ORGANIC LETTERS

2011
Vol. 13, No. 7
1626–1629

One-Pot Synthesis of Pyrrolo-[3,2-*d*]pyridazines and Pyrrole-2,3-diones via Zirconocene-Mediated Four-Component Coupling of Si-Tethered Diyne, Nitriles, and Azide

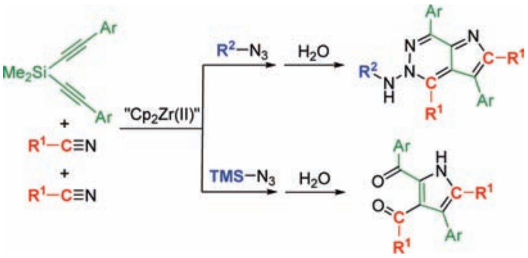
Shaoguang Zhang,[†] Jing Zhao,[‡] Wen-Xiong Zhang,[†,§] and Zhenfeng Xi*,[†]

Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, China

zfxi@pku.edu.cn

Received January 6, 2011

ABSTRACT



A one-pot synthesis of pyrrolo[3,2-*d*]pyridazine derivatives via zirconocene-mediated four-component coupling of one Si-tethered diyne, two nitriles, and one azide is reported. When $TMSN_3$ was used, pyrrole-2,3-diones were formed in good yields. Further condensation of these highly functionalized pyrrole-2,3-diones with hydrazine and hydroxylamine afforded useful pyrrole-fused heterocycles.

Pyrrolo[3,2-*d*]pyridazines are a class of interesting and useful *N*-heterocycles.[1] However, synthetic methods for such heterocyclic compounds have been very limited. Most of the known pyrrolo[3,2-*d*]pyridazines are synthesized via condensation of pyrrole-2,3-diones with hydrazine. There are no reports on one-pot multicomponent synthesis of pyrrolo[3,2-*d*]pyridazines.[1,2] Moreover, synthetic methods for pyrrole-2,3-diones are also very limited.[2] On the other hand, transition-metal-mediated reactions of azides are of great importance and versatility in organic synthesis because azides can be readily transformed into a wide variety of valuable *N*-containing natural products and

---

[†] Peking University.
[‡] Chinese Academy of Sciences.
[§] Nankai University.

(1) For papers on pyrrolo[3,2-*d*]pyridazines: (a) Wiscount, C. M.; Williams, P. D.; Tran, L. O.; Embrey, M. W.; Fisher, T. E.; Sherman, V.; Homnick, C. F.; Staas, D. D.; Lyle, T. A.; Wai, J. S.; Vacca, J. P.; Wang, Z.; Felock, P. J.; Stillmock, K. A.; Witmer, M. V.; Miller, M. D.; Hazuda, D. J.; Day, A. M.; Gabryelski, L. J.; Ecto, L. T.; Schleif, W. A.; DiStefano, D. J.; Kochansky, C. J.; Reza Anari, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4581. (b) Dyck, B.; Markison, S.; Zhao, L.; Tamiya, J.; Grey, J.; Rowbottom, M. W.; Zhang, M.; Vickers, T.; Sorensen, K.; Norton, C.; Wen, J.; Heise, C. E.; Saunders, J.; Conlon, P.; Madan, A.; Schwarz, D.; Goodfellow, V. S. *J. Med. Chem.* **2006**, *49*, 3753. (c) Murineddu, G.; Cignarella, G.; Chelucci, G.; Loriga, G.; Pinna, G. A. *Chem. Pharm. Bull.* **2002**, *50*, 754. (d) Dal Piaz, V.; Giovannoni, M. P.; Castellana, C.; Palacios, J. M.; Beleta, J.; Doménech, T.; Segarra, V. *J. Med. Chem.* **1997**, *40*, 1417. (e) Meade, E. A.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1992**, *35*, 526.

