Synthesis of Heterocycles

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An Efficient, Facile, and General Synthesis of 1*H*-Indazoles by 1,3-Dipolar Cycloaddition of Arynes with Diazomethane Derivatives

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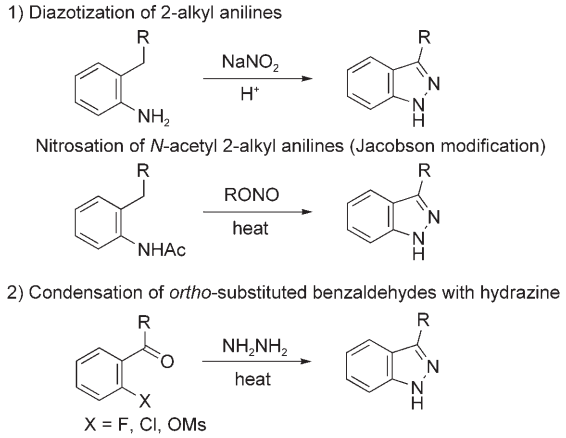
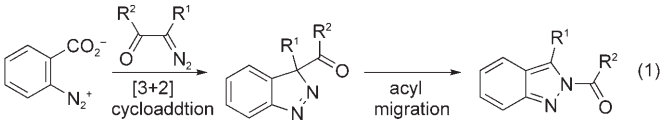
1*H*-Indazoles are pharmaceutically important compounds that display a wide range of pharmacological activities,[1] including antifertility, antiarthritic, anti-inflammatory, and contraceptive activity, as well as antagonistic activity towards the 5-HT_3 receptor. Because of this usefulness, considerable effort has been devoted to the development of efficient methods for the construction of indazole frameworks (Scheme 1).[2] The common synthetic routes are diazotization



Scheme 1. General methods for the synthesis of 1*H*-indazoles. Ms = methanesulfonyl.

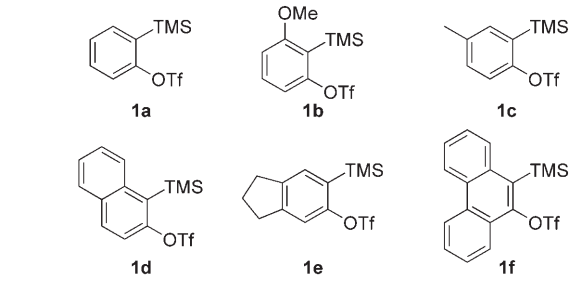
of the corresponding 2-alkyl anilines[2a] and nitrosation of the *N*-acetyl derivatives of 2-alkyl anilines (Jacobson modification);[2c–e] another attractive route is the condensation of *ortho*-substituted benzaldehydes with hydrazine.[2f,g] However, the reaction conditions of these methods are fairly harsh: Usually strong acids or high temperatures are required. An interesting approach is the 1,3-dipolar cycloaddition of benzyne (generated from diazotized anthranilic acid) with diazoalkanes.[3] For example, α-diazoketones (R^1 = alkyl, aryl) react with benzyne to give 3-acyl 3*H*-indazoles, which further isomerize to 2-acyl 2*H*-indazoles [Eq. (1)].[3c–e] However, this cycloaddition method has not been studied widely as

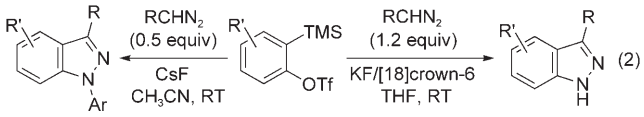


(1)

a result of the difficulty in generating arynes under the reported reaction conditions. The reaction is limited mostly to α-keto diazo compounds. Therefore, the development of an efficient and general synthetic approach to 1*H*-indazoles is desirable.

It is well known that benzyne is generated from 2-(trimethylsilyl)phenyl triflate (**1a**) under very mild conditions.[4] Accordingly, cycloadditions[5] and nucleophilic additions[6] with **1a** (via a benzyne intermediate) have been investigated extensively. In continuation of our interest in the development of efficient methods for the synthesis of nitrogen-containing heterocycles, such as tetrazoles and 1,2,3-triazoles, through 1,3-dipolar cycloaddition,[7] and in benzyne chemistry,[5c–f] we report herein a facile, efficient, and general procedure for synthesizing N-unsubstituted and 1-arylated 1*H*-indazoles. The [3+2] cycloaddition between arynes generated from silylaryl triflates and various diazomethane derivatives proceeded smoothly under very mild conditions to give, depending merely on the reaction conditions, 1*H*-indazoles or 1-aryl indazoles in good to high yields [Eq. (2)].





