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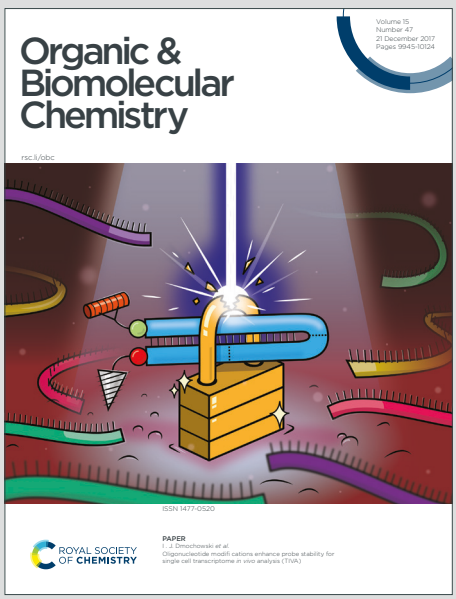

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Acid-Catalyzed Three-Component Addition of Carbonyl Compounds with 1,2,3-Triazoles and Indoles

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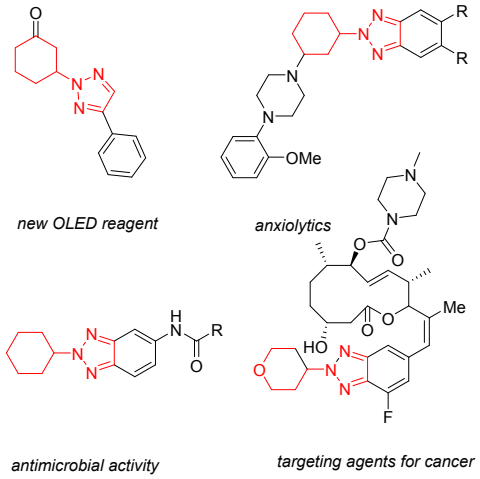
A facile and efficient acid-catalyzed three-component reaction of indoles, 1-tosyl-1,2,3-triazoles and carbonyl compounds has been developed. The use of TsOH with a small amount of water significantly promoted the reaction yield. This method provided a general and one-pot approach to structurally diverse *C3*-alkylated indole derivatives. The alkylation position exclusively occured at the N^2 position of triazoles. Various functional groups were tolerated under the optimized simple reaction conditions.

Organic compounds containing multiple nitrogen atoms have always been a hot spot pursued by organic chemists due to their outstanding application value in many fields such as material science,[1] biological research,[2] and medicinal chemistry.[3] Among them, compounds containing indole skeleton have undergone continuous research for decades.[4] On the other hand, N^2-alkylated triazoles exhibit a broad spectrum of biological activities,[5] such as anti-bacterial, anti-microbial, anti-tumor, antidepressant and so on. The combination of these two important nitrogen-containing molecules can provide more opportunities for further study of their bioactivities.

The rise of "click reactions" has made triazole compounds an important source for C-N bond construction. 1-Tosyl-4-aryl/alkyl-1,2,3-triazole was unstable because of the electron-withdrawing nature of the tosyl group. The triazole ring tends to open and form *N*-tosyl-α-diazo imine because of the weak N^1-N^2 bond.[6] Due to the unstable property of the triazole, most of the research mainly focused on the triazole ring opening transformation to provide a nitrogen atom, thus the atomic economy of the reaction is reduced. In recent years, considerable researches have been focused on keeping the triazole moiety in the product. Various reactions were realized involved the triazole functional group such as alkylation,[7] alkenyla tion,[8] and heterocyclization reactions at the N^1 position.[9] However, selectivity control is always a problematic issue along with this kind of reaction. Furthermore, the N^2 substituted products, especially N^2-heterocyclic products, have remarkable application value in both



Scheme 1 Examples of biologically active N^2-alkylated tria zoles.

