A Novel Synthesis of 2-Cyano-3,3-dimethylazetidines

Paul Sulmon, Norbert De Kimpe,* and Niceas Schamp

Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, State University of Gent, Coupure Links 653, B-9000 Gent, Belgium

A new route to 2-cyano-3,3-dimethylazetidines has been developed by reaction of β-chloroimines with potassium cyanide in methanol which involves nucleophilic addition and subsequent intramolecular nucleophilic substitution.

Azetidines have received considerable attention recently.[1—3] 2-Cyanoazetidines have already been prepared by hydrogen cyanide addition to 2,3-dihydro azetes,[4] by reaction of triphenylphosphine dibromide with azetidine-2-carboxamides,[5] or by ring contraction of α,γ-dibromopentanecarbonitriles with amines.[6] We now report a novel and simple synthesis of 2-cyano-3,3-dimethylazetidines (**3**) by reaction of β-chloroimines (**1**) with potassium cyanide in methanol under reflux (Table 1, Scheme 1). The yields are high and compounds (**3**) are produced exclusively. The formation of the four-membered heterocycle can be explained as originating from a nucleophilic addition of CN^- across the imino function, followed by intramolecular nucleophilic substitution and expulsion of Cl^-.

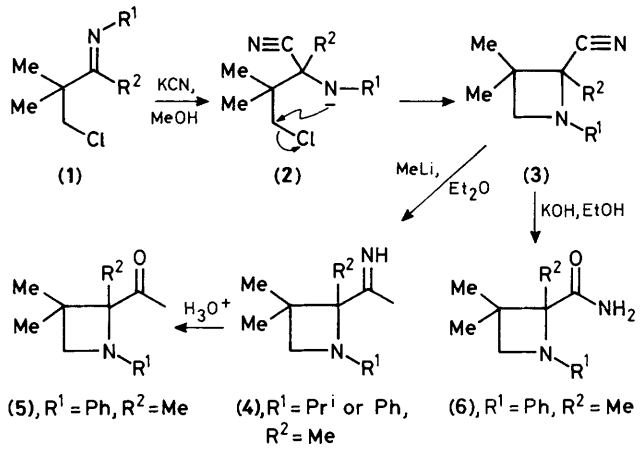
The stable cyanoazetidines (**3**) were converted quantitatively into the 2-imidoylazetidines (**4**) by reaction with methyl-lithium in diethyl ether, compounds (**4**) being hydrolysed to give the corresponding acylazetidines (**5**) in 80—90% yield with aqueous hydrogen chloride (Scheme 1). On reaction with potassium hydroxide in absolute ethanol the cyanoazetidines (**3**) were transformed into the carbamoyl derivatives (**6**) (Scheme 1).

The reactions of compounds (**1**) are analogous to those of

Table 1. Synthesis of 2-cyanoazetidines (**3**).[a]

R^1	R^2	Reflux time/h	% Yield of (**3**)
CH_2Ph	H	100	88[b]
Ph	Me	20	76[c,e]
CH_2Ph	Ph	6	93[b]
Bu^t	H	50	83[b]
CH_2Ph	Me	1	93[b]
Pr^i	Ph	12	89[b]
Pr^i	Me	2.5	82[d]; 96[b]

[a] Reaction conditions: KCN (2 equiv.) in methanol; all compounds gave spectral data (^1H and ^{13}C n.m.r., i.r., mass) in agreement with their structures and satisfactory analytical data. [b] Crude yield (no distillation, but purity >98%). [c] Yield after recrystallisation (m.p. 59 °C). [d] Yield after distillation (b.p. 82—85 °C). [e] ^{13}C N.m.r. ($CDCl_3$): 146.84 (s, quat. C), 129.08 (d, *meta*-C), 119.54 (d, *para*-C), 113.35 (d, *ortho*-C), 119.31 (s, C≡N), 66.55 (s, *C*C≡N), 60.80 (t, CH_2), 38.27 (s, *C*Me_2), 25.29, 22.28, and 20.33 (3 × q, 3 × Me); ^1H n.m.r. ($CDCl_3$): 1.34, 1.51, and 1.70 (each 3H, s, Me) 3.56 (2H, s, CH_2), and 6.60—7.60 (5H, m, Ph); i.r. (NaCl): ν (C≡N) 2230 cm^{-1}; *m/z* 200 (M^+, 14%), 174 (6), 173 (5), 145 (9), 144 (52), 143 (9), 129 (10), 118 (14), 117 (5), 106 (9), 105 (25), 104 (12), 91 (5), 78 (5), 77 (38), 55 (5), 51 (16), 44 (15), 43 (5), 42 (6), 41 (14), 40 (100), and 39 (10).



Scheme 1

the corresponding β-bromoketones with cyanide.[8] This high-yield synthesis of the cyanoazetidines (**3**) from β-chloroimines, which are easily accessible from the corresponding carbonyl compounds [hydroxymethylation using formaldehyde, followed by conversion into the chloro derivative (i, tosylation; ii, LiCl, dimethylformamide), then imine formation (analogous to ref. 9)], provides a new approach to this class of small heterocycles.[5,7] In addition, some 2-cyanoazetidines can be converted into useful medicinal products such as appetite depressants and products which can control obesity.[6]

We are indebted to the Belgian National Science Foundation and the I.W.O.N.L. for financial support.

Received, 18th February 1985; Com. 205

References

1 D. E. Davies and R. C. Storr, in 'Comprehensive Heterocyclic Chemistry', Vol. 7, Part 5, ed. W. Lwowski, Pergamon, Oxford, 1984, pp. 237—284.
2 J. A. Moore and R. S. Ayers, in 'Chemistry of Heterocyclic Compounds—Small Ring Heterocycles', Part 2, ed. A. Hassner, Wiley, New York, 1983, pp. 1—217.
3 N. H. Cromwell and B. Phillips, *Chem. Rev.*, 1979, **79**, 331.
4 J. C. Guillemin, J. M. Denis, and A. Lablache Combier, *J. Am. Chem. Soc.*, 1981, **103**, 468.
5 T. Masuda, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 3281.
6 E. H. Gold and D. M. Solomon, Ger. Offen 2 548 053 (1976), *Chem. Abstr.*, 1976, **85**, 46 359 g.
7 T.-Y Chen, M.-H. Hung, P.-T. Chen, and M. Ohta, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1179.
8 T. I. Temnikova, N. A. Venediktova, and S. N. Semenova, *Zh. Org. Khim.*, 1968, **4** (11), 2050.
9 N. De Kimpe, R. Verhé, L. De Buyck, L. Moens, and N. Schamp, *Synthesis*, 1982, 43.