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Novel Synthesis of 5-Amino-3-bromo-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile: A Versatile Intermediate for the Preparation of 5-Amino-3-aryl-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides

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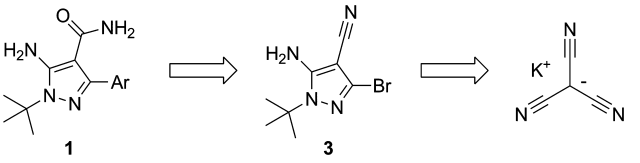
ABSTRACT



A simple, novel, and efficient route for the synthesis of 5-amino-3-aryl-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides 1 has been devised. Preparation of pyrazole bromide 3 from potassium tricyanomethanide can be accomplished in only two steps in good yield and features a selective Sandmeyer reaction on the corresponding diaminopyrazole. This allows for a more versatile synthesis of 5-amino-3-aryl-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides 1 than was previously possible.

Pyrazole[1] is an extensively utilized moiety, particularly in the field of medicinal chemistry, both as a pendant functional group and as a core template in a wide variety of therapeutic areas.[2] During the course of a medicinal chemistry campaign, a highly efficient and convergent synthesis of 5-amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1** was desired in order to rapidly access analogues at the 3-position (Figure 1). Our investigations into the literature revealed two main approaches to the synthesis of 5-amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1**. The first involves converting an acid chloride to 2-(methoxyarylmethylene)malononitrile (**4**), followed by ring closure with *tert*-butyl hydrazine, to afford the pyrazole **5** (Scheme 1).[3] While the first two steps are high yielding and robust, subsequent hydrolysis of the cyano group with sodium hydroxide, hydrogen peroxide, and tetrabutylammonium hydrogensulfate (TBAHS) to form carboxamide **1** is highly variable (15−75% reported yield). To address this liability, an alternate approach in which the carboxamide functionality can be incorporated into compound **6** prior to the pyrazole ring formation (Scheme 1) has been utilized.[4,5] This approach is more labor intensive. Additionally, both approaches require that each 3-aryl analogue be individually prepared in a linear fashion from the corresponding aryl acid chloride. We now report the development and application of an efficient three-step route to produce bromocarboxamide **2** that allows for a more versatile synthesis of various

(1) For recent reviews on the synthesis of pyrazoles, see: (a) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984–7034. (b) Yoon, J.-Y.; Lee, S.; Shin, H. *Curr. Org. Chem.* **2011**, *15*, 657–674. (c) Fustero, S.; Simon-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253–290.

(2) For recent reviews on pyrazoles in medicinal chemistry, see: (a) Keter, F. K.; Darkwa, J. *Biometals* **2012**, *25*, 9–21. (b) Tambe, S. K.; Dighe, N. S.; Pattan, S. R.; Kedar, M. S.; Musmade, D. S. *Pharmacologyonline* **2010**, *2*, 5–16. (c) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets in Heterocycl. Syst.* **2002**, *6*, 52–98.

(3) Adams, J. L.; Kasparec, J.; Silva, D. WO 03072541 A2, September 4, 2003.

(4) Davis, P. D.; Davis, J. M.; Moffat, D. F. C. WO 9740019 A1, October 30, 1997.

(5) Tominaga, Y.; Matsuoka, Y.; Oniyama, Y.; Uchimura, Y.; Komiya, H.; Hirayama, M.; Kohra, S.; Hosomi, A. *J. Heterocycl. Chem.* **1990**, *27*, 647–660.

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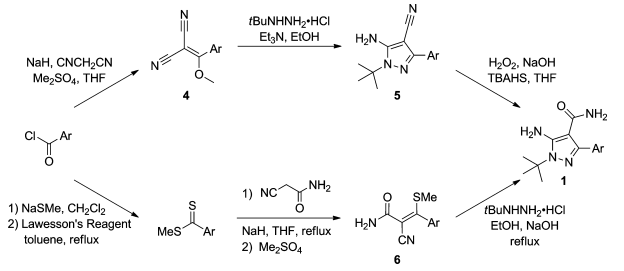
5-amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1** than was previously possible.