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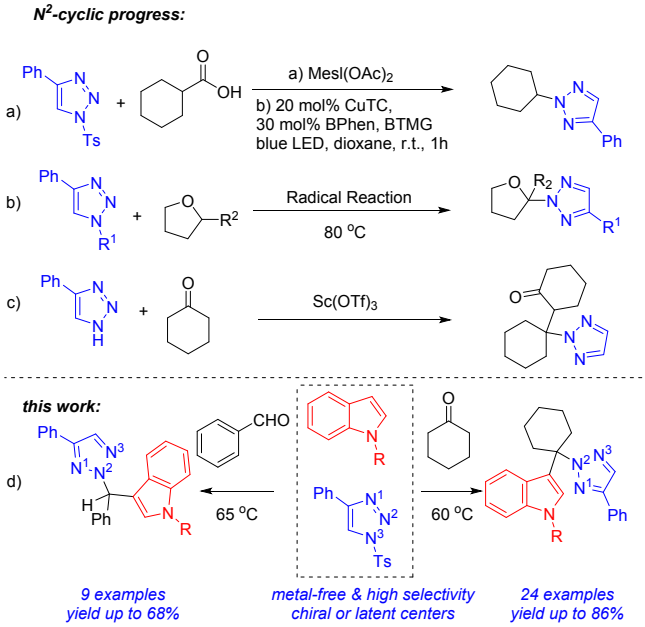
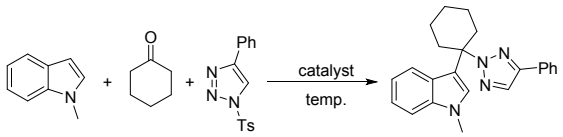


Scheme 2 Synthesis of N^2-alkylated triazoles

biomedicine and organic optoelectronic materials (Scheme 1). However, efficient related synthesis methods are rare and mostly of them are limited to two-component reactions. In 2018, David MacMillan and co-workers used cyclohexanecarboxylic acids and triazole compounds as the substrates to generate N^2 cyclohexyl products via decarboxylative coupling process under copper and photo-catalysed conditions (Scheme 2).[10] Subsequently, Xia and co-workers designed a free radical reaction pathway to realize the coupling of triazole and furan to obtain N^2 heterocyclic products, yet the products are limited to the five-membered ring.[11] Later in 2020, Tang first used cyclohexanone as the raw material for C-N bond synthesis to selectively give N^2 cyclohexyl products using treated triazoles.[12] These methods were proved to be versatile for the functionalization of 1,2,3-triazoles while maintaining the triazole motif in the product structure, general, efficient and multi-component synthetic methods for the preparation triazole derivatives are still desirable.[13] In recent years, our group have developed various methods for bis-functionalization of cyclohexanone's carbonyl group and its ortho carbon under transition-metal free conditions.[14] We envision that it might be possible to use cyclohexanone to connect the two important indole and triazole motifs in one-pot. Surprisingly, our preliminary studies revealed that the two functional molecules were not attached to the carbonyl group and its ortho site as expected, but to both carbonyl carbon (Scheme 2d). This special result encourages us to further optimized the reaction conditions systematically. Herein, we reported a simple and efficient method for the synthesis of indole derivatives via assembling of carbonyl compounds with indoles and triazoles under metal-free conditions.

To obtain optimization conditions for the three-component reaction, 1-methyl-1*H*-indole (**1a**), cyclohexanone (**2a**), and 4-phenyl-1-tosyl-1*H*-1,2,3-triazole (**3a**) were initially used as the standard substrates (Table 1). The desired product **4a** could be obtained in low yield even without any additional additives when the reaction was carried out at 60 °C in 1,2-dichlorobenzene (entry 1). To further improve the reaction yield, various acids were investigated for this kind of transformation based on our previous research. The addition of 10 mol% of HCl (6 mol/L) slightly improved the reaction yield to 28% (entry 2), indicating that acidic environment was effective. To our delight, the desired product **4a** was obtained in 54% yield when catalytic amounts of TfOH was added, showing that organic acid may more effective (entry 5). TsOH with a crystal water exhibited a gratifying yield of 60% (entry 6). To find the exact role of water in this kind of reaction, 2.5 eq. of H_2O was added to the reaction mixture and we were glad to find that the reaction yield could be further improved to 72% (entry 14). The reaction solvent is important to the reaction and lower yield was observed when the reaction was carried out under toluene (entry 7). Other non-polar solvents such as cyclohexane were not as effective as polar solvents. Better yields were achieved when the reaction was carried out in polar solvents such as DCM, PhCl and *o*-dichlorobenzene (entries 8-10). However, no product was found in DMSO (entry 9). Good yield was still achieved when the reaction was carried at 50 °C or 70 °C (entries 11-12). Extending the reaction time to 28 hours can slightly increase the yield to 76% (entry 14). However, further extension of the reaction time will decrease the yield (see SI). Meanwhile, substrate ratio investigation indicated that a slight excess of cyclohexanone substrate was essential and the yield was decreased when the amount of **2a** reduced (entry 15).

