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tert-Butyl Hydroperoxide-Mediated Oxo-Sulfonylation of 2*H*-Indazoles with Sulfinic Acid toward Indazol-3(2*H*)-ones

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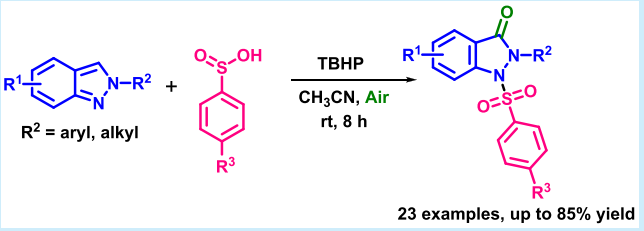
ABSTRACT: A new and efficient oxo-sulfonylation protocol has been established for the synthesis of N-sulfonylated indazolones employing sulfinic acid as a sulfonylating agent using *tert*-butyl hydroperoxide (TBHP) under ambient air. A series of structurally diverse 1-sulfonylindazol-3(2*H*)-one derivatives were obtained in good yields. A radical reaction mechanism has been proposed for this transformation.



Sulfur-containing organic compounds have a great importance in pharmaceutical chemistry, optical chemistry, and industrial research.[1] Introducing a sulfur-containing group on aryl and heteroaryl moieties enhances its biological activity.[2] Among the different sulfur-containing moieties, sulfonamide plays a prevalent role in pharmaceutical, agrochemical, and synthetic chemistry.[3] This moiety is the core structure of various drugs (Figure 1)[4a] and bioactive

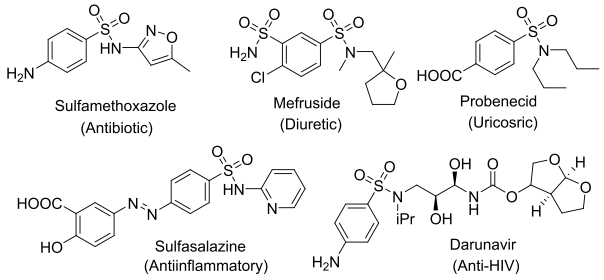


Figure 1. Sulfonamide-containing drugs.

compounds[4b] possessing antibacterial, antitumor, anti-inflammatory, and anti-HIV properties and of several pesticides[4c] including asulam, orzalin, fomesafen, halosafen, sulfentrazone, etc. Therefore, development of a competent method for the construction of a sulfonamide bond has drawn significant attention to the synthetic organic community.[5]

Indazolone, a nitrogen-containing heterocycle, is widely distributed in a large variety of biologically and pharmaceutically active molecules and natural products as shown in Figure 2.[6] It exhibits promising pharmacological properties such as anti-inflammatory,[7a] antihyperlipidemic,[7b] antipyretic,[7c] analgesic,[7d] etc. Moreover, there are a number of drugs containing this scaffold, and they have been utilized as a pathway-selective estrogen receptor,[8a] an inhibitor against sodium nitroprusside-induced apoptosis,[8b] an antiplatelet agent,[8c] and a selective

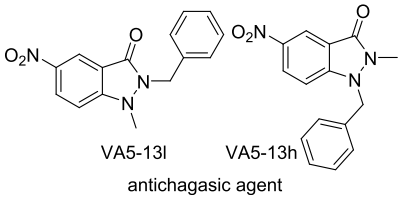


Figure 2. Examples of some indazol-3(2*H*)-one-based drugs.

rhokinase inhibitor.[8d] Therefore, it has been receiving significant attention for the synthesis of indazolones due to its wide-ranging biological implications.[9] However, as far as we know, there is no report on the direct synthesis of indazolone derivatives from 2*H*-indazoles. Based on our previous experiences on functionalization of 2*H*-indazoles,[10] as well as considering the importance of both indazol-3(2*H*)-one and sulfonamide, herein we presented a new method for the synthesis of 1-sulfonylindazol-3(2*H*)-one from 2*H*-indazole using sulfinic acid as a sulfonylating agent under ambient air (Scheme 1).

