

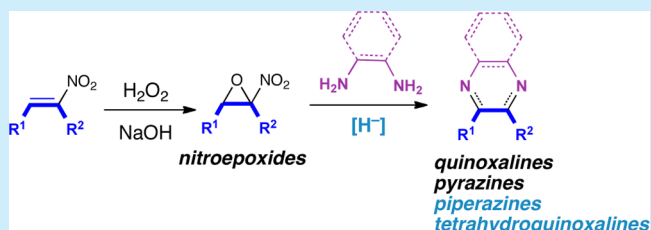
Nitroepoxides as Versatile Precursors to 1,4-Diamino Heterocycles

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S Supporting Information

ABSTRACT: Nitroepoxides are easily transformed into 1,4-diamino heterocycles such as quinoxalines and pyrazines by treatment with 1,2-benzenediamines and ammonia, respectively. Additionally, related saturated heterocycles, such as piperazines and tetrahydroquinoxalines, can be accessed by treatment with 1,2-diamines and a reducing agent. These transformations are efficient, provide access privileged, bioactive structures, and produce minimal waste.

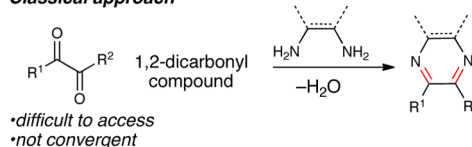


Diamino heterocycles, such as quinoxalines, tetrahydroquinoxalines, piperazines, and pyrazines, find numerous applications in medical and material science. For example, quinoxaline derivatives have been reported as anticancer,¹ antiviral,² antibacterial,³ and antiinflammatory agents⁴ and as kinase inhibitors⁵ and antibiotics.⁶ In addition, the quinoxaline moiety has been recently incorporated in materials with interesting properties such as solar cells.⁷ Compounds containing the pyrazine heterocycle find numerous applications in materials science,⁸ medicinal chemistry,⁹ compounds that are responsible for the flavor and aroma of several foodstuffs and wines,¹⁰ and compounds with herbicidal activity.¹¹ Recently, tetrasubstituted pyrazines have been discovered as semi-chemicals in orchids.¹² Compounds that possess a tetrahydroquinoxaline system have been studied as potent cholesteryl ester transfer protein inhibitors,¹³ anticonvulsants,¹⁴ potassium channel openers,¹⁵ and anti-HIV agents.¹⁶ The piperazine moiety has been classified as a “privileged scaffold” in medicinal chemistry¹⁷ and is frequently found in many natural products as well as being a large class of biologically active compounds (Figure 1).

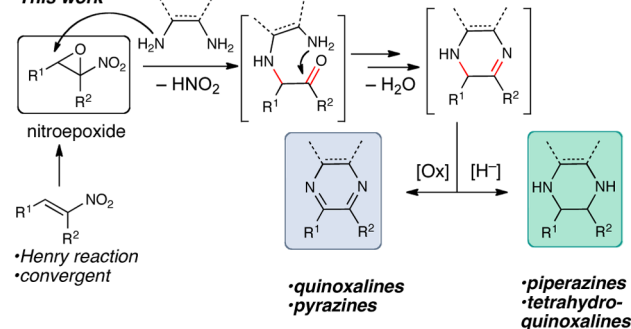
A common method for the preparation of the aforementioned heterocycles is the condensation of 1,2-dicarbonyl compounds with 1,2-diamines.¹⁸ General synthetic approaches to differently substituted 1,2-dicarbonyl compounds are usually step intensive and typically involve redox approaches. A convergent route could potentially involve the use of carbonyl anion synthons, but again, the oxidation states of the initial product require modification. Although interesting approaches have been reported to circumvent this limitation,¹⁹ we envisaged that nitroepoxides could be convenient and enabling starting materials for the preparation of 1,4-diamino heterocycles.

