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One-Pot Synthesis of *N*-Arylpyrazoles from Arylhalides

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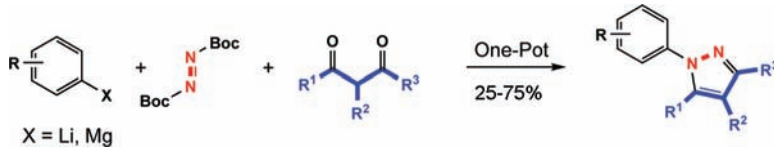
ABSTRACT



A simple one-pot method for the synthesis of diversely functionalized pyrazoles from aryl nucleophiles, di-*tert*-butylazodicarboxlate, and 1,3-dicarbonyl or equivalent compounds is presented.

N-Arylpyrazoles, although virtually unknown in natural products, are an important structural class in pharmaceuticals and agrochemicals including Celebrex (**1**), Pyracolfos, and Fipronil (**2**) (Figure 1).[1] Currently, two methods predominate in the synthesis of this key structure. The first is direct N-arylation of a 1 *H*-pyrazole via either a direct SN_{Ar} substitution or a transition-metal-catalyzed C−N cross-coupling reaction, and the second is the cyclocondensation of an arylhydrazine with a 1,3-difunctionalized three-carbon donor such as a diketone or β-aminoacrolein.[2] Even though transition-metal-catalyzed N-arylation using a variety of nitrogen nucleophiles has made tremendous progress in the past decade, including the use of palladium,[3] copper,[4−9] or iron,[10] these reactions still have limitations including non-generalization, lack of application to systems with sensitive functional groups, and limited examples of the use of 1*H*-pyrazoles as the nucleophilic component.[11] Conversely, the cyclocondensation method requires access to an appropriately substituted arylhydrazine, an often multistep synthesis when not commercially available, and further limited by compatibility of the free hydrazine with other functionality in the intermediate. Preparation of arylhydrazines from anilines via diazotization−reduction does not lend well to complex molecules with susceptible moieties. Additionally, these preparations of hydrazines usually are not appropriate at scale due to thermal instability and explosive characteristics of the intermediates. An ideal protocol would install the desired pyrazole onto an aryl halide, or even Ar-H, precursor in a functional group-tolerant, time-efficient, one-pot procedure.

In our research, we required access to *N*-arylpyrazole **4** (Scheme 1), with initial attempts focused on metal-catalyzed arylation using 4-chloro-1*H*-pyrazole under a variety of conditions. Unfortunately, all gave only low yields and required long reaction times (up to 5 days). Attempts to increase the rate or yield of the reaction by changing the

(1) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley & Sons: New York, 2004; pp 179−184.
(2) Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Rev. Dev.* **2008**, *12*, 480–489.
(3) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.
(4) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.
(5) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.
(6) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695–709.
(7) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.—Eur. J.* **2004**, *10*, 5607–5622.
(8) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
(9) Zhu, L.; Guo, P.; Li, G.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007**, *72*, 8535–8538.
(10) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862–8865.
(11) For an example of the state of the art, CuI-catalyzed N-arylation of pyrazole or 3-methyl-1*H*-pyrazole proceeded in 71% and 50% yield, respectively, after 40 h reaction time. Regioselectivity of arylation of 3-methyl-1*H*-pyrazole was 5:1 favoring the opposite regioisomer to the analogous example in our own work (Table 1, entry 4). See: Zhu, L.; Li, G.; Luo, L.; Guo, P.; Lan, J.; You, J. *J. Org. Chem.* **2009**, *74*, 2200–2202.

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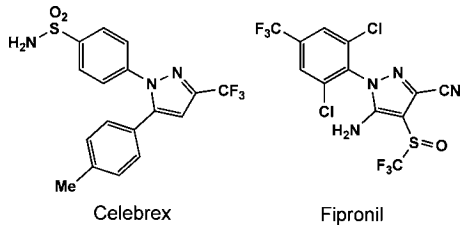
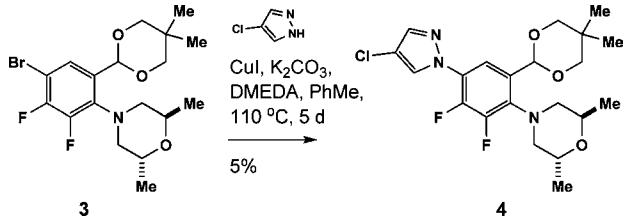


Figure 1. Important *N*-arylpyrazoles.

reaction conditions led to SN_{Ar} displacement of the aryl fluorine by the pyrazole nucleophile. Switching the pyrazole partner to 4-methyl-1*H*-pyrazoles or 1*H*-pyrazole had little impact on increasing the yield. Other reactions for the direct formation of the C−N bond from a pyrazole coupling using the boronic acid analog of **3** also failed.[12]

Scheme 1. CuI-Catalyzed Coupling of **3** with 4-Chloropyrazole



With these results, we turned our attention to the cyclocondensation reaction method, which would require the corresponding aryl hydrazine, a nontrivial transformation from **3**.

