Expedient Entry into 1,4-Dihydroquinoxalines and Quinoxalines via a Novel Variant of Isocyanide-Based MCR

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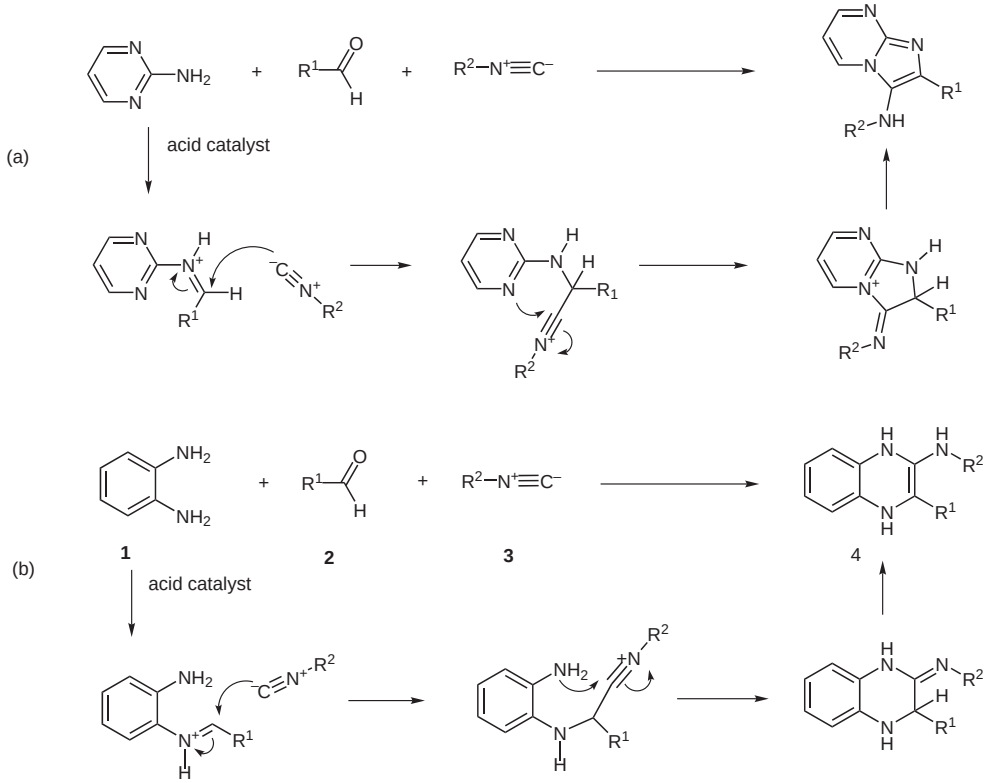
Abstract: A novel multicomponent reaction of *o*-phenylenediamines with aldehydes and isonitriles yields 1,4-dihydroquinoxalines. These intermediates are unstable under reaction conditions. They undergo oxidation with DDQ to furnish 33−54% isolated yields of the respective quinoxalines. This reaction is general for aromatic 1,2-diamines. Monoalkylated aryl 1,2-diamines lead to stable 1,4-dihydroquinoxalines.

Key words: combinatorial chemistry, dehydrogenations, multicomponent reactions, isocyanides, quinoxalines

Recent developments in the multicomponent reactions (MCR)[2] involving isocyanides and substrates containing two reacting functionalities have further confirmed their utility in generating complex scaffolds in a single chemical event. Notable examples include: i) Groebke reaction of 2-aminoazines and azoles,[3,4] ii) ring-forming Ugi-type reactions of various aldehydo and keto acids,[5,6] iii) aqueous-phase β-lactam synthesis from β-amino acids,[7] and many others.

In the course of our research on the Groebke-type reactions,[8,9] we explored the opportunities for other nitrogen nucleophiles (e.g., free amino group) within the aldimine moiety to intercept the initial reactive intermediate.[10] Herein we would like to report that, according to this rationale, the use of *o*-phenylenediamine (**1**) in the reaction with equimolar amounts of an aldehyde **2** and an isonitrile **3** leads to the formation of 1,4-dihydroquinoxalines **4** (Scheme 1).

