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Iron-Catalyzed C–H Sulfonylmethylation of Indoles in Water–PEG400

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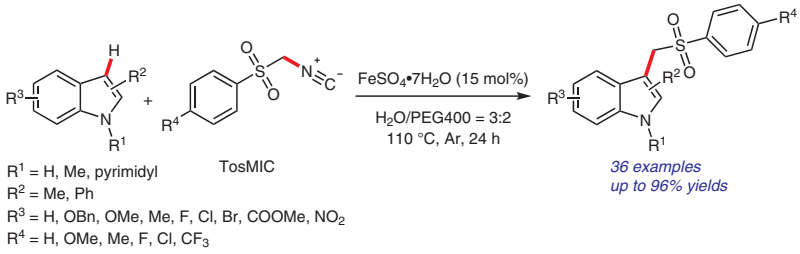

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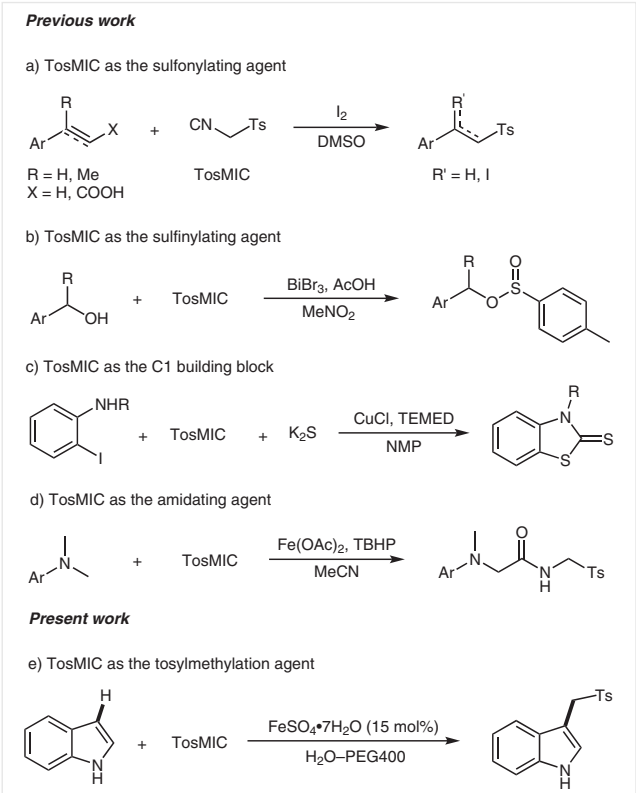
Abstract An iron-catalyzed C–H sulfonylmethylation of indoles in water–PEG400 has been developed using *p*-toluenesulfonylmethyl isocyanide. This protocol enables direct regioselective construction of Csp^2–Csp^3 bond at the C3 position of indoles with a broad range of substrate compatibility in moderate to good yields, which is cost-effective and environmentally friendly.

Key words indoles, sulfonylmethylation, *p*-toluenesulfonylmethyl isocyanide

As a representative nitrogen-containing heterocycle, indole has served as a privileged scaffold in various natural products, drugs, and functional molecules.[1] Over the past decades, considerable attention has been received in the synthesis of indole skeleton[2] and regioselective functionalization[3] at the C2 and C3 position due to inherent reactivity of the pyrrole core. Up to now, significant progress has been made for arylation,[4] alkenylation,[5] alkynylation,[6] amination,[7] acylation,[8] sulfuration,[9] and alkylation[10] of indoles. On the other hand, sulfonyl methylated indoles[11] are common pharmacophores with wide applications in pharmaceuticals.[12] Meanwhile, the arylsulfonyl functionality is a versatile synthetic intermediate, which can be utilized to fulfill multiple transformations.[13] However, the direct sulfonylmethylation of indoles are still less explored.[14]

p-Toluenesulfonylmethyl isocyanide (TosMIC) is a unique synthon in organic synthesis to access various heterocycles via 1,3-dipolar cycloadditions.[15] Meanwhile, TosMIC has also found to be a sulfonylating agent to access benzoheteroles, α-sulfonated carbonyl compounds, and vinyl, allyl, and β-iodo vinylsulfones (Scheme 1, a).[16] Also, sulfination of alcohols with TosMIC has been reported (Scheme 1, b).[17] In addition, TosMIC can act as a C1 building block to construct benzothiazolethiones (Scheme 1, c).[18] Moreover, TosMIC was utilized to realize C–H amidation with propargylic alcohols[19a] and anilines[19b] (Scheme 1, d). Considering the versatility of TosMIC in organic chemistry, it is advisable to utilize TosMIC to realize other transformations.



