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Synthesis of substituted indazoles from N-tosylhydrazones using ionic liquid

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ABSTRACT

The use of 1H-indazole as anti-cancer, anti-inflammatory, and anti-microbial agents has been documented in recent patents and publications. Although many new methodologies have been reported to synthesize 1H-indazoles, a mild, general method still remains an ongoing challenge. Under different reaction conditions N-Tosylhydrazones can be used to afford a variety of indazoles. We are interested in synthesizing a range of indazoles by using environment friendly ionic liquid as solvent, co-solvent and catalyst. The synthesis of 1H-indazoles under these conditions is extremely mild compared with previous synthetic approaches and affords the desired compounds in good to excellent yields.

Key words: Ionic liquid, N-Tosylhydrazones, DABCO, Indazole

INTRODUCTION

Indazole derivatives are a versatile class of compounds that have found use in biology, catalysis, and medicinal chemistry.[1] Although rare in nature,[2] indazoles exhibit a variety of biological activities such as HIV protease inhibition,[3] antiarrhythmic and analgesic activities,[4] antitumor activity,[5] and antihypertensive properties.[6] Derivatives of indazoles exhibit a broad spectrum of bioactivities including anti-inflammatory,[7] anti-tumor,[8] anti-HIV,[9] anti-cancer,[10] anti-platelet,[11] and serotonin 5-HT3 receptor antagonist activities.[12] Their desirable properties render them attractive targets for drug discovery,[13] and as such, numerous syntheses of the indazole core have been described.[14]With the growing interest in indazole derivatives, preparation of the indazole skeleton has been pursued for a long time by synthetic organic chemists, and recent developments have allowed for indazoles to be accessed from easily obtained starting materials under milder conditions in fewer steps.[15−18] Classical routes to 1*H*-indazoles typically require harsh or inconvenient conditions such as diazotizations and nitrosation reactions.[19] The large number of recently published methods that aim to improve the traditional routes to 1*H*indazole signifies the importance of these compounds.

Ionic liquids (ILs) has attracted the attention on scientific community in the last decade, due their particular properties [20] and their applications in Organic Synthesis [21], catalysis [22], biocatalysis [23], liquid-liquid separations [24], extraction [25] and dissolution (cellulose in microwave [26] and petroleum asphaltenes in microwave [27]) processes, nanomaterials synthesis [28], polymerization reactions [29] and electrochemistry [30]. ILs are an excellent alternative to substitute volatile organic solvents in more environmental friendly technologies

("green technologies"), since their very low vapor pressures, their thermal and chemical stability, their ability to act as catalyst, and their non-flammability and non-corrosives properties

EXPERIMENTAL SECTION

General Considerations.
All reagents and catalyst purchased from commercial sources were used as received. The solvents ionic liquid was prepared by reported procedure and used. The silica gel column chromatography was used for sepration. DABCO was used as received. All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra are referenced to the residual solvent signals (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C in $CDCl_3$; 2.05 ppm for ^{1}H and 29.8 ppm for ^{13}C in acetone-d6). All aryne reactions were carried out in oven-dried glassware and were magnetically stirred.

General Procedure To Prepare N-Tosylhydrazones (2).
To a solution of p-toluenesulfonyl hydrazide (1.02 g, 5.5 mmol, 1.1 equiv) in 5 mL of MeOH was added an aldehyde (5 mmol) slowly (liquid aldehyde was added dropwise, and solid aldehyde was added in small portions). The mixture was stirred at room temperature for 2 h. MeOH was evaporated in vacuo, and the residue was recrystallized from MeOH to afford the N-tosylhydrazones, which were used directly to the aryne reactions.

Hydrazone 2a. The general procedure was applied to 680 mg of 4- methoxybenzaldehyde to afford 1.37 g of 2a (90%) as white solid, mp 105−106 °C (lit.23d 110−111 °C); 1H NMR (400 MHz, CDCl3) δ 8.01 (s, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.73 (s, 1 H), 7.55−7.47 (m, 2H), 7.30 (d, J = 8.1 Hz, 2 H), 6.87−6.85 (m, 2 H), 3.81 (s, 3 H), 2.40 (s, 3 H).

