Isocyanide-Based Three-Component Synthesis of Pyrano-pyrido-quinoxalines

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Pyrano-pyrido-quinoxaline derivatives were synthesized in good yields by a three-component reaction of isocyanides, dialkyl acetylenedicarboxylates, and pyrido[1,2-*a*]quinoxaline-triones in DMF at 100°.

Introduction. – Within the past decade, the resurgence of interest in multi-component reactions (MCRs) has been driven, not only due to their convergent nature, superior atom economy, and straightforward experimental procedures, but also because of their value to the pharmaceutical industry for construction of low-molecular-weight compound libraries through combinatorial strategies and parallel synthesis [1–3]. Isocyanide-based multicomponent reactions (IMCRs) are particularly interesting as they are more versatile and diverse than other MCRs [4][5]. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, functional-group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. MCRs involving isocyanides have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [6–12].

It has been shown that isocyanides add to activated alkynes to generate zwitterionic species, which have been captured by CH acids to produce various heterocycles [13–24]. Although three-component reaction of isocyanide, activated alkynes, and CH acid has been applied to the synthesis of various heterocycles, to the best of our knowledge, this synthetic strategy has not been applied to the synthesis of substituted pyrano-pyrido-quinoxalines.

Quinoxaline and its derivatives are important heterocyclic compounds with wide applications in medicinal chemistry, as antidiabetic, anticancer, antibacterial, antiviral, and antifungal agents [25–28]. Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotics, such as echinomycin, actinomycin, and leromycin, compounds with reported inhibition of the growth of *Gram*-positive bacteria and activity against various tumors [29][30]. A number of fused (or substituted) quinoxalines, **I**–**III**, have been demonstrated to possess antidepressant, excitatory amino acid antagonistic, and antiglaucoma activities [31–33], respectively. Imidazo-quinoxaline **IV** [34] and isoindolo-quinoxalies **V** [35] have turned out to be a highly selective and potent inhibitor of IKK-2, and to exhibit antiproliferative activity, respectively (*Fig.*).

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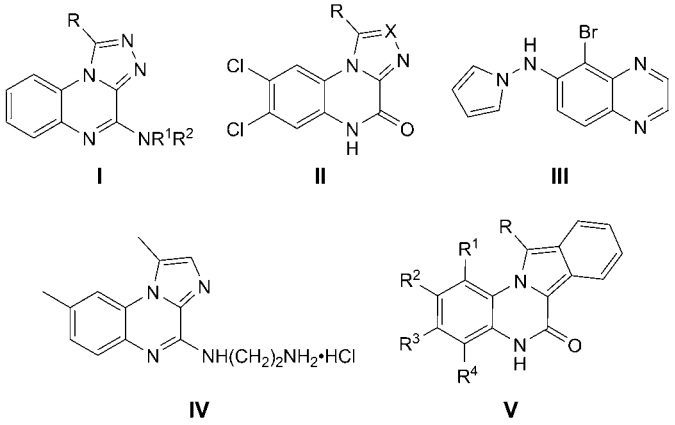
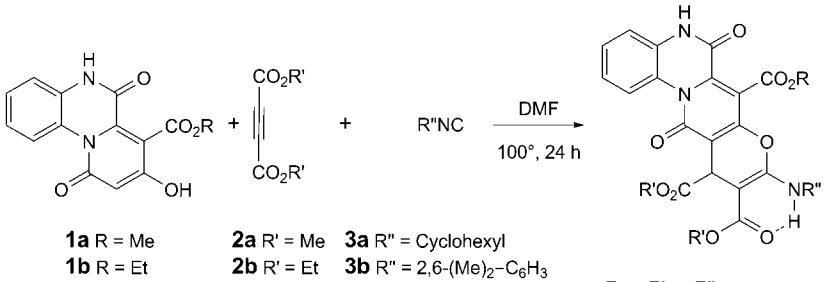


Figure. *Structures of some quinoxalines with biological activities*

As continuation of our studies of isocyanide-based multicomponent reactions [36–38] and synthesis of biologically active heterocyclic compounds [39–43], herein, we report an efficient isocyanide-based three-component reaction for the synthesis of pyrano-pyrido-quinoxaline.

