Pergamon

Tetrahedron Letters 42 (2001) 3921–3923

TETRAHEDRON LETTERS

Grob-type fragmentation of *N*-alkyl-2-cyano-5-bromopiperidines to unsaturated imidoyl cyanides

Erick Rosas Alonso,[a] Kourosch Abbaspour Tehrani,[a,†] Mark Boelens,[a] David W. Knight,[b] Valentina Yu[c] and Norbert De Kimpe[a,*]

[a]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*

[b]*Department of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, UK*

[c]*Institute of Chemical Sciences, Department of Physiologically Active Substances, Chokan Valihanov Street, 480100 Almaty, Kazakhstan*

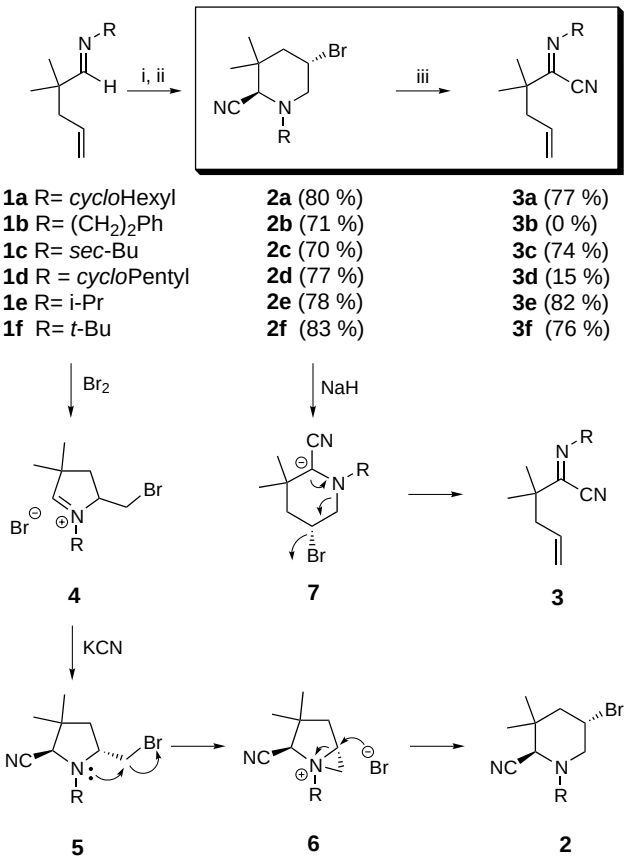
Received 19 February 2001; accepted 6 April 2001

Abstract—2-Cyano-5-bromopiperidines, derived from the stereoselective addition of cyanide to 5-bromomethyl-1-pyrrolinium salts, underwent a Grob fragmentation by reaction with sodium hydride in dimethylformamide, affording unsaturated imidoyl cyanides.

α-Imino nitriles (imidoyl cyanides) are a rather unexplored class of compounds. Although they were first cited long ago,[1] only a few reports regarding their synthesis have appeared in the literature.[2] Imidoyl cyanides, sometimes present as by-products in the synthesis of other compounds,[2c] have been utilized as precursors for the preparation of α,β-unsaturated imidoyl cyanides and α-alkylthio or other α-functionalized imidoyl cyanides.[3]

Previous routes to α-imino nitriles include the dimerization of isocyanides by $BF_3{\cdot}OEt_2$,[4] cyanation of imidoyl halides,[5] reaction of α,β-unsaturated aldehydes with α-(*N*-monoalkylamino)isobutyronitriles,[6] halogenation of α-cyanoenamines with *N*-halosuccinimides,[4] *N*-chlorination/dehydrochlorination of α-amino nitriles[2c,7] or reaction of acetals with *t*-butyl isocyanide/Et_2AlCl.[8]

In this paper, we wish to report a new method for the synthesis of imidoyl cyanides **3**. The synthetic strategy is depicted in Scheme 1. Our approach involves the electrophile-induced cyclization of easily accessible *N*-(4-penten-1-ylidene)amines **1**[9] by bromine in dichloromethane to yield the pyrrolinium species **4**,[10] which, after treatment with two equivalents of potassium cyanide in a biphasic system (THF/H_2O, 1:1), afforded 2-cyano-5-bromopiperidines **2** in good yields.[11]