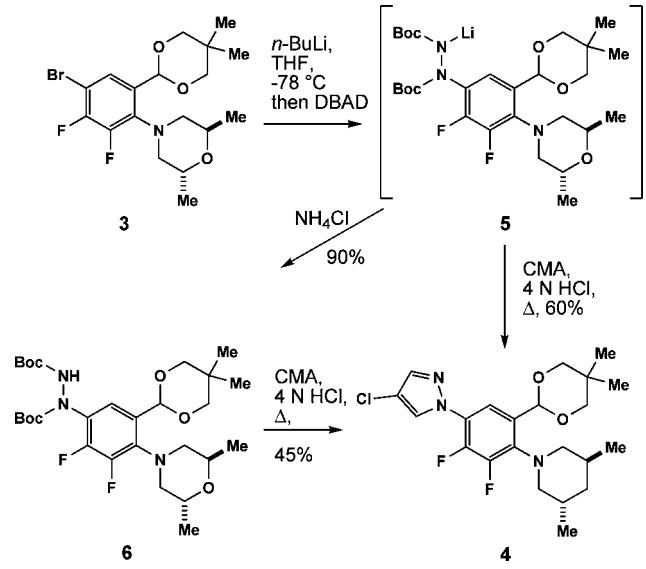
Fortunately, a literature search provided a route to install the hydrazine via the addition of an aryllithium species to an azodicarboxylate.[13] This method would give access to the bis-Boc protected aryl hydrazine by using di-*tert*-butyl azodicarboxylate (DBAD) as the hydrazine source.

Using this method allowed for the formation of **5**, which after isolation gave the derived bis-Boc hydrazine **6** (Scheme 2). Attempts to form the free hydrazine from **6** failed to give an isolable product, however, in situ deprotection using 4 N HCl in dioxane in the presence of chloromalonaldehyde (CMA) led to **4** in 45% yield. With this success, isolation of **6** appeared inconsequential, and it was found that the two reactions could be combined into a one-pot procedure. To this end, **3** was converted to its derived aryllithium by standard lithium-halogen exchange in THF at −78 °C then reacted with DBAD and allowed to warm to room temperature. The resulting lithium *N*-arylhydrazine intermediate **5** was then quenched with 4N HCl/dioxane followed by the addition of 2-chloromalonaldehdye and heating to reflux for

(12) Sreedhar, B.; Venkanna, G. T.; Shiva Kumar, K. B.; Balasubrahmanyam, V. *Synthesis* **2008**, *5*, 795–799.

(13) Demers, J. P.; Klaubert, D. H. *Tetrahedron Lett.* **1987**, *28*, 4933–4934.

Scheme 2. Alternative Synthesis of **4**



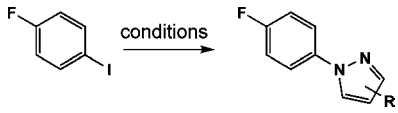
10 min to give the desired pyrazole product **4** in 60% yield after workup and purification.[14]

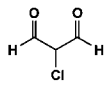
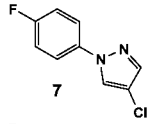
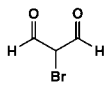
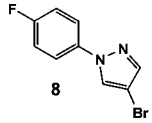
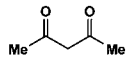
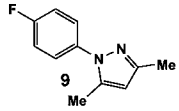
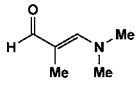
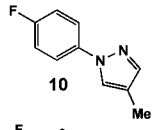
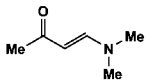
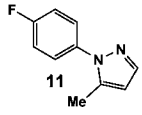
With a quick and simple one-pot procedure in hand, we set out to demonstrate the scope and utility of the procedure by the synthesis of a wide assortment of substituted pyrazoles. The one-pot procedure works well with a 1,3-dialdehyde, 1,3-diketone, β-aminoacrolein, or β-aminovinylketone as the three-carbon donor (Table 1).