Results and Discussion. – The three-component condensation reactions of pyrido[1,2-*a*]quinoxaline-4-carboxylate **1** with dialkyl acetylenedicarboxylates **2** in the presence of isocyanides **3** proceeded rapidly in DMF at 100° and were complete after 24 h. Corresponding pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxalines **4** were synthesized *via* the formation of three new bonds by a [CCO + CC + C] condensation strategy in good yields (*Scheme 1*).

Scheme 1. *Synthesis of Pyrano-pyrido-quinoxaline* **4**



1a R = Me
1b R = Et

2a R' = Me
2b R' = Et

3a R" = Cyclohexyl
3b R" = 2,6-$(Me)_2$–C_6H_3

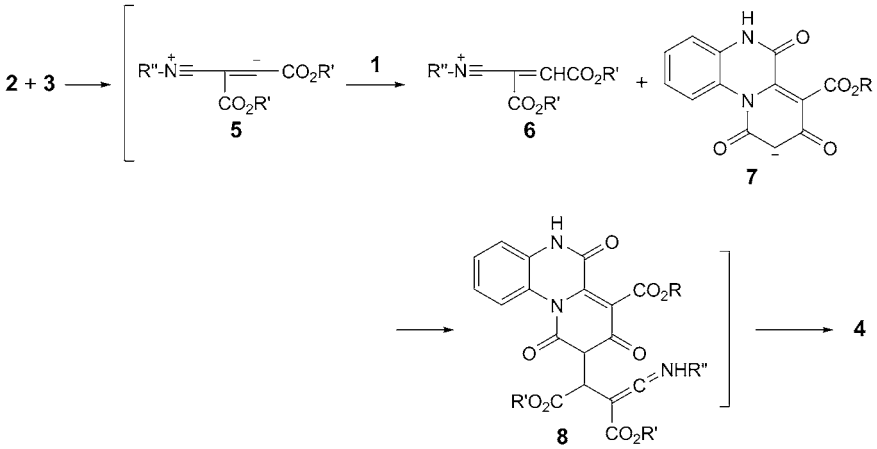
	R	R'	R"	Yield [%]
4a	Me	Me	Cyclohexyl	82
4b	Me	Me	2,6-Me_2–C_6H_3	78
4c	Me	Et	Cyclohexyl	75
4d	Me	Et	2,6-Me_2–C_6H_3	74
4e	Et	Me	Cyclohexyl	80
4f	Et	Et	2,6-Me_2–C_6H_3	76

The structures of the isolated products **4a**–**4f** were deduced from their elemental analyses, IR, and ^{1}H- and ^{13}C-NMR spectra. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular-ion peak at appropriate *m*/*z* value.

The mass spectrum of **4a** showed the molecular-ion peak at *m*/*z* 537. The IR spectrum of **4a** exhibited absorption bands due to C=O groups at 1738, 1706, 1700, 1650, and 1622 cm^{-1}, and a broad absorption band for the NH groups was observed at 3338 and 3325 cm^{-1}. The ^{1}H-NMR spectrum of **4a** consisted of *multiplet*s for the cyclohexyl rings (δ(H) 1.28–2.07) and the H–C–N resonance (δ(H) 3.40), four sharp *singlet*s for the three MeO groups (δ(H) 3.48, 3.57 and 3.86), and an allylic CH signal (δ(H) 4.64). A broad resonance (δ(H) 12.09) was observed for the amide NH group, along with a *doublet* (δ(H) 9.21, J = 8.8) for the NH of isocyanide moiety. The NH of isocyanide moiety at δ(H) 9.21 was strongly deshielded as a result of extensive intramolecular H-bonding as shown in *Scheme 1*. The aromatic H-atoms give rise to characteristic signals in the aromatic region of the spectrum. Due to the very low solubility of product **4a**, we were unable to obtain the ^{13}C-NMR spectrum.

