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Imidazo[1,2-*a*]quinoxalines Accessed via Two Sequential Isocyanide-Based Multicomponent Reactions

Mikhail Krasavin,* Sergey Shkavrov, Vladislav Parchinsky, and Konstantin Bukhryakov

Chemical Diversity Research Institute, 2a Rabochaya Street, Khimki, Moscow Region, 141400, Russia

myk@chemdiv.com

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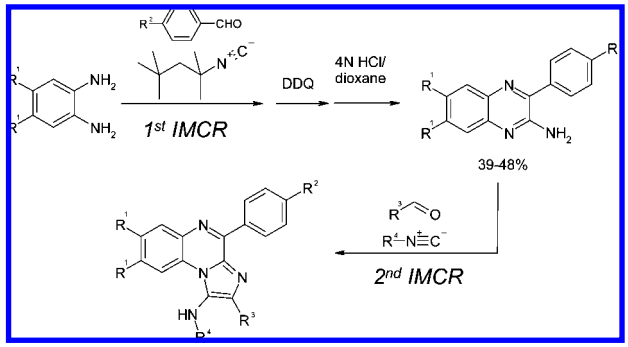
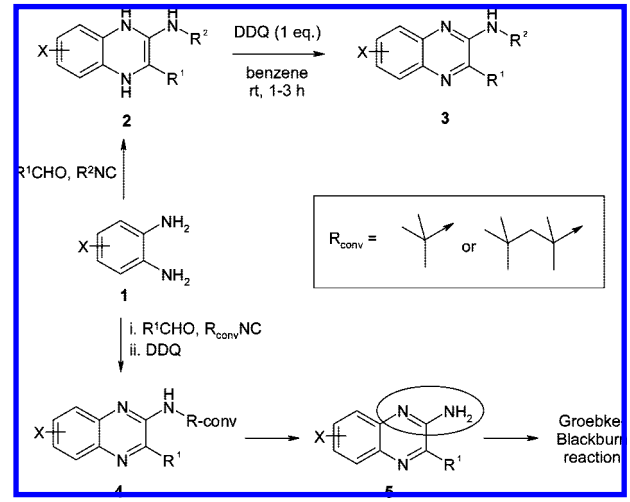


A novel synthetic protocol toward imidazo[1,2-*a*]quinoxalines has been developed. It includes two isocyanide-based multicomponent reactions sequentially introducing four diversity elements to the final products.

Isocyanide-based multicomponent reactions (IMCRs) continue to unveil their potential as a powerful tool for constructing skeletally diverse drug-like compounds.[1] The broad range of molecular scaffolds that have been crafted via IMCRs extends from classical linear "Ugi" compounds[2] through a variety of cyclic peptoid compounds resulting from the use of bifunctional (e.g., tethered carboxy carbonyl[3]) reagents, and to novel bicyclic heterocycles (such as imidazo[1,2-*x*]azines and -azoles,[4] or tetrahydropyrazines[5]) that have sprung up from applications of the Groebke−Blackburn reaction (GB-MCR)[6] and versions thereof.[7]

SCHEME 1. Synthesis of Quinoxalines by IMCR of Substituted *o*-Phenylenediamines[10] and IMCR/IMCR Coupling Strategy Explored in This Work



Additionally, various premeditated post-IMCR events have allowed reaching even higher levels of molecular complexity in a few chemical events.[8] Of particular interest is such an IMCR/post-IMCR tandem design that would allow the product of initial IMCR to be a substrate for another IMCR and so on, thus multiplying the diversity and/or complexity of resulting compounds. This strategy has been reduced to practice in recent work by Wessjohann[9] in which sequential Ugi reactions led to biologically active peptoid structures containing as many as eight amide units.

