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Microwave-Assisted Synthesis of 2-Pyridinylethyl Indazoles

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Abstract

An atom-economic pathway to obtain N-alkyl indazoles bearing pyridine from indazoles and vinylpyridines in water is reported. Assisted with microwave irradiation, the reaction could be completed within 20 minutes, affording N1 or N2 alkylation indazoles in high yields. 4-Vinylpyridines gave N1 alkylated products exclusively.

Key Words: Alkyl indazole, microwave, pyridine, alkylation

Introduction

The indazole ring is a commonly used motif in the discovery of biologically active molecules. [1] The manipulation of substitution pattern is crucial for designing pharmaceutical molecules bearing indazoles. We are interested in the introduction of a pyridinyl alkyl group into indazoles because some pyridinyl alkyl indazoles have shown important biological properties. For example, Compounds **A** are inhibitors for type III receptor tyrosine kinase (Figure 1). [2] Compounds **B** are thrombin inhibitors, which could be used for the treatment of thromboembolic diseases. [3] The general method to synthesize alkyl indazoles is nucleophilic substitution between indazoles and alkyl halides (Figure 2, eq 1). [4] However, it is still a challenge for the reaction of an alkyl halide bearing a nitrogen-containing heterocycle. For example, the reaction of 2-bromo-ethyl pyridine with indazoles is very sluggish (Eq 2). [3] The reason is that these halides would rather react with themselves to form pyridium salts than react with indazoles. We envisioned that using vinylpyridines as the alkylation reagent would avoid this side reaction, thus increasing the alkylation efficiency.

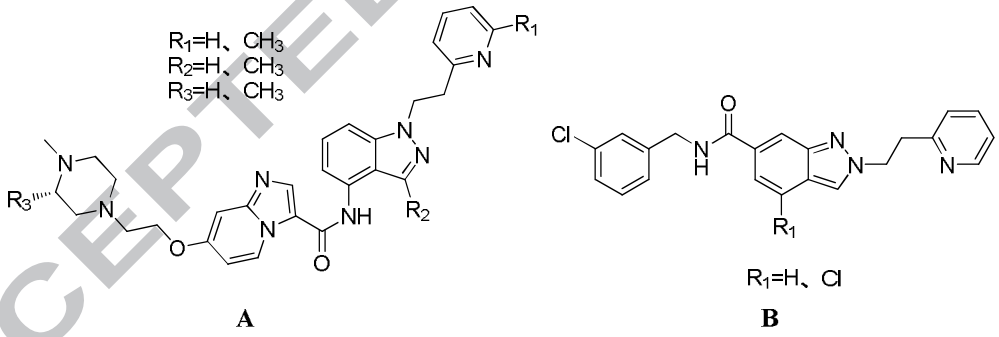


Figure 1. Biologically active N pyridinyl alkyl indazoles

Microwave as a green energy becomes more and more popular in the modern organic synthesis. Microwave can not only reduce energy consumption, but also shorten the reaction time, thereby increasing efficiency. [4] Using water as solvent provides opportunities for clean processing and pollution prevention. [5] However, most organic compounds hardly dissolve in water at ambient condition, which limit the application of

water. The supposed near-critical region of water at temperatures between 150 and 300 □ is of great importance to organic synthesis. [6] Organic compounds become more soluble in near-critical region of water. With the help of commercial microwave equipment, it is easy to use near-critical water as the solvent. Herein, we reported a microwave assisted synthesis of pyridinyl alkyl indazoles in water (Figure 2, eq 3).

