Tetrahedron Letters 49 (2008) 4579–4581

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient route to 3-aminoindazoles and 3-amino-7-azaindazoles

Michael J. Burke [a,*], Brian M. Trantow [b]

[a] Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd., Ridgefield, CT 06877, United States
[b] Stanford University, Department of Chemistry, 333 Campus Dr., Stanford, CA 94305, United States

ARTICLE INFO

Article history:
Received 27 March 2008
Revised 5 May 2008
Accepted 21 May 2008
Available online 27 May 2008

Keywords:
Indazole
Thioamide
Azaindazole

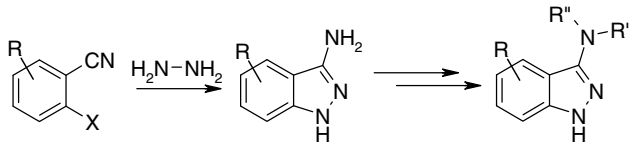
ABSTRACT

A non-acidic procedure for the preparation of 3-aminoindazoles and 3-amino-7-azaindazoles from 2-fluoroaryl carboxylic acids is reported. The synthesis starts from readily available starting materials and uses mild and practical reaction conditions in a three-step overall procedure. Products were isolated for a number of examples, but yields varied significantly depending on electronic nature of the substituents.

Recently, there has been great interest in the use of 3-aminoindazoles as agents interacting with a variety of biological targets including kinases,[1] Factor XIa,[2] CB1,[3] and PARP1.[4] The methods for the preparation of these compounds typically involved the reaction of a 2-haloaryl nitrile with hydrazine to provide the 3-aminoindazole, of which the amine must be further elaborated (Scheme 1).

Alternatively, use of either 3-chloroindazole[3,5] or imidoyl chlorides, prepared with $SOCl_2$ or $POCl_3$,[6] can be reacted with the desired amine; however, metal catalysis or protecting group manipulation is required for these reactions to succeed.

Recently, we required a general method for the preparation of 3-aminoindazoles which avoided the use of harshly acidic conditions, protecting groups, or metal catalysis while allowing for the incorporation of elaborated amines. Literature examination revealed only two examples of a two-step procedure requiring both acidic and basic steps through use of a thioamide and hydrazine.[7] The work described herein represents a milder approach to the preparation of these cores using representative amines and 2-fluoroaryl acids as starting points (Scheme 2).



Scheme 1. 3-Aminoindazole preparation from *o*-halo arylnitriles.

Acids **1**–**3** were coupled with amines **a**–**d** using HATU/TEA in DMF to prepare amides **4–6** in excellent yields.[8] Attempts to directly convert these amides to the desired indazoles via reaction with hydrazine under a variety of conditions were unsuccessful as the intermediate aminoamidine could not be detected. In order to increase the reactivity of these amides, they were converted to their corresponding thioamide derivatives (**7–9**) in good yield with Lawesson's Reagent in toluene or THF.[9] The desired products can then be prepared by simple dissolution of the thioamide in anhydrous DMSO and heating with an excess of anhydrous hydrazine.[10] The products prepared in this manner are summarized in Table 1 below.

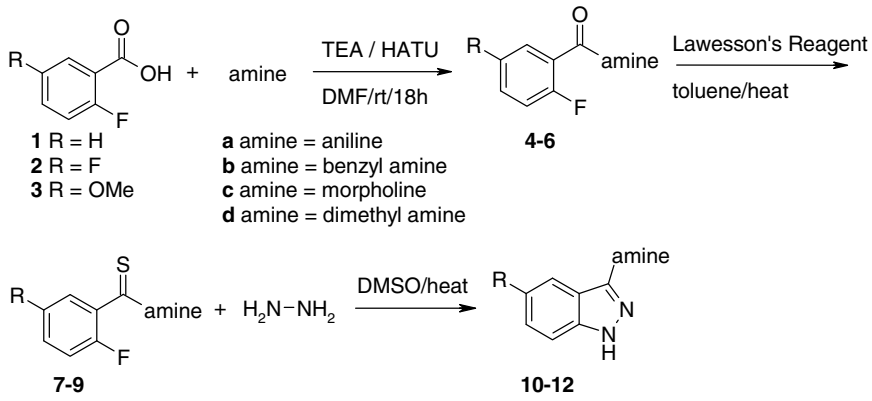
Examination of the effect of substitution *para* to the fluoro atom shows that the electron-donating *p*-methoxy substituent negatively affects the yield of indazole product when compared to the outcome with the electron-withdrawing *p*-fluoro substituent. It was also evident that the preparation of these methoxy derivatives required higher temperatures for the reaction to proceed relative to the electronically neutral proton and electronically deficient fluoro groups.