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4a

Entry	Acid	Solvent	Temp.(°C)	Yield (%)[b]
1	—	*o*-DCB	60	17
2	HCl	*o*-DCB	60	33
3	H_3PO_4	*o*-DCB	60	28
4	AcOH	*o*-DCB	60	28
5	TfOH	*o*-DCB	60	54
6	TsOH • H_2O	*o*-DCB	60	60
7	TsOH • H_2O	Toluene	60	45
8	TsOH • H_2O	DCM	60	55
9	TsOH • H_2O	DMSO	60	0
10	TsOH • H_2O	PhCl	60	58
11	TsOH • H_2O	*o*-DCB	50	48
12	TsOH • H_2O	*o*-DCB	70	57
13[c]	TsOH • H_2O	*o*-DCB	60	72
14[c,d]	TsOH • H_2O	*o*-DCB	60	76
15[c,e]	TsOH • H_2O	*o*-DCB	60	53

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), acid (10 mol%), solvent (1 ml), 60 °C for 24 h under air. [b] Isolated yield. [c] H_2O (2.5 eq.). [d] For 28 h. [e] **2a** (0.2 mmol).

With the optimized conditions in hand, we first investigated the substrate scope of indole derivatives and the results were summarized in Table 2. Various indoles bearing electron-withdrawing and electron-donating substituents at the indole benzene ring could be used to generate the expected products in moderate to excellent yields. Functional groups such as methyl,

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methoxy and OBn were all well tolerated under the given reaction conditions (**4b-4d**). Notably, reactive halogen substituents such as fluoro, chloro and bromo could even slightly improve the reaction yields (**4e-4g**), allowing to access more complex molecules through next coupling of these halogen-substituted products. The substituent position in the benzene ring of indole substrates did not significantly affect the reaction yield and good yields could be obtained when the substituents were located at C^6 (**4h-4j**). Moderate yield still could be achieved when a methyl group presented at the C^7 position(**4k**). In addition, better yield was obtained when *N*-methyl indole was replaced by *N*-ethyl indole (**4l**).

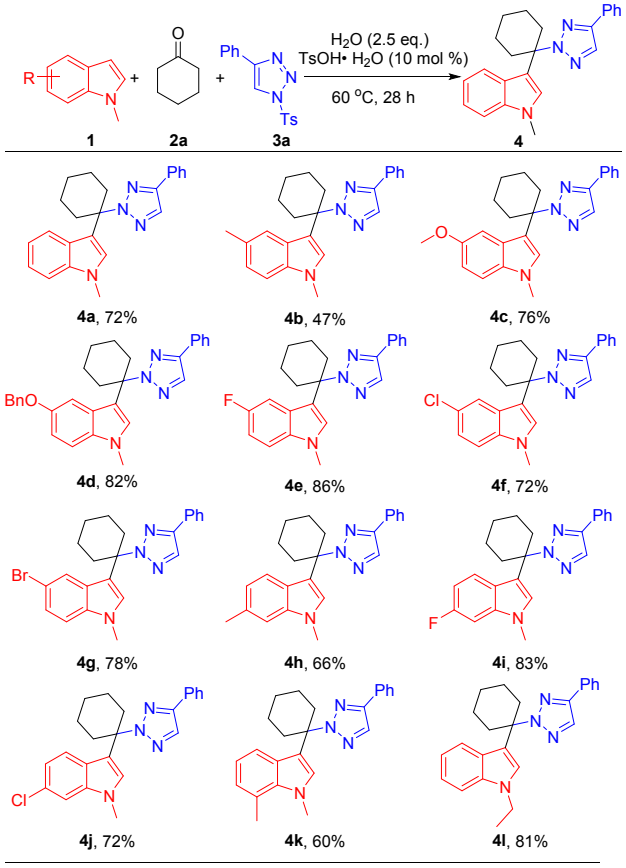
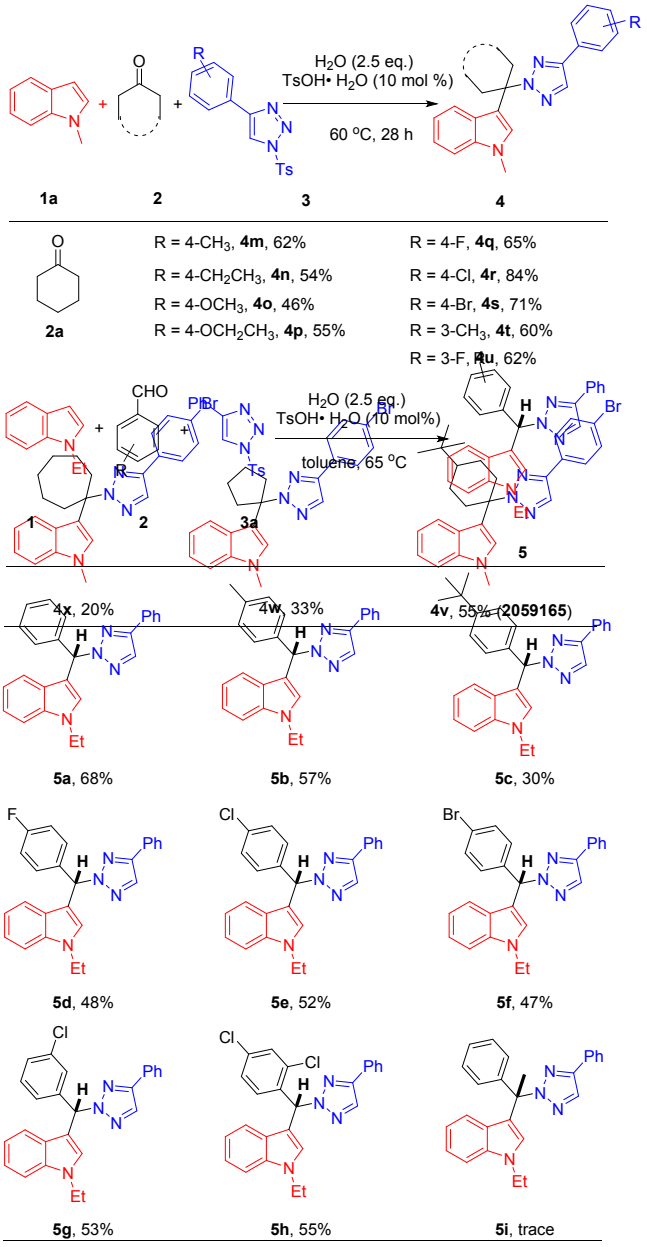