(2) For papers on pyrrole-2,3-diones, see: (a) Anary-Abbasinejad, M.; Charkhati, K.; Anakari-Ardakani, H. *Synlett* **2009**, 1115. (b) Barik, R.; Kumar, C. V.; Das, P. K.; George, M. V. *J. Org. Chem.* **1985**, *50*, 4309.

(3) For reviews on azides, see: (a) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

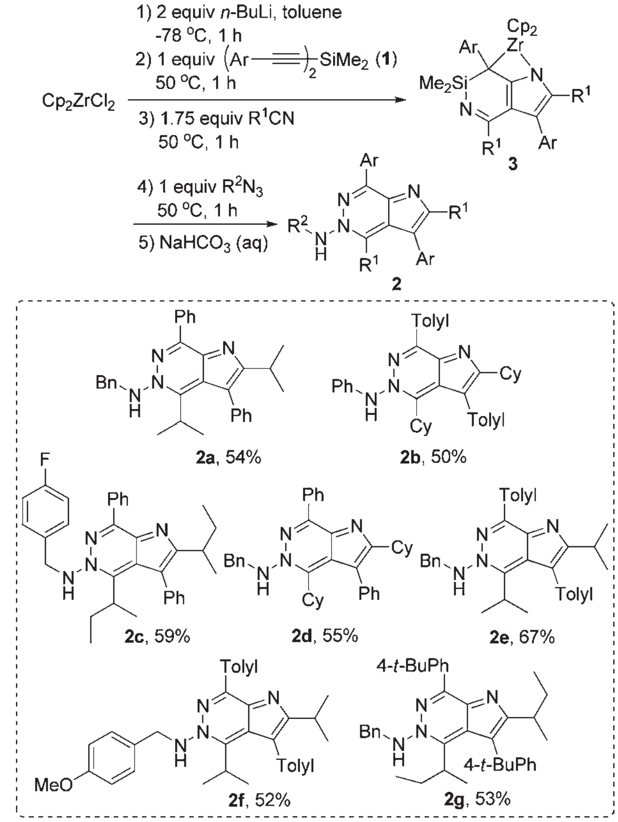
10.1021/ol200038n

medicinal agents,[3,4] such as aziridine,[5a] amide,[5b−d] amine,[5e,f] nitrile,[5g] triazoles,[6a−f] tetrazoles,[6g,h] and other related *N*-heterocycles.[7] Some nucleophilic reactions of organometallic reagents to organic azides have also been reported.[8]

During our investigation of zirconocene-mediated multicomponent reactions involving Si-tethered diynes **1**, nitriles, and other unsaturated substrates such as aldehyde, formamide, and isocyanide,[9,10] we were curious about whether azides could be used in this reaction, expecting formation of new types of *N*-heterocycles. Thus, herein we report a one-pot synthesis of pyrrolo[3,2-*d*]pyridazine derivatives **2** via zirconocene-mediated cyclization of one Si-tethered diyne **1**, two nitriles, and one azide. We also report here an efficient synthesis toward pyrrole-2,3-diones via the zirconocene-mediated cyclization of Si-tethered diyne **1**, nitriles, and $TMSN_3$ as a special azide. These functionalized pyrrole-2,3-diones could be efficiently further transformed into pyrrole-fused heterocycles.

Reactive organometallic intermediates **3** could be synthesized in situ in high yields via a one-pot multicomponent coupling process from Cp_2ZrBu_2, Si-tethered diyne (**1**), and nitriles, as we previously reported (see the Supporting Information).[9b−d] Treatment of **3a** (Ar = Ph, R^1 = *i*-Pr) with benzyl azide BnN_3 at 50 °C for 1 h followed by quenching with saturated aqueous $NaHCO_3$ afforded a yellow solid **2a** in 54% isolated yield (Scheme 1). The structure of product **2a** was confirmed as a pyrrolo[3,2-*d*]-pyridazine derivative by X-ray single-crystal structure analysis (Figure 1). As given in Scheme 1, various aryl or