Nitroepoxides are an underdeveloped class of compounds with wide potential for use in chemical synthesis.²⁰ These interesting small molecules can be easily prepared through the straightforward epoxidation of nitroalkenes, which in turn are readily accessed from a standard nitroaldol/Henry reaction (Figure 1). We previously reported the derivatization of

Classical approach



This work



Examples of biologically active heterocycles

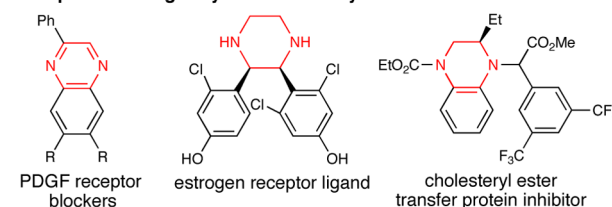


Figure 1. Reaction design for heterocycles.

nitroepoxides into vicinal diamines by treatment with an amine and then a reductive agent,²¹ and we now report the transformations of nitroepoxides into heterocycles with two nitrogen atoms. Our strategy revolves around the reaction between nitroepoxide and 1,2-diamine to afford an α -iminoamine intermediate (Figure 1). This key intermediate

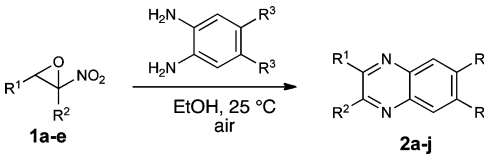
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can be processed in two ways: the exposure to air produces the oxidized aromatic heterocycle while the in situ addition of a reducing agent directly accesses the saturated analogue.

We began our studies of the preparation of quinoxalines by combining nitroepoxide **1a** with 1,2-benzenediamine (1.5 equiv) in 1,2-dichloroethane. We were pleased to see that the reaction afforded quinoxaline **2a** (Table 1, entry 1) under very

Table 1. Synthesis of Quinoxalines^a



entry	R ¹ , R ²	epoxide	R ³	diamine	yield ^b (%)
1 ^c	Ph, Me	1a	H	2a	72
2	Ph, Me	1a	H	2a	86
3	Ph, Me	1a	Cl	2b	82
4	<i>p</i> -F-Ph, Me	1b	H	2c	80
5	<i>p</i> -F-Ph, Me	1b	Cl	2d	75
6	<i>p</i> -Me-Ph, Me	1c	H	2e	78
7	<i>p</i> -Me-Ph, Me	1c	Cl	2f	70
8	<i>p</i> -F-Ph, Et	1d	H	2g	80
9	<i>n</i> -Pr, Me	1e	H	2h	63
10	<i>n</i> -Pr, Me	1e	Cl	2i	48

^aReactions were carried out using nitroepoxide (1.0 equiv) and 1,2-benzenediamine (1.5 equiv) at room temperature for 16 h. ^bYield of isolated product. ^cReaction was performed using 1,2-dichloroethane as a solvent.

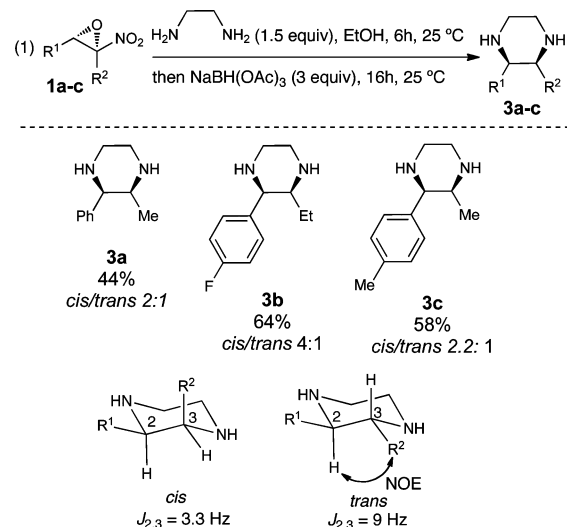
mild conditions. In order to improve the yield of the reaction, other conditions were evaluated. Higher yield was obtained by using ethanol as a solvent and performing the reaction in the presence of air²² (Table 1, entry 2). The improvement of the yield with ethanol as the solvent is most likely due to the higher solubility of the reactants and to the unreactivity of the solvent with diamines compared to 1,2-dichloroethane.²³ Under these conditions, the color of the reaction mixture turns an intense red as an indicator of reaction completion and was general all cases studied to date. Various nitroepoxides were subjected to reaction conditions to explore the scope of the process. Nitroepoxides **1a–d** having an aryl group and an alkyl group gave a higher yield (Table 1, entries 1–8), while compound **1e** having an alkyl group in both positions gave a lower yield (Table 1, entries 9 and 10).