Attempts to use hydroxylamine, in place of hydrazine in this method, failed to produce the desired 3-amino-1,2-benzisoxazoles as the oxygen atom failed to displace the *o*-fluoro group, even as the intermediate hydroxyamidine was observed by mass spectroscopy. Similarly, other attempts using substituted hydrazines in efforts to provide N1 alkylated 3-aminoindazoles gave complex mixtures of products.

In order to determine if the methodology could be extended to the preparation of azaindazoles, we investigated the use of either nicotinic or isonicotinic acids as starting materials and found that success depended on the position of the pyridyl nitrogen relative to the halogen atom.

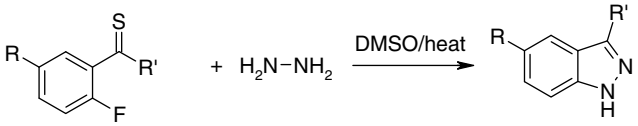
* Corresponding author. Tel.: +1 203 798 4180; fax: +1 203 791 6072.
E-mail address: michael.burke@boehringer-ingelheim.com (M. J. Burke).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.100



Scheme 2. Procedure for the preparation of 3-aminoindazoles.

Table 1
Yields and compounds prepared upon reaction of hydrazine with thioamides



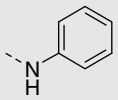
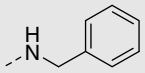
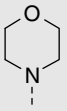
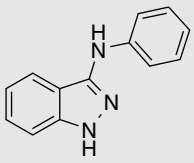
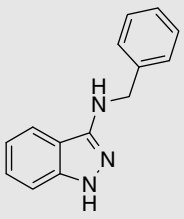
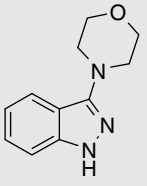
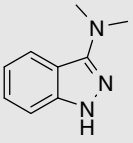
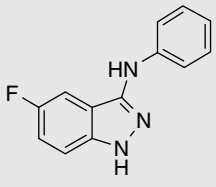
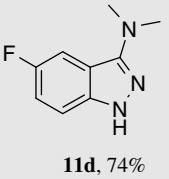
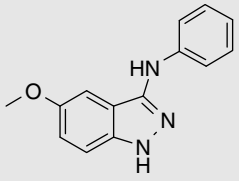
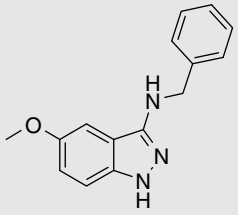
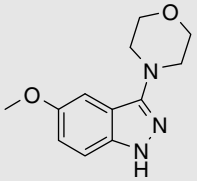
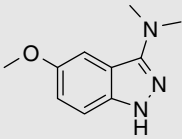
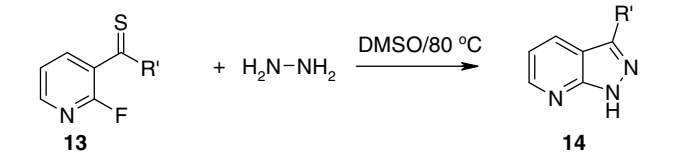
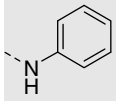
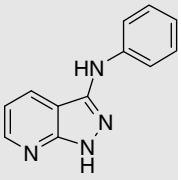
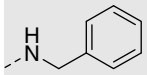
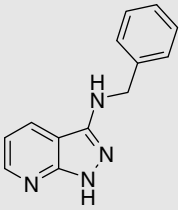
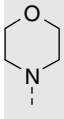
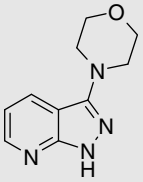
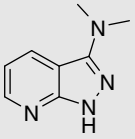
R	R′			
				
H	 **10a**, 73%	 **10b**, 75%	 **10c**,76%	 **9d**, 56%
F	 **11a**, 86%	 **11b**, 70%	 **11c**, 65%	 **11d**, 74%
OMe	 **12a**, 22%	 **12b**, 19%	 **12c**, 27%	 **12d**, 16%

Table 2
Preparation of 3-amino-7-azaindazoles



13 **14**

R′	Product, yield
 **13a**	 **14a**, 73%
 **13b**	 **14b**, 84%
 **13c**	 **14c**, 80%
 **13d**	 **14d**, 57%

Using 2-fluoro nicotinic acid as a starting point, decreased reaction temperatures and extended reaction times were required for the preparation of the thioamides **13a–d**. Under standard conditions, displacement of the fluoro atom by thiol, presumably originating from decomposition of Lawesson's reagent was the major product. Attempts to limit this through the use of 0.25 mol equiv of Lawesson's reagent created long reaction times and incomplete conversion to product. Once conditions were optimized, the thioamide reaction with hydrazine proceeded quite smoothly to produce products **14a–d** as can be seen in Table 2.

