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The regioselective catalyst-free synthesis of bis-quinoxalines and bis-pyrido[2,3-*b*]pyrazines by double condensation of 1,4-phenylene-bis-glyoxal with 1,2-diamines

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Abstract: The oxidation of 1,4-diacetylbenzene using several oxidizing agents gave 1,4-phenylene-bis-glyoxal in 61–85% yields. A convenient and efficient synthesis of bis-quinoxaline and bis-pyrido[2,3-*b*]pyrazine derivatives involves the double condensation of 1,2-diamines with 1,4-phenylene-bis-glyoxal in ethanol under reflux conditions. The structures of the new products were defined by proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), Fourier-transform infrared spectroscopy (FT-IR) and mass spectrometry (MS).

Keywords: 1,2-diamines; 1,4-phenylene-bis-glyoxal; bis-pyrido[2,3-*b*]pyrazines bis-quinoxalines; regioselectivity; selenium dioxide.

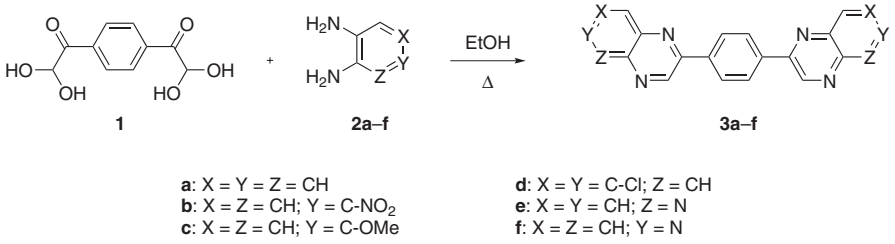
Introduction

Glyoxals are important building blocks in organic synthesis, particularly in the synthesis of biologically active heterocyclic compounds [1–9] including quinoxaline derivatives [10–26]. Synthesis of a quinoxaline by the reaction of a glyoxal with a 1,2-diamine is part of the general strategy involving the reaction of 1,2-dicarbonyl compounds with 1,2-diamines [27–30]. In continuation of our studies on the development of new synthetic routes to heterocyclic compounds using arylglyoxals, herein we report the synthesis of new bis-quinoxaline derivatives **3a–f** in a 68–94% yield via condensation of 1,4-phenylene-bis-glyoxal as its hydrate **1** (structure in Scheme 1) and 1,2-diamines **2a–f** in ethanol under reflux conditions.

Results and discussion

The glyoxal hydrate **1** was synthesized by oxidation of 1,4-diacetylbenzene using different oxidizing agents in a 61–85% yield. The SeO_2/dioxane/H_2O system is preferred to other oxidizing agents as its use provides product **1** in an 85% yield after crystallization from water. The use of other oxidizing systems described in the literature, namely HBr/DMSO/H_2O, $CuCl_2$/DMSO/H_2O and I_2/CuO/DMSO, furnished compound **1** in the respective yields of 73%, 65% and 61%.

The condensation of compound **1** with 1,2-diamines **2a–f** in ethanol under reflux gave the desired bis-quinoxalines and bis-pyrido[2,3-*b*]pyrazines under catalyst-free conditions in a 68–89% yield (Scheme 1). The use of unsymmetrical aromatic diamines **2b**, **2e** and **2f** could in principle lead to isomeric products, but the formation of a single product in each case shows that the reactions are regioselective. As can be seen, in the condensation of bis-glyoxal **1** with 4-nitro-1,2-diaminobenzene (**2b**) and



Scheme 1

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aminopyridines **2e** or **2f**, the more nucleophilic 1-amino group attacks the formyl group in the first step, and the condensation of the less reactive 2-amino group with the keto groups occurs in the second step, leading to the formation of bis-quinoxaline **3b**. The reactions of aminopyridines **2e** and **2f** with **1** follow a similar pattern and furnish regioselectively the respective bis-pyrido[2,3-*b*]pyrazines **3e** and **3f**. This reactivity pattern is in full agreement with previous mechanistic studies on the construction of fused pyrazines [27–30].