Following the success of the quinoxaline study, we then evaluated a one-pot procedure for the preparation of 2,3-disubstituted piperazines starting from nitroepoxides. Piperazines **3a–c** were prepared using the same procedure as the one reported by us for the preparation of diamines²¹ but using 1,2-ethylenediamine instead of an amine and ethanol as a solvent instead of 1,2-dichloroethane (eq 1, Scheme 1). The reaction afforded piperazines **3a–c** as a mixture of *cis/trans* isomers, with the *syn* isomer predominating.

The stereochemistry of the piperazines **3a–c** was assigned by NMR coupling constants ($J_{2,3}$ for *trans*, higher than for *cis*) and by NOE experiments (Scheme 1).

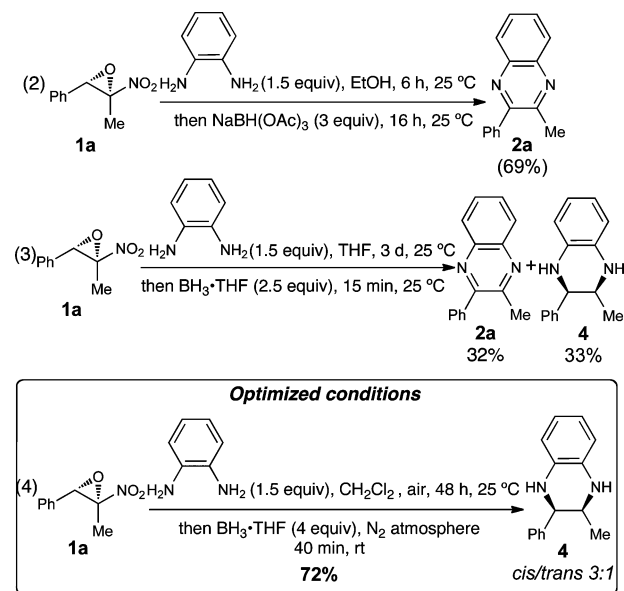
Although approaches for the preparation of oxopiperazines²⁴ or 2-substituted piperazines have been reported,²⁵ procedures for the preparation of 2,3-disubstituted piperazines are scarce.²⁶ Methods for the preparation of tetrahydroquinoxalines suffer from the same drawbacks as quinoxalines, since they are usually

Scheme 1. Synthesis of Piperazines **3a–c**



prepared through reduction of quinoxalines.²⁷ We evaluated a one-pot process for the preparation of tetrahydroquinoxalines starting from nitroepoxides (Scheme 2). We initially applied

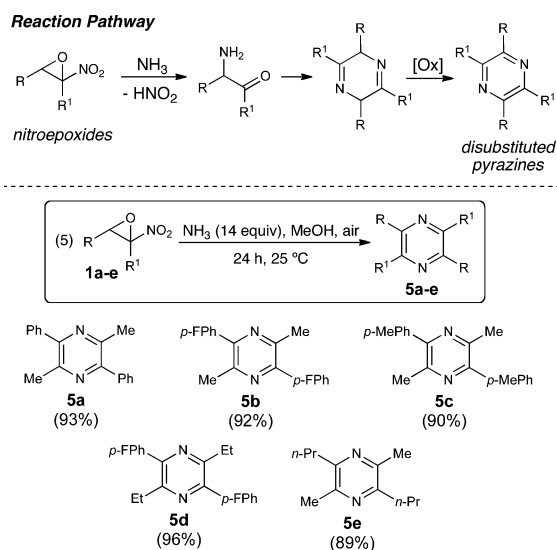
Scheme 2. Optimization of Conditions for the Synthesis of Tetrahydroquinoxaline **4**



