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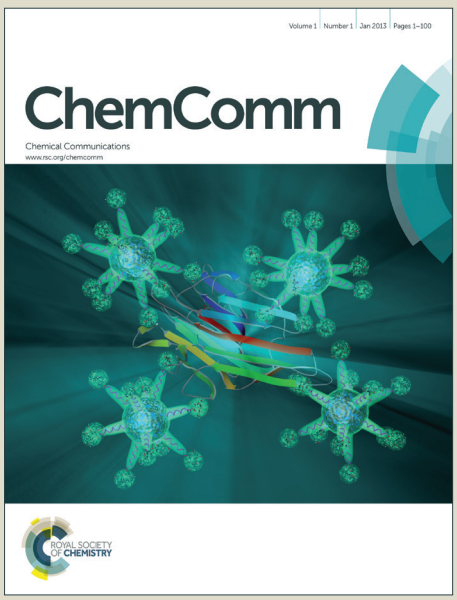

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ARTICLE TYPE

Synthesis of 1*H*-Indazoles from *N*-Tosylhydrazones and Nitroaromatic Compounds

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A new method for the synthesis of 1*H*-Indazoles from readily available *N*-tosylhydrazones and nitroaromatic compounds has been developed. This transformation is under transition-metal-free conditions and shows wide substrate scope. The method has been successfully applied to the formal synthesis of a bioactive compound, WAY-169916.

Owing to their diverse pharmacological activities, 1*H*-indazoles are frequently found in drugs and drug candidates as demonstrated by the examples shown in Figure 1.[1] Besides, 1*H*-indzoles also find applications in other area, such as being ligands in metal complexes.[2] Due to the importance of this type of compounds, many efficient methods have been developed to access 1*H*-indazoles. Among them, diazotization or nitrosation of *ortho*-alkyl-substituted anilines (Jacobson modification, Scheme 1a),[3] condensation of *ortho*-substituted arylaldehydes or ketones with hydrazines (Scheme 1b),[4] and [3+2] cyclization of diazomethanes with benzynes (Scheme 1c)[5] are the three most commonly explored strategies. Recently, the rapid development of transition-metal catalysis has opened alternative ways to access these structures. 1*H*-Indazoles are synthesized by transition-metal-catalyzed intramolecular amination of *o*-halo arylhydrazones or direct C-H amination of arylhydrazones (Scheme 1d).[6] Despite the success of these synthetic methods,

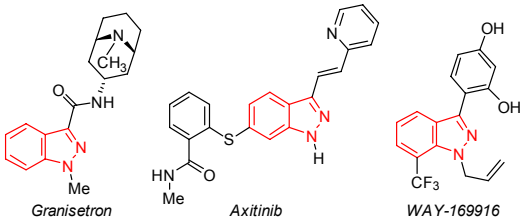

Figure 1 Some drugs and drug candidates containing 1*H*-indazole structure.

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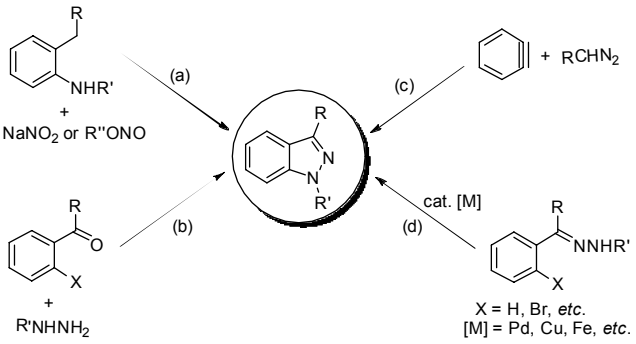
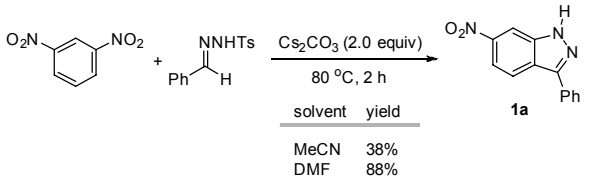
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/b000000x/



Scheme 1 The reported strategies for the synthesis of 1*H*-indazoles.

some drawbacks still remain, such as the use of toxic hydrazines, low regioselectivity of the reactions, and the need of pre-functionalization of starting materials. Therefore, further development of efficient methods is highly demanded.

On the other hand, *N*-tosylhydrazones have emerged as useful reagents in transition-metal-catalyzed cross-coupling reactions.[7] In this context, we have recently reported the direct aromatic C-H bond functionalization with *N*-tosylhydrazones.[8] As a continuation, we have conceived to extend this type of reaction with electron-deficient arenes such as 1,3-dinitrobenzene in Cu(I)-catalyzed direct C-H bond functionalization. In the control experiments, we found with surprise that in the absence of Cu(I) catalyst, 1,3-dinitrobenzene reacts directly with *N*-tosylhydrazone to give 6-nitro-3-phenyl-1*H*-indazole **1a** under basic conditions (Scheme 2). Changing the solvent from MeCN to DMF significantly improved the yield of **1a**.