Conclusion

A double condensation of 1,4-phenylene-bis-glyoxal with various 1,2-diamines furnished bis-quinoxaline derivatives **3a–f** in high to excellent yields. The simplicity of operation, high yields and regioselectivity are the key advantages of this method.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. Infrared spectra were measured on a Spectrum RXI, Perkin Elmer, UK Fourier-transform infrared (FT-IR) instrument using KBr disks. The ^{1}H (300 MHz) and ^{13}C (75 MHz) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX-300 Avance spectrometer in DMSO-d_6, $CDCl_3$ and C_6D_6 relative to tetramethylsilane (TMS) as the internal reference. Thin layer chromatography (TLC) was carried out on a pre-coated aluminum sheet with silica gel 60F 254 obtained from Merck, and detection was made with the help of an ultraviolet (UV) lamp (λ 254 nm). Mass analysis was performed on an Agilent Technology (HP) 5973 Network Mass Selective Detector and high-resolution mass spectra were recorded on a Kratos mass spectrometry (MS) 25RF spectrometer.

Synthesis of 1,1′-(1,4-phenylene)bis(2,2-dihydroxyethanone) (1)

A solution of selenium dioxide (1.55 g, 14 mmol) in 90% aqueous dioxane (10 mL) was treated at 100°C with a solution of 1,4-diacetylbenzene (1.62 g, 10 mmol) in dioxane (12 mL). The mixture was heated under reflux for 14 h and the precipitated selenium was removed by filtration. The solution was cooled and the resultant pale yellow precipitate of product **1** was collected and crystallized from water: yield 1.92 g (85%); mp 141–142°C; IR: ν_{max} 3428, 3377, 2975, 1670, 1505, 1446, 1407, 1297, 1121, 1037, 962, 873, 801, 696, 584, 517 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.15 (s, 4H), 6.90 (d, J = 7.2 Hz, 4H, 4 × OH, exchanged by D_2O addition), 5.68 (bt, J = 7.2 Hz, 2H, changed to a singlet after D_2O addition); ^{13}C NMR (DMSO-d_6): δ 196.5, 137.4, 129.7, 89.9; MS: *m/z* (%) 226 ([M]$^+$, 59), 184 (100), 163 (58), 149 (65), 133 (76), 105 (59), 91 (52), 77 (56), 55 (75). ESI-HRMS: Calcd. for $C_{10}H_{10}O_6$, [M]$^+$: *m/z* 226.0477. Found: *m/z* 226.0462.

General procedure for the synthesis of bis-quinoxalines and bis-pyrido[2,3-*b*]pyrazines (3a–f)

A mixture of 1,4-phenylene-bis-glyoxal (**1**, 1 mmol) and a 1,2-diamine (**2a–f**, 2 mmol) in absolute ethanol (10 mL) was heated under reflux for 10–15 h, then cooled and the resultant precipitate of **3a–f** was filtered, washed with ethanol and crystallized from ethanol.

1,4-Bis-(quinoxalin-2-yl)benzene (3a) Reaction time 12 h; yield 82% of light yellow powder; mp 264–266°C; IR: ν_{max} 3054, 1678, 1609, 1574, 1545, 1490, 1462, 1426, 1370, 1320, 1262, 1231, 1208, 1130, 1054, 1014, 956, 847, 756, 674, 630, 601, 566 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 2H), 8.45 (s, 4H), 8.24–8.16 (m, 4H), 7.85–7.80 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 150.9, 142.4, 141.8, 138.3, 130.5, 129.9, 129.7, 129.2, 128.2; EI-MS: *m/z* (%) 335 ([M + 1]$^+$, 28), 334 [M]$^+$ (100), 307 (11), 306 (17), 204 (12), 76 (19). ESI-HRMS. Calcd. for $C_{22}H_{14}N_4$, [M]$^+$: 334.1218. Found: *m/z* 334.1205.

1,4-Bis(6-nitroquinoxalin-2-yl)benzene (3b) Reaction time 15 h; yield 68% of orange powder; mp 235–236°C; IR: ν_{max} 3047, 1578, 1554, 1348, 1320, 1280, 1193, 1078, 1050, 964, 844, 831, 792, 742 cm^{-1}; ^{1}H NMR (C_6D_6): δ 9.16 (s, 1H), 9.13 (s, 1H), 8.20 (s, 4H), 8.10 (d, J = 9 Hz, 2H), 7.98 (d, J = 9 Hz, 2H), 7.10 (bs, 2H); ^{13}C NMR (C_6D_6): δ 138.5, 137.7, 136.1, 135.7, 133.7, 127.6, 126.9, 124.6, 124.0, 123.8; EI-MS: *m/z* (%) 425 ([M + 1]$^+$, 27), 424 ([M]$^+$, 100), 394 (25), 382 (11), 351 (14), 75 (13). ESI-HRMS. Calcd. for $C_{22}H_{12}N_6O_4$, [M]$^+$: *m/z* 424.0920. Found: *m/z* 424.0907.

