ORGANIC LETTERS

2011
Vol. 13, No. 5
1060–1063

Facile Syntheses of Novel Benzo-1,3-dioxolo-, Benzothiazolo-, Pyrido-, and Quinolino-fused 5*H*-Benzo[*d*]-pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-Pyrazoles

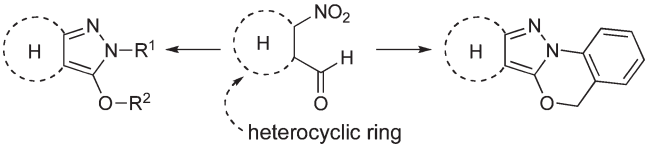
Belem Avila,[†] Danielle M. Solano,[†,‡] Makhluf J. Haddadin,[§] and Mark J. Kurth*[,†]

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States, and Department of Chemistry, American University of Beirut, Beirut, Lebanon

mjkurth@ucdavis.edu

Received December 22, 2010

ABSTRACT



A number of novel benzo-1,3-dioxolo-, benzothiazolo-, pyrido-, and quinolino-fused 5*H*-benzo[*d*]pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-pyrazoles were synthesized utilizing an easy and effective *N,N*-bond forming heterocyclization reaction. In so doing, the substrate scope of this heterocyclization reaction, which starts with *o*-nitroheterocyclic aldehydes, was expanded to provide several unique heterocyclic compounds for biological screening. This work further demonstrates the versatility of this simple, base-mediated, one-pot heterocyclization method in the construction of novel heterocycles.

Indazoles (e.g., benzo-fused pyrazoles) have been shown to display a wide array of biological activities, including antiangiogenic,[1] antiviral,[2] and anti-inflammatory applications.[3] These biological activities have prompted synthetic chemists to develop new methodologies to synthesize and functionalize the indazole ring system.[3] In that regard, the literature contains examples of heterocyclization routes to indazole derivatives;[4,5] however, of the two indazole isomers, 2*H*-indazoles are considerably less studied.[6] Of special interest, pyrazolopyridines have been shown to have improved log *P* and water solubilities

[†] University of California.
[‡] Present address: Department of Chemistry, California State University, 9001 Stockdale Hwy, Bakersfield, California 93311.
[§] American University of Beirut.

(1) Huang, L.-J.; Shih, M.-L.; Chen, H.-S.; Pan, S.-L.; Teng, C.-M.; Lee, F.-Y.; Kuo, S.-C. *Bioorg. Med. Chem.* **2006**, *14*, 528.
(2) Kim, D.; Wang, L.; Caldwell, C. G.; Chen, P.; Finke, P. E.; Oates, B.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Carver, G.; Carella, A.; Holmes, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3103.
(3) Schmidt, A.; Beutler, A.; Snovydovych, B. *Eur. J. Org. Chem.* **2008**, 4073.
(4) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2007**, *9*, 4947.
(5) (a) Hurst, J. *J. Chem. Soc. (C)* **1968**, 1487. (b) Foster, H.; Hurst, J. *J. Chem. Soc., Perkin Trans. I* **1973**, 319. (c) Chapman, D.; Hurst, J. *J. Chem. Soc., Perkin Trans. I* **1980**, 2398.
(6) (a) Stadlbauer, W.; Camp, N. In *Science of Synthesis: Houben-Weyl, Methods of Molecular Transformations*; Bellus, D., Ley, S. V., Noyori, R., Regitz, M., Schaumann, E., Shinkai, E., Thomas, E. J., Trost, B. M., Reider, P. J., Eds.; Thieme: Stutggart, 2002; Vol. 12, p 227. (b) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234.

10.1021/ol103108z
Published on Web 02/04/2011

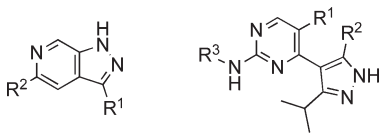
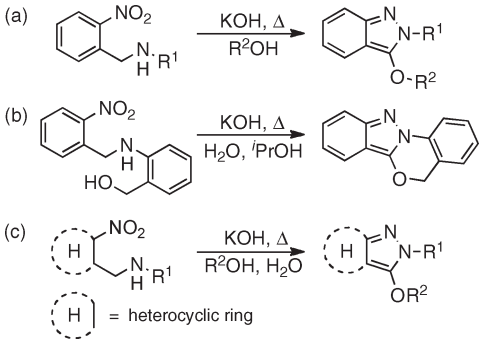


