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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 occurs under transition-metal-free conditions and shows a 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 Fig. 1.[1] Besides, 1*H*-indazoles also find applications in other areas, such as being ligands in metal complexes.[2] Due to the importance of these types 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, 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

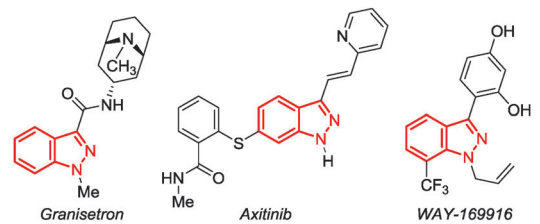
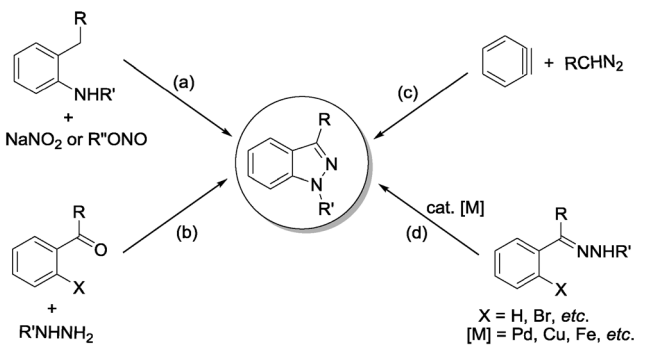


Fig. 1 Some drugs and drug candidates containing the 1*H*-indazole structure.



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

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 the 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**.

This unusual reaction raises an 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

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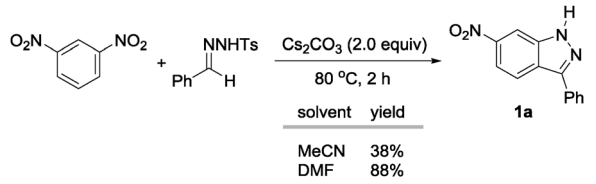
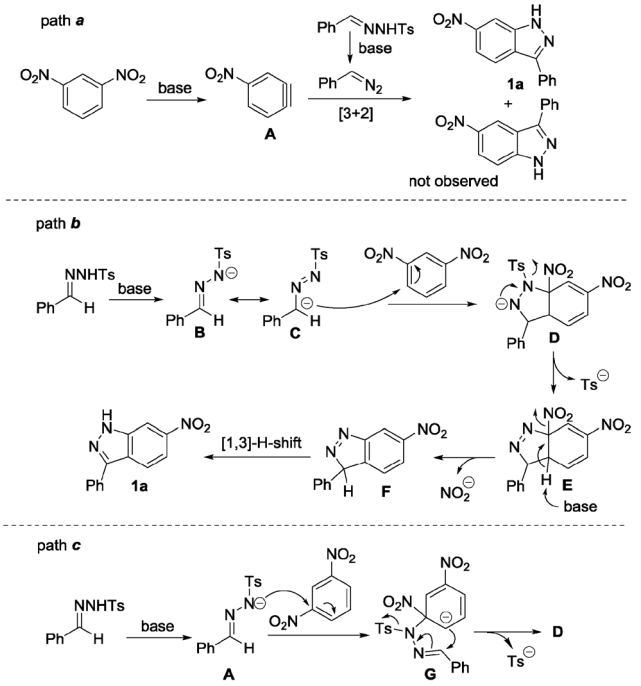


Scheme 2 Reaction of 1,3-dinitrobenzene with *N*-tosylhydrazone under transition-metal-free conditions.

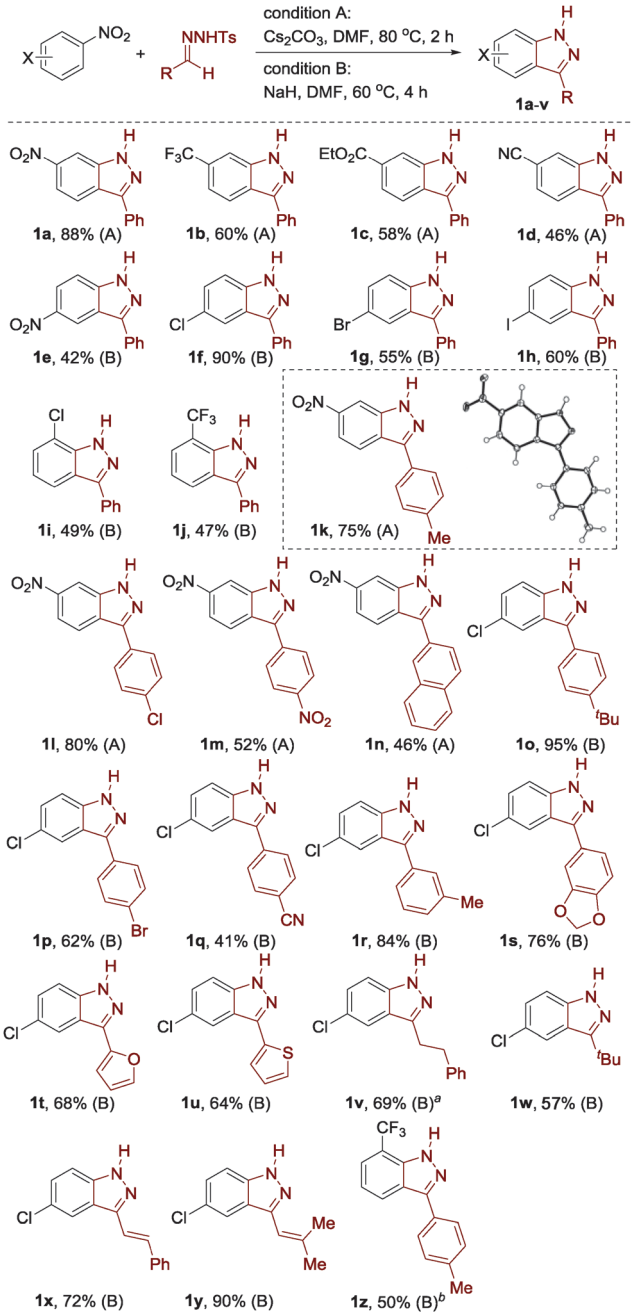


Scheme 3 Possible reaction mechanisms.

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. Paths **b** and **c** cannot be distinguished with currently available experimental evidence.

Since this highly efficient reaction can serve as a new methodology for the synthesis of 1*H*-indazoles, 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



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).

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 and 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

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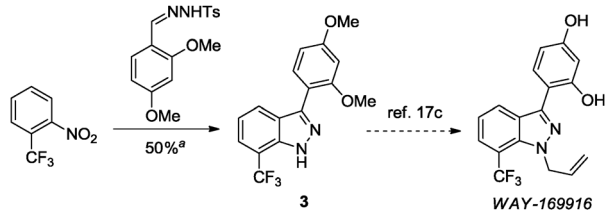

Scheme 5 Application to the formal synthesis of WAY-169916. [a] Reaction conditions: 1-nitro-2-(trifluoromethyl)benzene (0.3 mmol), *N*-tosylhydrazone (0.45 mmol), NaH (1.35 mmol), TBAB (0.3 mmol), DMF (2.0 mL), 110 °C.

1*H*-indazoles (**1i–j**) were 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 gave 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 analysis.[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]

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 a 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 that this methodology would find applications in the synthesis of 1*H*-indazoles.

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