1a R= *cyclo*Hexyl	**2a** (80 %)	**3a** (77 %)
1b R= $(CH_2)_2$Ph	**2b** (71 %)	**3b** (0 %)
1c R= *sec*-Bu	**2c** (70 %)	**3c** (74 %)
1d R = *cyclo*Pentyl	**2d** (77 %)	**3d** (15 %)
1e R= i-Pr	**2e** (78 %)	**3e** (82 %)
1f R= *t*-Bu	**2f** (83 %)	**3f** (76 %)

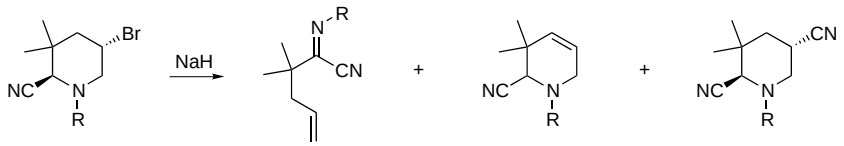
Scheme 1. *Reagents and conditions*: (i) 1 equiv. Br_2, CH_2Cl_2, 0°C, 20 min; (ii) 2 equiv. KCN, 1:1 THF:H_2O, rt, 4 h; (iii) 1.5 equiv. NaH, DMF, 40–80°C, 4–14 h.

Keywords: cyclization; piperidines; ring opening; Grob fragmentation; α-iminonitriles; imidoyl cyanides.

* Corresponding author. Tel.: +00 32 9 264 59 51; fax: +00 32 9 264 62 43; e-mail: norbert.dekimpe@rug.ac.be

† Postdoctoral Fellow of the F.W.O.-Flanders, Belgium.

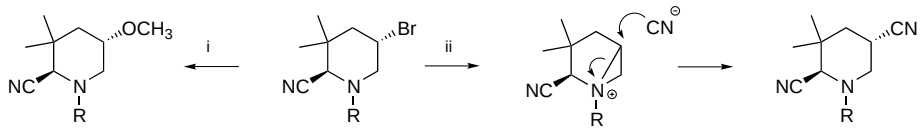
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00583-4



2a R= *cyclo*Hexyl	**3a** (77 %)	**8a** (0 %)
2b R= $(CH_2)_2Ph$	**3b** (0 %)	**8b** (53 %)
2c R= *sec*-Bu	**3c** (74 %)	**8c** (9 %)
2d R = *cyclo*Pentyl	**3d** (15 %)	**8d** (38 %)
2e R= i-Pr	**3e** (82 %)	**8e** (10 %)
2f R= *t*-Bu	**3f** (76 %)	**8f** (6 %)

9d (8 %)

Scheme 2.



10 (82 %) **2d** **11** **9d** (73%)

Scheme 3. *Reagents and conditions*: (i) 2 equiv. CH_3ONa, CH_3OH, Δ, 3 h; (ii) 1 equiv. KCN, CH_3OH, rt, 2 h.

These 2-cyanopiperidines, the formation of which can be rationalized through intermediates **5** and **6**, underwent a ring opening Grob-type elimination[12] when reacted with 1.5 equivalents of NaH in DMF, affording imidoyl cyanides **3**.[13]

The ring opening reaction of 2-cyanopiperidines **2** with sodium hydride led to the formation of side products **8**,[14] which were isolated during the purification of **3** (Scheme 2). The formation of these tetrahydropyridines **8** could not be avoided, even with smaller amounts of sodium hydride and lower temperatures. Interestingly, entry **2b** did not yield even a trace (GC) of the corresponding imidoyl cyanide upon treatment with sodium hydride. An explanation for this fact is still lacking. Surprisingly, the dicyanide **9d** constituted a third by-product arising during the course of the reaction of the 2-cyanopiperidine **2d** with sodium hydride.

The *trans* stereochemistry of **2** was determined based on previous data concerning *trans* stereoselective nucleophilic additions to cyclic iminium species.[15] Furthermore, the coupling constants for H-6_{eq} ($J=4.6$ Hz) in the ^1H spectrum of **2d** imply an equatorial–axial relationship with H-5. The bigger coupling constant of 11.5 Hz indicates an axial–axial relationship between H-6_{ax} and H-5.[16] A minimized energy molecular model of **2d** reveals an arrangement that matches this grouping.[17]

Additionally, compound **2d** was reacted with one equivalent of potassium cyanide in methanol, resulting in the formation of dicyanide **9d** (Scheme 3). The retention of configuration at C5 suggests that the mechanism operating is through the bicyclic species **11** by anchimeric assistance of the nitrogen atom. Treatment of **2d** with one equivalent of sodium methoxide afforded **10**, thus proving that no epimerization at C-2 could have occurred, even in the presence of base.