Figure 1. Pyrazolopyridine and 4-(pyrazol-4-yl)pyrimidines inhibitors.

compared to indoles and indazoles exhibiting protein kinase B/Akt inhibitory activities[7,4] and, more recently, 4-(pyrazol-4-yl)pyrimidines have been shown to selectively inhibit CDK4/6 (Figure 1).[8]

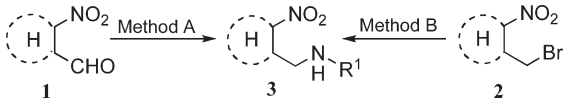
The benzo-1,3-oxazine ring system has also been shown to exhibit antihypertensive affects,[9] potency as antirheumatic agents,[10] and antianginal acitivity.[11] In contrast, heterocycle-fused 5*H*-benzo[*d*]pyrazolo[5,1-*b*][1,3]-oxazines, to the best of our knowledge, are unknown. This, together with the biological potential and intriguing structures of these compounds, prompted us to study the synthesis of this novel class of heterocycles.

Scheme 1. Synthetic Routes to Benzo-Fused [(a) and (b)] and Heterocycle-Fused (c) Pyrazoles



We have previously demonstrated that 3-alkoxy-2*H*-indazoles (Scheme 1a) and 5*H*-indazolo[3,2-*b*]benzo[*d*]-1,3-oxazines (Scheme 1b) can be obtained from *o*-nitroarylmethylamines via an *N*,*N*-bond forming heterocyclization reaction by treatment with KOH and water in alcoholic solvent.[12] It was also found that 5*H*-indazolo-[3,2-*b*]benzo[*d*][1,3]-oxazines can be obtained in a one-pot reaction starting with *o*-nitrobenzaldehyde.[12e] We envisaged that these methods (Scheme 1a/b) could be extended to the synthesis of a variety of novel heterocyclic analogs by, for example, introduction of a nitrogen atom in the benzo ring of 2*H*-indazoles or in any of the rings fused to this benzo ring (Scheme 1c). Indeed, a host of unique heterocycles can be envisioned in which the pyrazole ring is the common denominator and we report here that a number of benzo-1,3-dioxolo-, benzothiazolo-, pyrido-, quinolino-fused 5*H*-benzo[*d*]-pyrazolo[5,1-*b*]-[1,3]-oxazines and 1*H*-pyrazoles are accessible in moderate to high yields (35−88%) via this *N*,*N*-bond forming heterocyclization reaction.

Scheme 2. Synthesis of *o*-Nitroarylmethylamines[a]



[a] Method A: R^1NH_2 + acetic acid in MeOH; then $NaBH_3CN$/MeOH. Method B: R^1NH_2 (excess) in refluxing MeOH.

Scheme 2 demonstrates that *o*-nitroheterocyclic amine **3** can be accessed from either *o*-nitroheterocyclic aldehydes (**1**; Method A) or *o*-nitroheterocyclic halides (**2**; Method B). In Method A, the targeted *o*-nitroarylmethylamine **3** is obtained in nearly quantitative yield by utilizing an excess of amine. Moreover, the resulting *o*-nitroarylmethylamine generally does not require purification and crude **3** can be used directly in the subsequent heterocyclization with no significiant loss in yield or complication in product isolation/purification. In Method B, the starting *o*-nitroheterocyclic halide **2** is prepared in low yield (benzylic bromination; 30−40%) making this a generally less effective route to *o*-nitroarylmethylamine **3**.

All *o*-nitroheterocyclic aldehydes (**4a**−**e**, Scheme 3) except for **4e**, which was commercially available, were synthesized according to literature procedures.[13] Our targeting of heterocycle-fused pyrazoles started with treatment of the specific *o*-nitroheterocyclic aldehyde **4** with 2-aminobenzyl alcohol or *p*-bromoaniline followed by reduction of the resulting anil with $NaBH_3CN$ to obtain the *o*-nitroheterocyclic amine **3** (Scheme 3).

(7) Zhu, G.-D.; Gandhi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Olson, A.; Marsh, K. C.; Stoll, V. S.; Mamo, M.; Polakowski, J.; Campbell, T. J.; Martin, R. L.; Gintant, G. A.; Penning, T. D.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *J. Med. Chem.* **2007**, *50*, 2990.

