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N,N-Bond-Forming Heterocyclization: Synthesis of 3-Alkoxy-2*H*-indazoles

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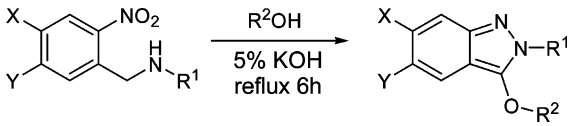
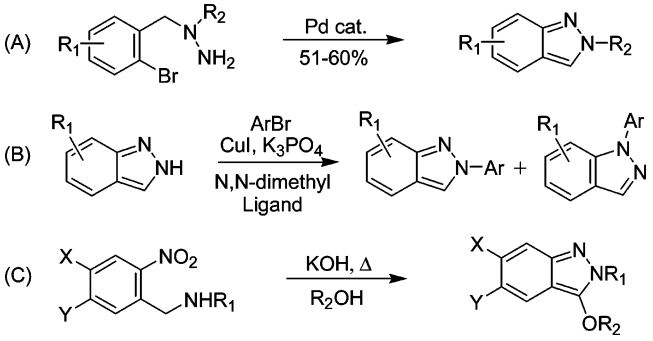


A one-step heterocyclization of *o*-nitrobenzylamines to 3-alkoxy-2*H*-indazoles is reported. The electronic nature of the nitrophenyl group, the steric and electronic nature of the R^1-functionalized benzylic amine, and the nature of the alcoholic solvent affect the efficiency of this heterocyclization reaction (∼40−90%).

Introduction

Seven of the top 10 selling drugs are nitrogen-containing heterocycles,[1] and these structural motifs are also found in many natural products.[2] Motivated by these synthetic challenges, chemists have developed an array of methods for the construction of these important heterocycles.[3] The indazole ring, the subject of our work, is an intriguing heterocycle with biological, agricultural, and industrial applications.[4] Within the indazole arena, the chemistry of 2*H*-indazoles has not been as well-explored as the chemistry of 1*H*-indazoles.[5] As outlined in Scheme 1, routes to 2*H*-indazoles include palladium-catalyzed cyclization[6] of substituted hydrazines and aryl bromides (Scheme 1A), metal reductions of *o*-nitrobenzylamines mediated by Sn, Zn, or Fe (generally giving low yields of the 2*H*-indazole as side products),[7] and *N*-alkylation or *N*-arylation of preformed 1*H*-indazoles at N2 (typically with limited regioselectivity) using CuI (Scheme 1B).[8] In addition, in a recent reinvestigation of a purported route to 2,1-benzisoxazoles,[9] we discovered a new route to 3-alkoxy-2*H*-indazoles from *o*-nitrobenzylamines (Scheme 1C).

SCHEME 1. Routes to 2*H*-Indazoles



This new method, while not fully explored in our original report, offered the advantage of requiring no expensive or toxic metals to mediate heterocycle formation and proceeded under mild base treatment at a relatively low temperature in an alcoholic solvent.[10] In addition to our route (Scheme 1C), we

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(1) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.
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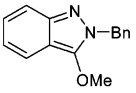
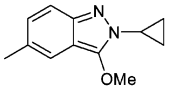
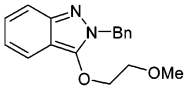
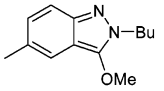
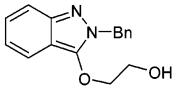
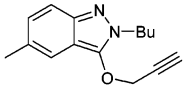
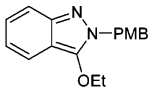
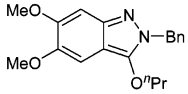
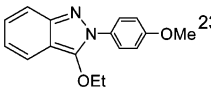
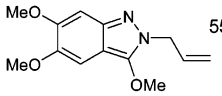
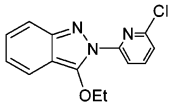
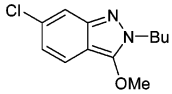
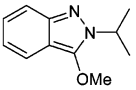
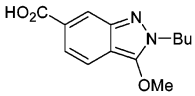
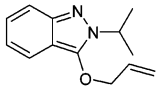
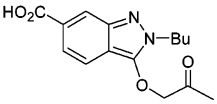
TABLE 1. ***N,N*-Bond-Forming Heterocyclization**[a,b]

