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Chemoselective Nucleophilic Attack of α,α-Dicyano Epoxides: A Simple Synthesis of α-Amino Amides, Epoxy Amidines and Their Cyclic Analogs

Dominique Hurtaud, Michèle Baudy-Floc'h,*
Albert Robert, and Philippe Le Grel

Chimie Structurale, URA CNRS 704, Université de Rennes I, Campus de Beaulieu 35042 Rennes Cédex, France

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Introduction

Nucleophilic reagents react with α-functionalized epoxides to give either ring-opened products or new functionalized epoxides.[1−7] In the case of *gem*-dicyano epoxides **1** these two possibilities have already been observed. Protic nucleophiles, such as water, primary alcohols, phenol, and thiophenol directly open the *gem*-dicyano epoxides **1**.[8] The nucleophile reacts selectively on the carbon bearing the R^1 and R^2 groups. It seems likely that the first step of the reaction is the protonation of the ring oxygen, followed by the regioselective reaction of the nucleophile with the most positive center (Scheme 1). The reaction leads to α-functionalized acid derivatives.

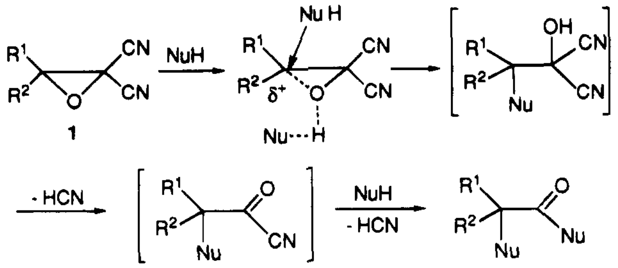
On the other hand, other selective reactions at one cyano group, without ring opening, have been observed, for instance the reaction of sodium borohydride which leads to α-cyano-α-aminomethyl epoxides (Scheme 2).[9]

In this paper we will show that primary or secondary amines react with *gem*-dicyano epoxides to give either ring-opened products or new α-functionalized epoxides. Depending on the degree of substitution on the epoxide, this reaction may give either α-amino amides or epoxy amidines. Such a reaction is also of interest since to date, only two epoxy amidines are described in the literature and these compounds possess antibiotic properties.[10]

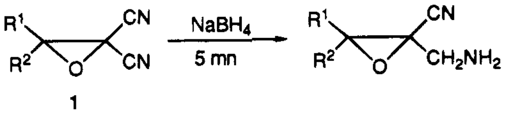
Results and Discussion

Trisubstituted epoxides **1** (R^2 = H) are selectively opened by the amines to lead, after the loss of two hydrogen cyanide molecules to the α-amino amides **3** (15−50%) and to the cyano amines **4** (5−10%) as byproducts in proportions **3**/**4**: 80/20. Tetrasubstituted epoxides **1** ($R^2 \neq$ H) react with amines in a very different way. The reaction involves nucleophilic attack on the nitrile group to give epoxy amidines **5** (50%). If $R^1 \neq R^2$, we obtained a mixture of two diastereoisomers, *E*-**5c** and *Z*-**5d**, in equivalent proportions.

Scheme 1



Scheme 2



We propose that the course of the reaction can be accounted for by assuming that if the carbon β to the epoxide is not hindered (R^2 = H), the amine slowly ring opens the epoxide according to Scheme 1 to give **3** (the formation of the byproduct cyano amine **4** is not so easily explained[11]). When $R^2 \neq$ H, the amine attacks one nitrile group of the epoxide to give the amidine **5** (Scheme 3). The formation of amidines **5** is in good agreement with the addition of amine on a nitrile bearing an electron-withdrawing group already described in the literature.[12]

The reaction of amines with cyano epoxides **1** is quite general and can be extended to diamines. Examples given in Scheme 4 show that diamines react with **1** to open a new route to epoxides α-substituted by an imidazoline or a tetrahydropyrimidine ring **6** (30%) when R^1 and $R^2 \neq$ H, while a piperazinone **7** (10%) is obtained when R^2 = H.

Conclusions

In summary we have shown that basic nucleophiles such as amines react selectively and reversibly at one nitrile group of the tetrasubstituted epoxides **1** and open a route to new substituted epoxy amidines. The reversibility of this reaction allows a nucleophilic ring opening of the less hindered trisubstituted epoxides **1** (R^2 = H) and give α-amino substituted amides. The reaction is general and can be extended to the reaction of diamines with the epoxides **1** allowing either the preparation of imidazolino or tetrahydropyrimidino epoxides (R^2 and R^1 $\neq$ H) or piperazinones (R^2 =H).