(2)

In the cycloaddition between the commercially available silylaryl triflate **1a** and ethyl diazoacetate (**2a**), we focused initially on optimizing the conditions for the formation of the N-unsubstituted 1*H*-indazole **3a**. When the reaction of **1a** with **2a** (1.2 equiv) was carried out in the presence of KF

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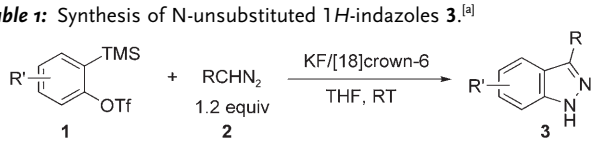
(3.0 equiv) and [18]crown-6 (3.5 equiv) in THF at room temperature for 24 h, 3-ethoxycarbonyl-1*H*-indazole (**3a**)[8a] was obtained in 80% yield (Table 1, entry 1). Although CsF or nBu$_4$NF could be used instead of KF to generate benzyne from **1a**, the yield of **3a** decreased to 63 and 54%, respectively (Table 1, entries 2 and 3).

Table 1: Synthesis of N-unsubstituted 1*H*-indazoles **3**.[a]

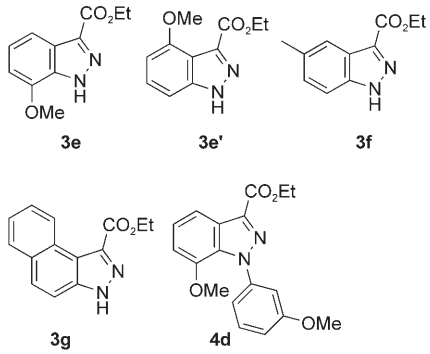


1 2 3

Entry	1	2	R	3	Yield [%][b]
1	**1a**	**2a**	CO_2Et	**3a**	80
2[c]	**1a**	**2a**	CO_2Et	**3a**	63
3[d]	**1a**	**2a**	CO_2Et	**3a**	54
4	**1a**	**2b**	CO_2tBu	**3b**	89
5[e]	**1a**	**2c**	TMS	**3c**	50
6	**1a**	**2d**	Ph	**3d**	90
7	**1b**	**2a**	CO_2Et	**3e**	83
8	**1c**	**2a**	CO_2Et	**3f/3f′**	82 (1:1)[f]
9	**1d**	**2a**	CO_2Et	**3g/3g′**	70 (1:1)
10	**1e**	**2a**	CO_2Et	**3h**	90
11	**1f**	**2a**	CO_2Et	**3i**	70

[a] The reaction of **1** (0.5 mmol) with **2** (0.6 mmol) was carried out in the presence of KF (3 equiv) and [18]crown-6 (3.5 equiv) in THF (0.25 M) at RT for 24 h unless otherwise noted. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl. [b] Yield of the isolated product. [c] The reaction was carried out in the presence of CsF (2.0 equiv) in CH_3CN. [d] The reaction was carried out in the presence of nBu$_4$NF (2.0 equiv) in CH_3CN. [e] The reaction was carried out in the presence of CsF (3.0 equiv) in CH_3CN/MeOH (10:1; 0.25 M); in product **3c**, R is H. [f] The ratio of regioisomers was determined by ^{1}H NMR spectroscopy.

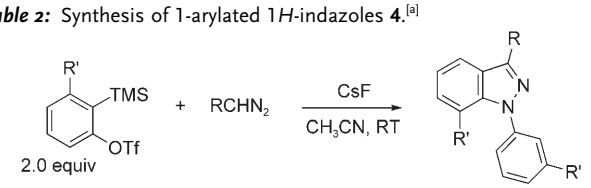
This cycloaddition reaction was extended to the substituted aryne precursors **1b–f** and various diazo compounds **2** to examine the regioselectivity of the reaction and to test the methodology for general utility for the synthesis of functionalized 1*H*-indazoles.[8b] Thus, the treatment of *tert*-butyl diazoacetate (**2b**) with **1a** under the standard reaction conditions gave the corresponding indazole **3b** in high yield (Table 1, entry 4). Trimethylsilyldiazomethane (**2c**) underwent the cycloaddition reaction in the presence of CsF in a mixture of CH_3CN and MeOH to give the 3-unsubstituted indazole **3c** (R = R′ = H) in 50% yield (Table 1, entry 5). The reaction of phenyldiazomethane (**2d**) with **1a** yielded 3-phenyl-1*H*-indazole (**3d**) in 90% yield (Table 1, entry 6). Not only **1a** (R′ = H), but also the substituted benzyne precursors **1b–f** underwent the cycloaddition reaction smoothly with ethyl diazoacetate (**2a**). 3-Methoxy-2-trimethylsilylphenyl triflate (**1b**) reacted cleanly with **2a** to afford the corresponding indazole **3e** as a single product in 83% yield (Table 1, entry 7); none of the regioisomeric indazole **3e′** was obtained. However, in the case of the benzyne precursors **1c** and **1d**, the reaction gave an approximately 1:1 mixture of regioisomers (Table 1, entries 8 and 9). The regioselective formation of **3e** can be explained by the electronic effect of the *meta* OMe group on the nucleophilic attack on the benzyne derivative.[6e] The benzyne precursors **1e** and **1f** underwent the cycloaddition reaction efficiently to give the indanyl and phenanthryl derivatives **3h** and **3i** in 90 and 70% yield, respectively (Table 1, entries 10 and 11).