X / Y / R^1 in $ArNO_2$[c] → (#)	2*H*-Indazole	yield	X / Y / R^1 in $ArNO_2$[c] → (#)	2*H*-Indazole	yield
X = H, Y = H, R^1 = Bn **3** → (**14**)		61%	X = H, Y = H, R^1 = *cyclo*-Pr **8** → (**22**)		41%
X = H, Y = H, R^1 = Bn **3** → (**15**)		75%	X = H, Y = Me, R^1 = *n*-Butyl **9** → (**23**)		60%
X = H, Y = H, R^1 = Bn **3** → (**16**)		71%	X = H, Y = Me, R^1 = *n*-Butyl **9** → (**24**)		0%
X = H, Y = H, R^1 = PMB **4** → (**17**)		60%	X = OMe, Y = OMe, R^1 = Bn **10** → (**25**)		11%
X = H, Y = H, R^1 = *p*-MeOPh **5** → (**18**)		23%	X = OMe, Y = OMe, R^1 = Allyl **11** → (**26**)		55%
X = H, Y = H, R^1 = 6-Cl-2-Pyr **6** → (**19**)		0%	X = Cl, Y = H, R^1 = *n*-Butyl **12** → (**27**)		67%
X = H, Y = H, R^1 = *i*-Pr **7** → (**20**)		71%	X = CO_2H, Y = H, R^1 = *n*-Butyl **13** → (**28**)		96%
X = H, Y = H, R^1 = *i*-Pr **7** → (**21**)		0%	X = CO_2H, Y = H, R^1 = *n*-Butyl **13** → (**29**)		0%

[a] Products were characterized by ^1H and ^{13}C NMR and IR. [b] Isolated yields after purification by chromatography on silica gel. [c] See **3**−**13** in Scheme 2.

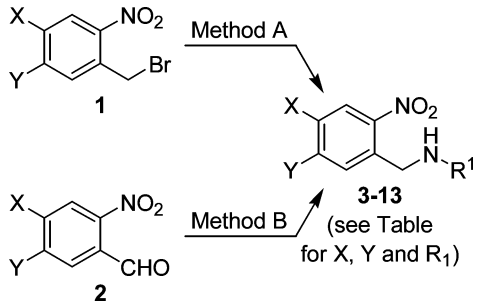
are aware of only one other strategy for the synthesis of 3-alkoxy-substituted 2*H*-indazoles. This approach involves *N*,*N*-bond-forming heterocyclization from *o*-azidobenzamides by treatment with thionyl chloride to give 3-chloro-2*H*-indazole. Upon subsequent alkoxide treatment, the 3-chloro-2*H*-indazole delivers the 3-alkoxyalkyl-2*H*-indazole.[11] However, the use of halogenating agents restricts the types of functional groups that can be incorporated. There are three other methods in addition to ours for the *N*,*N*-bond-forming heterocyclization to 2*H*-indazoles.[11,12]

Since the scope of our *o*-nitrobenzylamine → 2*H*-indazole cyclization reaction as well as the electronic requirements of the reactants were not explored in our first report, we set out to study this heterocyclization reaction in greater detail. Herein, we report the details of a study which culminates in the preparation of a small collection of unique 3-alkoxy-2*H*-indazoles (see Table 1).

