A New and Practical Procedure for the Bruylants Reaction. Zinc-Mediated Synthesis of Tertiary Homoallylamines and β-Aminoesters

Luca Bernardi,* Bianca F. Bonini, Elena Capitò, Gabriella Dessole, Mariafrancesca Fochi, Mauro Comes-Franchini, Alfredo Ricci*

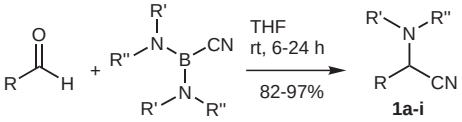
Dipartimento di Chimica Organica 'A. Mangini', Facoltà di Chimica Industriale, Università di Bologna, V. Risorgimento 4, 40136 Bologna, Italy
Fax +39(51)2093654; E-mail: nacca@ms.fci.unibo.it
Received 23 June 2003

Abstract: *N,N*-Disubstituted α-aminonitriles undergo Bruylants reaction under Barbier and Reformatsky conditions with activated halides, in the presence of zinc and 10 mol% HOAc. The high yields and the simple operational conditions make this reaction an appealing approach to *N,N*-disubstituted homoallylamines and β-aminoesters.

Key words: α-aminonitriles, Bruylants reaction, tertiary amines, zinc, metathesis

α-Aminonitriles are very popular bifunctional compounds useful not only as synthetic intermediates for α-aminoacids, but also as versatile synthons in organic chemistry.[1] The Strecker reaction which involves treatment of aldehydes with ammonia and hydrogen cyanide (or equivalents) provides one of the most popular and widely used routes to α-aminonitriles and has been applied on an industrial scale towards the synthesis of racemic α-aminoacids via hydrolysis of the intermediate α-aminonitriles. Moreover an emerging field of importance deals[2] with direct and viable methods for the synthesis of homochiral α-aminonitriles via catalytic asymmetric Strecker-type reactions. Besides these well established methodologies, very recently a Strecker-type aminative cyanation of aldehydes and ketones using bis(dialkylamino)cyanoboranes has been reported[3] disclosing a general and highly flexible new entry to these synthetically useful building blocks (Scheme 1). Regarding the further synthetic elaborations, whereas the hydrolysis and the reduction of the cyano group in *N,N*-disubstituted α-aminonitriles are well documented,[1a] the reaction sequence involving the addition of an organometallic reagent to the nitrile group, with formation of the intermediate imine, is more problematic. As a matter of fact only in particular circumstances[4] the addition reaction prevails over the replacement of the cyano group by a C-nucleophile. The latter pathway, known as Bruylants reaction, is an old widely used procedure[5] for the preparation of α-substituted tertiary amine moieties.[6] In the course of our ongoing research program aimed at the synthesis of new core units for HIV protease inhibitors,[7] we became interested in the synthesis of α-aminonitriles and in their reactivity towards organometallic reagents. Herein we report a general, concise and very simple procedure based on an unprecedented combination between the Bruylants and the Barbier or Reformatsky-type reactions, aimed at the straightforward transformation of α-aminonitriles into *N,N*-disubstituted homoallylic amines and β-aminoesters.

The α-aminonitriles **1a**–**i** were synthesized in very good yields following Suginome's procedure[3] (Scheme 1) using simple aldehydes and different bis(dialkylamino)cyanoboranes[8] as starting materials (Table 1).



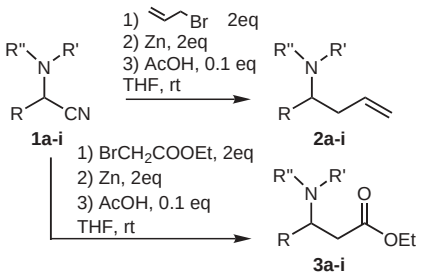
Scheme 1

Besides dialkyl substituted aminonitriles, we successfully extended this synthesis to derivatives bearing a reactive framework at nitrogen, e.g. a double bond, and removable groups, such as the benzyl and the *p*-methoxybenzyl (PMB) groups (entries 7–9).

