Synthesis of Functionalized Pyrazines and Quinoxalines from *Nef*-Isocyanide Adducts and 1,2-Diamines

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Alkyl 3-(alkylamino)-5,6-dicyanopyrazine-2-carboxylates and alkyl 3-(alkylamino)quinoxaline-2-carboxylates were obtained in good yields by treatment of *Nef*-isocyanide adducts with 1,2-diamines in MeCN.

Introduction. – The synthetic interest in isocyanides is traditionally associated with their interaction with aldehydes and ketones as disclosed in the *Ugi* and *Passerini* reactions [1][2]. Discovered much earlier by *Nef* [3], the reaction of isocyanides with acyl chlorides is, however, less documented [4–7]. This reaction gives imidoyl chloride intermediates, which can be either hydrolyzed to ketoamides or trapped to form various cyclic adducts [4]. In contrast to the *Ugi* and *Passerini* reactions, the interaction between isocyanides and acyl chlorides often requires heating to give adducts in moderate yields [8]. More efficient *Nef*-type reactions could be accomplished with highly electrophilic acid derivatives such as trifluoroacetic anhydride [9] or acyl bromides, which were shown to be more reactive than the corresponding chlorides [10].

Results and Discussion. – As part of our current studies on the development of new routes to synthesis of imidoyl chlorides [11–14] and quinoxalines [15], here we report a new one-pot synthesis of pyrazines and quinoxalines with imidoyl chloride intermediates. Thus, the *Nef* isocyanide adducts **3**, obtained from alkyl chlorooxalates **1** with isocyanides **2**, reacts at room temperature with 2,3-diaminomaleonitrile (=(*Z*)-2,3-diaminobut-2-enedinitrile; **4**) and benzene-1,2-diamine (**5**) to give alkyl 3-(alkylamino)-5,6-dicyanopyrazine-2-carboxylates **6** and alkyl 3-(alkylamino)quinoxaline-2-carboxylates **7** in moderate-to-good yields (*Scheme 1* and *Table*).

The structures of compounds **6** and **7** were deduced from their IR, and ^{1}H- and ^{13}C-NMR data. For example, the ^{1}H-NMR spectrum of **6a** in $CDCl_3$ exhibited three *singlet*s readily recognized as arising from ^{t}Bu (δ(H) 1.50), MeO (δ(H) 3.98), and NH (δ(H) 8.91) H-atoms. The ^{1}H-decoupled ^{13}C-NMR spectrum of **6a** exhibited ten signals in agreement with the proposed structure. The ^{1}H- and ^{13}C-NMR spectra of **6b**–**6d** are similar to those for **6a**, except for the signals of the alkyl groups.

A plausible pathway may be proposed to rationalize product formation (*Scheme 2*). Presumably, the *Nef* isocyanide adduct **3**, formed from acid chloride **1** and isocyanide **2**, is attacked by **4** to form the intermediate **8**, which then undergoes an intramolecular

Scheme 1

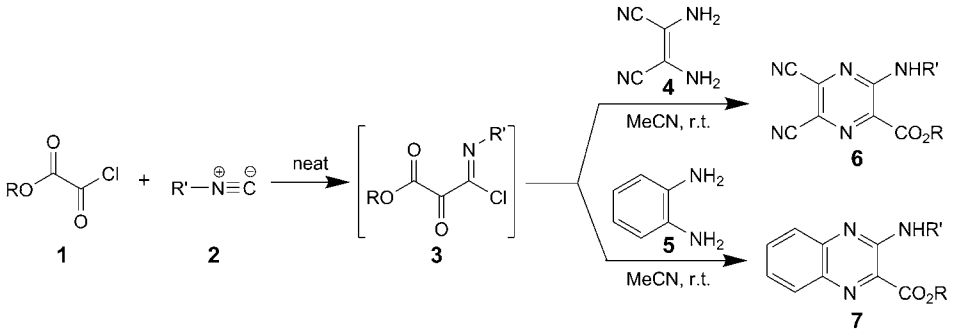
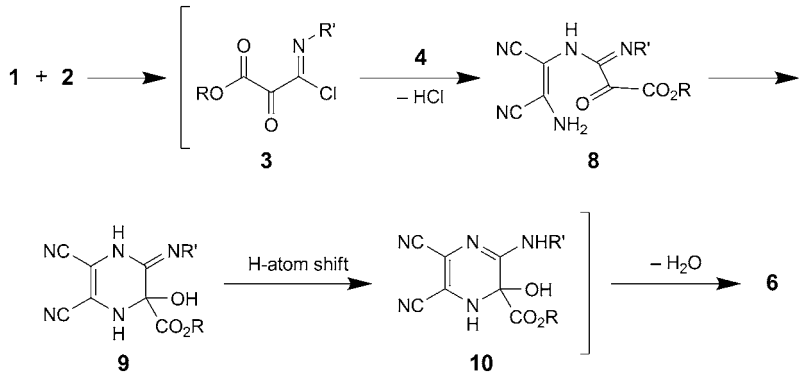


Table. *Conversions of* **4** *and* **5** *to* **6** *and* **7**, *Respectively*[a])

Amine	R	R'	Product	Yield [%]
4	Me	*t*-Bu	**6a**	57
4	Me	Cyclohexyl	**6b**	72
4	Et	*t*-Bu	**6c**	75
4	Et	Cyclohexyl	**6d**	86
5	Et	Cyclohexyl	**7a**	84
5	Et	*t*-Bu	**7b**	72
5	Me	Cyclohexyl	**7c**	62

[a]) For the reaction, see *Scheme 1*.