Although the mechanism of the reaction has not yet been established experimentally, a proposal is presented in *Scheme 2*. The 1:1 zwitterionic ionic intermediate **5**, formed from the isocyanide and the acetylenic ester, is protonated by **1** to furnish intermediate **6**, which is attacked by the anion of the CH-acidic **7** in a *Michael* fashion to produce ketenimine **8**. The latter then can undergo cyclization under the reaction conditions to afford the pyrano-pyrido-quinoxalines **4** (*Scheme 2*) [20–24].

Scheme 2. *Proposed Mechanism*



In conclusion, an efficient, atom-economical, and simple method for the preparation of pyrano-pyrido-quinoxalines of potential synthetic and biological interest is reported. The method is performed under neutral conditions, and the starting material can be used without any activation or modification. Moreover, it is worth noting that two C–C and one C–O bonds were formed with concomitant creation of a fused pyrano-pyrido-quinoxalines ring in this three-component process.

Experimental Part

General. The chemicals were obtained from *Fluka* and *Merck*, and were used without purification. Pyrido[1,2-*a*]quinoxalines **1** were prepared according to a literature procedure [44]. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *BOMEM MB*-series FT-IR apparatus; in cm^{-1}. ^{1}H-NMR Spectra: *BRUKER DRX-300 AVANCE* spectrometer recorded at 300.13 MHz; in (D_6)DMSO; δ in ppm rel. to Me_4Si (= 0 ppm), *J* in Hz. EI-MS (70 eV): *FINNIGAN-MAT 8430* mass spectrometer; in *m*/*z*. Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds **4a**–**4f**. To a magnetically stirred soln. of **1** (1 mmol) and **2** (1 mmol) in DMF (4 ml) was added, dropwise, a soln. of **3** (1 mmol) in DMF (2 ml) at r.t. over 10 min. The mixture was stirred for 24 h at 100° (as indicated by TLC). Then, the mixture was filtered off and washed with EtOH (10 ml) to afford the pure product **4**.

*Trimethyl 9-(Cyclohexylamino)-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4a**). Yield 82%. Yellow powder. M.p. 155–157°. IR (KBr): 3338, 3325 (NH), 1738, 1706, 1700, 1650, 1622 (C=O). ^{1}H-NMR: 1.28–2.07 (*m*, 5 CH_2 of cyclohexyl); 3.40 (*m*, CH–N); 3.48 (*s*, MeO); 3.57 (*s*, MeO); 3.86 (*s*, MeO); 4.64 (*s*, CH); 7.15–7.39 (*m*, 3 arom. H); 8.54 (br. *s*, 1 arom. H); 9.21 (*d*, *J* = 8.8, NH); 12.09 (*s*, NH). EI-MS: 537 (M^+). Anal. calc. for $C_{27}H_{27}N_3O_9$ (537.52): C 60.33, H 5.06, N 7.82; found: C 60.23, H 5.13, N 7.75.

*Trimethyl 9-[(2,6-Dimethylphenyl)amino]-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4b**). Yield 78%. Yellow powder. M.p. 179–181°. IR (KBr): 3350, 3314 (NH), 1750, 1740, 1682, 1664 (C=O). ^{1}H-NMR: 2.10 (br. *s*, 2 Me); 3.55 (*s*, MeO); 3.67 (br. *s*, 2 MeO); 4.70 (*s*, CH); 6.88–7.62 (*m*, 6 arom. H); 9.10 (br. *s*, 1 arom. H); 9.68 (br. *s*, NH); 11.93 (br. *s*, NH). EI-MS: 559 (M^+). Anal. calc. for $C_{29}H_{25}N_3O_9$ (559.52): C 62.25, H 4.50, N 7.51; found: C 62.13, H 4.42, N 7.43.