Attempts to extend the method to the preparation of additional isomeric azaindazoles have so far been unsuccessful. With 3-fluoroisonicotinic thioamides, no conditions were identified that provided for the preparation of the desired 6-azaindazole systems. Attempts to produce azaindazoles using 4-chloro-3-thionicotinic amides also failed as chloro displacement by hydrazine prevailed which in turn led to intractable products. Future investigations will examine the use of less reactive leaving groups, such as methoxy or thiomethyl in place of the halogen, to complete the aza series. Also, investigation is underway using 2-bromo substituents and metal catalysis for the preparation of 3-aminoazabenzisoxazole compounds, which are relatively underrepresented in the literature. This may also provide a means to improve the yields for electron-rich ring systems.

Acknowledgments

The authors would like to thank Dr. John Regan for strategic discussions; Mr. Mark Ralph for the preparation of some intermediates; as well as the Connecticut Business and Industry Association for the summer industrial tenure of Mr. Brian Trantow.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.100.

References and notes

1. (a) Klein, M.; Gericke, R.; Mederski, W.; Beier, N.; Lang, F. WO2007/090494, August 16, 2007.; (b) Bingaman, D. US 2006/0189608, August 24, 2006; (c) Harmange, J. -C.; Booker, S.; Bauer, D.; Kim, T. -S.; Cheng, Y.; Xu, S.; Ning, X.; Kim, J.; Tasker, A. WO2005/073224, August 11, 2005.; (d) Woods, K.; Fisher, J.; Claiborne, A.; Li, T.; Thomas, S.; Zhu, G.-D.; Diebold, R.; Liu, X.; Shi, Y.; Klinghofer, V.; Han, E.; Guan, R.; Magnone, S.; Johnson, E.; Bouska, J.; Olson, A.; de Jong, R.; Oltersdorf, T.; Luo, Y.; Rosenberg, S.; Giranda, V.; Li, Q. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 6832; (e) Stocks, M.; Barber, S.; Ford, R.; Leroux, F.; St. Gallay, S.; Teague, S.; Xue, Y. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3459.
2. Pinto, D.; Smallheer, J.; Corte, J.; Zilun, H.; Cavallaro, C.; Gilligan, P.; Quan, M. WO2007/070826, June 21, 2007.
3. Santhakumar, V.; Tomaszewski, M. WO2006/052190, May 18, 2006.
4. Guillemont, J.; Kennis, L.; Mertens, J.; Van Dun, J.; Somers, M.; Wouters, W. WO2006/003146, January 12, 2006.
5. Bouchet, P.; Lazaro, R.; Benchidmi, M.; Elguero, J. *Tetrahedron* **1980**, *36*, 3523.
6. (a) Leroy, V.; Lee, G.; Lin, J.; Herman, S.; Lee, T. *Org. Process Res. Dev.* **2001**, *5*, 179; (b) Watson, T.; Ayers, T.; Shah, N.; Wenstrup, D.; Webster, M.; Freund, D.; Horgan, S.; Carey, J. *Org. Process Res. Dev.* **2003**, *7*, 521.
7. Kennis, L. E., Vendenberk, J., Mertens, J. C. US 4, 958, 916, September 18, 1990.
8. *General procedure I for amide preparation: To o*-fluoro arylacid (1 equiv) in DMF (5 mL/3.5 mmol acid) were added triethylamine (1.5 equiv), amine (1.1 equiv), and HATU (1.1 equiv). This mixture was allowed to stirr for 18 h at room temperature, then diluted with EtOAc and transferred to a separatory funnel. The mixture was diluted with EtOAc and rinsed with saturated Na_2CO_3, water, and brine. The organics were then dried with Na_2SO_4, filtered, and evaporated. The residue was then purified via flash chromatography (hexanes/EtOAc) to provide the desired amide in yields of 80–95%.
9. *General procedure II for thioamide preparation: To o*-fluoro aryl amide (1 equiv) in toluene (5 mL/1.7 mmol) or THF (for azacompounds) was added Lawesson's Reagent (1 equiv) and the mixture was heated at 100 °C (40 °C for azacompounds). Upon completion (2–18 h), the reaction was filtered through Celite and the filtrate was evaporated. The residue was purified via flash chromatography (hexanes/EtOAc) to provide the desired thioamide in yields of 75–85%.
10. *General procedure III for indazole preparation: To o*-fluorothioamide (1 equiv) in anhydrous DMSO (5 mL/1.7 mmol) was added hydrazine (10 equiv) in one portion. The flask was then lowered into a preheated oil bath (150 °C e.g., **10a–11d**; 180 °C e.g., **12a–d**; and 80 °C e.g., **14a–d**) and allowed to stir. After 2 h, or until reaction appeared complete via MS, the reaction was cooled to room temperature, diluted with saturated Na_2CO_3, and extracted with Et_2O. The combined organics were rinsed with water, brine, dried with Na_2SO_4, filtered, and evaporated. The residue was then purified via flash chromatography (hexanes/EtOAC) to provide the desired products.