Though several variants in the use of the Bruylants reaction have been proposed so far, the use of preformed organometallic species and the frequent presence of stoichiometric amounts of additives such as $AgBF_4$ or AgOTf[6b,d] are common features of these reactions. In our approach to a revisited version of the Bruylants reaction, inspired by our recent findings in the indium-mediated addition of reactive halides to unsaturated N-containing molecules,[9] we envisaged the possibility of using a Barbier–type protocol to generate in situ the organometallic species.

Barbier-type allylation reaction of phenyl-(1-pyrrolidinyl)acetonitrile (**1a**) mediated by metals was extensively examined. Using indium this reaction proved to be inefficient and not reproducible. However, when mediated by zinc and in THF as the solvent, the same reaction was usually complete in less than 2 h to give the tertiary homoallylamine **2a** in good yield. A standard procedure using 2 equivalents of activated halide with respect to the starting α-aminonitrile followed by 2 equivalents of powdered zinc soon emerged as the best reaction conditions. The addition of a small amount of HOAc (10 mol%) was found to be crucial for the reaction to proceed (Scheme 2). At the

SYNLETT 2003, No. 12, pp 1778–1782
Advanced online publication: 19.09.2003
DOI: 10.1055/s-2003-41471; Art ID: G14603ST



Scheme 2

present state of the research, no other metals have been tested.

All the α-aminonitriles **1b**–**i** synthesised so far were then treated under the optimised conditions, furnishing the corresponding homoallylamines **2b**–**i** in good yields and purity in most cases, after basic work up (aq Na_2CO_3) and chromatography on silica gel or neutral alumina, to separate oligomeric by-products, formed in small amounts during the reaction (Table 1).[10] While both aliphatic and aromatic groups are well tolerated in α position to the cyano group (entries 1–3), the successful outcome of the allylation rather relies upon the substituents at nitrogen, since we observed a lowering in the yields when the steric hindrance becomes too severe, as in the case of the *N*,*N*-dibenzyl derivative **1g** (entry 7), or in the case of the morpholino derivative **1f** (entry 6). It is worthy to note that in these cases we could obtain an improvement in the yields by heating the reaction mixture to reflux for a few minutes immediately after the addition of HOAc.

We assume that the reaction proceeds through the formation of a highly reactive iminium ion (Figure 1),[11] as it is evidenced by the isolation of the corresponding homoallylic alcohol when the reaction was performed in wet THF. The role of HOAc is not clear at the moment, although we believe that it might be necessary for the activation of the metal surface thus facilitating the subsequent formation of the organozinc species.[12] However, we cannot exclude an involvement of the acid in the formation of the iminium ion, since it is known that Brønsted acids can promote the displacement of the cyano group in *N*,*N*-disubstituted α-aminonitriles.[1b]

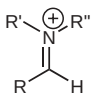
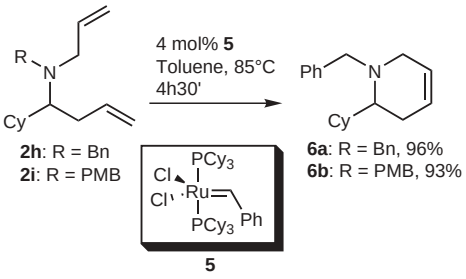


Figure 1 Postulated reaction intermediate

Inspired by the work of Mosset,[13] who also reported a 'Reformatsky-type' addition to iminium ions generated from enamines, we turned our attention to a different activated halide, namely ethyl bromoacetate.[14] And indeed, the 'Reformatsky-type' reaction, performed under the same conditions with aminonitriles **1a**–**i**, led to the expected tertiary β-aminoesters **3a**–**i** (Scheme 2).[10] Moreover, in this case the products were obtained in good yields and purity irrespectively of the steric hindrance of the substituents at nitrogen (Table 1).

The experimental procedure described here is straightforward and does not require the handling of reactive organometallic reagents or the use of stoichiometric amounts of metal salts to promote the formation of the intermediate iminium ion.[6b,d] Moreover, the scarce basicity of the organometallic species involved should prevent the deprotonation of the α-aminonitrile or of the intermediate iminium ion,[6b] which are often side reactions in Bruylants transformations.