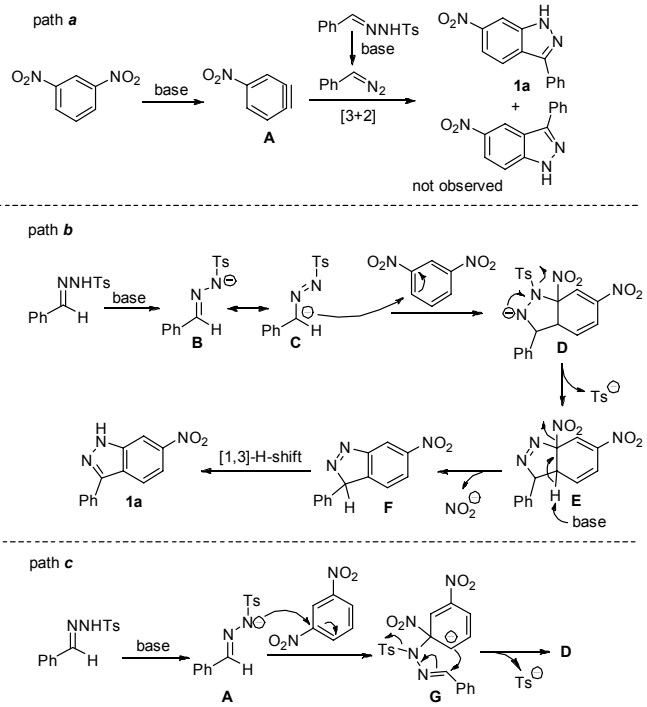


Scheme 2 Reaction of 1,3-dinitrobenzene with *N*-tosylhydrazone under transition-metal-free conditions.

This unusual reaction raises intriguing question concerning its reaction mechanism. As shown in Scheme 3, there are several

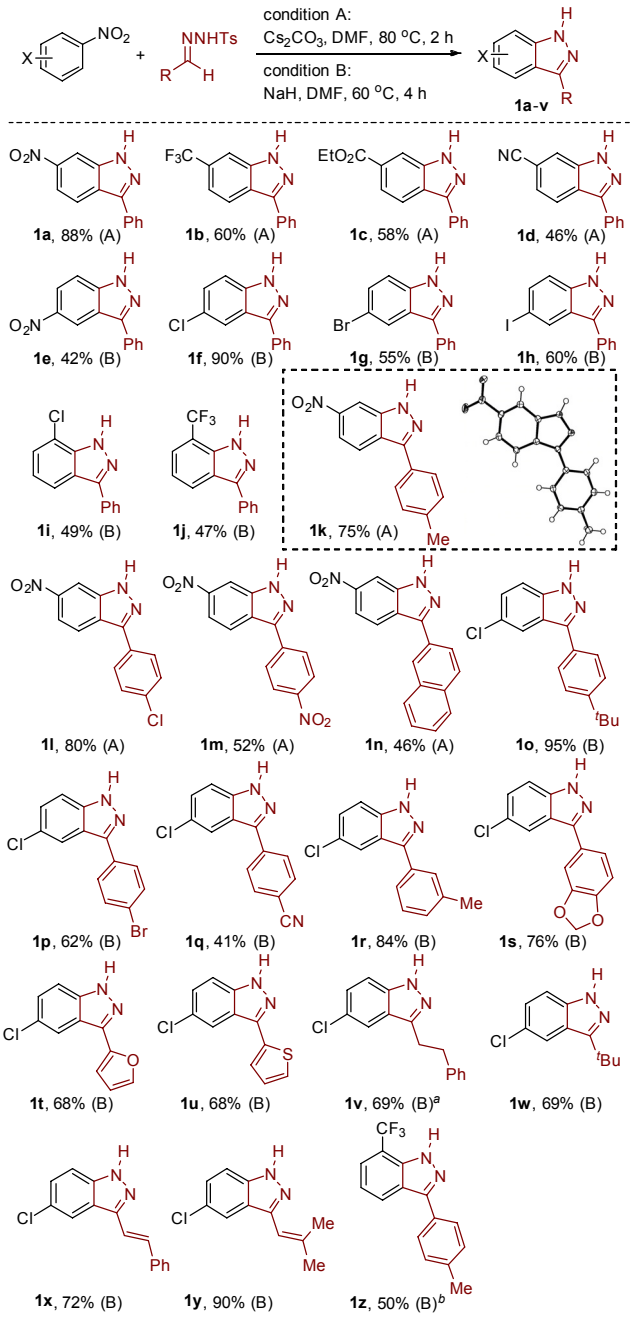
possible mechanisms for this reaction. Path ***a*** is based on [3+2] cycloaddition between diazo compounds and benzynes. It is known that diazo compounds are formed *in situ* from *N*-tosylhydrazones under basic conditions (Bamford-Stevens reaction),[9] while benzyne **A** may be generated *via* nitro-elimination under basic conditions.[10] However, careful analysis of the crude reaction mixture reveals that only one isomer could be identified.[11] This is not in agreement with the result of normal benzyne-involved [3+2] cycloaddition reactions, where the mixture of two regioisomers is usually produced.[12]

Path ***b*** starts with the deprotonation of *N*-tosylhydrazone. Then the deprotonated tosylhydrazone **B** (in resonance with **C**) undergoes nucleophilic addition to the less hindered *ortho* position of the nitro group of 1,3-dinitrobenzene to afford the intermediate **D**. Through intramolecular cyclization, nitro-elimination and [1,3]-H-migration, the final product **1a** is formed.[13] Path ***c***, which is similar to path ***b***, involves the direct nucleophilic attack of the nitro-attached carbon of the 1,3-dinitrobenzene substrate, giving intermediate **G**. While this step is thermodynamically disfavoured, the fast cyclization from **G** to **D** should drive the reaction forward. Path ***b*** and ***c*** cannot be distinguished with currently available experimental evidences.