We commenced our study by examining the reaction taking 2-phenyl-2*H*-indazole (**1a**) as a model substrate and 4-methylbenzenesulfinic acid (**2a**) as a sulfonylating agent (Table 1). At first, we carried out the reaction using 1.0 equiv of *tert*-butyl hydroperoxide (TBHP) in toluene at room temperature under ambient air for 8 h. Delightfully, 2-phenyl-1-tosyl-1,2-dihydro-3*H*-indazol-3-one (**3aa**) was obtained in 52% yield. Encouraged by this initial result, we examined the effect of a number of different solvents such as DMSO, DCM,

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Scheme 1. Synthesis of 1-Sulfonylindazol-3(2*H*)-one

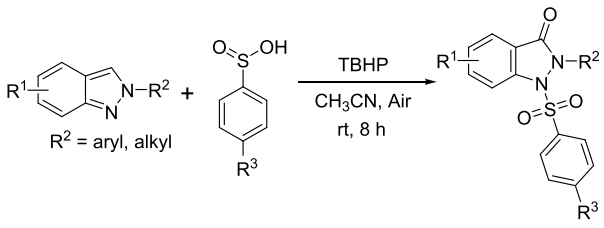
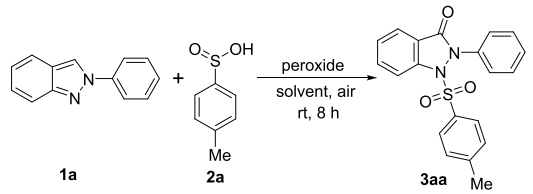


Table 1. Optimization of the Reaction Conditions for Oxo-Sulfonylation of 2*H*-Indazoles[a]



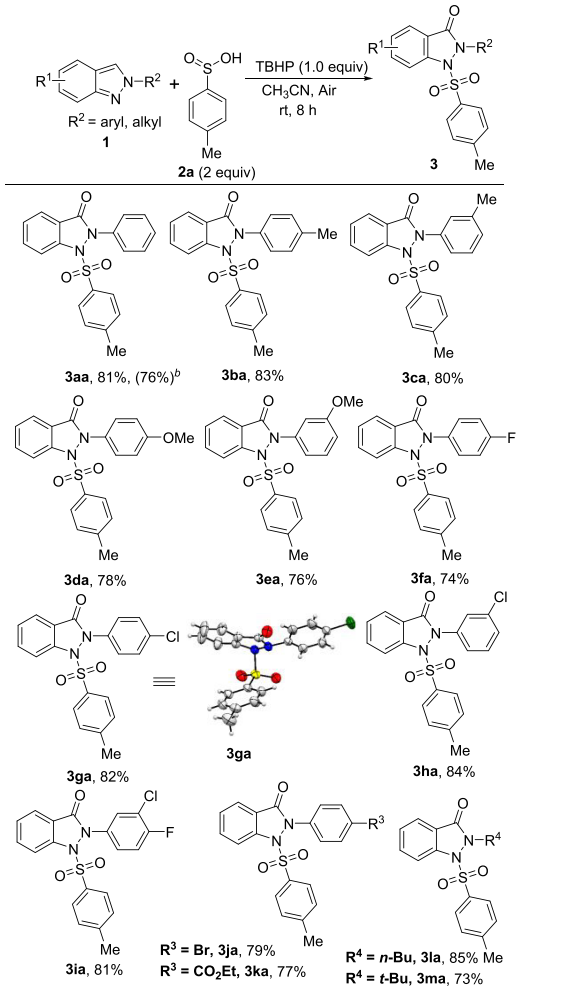
entry	peroxide (1 equiv)	solvent (2 mL)	yield (%)
1	TBHP	toluene	52
2	TBHP	DMSO	nr
3	TBHP	DCM	30
4	TBHP	DMAc	nr
5	TBHP	DMF	48
6	TBHP	1,2-DCE	37
7	TBHP	DCB	33
8	TBHP	1,4-dioxane	trace
9	TBHP	EtOH	nr
10	TBHP	propanol	trace
11	TBHP	CH_3CN	81
12	DTBP	CH_3CN	nr
13	DCP	CH_3CN	trace
14	TBPB	CH_3CN	nr
15	$K_2S_2O_8$	CH_3CN	nr
16	H_2O_2	CH_3CN	trace
17	O_2	CH_3CN	trace
18	TBHP	CH_3CN	41[b], 78[c]
19	TBHP	CH_3CN	39[d], 80[e]
20	TBHP	CH_3CN	68[f]