*10,11-Diethyl 7-Methyl 9-(Cyclohexylamino)-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4c**). Yield 75%. Cream powder. M.p. 195–197°. IR (KBr): 3385, 3335 (NH), 1727, 1706, 1678, 1664, 1620 (C=O). ^{1}H-NMR: 1.14 (*t*, *J* = 8.6, Me); 1.22 (*t*, *J* = 8.1, Me); 1.23–1.88 (*m*, 5 CH_2 of cyclohexyl); 3.46 (*m*, CH–N); 3.86 (*s*, MeO); 4.02–4.23 (*m*, 2 CH_2O); 4.62 (*s*, CH); 7.16–7.40 (*m*, 3 arom. H); 8.55 (*d*, *J* = 7.2, 1 arom. H); 9.19 (*d*, *J* = 8.9, NH); 12.08 (*s*, NH). EI-MS: 565 (M^+). Anal. calc. for $C_{29}H_{31}N_3O_9$ (565.57): C 61.59, H 5.52, N 7.43; found: C 61.65, H 5.46, N 7.57.

*10,11-Diethyl 7-Methyl 9-[(2,6-Dimethylphenyl)amino]-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4d**). Yield 74%. Cream powder. M.p. 176–178°. IR (KBr): 3433, 3343 (NH), 1742, 1730, 1702, 1672 (C=O). ^{1}H-NMR: 1.17 (*t*, *J* = 7.1, Me); 1.29 (*t*, *J* = 8.4, Me); 2.10 (*s*, Me); 2.20 (*s*, Me); 3.15 (*s*, MeO); 4.04–4.26 (*m*, 2 CH_2O); 4.71 (*s*, CH); 7.11–7.38 (*m*, 6 arom. H); 9.16 (*d*, *J* = 9.0, 1 arom. H); 9.80 (br. *s*, NH); 11.98 (br. *s*, NH). EI-MS: 587 (M^+). Anal. calc. for $C_{31}H_{29}N_3O_9$ (587.58): C 63.37, H 4.97, N 7.15; found: C 63.30, H 4.92, N 7.06.

*7-Ethyl 10,11-Dimethyl 9-(Cyclohexylamino)-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4e**). Yield 80%. Yellow powder. M.p. 209–210°. IR (KBr): 3440, 3385 (NH), 1735, 1690, 1681 (C=O). ^{1}H-NMR: 1.20–1.87 (*m*, 5 CH_2 of cyclohexyl, Me); 3.48 (br. *s*, CH–N); 3.58 (*s*, MeO); 3.73 (*s*, MeO); 4.34–4.36 (*m*, CH_2O); 4.64 (*s*, CH); 7.17–7.68 (*m*, 3 arom. H); 8.54 (*d*, *J* = 8.3, 1 arom. H); 9.20 (*d*, *J* = 8.8, NH); 12.09 (*s*, NH). EI-MS: 551 (M^+). Anal. calc. for $C_{28}H_{29}N_3O_9$ (551.54): C 60.97, H 5.30, N 7.62; found: C 60.88, H 5.21, N 7.67.

*Triethyl 9-[(2,6-Dimethylphenyl)amino]-6,12-dihydro-6,12-dioxo-5*H,*11*H-*pyrano[2′,3′:4,5]pyrido[1,2-*a*]quinoxaline-7,10,11-tricarboxylate* (**4f**). Yield 76%. Yellow powder. M.p. 124–126°. IR (KBr): 3337, 3289 (NH), 1735, 1700, 1677, 1650 (C=O). ^{1}H-NMR: 1.12–1.28 (*m*, 3 Me); 2.07 (*s*, Me); 2.19 (*s*, Me); 4.06–4.38 (*m*, 3 CH_2O); 4.70 (*s*, CH); 6.91–7.35 (*m*, 6 arom. H); 9.16 (*d*, *J* = 7.5, 1 arom. H); 9.77 (*d*, *J* = 9.7 NH); 11.97 (br. *s*, NH). EI-MS: 601 (M^+). Anal. calc. for $C_{32}H_{31}N_3O_9$ (601.60): C 63.89, H 5.19, N 6.98; found: C 63.95, H 5.11, N 7.07.

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