Experimental Section

^{1}H NMR spectra were recorded at 80 MHz on a Bruker WP 80 spectrometer and ^{13}C NMR spectra at 75 MHz on a Bruker AM 300 spectrometer with tetramethylsilane as internal reference. Mass spectra were determined with a Varian Mat 311 spectrometer. IR spectra were

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(1) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367.

(2) Gorzynski, J. *Synthesis* **1984**, 629−656.

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(4) Taylor, E. C.; Maryanoff, C. A. *J. Org. Chem.* **1980**, *45,* 2512−2516.

(5) Guillemet, M.; Baudy-Floc'h, M.; Robert, A. *J. Chem. Soc. Chem.Commun.* **1991**, 906−907.

(6) Jaime, C.; Ortuno, R. M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139−141.

(7) Sabate-Alduy, B.; Bercot, Lematre, *Bull. Soc. Chim. Fr.* **1974**, 1942−1948.

(8) Florac, C.; Le Grel, P.; Baudy-Floc'h, M.; Robert, A. *Synthesis* **1991**, 741−743.

(9) Mauger, J.; Robert, A. *Tetrahedron* **1988**, *44*, 2493−2502.

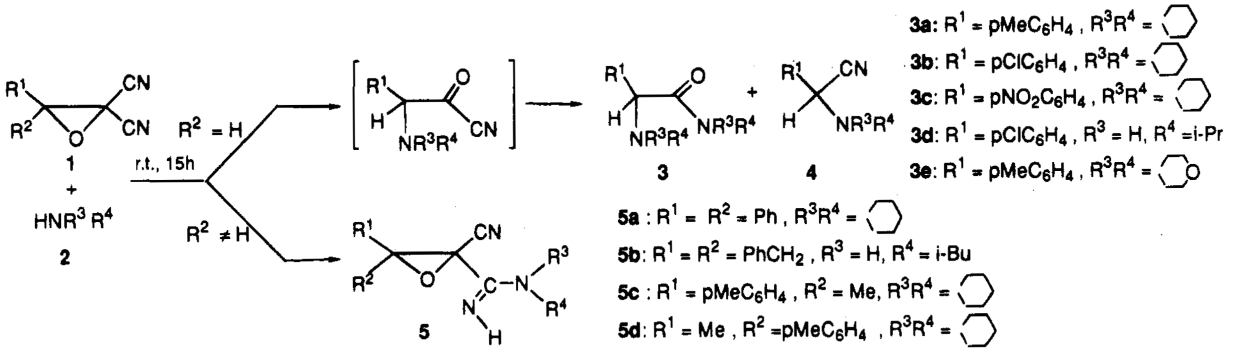
(10) Christensen, B. G.; Beattie, T. R.; Graham, D. W.; Merck and Co. Fr Patent 2 034 480, 1971; *Chem. Abstr.* **1971**, *75*, 88759m.

(11) We have shown that some nucleophiles under basic conditions and in the absence of water react with **1** (R^2 = H) to give the aldehyde R^1CHO.[5] It is possible that **4** arises from the reaction of such an aldehyde with cyanide ion and the amine present in the medium. When *p*-MeC_6H_4CHO was added to a medium consisting of epoxide **1** (R^1 = *p*-ClC_6H_4) and piperidine we in fact were able to characterize **4** (R^1 = *p*-MeC_6H_4) together with **4** (R^1 = *p*-ClC_6H_4). But a decarbonylation mechanism could also explain the formation of **4** as mentioned by a referee.

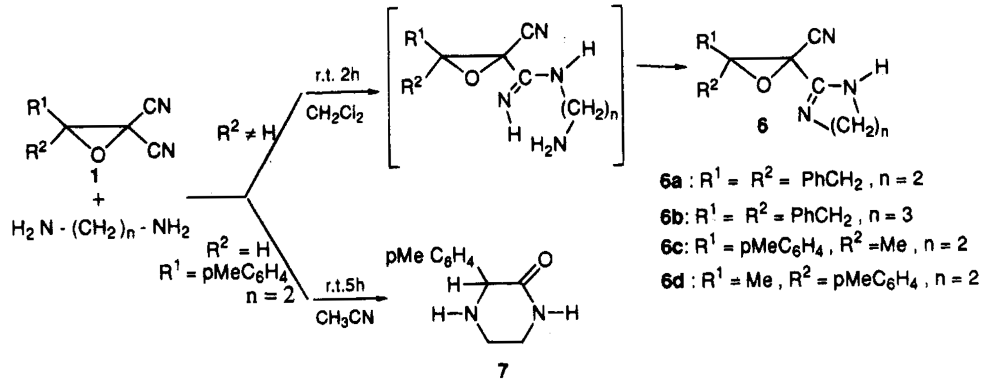
(12) Patai, S. *The Chemistry of amidines and imidates*; John Wiley and Sons: London, 1975.