[a]All reactions were performed with **1a** (0.2 mmol), **2a** (2.0 equiv), peroxide (1.0 equiv), and solvent (2.0 mL) for 8 h at rt. [b]0.5 equiv of TBHP used. [c]2.0 equiv of TBHP used. [d]1.0 equiv of sulfinic acid used. [e]3.0 equiv of sulfinic acid used. [f]Stirred at 60 °C. nr = no reaction.

DMAc, DMF, 1,2-DCE, DCB, 1,4-dioxane, EtOH, propanol, and CH_3CN (Table 1, entries 2−11). Among them, a better result was found in CH_3CN, producing the desired product in 81% yield. Probably, solubility and radical stability make CH_3CN an effective solvent for this reaction. After that, the reaction was performed using different peroxides like di-*tert*-butyl peroxide (DTBP), dicumyl peroxide (DCP), *tert*-butyl peroxybenzoate (TBPB), $K_2S_2O_8$, and H_2O_2, but they were not effective for this transformation (Table 1, entries 12−16). A trace amount of oxo-sulfonylated product was obtained in the absence of TBHP using only the O_2 balloon (Table 1, entry 17). The yield of the reaction did not improve with increasing the amount of both TBHP and sulfinic acid, whereas an inferior result was observed with diminishing the amount of both of them (Table 1, entries 18 and 19). Further screening of reaction temperature showed that the reaction worked well at ambient temperature (Table 1, entry 20). Finally, we got the optimized reaction conditions using 2.0 equiv of sulfinic acid and 1.0 equiv of TBHP in CH_3CN under ambient air at room temperature for 8 h (Table 1, entry 11). Other sulfonylating agents like *p*-toluenesulfonyl chloride, sodium *p*-toluenesulfinate, and *p*-toluenesulfonic acid were unable to produce the desired oxo-sulfonylated products.

Having the optimized reaction conditions in hand, next we focused on the synthesis of a variety of structurally diverse 2*H*-indazoles (Scheme 2). A library of 2-phenyl-2*H*-indazoles

Scheme 2. Substrate Scope of 2*H*-Indazoles[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv), TBHP (1.0 equiv), and CH_3CN (2.0 mL) for 8 h at rt. [b]On a 5.0 mmol scale.

reacted with 4-methylbenzenesulfinic acid (**2a**) to afford the oxo-sulfonylated products ranging from 73% to 84% yields (**3aa**−**3ma**). 2-Phenyl-2*H*-indazoles having electron-donating groups like −Me and −OMe at the aromatic ring (**1b**−**1e**) nicely reacted with **2a** to produce the desired products in up to 83% yields (**3ba**−**3ea**). Halogen-containing 2-phenyl-2*H*-indazoles also afforded the corresponding products in good yields (**3fa**−**3ja**). The structure of 2-(4-chlorophenyl)-1-tosyl-1,2-dihydro-3*H*-indazol-3-one (**3ga**) was confirmed by the single-crystal X-ray analysis. To our delight, ethyl 4-(2*H*-indazol-2-yl)benzoate (**1k**) successfully produced ethyl 4-(3-oxo-1-(phenylsulfonyl)-1,3-dihydro-2*H*-indazol-2-yl)benzoate (**3ka**) in 77% yield. Moreover, *n*-butyl- and *tert*-butyl-substituted 2*H*-indazole were well tolerable for such a

