Tetrahedron 69 (2013) 3907–3912

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

A method for the regioselective synthesis of 1-alkyl-1*H*-indazoles

Han-Jun Liu [a], Shiang-Fu Hung [a], Chuan-Lin Chen [b], Mei-Huey Lin [a,*]

[a] Department of Chemistry, National Changhua University of Education, Changhua 50007, Taiwan
[b] Department of Biomedical Imaging and Radiological Sciences, National Yang-Ming University, Taipei 112, Taiwan

ARTICLE INFO

Article history:
Received 2 January 2013
Received in revised form 6 March 2013
Accepted 9 March 2013
Available online 14 March 2013

Keywords:
Regioselective
Indazoles
2-Halobenzonitriles
N-Alkylhydrazines
Deamination

ABSTRACT

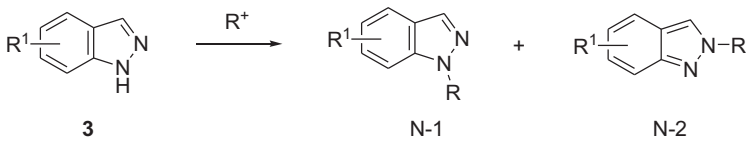
A method for the regioselective synthesis of 3-unsubstituted 1-alkyl-1*H*-indazoles, starting with 2-halobenzonitriles and *N*-alkylhydrazines, is described. The two-step reaction pathway proceeds through the intermediacy of 1-alkyl-3-amino-1*H*-indazoles followed by reductive deamination.

1. Introduction

The indazole ring system is recognized to be a highly effective pharmacophore in medicinal chemistry as well as being the core of important nitrogen-containing heterocycles that show a broad range of biological activities, such as nitric oxide synthase[1] and HIV protease[2] inhibitors, anti-inflammatory,[3] antitumor,[4] and anti-cancer[5] agents, and serotonin 5-HT3 receptor antagonists.[6] A variety of methods for the preparation of indazoles have been reported.[7] The developed approaches include diazotization of 2-alkylaniline derivatives followed by cyclization under basic conditions,[8] base promoted cyclization of (*o*-alkylaryl)azosulfides derived from 2-alkylaniline derivatives,[9] [3+2] cycloadditions of arynes with diazo compounds or hydrazones,[10] condensation reactions of *o*-haloaryl carbonyls or salicylaldehydes with hydrazine,[11] and cyclization reactions of *o*-aminobenzoximes in the presence of bases.[12] Although methods for regioselective synthesis of indazoles have been described,[12–20] only a few of these are applicable to the regioselective synthesis of 1-alkyl-1*H*-indazoles.[13,14,15b,16,20] Thus, methods for the regioselective synthesis of 1-alkyl-1*H*-indazoles remain in demand.

2. Results and discussion

As a part of a recent research effort, we required 3-unsubstituted 1-alkyl-1*H*-indazoles as synthetic intermediates. The most straightforward route to access these substances involves treatment of 3-unsubstituted 1*H*-indazoles with alkylating agents. However, the regiochemistry of these processes is highly dependent on the nature of alkylating agent and, in general, mixtures of *N*-1 and *N*-2 alkylated products are typically produced (Eq. 1). For example, methylation of 5-nitro-1*H*-indazole using iodomethane (NaH, THF, 0 °C, 2 h) results in formation of a mixture of 5-nitro-1-methyl-1*H*- and 5-nitro-2-methyl-2*H*-indazoles in a 55:45 ratio. Moreover, varying the solvent, temperature and base employed in this reaction failed to improve the selectivity.



3 N-1 N-2 **Eq (1)**

A common method for the preparation of 3-substituted 1-alkyl-1*H*-indazoles involves cyclization of an arylhydrazone, derived

* Corresponding author. Tel.: +886 4 7232105x3543; fax: +886 4 7211190; e-mail address: mhlin@cc.ncue.edu.tw (M.-H. Lin).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.03.042

from reaction of an arylketone possessing a leaving group in the *ortho*-position with an alkylhydrazine.[14,16] We envisioned that 3-unsubstituted 1-alkyl-1*H*-indazoles could be generated utilizing an analogous process in which an arylketone is replaced by an arylaldehyde. However, treatment of methylhydrazine and a mesylate, derived from reaction of 5-bromo-2-hydroxy-benzaldehyde with mesyl chloride, in refluxing xylene in the presence of NH_4OAc for 3 h gave only the corresponding hydrazone product, and an increase in the time for this reaction to 14 h resulted in the formation of multiple products.

Owing to these observations, our attention turned to the use of other substrates. 3-Aminoindazoles, obtained by using a variety of methods,[21–23] are known to have valuable biological activities in several therapeutic areas.[24] Wheeler et al. described a procedure for the regioselective synthesis of 3-amino-1-methyl-1*H*-indazoles utilizing reactions of 2-fluorobenzonitriles with methylhydrazine.[20] We hypothesized that this process, when coupled with the novel reductive deamination reaction of arylamines that produces aromatic hydrocarbons described by Doyle and Picciionello et al.,[24,25] would serve as a regioselective two-step method for the preparation of 3-unsubstituted 1-alkyl-1*H*-indazoles. The viability of this proposal was demonstrated in the studies described below.

