Synthesis of 2*H*-Indazoles by the [3 + 2] Cycloaddition of Arynes and Sydnones
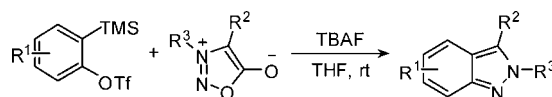
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ABSTRACT

A rapid and efficient synthesis of 2*H*-indazoles has been developed, which involves the [3 + 2] dipolar cycloaddition of arynes and sydnones. The process proceeds under mild reaction conditions in good to excellent yields.

The indazole ring system has long been recognized as a "privileged structure" in heterocyclic chemistry due to its pronounced biological activities. As bioisosteres of catechol derivatives, indazole derivatives are natural PDE-4 inhibitors and exhibit NOS inhibition and anti-inflammatory activity, as well as anticancer activities.[1] The isomeric form of indazole, namely 2*H*-indazole, is a potential pharmacophore with various derivatives exhibiting potent affinity for 5-HT$_{1A}$ receptors[2] and good affinity to the imidazoline I$_2$ receptor with low affinity to the α_2-adrenoceptor.[3]

Compared with 1*H*-indazoles, 2*H*-indazoles have been much less studied in part due to the difficulty in their preparation. Most existing methods give mixtures of 1*H*- and 2*H*-indazoles,[4] and the selective preparation of 2*H*-indazoles remains challenging. Although recently several promising synthetic routes to 2*H*-indazoles have been reported,[5] the demand for new, efficient, and selective methods to prepare 2*H*-indazoles using readily available starting materials under mild reaction conditions still exists. Herein, we wish to disclose our preliminary results using aryne 1,3-dipolar cycloaddition chemistry[6−8] to afford 2*H*-indazoles.

Arynes have demonstrated excellent reactivity as dipolarophiles in various 1,3-dipolar cycloaddition reactions, affording important heterocycles in good yields under mild

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reaction conditions. However, to date, only linear dipoles have been systematically investigated, and reactions with cyclic dipoles have only been briefly examined using diazotized anthranilic acid,[9] which is difficult to handle. Sydnone,[10] as a representative stable and isolable cyclic 1,3-dipole that itself bears interesting biological activity,[11] has been widely used in dipolar cycloadditions with various dipolarophiles to yield important heterocyclic products.[12] Unlike linear 1,3-dipoles, sydnone, as well as some other mesoionic rings, affords a bicyclic adduct that is typically unstable after cycloaddition. That adduct typically readily undergoes spontaneous extrusion of a molecule of CO_2 in a retro-[4 + 2] fashion to reestablish a planar structure with a reorganization of electrons. Hence, the reaction of sydnones with arynes (Scheme 1)[9] would be an ideal method to

Scheme 1. Proposed Cycloaddition of Sydnones and Arynes
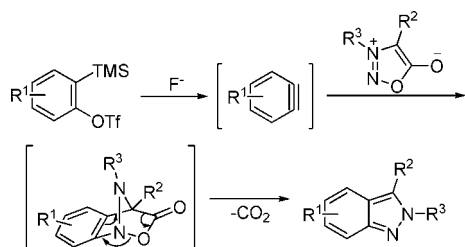
produce the 2H-indazole skeleton and should provide further insights into the underexplored reactivity of arynes in 1,3-dipolar cycloaddition reactions.

The preparation of sydnones is readily achieved according to literature procedures,[13] albeit in variable yields.

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The most easily accessed sydnone, N-phenylsydnone (**2a**),[13a] has first been investigated as a representative substrate to test the feasibility of the reaction (Table 1).

Table 1. Reaction Optimization[a]

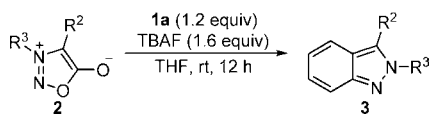| entry	**1a** (equiv)	fluoride source (equiv)	solvent	temp (°C), time (h)	yield[b] (%)
1	1.5	CsF (2.5)	MeCN	rt, 36	69[c]
2	1.5	CsF (2.5)	THF	70, 24	90
3[d]	1.5	TBAF (2.5)	MeCN	rt, 12	95[e]
4[d]	1.5	TBAF (2.5)	THF	rt, 12	94
5[d]	1.2	TBAF (1.6)	THF	rt, 12	98
6[f]	1.2	TBAF (1.6)	THF	rt, 12	97

[a] All reactions were carried out on 0.4 mmol of **2a** at a concentration of 0.1 M. [b] Isolated yield. [c] Incomplete conversion even after 2 days. [d] Solid anhydrous TBAF was used. [e] The product is significantly yellow, although no apparent impurity was detected by NMR spectroscopy. [f] A THF solution (1 M) was used.

Table 2. Reaction with Other Aryne Precursors[a]

entry	aryne precursor	product	yield[b] (%)
1	**1b**	**3b**	97
2	**1c**	**3c**	95
3	**1d**	**3d**	93[c]
4	**1e**	**3e**	33[d]

[a] All reactions were carried out on 0.4 mmol of **2a** at a concentration of 0.1 M. [b] Isolated yield. [c] A 1:1 mixture of the 5-Me isomer and the 6-Me isomer was obtained. [d] See the Supporting Information for the structure assigment. A side product was also isolated.