In short, a unique synthesis of unsaturated imidoyl cyanides has been accomplished. To the best of our knowledge, this Grob elimination represents a new general approach to the preparation of this type of compound, starting from an azaheterocycle. Possible synthetic applications of imidoyl cyanides **3** will be further explored, as they represent potential precursors towards the synthesis of a variety of other compounds.

Acknowledgements

The 'Fund for Scientific Research-Flanders (Belgium)' (F.W.O.-Vlaanderen), the IWT and INTAS (Grant 97-00217) are greatly acknowledged for financial support. E.R.A. is indebted to the Mexican National Council for Science and Technology (CONACyT).

References

1. Sachs, F. *Berichte* **1901**, *34*, 494–495.
2. See for instance: (a) Sandhu, J. S.; Mohan, S.; Kapoor, A. L. *Chem. Ind.* **1971**, *9*, 504–505; (b) Rai, M.; Krishan, K.; Singh, A. *Indian J. Chem.* **1976**, *14B*, 376–377; (c) De Kimpe, N.; Verhé, R.; De Buyck, L.; Chijs, J.; Schamp, N. *Synthesis* **1978**, *12*, 895–897; (d) Takahashi, K. *Synthesis* **1978**, 892–893; (e) Pochat, F. *Tetrahedron Lett.* **1981**, *22*, 955–956.
3. De Kimpe, N.; Verhé, R.; De Buyck, L.; Chijs, J.; Schamp, N. *Bull. Soc. Chim. Belg.* **1979**, *88*, 695–717.
4. Saegusa, T.; Taka-ishi, N.; Ito, Y. *J. Org. Chem.* **1969**, *34*, 4040–4046.
5. Ta-Shma, R.; Rapoport, Z. *J. Chem. Soc., Perkin Trans. 2* **1977**, *5*, 659–667.