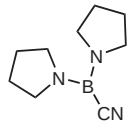
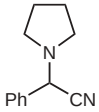
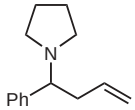
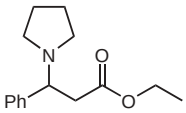
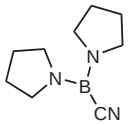
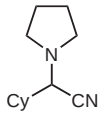
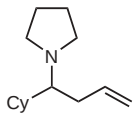
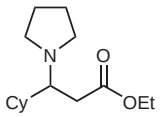
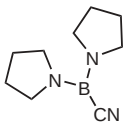
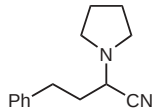
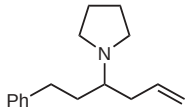
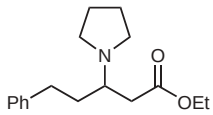
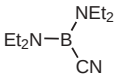
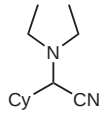
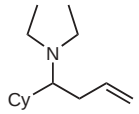
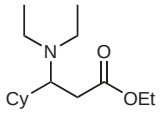
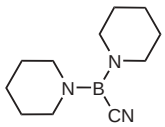
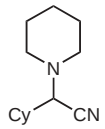
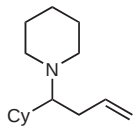
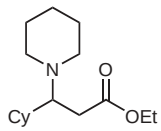
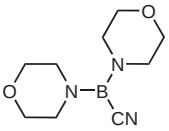
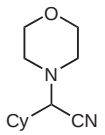
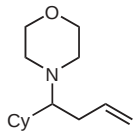
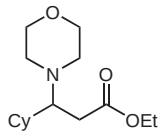
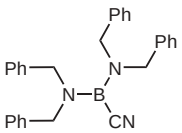
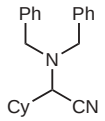
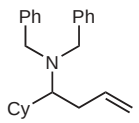
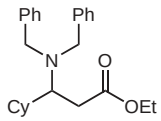
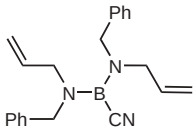
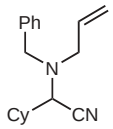
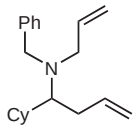
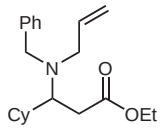
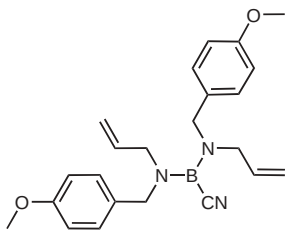
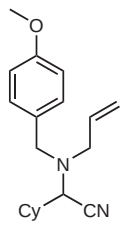
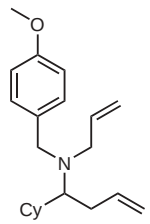
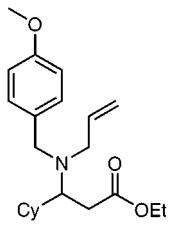
The possibility of obtaining tertiary homoallylamines bearing a double bond at nitrogen can be chemically exploited to synthesise, via ring closing metathesis (RCM), simple nitrogen containing heterocycles, such as the tetrahydropyridines **6a**,**b**,[15] employing Grubbs' catalyst **5** (Scheme 3).[16] Since the Bruylants reaction and the RCM tolerate well both benzyl and PMB protecting groups, the latter removable without affecting the double bond,[17] this sequence could represent in principle a simple and rapid access to unprotected 2-substituted piperidines and 1,2,3,6-tetrahydropyridines, structures widely found in biologically active natural products and pharmaceuticals.[18]