Results and Discussion

As outlined in Scheme 2, the starting *o*-nitrobenzylamines were readily prepared from either benzyl halide **1** (Method A) or benzyladehyde **2** (Method B). Method A was used to synthesize amines **3**, **4**, and **7**−**13**. By employing an excess of the amine,[13] the targeted benzylamines were obtained in nearly quantitative yields. However, arylamine derivatives were not reactive enough for Method A and, consequently, substrates **5** and **6** were prepared by way of the corresponding imine of **2** via Method B. This protocol worked well for both electron-rich (e.g., 4-methoxyanaline) and electron-poor (e.g., 6-chloro-2-aminopyridine) systems (98 and 73% yield, respectively).[14]

SCHEME 2. Synthesis of *o*-Nitrobenzylamines[a]



[a] Method A: R^1NH_2 (excess; used to prepare all amines except **5** and **6**). Method B: R^1NH_2, neat, 150 °C, then $NaBH_4$/MeOH.

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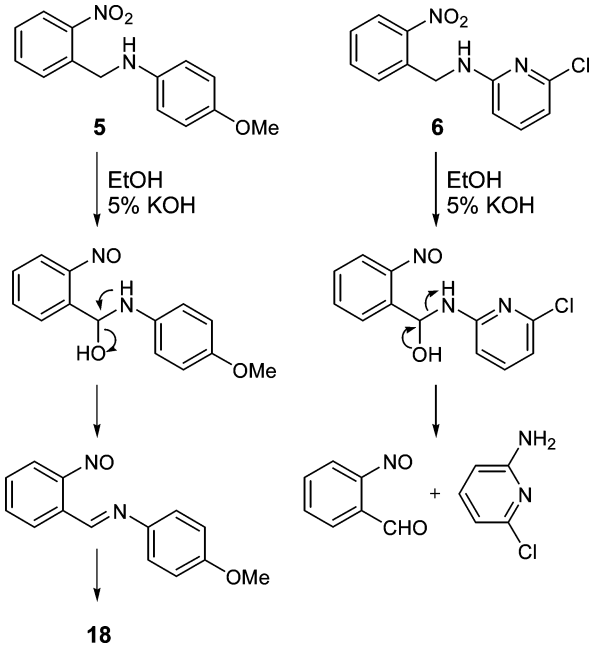
(14) Johnston, D.; Smith, D. M.; Shepherd, T.; Thompson, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, *3*, 495.

SCHEME 3. Aryl Amine Derivatives



With a variety of *o*-nitrobenzylamines in hand (**3**−**13**), we turned to study the *N,N*-bond-forming heterocyclization reaction. Our results are outlined in the table with variables including: (1) the electronic nature of the nitrophenyl group, (2) the steric and electronic nature of the benzylic amine R^1 group, and (3) the nature of the alcoholic solvent.

As illustrated with 2*H*-indazoles **14**, **22**, **25**, **27**, and **28**, the reaction is quite tolerant of electronic variation in the nitrophenyl group. Benzoic acid derivative **13** was particularly effective in this transformation, either as a consequence of the electron-withdrawing nature of the carboxyl group or as a result of the improved solubility of the intermediates in the formation of **28**.

This heterocyclization reaction tolerates a variety of R^1 groups in **3**−**13** with the exception that arylamine derivatives give variable results. Specifically, as depicted in Scheme 3, the *N*-4-methoxyphenyl-2-nitrobenzylamine analogue **5** cyclized to indazole **18** in poor yield (23%), while *N*-(6-chloropyridin-2-yl)2-nitrobenzylamine **6** failed to undergo heterocyclization to indazole **19**. We believe the electron-withdrawing chloropyridyl moiety favors hemiaminal retrocondensation to the nitroso aldehyde rather than dehydration to the imine. Presumably, this dehydration does occur in the reaction of **5** (albeit to a lesser extent than with nonarylamines **3**−**4** and **7**−**13**), and the resulting nitroso imine undergoes heterocyclization to 2*H*-indazole **18**. Indeed, 6-chloropyridin-2-ylamine was isolated in 60% yield, together with 2-nitrosobenzaldehyde, when **6** was treated with ethanolic KOH.