Scheme 1. Synthesis of 5-Amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides from Acid Chlorides



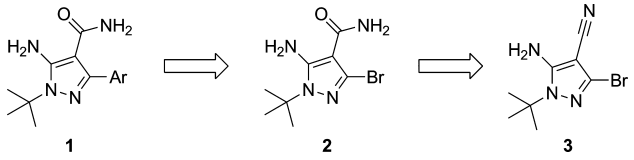
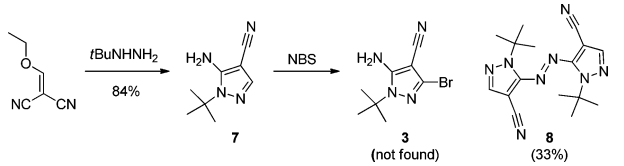


Figure 1. Retrosynthesis of 5-amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1** from 5-amino-3-bromo-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile (**3**).

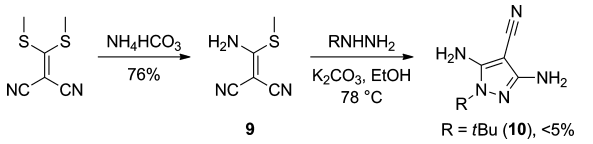
Our proposal was to efficiently prepare the bromo-intermediate **2** on scale which would enable the installation of a C-3 aryl group as the last step in the synthesis. Retrosynthetically, compound **2** would then be derived from compound **3** (Figure 1). Attempted bromination of 1-*tert*-butyl pyrazole[6] **7** resulted exclusively in the formation of diazenyl byproduct **8** instead of the desired bromide **3**, which was undetectable (Scheme 2).[7]

Scheme 2. Attempted Bromination of 5-Amino-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile (**7**)



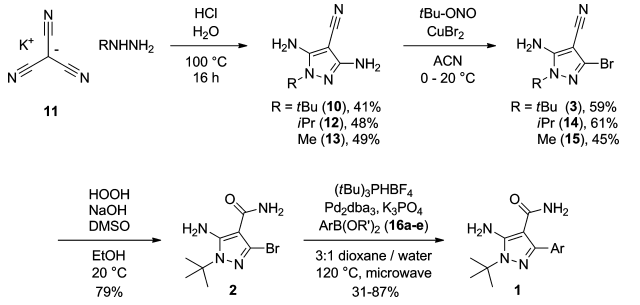
We postulated that the bromo intermediate **3** could instead be formed from diaminopyrazole **10** via a selective Sandmeyer reaction. The key intermediate **10** could be synthesized from malononitrile derivative **9**, but in very low yield (< 5%) (Scheme 3).[8] While this method was reported to provide the corresponding *N*-1-methyl and *N*-1-unsubstituted compounds in high yields (> 80% reported yield), the use of this reaction was impractical for generating preparative quantities of the *N*-1-*tert*-butyl intermediate **10**.

Scheme 3. Synthesis of 3,5-Diamino-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile (**10**) from Malononitrile Derivative **9**



Potassium tricyanomethanide (**11**) has been reported in the literature for the successful preparation of *N*-1-methyl-3,5-diamino-4-cyanopyrazole (**13**).[9] We hypothesized that this same reagent could also be used to form the desired *tert*-butyl intermediate **10**. Gratifyingly, treatment of potassium tricyanomethanide (**11**) with *tert*-butylhydrazine afforded 3,5-diamino-1-(*tert*-butyl)-1*H*-pyrazole-4-carbonitrile (**10**) in 41% isolated yield on a multigram scale. Similarly, this method was applied to the synthesis of *N*-1-*iso*-propyl intermediate **12** and *N*-1-methyl intermediate **13** in 48% and 49% yields, respectively (Scheme 4).