Table 2 Substrate scope with *N*-methyl indole[a]

[a] Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), acid (10 mol%), H_2O (2.5 eq.), solvent (1 ml), 60 °C for 28 h under air.

Table 3 Substrate scope with respect to 4-phenyl-1-tosyl-1*H*-1,2,3-triazole derivatives[a]



[a] Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), **3** (0.2 mmol), acid (10 mol%), H_2O (2.5 eq.), solvent (1 ml), 60 °C for 28 h under air.

Table 4 Substrate scope with respect to benzaldehyde[a]

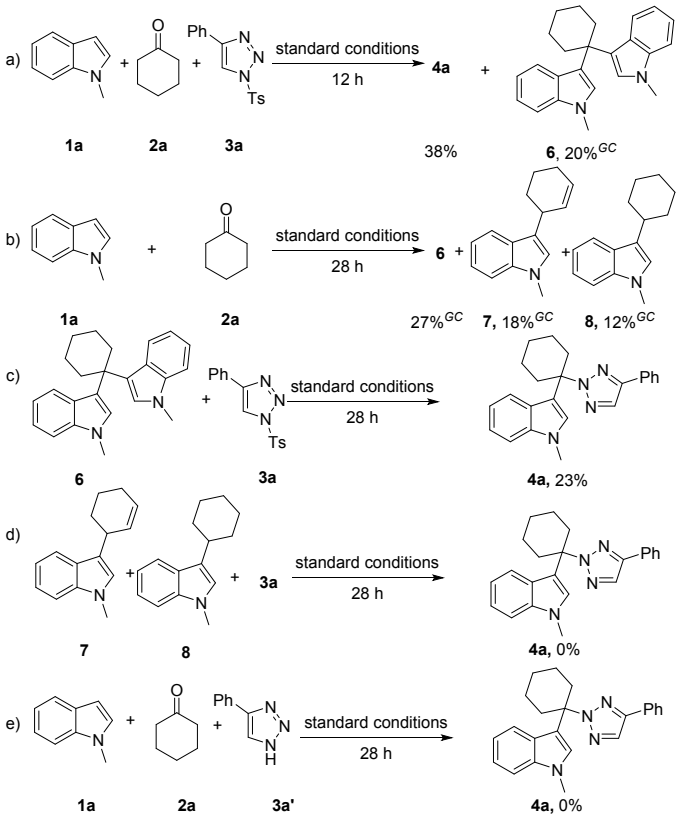
[a] **1** (0.2 mmol), **2** (0.4 mmol), **3a** (0.2 mmol), catalyst (10 mol%), H_2O (2.5 eq.) and solvent (1 ml) at 65 °C for 28 h under air.