1-Aryl 1*H*-indazoles are also considered to be very important biologically active molecules.[1] The Pd-catalyzed cyclization of aryl hydrazones of 2-halobenzaldehydes[9] and the Cu-catalyzed N arylation of indazoles[10] were developed as useful methods for synthesizing 1-aryl indazoles. However, these reactions usually require high temperatures. Furthermore, only indazoles that are not substituted at the 3-position can be synthesized by these methods; 3-substituted derivatives are not available. Liu and Larock reported recently the simple N arylation of various amines with *o*-silylaryl triflates under very mild conditions.[6d,e] It occurred to us that a combination of our new method (Table 1) and the protocol of Liu and Larock would enable the synthesis of N-arylated 1*H*-indazoles in a simple and efficient one-pot procedure (Table 2).

The 1-arylated indazole **4a** was obtained readily in 62% yield without formation of the N-unsubstituted indazole when **1a** (2.0 equiv) was treated with **2a** in the presence of excess KF/[18]crown-6 at room temperature (Table 2, entry 1). However, when CsF was used instead of KF/[18]crown-6 to generate benzyne, the yield increased to 79%, and the time required for the reaction to reach completion decreased significantly to 24 h (Table 2, entry 2). Under these optimal

Table 2: Synthesis of 1-arylated 1*H*-indazoles **4**.[a]



1 2 4

Entry	1	2	R	4	R′	Yield [%][b]
1[c]	**1a**	**2a**	CO_2Et	**4a**	H	62
2	**1a**	**2a**	CO_2Et	**4a**	H	79
3	**1a**	**2d**	Ph	**4b**	H	56
4	**1a**	**2e**	4-$CF_3C_6H_4C(O)$	**4c**	H	90
5	**1b**	**2a**	CO_2Et	**4d**	OMe	68

[a] The reaction of **1** (0.5 mmol) and **2** (0.25 mmol) was carried out in the presence of CsF (6.0 equiv) in CH_3CN (0.12 M) at RT for 24 h unless otherwise noted. [b] Yield of the isolated product. [c] The reaction was carried out in the presence of KF (6.0 equiv) and [18]crown-6 (7.0 equiv) in THF for 48 h.

reaction conditions, phenyldiazomethane (**2d**) also reacted well with **1a** to afford 1,3-diphenylindazole (**4b**) in 56% yield (Table 2, entry 3). Similarly, the treatment of **1a** with the benzoyl diazomethane **2e** gave the corresponding 1-arylated indazole **4c** in high yield (Table 2, entry 4). The analogous reaction with the silylaryl triflate **1b** afforded the *meta* isomer **4d** in 68% yield with excellent regioselectivity (Table 2, entry 5). This result clearly indicates that the nucleophile reacts at the position *meta* to a methoxy group rather than at the *ortho* position.

In summary, we have developed a facile, efficient, and general method for the synthesis of N-unsubstituted indazoles and 1-arylated indazoles by the 1,3-dipolar cycloaddition of benzynes with diazomethane derivatives. By changing the reaction conditions, the controlled synthesis of either of the two products is possible. A variety of indazoles can be obtained in good to high yields under very mild conditions. Further studies on the application of the present methodology to the synthesis of biologically active compounds are in progress.

Experimental Section

Synthesis of **3a**: Ethyl diazoacetate (**2a**; 62 μL, 0.6 mmol) was added to a solution of **1a** (125 μL, 0.5 mmol), KF (87 mg, 1.5 mmol), and [18]crown-6 (462 mg, 1.75 mmol) in THF (2 mL) under an argon atmosphere in a pressure vial. The reaction mixture was stirred at room temperature for 24 h, then filtered through a short pad of Florisil and eluted with ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (eluent: hexane/EtOAc) to afford **3a** (76.5 mg, 80%).

Synthesis of **4a**: Ethyl diazoacetate (**2a**; 26 μL, 0.25 mmol) was added to a solution of **1a** (125 μL, 0.5 mmol) and CsF (228 mg, 1.5 mmol) in CH_3CN (2.0 mL) under an argon atmosphere in a pressure vial. The reaction mixture was stirred at room temperature for 24 h, then filtered through a short pad of Florisil and eluted with ethyl acetate. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (eluent: hexane/EtOAc) to afford **4a** (52.6 mg, 79%).

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