Scheme 4. Synthesis of 5-Amino-3-substituted-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1** from Potassium Tricyanomethanide (**11**)



With the desired 3,5-diamino-pyrazole **10** (R = *t*Bu) in hand, we carried out the proposed Sandmeyer reaction. We hypothesized that the 3-bromo regioisomer would be afforded as the major product due to the steric hindrance adjacent to the 5-amino group. Indeed, the Sandmeyer reaction afforded **3** selectively in 59% yield (Scheme 4). Similarly, when the pyrazole N-1 nitrogen was substituted with *iso*-propyl (**12**) the Sandmeyer reaction was regioselective for the 3-amino group and afforded the 3-bromo regioisomer **14** as the major product. Excellent selectivity

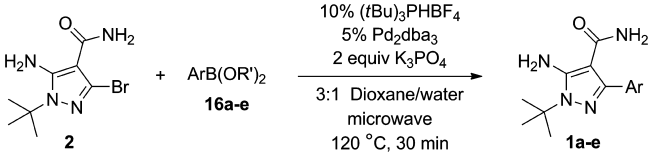
(6) Prepared according to the method described in: Bulawa, C. E.; Devit, M.; Elbaum, D. WO 2009062118 A2, May 14, 2009.

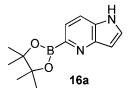
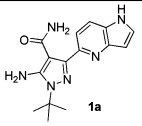
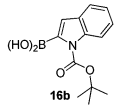
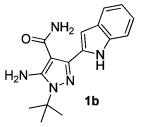
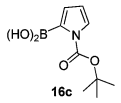
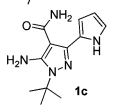
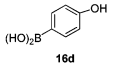
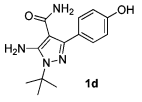
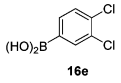
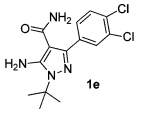
(7) Salaheldin, A. M.; Oliveira-Campos, A. M. F.; Rodrigues, L. M. *Tetrahedron Lett*. **2007**, *48*, 8819–8822.

(8) Ried, W.; Aboul-Fetouh, S. *Tetrahedron* **1988**, *44*, 7155–7162.

(9) Percival, A.; Judson, P. N. U.S. Patent 4,163,846, August 7, 1979.

Table 1. Examples of Suzuki−Miyaura Cross-Coupling of Bromopyrazole **2** with Boronates **16a**−**e**[a]



entry	aryl boronate	product	% isolated yield
1	 16a	 1a	87
2	 16b	 1b	25
3	 16c	 1c	31
4	 16d	 1d	48
5	 16e	 1e	34

[a] All reaction used 1 equiv of pyrazole bromide **2** and 1.0−1.1 equiv of aryl boronate **16**, on 100−150 mg scale.

was also observed in the formation of the N-1 methyl derivative **15**. The 5-bromo regioisomer was not observed in all the substrates studied.

Hydrolysis of the cyano group proceeded cleanly to provide the carboxamide **2** in 79% yield. 5-Amino-3-bromo-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamide (**2**) was then coupled successfully with the corresponding boronates or boronic acids **16a**−**e** via Suzuki−Miyaura reaction under microwave heating. The desired 3-aryl and 3-heteroaryl substituted pyrazoles **1a**−**e** were formed in generally good yields (31−87%, Table 1). The *tert*-butoxy carbonyl (*t*Boc) indole protecting group was removed *in situ* under the Suzuki−Miyaura reaction conditions (entries 2, 3).

In summary, a simple, novel, and efficient route for the synthesis of 5-amino-3-aryl-1-(*tert*-butyl)-1*H*-pyrazole-4-carboxamides **1** was developed. Preparation of the previously unknown pyrazole bromide **3** from potassium tricyanomethanide (**11**) can be accomplished in only two steps in good yield and features a selective Sandmeyer reaction on diaminopyrazole **10**. The synthesis is also scalable and requires only a single chromatographic purification. Importantly, C-3 can conveniently be diversified in the final step. The chemistry illustrated here provides a new route by which numerous and diverse medicinally useful pyrazole compounds can be readily accessed.

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

The authors declare no competing financial interest.