This reaction proceeded smoothly with a variety of reactants (Table 1) in methanol at room temperature using equimolar amount of HCl (concd) as a catalyst. In 18 hours, 1,4-dihydroquinoxalines **4a−h** were detected as major components of the reaction mixture by LCMS anal-



Scheme 1 The Groebke reaction of 2-aminopyrimidine (a) and the novel reaction of *o*-phenylenediamines described in this work (b).

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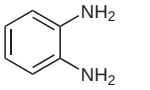
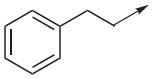
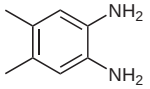
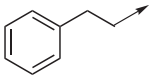
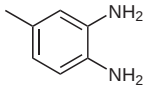
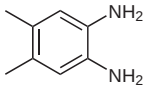
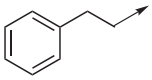
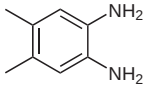
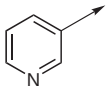
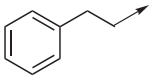
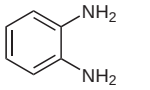
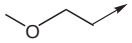
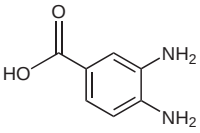
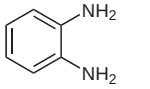
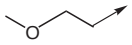
Table 1 Quinoxalines **5a–h** Synthesized in this Work

Entry	Diamine **1**	R^1	R^2	Yield of **5** (%)[c]
1		Ph		54
2		Ph		50
3		Ph		53[a]
4				43
5				33
6		Ph		48
7		Ph		35[b]
8				43

[a] The product was isolated chromatographically as 1:1 mixture of isomers.
[b] The product was obtained as a single isomer after chromatography (<5% of the other isomer was present in crude reaction mixture by LCMS analysis).
[c] The yield for two steps (% from **1**) after chromatography.

ysis, accompanied by minor byproducts.[11] During attempted chromatographic isolation of **4a–h**, these compounds were found to be unstable. Exposure of **4a–h** to air led to the formation of variable amounts of the respective quinoxalines **5a–h**. Efficient conversion of the product mixture into a single isolable product was achieved by brief exposure of crude reaction mixtures containing **4a–h** to DDQ/benzene system at room temperature. As expected, this furnished **5a–h** (Scheme 2, Table 1).[12] The identity of synthesized quinoxalines **5** has been confirmed by the X-ray analysis of a representative compound **5b** (Figure 1).[13]

Several relevant molecules have been reported as biologically active substances. A number of antifolate agents[14] and kinase inhibitors[15] based on this chemotype appeared in the literature. Notably, their synthesis generally involved multistep reaction sequences. The method reported herein offers a convenient and conceptually new alternative to combinatorial synthesis of 2-(alkylamino)-3-arylquinoxalines. In addition, it offers considerable

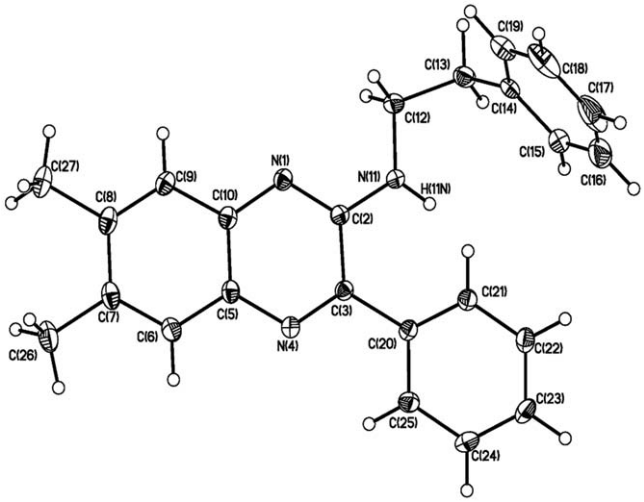
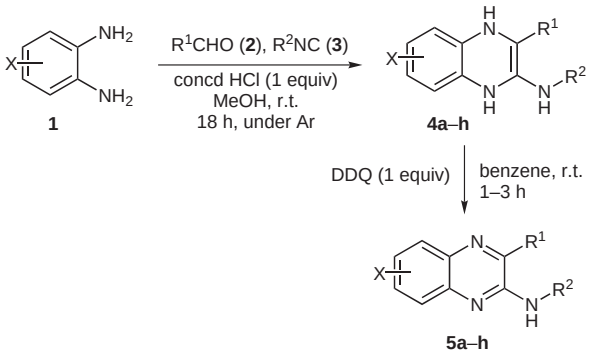


Figure 1 X-ray structure of the compound **5b**.