Scheme 2



cyclization reaction to afford **9**. This intermediate is converted to **6** by H-atom shift and elimination of H_2O.

In summary, we have developed a simple, one-pot synthesis of functionalized 3-(alkylamino)-5,6-dicyanopyrazines and 3-(alkylamino)quinoxalines by treatment of *Nef* isocyanide adducts with 1,2-diamines in MeCN. Short reaction times and readily available starting materials are the main advantages of this protocol.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm, J in Hz. MS: *Finnigan-MAT-8430EI-MS* mass spectrometer; at 70 eV; in *m/z* (rel. %). Elemental analyses: *Vario EL III CHNOS* elemental analyzer.

General Procedure for Synthesis of Compounds **6** *and* **7**. Isocyanide **2** (1.0 mmol) was added to acyl chloride **1** (1 mmol) under solvent-free conditions at r.t., and the mixture was stirred for 10 min, then MeCN (2 ml) and 1,2-diamine (**4** or **5**, 1 mmol) were added. The mixture was stirred for 2–4 h at r.t. and then concentrated under reduced pressure. The crude compound was purified by flash column chromatography (hexane/AcOEt 4:1) to give the product.

*Methyl 3-[(*tert*-Butyl)amino]-5,6-dicyanopyrazine-2-carboxylate* (**6a**). Yellow powder. Yield: 0.15 g (57%). M.p. 175–177°. IR (KBr): 3329 (NH); 2354, 2223 (CN), 1704 (C=O). ^1H-NMR: 1.50 (*s*, *t*-Bu); 3.98 (*s*, MeO); 8.91 (*s*, NH). ^{13}C-NMR: 29.6 (Me_3C); 55.2 (Me_3C); 55.3 (MeO); 114.4 (CN); 115.0 (CN); 118.6 (C); 129.0 (C); 136.0 (C); 154.2 (C); 166.4 (C=O). EI-MS: 259 (5, M^+), 244 (65), 212 (24), 184 (57), 170 (14), 77 (28), 59 (47), 57 (100). Anal. calc. for $C_{12}H_{13}N_5O_2$ (259.11): C 55.59, H 5.05, N 27.01; found: C 55.80, H 5.21, N 26.87.

Methyl 5,6-Dicyano-3-(cyclohexylamino)pyrazine-2-carboxylate (**6b**). Yellow powder. Yield: 0.20 g (72%). M.p. 135–137°. IR (KBr): 3329 (NH); 2223, 2354 (CN); 1704 (C=O), 1204. ^1H-NMR: 1.27–2.02 (*m*, 5 CH_2); 4.03 (*s*, MeO); 4.06–4.08 (*m*, CHN); 8.73 (*d*, J = 6.3, NH). ^{13}C-NMR: 24.3 (2 CH_2); 25.1 (CH_2); 31.9 (2 CH_2); 50.2 (CH); 53.7 (MeO); 113.0 (CN); 113.6 (CN); 117 (C); 127.2 (C); 135.6 (C); 152.5 (C); 164.8 (C=O). EI-MS: 285 (23, M^+), 270 (1), 242 (35), 228 (100), 210 (39), 196 (29), 182 (32), 155 (9), 81 (38), 55 (86). Anal. calc. for $C_{14}H_{15}N_5O_2$ (285.12): C 58.94, H 5.30, N 24.55; found: C 59.18, H 5.53, N 24.26.

*Ethyl 3-[(*tert*-Butyl)amino]-5,6-dicyanopyrazine-2-carboxylate* (**6c**). Yellow powder. Yield: 0.20 g (75%). M.p. 170–172°. IR (KBr): 3323 (NH), 2228 (CN), 1699 (C=O), 1206. ^1H-NMR: 1.43 (*t*, J = 7.1, Me); 1.50 (*s*, *t*-Bu); 4.44 (*q*, J = 7.1, CH_2O); 8.94 (*s*, NH). ^{13}C-NMR: 15.4 (Me); 29.6 (Me_3C); 55.2 (Me_3C); 64.8 (CH_2O); 114.5 (CN); 115.1 (CN); 118.6 (C); 129.4 (C); 135.8 (C); 154.2 (C); 166.0 (C=O). EI-MS: 273 (12, M^+), 258 (53), 212 (17), 184 (20), 170 (8), 69 (12), 57 (100). Anal. calc. for $C_{13}H_{15}N_5O_2$ (273.12): C 57.13, H 5.53, N 25.63; found: C 56.87, H 5.41, N 25.82.