Scheme 1. One-Pot Synthesis of Pyrrolo[3,2-*d*]pyridazine Derivatives **2** via Zirconocene-Mediated Cyclization of One Si-Tethered Diyne **1**, Two Nitriles, and One Azide



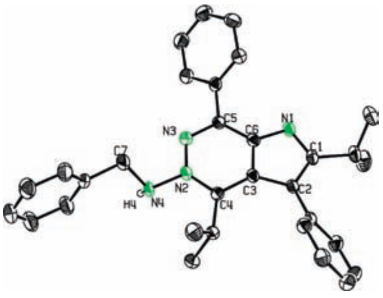


Figure 1. Single-crystal X-ray structure of **2a**. Hydrogen atoms are omitted for clarity except polar N−H bonds. Selected bond lengths (Å): N1−C1 1.390(2), N1−C6 1.363(2), N2−N3 1.350(2), N2−C4 1.372(2), N3−C5 1.327(2), N4−N2 1.438(2).

---

(4) (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095. (b) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712. (c) Griffin, R. J. The Medicinal Chemistry of the Azido Group. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science B.V.: Amesterdam, 1994; Vol. 31, Chapter 3, pp 121.

(5) (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (b) Lin, F. L.; Hoyt, H. M.; van Halbeek, H.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2005**, *127*, 2686. (c) Burés, J.; Martín, M.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **2009**, *74*, 2203. (d) Saxon, E.; Bertozzi, C. R. *Science* **2000**, *287*, 2007. (e) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906. (f) Benati, L.; Bencivenni, G.; Leardini, R.; Nanni, D.; Minozzi, M.; Spagnolo, P.; Scialpi, R.; Zanardi, G. *Org. Lett.* **2006**, *8*, 2499. (g) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094.

(6) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8881. (c) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235. (d) Yan, Z.-Y.; Zhao, Y.-B.; Fan, M.-J.; Liu, W.-M.; Liang, Y.-M. *Tetrahedron* **2005**, *61*, 9331. (e) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (f) Shao, C.; Wang, X.; Xu, J.; Zhao, J.; Zhang, Q.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 7002. (g) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110. (h) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 12210.

(7) (a) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2008**, *73*, 3928. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (c) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266. (d) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (e) Shou, W. G.; Li, J.; Guo, T.; Lin, Z.; Jia, G. *Organometallics* **2009**, *28*, 6847.

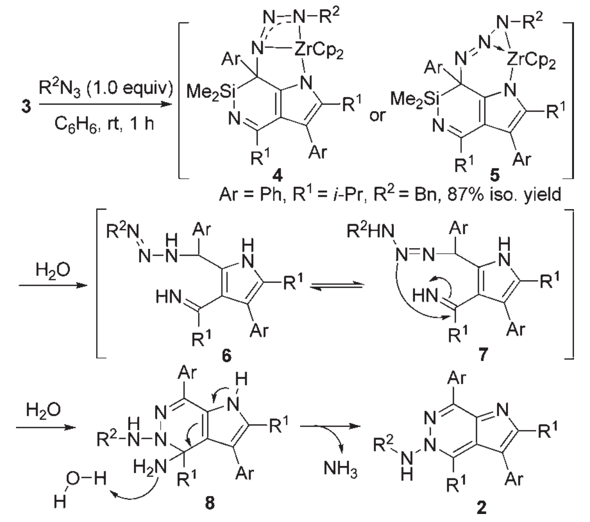
(8) (a) Trost, B. M.; Pearson, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 1054. (b) Kabalka, G. W.; Li, G. *Tetrahedron Lett.* **1997**, *38*, 5777.