the same conditions as mentioned above for the preparation of piperazines over nitroepoxide **1**, but using 1,2-benzenediamine instead of ethylenediamine. However, the main product of the reaction was quinoxaline **2a** (eq 2, Scheme 2). Tetrahydroquinoxaline **4** was obtained when borane–tetrahydrofuran complex was used as a reductive agent in tetrahydrofuran as a solvent.²⁸ However, the yield was low, and the main product of the reaction was quinoxaline **2a** (eq 3, Scheme 2). Finally, nitroepoxide **1a** was transformed into tetrahydroquinoxaline **4** in higher yield by treatment with 1,2-benzenediamine in dichloromethane as a solvent for 48 h and then addition of borane–tetrahydrofuran complex (4 equiv) (eq 4, Scheme 2). The stereochemistry of tetrahydroquinoxaline **4** was assigned by NMR as for piperazines **3a–c**.

Although other approaches have been reported,²⁹ pyrazines are commonly prepared from α -aminoaldehydes.³⁰ We envisioned a preparation of pyrazines starting from nitroepoxides using dry ammonia in methanol. Ammonia would attack the nitroepoxide to give an α -amino ketone which could dimerize to afford a dihydropyrazine intermediate which upon oxidation could afford pyrazine (Scheme 3). When nitro-

Scheme 3. Synthesis of Pyrazines



epoxides **1a–e** were treated with a solution of ammonia in methanol³¹ in the open air pyrazines **5a–e** were obtained as the single compound of the reaction³² in high yield (eq 5, Scheme 3).