Hydrazone 2b. The general procedure was applied to 530 mg of benzaldehyde to afford 0.70 g of 2b (51%) as white solid, mp 120−121°C (lit.23d 127−128 °C); 1H NMR (400 MHz, CDCl3) δ 7.94 (s, 1H), 7.88 (d, J = 8.3 Hz, 2 H), 7.75 (s, 1 H), 7.59−7.57 (m, 2 H),7.38−7.34 (m, 3 H), 7.31 (d, J = 8.1 Hz, 2 H), 2.41 (s, 3 H). Hydrazone 2c. The general procedure was applied to 925 mg of 4-bromobenzaldehyde to afford 1.60 g of 2c (91%) as white solid, mp 171−171.5 °C; 1H NMR (400 MHz, CDCl3) δ 7.89 (s, 1 H), 7.86 (d, J = 8.3 Hz, 2 H),7.69 (s, 1 H), 7.51−7.42 (m, 4 H),7.32 (d, J = 8.1 Hz, 2 H), 2.41 (s, 3 H).

Hydrazone 2d. The general procedure was applied to 755 mg of 3-nitrobenzaldehyde to afford 0.70 g of 2d (44%) as white solid, mp 153−154 °C (lit.23d 154−156 °C); 1H NMR (400 MHz, CDCl3) δ8.37 (t, J = 1.8 Hz, 1 H), 8.28 (s, 1 H), 8.21 (ddd, J = 8.2, 2.2, 1.0 Hz,1 H), 7.93 (d, J = 7.8 Hz, 1 H), 7.90 (d, J = 8.3 Hz, 2 H), 7.82 (s, 1 H),7.55 (t, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.1 Hz, 2 H), 2.42 (s, 3 H).

Hydrazone 2e. The general procedure was applied to 700 mg of 2-chlorobenzaldehyde to afford 1.30 g of 2e (84%) as white solid, mp 137−138 °C (lit.35 154−156 °C); 1H NMR (400 MHz, CDCl3) δ 8.16 (s, 1 H), 7.95−7.90 (m, 2 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.34−7.31 (m,3 H), 7.30−7.24 (m, 2 H), 2.42 (s, 3 H).

Hydrazone 2f. The general procedure was applied to 875 mg of 2,6-dichlorobenzaldehyde to afford 1.58 g of 2f (92%) as white solid, mp 182−182.5 °C; 1H NMR (400 MHz, acetone-d6) δ 10.7 (s, 1 H), 8.16(s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.46−7.36 (m, 5 H), 2.41 (s, 3 H).

Hydrazone 2g. The general procedure was applied to 830 mg of 3,4-dimethoxybenzaldehyde to afford 1.25 g of 2g (75%) as white solid, mp 129−130 °C; 1H NMR (400 MHz, CDCl3) δ 7.87−7.85 (m, 2 H), 7.70 (s, 1 H), 7.31 (d, J = 7.9 Hz, 2 H), 7.26 (s, 1 H), 7.24 (d,J = 1.8 Hz, 1 H), 7.01 (dd, J = 8.2, 1.9 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.41 (s, 3 H)

Hydrazone 2h. The general procedure was applied to 535 mg of nicotinaldehyde to afford 0.82 g of 2h (60%) as brown solid, mp 154−155 °C (lit.36 155−156 °C); 1H NMR (400 MHz, acetone-d6) δ 10.48 (s, 1 H), 8.74 (d, J = 1.9 Hz, 1 H), 8.56 (dd, J = 4.8, 1.7 Hz, 1 H), 8.03(s, 1 H), 8.01 (dt, J = 8.1, 1.9 Hz, 1 H), 7.87−7.81 (m, 2 H),7.42−7.38 (m, 3 H), 2.39 (s, 3 H).

Hydrazone 2i. The general procedure was applied to 560 mg of thiophene-2-carbaldehyde to afford 1.10 g of 2i (79%) as brown solid, mp 134−135 °C (lit.37 140−141 °C); 1H NMR (400 MHz, CDCl3) δ 7.98 (s, 1 H), 7.85 (d, J

= 8.3 Hz, 2 H), 7.77 (s, 1 H), 7.36 (d, J = 5.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.20 (dd, J = 3.6, 0.7 Hz, 1 H),7.01 (dd, J = 5.0, 3.7 Hz, 1 H), 2.41 (s, 3 H).

Hydrazone 2j. The general procedure was applied to 430 mg of pivalaldehyde to afford 0.35 g of 2j (28%) as white solid, mp 107−108°C (lit.38 110−112 °C); 1H NMR (400 MHz, CDCl3) δ 7.80 (d, J =8.3 Hz, 2 H), 7.34 (s, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.06 (s, 1 H),2.43 (s, 3 H), 1.00 (s, 9 H).