(9) (a) Zhang, S.; Zhang, W.-X.; Zhao, J.; Xi, Z. *J. Am. Chem. Soc.* **2010**, *132*, 14042. (b) Zhang, S.; Zhang, W.-X.; Xi, Z. *Chem.—Eur. J.* **2010**, *16*, 8419. (c) Zhang, S.; Sun, X.; Zhang, W.-X.; Xi, Z. *Chem.—Eur. J.* **2009**, *15*, 12608. (d) Zhang, W.-X.; Zhang, S.; Sun, X.; Nishiura, M.; Hou, Z.; Xi, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 7227. (e) Sun, X.; Wang, C.; Li, Z.; Zhang, S.; Xi, Z. *J. Am. Chem. Soc.* **2004**, *126*, 7172. See also: (f) Xi, Z.; Fischer, R.; Hara, R.; Sun, W.; Obora, Y.; Suzuki, N.; Nakajima, K.; Takahashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 12842. (g) Takahashi, T.; Xi, Z.; Obora, Y.; Suzuki, N. *J. Am. Chem. Soc.* **1995**, *117*, 2665.

(10) For recent multicomponent syntheses of heterocycles, see: (a) Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133. (c) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005. (d) Marek, I., Ed. *Tetrahedron Symposia-in-Print* 2005, *67*, 11299. (e) Jiang, B.; Tu, S.-J.; Kaur, P.; Wever, W.; Li, G. G. *J. Am. Chem. Soc.* **2009**, *131*, 11660. (f) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

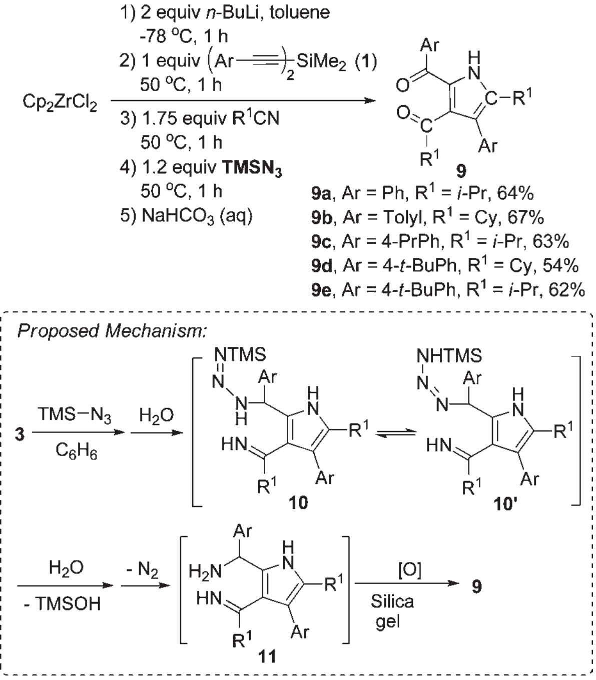
benzyl azides with both electron-withdrawing groups (F) and electron-donating groups (MeO) could be applied to afford pyrrolo[3,2-*d*]pyridazine derivatives **2** in good isolated yields.

Scheme 2. Proposed Mechanisms



Shown in Scheme 2 is a proposed mechanism for the reaction of azides with the reactive organometallic intermediate **3**. The hydrolysis mechanism of the reaction mixture affording the pyrrolo[3,2-*d*]pyridazine derivative product **2** is also given in Scheme 2. We suggest 1,1-insertion of an azide into the C−Zr bond of **3** and delocalization would lead to formation of triazenido-ligated zirconium intermediate **4**. According to the literature,[11] a 1,3-insertion of an azide into the C−Zr bond of **3** may be also possible to generate the intermediate **5**.[12] Although it is not clear which one is formed in this reaction, only one insertion organometallic intermediate, either **4a** or **5a**, was obtained in 87% isolated yield and characterized by NMR spectroscopy. Hydrolysis of the insertion product, either **4** or **5**, would afford pyrrole derivatives **6** or **7**. These intermediates **6** and/or **7** would undergo cyclization of the triazene moiety with the imine C=N bond to afford **8**.[13] Dehydration and aromatization of **8** led to the final product **2**.