(8) Cho, Y. S.; Borland, M.; Brain, C.; Chen, C. H.-T.; Cheng, H.; Chopra, R.; Chung, K.; Groarke, J.; He, G.; Hou, Y.; Kim, S.; Kovats, S.; Lu, Y.; O'Reilly, M.; Shen, J.; Smith, T.; Trakshel, G.; Vogtle, M.; Xu, M.; Sung, M. J. *J. Med. Chem.* **2010**, *53*, 7938.

(9) Clark, R. D.; Caroon, J. M.; Kluge, A. F.; Repke, D. B.; Roszkowski, A. P.; Strosberg, A. M.; Baker, S.; Bitter, S. M.; Okada, M. D. *J. Med. Chem.* **1983**, *26*, 657.

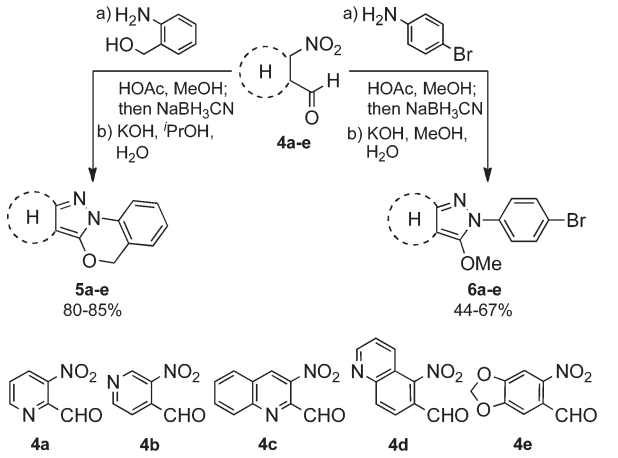
(10) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105.

(11) Benedini, F.; Bertolini, G.; Cereda, R.; Dona, G.; Gromo, G.; Levi, S.; Mizrahi, J.; Sala, A. *J. Med. Chem.* **1995**, *38*, 130.

(12) (a) Kurth, M. J.; Olmstead, M. M.; Haddadin, M. J. *J. Org. Chem.* **2005**, *70*, 1060. (b) Mills, A. D.; Nazer, M. Z.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2006**, *71*, 2687. (c) Mills, A. D.; Maloney, P.; Hassanein, E.; Haddadin, M. J.; Kurth, M. J. *J. Comb. Chem.* **2007**, *9*, 171. (d) Butler, J. D.; Solano, D. M.; Robins, L. I.; Haddadin, M. J.; Kurth, M. J. *J. Org. Chem.* **2008**, *73*, 234. (e) Solano, D. M.; Butler, J. D.; Haddadin, M. J.; Kurth, M. J. *Org. Synth.* **2010**, *87*, 339.

(13) (a) Niu, C.; Li, J.; Doyle, T. W.; Chen, S.-H. *Tetrahedron* **1998**, *54*, 6311. (b) Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219. (c) Yan, M.-C.; Tu, Z.; Lin, C.; Ko, S.; Hsu, J.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 1565. (d) Godard, A.; Queguiner, G. *J. Heterocycl. Chem.* **1980**, *17*, 465. (e) Couch, G. D.; Knox, R. J.; Moody, C. J. *Tetrahedron* **2008**, *64*, 2816.

Scheme 3. Route to Heterocycle-Fused Pyrazoles



As previously mentioned, these amine intermediates were not isolated, but were further treated with aqueous KOH in ^{i}PrOH (for **5a**−**e**) or in MeOH (for **6a**−**e**) to effect the heterocyclization leading to a series of heterocycle-fused pyrazole derivatives. The overall yields ranged from 80 to 85% for **5a**−**e** and 44−67% for **6a**−**e** (Scheme 3).

Interestingly, the heterocyclization reactions which give pyrido- and quinolino-fused 1*H*-pyrazoles (Table 1) were effected at room temperature − a deviation from the previously reported methods (Scheme 1a/b) where heating to 60 °C was required. This relative ease of formation of heterocycles **5a**−**c** and **6a**−**c** is likely due to the increased acidity of the benzylic hydrogen **4a**−**c**. In the synthesis of **5a**−**c**, ^{i}PrOH was used as solvent in the *N*,*N*-bond forming heterocylization reactions; when MeOH was used, LC/MS of the crude reaction mixture indicated some indazolone formation.[14] However, when targeting heterocycle-fused pyrazoles **6a**−**c**, MeOH was used as reactant and solvent and no indazolone was observed.