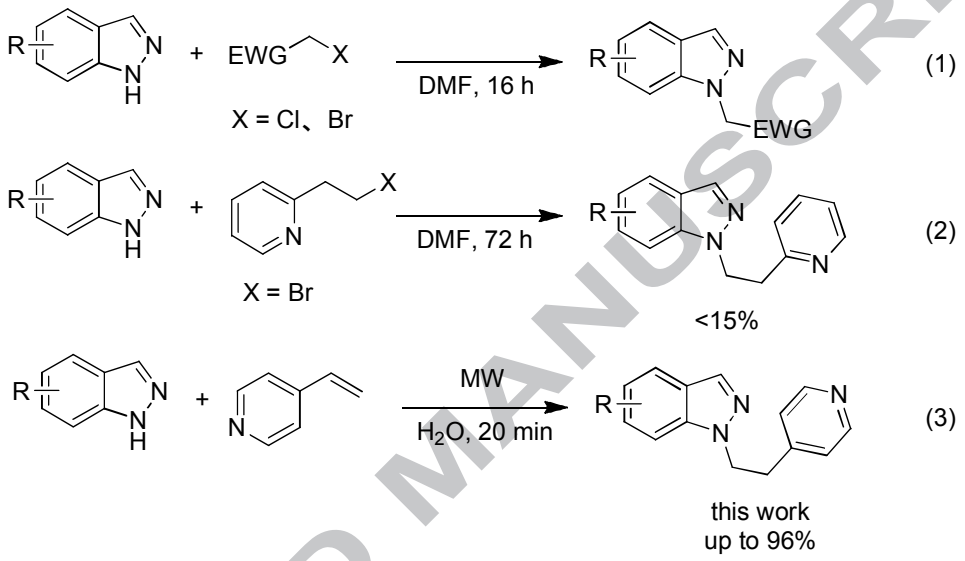
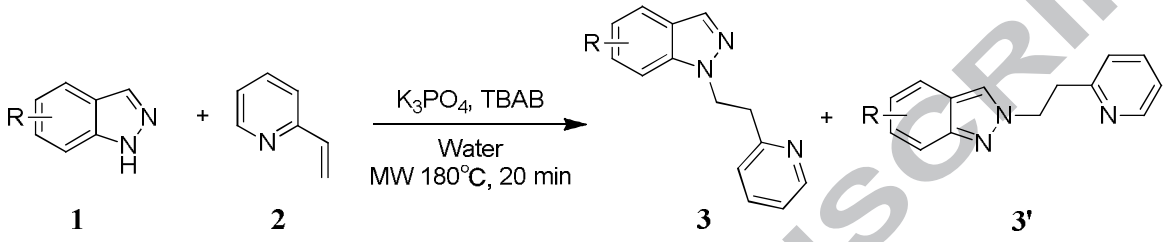


Figure 2. Methods for alkylation of indazoles

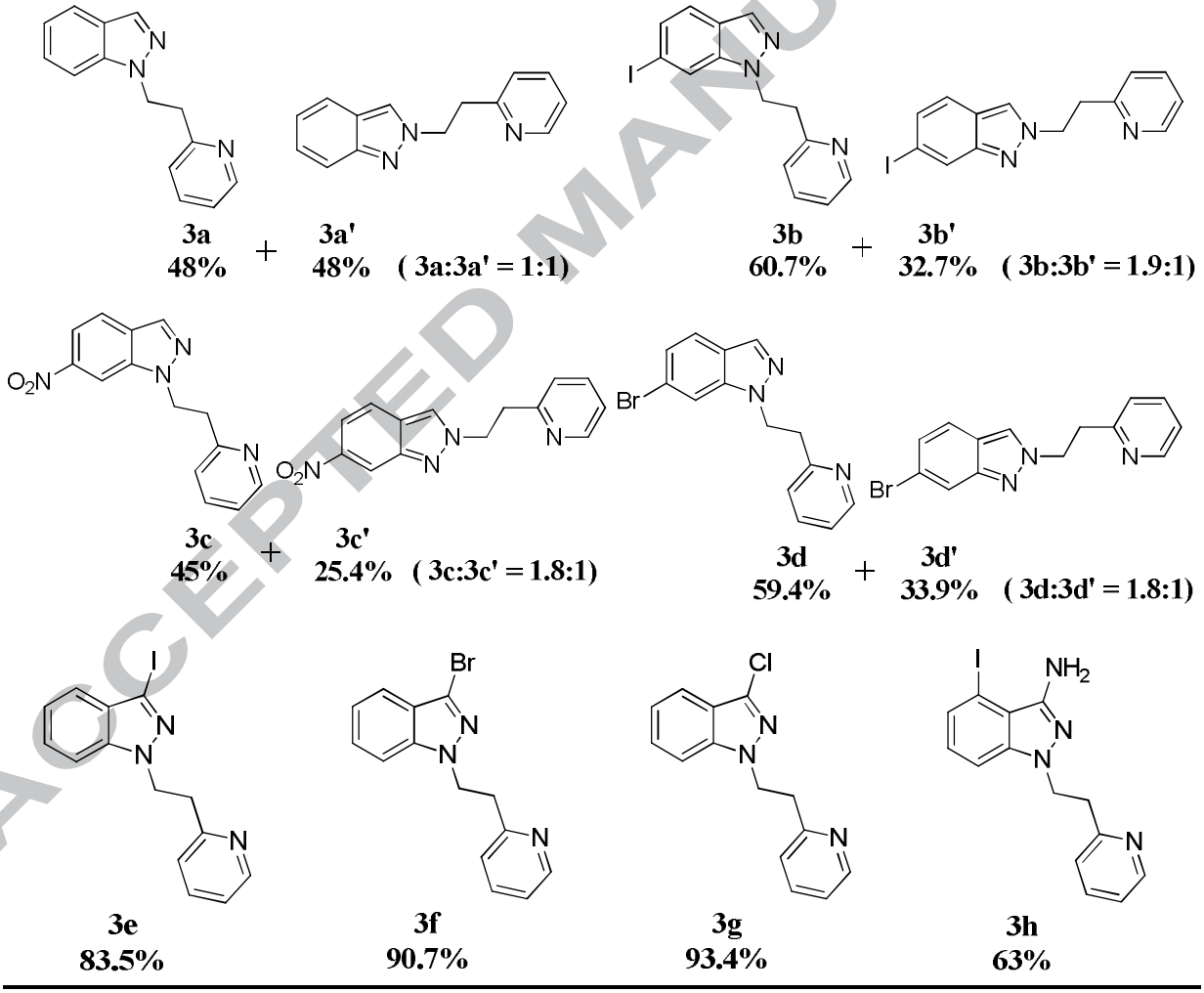
Assisted with microwave irradiation for 20 min at 180 ℃, the reaction of 2-vinylpyridine with indazole was completed. Two products **3a** (R_f =0.4) and **3a′** (R_f =0.2) were isolated by chromatograph in 1:1 ratio (Table 1).[7] Then a variety of substituted indazoles were tested (Table 1). All of substituted indazoles afforded pyridinyl alkyl indazoles in high yields except 6-nitroindazole (**3c** and **3c′**). C3-substituted indazoles provided N1 alkylation products exclusively in high yields (**3e-3h**). Generally, the selective alkylation of C3-unsubstituted indazoles at the N1 position is difficult. [8] Fortunately, when 4-vinylpyridine was used as the alkylation reagent, we found that only N1 alkylated products were isolated in high yields (Table 2). The mechanism of this reaction should be the classic Michael addition mechanism. [9] The reason why 4-vinylpyridine affords high regioselectivity products is uncertain.