Recently we described a novel IMCR process involving aromatic 1,2-diamines **1**, aldehydes, and isocyanides that led to redox-unstable 1,4-dihydroquinoxalines **2**. These were quickly oxidized with DDQ into stable quinoxalines **3** contaning three elements of diversity resulting from the three reactants.[10] This two-step sequence represented a conceptually new method for preparing substituted quinoxalines. We reasoned that if we use a convertible isocyanide, such as *tert*-butylisocyanide[11] or 1,1,3,4-tetramethylbutylisocyanide (Walborsky reagent[12]), to construct quinoxalines **4** using the same two-step sequence, then the R_{conv} group could be removed (still leaving behind two diversity elements from the first IMCR) and the resulting 2-aminoquinoxalines **5** could serve as substrates for GB-MCR, i.e., the second IMCR in a row (Scheme 1). Herein we report our results on the feasibility of the above strategy.

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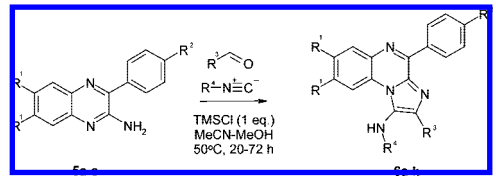
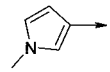
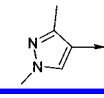
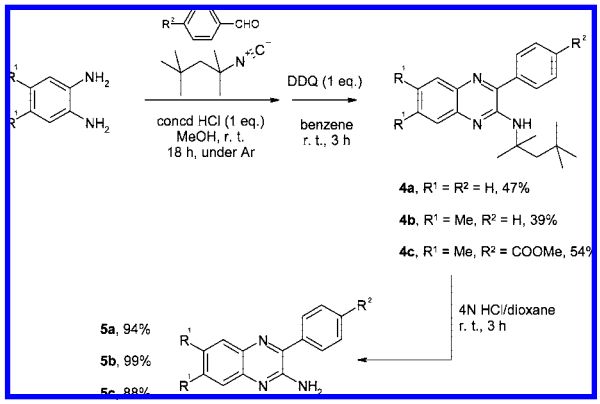
TABLE 1. TMSCl-Promoted GB-MCR of Aminoquinoxalines 5a−c



Product	R^1	R^2	R^3	R^4	Reaction time, h	Yield, %
6a	H	H	4-FPh	*i*-PrO$(CH_2)_3$	20	65
6b	H	H	*n*-Pr	4-MeOPhCH_2	48	45
6c	H	H	4-(*n*-BuO)Ph	*i*-Pr$(CH_2)_2$	48	52
6d	H	H	3,4,5-$(MeO)_3$Ph	4-MeOPhCH_2	72	68
6e	Me	H	3-Py	EtO$(CH_2)_3$	20	73
6f	Me	H	4-(*i*-PrO)Ph	EtO_2CCH_2	48	56
6g	Me	H		Cyclopentyl	72	34
6h	Me	H	4-NCPh	*t*-Bu	20	72
6i	Me	COOMe	*n*-Pr	*t*-Bu	48	64
6j	Me	H	*n*-Pr	*t*-Bu	48	71
6k	Me	H		EtO$(CH_2)_3$	72	49

SCHEME 2. Preparation of 5a−c as Substrates for the Groebke−Blackburn Reaction



Between the two convertible isocyanides that proved to work well in GB-MCR (vide supra), we chose the Walborsky reagent for our studies. Although it is more expensive than *tert*-butylisocyanide, its removal requires only brief exposue to mineral acid (such as 4 N HCl in dioxane[13]) while removing *t*-BuNC with TFA involves inevitable (albeit sometimes useful[11]) intermediacy of the respective trifluoroacetamides and the need to hydrolyze the latter that limits the process's functional group tolerance. The three isooctylamino quinoxalines **4a−c** were synthesized in good yields as described earlier.[10] Treatment of **4a−c** with 4 N HCl in dioxane led to nearly quantitative yields of the primary amines **5a−c** (Scheme 2).