Scheme 1 Different transformations of TosMIC

Our group has been interested in developing an efficient methodology to achieve C–H functionalization of (hetero)aromatics.[20] Very recently, we have also reported C–H arylation, alkylation of indoles, and C–H allylation of indolines with arylboronic acids,[21a] maleimides,[21b] and vinyl-

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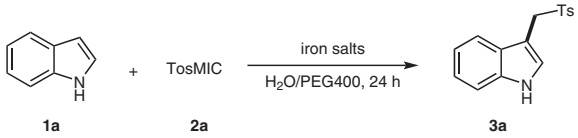
cyclopropanes.[21c] As a continuation of our previous work, we herein describe the regioselective C3-sulfonylmethylation of indoles using TosMIC as the reaction partner (Scheme 1, e). This work presents a supplement and improvement of a previous report,[20c] wherein unprotected 1*H*-indole gave a poor yield. Specially, the current protocol utilizes iron salt as the catalyst, and a mixture of water and PEG400 was utilized as the nontoxic media, which is more cost-effective and environmentally benign.

To begin with, 1-*H* indole (**1a**) and TosMIC (**2a**) were utilized as the model substrates to optimize the reaction conditions (Table 1). To our delight, the desired C3-tosylmethylated indole **3a** was obtained in 58% yield in the presence of $FeCl_3$ (30 mol%) in mixture solvent of H_2O and PEG400 (v/v = 7:3) at 130 °C for 24 h. Subsequently, various iron salts were screened, which indicated that $FeSO_4{\cdot}7H_2O$ was the best choice to afford product **3a** in 73% yield (Table 1, entries 1–6). Next, the amount of $FeSO_4{\cdot}7H_2O$ was adjusted, and the yield (68%) was not significantly decreased using 15 mol% $FeSO_4{\cdot}7H_2O$ (Table 1, entry 8). A survey of mixed solvent ratios revealed that H_2O/PEG400 (v/v = 3:2) was beneficial to give **3a** in 81% yield (Table 1, entry 10). To further improve the reaction efficiency, the reaction temperature was modulated. Product **3a** could be isolated in 86% yield at 110 °C, while conducting the reaction at 100 °C led to a decreased yield (Table 1, entries 11 and 12). Moreover, it was found that either shortening or extending the reaction time would provide **3a** in a decreased yield (Table 1, entries 13 and 14). When the reaction was carried out under air or oxygen atmosphere, **3a** was generated in 68% and 35% yields, respectively (Table 1, entries 15 and 16). Moreover, other nonaqueous solvents, namely toluene, DMF, and MeOH, with different polarity and protic nature, were evaluated (Table 1, entries 17–19). No product was detected when toluene and DMF were utilized, while product **3a** was obtained in 55% yield in MeOH, suggesting an S_N1-type mechanism might be involved. Finally, other metal-based Lewis acids were also investigated, which all gave inferior results (see Table S1 in the Supporting Information).

With the optimized conditions in hand, the substrate scope of indoles was investigated (Scheme 2).[22] In general, a wide range of functional groups, including fluoro (**3b**, **3k**, **3o**), chloro (**3c**), ester (**3d**, **3l**), methoxy (**3e**, **3j**, **3q**), and

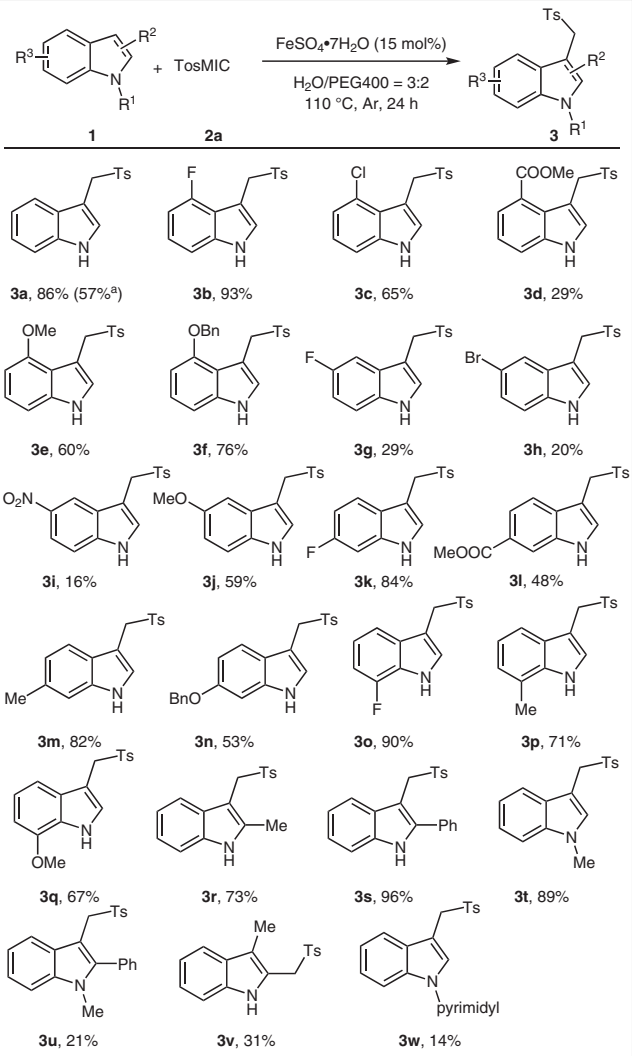
Table 1 Optimization of Reaction Conditions for C3-Sulfonylmethylindoles[a]