General Procedure To Prepare 3-Substituted Indazoles (3) from N-Tosylhydrazones (2)

To an oven-dried 25 mL round bottom flask equipped with a stirrer bar was added 0.4 mmol of N-tosylhydrazone 2, followed by the aryne precursor (0.48 mmol, 1.2 equiv). IL (15 mL) was added, followed by DABCO (0.1mmol, 0.25 equiv) and CsF (ca. 180−185 mg, 1.2 mmol, 3 equiv). The flask was topped with a refluxing condenser, and the reaction mixture was stirred at 65 °C for 14h, cooled to room temperature, poured into brine, and extracted with EtOAc. The combined extracts were dried over MgSO4, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the indazoles 3.

5,6-Dimethoxy-3-(4-methoxyphenyl)-1H-indazole (3b). The general procedure was applied to 122 mg of 2a and 172 mg of 1b to afford 64 mg of 3b (54%) as white solid, mp 209−210 °C; Rf = 0.45 (EtOAc); 1H NMR (400 MHz, CDCl3) δ 11.66 (s, 1 H), 7.93 (d, J = 8.6 Hz, 2 H), 7.20 (s, 1 H), 7.08 (d, J = 8.7 Hz, 2 H), 6.38 (s, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.70 (s, 3 H); 13C NMR (100 MHz,CDCl3) δ 159.4, 150.8, 146.4, 144.4, 137.4, 128.9, 126.5, 114.5, 113.6,99.8, 91.5, 55.1, 55.8, 55.3.

7-Methoxy-3-(4-methoxyphenyl)-1H-indazole (3c). The general procedure was applied to 122 mg of 2a and 158 mg of 1c to afford 61 mg of 3c (58%) as white solid. The major isomer can be separated: mp 149−151 °C; Rf = 0.35 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.22 (s, 1 H), 7.92 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.14 (t, J = 7.8 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 7.5 Hz, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 159.6, 145.7, 145.3, 133.8, 128.7, 126.3, 122.4, 121.9, 114.3,113.2, 105.0, 55.5, 55.3.

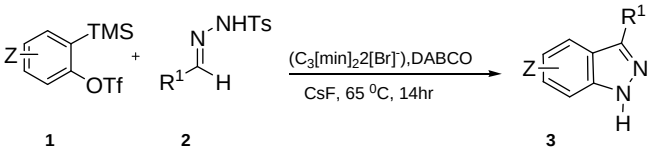
3-Phenyl-1H-indazole (3d). The general procedure was applied to 110 mg of 2b and 143 mg of 1a to afford 64 mg of 3d (80%) as white solid, mp 116−117 °C (lit.41 115−116 °C); Rf = 0.43 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 12.53 (s, 1 H), 8.08 (d, J =7.5 Hz, 2 H), 8.05 (d, J = 8.4 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 2 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.33 (t, J= 7.6 Hz, 1 H), 7.22 (t, J = 7.5 Hz, 1 H),7.09 (d, J = 8.3 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 145.5,141.6, 133.5, 129.0, 128.2, 127.8, 126.7, 121.2, 120.9, 120.8, 110.4;

3-(4-Bromophenyl)-1H-indazole (3e). The general procedure was applied to 142 mg of 2c and 143 mg of 1a to afford 92 mg of 3e (83%) as slightly yellow solid, mp 135−137 °C; Rf = 0.42 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.40 (s, 1 H), 8.00 (d, J =8.2 Hz, 1 H), 7.91−7.82 (m, 2 H), 7.68−7.61 (m, 2 H), 7.50 (t, J = 8.4Hz, 1 H), 7.44 (dd, J = 8.0, 7.1 Hz, 1 H), 7.29−7.22 (m, 1 H); 13C NMR (100 MHz, CDCl3) δ 144.6, 141.6, 132.4, 132.1, 129.1, 127.0,122.3, 121.7, 120.8, 120.7, 110.2.