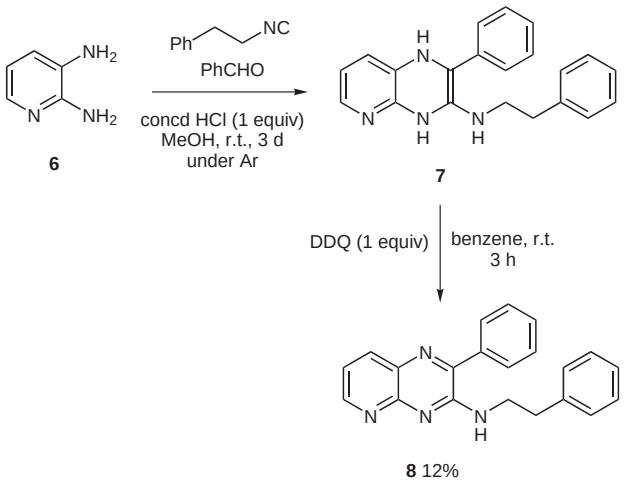


Scheme 2 Synthesis of quinoxalines **5a–h** via intermediate formation of 1,4-dihydroquinoxalines **4a–h**.

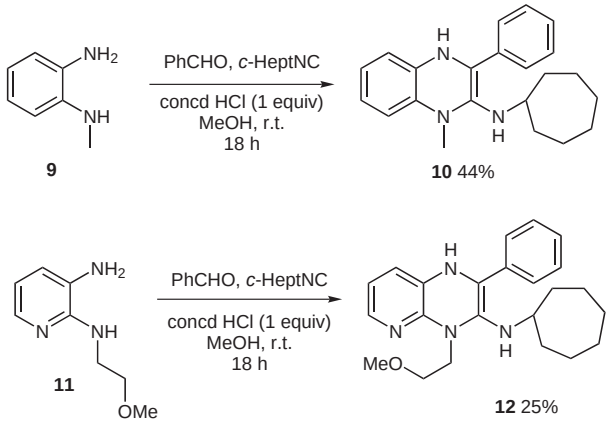
flexibility with respect to functional group (e. g., **5g**). To the best of our knowledge, this new isocyanide-based multicomponent reaction is the first example of the anilinic amino group functioning as internal nucleophile to intercept the isonitrile interacting with an aldimine moiety. We further established that this two-step addition–oxidation protocol can be extended to the synthesis of pyrido[2,3-*b*]pyrazine **8** from 2,3-dimiaminopyridine (**6**),[16] albeit in low yield (Scheme 3).

In order to confirm the intermediacy of 1,4-dihydroquinoxalines **4** in the preparation of the isolated quinoxalines **5**, we tested the same multicomponent reaction using monoalkylated diamines **9** and **11**. Gratifyingly, the reaction mixtures contained products **10**[17] and **12**[18] isolated in moderate yields (Scheme 4). These heterocyclic compounds are flavin analogues posing interest as molecular probes[19] and catalysts for biomimetic oxidations.[20]

In conclusion, we have discovered a novel variant of isocyanide-based MCR involving aromatic 1,2-diamines and demonstrated its preparative value in efficient two-step synthesis of medicinally important 2-(alkylamino)-3-arylquinoxalines **5a–h**. This reaction could be extended to the heterocyclic 1,2-diamines and N-monoalkylated diamines. The potential of this new ring-forming MCR war-



Scheme 3



Scheme 4 Air-stable 1,4-dihydroquinoxaline **10** and 1,4-dyhydropyrido[2,3-*b*]pyrazine **12** prepared from monoalkylated diamines (**9** and **11**, respectively).

rants future studies to expand scope and optimize yields of the target compounds.