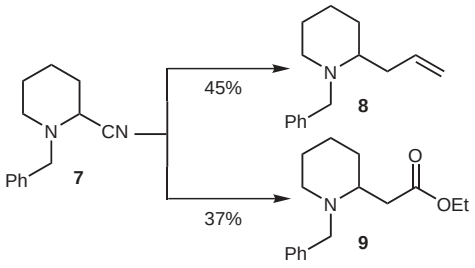
Scheme 3

Moreover, we thought that this new and simple protocol for the Bruylants reaction could be a useful tool in alkaloid chemistry for the introduction of reactive side chains in nitrogen containing heterocycles. To this purpose, we performed, on the *N*-benzyl-2-cyano-piperidine **7**,[19] both the Barbier and the 'Reformatsky-type' reactions obtaining the substituted piperidines **8** and **9**, respectively, albeit in modest yields (Scheme 4). In this particular case, however, the Reformatsky reaction is much more efficient, in terms of the yield of **9**, when carried out with a pre-formed organozinc species.[14] Moreover, even though also direct addition of organozinc reagents to the iminium ion precursor of **7**[19] might afford compounds **8** and **9**, a limit of this more straightforward route could lie in the possible incompatibility of the organometallic species with the conditions of the modified Polonovski–Potier reaction.

Table 1 Cyanoboranes, α-Aminonitriles and Products Obtained by the Bruylants Reaction under Barbier and Reformatsky Conditions

Entry	Bis(dialkylamino)cyano boranes	α-Aminonitriles **1** (isolated yield%)	Homoallylamines **2** (isolated yield%)	β-Aminoesters **3** (isolated yield%)
1		 **1a** (88)	 **2a** (65)	 **3a** (75)
2		 **1b** (86)	 **2b** (82)	 **3b** (45)
3		 **1c** (90)	 **2c** (75)	 **3c** (50)
4		 **1d** (86)	 **2d** (92)	 **3d** (75)
5		 **1e** (93)	 **2e** (77)	 **3e** (87)
6		 **1f** (90)	 **2f** (Traces, 66[a])	 **3f** (80)
7		 **1g** (94)	 **2g** (15, 38[a])	 **3g** (87)
8		 **1h** (97)	 **2h** (67)	 **3h** (70)
9		 **1i** (82)	 **2i** (72)	 **3i** (84)

[a] Heating the reaction mixture to reflux for 2 min after the addition of HOAc.



Scheme 4

In summary, we developed a new procedure for the Bruylants reaction, simply consisting in mixing an α-aminonitrile, an activated halide and zinc powder in THF, in the presence of 10 mol% HOAc. The method presented here therefore avoids the use of preformed organometallic species and does not need stoichiometric metal salts to promote the loss of the cyano group. The resulting tertiary homoallylamines and β-aminoesters are generally formed in good yields and can be used for further synthetic transformations.

Further studies will be aimed at clarifying the mechanism of the reaction, with particular attention at the role played by HOAc. Moreover, the scope of the reaction will be expanded to other activated halides.

Acknowledgement

The financial support by the University of Bologna (Funds for Selected Research Topics, A. A. 1999–2001), by the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' 2002–2003, and by the ex-60% MURST-Funding 2002 is gratefully acknowledged.

References

(1) (a) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148. (b) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (c) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

(2) Yet, L. *Angew.Chem. Int. Ed.* **2001**, *40*, 875; and references therein.

(3) Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, 1392.

(4) Leclerc, E.; Vrancken, E.; Mangeney, P. *J. Org. Chem.* **2002**, *67*, 8928.

(5) Bruylants, P. *Bull. Soc. Chim. Belg.* **1924**, *33*, 467.

(6) For recent examples of the use of the Bruylants reaction in synthesis, see: (a) Enders, D.; Thiebes, C. *Synlett* **2000**, 1745. (b) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085. (c) Suau, R.; Najera, F.; Rico, R. *Tetrahedron* **2000**, *56*, 9713. (d) Schneider, C.; Börner, C. *Synlett* **1998**, 652. (e) Bonjoch, J.; Fernàndez, J.-C.; Terricabras, D.; Valls, N. *Tetrahedron* **1997**, *53*, 9407. (f) Yue, C.; Gauthier, I.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 4949. (g) Hammon, J.; Vignon, J.; Kamenka, J. M. *Eur. J. Med. Chem.* **1996**, *31*, 489. (h) Bacque, E.; Paris, J.-M.; Le Bitoux, S. *Synth. Commun.* **1995**, *25*, 803. (i) Aitken, D. J.; Beaufort, V.; Chalard, P.; Cladière, J.-L.; Dufour, M.; Pereira, E.; Théry, V. *Tetrahedron* **2002**, *58*, 5933.