0022-3263/94/1959-4701$04.50/0

Scheme 3



Scheme 4



determined with a Perkin-Elmer 225 or 1420 spectrometer. Melting points were taken with a Kofler hot stage apparatus.

α-Amino Amides 3. General Procedure. To a solution of epoxide **1** ($R^2 = H$)[13] (5 mmol) in dry acetonitrile (30 mL) was added amine **2** (15 mmol). The mixture was stirred at room temperature for 15 h and then evaporated. By addition of petroleum ether, some impurities precipitated, and the organic layer was filtered and evaporated. The α-amino amide **3** was obtained after separation from **4** by silica gel (Merck 90) column chromatography using ether/petroleum ether as eluent. The α-amino amides are then purified by recrystallization from hexane.

3a: 35%; mp 85 °C; R_f (Et_2O/petroleum ether) 0.09 (1/1); ^1H NMR δ ($CDCl_3$) 1.50 (m, 12H), 2.31 (s, 3H), 2.46 (m, 4H), 3.50 (m, 4H), 4.27 (s, 1H), 7.20 (m, 4H); ^{13}C NMR δ ($CDCl_3$/TMS) 21 (CH_3), 24 (CH_2), 26 (CH_2), 26 (CH_2), 43 (CH_2), 46 (CH_2), 53 (CH_2), 72 (CH), 129 (2 aromatic carbons), 133 (C-quaternary), 137 (C-quaternary), 169 (CO); IR (Nujol) 1630 cm^{-1}; MS calcd for $C_{19}H_{28}N_2O$: *m/z* (rel intensity) = 300 $M^{\bullet+}$ (0.13), 299 (0.03), 189 (9.8), 188 (100), 132 (11), 131 (1.3), 112 (1.2), 105 (8.7), 91 (1.7), 84 (6.9), 28 (2.7); HRMS calcd for $C_{19}H_{27}N_2O$ $(M-H^{\bullet})^+$ 299.2123, found 299.211. Anal. Calcd for $C_{19}H_{28}N_2O$: C, 75.96; H, 9.39; N, 9.32. Found: C, 75.91; H, 9.28; N, 9.38.

3b: 50%; mp 136 °C; R_f (Et_2O/petroleum ether) 0.17 (1/1); ^1H NMR δ ($CDCl_3$) 1.50 (m, 12H), 2.45 (m, 4H), 3.50 (m, 4H), 4.27 (s, 1H), 7.32 (s, 4H); IR (Nujol) 1625 cm^{-1}. Anal. Calcd for $C_{18}H_{25}N_2OCl$: C, 67.38; H, 7.85; N, 8.73; Cl, 11.05. Found: C, 67.68; H, 8.06; N, 8.93; Cl, 11.12.

3c: 30%; mp 152 °C; R_f (Et_2O/petroleum ether) 0.13 (1/1); ^1H NMR δ ($CDCl_3$) 1.50 (m, 12H), 2.45 (m, 4H), 3.55 (m, 4H), 4.45 (s, 1H), 7.90 (AB, 4H, $J = 8$ Hz); IR (Nujol) 1625 cm^{-1}. Anal. Calcd for $C_{18}H_{25}N_3O_3$: C, 65.24; H, 7.60; N, 12.68. Found: C, 65.09; H, 7.70; N, 12.57.

3d: 15%; mp 72 °C; R_f (Et_2O/petroleum ether) 0.24 (7/3); ^1H NMR δ ($CDCl_3$) 1.10 (d, 6H), 1.20 (d, 6H), 1.97 (br, NH), 2.80 (sept, 1H), 4.12 (s, 1H), 4.16 (s, 1H), 7.25 (s, 4H); IR (Nujol) 3305, 1650 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_2OCl$: C, 62.56; H, 7.87; N, 10.42; Cl, 13.19. Found: C, 62.29; H, 7.69; N, 10.49; Cl 13.04.