As expected, the condensation reaction exhibits the regioselectivity typically observed and, thus, fills a niche in pyrazole synthesis methodology. The aryl halide coupling component one might use in a transition metal catalyzed, or SN_{Ar} approach leads to the contrasteric cyclocondensation product (as in entry 5) that would not be normally accessible using these methodologies. By substituting sulfuric acid for HCl in the general procedure, 3-bromopyrazole **8** was formed in 68% from 2-bromomalonaldehyde (entry 2). Using sulfuric acid in this case instead of 4 N HCl in dioxane circumvented competitive bromide−chloride exchange that gave a mixture of **7** and **8** when bromomalonaldehyde was used. Ready access to 4-bromopyrazoles was a gratifying result because it allowed us to apply the wide diversity of known arylhalide

(14) **Representative Procedure: 4-Chloro-1-(4-fluorophenyl)-1*H*-pyrazole (8).** To a solution of 4-fluoroiodobenzene (222 mg, 1.0 equiv) in THF (4 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.42 mmol, 1.05 equiv). The reaction was stirred for 5 min, and then di-*tert*-butyl azodicarboxylate (242 mg, 1.05 equiv) in THF (1 mL) was added in one portion. The reaction changed from slightly yellow to amber color. The reaction was removed from the ice bath and allowed to warm to room temperature over 30 min. To the reaction mixture was added 2-chloromalonaldehyde (118 mg, 1.05 equiv) followed by 4 N HCl in dioxane (∼5 mL). The reaction changed from an amber color to light yellow with the addition of the acid. The reaction was then heated to 80 °C for 10 min (the reaction turned dark amber color) then cooled to room temperature. The reaction was neutralized with sodium bicarbonate to pH ∼7 and extracted with ethyl acetate (5 mL × 3). The organic layer was dried with sodium sulfate, filtered, and concentrated to give an amber oil, which by TLC showed only one major spot above baseline (8:2 heptane/ethyl acetate). The reaction was purified via silica gel chromatography to give an off-white solid (125 mg, 64%).

Table 1. Survey of Three-Carbon Donors[a]



entry	3-carbon donor	product	yield (%)
1[a]		 **7**	64
2[b]		 **8**	68
3[a]		 **9**	67
4[a]		 **10**	74
5[a]		 **11**	50

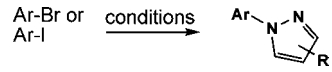
[a] Conditions: (a) 1 equiv of *n*-BuLi in THF at −78 °C, then DBAD and warm to 23 °C followed by addition of three-carbon donor and 4 N HCl/dioxane and reflux; (b) 1 equiv *of n*-BuLi in THF at −78 °C, then DBAD and warm to 23 °C followed by addition of three-carbon donor and 10% H_2SO_4/dioxane and reflux.

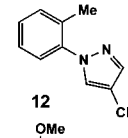
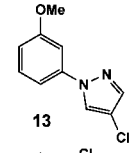
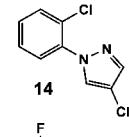
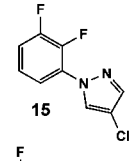
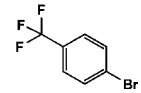
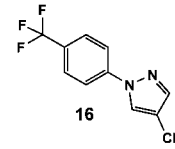
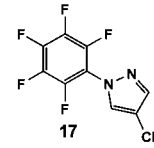
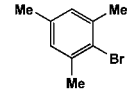
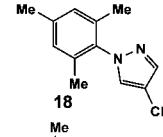
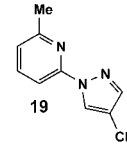
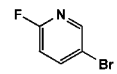
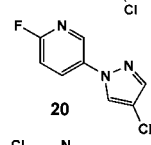
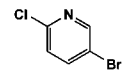
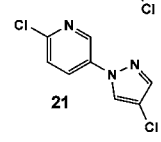
coupling reactions to the rapid diversification of substituents at the 4-position, including a subsequent application of our own protocol to append a second pyrazole to give **25** (Table 3).

We next turned our attention to varying the aryl component of the one-pot reaction, with an eye toward substrates whose functional groups might present problems with regioselectivity of substitution or functional group compatibility using other methods (Table 2). Entries 1−7 serve to establish the tolerability of simple arylbromide or aryliodide donors in the one-pot procedure. We were pleased to find even the hindered product **18** was accessible by this method. The reaction was found to be successful using lithium-halogen exchange on aryl-bromides or iodines in the presence of aryl-flourides or chloride. A variety of ring and substituent fluorination patterns was well tolerated. Trifluoromethyl (**16**), various difluoro (**15**, **22**, **23**), and even perfluoro (**17**) substitution gave useful yields of product. Halogenated pyridines were successfully employed to install the pyrazole group at either the 2- or 3- position including examples where SN_{Ar} susceptible 2-F or 2-Cl moieties were preserved (entries 9−10). Somewhat surprisingly, attempts to substitute a pyridine 4-position using the one-pot procedure met with failure.