To confirm the structures of N1 or N2 substituted indazoles, several NOESY experiments were carried out. As shown in Figure 3, the spectrum of compound **3d** displayed a cross-peak between H-7 and H-6, while compound **3d′** displayed the dipolar correlation between H-10 and H-6.

Table 1. Microwave-assisted alkylation of indazoles with 2-vinylpyridine[a]

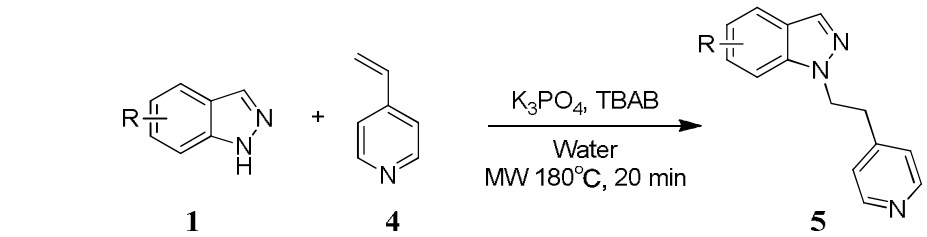


1 **2** **3** **3'**

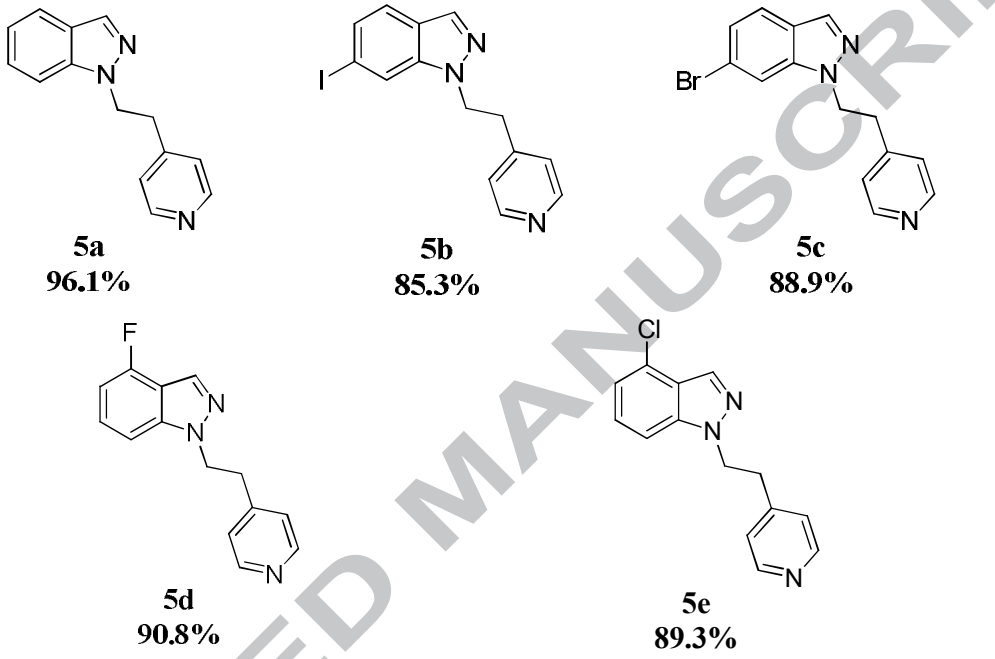


[a] Reaction conditions:**1** (0.5 mmol), **2** (1.5 mmol), K_3PO_4 (1 mmol), TBAB (20 mol%), H_2O (2 mL), 180℃ under microwave irradiation for 20 min. TBAB = Tetrabutyl ammonium bromide. Isolated Yields

Table 2. Selective alkylation of indazole with 4-vinylpyridie[a]



1 **4** **5**



5a 96.1%

5b 85.3%

5c 88.9%

5d 90.8%

5e 89.3%

[a] Reaction conditions:**1** (0.5 mmol), **4** (1.5 mmol), K_3PO_4 (1 mmol), TBAB (20 mol%), H_2O (2 mL), 180℃ under microwave irradiation for 20 min. TBAB = Tetrabutyl ammonium bromide. Isolated yields.

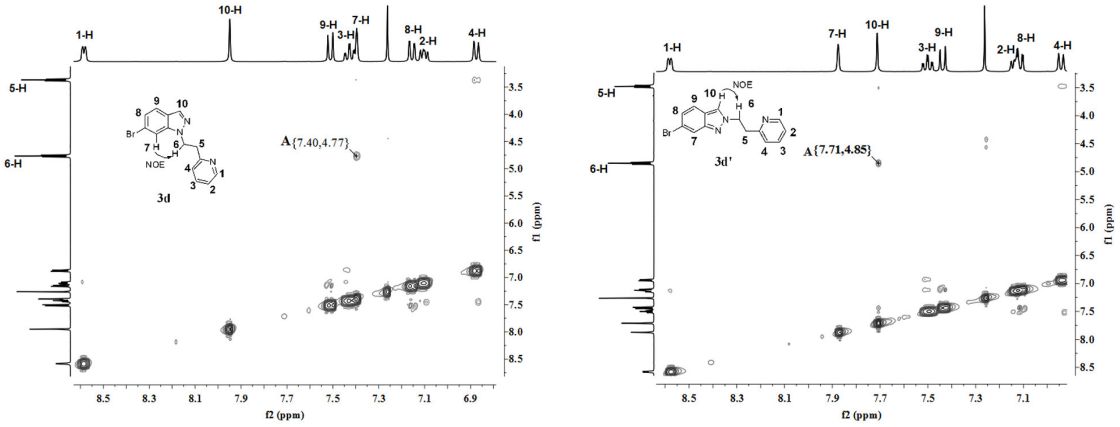


Figure 3. H-H NOESY of **3d** and **3d′**

Conclusion

We have reported a transition-metal-free hydroamination reaction to obtain N pyridinyl alkyl indazoles. It is possible to isolate the pure N1 substituted and N2 substituted indazole products respectively. These compounds may have potential application in the discovery of new biologically active compounds. This reaction meets some requirements of green chemistry [10] with atom economy, the utility of water as reaction medium, the absence of toxic catalysts and additives, while microwave is applied as clean and efficient energy to shorten reaction time.

Acknowledgements

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Supplementary data:

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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7. *General procedure for alkylation of indazoles:* To a 10 mL glass microwave vial equipped with a magnetic stir bar was charged with a mixture of 1H-indazoles (0.5 mmol, 1 equiv), 2-vinylpyridine or 4-vinylpyridine (1.5 mmol, 3 equiv), Potassium phosphate (1mmol, 2equiv) and TBAB (20 mol%, 0.1 mmol) in water (2 mL). The mixture was heated to 180 ℃ as fast as possible in microwave oven, and stirred for 20 min at 180 ℃. The resulting solution was cooled to temperature and extracted with EtOAc twice. The combined organic layer was washed with saturated salt water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by gradient elution (PE/AcOEt for starting materials, PE/AcOEt/TEA=100/50/3 for the pure N1 substituted products and PE/AcOEt/TEA=20/20/1 for N2 substituted products).
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10. The 12 principles of green chemistry are as follows: prevention, atom economy, less hazardous chemical synthesis, designing safer chemicals, safer solvents, design for energy efficiency, use of renewable feedstocks, reduce derivatives, catalysis, design for degradation, real-time analysis for pollution prevention, inherently safer chemistry for accident prevention.

Graphical Abstract

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