Scheme 3 Possible reaction mechanisms.

Since this highly efficient reaction can serve as a new methodology for the synthesis of 1*H*-indazole, we then proceeded to study the scope of the reaction (Scheme 4). For the nitrobenzenes, it turned out that *m*-CF_3-, *m*-EtO_2C-, and *m*-NC-substituted ones were suitable substrates, affording the corresponding products **1b-d** in moderate yields. For *para*- or *ortho*-substituted nitrobenzenes, strong base NaH is needed instead of Cs_2CO_3.[14] For *para*-substituted nitrobenzenes, in addition to 1,4-dinitrobenzene, structures containing weak electron-withdrawing substituents (Cl, Br, I) could also be employed as the right substrates to give the corresponding products **1e-h** in moderate to excellent yields. As for *ortho*-substituted nitrobenzene, the corresponding 1*H*-indazoles (**1i-j**) were

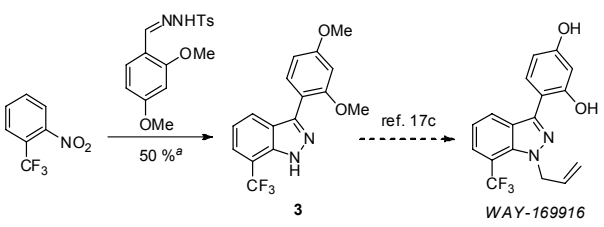


Scheme 4 Reaction scope of transition-metal-free synthesis of 1*H*-indazoles. Reaction conditions A: nitroarene (0.3 mmol), *N*-tosylhydrazone (0.36 mmol) and Cs_2CO_3 (1.08 mmol) in DMF (2.0 mL) at 80 °C for 2 h; Reaction conditions B: nitroarene (0.3 mmol), *N*-tosylhydrazone (0.36 mmol) and NaH (1.08 mmol) in DMF (2.0 mL) at 60 °C for 4 h. All the yields refer to isolated yields.[a] 110 °C; [b] additive: tetrabutylammonium bromide (TBAB) (0.3 mmol).

obtained in low yields, presumably attributed to the *ortho* effect.[15]

Next, we examined the substrate scope of the *N*-tosylhydrazones. For the reactions with 1,3-dinitrobenzene, *N*-tosylhydrazones derived from aldehydes with weak electron-donating or -withdrawing groups worked smoothly (**1k-l**). However, those derived from the aldehydes bearing strong electron-withdrawing or bulky substituents give only diminished yields of the corresponding products (**1m-n**). For the reactions with 1-chloro-4-nitrobenzene, the results were somewhat similar (**1o-s**). *N*-Tosylhydrazones derived from heteroaromatic aldehydes also worked well to give the corresponding products in moderate yields (**1t-u**). Besides, the *N*-tosylhydrazones derived from alkyl aldehydes and alkenyl aldehydes could also be used to afford 3-alkyl or alkenyl–substituted indazoles in good yields (**1v-y**). Finally, the reaction with 1-nitro-2-(trifluoromethyl)benzene afforded moderate yield of the product (**1z**). For one of the products **1k**, the structure is unambiguously confirmed by X-ray diffraction.[16]

WAY-169916 is the first example of an ER ligand that has broad *anti*-inflammatory activity *in vivo* with the potential use in the treatment of rheumatoid arthritis but lacks the classical proliferative effects associated with estrogens.[17] The access to this molecule from previous reports calls for *multi*-step synthesis. Herein, the current methodology has been employed to prepare the key intermediate **3** in one step from the readily available starting materials (Scheme 5). The intermediate **3** could be easily transformed to WAY-169916 according to the literature.[17c]



Scheme 5 Application to the formal synthesis of WAY-169916. [a]Reaction conditions: 1-nitro-2-(trifluoromethyl)benzene (0.3 mmol), *N*-tosylhydrazone (0.45 mmol), NaH (1.35 mmol), TBAB (0.3 mmol), DMF (2.0 mL), 110 ^{o}C.

In conclusion, we have developed a straightforward method for the synthesis of 1*H*-indazoles from *N*-tosylhydrazones and nitroaromatic compounds. The reaction is efficient and shows wide substrate scope. Compared with the existing methods, ready availability of the starting materials, easy operation, and no need for transition-metal catalysts are its attractive features. With these merits, we expect this methodology would find applications in the synthesis of 1*H*-indazoles.

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