In summary, we report herein that aromatic heterocycles such as quinoxalines and pyrazines can be easily prepared by treating nitroepoxides with 1,2-benzenediamines and ammonia, respectively. These reactions give very high yields using environmentally friendly ethanol as a solvent. Piperazines can also be prepared in a one-pot procedure when nitroepoxides are treated with 1,2-ethylenediamine and then sodium triacetoxyborohydride as a reductive agent in ethanol. In addition, tetrahydroquinoxalines can be easily obtained by using 1,2-benzenediamine in dichloromethane and then borane–tetrahydrofuran complex as a reductive agent. Further investigations of the utility of nitroepoxides in synthesis are ongoing and will be reported in the future.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Hazeldine, S. T.; Polin, L.; Kushner, J.; Paluch, J.; White, K.; Edelstein, M.; Palomino, E.; Corbett, T. H.; Horwitz, J. P. *J. Med. Chem.* **2001**, *44*, 1758–1776. (b) Kong, D.; Park, E. J.; Stephen, A. G.; Calvani, M.; Cardellina, J. H.; Monks, A.; Fisher, R. J.; Shoemaker, R. H.; Melillo, G. *Cancer Res.* **2005**, *65*, 9047–9055.
- (2) (a) El-Ashry, E. S. H.; Abdel-Rahman, A. A. H.; Rashed, N.; Rasheed, H. A. *Pharmazie* **1999**, *54*, 893–897. (b) You, L.; Cho, E. J.; Leavitt, J.; Mad, L.; Montelione, G. T.; Anslyn, E. V.; Krug, R. M.; Ellington, A.; Robertus, J. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3007–3011.
- (3) Badran, M. M.; Abonzid, K. A.; Hussein, M. H. *Arch. Pharm. Res.* **2003**, *26*, 107–113. Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, S604–S606.
- (4) Abu-Hashem, A. A.; Gouda, M. A.; Badria, F. A. *Eur. J. Med. Chem.* **2010**, *45*, 1976–1981.
- (5) (a) Khattab, S. N.; Hassan, S. Y.; Bekhit, A. A.; El Massry, A. M.; Langer, V. *Eur. J. Med. Chem.* **2010**, *45*, 4479–4489. (b) Srinivas, C.; Kumar, C. N. S. P.; Rao, V. J.; Palaniappan, S. *J. Mol. Catal. A: Chem.* **2007**, *26*, 227–230.
- (6) (a) Myers, M. R.; He, W.; Hanney, B.; Setzer, N.; Maguire, M. P.; Zulli, A.; Bilder, G.; Galzciniski, H.; Amin, D.; Needle, S.; Spada, A. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3091–3095. (b) Dietrich, B.; Diederchsen, U. *Eur. J. Org. Chem.* **2005**, *40*, 147–153.
- (7) Li, H.; T. Koh, T. M.; Hagfeldt, A.; Gratzel, M.; Mhaisalkar, S. G.; Grimsdale, A. C. *Chem. Commun.* **2013**, *49*, 2409–2411.
- (8) (a) Mondal, R.; Ko, S.; Bao, Z. *J. Mater. Chem.* **2010**, *20*, 10568–10576. (b) Wriedt, M.; Jess, I.; Näther, C. *Eur. J. Inorg. Chem.* **2009**, 363–372. (c) Liu, H.-Y.; Wu, H.; Ma, J.-F.; Yang, J.; Liu, Y.-Y. *Dalton Trans.* **2009**, *38*, 7957–7961.
- (9) (a) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, S604–S606. (b) Niculescu-Duvaz, I.; Roman, E.; Whittaker, S. R.; Friedlos, F.; Kirk, R.; Scanlon, I. J.; Davies, L. C.; Niculescu-Duvaz, D.; Marais, R.; Springer, C. J. *J. Med. Chem.* **2008**, *51*, 3261–3274. (c) Cheng, X.-C.; Liu, X.-Y.; Xu, W.-F.; Guo, X.-L.; Zhang, N.; Song, Y.-N. *Bioorg. Med. Chem.* **2009**, *17*, 3018–3024. (d) Zitko, J.; Dolezal, M.; Svobodova, M.; Vejsova, M.; Kucera, R.; Jilek, P. *Bioorg. Med. Chem.* **2011**, *19*, 1471–1476. (e) Dubuisson, M. L. N.; Rees, J.-F.; Merchand-Brynaert, J. *Mini-Rev. Med. Chem.* **2004**, *4*, 421–435.
- (10) (a) Maga, J. A.; Sizer, C. E. *J. Agric. Food Chem.* **1973**, *21*, 22–30. (b) Rohovec, J.; Kotek, J.; Peters, J. A.; Maschmeyer, T. *Eur. J. Org. Chem.* **2001**, *36*, 3899–3901. (c) Lacey, M. J.; Allen, M. S.; Harris, R. L. N.; Brown, W. V. *Am. J. Enol. Viticul.* **1991**, *42*, 103–108. (d) Allen, M. S.; Lacey, M. J.; Boyd, S. J. *J. Agric. Food Chem.* **1995**, *43*, 769–772. (e) Adams, A.; de Kimpe, N. *Food Chem.* **2009**, *115*, 1417–1423.
- (11) Doležal, M.; Krl'ov, K. *Synthesis and Evaluation of Pyrazine Derivatives with Herbicidal Activity In Herbicides, Theory and Applications*; Soloneski, S.; Larramendy, M. L., Eds.; InTech: Rijeka, 2011; Chapter 27, pp 581–610.
- (12) Bohman, B.; Jeffares, L.; Flematti, G.; Byrne, L. T.; Skelton, B. W.; Phillips, R. D.; Kingsley, W. D.; Peakall, R.; Barrow, R. A. *J. Nat. Prod.* **2012**, *75*, 1589–1594.
- (13) Eary, C. T.; Jones, Z. S.; Groneberg, R. D.; Burgess, L. E.; Mareska, D. A.; Drew, M. D.; Blake, J. F.; Laird, E. R.; Balachari, D.; O'Sullivan, M.; Allen, A.; Marsh, V. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2608–2613.
- (14) Pouw, B.; Nour, M.; Matsumoto, R. R. *Eur. J. Pharmacol.* **1999**, *386*, 181–186.
- (15) Matsumoto, Y.; Tsuzuki, R.; Matssuhisa, A.; Yoden, T.; Yamagiwa, Y.; Yanagisawa, I.; Shibnuma, T.; Nohira, H. *Bioorg. Med. Chem.* **2000**, *8*, 393–404.