6. Yanosvskaya, L.; Shachidayatov, C.; Prokofiev, E.; Andrianova, G.; Kucherov, V. *Tetrahedron* **1968**, *24*, 4677–4679.
7. De Corte, B.; Denis, J. M.; De Kimpe, N. *J. Org. Chem.* **1987**, *58*, 1147–1149.
8. Pellissier, H.; Gil, G. *Tetrahedron Lett.* **1988**, *29*, 6773–6774.
9. De Kimpe, N.; Boelens, M.; Contreras, J. *Tetrahedron Lett.* **1996**, *37*, 3171–3174.
10. De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* **1994**, *35*, 1925–1928.
11. Representative procedure for the synthesis of 2-cyanopiperidines **2**: To a solution of 10 mmol of potassium cyanide in 20 ml of THF and 20 ml of distilled water, 5 mmol of the corresponding finely powdered 1-pyrrolinium salt **4** were added. The reaction mixture was stirred for 4 h at room temperature. After separation of the THF layer, the aqueous phase was extracted twice with ether, and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the resulting oil was purified by flash chromatography. Compound **2a** (5-bromo-1-cyclohexyl-3,3-dimethylpiperidine-2-carbonitrile): light-yellow oil, ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.12 (6H, s, $(CH_3)_2C$); 1.16–1.36 (4H, m, $(CH_2)_2$); 1.56–1.98 (8H, m, $(CH_2)_3$ and $(CH_3)_2CC\underline{H}_2$); 2.38–2.48 (1H, m, NCH_{cyclo}); 2.76 (1H, dd, $J_1=11.5$ Hz, $J_2=11.5$ Hz, $NC\underline{H}(H)$); 3.28 (1H, dd, $J_1=11.6$ Hz, $J_2=4.6$ Hz, $NCH(\underline{H})$); 3.46 (1H, s, CHCN); 4.03–4.15 (1H, m, CHBr); ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.03 and 27.30 ($(CH_3)_2$); 24.62; 24.69; 25.29; 29.45; 29.42 ($(CH_2)_5$); 36.34 ($\underline{C}(CH_3)_2$); 43.85 (CHBr); 45.05 ($\underline{C}H_2C(CH_3)_2$); 52.81 ($CH_2N$); 58.60 ($\underline{C}HCN$); 61.48 ($NCH_{cyclo}$); 116.33 (C≡N). MS (70 eV) m/z (%): 298/300 (M^+, 14); 283/5 (5); 270/2 (4); 255/57 (100); 242/44 (22); 229/31 (13); 219 (33); 163 (10); 105 (29); 83 (12); 69 (13); 67 (10); 57 (17); 55 (25); 43 (16); 41 (24). IR (NaCl, cm^{-1}): $\nu_{CN}=2221$; $R_f=0.23$ (hex/CH_2Cl_2, 95/5).
12. (a) Grob, C. A. *Angew. Chem.* **1976**, *88*, 621–627; (b) Gleiter, R.; Stohrer, W. D. *Helv. Chim. Acta* **1972**, *55*, 893–906 and references cited therein.
13. Typical experimental procedure for the synthesis of imidoyl cyanides **3**: To a solution of 5 mmol of the corresponding 2-cyanopiperidine **2** in 10 ml of DMF, 7.5 mmol of NaH (60% dispersion in mineral oil) were added. The reaction mixture was stirred at 80°C for 4 h. After this period, the reaction was carefully quenched with water, extracted twice with ether, and the combined extracts were dried over $MgSO_4$. Imidoyl cyanides **3** were obtained after purification by flash chromatography. Compound **3a** [2-(cyclohexylimino)-3,3-dimethyl-5-hexenenitrile]: light-yellow oil, ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.19 (6H, s, $(CH_3)_2$); 1.26–1.83 (10H, m, $(CH_2)_5$); 2.32 (2H, d, $J=7.3$ Hz, $C\underline{H}_2C(CH_3)_2$); 3.61–3.68 (1H, m, NCH); 5.04–5.11 (2H, m, $=CH_2$); 5.59–5.75 (1H, m, $C\underline{H}=CH_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 23.00 and 24.41 and 32.45 ($3\times CH_2$); 23.74 ($C(\underline{C}H_3)_2$); 40.77 ($\underline{C}(CH_3)_2$); 43.14 ($\underline{C}H_2C(CH_3)_2$); 65.69 (CHN); 108.66 (C≡N); 117.41 ($=CH_2$); 132.25 (=CH); 147.33 (C=N). MS (70 eV) m/z (%): 218 (M^+, 12); 203 (9); 188 (9); 137 (18); 80 (100); 76 (36); 55 (39); 47 (90); 43 (45); 41 (51). IR (NaCl, cm^{-1}): $\nu_{C=C+C=N}=1618$, 1625; $R_f=0.18$ (hex/CH_2Cl_2, 7/3).
14. As an example, the spectral data of 1-isopropyl-3,3-dimethyl-1,2,3,6-tetrahydro-2-pyridinecarbonitrile **8e** are given: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.12 and 1.15 (6H, 2×d, $J=6.6$ Hz, $CH(C\underline{H}_3)_2$); 1.18 (6H, s, $C(CH_3)_2$); 2.81 (1H, septet, $J=6.6$ Hz, $C\underline{H}(CH_3)_2$); 3.10 (1H, dt, $J_1=17.0$ Hz, $J_2=2.0$ Hz, $\underline{H}CHCH=$); 3.30 (1H, ddd, $J_1=17.0$ Hz, $J_2=4.2$ Hz, $J_3=2.0$ Hz, $HC\underline{H}CH=$); 3.60 (1H, s, CHCN); 5.41 (1H, m, $C\underline{H}=CHCH_2$); 5.62 (1H, ddd, $J_1=9.9$ Hz, $J_2=4.2$ Hz, $J_3=2.0$ Hz, $CH=C\underline{H}CH_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.71 and 20.20 ($2\times CH(CH_3)_2$); 25.71 and 27.64 ($C(\underline{C}H_3)_2$); 36.32 ($\underline{C}(CH_3)_2$); 45.62 (CH_2); 53.03 ($\underline{C}H(CH_3)_2$); 58.08 ($\underline{C}HCN$); 116.89 (CN); 123.41 and 132.34 (CH=CH). MS (70 eV) m/z (%): 178 (M^+, 12); 164 (6); 163 (30); 94 (7); 83 (10); 82 (100); 81 (17); 67 (35); 54 (7); 43 (17). IR (NaCl, cm^{-1}): $\nu_{max}=2215$; $R_f=0.35$ (hex/AcOEt, 9/1).
15. Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5743–5746.
16. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1983; p. H185.
17. This calculation was carried out by means of the program Chem 3D Pro® Molecular Modeling and Analysis, version 3.5 using the MNDO computation option.