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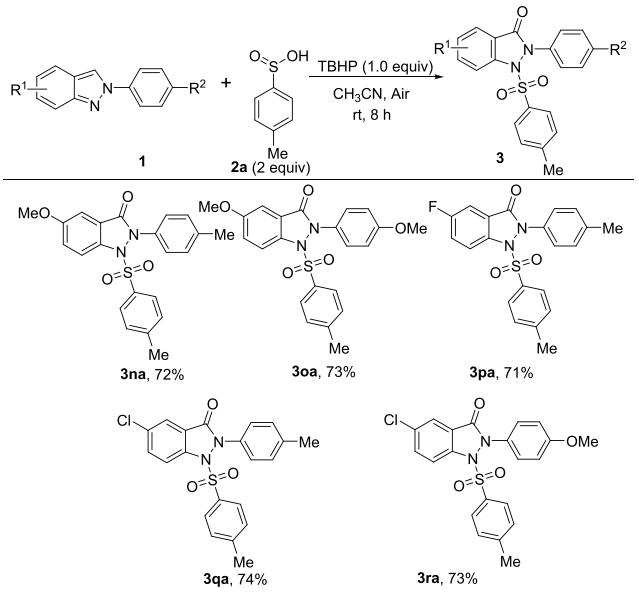
transformation (**3la** and **3ma**). However, *ortho*-substituted 2*H*-indazoles and 2-benzyl-2*H*-indazole did not give the desired products. Anthranil and indole were also unable to produce the oxo-sulfonylated product under the reaction conditions. Further signifying the synthetic applicability of this process, a gram-scale synthesis of 2-phenyl-1-(phenylsulfonyl)-1,2-dihydro-3*H*-indazol-3-one (**3aa**) was carried out using 2-phenyl-2*H*-indazole (**1a**) in 5.0 mmol scale under the optimized reaction conditions. Pleasingly, the desired product was obtained in 76% yield.

Additionally, substitutions at the arene part of 2*H*-indazoles were also examined (Scheme 3). 5-Methoxy-2-(*p*-tolyl)-1-tosyl-1,2-dihydro-3*H*-indazol-3-one and 5-methoxy-2-(4-methoxyphenyl)-1-tosyl-1,2-dihydro-3*H*-indazol-3-one (**3na** and **3oa**) were obtained in 72% and 73% yields, respectively. C-5 halogen-substituted (−F and −Cl) 2*H*-indazole resulted in the desired products in up to 74% yield (**3pa**−**3ra**).

Scheme 3. Substrate Scope[a]

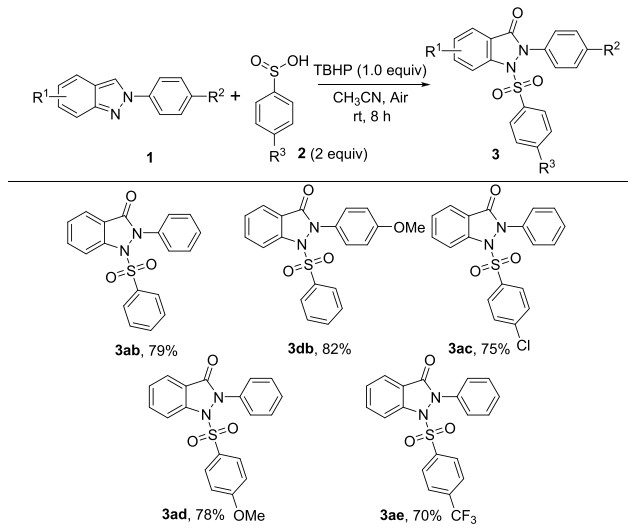


[a]Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv), TBHP (1.0 equiv), and CH_3CN (2.0 mL) for 8 h at rt.

We next turned our attention to the scope of sulfinic acids (Scheme 4). Benzenesulfinic acid, 4-chlorobenzenesulfinic acid, 4-methoxybenzenesulfinic acid, and 4-(trifluoromethyl)-benzenesulfinic acid afforded the desired products (**3ab**, **3db**, **3ac**, **3ad**, and **3ae**) in moderate to good yields.