- (16) Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Klabe, R. M.; Erickson-Vitanen, S.; Trainor, G. L.; Rogers, J. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729–1731.
- (17) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (b) Tullberg, M.; Grötl, M.; Luthman, K. *J. Org. Chem.* **2007**, *72*, 195–199.
- (18) (a) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873–4876. (b) Ajaikumar, S.; Pandurangan, A. *Appl. Catal. A: Gen.* **2009**, *357*, 184–192. (c) Heravi, M. M.; Bakhtiari, K.; Oskooie, H.; Taheri, S. *Heteroatom. Chem.* **2008**, *19*, 218–220. (d) Adlington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 668–679. (e) China Raju, B.; Dharma Theja, N.; Ashok Kumar, J. *Synth. Commun.* **2009**, *39*, 175–188. (f) Hou, J.-T.; Liu, Y. H.; Zhang, Z. H. *J. Heterocycl. Chem.* **2010**, *47*, 703–706. (g) Sadjadi, S.; Sadjadi, S.; Hekmatshoar, R. *Ultrason. Sonochem.* **2010**, *17*, 764–767. (h) Mantel, M. L. H.; Lindhardt, A. T.; Lupp, D.; Skrydstrup, T. *Chemistry* **2010**, *16*, 5437–5442.
- (19) (a) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715–5724. (b) Philips, E. M.; Chan, A.; Scheidt, K. A. *Aldrichimica Acta* **2009**, *42*, 55–56.
- (20) (a) Weiß, K. M.; Wei, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2011**, *9*, 3457–3461. (b) Evans, L. A.; Adams, H.; Barber, C. G.; Caggiano, L.; Jackson, R. F. W. *Org. Biomol. Chem.* **2007**, *5*, 3156–3163. (c) Vankar, Y. D.; Shah, K.; Bawa, A.; Singh, S. P. *Tetrahedron* **1991**, *47*, 8883–8906. (d) Newman, H.; Angier, R. B. *Tetrahedron* **1970**, *26*, 825–836.
- (21) Agut, J.; Vidal, A.; Rodríguez, S.; González, F. V. *J. Org. Chem.* **2013**, *78*, 5717–5722.
- (22) It is probable that atmospheric oxygen oxidizes the dihydroquinoxaline intermediate to quinoxaline (see Figure 1).
- (23) Monopoli, A.; Contugno, P.; Cortese, M.; Calvano, D. C.; Ciminale, F.; Nacci, A. *Eur. J. Org. Chem.* **2012**, *47*, 3105–3111.
- (24) (a) De Risi, C.; Pelà, M.; Polline, G. P.; Trapella, C.; Zanirato, V. *Tetrahedron: Asymmetry* **2010**, *21*, 255–274. (b) Neves, N. D.; Raymond, M.; Beauchemin, A. M. *Heterocycles* **2014**, *88*, 639–650. (c) Bull, S. D.; Davies, S. G.; Garner, A. C.; Parkes, A. L.; Roberts, P. M.; Sellers, T. G. R.; Smith, A. D.; Tamayo, J. A.; Thomson, J. E.; Vickers, R. J. *New J. Chem.* **2007**, *31*, 486–495.
- (25) (a) Kour, H.; Paul, S.; Singh, P. P.; Gupta, M.; Gupta, R. *Tetrahedron Lett.* **2013**, *54*, 761–764. (b) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329–332.
- (26) Gust, R.; Keilitz, R.; Schmidt, K. *J. Med. Chem.* **2002**, *45*, 2325–2337.
- (27) Figueras, J. *J. Org. Chem.* **1966**, *31*, 803–806.
- (28) McKinney, A. M.; Jackson, K. R.; Salvatore, R. N.; Savrides, E.; Edattel, M. J.; Gavin, T. J. *J. Heterocycl. Chem.* **2005**, *42*, 1031–1034.
- (29) Beauchemin, A. *Org. Biomol. Chem.* **2013**, *9*, 7039–7050.
- (30) Badrinarayanan, S.; Sperry, J. *Org. Biomol. Chem.* **2012**, *10*, 2126–2132.
- (31) Commercial 7 N solution of ammonia in methanol was used.
- (32) Partial decomposition of pyrazines **5a–e** was observed when they were purified through silica gel chromatography. After usual workup, pyrazines **5a–e** were found to be highly pure (see the Supporting Information).