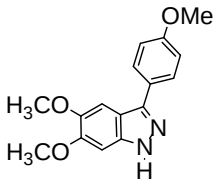
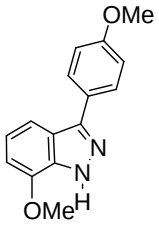
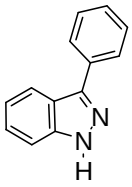
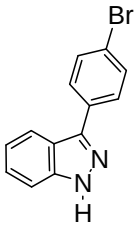
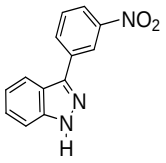
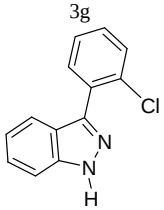
3-(3-Nitrophenyl)-1H-indazole (3f). The general procedure was applied to 128 mg of 2d and 143 mg of 1a to afford 53 mg of 3f (53%) as glassy yellow solid, mp 188−189 °C; Rf = 0.33 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, acetone-d6) δ 12.78 (s, 1 H), 8.88 (t,J = 1.9 Hz, 1 H), 8.54−8.51 (m, 1 H), 8.27 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1 H), 7.85 (t, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.4Hz, 1 H), 7.48 (dt, J = 7.5, 0.8 Hz, 1 H), 7.32 (dt, J = 7.6, 0.8 Hz, 1H); 13C NMR (100 MHz, acetone-d6) δ 149.7, 143.1, 142.7, 136.8,133.6, 131.1, 127.4, 122.9, 122.7, 122.0, 121.3, 121.1, 111.6.

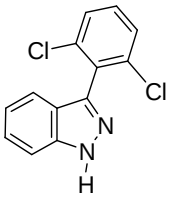
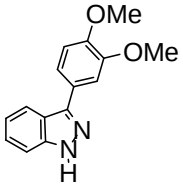
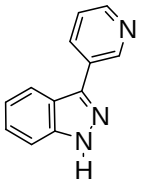
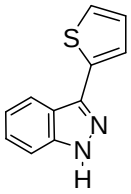
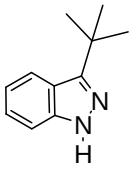
3-(2-Chlorophenyl)-1H-indazole (3g). The general procedure was applied to 124 mg of 2e and 143 mg of 1a to afford 70 mg of 3g (75%) as white solid, mp 140−141 °C; Rf = 0.38 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.71 (s, 1 H), 7.72 (d, J = 8.2 Hz, 1 H),7.63−7.62 (m, 1 H), 7.60−7.56 (m, 1 H), 7.47−7.37 (m, 4 H), 7.21 (ddd, J = 7.9, 6.4, 1.3 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 143.8,140.8, 133.8, 132.4, 132.2, 130.2, 129.7, 126.9, 126.7, 121.9, 121.4,121.0, 110.2.

Table. Conversion N-Tosylhydrazones to Indazole



1 **2** **3**

Entry	Z	R^1	Product	Yield
1	4,5-$(MeO)_2$ 1b	2a 4-$(OMe)C_6H_4$	3b 	54
2	3-MeO 1c	2a	3c 	58
3	H 1a	2b Ph	3d 	80
4	H 1a	2c R^1=4-BrC_6H_4	3e 	83
5	H 1a	2d R^1=3-$(O_2N)C_6H_4$	3f 	53
6	H 1a	2e R^1=2-ClC_6H_4	3g 	75

			3h	
7	H 1a	2f R^1=2,6-$Cl_2C_6H_3$		73
			3i	
8	H 1a	2g 3,4-$(OMe)_2C_6H_3$		82
			3j	
9	H 1a	2h 3-pyridyl		66
			3k	
10	H 1a	2i 2-thiophenyl		34
			3l	
11	H 1a	2j t-Bu		29

3-(2,6-Dichlorophenyl)-1H-indazole (3h). The general procedure was applied to 138 mg of 2f and 143 mg of 1a to afford 79 mg of 3h (73%) as white solid, mp 160−161 °C; Rf = 0.47 (2:1 hexanes/ EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.71 (s, 1 H), 7.53−7.47 (m, 4 H), 7.45−7.40 (m, 1 H), 7.37 (dd, J = 8.7, 7.4 Hz, 1 H), 7.20 (ddd, J = 7.9, 6.8, 0.9 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 141.4,140.6, 136.7, 131.2, 130.5, 128.2, 126.9, 122.1, 121.2, 120.6, 110.2.