To our delight, this reaction proceeded readily, a range of reaction conditions proved operational, and excellent yields of the desired product, 2-phenyl-2H-indazole (**3a**), could be realized. Somewhat surprisingly, however, the arguably most widely used conditions for generating

Table 3. Reaction with Other Sydnones[a]

entry	sydnone	product	yield[b] (%)	entry	sydnone	product	yield[b] (%)
1	2b	3f	95	7	2h	3l	~79[c]
2	2c	3g	94	8	2i	3m	72[d]
3	2d	3h	91	9	2j	3n	70[e]
4	2e	3i	93	10	2k	3o	79
5	2f	3j	91	11	2l	3p	63[f]
6	2g	3k	71	12	2m	3q	70

[a] All reactions were carried out on approximately 0.4 mmol of sydnone at a concentration of 0.1 M. [b] Isolated yield. [c] The reaction afforded a 52% yield of pure **3l**, together with another fraction of impure **3l** (32% by weight, approximately 80−85% purity) that was very hard to purify. [d] With 15% recovery of **2i**. [e] With 19% recovery of **2j**. [f] This reaction was performed with 1.6 equiv of **1a** and 2.4 equiv of TBAF.

benzyne, namely CsF in acetonitrile, seemed to be the worst choice here, with only a 69% yield and incomplete conversion of **2a**, even upon prolonged reaction times (entry 1). Running the reaction in THF at 70 °C led to complete conversion of **2a** with a much improved 90% yield (entry 2). Finally, replacing CsF with TBAF (entries 3 and 4) resulted in the ideal situation; not only were high yields obtained, but the reaction time could be significantly shortened. THF and acetonitrile afforded no apparent difference in yields, but the reaction performed in acetonitrile led to a yellow product as opposed to the white product obtained when using THF. For this reason, we

prefer to carry out the reaction in THF rather than acetonitrile. Finally, using THF as the solvent, the loadings of both **1a** and fluoride could be reduced while maintaining a near-quantitative yield (entry 5). The use of either solid TBAF or a THF solution of TBAF afforded similar results. The reaction as described affords a clean, spot-to-spot tranformation, except for perhaps a trace of unreacted sydnone. No other spots were observed on TLC analysis. Therefore, these reaction conditions served as our standard to study other substrates in this cycloaddition. It should be noted that a possible side-product arising from the [4 + 2] cycloaddition of the product **3a** with another

molecule of benzyne to yield a bicyclic system was not observed under any of the reaction conditions.

Different aryne precursors were screened next (Table 2), and the results proved quite satisfactory. Symmetrical benzyne precursors **1b** and **1c** gave near-quantitative yields as well (entries 1 and 2). An unsymmetrical benzyne precursor **1d**, which is neither electronically nor sterically biased, generated a 1:1 mixture of two regioisomers in a 93% combined yield (entry 3). The commonly used, both electronically and sterically biased unsymmetrical benzyne precursor **1e** afforded a single regioisomer (entry 4), but in only a 33% yield.[14] Although the regioselectivity of this aryne has been previously observed and suggested to involve more favorable nucleophilic attack at the meta position for both electronic and steric reasons,[7e,15] the regioselectivity of this specific reaction seems somewhat counterintuitive, as one would anticipate that the *C*-4 enolate position of the sydnone would serve as the nucleophile, as seen in the acylation and halogenation reactions of sydnones.[10a] However, computational studies have demonstrated that unlike that of regular azomethine imines, the LUMO of sydnones has the coefficients of *N*-2 and *C*-4 quite close,[16] rendering its *N*-2 position similar in reactivity. In fact, the cycloaddition of sydnones with unsymmetrical alkynes generally comes with low regioselectivity.[10a] Calculations have shown that the *N*-2 position of sydnone carries a significant negative charge, while the *C*-4 position remains neutral or slightly positive.[17] Therefore, it would not be too surprising for **2a** to react with 3-methoxybenzyne with the *N*-2 position as the nucleophile.

The scope of the reaction was then further tested using a range of sydnones (Table 3). As can be seen, the reaction works best for simple *N*-substituted sydnones (entries 1−3), where near-quantitative yields are easily obtained. Substitution at the 3-position is tolerated. Aryl groups (entries 4−6), heterocyclic aryl groups (entries 7 and 8), an alkynyl group (entry 9), and a vinyl group (entry 10) at this position all afford reasonable results, although in some cases (entries 8 and 9) incomplete conversions have been observed. Some-

what surprisingly, alkyl groups at the 3-position do not always afford high yields. When 3-isobutyl-2-arylsydnone **2l** was used, the reaction afforded only a 23% yield with ∼10% recovery of the sydnone under our standard conditions (1.2 equiv of **1a**, 1.6 equiv of TBAF). An excess of the benzyne precursor had to be employed to push the reaction to completion, but the 63% yield remains only moderate (entry 11).[18] On the contrary, sydnone **2m** with its 3,4-alkyl substituents tethered in a ring reacted smoothly (entry 12), and a 70% yield of the product **3q** was easily obtained. This product and derivatives might serve as a structural analogue of withasomnine **1**[19] for screening of its CNS and circulatory system depressant properties.

In summary, we have developed a method for the preparation of 2*H*-indazoles starting from arynes and easily obtained sydnones by a sequence involving [3 + 2] dipolar cycloaddition/decarboxylation. Compared with literature protocols, our reaction offers very mild conditions, high yields, and excellent selectivity. The versatility of the reaction makes it ideal for medicinal chemistry. A more detailed study of this cycloaddition, including more functional groups and a wider range of substrates, as well as studies of arynes with other representative dipoles, is actively under way in our laboratories.

Supporting Information Available: Preparation of sydnones, experimental details, and characterization of both sydnones and the final products, including full ^{1}H and ^{13}C NMR spectra of the 2*H*-indazoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) There is a significant side product in this reaction, whose identity is currently under investigation. The results will be published in due course.

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