1,4-Bis(6-methoxyquinolin-2-yl)benzene (3c) Reaction time 10 h; yield 89% of brown powder; mp 267–268°C; IR: ν_{max} 3047, 1616, 1498, 1374, 1321, 1261, 1217, 1201, 1173, 1122, 1060, 1026, 958, 846, 830, 779 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.52 (s, 2H), 8.55(s, 4H), 8.03 (d, J = 8.7 Hz, 2H), 7.54 (s, 2H), 7.51 (d, J = 8.7 Hz, 2H), 3.86 (s, 6H); ^{13}C NMR spectrum could not be recorded due to low solubility of the sample; EI-MS: *m/z* (%) 395 ([M + 1]$^+$, 29), 394 ([M]$^+$, 100), 262 (10), 197 (7), 106 (12), 63 (10). ESI-HRMS. Calcd. for $C_{24}H_{18}N_4O_2$, [M]$^+$: *m/z* 394.1430. Found: *m/z* 394.1416.

1,4-Bis(6,7-dichloroquinoxalin-2-yl)benzene (3d) Reaction time 12 h; yield 78% of gray powder; mp 190–191°C; the ^{1}H NMR and ^{13}C NMR spectra could not be recorded due to low solubility of the sample; IR: ν_{max} 3066, 3045, 1544, 1459, 1418, 1317, 1274, 1177, 1111, 1058, 1016, 945, 928, 900, 878, 840, 810, 660, 624 cm^{-1}; EI-MS: *m/z* (%) 478 ([M + 6]$^+$, 14), 474 ([M + 4]$^+$, 52), 472 ([M + 2]$^+$, 100), 470 ([M]$^+$, 80), 300 (17), 272 (15), 237 (11), 170 (13), 146 (32), 144 (50), 109 (30), 74 (12). ESI-HRMS. Calcd. for $C_{22}H_{10}Cl_4N_4$, [M]$^+$: *m/z* 469.9660. Found: *m/z* 469.9648.

1,4-Bis(pyrido[2,3-*b*]pyrazine-2-yl)benzene (3e) Reaction time 10 h; yield 80% of brown powder; mp 320–321°C; IR: ν_{max} 3413, 3067, 2372, 1546, 1461, 1310, 209, 1125, 1061, 952, 848, 794 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.29 (s, 2H), 9.25 (bs, 2H) 8.82 (s, 4H), 8.54 (d, J = 7.8 Hz, 2H), 7.77 (dd, J_1 = 8.4 Hz, J_2 = 4.5 Hz, 2H); ^{13}C NMR spectrum could not be recorded due to low solubility of the sample; EI-MS: *m/z* (%) 337 ([M + 1]$^+$, 24), 336 ([M]$^+$, 100), 308 (9), 233 (20), 205 (9), 104 (10), 77 (14). ESI-HRMS. Calcd. for $C_{20}H_{12}N_6$, [M]$^+$ *m/z* 336.1123. Found: *m/z* 336.1111.

1,4-Bis(pyrido[3,4-*b*]pyrazine-2-yl)benzene (3f) Reaction time 10 h; yield 78% of creamy powder; mp 248–249°C; IR: ν_{max} 3216, 2373, 1547, 1419, 1317, 1235, 1054, 960, 854, 837, 584 cm^{-1}; ^{1}H NMR ($CDCl_3$):

δ 9.62 (s, 2H), 9.55 (s, 2H), 8.90 (d, J = 5.7 Hz, 2H), 8.52 (s, 4H), 8.04 (d, J = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 154.2, 147.7, 145.2, 144.8, 136.8, 128.9, 128.5, 121.9, 121.5; EI-MS: *m/z* (%) 337 ($[M+1]^+$, 22), 336 ($[M]^+$, 100), 309 (13), 308 (15), 233 (11), 77 (11), 50 (32). ESI-HRMS. Calcd. for $C_{20}H_{12}N_6$, $[M]^+$: *m/z* 336.1123. Found: *m/z* 336.111.