Ethyl 5,6-Dicyano-3-(cyclohexylamino)pyrazine-2-carboxylate (**6d**). Yellow powder. Yield: 0.25 g (86%). M.p. 154–156°. IR (KBr): 3330 (NH), 2355, 2226 (CN), 1693 (C=O), 1196. ^1H-NMR: 1.47–1.99 (*m*, 5 CH_2); 1.42 (*t*, J = 7.1, Me); 4.05 (*m*, CHN); 4.43 (*q*, J = 7.1, CH_2O); 8.76 (*d*, J = 6.8, NH). ^{13}C-NMR: 14.0 (Me); 24.2 (2 CH_2); 25.3 (CH_2); 31.9 (2 CH_2); 50.1 (CH); 63.2 (CH_2O); 113.0 (CN); 113.6 (CN); 117.2 (C); 127.5 (C); 135.4 (C); 152.5 (C); 164.4 (C=O). EI-MS: 299 (21, M^+), 270 (13), 242 (91), 210 (20), 170 (42), 81 (37), 69 (44), 55 (100). Anal. calc. for $C_{15}H_{17}N_5O_2$ (299.14): C 60.19, H 5.72, N 23.40; found: C 60.32, H 5.84, N 23.15.

Ethyl 3-(Cyclohexylamino)quinoxaline-2-carboxylate (**7a**). Pale yellow powder. Yield: 0.25 g (84%). M.p. 89–91°. IR (KBr): 3357 (NH), 1690 (C=O), 1458, 1214. ^1H-NMR: 1.37–2.08 (*m*, 5 CH_2); 1.44 (*t*, J = 7.1, Me); 4.14–4.20 (*m*, CH); 4.49 (*q*, J = 7.1, CH_2O); 7.28 (*t*, J = 8.2, CH); 7.54 (*t*, J = 8.3, CH); 7.60 (*d*, J = 8.4, CH); 7.90 (*d*, J = 8.3, CH); 7.94 (*d*, J = 7.3, NH). ^{13}C-NMR: 15.6 (Me); 26.1 (2 CH_2); 27.2 (CH_2); 33.9 (2 CH_2); 50.0 (CH); 63.8 (CH_2O); 124.9 (C); 125.7 (CH); 127.4 (CH); 131.6 (CH); 133.8 (CH); 136.8 (C); 145.8 (C); 152.7 (C); 167.6 (C=O). EI-MS: 299 (22, M^+), 242 (16), 170 (50), 155 (11), 145 (100), 129 (30), 81 (22), 69 (65), 55 (74). Anal. calc. for $C_{17}H_{21}N_3O_2$ (299.16): C 68.20, H 7.07, N 14.04; found: C 67.94, H 7.21, N 13.92.

*Ethyl 3-[(*tert*-Butyl)amino]quinoxaline-2-carboxylate* (**7b**). Pale yellow powder. Yield: 0.19 g (72%). M.p. 80–82°. IR (KBr): 3364 (NH), 1698 (C=O), 1460, 1212. ^1H-NMR: 1.46 (*t*, J = 7.0, Me); 1.52 (*s*, *t*-Bu); 4.49 (*q*, J = 7.0, CH_2O); 7.31 (*t*, J = 7.8, CH); 7.57 (*t*, J = 7.35, CH); 7.65 (*d*, J = 8.0, CH); 7.91 (*d*, J = 8.3, CH); 8.05 (*s*, NH). ^{13}C-NMR: 15.6 (Me); 30.1 (Me_3C); 53.2 (Me_3C); 63.8 (CH_2O); 125.8 (CH); 127.8 (CH); 131.6 (CH); 131.9 (C); 133.7 (CH); 136.5 (C); 145.2 (C); 153.1 (C); 167.8 (C=O). EI-MS: 273 (6, M^+), 184 (39), 170 (23), 141 (51), 125 (29), 83 (84), 69 (29), 57 (100). Anal. calc. for $C_{15}H_{19}N_3O_2$ (273.33): C 65.91, H 7.01, N 15.37; found: C 66.08, H 7.14, N 15.46.

Methyl 3-(Cyclohexylamino)quinoxaline-2-carboxylate (**7c**). Pale yellow powder. Yield: 0.17 g (62%). M.p. 115–117°. IR (KBr): 3433 (NH), 1691 (C=O). ^{1}H-NMR: 1.24–2.09 (*m*, 5 CH_2); 4.22–4.24 (*m*, CH); 4.05 (*s*, MeO); 7.17–7.91 (*m*, CH); 7.93 (*d*, J = 8.4, NH). ^{13}C-NMR: 24.6 (2 CH_2); 25.8 (CH_2); 32.5 (2 CH_2); 53.2 (CH); 54.0 (MeO); 124.5 (C); 125.0 (CH); 127.5 (CH); 130.1 (CH); 133.1 (CH); 136.3 (C); 145.1 (C); 153.4 (C); 167.5 (C=O). EI-MS: 285 (4, M^+), 228 (4), 129 (12), 118 (27), 97 (16), 81 (42), 69 (100), 56 (95). Anal. calc. for $C_{16}H_{19}N_3O_2$ (285.15): C 67.35, H 6.71, N 14.73; found: C 67.18, H 6.84, N 14.91.

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