Scheme 3. One-Pot Synthesis of Pyrrole-2,3-diones **9** via Zirconocene-Mediated Cyclization of Si-Tethered Diyne **1**, Nitriles, and $TMSN_3$



Unexpectedly, when $TMSN_3$ was used as an azide in this zirconocene-mediated reaction, pyrrole-2,3-diones **9** were formed in good isolated yields (Scheme 3). The structure of product **9a** was determined by single-crystal X-ray structural analysis (Figure 2). Si-tethered diynes with functional groups as well as bulky nitriles like *t*-BuCN could not lead to products **9** because their corresponding intermediates **3** could not be formed efficiently. On mechanistic aspects, we proposed that after insertion of $TMSN_3$ into the C−Zr bond, hydrolytic cleavage of N−Si and N−Zr bonds would give triazene **10** or **10′**. Hydrolysis of N-$SiMe_3$ bond followed by elimination of dinitrogen would afford the

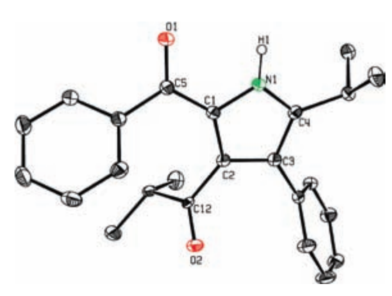


Figure 2. Single-crystal X-ray structure of **9a**. Hydrogen atoms are omitted for clarity except polar N−H bonds. Selected bond lengths (Å): C5−O1 1.224(3), C12−O2 1.200(3), N1−C1 1.368(3), N1−C4 1.340(3).

---

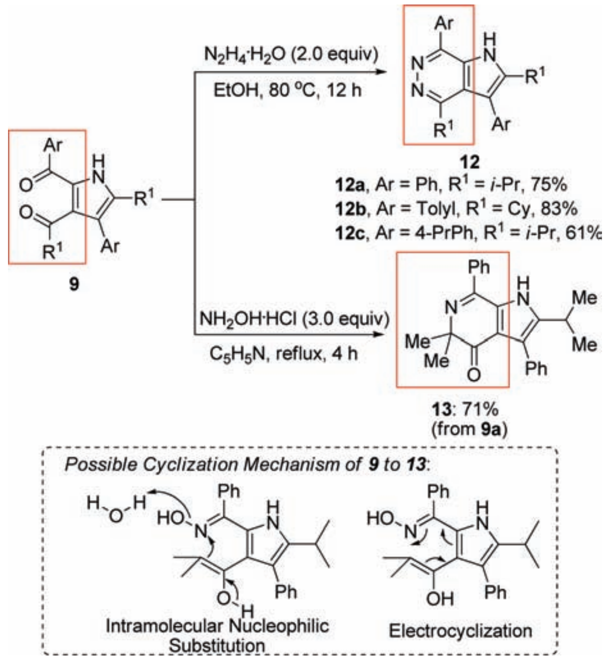
[11] (a) Deng, L.; Chan, H.-S.; Xie, Z. *J. Am. Chem. Soc.* **2005**, *127*, 13774. (b) Meyer, K. E.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 974. (c) Luker, T.; Whitby, R. J.; Webster, M. *J. Organomet. Chem.* **1995**, *492*, 53. (d) Vaughan, G. A.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1990**, *112*, 7994.

[12] Insertion of nitriles or diazo compounds to form azazirconacycles:(a) Knobloch, D. J.; Benito-Garagorri, D.; Bernskoetter, W. H.; Keresztes, I.; Lobkovsky, E.; Toomey, H.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 14903. (b) Ugolotti, J.; Kehr, G.; Fröhlich, R.; Grimme, S.; Erker, G. *Chem. Commun.* **2009**, 6572. (c) Cadierno, V.; Zablocka, M.; Donnadieu, B.; Igau, A.; Majoral, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4524. (d) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802. (e) Zippel, T.; Arndt, P.; Ohff, A.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Organometallics* **1998**, *17*, 4429. (f) Hanna, T. A.; Baranger, A. M.; Bergman, R. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 653. For triazenido-ligated zirconacycles, see:(g) Guzei, I. A.; Liable-Sands, L. M.; Rheingold, A. L.; Winter, C. H. *Polyhedron* **1997**, *16*, 4017.