The starting diamine **1** (10 mmol) was dissolved in anhyd MeOH (50 mL) and the solution was thoroughly degassed by freeze-thaw technique. Concentrated HCl (10 mmol) and equimolar amounts of aldehyde **2** and isonitrile **3** were added to the resulting solution. The reaction mixture was stirred at r.t. for 18 h under argon. Methanol was evaporated in vacuo. The residue was partitioned between sat. aq $NaHCO_3$ and $CHCl_3$. Aqueous layer was further extracted with $CHCl_3$. Combined organic extracts were dried over anhyd $MgSO_4$, filtered, and concentrated in vacuo. Crude product was washed with dry benzene (ca. 100 mL) and a solution of DDQ in 5 mL of benzene was added dropwise. The resulting mixture was stirred at r.t. for 1−3 h. The precipitate of hydroquinone was filtered off and washed with toluene. The combined filtrate and washings were concentrated in vacuo. Quinoxalines **5a−h** were isolated chromatographically (SiO_2) using EtOAc−hexane mixtures as eluent.

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References and Notes

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(10) (a) One example of an aliphatic diamine participating in the intramolecular Ugi-type MCR has been reported in:Keung, W.; Bakir, F.; Patron, A. P.; Rogers, D.; Priest, C. D.; Darmohusodo, V. *Tetrahedron Lett.* **2004**, *45*, 733. (b) An account of the use of ethylene diamines appeared in print when the present manuscript was in preparation: Kysil, V.; Tkachenko, S.; Khvat, A.; Williams, C.; Tsirulnikov, S.; Churakova, M.; Ivachtchenko, A. *Tetrahedron Lett.* **2007**, *48*, 6239.
(11) (a) One of the redundant byproducts was identified as 2-(R^1)-substituted benzimidazole, presumably formed from the oxidative cyclization of the intermediate aldimine. This observation is in accordance with our previous results, see ref. 11b. The unwanted benzimidazole formation could be minimized by thorough exclusion of air from the reaction medium. (b) Krasavin, M.; Kobak, V. V.; Bondarenko, T. Y.; Kravchenko, D. V. *Heterocycles* **2005**, *65*, 2189.
(12) **Analytical Data for Selected Compounds**
Compound **5b**: pale yellow solid, mp 156−157ºC. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.50−7.59 (m, 7 H), 7.21−7.31 (m, 5 H), 6.34 (s, 1 H, NH), 3.64 (unresolved dd, 2 H, $NHCH_2$), 2.93 (unresolved t, 2 H, $NHCH_2CH_2$), 2.37 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.0, 145.7, 140.3, 140.1, 139.6, 137.3, 135.5, 133.5, 129.6, 129.2 (two signals overlapped), 128.9, 128.8, 128.2, 126.4, 125.7, 42.9, 34.7, 20.2, 19.7. LCMS: *m/z* = 354 [M + 1]. HRMS (EI): *m/z* calcd for $C_{24}H_{23}N_3$: 353.4710; found: 353.4711.
Compound **5g**: grey solid, mp 203 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.95 (br s, 1 H, COOH), 8.33 (d, *J* = 1.5 Hz, 1 H), 8.04 (dd, *J* = 8.6, 1.8 Hz, 1 H), 7.74 (m, 2 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 7.55 (m, 3 H), 6.61 (d, *J* = 6.6 Hz, 1 H, NH), 4.46 (m, 1 H, NHCH), 2.00 (m, 2 H), 1.65 (m, 2 H), 1.54 (m, 4 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.5 (COOH), 150.9, 148.2, 144.3, 136.7, 135.6, 130.8, 130.1, 129.8, 129.3, 128.9, 126.1, 125.8, 52.9, 32.2, 24.0. LCMS: *m/z* = 334 [M + 1]. HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_3O_2$: 333.3933; found: 333.3932.
Compound **5h**: yellow sticky solid, mp 68–69 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.86 (dd, *J* = 3.8, 0.9 Hz, 1 H), 7.83 (dd, *J* = 5.1, 0.9 Hz, 1 H), 7.78 (dd, *J* = 8.2, 1.1 Hz, 1 H), 7.62 (dd, *J* = 8.4, 1.1 Hz, 1 H), 7.55 (ddd, *J* = 8.4, 6.8, 1.1 Hz, 1 H), 7.37 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H), 7.27 (dd, *J* = 5.1, 3.8 Hz, 1 H), 6.87 (t, *J* = 5.3 Hz, $NHCH_2$), 3.70 (dt, J_d = 5.3, J_t = 5.1 Hz, 2 H, $NHCH_2$), 3.62 (t, *J* = 5.1 Hz, 2 H, $MeOCH_2$), 3.31 (s, 3 H, OCH_3). ^{13}C NMR (75 MHz, DMSO-