(7) Bernardi, L.; Bonini, B. F.; Dessole, G.; Fochi, M.; Comes-Franchini, M.; Gavioli, S.; Ricci, A.; Varchi, G. *J. Org. Chem.* **2003**, *68*, 1418.

(8) The cyanoboranes were obtained, according to ref.[3], using a one pot procedure starting from the corresponding *N*-silylamines, BCl_3 and TMSCN, and were directly used after evaporation of the solvent, without purification.

(9) Bernardi, L.; Cerè, V.; Femoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, *68*, 3348.

(10) **Zinc-Mediated Bruylants Reaction – General procedure:** To a stirred solution of the α-aminonitrile **1** (0.5 mmol) in dry THF (1 mL) were sequentially added allyl bromide or ethyl bromoacetate (1 mmol), zinc dust (1 mmol), and HOAc (0.05 mmol in 0.05 mL of dry THF). A slightly exothermic reaction occurred. The mixture was stirred at r.t. for 2 h, quenched with sat. Na_2CO_3 and then extracted three times with Et_2O. The organic extracts were dried ($MgSO_4$), filtered, evaporated and the crude product purified by chromatography on silica gel or neutral Al_2O_3 (hexane/EtOAc mixtures). Selected data for representative examples: **1-(1-Phenyl-3-butenyl)-pyrrolidine (2a).** Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.05 (m, 5 H), 5.53–5.39 (m, 1 H), 4.90–4.72 (m, 2 H), 3.06 (dd. *J* = 4.2, 9.3 Hz, 1 H), 2.65–2.55 (m, 1 H), 2.52–2.40 (m, 3 H), 2.38–2.20 (m, 2 H), 1.79–1.60 (m, 4 H). ^{13}C NMR (70 MHz, $CDCl_3$): δ = 142.5, 135.4, 128.2, 128.0, 126.9, 116.4, 70.9, 52.7, 40.5, 23.2. HRMS: exact mass calcd for $C_{14}H_{19}N$ [M + Na]$^+$ 224.1415. Found: 224.1399. ***N*-Allyl-*N*-benzyl-1-cyclohexyl-3-buten-1-amine (2h).** Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.08 (m, 5 H), 5.96–5.60 (m, 2 H), 5.17–4.80 (m, 4 H), 3.79 (d, *J* = 14.4 Hz, 1 H), 3.54 (d, *J* = 14.1 Hz, 1 H), 3.22 (ddt, J_t = 1.7 Hz, J_d = 4.9 Hz, J_d = 14.2 Hz, 1 H), 3.08 (dd, *J* = 7.5 Hz, *J* = 14.4 Hz, 1 H), 2.42–2.22 (m, 2 H), 2.18–2.03 (m, 1 H), 2.00–1.90 (m, 1 H), 1.70–1.50 (m, 4 H), 1.45–1.30 (m, 3 H), 1.22–0.71 (m, 3 H). ^{13}C NMR (70 MHz, $CDCl_3$): δ = 141.0, 139.0, 138.0, 128.7, 128.0, 126.5, 116.1, 115.1, 62.9, 54.4, 53.6, 40.7, 32.1, 31.1, 31.0, 26.7, 26.6. HRMS: exact mass calcd for $C_{20}H_{29}N$ [M + H]$^+$ 284.2378. Found: 284.2388. **Ethyl 3-Phenyl-(1-pyrrolidinyl)propanoate (3h).** Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.05 (m, 5 H), 3.88 (q, *J* = 7.2 Hz, 2 H), 3.63 (dd. *J* = 5.7, 9.0 Hz, 1 H), 2.90 (dd. *J* = 5.7, 14.7 Hz, 1 H), 2.63 (dd. *J* = 9.0, 14.7 Hz, 1 H), 0.99 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (70 MHz, $CDCl_3$): δ = 171.5, 141.5, 128.1, 128.0, 127.4, 66.4, 60.2, 52.1, 41.6, 23.2, 13.9. IR (thin layer): ν = 1728 cm^{-1}. HRMS: exact mass calcd for $C_{15}H_{21}NO_2$ [M + H]$^+$ 248.1651. Found: 248.1667. **Ethyl 3-[Allyl(benzyl)amino]-3-cyclohexylpropanoate (3h).** Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.18 (m, 5 H), 5.89–5.86 (m, 1 H), 5.21–5.02 (m, 2 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.75 (d, *J* = 14.1 Hz, 1 H), 3.43 (d, *J* = 14.1 Hz, 1 H), 3.18 (m, 1 H), 3.01–2.86 (m, 2 H), 2.58 (dd, *J* = 5.1 Hz, *J* = 15.0 Hz, 1 H), 2.26 (dd, *J* = 7.2 Hz, *J* = 15.0 Hz, 1 H), 2.18–2.14 (m, 1 H), 1.80–1.58 (m, 4 H), 1.40–1.05 (m, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 0.98–0.80 (m, 2 H). ^{13}C NMR (70 MHz, $CDCl_3$): δ = 173.8, 140.3, 137.3, 128.8, 128.0, 126.6, 116.6, 61.0, 60.3, 54.1, 53.1, 41.1, 33.3, 31.0, 30.3, 26.5, 26.4, 26.3, 14.2. IR (thin layer): ν = 1734 cm^{-1}. HRMS: exact mass calcd for $C_{21}H_{31}NO_2$ [M + Na]$^+$ 352.2252. Found: 352.2237.