[13] For cyclization of triazenes, see: (a) Vinogradova, O. V.; Sorokoumov, V. N.; Balova, I. A. *Tetrahedron Lett.* **2009**, *50*, 6358. (b) Kimball, D. B.; Herges, R.; Haley, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 1572. (c) Kimball, D. B.; Haley, M. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3338.

imine **11**, which might be oxidized and hydrolyzed on the silica gel during column chromatography to give the final product pyrrole-2,3-dione **9** (see the Supporting Information for more discussion). Although plenty of synthetic methods for pyrrole derivatives have been developed,[7d,14] synthetic methods for pyrrole-2,3-diones, which are highly functionalized pyrroles, are very rare.[2]

Scheme 4. Preparation of Pyrrole-Fused *N*-Heterocyclic Compounds via Annulation of Pyrrole-2,3-diones **9**



The two carbonyl groups on the pyrrole ring of **9** are expected to be very useful for the preparation of other valuable pyrrole-fused *N*-heterocyclic compounds via conventional annulation methods.[15] As a demonstration of their further application, condensation of **9** with hydrazine hydrate and hydroxylamine hydrochloride was carried out, and the pyrrole-fused heterocycles pyrrolo[3,2-*d*]pyridazine **12** and pyrrolo[2,3-*c*]pyridinone **13** were generated in high isolated yields, respectively (Scheme 4).

Condensation of **9** with hydrazine hydrate in ethanol at 80 °C gave pyrrolo[3,2-*d*]pyridazines **12** as products.[1] However, surprisingly, condensation of **9a** with hydroxylamine hydrochloride in refluxing pyridine led to the pyrrolo[2,3-*c*]pyridinone **13** as the single product. The carbonyl group adjacent to the *i*-Pr group was untouched; instead, the C_{sp3}−H bond of *i*-Pr was coupled with the in situ generated oxime moiety to form the pyridinone ring via intramolecular nucleophilic substitution or 6π-electrocyclization (see the Supporting Information for more discussion). The structure of product **13** was determined by single-crystal X-ray structural analysis (Figure 3).

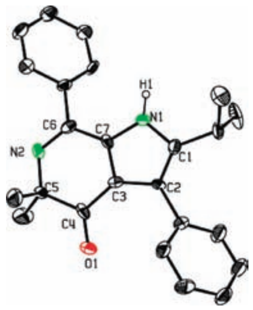


Figure 3. Single-crystal X-ray structure of **13**. Hydrogen atoms are omitted for clarity except polar N−H bonds. Selected bond lengths (Å): C4−O1 1.229(5), N1−C1 1.410(5), N1−C7 1.387(5), N2−C5 1.434(5), N2−C6 1.291(5).

In conclusion, novel synthetic methods for pyrrolo[3,2-*d*]pyridazines and pyrrole-2,3-diones have been realized via a zirconocene-mediated one-pot multicomponent coupling process.

Acknowledgment. This work was supported by the Natural Science Foundation of China, and the Major State Basic Research Development Program (2011CB808705).

Supporting Information Available. Details for proposed mechanisms, experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds, and crystallographic data for **2a**, **9a**, **13** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

---

(14) (a) Luh, T. Y.; Lee, C. F. *Eur. J. Org. Chem.* **2005**, 3875. (b) Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4031. (c) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046. (d) Li, Q.; Fan, A.; Lu, Z.; Cui, Y.; Lin, W.; Jia, Y. *Org. Lett.* **2010**, *12*, 4066. (e) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585.

(15) For reviews on the synthesis of *N*-heterocycles from 1,4-dicarbonyl compounds, see: (a) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, *20*, 3095. (b) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238.