The latter were now used as substrates for GB-MCR. Among the range of conditions described for this reaction, we narrowed our choice to the protocol involving TMSCl as a promoter, that has given us[14] and others[5] superior results compared to other catalysts or promoters such as lanthanide Lewis acids[6b] or mineral acids.[6a] An equimolar amount of TMSCl effectively promoted GB-MCR and versions thereof both in pure acetonitrile[14] and methanol.[5] When attempting GB-MCR with **5a−c**, we found that these substrates were poorly soluble in pure acetonitrile, thus giving only partial conversions.

Acetonitrile−methanol mixtures, however, dissolve aminoquinoxalines and we used this reaction medium throughout the study. To our delight, the products with the desired molecular weight were present in the reaction mixtures as single isomer (as evidenced by a single product LCMS peak and verified by ^{1}H NMR analysis of the crude products giving only one set of signals corresponding to the target imidazo[1,2-*a*]quinoxalines), thus confirming that the reaction was free from the regiochemical ambiguity noted for such processes by us[15] and others.[16] The products **6a−k** were isolated chromatographically in satisfactory yields (Table 1). Their identity as the target imidazo[1,2-*a*]quinoxalines was further confirmed by ^{1}H and ^{13}C NMR and elemental analyses and single-crystal X-ray analysis of a representative compound (**6f**, see the Supporting Information).

Crystallographic information was particularly important in confirming that the GB-MCR had taken the desired regiochemical course (**6** vs **7**). This is further confirmed by NOESY information obtained for compounds **6c** (Figure 1).

In conclusion, we developed a synthetic strategy to prepare substituted imidazo[1,2-*a*]quinoxalines **6** that have not been described in the literature. The conceptually new protocol includes two coupled IMCR processes: the earlier described synthesis of quinoxalines from *o*-phenylenediamines and the Groebke−Blackburn multicomponent reaction. The simplicity of the reaction design and the possibility to synthesize novel heterocycles **6** with four diversity elements in only four chemical operations (including two chromatographic purifications) makes the described methodology a tool of choice to construct these

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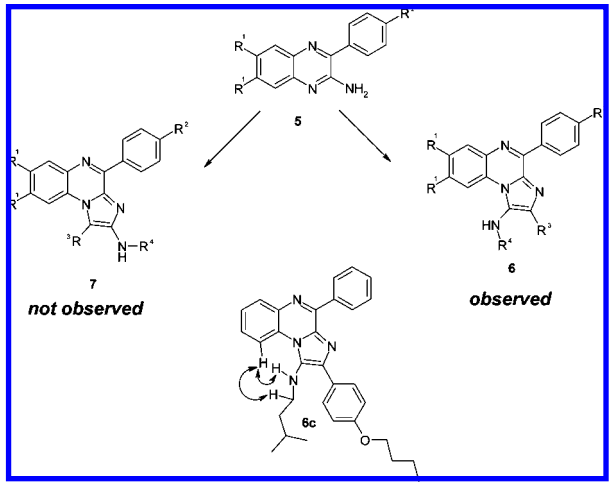

FIGURE 1. Possible regiochemical outcomes[15,16] of the GB-MCR of **5** and through-space interactions observed in the NOESY spectrum of **6c**.

medicinally relevant[17] compounds. Biological profiling of the described compounds is currently underway in our laboratories. The results of these studies will be disclosed in due course.

Experimental Section

Typical Procedure 1: Synthesis of Quinoxalines 4. The starting *o*-phenylenediamine (10 mmol) was dissolved in anhydrous methanol (50 mL) and the solution was thoroughly degassed by freeze−thaw technique. To the solution were added concentrated HCl (10 mmol) and equimolar amounts of the aldehyde and the isocyanide. The reaction mixture was stirred in argon atmosphere at rt for 18 h. The methanol was evaporated in vacuo. The residue was partitioned between sat. aq $NaHCO_3$ and chloroform and the aqueous layer was further extracted with chloroform. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was taken up in dry benzene (the amount of benzene was such that the mixture is transparent to slightly cloudy, usually ≤50 mL on the scale described) and a solution of DDQ in a small amount of benzene was added dropwise. The resulting mixture was stirred at rt for 1−3 h. The precipitate of hydroquinone was filtered off and washed with toluene. The combined filtrate and washings were concentrated in vacuo and the quinoxalines **4** were isolated chromatographically (SiO_2) with ethyl acetate−hexane mixtures as eluent.