3-(3,4-Dimethoxyphenyl)-1H-indazole (3i). The general procedure was applied to 134 mg of 2g and 143 mg of 1a to afford 86 mg of 3i (82%) as white solid, mp 147−149 °C; Rf = 0.13 (2:1 hexanes/ EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.44 (s, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.57−7.53 (m, 2 H), 7.45−7.40 (m, 2 H), 7.26−7.22 (m,1 H), 7.03 (d, J = 8.1 Hz, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 149.4, 149.2, 145.5, 141.7, 126.8, 126.4, 121.2,121.1, 120.8, 120.2, 111.4, 110.7, 110.2, 56.0, 55.9;

3-(Pyridin-3-yl)-1H-indazole (3j). The general procedure was applied to 110 mg of 2h and 143 mg of 1a to afford 53 mg of 3j (66%) as brown solid, mp 184−185 °C; Rf = 0.40 (10:1 CH2Cl2/ MeOH); 1H NMR (400 MHz, CDCl3) δ 10.55 (s, 1 H), 9.27 (d, J = 1.0 Hz, 1 H), 8.70−8.68 (m, 1 H), 8.29 (dt, J = 7.9, 1.7 Hz, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.48−7.45 (m, 2 H),7.31−7.26 (m, 1 H); 13C NMR (100 MHz, acetone-d6) δ 149.6, 148.8,142.9, 142.2, 134.7, 130.9, 127.3, 124.6, 122.3, 121.5, 121.3, 111.4.

3-(Thiophen-2-yl)-1H-indazole (3k). The general procedure was applied to 112 mg of 2i and 143 mg of 1a to afford 29 mg of 3k (34%) as brown solid, mp 151−153 °C (lit.42 137 °C); Rf = 0.47 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 10.06 (s, 1 H), 8.07 (dt, J = 8.2, 0.9 Hz, 1 H), 7.68 (dd, J = 3.6, 1.1 Hz, 1 H), 7.51 (dt, J = 8.4, 0.9 Hz, 1 H), 7.46−7.42 (m, 1 H), 7.38 (dd, J = 5.1, 1.1 Hz, 1 H), 7.29−7.25 (m, 1 H), 7.19 (dd, J = 5.1, 3.6 Hz, 1 H); 13C NMR (100 MHz, CDCl3) δ 141.5, 140.7, 135.8, 127.7, 127.1, 125.2, 124.9, 121.6,120.8, 120.4, 110.3.

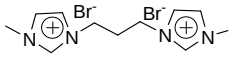
3-tert-Butyl-1H-indazole (3l). The general procedure was applied to 102 mg of 2j and 143 mg of 1a to afford 23 mg of 3l (29%) as white solid, mp 152−154 °C; Rf = 0.46 (2:1 hexanes/EtOAc); 1H NMR (400 MHz, CDCl3) δ 9.72 (s, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.36 (dt, J = 7.4, 0.9 Hz, 1 H), 7.13 (J = 7.6, 0.9 Hz, 1 H), 1.54 (s, 9 H); 13C NMR (100 MHz, CDCl3) δ 154.5, 141.8, 126.2,122.1, 120.5, 119.8, 110.0, 33.7, 30.0.

RESULTS AND DISCUSSION

Reaction of N-Tosylhydrazones To Prepare 3-Substituted Indazoles.

Through our survey of reaction conditions Ionic liquid here also as phase transfer catalyst. The scope of this reaction was then studied (Table).Different arynes reacted smoothly (entries 1 and 2). N- Tosylhydrazones derived from aromatic (entries 3−8) and heteroaromatic aldehydes (entries 9 and 10) were all successfully transformed to the desired indazoles, despite the lower yields for the latter. Hydrazones derived from primary or secondary aliphatic aldehydes afforded only complex mixtures. Nonetheless, 2j derived from a tertiary aldehyde allowed for a marginal success (entry 11).

Encouraged by this result, we have focused attention on the use of $C_3[min]_2 2[Br^-]$ (dicationic ionic liquid) as solvent as well as catalyst. It was found that the ionic liquid worked well and the conversion found to take place rapidly giving excellent yield.



3-methyl-1-[3-(metnyl-1H-imidazolium-1-yl)propyl]-1H-imidazolium dibromide
($C_3[mim]_2 2[Br^-]$)

CONCLUSION

Here we have used ionic liquid as a green solvent for the synthesis of indazole . Although we have developed aryne reactions to prepare 3-substituted 1H-indazoles using N-Tosylhydrazones .Specifically, N-Tosylhydrazones can afford 3-substituted 1H-indazoles. Compared with the early discoveries in aryne reactions to indazoles, our methods allow for indazoles bearing more diverse substitutions at 3-positions. Introduction of aryl and vinyl groups have been successful, and the introduction of alkyl groups has been partially resolved. With the rapid development of aryne chemistry, construction of more heterocyclic scaffolds through aryne processes can be expected in the future.

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