(11) The addition of allylzinc species to preformed iminium ions has been previously reported: Courtois, G.; Harama, M.; Mi giniac, P. *J. Organomet. Chem.* **1981**, *218*, 275; see also ref. 6d.

(12) It has already been shown that HOAc is able to accelerate zinc-mediated allylation of aldehydes under Barbier conditions: Oda, Y.; Matsuo, S.; Saito, K. *Tetrahedron Lett.* **1992**, *33*, 97.
(13) (a) Bossard, F.; Dambrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.* **1995**, *34*, 6055. (b) Tussa, L.; Lebreton, C.; Mosset, P. *Chem.–Eur. J.* **1997**, *3*, 1064.
(14) A Bruylants reaction on *N*-benzyl-2-cyano-piperidine, involving a preformed organozinc species generated from ethyl bromoacetate has been once reported: Dartiguelongue, C.; Payan, S.; Duval, O.; Gomes, L. M.; Waigh, R. D. *Bull. Soc. Chim. Fr.* **1997**, *134*, 769.
(15) For a review of the application of RCM to the synthesis of nitrogen-containing compounds see: Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75.
(16) To a solution of homoallylamine **2** (0.11 mmol) in dry, degassed toluene (3.5 mL) was added ruthenium alkylidene **5** (4 mol%). The solution was stirred at 85 °C for 4 h 30 min, then pentane was added, followed by celite and charcoal. The mixture was stirred at r.t. overnight, then filtered and concentrated. Chromatography on silica gel (hexane/EtOAc) afforded tetrahydropyridines **6**.
(17) Smith, A. B. III; Leahy, J. W.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Am. Chem. Soc.* **1992**, *114*, 2995.
(18) Michael, J. P. In *The Alkaloids*, Vol. 55; Cordell, G. A., Ed.; Academic Press: San Diego, **2001**.
(19) *N*-Benzyl-2-cyano-piperidine was prepared in 62% yield by a modified Polonovski-Potier reaction, treating *N*-benzyl-piperidine *N*-oxide with TFAA and KCN (caution!), as described in the literature for similar compounds: Compernolle, F.; Ashty Saleh, M.; Van den Branden, S.; Toppet, S.; Hoornaert, G. *J. Org. Chem.* **1991**, *56*, 2386.