We recognized the possibility of directly functionalizing an Ar-H precursor. Initially we had sought to perform the

Table 2. Survey of Aryl Donors[a]

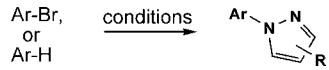


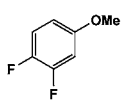
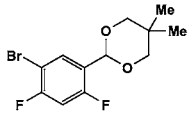
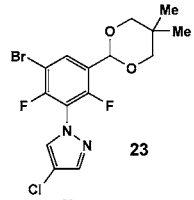
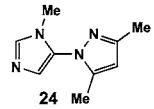
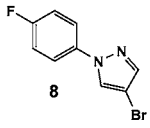
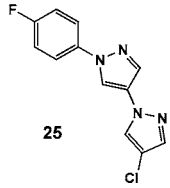
entry	aryl donor	product	yield (%)
1		 **12**	73
2		 **13**	60
3		 **14**	54
4		 **15**	60
5		 **16**	75
6		 **17**	75
7		 **18**	43
8		 **19**	64
9		 **20**	58
10		 **21**	67

[a] Conditions: 1 equiv of *n*-BuLi in THF at −78 °C, then DBAD and warm to 23 °C followed by addition of chloromalonaldehyde and 4 N HCl/dioxane then reflux.

Lewis acid catalyzed electrophilic amination using DBAD reported by Yadav and et al., however, in our hands this reaction was too unreliable to use in the one-pot method.[15,16] Alternatively, direct lithiation of activated arenes using LHMDS proved successful (entries 1 and 2, Table 3)

Table 3. Additional Examples[a]



entry	aryl donor	product	yield (%)
1[a]		 **22**	25
2[a]		 **23**	61
3[b]		 **24**	45
4[c]	 **8**	 **25**	50

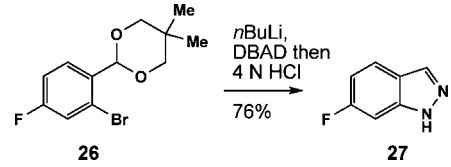
[a] Conditions: (a) 1.0 M LiHMDS, THF, −78 °C, DBAD, warm to 23 °C, then three-carbon donor, 4 N HCl/dioxane, reflux; (b) 2 M EtMgCl, THF, −78 °C, DBAD, warm to 23 °C, then acetoacetone, 4 N HCl/dioxane then reflux; (c) *n*-BuLi, THF, −78 °C, then DBAD and warm to 23 °C followed by addition of chloromalonaldehyde and 4 N HCl/dioxane then reflux.

demonstrating that lithium−halogen exchange was not critical for the reaction to occur. Entry 2 demonstrates the advantage of this option in which an aryl bromide was carried through untouched and lithium-halogen exchange would have given a different product. Five membered ring heteroaryl bromides were substrates as well. The imidazole−pyrazole **24** was synthesized in 45% via the 2-imidazolemagnesium chloride instead of the lithium species (entry 3). The halopyrazole product **8** is, itself, a substrate for a second iteration of the one-pot pyrazole procedure to give the unique bis-pyrazole **25** (entry 4).

We were pleased to find that this method was applicable to the one-pot formation of other N-functionalized arenes as well.

For example, an indazole was synthesized by, first, protection of 2-bromo-4-fluorobenzaldehyde using neopentyl glycol and catalytic *p*-toluenesulfonic acid to give **26** in quantitative yield (Scheme 3). Then lithium-halogen exchange followed by addition of DBAD gave a presumed lithiated arylhydrazine intermediate, which, upon treatment with 4 N HCl in dioxane, underwent hydrazine deprotection, triggering spontaneous cyclization with expulsion of neopentyl glycol to form the indazole **27** in 76% yield.

Scheme 3. Indazole Synthesis



26 **27**

This method is complementary to the method developed by Verma and LaFrance in which *o*-fluorobenzaldehydes are treated with hydrazine followed by cyclodehydration.[17]

In summary, we have reported a quick and simple one-pot synthesis of *N*-arylpyrazoles that can be readily adapted to the synthesis of indazoles as well. A wide variety of pyrazoles was formed that compliments the currently available methods in both substrate scope and compatibility, reaction time, and ease of synthesis. This, along with easy access to the previously challenging 4-halogenated *N*-arylpyrazoles, demonstrates this method as a tool for the rapid introduction of a functionalized pyrazole into an aryl or heteroaryl template.[18]

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Supporting Information Available: Procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Verma, S. K.; LaFrance, L. V. *Tetrahedron Lett.* **2009**, *50*, 383–385.

(18) We occasionally observed formation of *N*-butylpyrazoles as side products of unreacted *n*-BuLi addition to DBAD. Although we did not pursue this avenue of research, we believe the scope may extend beyond aryl and heteroaryl substrates.