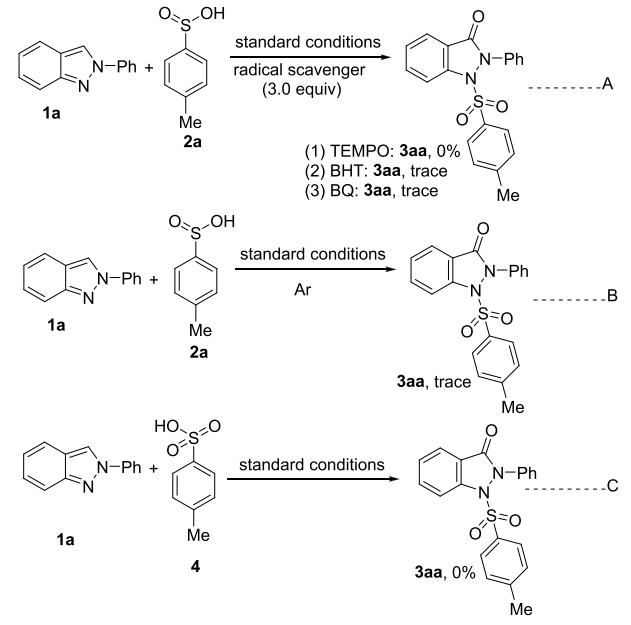
To establish the possible mechanism, some control experiments were carried out as shown in Scheme 5. The formation of a trace amount of desired product in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 1,4-benzoquinone (BQ) suggests the radical pathway of this protocol (Scheme 5, eq A). The present reaction did not give the expected product at all under an inert atmosphere (Scheme 5, eq B). Therefore, the oxygenation was probably triggered by aerial oxygen. However, we are unable to do an $^{18}O_2$ experiment. The desired product was not obtained by replacing sulfinic acid with sulfonic acid (Scheme 5, eq C). This result indicates that sulfonic acid was not the intermediate of this present reaction. However, disulfide product was not formed under the optimized reaction conditions.

Scheme 4. Substrate Scope of Sulfinic Acids[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), TBHP (1.0 equiv), and CH_3CN (2.0 mL) for 8 h at rt.

Scheme 5. Mechanistic Experiments



On the basis of the control experimental results and literature reports,[11−14] a probable mechanism is illustrated in Scheme 6. Initially sulfinic acid generates the sulfinic radical **A** in the presence of TBHP.[11] Next the sulfinic radical adds to the N-1 position of 2-phenyl-2*H*-indazole to produce intermediate **B** which then converts to intermediate **C** via aerial oxygen abstraction[12] at the C-3 position of 2-phenyl-2*H*-indazole. Next intermediate **C** takes a hydrogen radical from sulfinic acid to generate intermediate **D**. Lastly, the desired product (**3aa**) is formed by the elimination of water from the intermediate **D**.[13]

In summary, a simple and facile oxo-sulfonylation protocol has been reported for the synthesis of 1-sulfonylindazol-3(2*H*)-one at ambient air under metal-free conditions. Mild conditions, broad substrate suitability, scalability, and room temperature make this protocol relevant for functionalization

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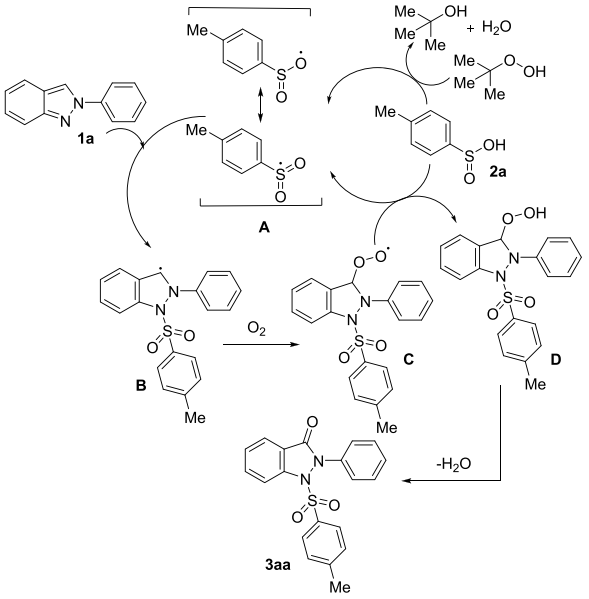
Scheme 6. Plausible Mechanistic Pathway



of biologically active heterocycles. To our knowledge this is the first report for the synthesis of an indazol-3(2*H*)-one derivative from easily accessible indazoles. We believe that our current oxo-sulfonation protocol will gain high synthetic value in both academia and industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04617.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1973641 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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