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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

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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 anti-angiogenic,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 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 (see 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 activity.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.

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Supporting Information: Full experimental details and characterization data (IR, ¹H NMR, ¹³C NMR, and ESI MS) of all new compounds are available free of charge via the Internet at <http://pubs.acs.org>.

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 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 significant 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 NaBH₃CN to obtain the *o*-nitroheterocyclic amine **3** (Scheme 3).

As previously mentioned, these amine intermediates were not isolated, but were further treated with aqueous KOH in ⁱPrOH (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 80-85% for **5a-e** and 44-67% for **6a-e** (Scheme 3).

Interestingly, the heterocyclization reactions which give pyrido- and quinolino-fused 1*H*-pyrazoles (see 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**, ⁱPrOH was used as solvent in the *N,N*-bond forming heterocyclization 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.

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-nitrobenzothiazole (**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-methyl-benzothiazole (**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 in carbon tetrachloride (AIBN catalyst), under reflux for 12 h, to give 7-bromomethyl-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 ($\rightarrow$ **11**) or in MeOH ($\rightarrow$ **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-carbaldehyde¹⁷ (**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 $\rightarrow$ nitro air oxidation¹⁹ outcompetes *N,N*-bond formation to deliver **17** rather than the targeted heterocycle **15**. This difficulty in formation of thieno-fused *1H*-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 publications,^{12,14} we propose to call this method the “Davis-Beirut” reaction in recognition of the merits of international collaboration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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18. The structure of **17** has been independently verified through its direct preparation by condensation of **13** with *o*-fluoroaniline; see Supporting Information.
19. We have observed nitroso $\rightarrow$ nitro air oxidation in a related system (*o*-nitrosoaniline $\rightarrow$ *o*-nitroaniline); unpublished results.

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

Scheme 1.

Synthetic routes to benzo-fused [(a) and (b)] and heterocycle-fused (c) pyrazoles.

Scheme 2. Synthesis of *o*-nitroarylmethylamines.^a^a**Method A:** R_1NH_2 + acetic acid in MeOH; then $\text{NaBH}_3\text{CN}/\text{MeOH}$.**Method B:** R_1NH_2 (excess) in refluxing MeOH.

Scheme 3.
Route to heterocycle-fused pyrazoles.

Scheme 4.

Synthesis of benzothiazolo-fused 5H-benzo-[d]pyrazolo[5,1-b][1,3]-oxazines and 1H-pyrazoles.^{a,b}

^aProducts were characterized by ^1H , ^{13}C NMR, IR, and ESI MS.

^bIsolated yields after purification by chromatography on silica gel.

Scheme 5.
Attempted synthesis of a thieno-fused 1H-pyrazole.

Table 1Synthesis of pyrido- and quinolino-fused 5*H*-benzo[*d*]pyrazolo[5,1-*b*][1,3]-oxazines and 1*H*-pyrazoles.^{a,b}

<i>o</i> -nitroheterocyclic 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 ¹H, ¹³C 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}

<i>o</i> -nitroheterocyclic aldehyde ^c	product	yield
4d → 5d		78%
4d → 6d		54%
4e → 5e		88%
4e → 6e		44%

^aProducts were characterized by ¹H, ¹³C NMR, IR, and ESI MS.

^bIsolated yields after purification by chromatography on silica gel.

^cSee 4d-e in Scheme 3.