d_6): δ = 149.4, 140.9, 140.8, 140.0, 136.4, 130.3, 130.0, 128.7, 128.4, 128.2, 125.9, 124.8, 70.3, 58.4, 40.7. LCMS: *m/z* = 286 [M + 1]. HRMS (EI): *m/z* calcd for $C_{15}H_{15}N_3OS$: 285.3703; found: 285.3703.

(13) Crystallographic data (excluding structure factors) for the structure **5b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 671798. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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(16) **Characterization Data for 8**
Brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.79 (dd, *J* = 5.1, 1.8 Hz, 1 H), 8.50 (d, *J* = 7.3 Hz, 1 H), 7.73 (br s, 1 H, NH), 7.64 (m, 2 H), 7.53−7.59 (m, 4 H), 7.28−7.35 (m, 4 H), 7.22 (m, 1 H), 3.72 (dd, *J* = 14.2, 7.2 Hz, 2 H, $NHCH_2CH_2$), 2.98 (t, *J* = 7.2 Hz, 2 H, $NHCH_2CH_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.4, 151.6, 147.0, 142.1, 136.7, 135.0, 134.9, 133.6, 130.1, 129.6, 128.5, 127.9, 127.2, 126.4, 125.8, 43.6, 35.2. LCMS: *m/z* = 327 [M + 1]. HRMS (EI): *m/z* calcd for $C_{21}H_{18}N_4$: 326.4044; found: 326.4047.

(17) **Characterization Data for 10**
Off-white solid, mp 110–112 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.24 (m, 3 H), 7.15 (m, 2 H), 6.86 (m, 1 H), 6.83 (m, 1 H), 6.72 (ddd, *J* = 7.6, 7.5, 1.6 Hz, 1 H), 6.53 (dd, *J* = 7.5, 1.6 Hz, 1 H), 5.47 (s, 1 H, dihydroquinaxoline-NH), 4.24 (br s, 1 H, NH-*cyclo*C_7H_{13}), 3.52 (s, 3 H, NCH_3), 3.48 (m, 1 H, NHCH), 1.72−1.82 (m, 2 H), 1.44−1.67 (m, 8 H), 1.18−1.35 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 149.8, 140.5, 132.1, 132.0, 128.8, 127.7, 126.4, 120.3, 119.9, 114.5, 113.0, 58.7, 53.4, 37.2, 36.6, 30.6, 28.3, 28.1, 24.7, 24.5. LCMS: *m/z* = 334 [M + 1]. HRMS (EI): *m/z* calcd for $C_{22}H_{27}N_3$: 333.4806; found: 333.4803.

(18) **Characterization Data for 12**
Brown viscous oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (dd, *J* = 4.9, 1.3 Hz, 1 H), 7.89 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.56 (m, 2 H), 7.51 (m, 3 H), 7.07 (dd, *J* = 4.9, 7.6 Hz, 1 H), 4.55 (t, *J* = 6.3 Hz, 2 H, $MeOCH_2$), 3.65 (t, *J* = 6.3 Hz, 2 H, $NHCH_2$), 3.30 (s, 3 H, OCH_3), 3.24 (m, 1 H, NHCH), 1.44 (m, 2 H), 1.30−1.40 (m, 6 H), 1.21 (m, 2 H), 0.95 (m, 2 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 154.2, 149.0, 146.1, 139.8, 139.5, 136.1, 130.0, 129.0, 127.4, 117.1, 114.2, 68.3, 58.4, 58.0 (one signal obscured by DMSO sept). LCMS: *m/z* = 379 [M + 1]. HRMS (EI): *m/z* calcd for $C_{23}H_{30}N_4O$: 378.5218; found: 378.5221.

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