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References

[1] Zaliani, V.; Cocconcelli, G.; Fantini, M.; Ghiron, C.; Rivara, M. A practical synthesis of 2,4(5)-diarylimidazoles from simple building blocks. *J. Org. Chem.* **2007**, *72*, 4551–4553.

[2] Juspin, T.; Terme, T.; Vanelle, P. Rapid access to diphenyl- and acenaphthoquinoline derivatives. *Synfacts* **2009**, *9*, 1485–1489.

[3] Fischer, B.; Kabha, E.; Gendron, F. P.; Beaudoin, A. R. Analytical ancestry: "firsts" in fluorescent labeling of nucleosides, nucleotides, and nucleic acids. *J. Med. Chem*. **2000**, *19*, 1033–1034.

[4] Prashanthukumar, B. R.; Sharma, G. K.; Srinath, S.; Noor, M.; Suresh, B.; Srinivasa, B. R. Synthesis and biological evaluation of newer benzofuran derivatives as potential anticancer and anathematic agents. *J. Heterocycl. Chem*. **2009**, *46*, 278.

[5] Robjohn, N. Selenium dioxide oxidation. *Org. React*. **1949**, *5*, 331.

[6] Robjohn, N. Selenium dioxide oxidation. *Org. React*. **1976**, *24*, 261.

[7] Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Weaver, W. M. Conversion of aldehydes to amides via dimethyl sulfoxide oxidation of the corresponding α-aminonitriles. *J. Am. Chem. Soc*. **1957**, *79*, 6562.

[8] Schaefer, J. P. Selenium dioxide oxidations. I. studies on the mechanism of oxidation of 1,2-dibenzoylethane. *J. Am. Chem. Soc*. **1962**, *84*, 713–716.

[9] Zhiling, C.; Dahua, Sh.; Ying, Q.; Chuanzhou, T.; Weiwei, L.; Guowei, Y. A new method for synthesis of 3,6-diacetyl-9-ethylcarbazole and its oxidation to the corresponding diglyoxal using several oxidizing agents. *Molecules* **2013**, *18*, 15717–15723.

[10] Zarranz, B.; Jaso, A.; Aldana, I.; Monge, A. Synthesis and anticancer activity evaluation of new 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide derivatives. *J. Med. Chem*. **2004**, *12*, 3711–3721.

[11] Grande, F.; Aiello, F.; Grazia, O. D.; Brizzi, A.; Garofalo, A.; Neamati, N. Synthesis and antitumor activities of a series of novel quinoxalin hydrazides. *J. Med. Chem*. **2005**, *15*, 288–294.

[12] Ali, M. M.; Ismail, M. M. F.; El-Gaby, M. S. A.; Zahran, M. A.; Ammar, T. A. Synthesis and anti-microbial activity of some novel quinoxaline derivatives. *Molecules* **2000**, *5*, 864–873.

[13] Seitz, L. E.; Suling, W. J.; Reynolds, R. C. Synthesis and antimycobacterial activity of pyrazine and quinoxaline derivatives. *J. Med. Chem*. **2002**, *45*, 5604–5606.

[14] Jaso, A.; Zarranz, B.; Aldana, I.; Monge, A. Synthesis of new quinoxaline-2-carboxylate 1,4-dioxide derivatives as antimycobacterium tuberculosis agents. *J. Med. Chem*. **2005**, *48*, 2019–2025.

[15] Bailly, C.; Echepare, S.; Gago, F.; Waring, M. Recognition elements that determine affinity and sequence-specific binding to DNA of 2QN, a biosynthetic bis-quinoline analogue of echinomycin. *J. Med. Chem*. **1999**, *14*, 291–303.

[16] Gomtsyan, A.; Bayburt, E. K.; Schmidt, R. G.; Zheng, G. Z.; Perner, R. J.; Didomenico, S.; Koeni, J. R.; Turner, S.; Jinkerson, T.; Drizin, I.; et al. Novel transient receptor potential vanilloid 1 receptor antagonists for the treatment of pain: structure-activity relationships for ureas with quinoline, isoquinoline, quinazoline, phthalazine, quinoxaline, and cinnoline moieties. *J. Med. Chem*. **2005**, *48*, 744–752.

[17] Perumal, R. V.; Mahesh, R. Synthesis and biological evaluation of a novel structural type of serotonin 5-HT3 receptor antagonists. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2769–2772.