3e: 15%; oil; R_f (Et_2O/petroleum ether) 0.03 (7/3); ^1H NMR δ ($CDCl_3$) 2.30 (s, 3H), 2.50 (m, 4H), 3.52 (m, 8H), 3.70 (m, 4H), 4.16 (s, 1H), 7.22 (m, 4H); IR (Nujol) 1630 cm^{-1}; MS calcd for $C_{17}H_{24}N_2O_3$: m/z (rel intensity): 304 $M^{\bullet+}$ (0.02), 303 (0.06), 191 (18.5), 190 (100), 132 (2.6), 131 (2.2), 130 (2), 119 (7.2), 105 (8.9), 104 (2.8), 103 (2.2), 91 (5.1), 86 (2.3,; 77 (2.1), 70 (2), 56 (3.5), 42 (2.9), 28 (5.1); HRMS calcd for $C_{17}H_{23}N_2O_3$ $(M - H^{\bullet})^+$ 303.1709, found 303.169. Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.96; H, 7.67; N, 9.08.

Epoxy-amidines 5. General Procedure. To a solution of epoxide **1** ($R^2 \neq H$)[14] (5 mmol) in dry acetonitrile (30 mL) was added amine **2** (15 mmol). The mixture was stirred at room temperature for 15 h, then evaporated. The residue was purified by silica gel (Merck 90) column chromatography using ether/petroleum ether as eluent. Evaporation of the solvent gave the epoxy-amidines, **5a** and **5b** which were recrystallized from hexane. The two diastereoisomers **5c** and **5d** were separated and isolated as oils. The magnetic anisotropy of the aromatic group allows the characterization of the nmr signals of the protons of **5c** and **5d**.

5a: 50%; mp 124 °C; R_f (Et_2O/petroleum ether) 0.18 (4/6); ^1H NMR δ ($CDCl_3$) 1.55 (m, 6H), 3.42 (m, 4H), 6.7 (s, 1H, NH), 7.4 (m, 10H); ^{13}C NMR δ ($CDCl_3$/TMS) δ 24 (CH_2), 25 (CH_2), 46 (CH_2), 59 (CCN), 74 (PhCPh), 115 (CN), 127, 127.4, 128.5, 128.9, 129.3, 129.5 (arom), 133.1

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[13] Baudy, M.; Robert, A.; Foucaud, A. *J. Org. Chem.* **1978**, *43*, 3732–3736.

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(C-quaternary), 135 (C-quaternary), 156 (N=CN); IR (Nujol) 3310, 2230, 1600 cm^{-1}; MS calcd for $C_{21}H_{21}N_3O$: *m/z* (rel intensity) 331 (22), 330 (40.8), 314 (25.2), 302 (8.6), 230 (4.6), 110 (28.7), 105 (53.3), 84 (100), 83 (18.9), 77 (32.4), 69 (16.4), 55 (30.2), 42 (22.3), 41 (21.7), 28 (18), 27 (10.6); HRMS calcd for $C_{21}H_{20}N_3O$ $(M - H^{\bullet})^+$ 330.1606, found 330.160. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 76.07; H, 6.62; N, 12.19.

5b: 50%; oil, R_f (Et_2O/petroleum ether) 0.34 (5/5); ^1H NMR δ ($CDCl_3$) 0.95 (d, 6H), 2.37 (m, 1H), 2.77 (s, 2H), 3.02 (d, 2H), 3.06 (s, 2H), 5.52 (s, 1H, NH), 7.5 (m, 11H, Ph + NH); IR (Nujol) 3360, 2245, 1665 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_3O$: C, 76.08; H, 7.20; N, 12.10. Found: C, 76.47; H, 7.28; N, 12.40.

5c (*E* isomer): 20%; oil, R_f (Et_2O/petroleum ether) 0.70 (6/4); ^1H NMR δ ($CDCl_3$) 1.62 (m + s, 9H), 2.32 (s, 3H), 3.45 (m, 4H), 6.07 (s, 1H, NH), 7.28 (s, 4H); IR (Nujol) 3310, 2235, 1605 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 71.67; H, 7.60; N, 14.40.

5d (*Z* isomer): 20%; oil, R_f (Et_2O/petroleum ether) 0.90 (6/4); ^1H NMR δ ($CDCl_3$) 1.45 (m, 6H), 2.00 (s, 3H), 2.27 (s, 3H), 3.17 (m, 4H), 7.11 (s, 4H), 7.32 (s, 1H, NH); IR (Nujol) 3310, 2240, 1605 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found: C, 71.43; H, 7.57; N, 14.48.