Subsequently, we shift the focus of the reaction on 4-phenyl-1-tosyl-1*H*-1,2,3-triazole derivates with cyclic ketones and *N*-methyl indole to explore whether the difference of the substituents will affect the chemical selectivity of the product (Table 3). When the substituents are electron donating groups such as methyl, ethyl, methoxy and ethoxy, the reaction could be smoothly proceeded to give the desired products in moderate yields (**4m-4p**). When the electron-withdrawing substituent on

the benzene ring such as fluoro, chloro and bromo were existed, the reaction results were even better, delivering the N^2-cyclohexyl products in good yields (**4q**-**4s**). The electronic effect of the meta substituent did not show significant effect on the reaction yield and selectivity (**4t**-**4u**). The structure of **4v** was further confirmed by single-crystal X-ray diffraction. Other cyclic ketones, such as cyclo pentanone and cycloheptanone were investigated under similar reac tion conditions and lower reaction yields were achieved (**4w** and **4x**).

Furthermore, other carbonyl compounds such as aromatic aldehydes were also able to apply for this kind addition after some fine- tuning of the conditions (Table 4). Aromatic aldehydes with various substituents could smoothly react with indole derivatives and 4- phenyl-1-tosyl-1*H*-1,2,3-triazole (**3a**) to form a chemically selective product **5** with a chiral center.

When benzaldehyde was used, the corresponding product **5a** was obtained in 68% yield. Electron-donating alkyl substituents such as methyl and tert-butyl both gave lower yields of N^2-selective products (**5b** and **5c**). Electron-withdrawing substituents such as fluoro, chloro and bromo were all able to be tolerated under the given reaction conditions, leading to moderate yields of the desired products (**5d**-**5f**). However, benzaldehydes with strong electron-withdrawing groups such as nitro and trifluoromethyl, only gave trace amount of the desired product and a large amount of raw materials were left. The position of the substituent did not affect the result of the reaction obviously (**5g** and **5h**). When aromatic ketones such as acetophenone were treated under the optimized reaction conditions, we found that the reaction activity of acetophenone was

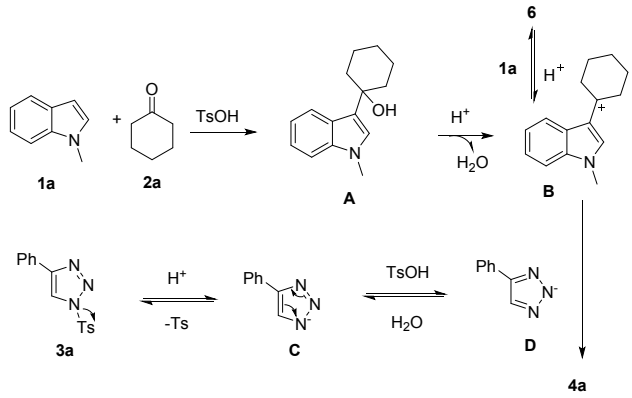


very low and only a small amount of reaction product was detected (**5i**).

Scheme 3 Control Experiments

In order to explore the mechanism of the reaction, we carried out a series of control experiments (Scheme 3). When the reaction time was shortened to 12 hours, we found that in addition to the target product **4a** (38% isolated yield), there was a condensation by-product **6** (20% yield detected by GC) which was generated by addition reaction of two molecules of indole with cyclohexanone (Scheme 3a). In the absence **3a**, **6**-**8** were observed by GC-MS analysis and based on the basis of our previous studies (Scheme 3b).[14b] Equivalent compound **6** reacted with **3a** to give the desired product **4a** in low yield (Scheme 3c). However, treatment of possible intermediates **7** and **8** could not give the product **4a** under the standard reaction conditions (Scheme 3d). Interestingly, when 4-phenyl-1*H*-1,2,3-triazole (**3a'**) was used instead of **3a** for this reaction, no desired product **4a** could be obtained (Scheme 3e). This reaction indicated that the Ts group was not removed in the first step.

Based on the control experimental results and previous related literature,[14] we proposed a possible reaction mechanism for this kind of transformation (Scheme 4). Initially, addition of indole with cyclohexanone under acidic conditions form the corresponding intermediate **B**. On the same time, 4-phenyl-1-tosyl-1*H*-1,2,3-triazole (**3a)** proceeds a classic autocatalysis process in the presence of *p*-toluene sulfonic acid providing a nitrogen anion **D** after a series of electron transfer.[15] The combination of **B** and **D** generates the desired product **4a**. Meanwhile, carbocation **B** can also undergo nucleophilic addition with another molecule of indole to form **6**.



Scheme 4 Possible reaction mechanism.

In summary, we developed a gentle and efficient method for the addition of carbonyl compounds with indoles and 1,2,3-triazoles in the absence of metal-catalyst. The reaction selectivity could be well controlled under this simple and mild reaction conditions. Two important functional molecules were selectively added to the same carbonyl carbon site. When aromatic aldehydes were used for this kind of reaction, a chiral center was generated which provided more opportunities for further functionalization.

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