As the results displayed in Scheme 1 and Table 1 show, reactions of members of a series of 2-halobenzonitriles, containing either electron-donating or -withdrawing groups, with methylhydrazine in ethanol efficiently produce the corresponding 3-amino-1-methyl-1*H*-indazoles **2**. Reductive deamination reactions of the 3-amino-1-methyl-1*H*-indazole products **2** with *tert*-butyl nitrite in either $CHCl_3$, DMF or THF generated 3-unsubstituted-1-methyl-1*H*-indazoles **3** in high yields. It should be noted that the deamination reaction of 3-amino-1-methyl-5-nitro-1*H*-indazole (**2e**) in THF or $CHCl_3$ gave a product that was expected to be 1-methyl-5-nitro-1*H*-indazole (**3e**). In order to confirm its structure, this substance was subjected to catalytic hydrogenation, which yielded 1-methyl-5-amino-1*H*-indazole.

4. Experimental section

4.1. General

All commercially available chemicals were used without further purification. TLC analyses were run on a TLC glass plate (Silica gel 60 F_{254}) and were visualized using UV and a solution of phosphomolybdic acid in ethanol (5 wt %) or *p*-anisaldehyde stain. Flash chromatography was performed using silica gel (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.24, δ_C (central line) 77.0]. Mass spectra were recorded under fast atom bombardment (FAB) or electron impact ionization (EI) conditions. High-resolution mass spectra were recorded by electron impact ionization with a magnetic sector analyzer.

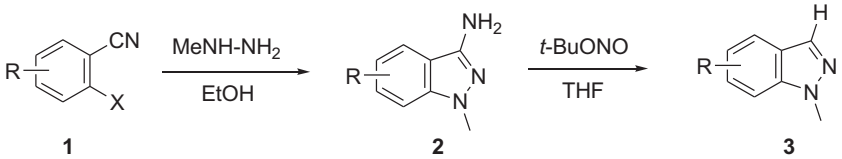
4.2. Synthesis

*4.2.1. General procedure for synthesis of 3-amino-1-methyl-1H-indazole **2**.* A mixture of benzonitrile **1** (10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) was heated to reflux overnight. The mixture was cooled to rt and then concentrated. H_2O (10.0 mL) and EtOAc (20.0 mL) were added to the residue. The organic layer was washed with H_2O (10.0 mL), brine (10.0 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was subjected to silica-gel chromatography by using EtOAc/hexanes (1:1) as eluent to give the product **2**.

*4.2.1.1. 1-Methyl-1H-indazol-3-ylamine (**2a**).* As described in the general procedure, reaction of 2-fluorobenzonitrile **1a** (1.21 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.35 g, 92%). Solid (EtOAc/hexanes=3:1), mp 94–95 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.13 (br s, 2H), 6.96 (dd, *J*=8.6, 7.2 Hz, 1H), 7.15 (d, *J*=8.6 Hz, 1H), 7.30 (dd, *J*=8.0, 7.2 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6 (CH_3), 108.5 (CH), 114.3 (C), 118.2 (CH), 119.4 (CH), 126.7 (CH), 141.3 (C), 146.9 (C); MS *m*/*z* (rel intensity) 148 (M^++H, 100), 133 (5). These data are in agreement with those reported in the literature.[26]

*4.2.1.2. 4-Fluoro-1-methyl-1H-indazol-3-amine (**2b**).* As described in the general procedure, reaction of 2,6-difluorobenzonitrile **1b** (1.39 g, 10.0 mmol) and methylhydrazine (2.8 mL, 50.0 mmol) in EtOH (10.0 mL) afforded the title compound (1.42 g, 86%). Solid (EtOAc/hexanes=1:1), mp 125–126 °C; TLC (EtOAc/hexanes (1:1)) R_f=0.2; IR (neat) 3438, 3308, 3206, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.12 (br s, 2H), 6.54 (dd, *J*=9.0, 6.0 Hz, 1H), 6.88 (d, *J*=6.0 Hz, 1H), 7.18 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 35.0 (CH_3), 102.7 (CH), 104.6 (CH), 128.2 (CH), 144.0 (C), 145.5 (C), 155.1 (C), 158.4 (C); MS *m*/*z* (rel intensity) 165 (M^+, 100), 122 (28); HRMS $[M]^+$ for $C_8H_8N_3$: 165.0702, found 165.0708.

*4.2.1.3. 5-Fluoro-1-methyl-1H-indazol-3-amine (**2c**).* As described in the general procedure, reaction of 2,5-difluorobenzonitrile



Scheme 1. Regioselective synthesis of 1-methyl-1*H*-indazoles via 1-methyl-3-amino-1*H*-indazoles.

In order to determine if this methodology is suitable for the preparation of other 1-alkyl-1*H*-indazoles, reactions of ethyl hydrazine and benzyl hydrazine with the respective benzonitriles **1b** and **1e** were examined. As the results displayed in Scheme 2 show, application of the two-step procedure gave the corresponding 1-ethyl- (**3j**) and 1-benzyl- (**3i**) 1*H*-indazoles in high yields. Other hydrazines, such as phenylhydrazine (Ph–NH–NH_2) and isopropylhydrazine (Me_2CH–NH–NH_2) were examined and both reactions gave a mixture of multiple products. Based on the results, a plausible mechanism is proposed and shown in Scheme 3.

3. Conclusion

In summary, the study described above has resulted in the development of an alternative, two-step method for the regioselective synthesis of 3-unsubstituted 1-alkyl-1*H*-indazoles starting with *N*-alkylhydrazines and 2-halobenzonitriles.