Table 1. Synthesis of Pyrido- and Quinolino-Fused 5*H*-Benzo-[*d*]pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-Pyrazoles[a,b]

o-nitro-heterocyclic aldehyde[c]		product	yield
4a	→	**5a**	85%
4a	→	**6a**	67%
4b	→	**5b**	81%
4b	→	**6b**	61%
4c	→	**5c**	80%
4c	→	**6c**	55%

[a] Products were characterized by ^{1}H, ^{13}C NMR, IR, and ESI MS. [b] Isolated yields after purification by chromatography on silica gel. [c] See **4a**−**c** in Scheme 3.

Table 2. Synthesis of Quinolino- and Benzo-1,3-dioxolo-fused 5*H*-Benzo[*d*]pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-Pyrazoles[a,b]

o-nitro-heterocyclic aldehyde[c]		product	yield
4d	→	**5d**	78%
4d	→	**6d**	54%
4e	→	**5e**	88%
4e	→	**6e**	44%

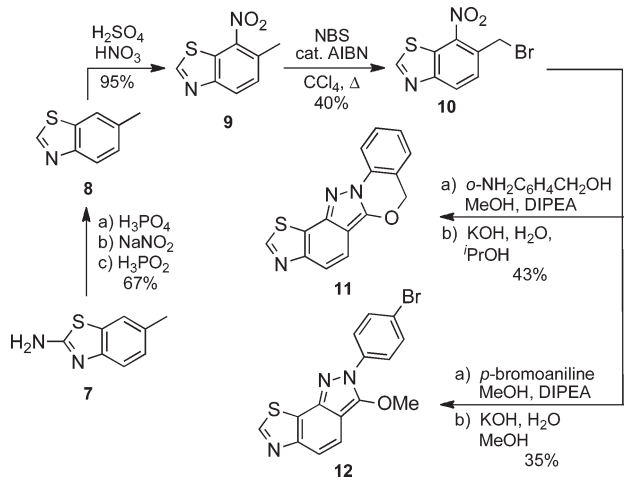
[a] Products were characterized by ^{1}H, ^{13}C NMR, IR, and ESI MS. [b] Isolated yields after purification by chromatography on silica gel. [c] See **4d**−**e** in Scheme 3.

Next, a study of quinolino- and benzo-1,3-dioxolo-fused analogs of **5** and **6** were explored (Table 2). Compounds **5d**,**e** and **6d**,**e** were synthesized by the same methods employed for **5a-c**/**6a-c** (Scheme 3). It is interesting to note that reactions of **4e** → **5e** and **4e** → **6e** proceed well (yields of 44% and 88%, respectively) despite the fact that starting material **4e** is relatively electron rich.

Benzothiazolo-fused pyrazoles **11** and **12** (Scheme 4) are additional examples of benzo-fused heterocyclic pyrazoles attainable by this method. To synthesize these compounds, the key synthetic intermediate, 6-bromomethyl-7-nitro-benzothiazole (**10**), was synthesized in three steps (25% overall yield) from 6-methyl-2-benzothiazolamine (**7**).[15,16] Step one involved deamination of **7** with phosphoric acid and sodium nitrite followed by reduction with hypophosphorous acid to give 6-methylbenzothiazole (**8**). Subsequent regioselective nitration delivered 6-methyl-7-nitrobenzothiazole (**9**) in improved yield (95%) when purified by flash chromatography instead of recrystallization. Nitrobenzothiazole **9** was then reacted with stoichiometric NBS

(14) Oakdale, J. S.; Solano, D. M.; Fettinger, J. C.; Haddadin, M. J.; Kurth, M. J. *Org. Lett.* **2009**, *11*, 2760.
(15) Matveev, M.; Ponyaev, A. I.; El'tsov, A. V. *Russ. J. Gen. Chem.* **2001**, *71*, 1286.
(16) Katritzky, A. R.; Rogovoy, B. V.; Chassaing, C.; Vvedensky, V.; Forood, B.; Flatt, B.; Nakai, H. *J. Heterocycl. Chem.* **2000**, *37*, 1655.