Epoxy Imidazolines and Epoxy Tetrahydropyrimidine 6. General Procedure. To a solution of epoxide **1** ($R^2 \neq H$) (5 mmol) in dry CH_2Cl_2 (30 mL) was added diamine (5 mmol). The mixture was stirred at room temperature for 2 h and then evaporated. The residue was purified by silica gel (Merck 90) column chromatography using ether/petroleum ether as eluent. Evaporation of the solvent gave the epoxy imidazolines **6a**, **6c** and **6d** or the epoxy tetrahydropyrimidine **6b**. The two diastereoisomers **6c** and **6d** could be separated by column chromatography.

6a: 30%; mp 103 °C; R_f (Et_2O/petroleum ether) 0.22 (6/4); ^1H NMR δ ($CDCl_3$) 2.87 (s, 2H), 3.07 (s, 2H), 3.2–4.2 (m, 4H), 4.92 (s, 1H), 7.0–7.4 (m, 10H); ^{13}C NMR δ ($CDCl_3$/TMS) δ 19 (CCH_3), 21 (p-$CH_3C_6H_4$), 50 (2 carbons, CH_2), 56 (CCN), 70 (CCH_3), 115 (CN), 126, 129 (arom), 133.2 (C-arom-quaternary), 139 (C-arom-quaternary), 159 (N=CN); IR (Nujol) 3160, 2235, 1595 cm^{-1}; MS calcd for $C_{20}H_{19}N_3O$ *m/z* (rel intensity) 317 $M^{\bullet +}$ (4.1), 227 (11.2), 226 $[M - \dot{C}H_2Ph]^+$ (32.5), 210 (18.4), 199 (31), 198 (10.6), 136 (76.9), 125 (18.7), 124 (24.6), 115 (12.9), 91 (100), 65 (39.5), 44 (16.4), 28 (13.7), 18 (11.8); HRMS calcd for $C_{20}H_{19}N_3O$ 317.1528, found 317.152. Anal. Calcd for $C_{20}H_{19}N_3O$: C, 76.08; H, 7.20; N, 12.10. Found: C, 76.47; H, 7.28; N, 12.40.

6b: 30%; oil; R_f (Et_2O/petroleum ether) 0.22 (1/1); ^1H NMR δ ($CDCl_3$) 1.75 (quint, 2H), 2.80 (s, 2H), 3.05 (AB, 2H), 3.37 (t, 4H), 4.92 (s, 1H), 7.25 (m, 10H); IR (Nujol) 3400, 2240, 1640 cm^{-1}. Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.13; H, 6.34; N, 12.69. Found: C, 76.37; H,6.28; N, 12.48.

6c (*E* isomer): 15%; mp 132 °C; R_f (Et_2O/petroleum ether) 0.13 (9/1); ^1H NMR δ ($CDCl_3$) 1.77 (s, 3H), 2.35 (s, 3H), 3.73 (m, 4H), 4.50 (s, 1H), 7.25 (AB, 4H); IR (Nujol) 3150, 2240, 1600 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.26; N, 17.41. Found: C, 69.21; H, 5.99; N, 17.24.

6d (*Z* isomer): 15%; mp 155 °C; R_f (Et_2O/petroleum ether) 0.36 (9/1); ^1H NMR δ ($CDCl_3$) 1.91 (s, 3H) 2.32 (s, 3H), 3.32 (m, 4H), 6.45 (s, 1H), 7.20 (s, 4H); IR (Nujol) 3150, 2240, 1600 cm^{-1}. Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.26; N, 17.41. Found: C, 69.36; H, 5.98; N, 17.12.

Piperazinone 7. To a solution of epoxide **1** ($R^2 = H$) (5 mmol) in dry acetonitrile (30 mL) was added ethylenediamine (5 mmol). The mixture was stirred at room temperature for 5 h and then evaporated. The residue was purified by silica gel (Merck 90) column chromatography using ether/petroleum ether as eluent. Evaporation of the solvent gave the piperazinone **7**.

7: 10%; mp 130–132 °C; R_f (Et_2O/petroleum ether) 0.03 (7/3); ^1H NMR δ ($CDCl_3$) 2.30 (s, 3H), 3.27 (m, 4H), 4.45 (s, 1H), 7.17 (m, 4H); IR (Nujol) 3240, 3180, 1670 cm^{-1}; MS calcd for $C_{11}H_{14}N_2O$ m/z (rel intensity) 190 $M^{\bullet +}$ (46.5), 162 (28.2), 161 (54.4), 147 (13.7), 133 (40.1), 132 (100), 131 (16.6), 119 (27.8), 118 (81.4), 117 (19.0), 105 (80.7), 91 (20.5), 77 (11.3), 71 (15.0), 45 (13.6), 30 (17.6), 28 (20.6).