4b: gray solid, mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 5.9 Hz, 3H), 7.52 (m, 4H), 4.98 (s, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 1.96 (s, 2H), 1.57 (s, 6H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 145.8, 139.8, 138.8, 137.2, 134.6, 133.0, 128.8, 128.1, 127.8, 125.6, 55.5, 51.1, 31.3, 31.1, 28.8, 19.8, 19.4; LCMS (M + H) 362. Anal. Calcd for $C_{24}H_{31}N_3$: C, 79.73; H, 8.64; N, 11.62. Found: C, 79.69; H, 8.60; N, 11.59.

Typical Procedure 2: Isooctyl Group Removal To Prepare 5. Isooctylaminoquinoxalines **4** (5 mmol) were dissolved in 4 N HCl in dioxane and the solution was stirred at rt for 3 h. The reaction mixture was carefully added to ice-cold sat. aq $NaHCO_3$ solution and, when CO_2 evolution seized, the mixture was extracted with ethyl acetate (3 × 50 mL). Combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The products were at least 90% pure as judged by ^{1}H NMR and were used in the next step without further purification.

5b: white solid, mp 171−173 °C (methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.0, 1.5 Hz, 2H), 7.72 (s, 1H), 7.52 (m, 3H), 7.45 (s, 1H), 5.16 (s, 2H), 2.38 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 144.2, 139.8, 139.3, 137.0, 136.6, 134.6, 129.0, 128.7, 128.0, 124.7, 20.0, 19.5; LCMS (M + H) 250. ANal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 77.13; H, 6.11; N, 16.89.

Typical Procedure 3: The Groebke−Blackburn Reaction To Prepare 6. A solution of **5** (1 mmol) in 50:50 MeOH/MeCN (10 mL) was treated with an aldehyde (1 mmol) and the mixture was stirred at rt for 3 h. To the resulting solution (often cloudy) was added TMSCl (1 mmol) in a minimum volume of DCM, then the mixture was stirred for an additional 30 min, an isocyanide (1 mmol) was added, and the mixture was heated at 50 °C over 20−72 h. When the reaction was complete (as judged by TLC and LCMS analyses), the mixture was cooled to rt and partitioned between sat. aq $NaHCO_3$ (25 mL) and ethyl acetate (25 mL). The aqueous layer was further extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Chromatography on silica gel with an appropriate gradient (0−10%) of methanol in DCM provided the target compounds **6a**−**k** in yields indicated in Table 1.

6e: brown sticky solid; ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.29 (s, 1H), 8.86 (s, 1H), 8.75 (d, J = 7.9 Hz, 2H), 8.56 (d, J = 3.8 Hz, 1H), 8.45 (d, J = 7.9 Hz, 1H), 7.76 (s, 1H), 7.53 (m, 4H), 5.24 (t, J = 5.3 Hz, 1H), 3.47 (t, J = 6.0 Hz, 2H), 3.34 − 3.42 (m, 2H), 3.11 (q, J = 6.1 Hz, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.86 (m, 2H), 1.08 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 Hz, d_6-DMSO) δ 147.6, 147.5, 137.0, 136.1, 134.8, 134.5, 134.4, 133.6, 133.4, 133.3, 129.9, 129.6, 127.8, 126.1, 123.7, 116.0, 95.6, 67.8, 65.4, 45.9, 29.7, 20.2, 19.3, 15.1; LCMS (M + H$^+$) 452. Anal. Calcd for $C_{28}H_{29}N_5O$: C, 74.48; H, 6.47; N, 15.51. Found: C, 74.54; H, 6.49; N, 15.55.

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Supporting Information Available: Characterization data for the newly synthesized compounds (**4a**−**c**, **5a**−**c**, **6a**−**k**) and an X-ray crystallographic file (CIF) for compound **6f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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