When X and Y in the *o*-nitrobenzylamine are electron-donating groups (e.g., methoxy in **10** and **11**), the yield of indazole decreased. We believe this drop in reaction productivity is a consequence of decreased acidity at the benzylic position in the starting *o*-nitrobenzylamine. In contrast, when X is an electron-withdrawing group, such as a carboxylate, the indazole yield increased (**13** → **28**; 96%).

The alcohols found to be acceptable in this reaction (Scheme 1C) were methanol, ethanol, ethylene glycol, and ethylene glycol monomethyl ether. Reactions run in propargyl alcohol, ethanolamine, furfuryl alcohol, and allyl alcohol did not produce indazole products (*o*-nitrobenzylamine decomposition was observed). Results with *n*-propanol were marginal (cf., **10** → **25**; 11%). Collectively, these results suggest that subtle changes in solvent properties (chemical reactivity, dielectric constant, dipole moment, eluotropic value, miscibility, polarity index, viscosity, etc.) rather strikingly mediated the effectiveness of this heterocyclization reaction.

In summary, the one-step heterocyclization of *o*-nitrobenzylamines to 3-alkoxy-2*H*-indazoles is reported in generally fair yields (∼40−90%).

Experimental Section

General Procedures for the Synthesis of 2*H*-Indazoles. A solution of nitrobenzyl bromide (1.2 mmol) in tetrahydrofuran (2 mL) was added dropwise to a solution of the amine (12.0 mmol) in tetrahydrofuran (2 mL). The reaction was allowed to stir for 4 h and then concentrated. The resulting crude reaction mixture was diluted with EtOAc, washed consecutively with aq sodium bicarbonate and brine, dried over sodium sulfate, and concentrated. ^{1}H NMR spectra indicated that most amines were pure enough to be used directly in the cyclization reaction (the remainder were purified by flash chromatography). Benzyl(2-nitrobenzyl)amine, 4-methoxybenzyl(2-nitrobenzyl)amine, and 4-methoxyphenyl(2-nitrobenzyl)amine were synthesized by the respective literature methods.[10,15,16]

Next, these 2-nitrobenzylamines were added to solutions of 5% KOH in the appropriate alcoholic solvent (5 mL). Each reaction was allowed to stir for 6 h at 60 °C and then concentrated. The crude reaction mixture was taken up with EtOAc (100 mL), washed consecutively with water (100 mL), sodium bicarbonate (100 mL), and brine (100 mL) and then dried over sodium sulfate, concentrated, and purified by flash chromatography to afford the 2*H*-indazole.

2-Benzyl-3-methoxy-2*H*-indazole (14). Benzyl(2-nitrobenzyl)-amine (**3**) was prepared according to literature methods.[9] Crude amine **3** (0.300 g, 1.239 mmol) gave **14** (R_f = 0.37 (2:5, hexane/ethyl acetate) as a light yellow oil (61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.7 Hz, 1.2, 1H), 7.57 (dd, J = 8.1 Hz, 0.9 Hz, 1H), 7.32−7.18 (m, 6H), 6.92 (dt, J = 6.6 Hz, 0.9 Hz, 1H), 5.44 (s, 2H), 4.21 (s, 3H); ^{13}C NMR δ 147.3, 146.6, 136.3, 128.6, 127.7, 127.5, 126.1, 119.6, 119.4, 117.7, 106.8, 60.4, 52.0; IR (neat) 1624, 1526, 1510, 1406, 1385, 1113, 737, 701 cm^{-1}; HPLC purity = 97%; HREIMS calcd for $C_{15}H_{14}N_2O$ (M^+), 238.1106; found, 238.1104.

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Supporting Information Available: Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **14**−**18**, **20**, **22**−**23**, and **25**−**28** are available free of charge via the Internet at http://pubs.acs.org.

JO0524831

(15) Kienzle, F.; Kaiser, A.; Chodnekar, M. S. *Eur. J. Med. Chem.* **1982**, *17*, 547.
(16) Frontana-Uribe, B. A.; Moinet, C. *Tetrahedron* **1998**, *54*, 3197.