Scheme 4. Synthesis of Benzothiazolo-Fused 5*H*-Benzo-[*d*]pyrazolo-[5,1-*b*][1,3]-oxazines and 1*H*-Pyrazoles[a,b]



[a] Products were characterized by ^{1}H, ^{13}C NMR, IR, and ESI MS. [b] Isolated yields after purification by chromatography on silica gel.

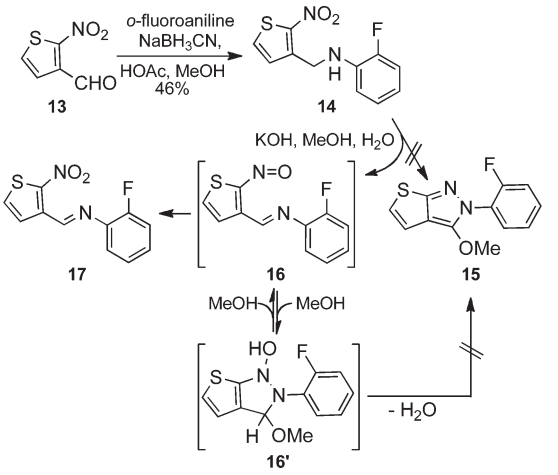
in carbon tetrachloride (AIBN catalyst), under reflux for 12 h, to give 7-bromo-methyl-6-nitrobenzothiazole (**10**) in 40% yield. Benzyl bromide **10** was then *N*-alkylated with excess 2-aminobenzyl alcohol, or *p*-bromoaniline, to generate the corresponding *o*-nitroarylmethylamines in MeOH which, without isolation, was treated with aqueous KOH in ^{i}PrOH (→ **11**) or in MeOH (→ **12**) to deliver benzothiazolo-fused pyrazoles **11** and **12** in 43 and 35% yields, respectively.

Finally, with these successes in preparing the unique heterocycles delineated above through this easy and effective *N*,*N*-bond forming heterocyclization methodology, we attempted to synthesize thiophene-fused pyrazole **15** (Scheme 5). *N*-((2-Nitrothiophen-3-yl)methyl)aniline **14** was obtained from 2-nitrothiophene-3-carbaldehyde[17] (**13**) and 2-fluoroaniline by reductive amination. Subjecting **14** to heterocyclization conditions at 0 °C (significant decomposition ensued at room temperature), failed to deliver the anticipated thieno-fused pyrazole **15**. Rather, the major product of this reaction proved to be 2-fluoro-*N*-((2-nitrothiophen-3-yl)methylene)aniline (**17**).[18] We speculate that nitroso imine **16** is the initial product of this reaction,[12a,b] but subsequent nitroso → nitro air oxidation[19] out-competes *N*,*N*-bond formation to deliver **17** rather than

(17) Makosza, M.; Owczarczyk, Z. *Tetrahedron Lett.* **1987**, *28*, 3021.

(18) The structure of **17** has been independently varified through its direct preparation by condensation of **13** with *o*-fluoroaniline; see Supporting Information.

Scheme 5. Attempted Synthesis of a Thieno-Fused 1*H*-Pyrazole



the targeted heterocycle **15**. This difficulty in formation of thieno-fused 1*H*-pyrazole **15** appears to derive from the weak acidity of the sp^3 hybridized proton of **16′**, which thus impedes 1,4-elimination of water. However, this tentative explanation remains to be supported by further investigation.

In summary, several unique pyrazole-based heterocycles were synthesized by a one-pot, *N*,*N*-bond forming heterocyclization of *o*-nitroarylmethylamines. These novel heterocycles have been submitted to the NIH Molecular Libraries Small Molecule Repository (MLSMR) for high-throughput biological screening. In view of the utility of this *N*,*N*-bond forming heterocyclization, which has been demonstrated in the synthesis of a wide variety of often complex heterocycles in this work as well as in six earlier pulications,[12,14] we propose to call this method the "Davis-Beirut" reaction in recognition of the merits of international collaboration.

Acknowledgment. Financial support was provided by the National Science Foundation (CHE-0910870, CHE-0449845) and the National Institutes of Health (GM089153). B.A. thanks the Bristol-Myers Squibb Graduate Minority Chemist Fellowship and Alfred P. Sloan Minority Ph.D. Program for fellowship support.

Supporting Information Available. Full experimental details and characterization data (IR, ^{1}H NMR, ^{13}C NMR, and ESI MS) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) We have observed nitroso → nitro air oxidation in a related system (*o*-nitrosoaniline → *o*-nitroaniline); unpublished results.