | 0 | 30 min | 74 |

[a] nd: not determined. $^1$H NMR analysis of the crude product indicated a 1:1 mixture of EtNHBoc and **2a**.

**Table 3**
Amination of $R_2Zn$ with oxaziridine **1a** in 1:4 $Et_2O$/hexane mixture at 0 °C

| Entry | R | Reaction time (min) | Yield of **3** (%) |
|---|---|---|---|
| 1 | *n*Bu | 40 | 71 |
| 2 | *s*Bu | 60 | 28 |
| 3 | *t*Bu | 60 | 21 |
| 4 | Cyclohexyl | 120 | 40 |
| 5 |  | 330 | 39[a] |
| 6 | Phenyl | 120 | 43 |
| 7 | 4-Methoxyphenyl | 90 | 29 |

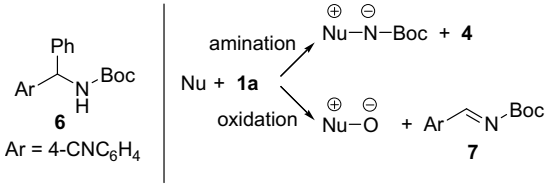
[a] New compound: $[\alpha]_D$ −10.5 (*c* 1, MeOH), mp = 60 °C.

These optimized reaction conditions (0 °C, hexane as the major solvent constituent, oxaziridine **1a**) allowed us to synthesize several *N*-Boc primary amines in 21–71% yields (Table 3).[14] The yield of *N*-Boc butylamine was increased under these conditions (entry 1 and Table 1, entry 2). Steric hindrance of dialkylzincs, pre-prepared from corresponding organolithium and anhydrous $ZnCl_2$ in ether,[7b,c] resulted in longer reaction times and reduced yields (entries 2–4).

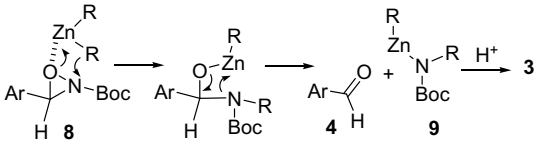
Optically active *N*-Boc *cis*-pinan-2-ylmethyl amine was obtained in 39% yield from the corresponding enantiopure chiral diorganozinc reagent prepared from (−)-β-pinene (entry 5).[15] Amination of diarylzinc reagents, pre-prepared from the corresponding Grignard reagent, proceeded in fair yields even in the absence of magnesium salts which were precipitated in dioxane and then filtered (entries 6–7).[7b,c] In the case of diphenylzinc, solvent composition proved to be essential since reaction at 0 °C in ether/dioxane resulted in a very complex mixture from which unexpected *N*-Boc amine **6** was isolated in 35% yield (Scheme 3).[16]

Depending on the nature of the nucleophile (amine, phosphine or sulfide) and of the solvent, oxaziridine **1a** was shown to behave as an aminating reagent and also as an oxidant (Scheme 3).[4b] Parallel oxidation of $Ph_2Zn$ by **1a** producing *N*-Boc imine **7** may have occurred in ethereal solvent. As **7** is an excellent Michael acceptor,[17] its further trapping by diphenylzinc may be postulated to explain isolation of **6**.

The presence of two heteroatoms and a weak N–O bond in oxaziridine **1a** seems to be essential to explain its high reactivity towards diorganozinc reagents (Scheme 4). We propose that the




**Scheme 3.** Compound **6** formula and competitive amination or oxidation of nucleophile Nu by *N*-Boc oxaziridine **1a**.




**Scheme 4.** Plausible mechanism for dialkylzinc amination by *N*-Boc oxaziridine **1a**.

oxygen atom of oxaziridine **1a** acts as a Lewis base which coordinates to the zinc atom to form zincate complex **8.** So, attack of the electrophilic nitrogen by the organo moiety R is activated and followed by fragmentation of the adduct to give **4** and **9**. Similar activation of intermediate **9** is probably disfavoured because of a weaker Lewis acidity, so resulting in no transformation of the second organo moiety R. In order to promote the amination reaction, competing Lewis bases such as ethereal solvent must be avoided.

In conclusion, we have shown that *N*-Boc oxaziridine **1a** reacts with diorganozinc reagents **2** (M = ½Zn) without any additives at 0 °C in hexane/ether solvent. We suggest that the presence of two heteroatoms in oxaziridine **1a** allows Lewis base activation of this reaction. Furthermore, *N*-Boc protected primary amines are obtained in fair to good yields.

## Acknowledgements

Université de Rennes 1 and CNRS (UMR 6510) are acknowledged for financial support. M.G. thanks the Ministère de l'enseignement supérieur et de la recherche for a doctoral fellowship. We gratefully acknowledge Nicolas Richy for technical help and Dr. Émilie Genin for critical reading of the manuscript.