[18] Tandon, V. K.; Yadav, D. B.; Maurya, H. K., Chaturvedi, A. K.; Shukla, P. K. Design, synthesis, and biological evaluation of 1,2,3-trisubstituted-1,4-dihydrobenzo[*g*]quinoxaline-5,10-diones and related compounds as antifungal and antibacterial agents. *J. Med. Chem*. **2006**, *14*, 6120–6126.

[19] Carta, A.; Loriga, M.; Paglietti, G.; Mattana, A.; Fiori, P. L.; Mollicotti, P.; Echi, L.; Zanetti, S. Synthesis, anti-mycobacterial, anti-trichomonas and anti-candida in vitro activities of 2-substituted-6,7-difluoro-3-methylquinoxaline-1,4-dioxides. *J. Med. Chem*. **2004**, *39*, 195–203.

[20] Mashevskaya, I.; Makhmudov, R. R.; Aleksandrova, G. A.; Golovnira, O. V.; Duvalov, A. V.; Maslivets, A. N. Synthesis and study of the antibacterial and analgesic activity of 3-acyl-1,2,4,5-tetrahydro-[1,2-*a*]quinoxaline-1,2,4-triones. *Pharm. Chem. J*. **2001**, *35*, 196–198.

[21] Vyas, D. A.; Chauhan, N. A.; Parikh, A. R. Synthesis and antimicrobial activity of quinoxaline based thiazolidinones and azetidinones. *Indian J. Chem*. **2007**, *46B*, 1699–1702.

[22] Burguete, A.; Pontiki, E.; Litina, D. H.; Villar, R.; Vicente, E.; Solano, B.; Ancizu, S.; Aldana, I.; Monge, A. Synthesis and anti-inflammatory/antioxidant activities of some new ring substituted 3-phenyl-1-(1,4-di-*N*-oxide quinoxalin-2-yl)-2-propen-1-one derivatives and of their 4,5-dihydro-(1*H*)-pyrazole analogues. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6439–6443.

[23] Wagle, S.; Adhikari, A. V.; Kumari, N. S. Synthesis of some new 2-(3-methyl-7-substituted-2-oxoquinoxalinyl)-5-(aryl)-1,3,4-oxadiazoles as potential nonsteroidal anti-inflammatory and analgesic agents. *Indian J. Chem*. **2008**, *47B*, 439–448.

[24] Kim, Y. B.; Kim, Y. H.; Park, J. Y.; Kim, S. K. Synthesis and biological activity of new quinoxaline antibiotics of echinomycin analogues. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 541–544.

[25] Palanaki, M. S. S.; Dneprovskaia, E.; Doukas, J.; Fine, R. M.; Hood, J.; Kang, X.; Lohse, D.; Martin, M.; Noronha, G.; Soll, R. M.; et al. Discovery of 3,3′-(2,4-diaminopteridine-6,7-diyl) diphenol as an isozyme-selective inhibitor of PI3K for the treatment of ischemia reperfusion injury associated with myocardial infarction. *J. Med. Chem*. **2007**, *50*, 4279–4294.

[26] Bandyopadhayay, D.; Cruz, J.; Morales, D. L.; Arman, H.; Cuate, E.; Lee, Y. S.; Banik, B. K.; Kim, D. An expeditious green route toward 2-aryl-4-phenyl-1*H*-imidazoles. *J. Med. Chem*. **2013**, *5*, 1377.

[27] Sako, M. Methods of Molecular Transformations. In *Science of Synthesis*. Yamamoto, Y., Ed. Houben-Weyl Thieme: Stuttgart, New York, 2003; Vol. 16, pp 1269–1290.
[28] Brown, D. J. A Series of Monographs; Quinoxalines: Supplement II. In *The Chemistry of Heterocyclic Compounds*. Taylor, E. C., Wipf, P., Eds. John Wiley & Sons: New Jersey, 2004; Vol. 61.
[29] Porter, A. E. A. Quinoxalines. In *Comprehensive Heterocyclic Chemistry A*. Katritsky, R., Rees, C. W., Eds. Oxford: Pergamum, 1984; p 157.
[30] Khalafy, J.; Poursattar Marjani, A.; Haghipour, M. Regioselective synthesis of 3-arylpyrido[2,3-*b*]pyrazines by reaction of arylglyoxals with 2,3-diaminopyridine. *Curr. Chem. Lett.* **2013**, *2*, 21–26.