## References and notes

1. (a) For recent general reviews: Ricci, A., Ed.Modern Amination Methods; Wiley-VCH & Sons: Weinheim, 2000; (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (c) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166; (d) Ricci, A., Ed.Amino Group Chemistry: From Synthesis to the Life Sciences; Wiley-VCH & Sons: Weinheim, 2007.
2. For recent reviews: (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947–1980; (b) Greck, C.; Genêt, J.-P. *Synlett* **1997**, 741–748; (c) Dembech, P.; Seconi, G.; Ricci, A. *Chem. Eur. J.* **2000**, *6*, 1281–1286; (d) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377–1385; (e) Erdik, E. *Tetrahedron* **2004**, *60*, 8747–8782.
3. For reviews on oxaziridines (a) Davis, F. A.; Chen, B.-C.; Zhou, P. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; Vol. 1, pp 559–621; (b) Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327–341.
4. (a) Vidal, J.; Guy, L.; Sterin, S.; Collet, A. *J. Org. Chem.* **1993**, *58*, 4791–4793; (b) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691–1709; (c) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845–8848; (d) Hannachi, J.-C.; Vidal, J.; Mulatier, J.-C.; Collet, A. *J. Org. Chem.* **2004**, *69*, 2367–2373.
5. (a) Andreae, S.; Schmitz, E.; Wulf, J. P.; Schulz, B. *Liebigs Ann. Chem.* **1992**, 239–256; (b) Page, P. C. B.; Limousin, C.; Murrell, V. L. *J. Org. Chem.* **2002**, *67*, 7787–7796.
6. (a) Enders, D.; Poiesz, C.; Joseph, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3709–3716; (b) Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron Lett.* **2000**, *41*, 2247–2251; (c) Armstrong, A.; Atkin, M. A.; Swallow, S. *Tetrahedron: Asymmetry* **2001**, *12*, 535–538; (d) Armstrong, A.; Edmonds, I. D.; Swarbrick, M. E.; Treweeke, N. R. *Tetrahedron* **2005**, *61*, 8423–8442.
7. (a) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: New York, 1996; (b) Knochel, P.; Jones, P. *Organozinc Reagents, A Practical Approach*; Oxford University Press: Oxford, 1999; (c) Nakamura, E. Organometallics in Synthesis. In Schlosser, M., Ed.; John Wiley & Sons: Chichester, 2002; pp 579–664; (d) *The Chemistry of Organozinc Compounds (Pata Series)*; Rappoport, Z., Marek, I., Eds.; Wiley-VCH & Sons: Chichester, 2006.
8. Coleman, G. H.; Hermanson, J. L.; Johnson, H. L . *J. Am. Chem. Soc.* **1937**, *59*, 1896–1897.
9. Velarde-Ortiz, R.; Guijarro, A.; Rieke, R. D. *Tetrahedron Lett.* **1998**, *39*, 9157–9160.
10. Sinha, P.; Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 3741–3744.
11. (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681; (b) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799–1801; (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219–224; (d) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364–366.
12. (a) Erdik, E.; Daşkapan, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3139–3142; (b) Daşkapan, T. *Tetrahedron Lett.* **2006**, *47*, 2879–2881.
13. Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.* **2005**, *7*, 713–716.
14. *Typical experimental procedure*: Under argon, commercial *n*BuLi in hexanes (1.6 M, 1.5 mL, 2.4 mmol) was added dropwise to a Schlenk tube cooled at 0 °C and containing $ZnCl_2$ in ether (1 M, 1.2 mL, 1.2 mmol) and anhydrous ether (3 mL). After 30 min. at 0 °C, the mixture was concentrated in vacuo to ca. 2 mL. This solution was added at 0 °C to a mixture of anhydrous hexane (7 mL), anhydrous ether (1 mL) and oxaziridine **1a** (242 mg, 1 mmol). After 40 min at 0 °C, TLC analysis showed that **1a** was consumed. Then aqueous HCl (0.15 M, 10 mL) was added to the reaction mixture. After extraction of the aqueous phase by ether (2 × 5 mL), the combined organic phases were successively washed by aqueous 1 M $NaHCO_3$ and water, then dried over $Na_2SO_4$ and concentrated in vacuo. Flash chromatography on silica gel (15 g, ether/AcOEt 95:5) afforded *N*-Boc butylamine (123 mg, 71%) as an oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.84 (t, $J$ = 7.2 Hz, 3 H), 1.25–1.41 (m, 13 H), 3.02 (m, 2 H), 4.57 (br s, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 12.7, 18.9, 27.4, 31.2, 39.3, 77.9, 155.0.
15. Langer, F.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 4591–4594.
16. *Compound* 6: white solid, mp 106 °C, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.45 (s, 9 H), 5.17 (br s, 1 H), 5.92 (br s, 1 H), 7.19–7.21 (m, 2 H), 7.31–7.36 (m, 3 H), 7.41 (d, $J$ = 8.3 Hz, 2 H), 7.64 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 28.3, 80.4, 111.1, 118.7, 127.5, 127.7, 128.1, 129.1, 129.9, 132.4, 132.8, 140.6, 154.9. EI-HRMS: $m/z$ calcd for $C_{15}H_{12}N_2O_2$ $[M-C_4H_8]^+$: 252.0900; found: 252.0891.
17. (a) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171; (b) Kantam, M. L.; Mahendar, K.; Sreedhar, B.; Choudary, B. M. *Tetrahedron* **2008**, *64*, 3351–3360; (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866–5867; (d) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707–1710; (e) Wu, P.; Sun, J. *Synth. Commun.* **2008**, *38*, 1003–1010; (f) Zhang, Y.; Liu, Y.-K.; Kang, T.-R.; Hu, Z.-K.; Chen, Y.-C. *J. Am. Chem. Soc.* **2008**, *130*, 2457–2459.