1a **2a** **3a**

Entry	Catalyst (mol%)	Solvent (ratio)	Atmosphere	Temp (°C)	Time (h)	Yield (%)[b]
1	$FeCl_3$ (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	58
2	$FeSO_4{\cdot}7H_2O$ (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	73
3	FeC_2O_4 (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	55
4	$FeCl_2{\cdot}4H_2O$ (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	66
5	$Fe(acac)_3$ (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	16
6	$Fe(NO_3)_3{\cdot}9H_2O$ (30)	H_2O/PEG_{400} (7:3)	Ar	130	24	46
7	$FeSO_4{\cdot}7H_2O$ (20)	H_2O/PEG_{400} (7:3)	Ar	130	24	67
8	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (7:3)	Ar	130	24	68
9	$FeSO_4{\cdot}7H_2O$ (10)	H_2O/PEG_{400} (7:3)	Ar	130	24	60
10	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	Ar	130	24	81
11	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	Ar	110	24	86
12	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	Ar	100	24	80
13	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	Ar	110	12	67
14	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	Ar	110	36	75
15	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	air	110	24	68
16	$FeSO_4{\cdot}7H_2O$ (15)	H_2O/PEG_{400} (3:2)	O_2	110	24	35
17	$FeSO_4{\cdot}7H_2O$ (15)	toluene	Ar	110	24	–
18	$FeSO_4{\cdot}7H_2O$ (15)	DMF	Ar	110	24	–
19	$FeSO_4{\cdot}7H_2O$ (15)	MeOH	Ar	110	24	55

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), iron salt, solvent (2 mL). Isolated yields.



Scheme 2 Substrate scope of indoles. *Reagents and conditions*: **1** (0.1 mmol), **2a** (0.3 mmol), $FeSO_4{\cdot}7H_2O$ (15 mol%), H_2O/PEG_{400} = 3:2 (2 mL), under Ar, 110 °C, 24 h. [a] Scale-up: **1a** (10 mmol, 1.17 g), **2a** (30 mmol, 5.86 g).

benzyloxy (**3f**, **3n**) at various positions of the benzene core were well tolerated under the current protocol. For C5-substituted indoles, products **3g–i** were isolated in low yields. Next, C2-methyl- and phenyl-substituted indoles were also tested to give the corresponding products **3r** and **3s** in 73% and 96% yields, respectively. Apart from 1*H*-indoles, *N*-methylindole was also proved to be the ideal substrate to provide product **3t** and **3u** in 89% and 21% yields. Interestingly, when the C3 position of indole was occupied, the C2-tosylmethylated product **3v** was obtained in 31% yield. Finally, we also attempted to achieve chelation-assisted functionalization, which unfortunately gave C3-tosylmethylated product **3w** in 14% yield. Luckily, the absolute configuration of **3w** was confirmed by X-ray diffraction (Figure S1 in the Supporting Information). To evaluate the synthetic utility of this protocol, a gram-scale reaction was conducted using 1*H*-indole (**1a**) and TosMIC (**2a**) as the substrate, which delivered product **3a** in 57% yield.

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Encouraged by the above results, the scope of the sulfonylmethylation reaction was further extended to different TosMIC derivatives (Scheme 3). It was found that *para*-substituted TosMICs bearing both electron-withdrawing (F, Cl, and CF_3) and electron-donating (OMe) groups could react with indoles smoothly to deliver products **4a–m** in 37–84% yields.

To explore the reaction mechanism, a set of control experiments were carried out (Scheme 4). Without $FeSO_4{\cdot}7H_2O$, the C3-sulfonylmethylated product could not be detected, indicating the necessity of iron salt. Next, the radical scavenger reactions were performed under the optimized conditions. It was found that C3-sulfonylmethylated product **3a** could still be isolated in 34% and 77% yield, respectively, when excess TEMPO (3 equiv) and BHT (3 equiv) was introduced into the catalytic system. Considering the preliminary results obtained in Table 1 (entries 17–19), it was postulated that an S_N1-type C–C bond formation would be the key step.

Iron metals could coordinate with isocyanides to form mixed ligand complexes, which underwent facile C–N cleavage to form carbon cation species due to the strong binding ability between iron and cyanide.[23] On the basis of the control experiments and previous reports,[20c,23] a plausible mechanism was proposed (Scheme 5). The catalytic cycle initiates with the activation of TosMIC (**2a**) with Fe^{2+} to produce the electrophilic species **A**, which was converted into intermediate **B**. Next, nucleophilic substitution of intermediate **B** by 1*H*-indole (**1a**) results in the formation of intermediate **C**. Finally, the desired product **3a** was achieved via H^+ elimination.

In summary, we herein disclosed iron-catalyzed sulfonylmethylation of indoles with TosMIC in a nontoxic medium. A wide range of indoles and substituted TosMIC proceeded smoothly to afford products in moderate to good yield. This methodology is environmentally benign, cost-effective, and additive-free.

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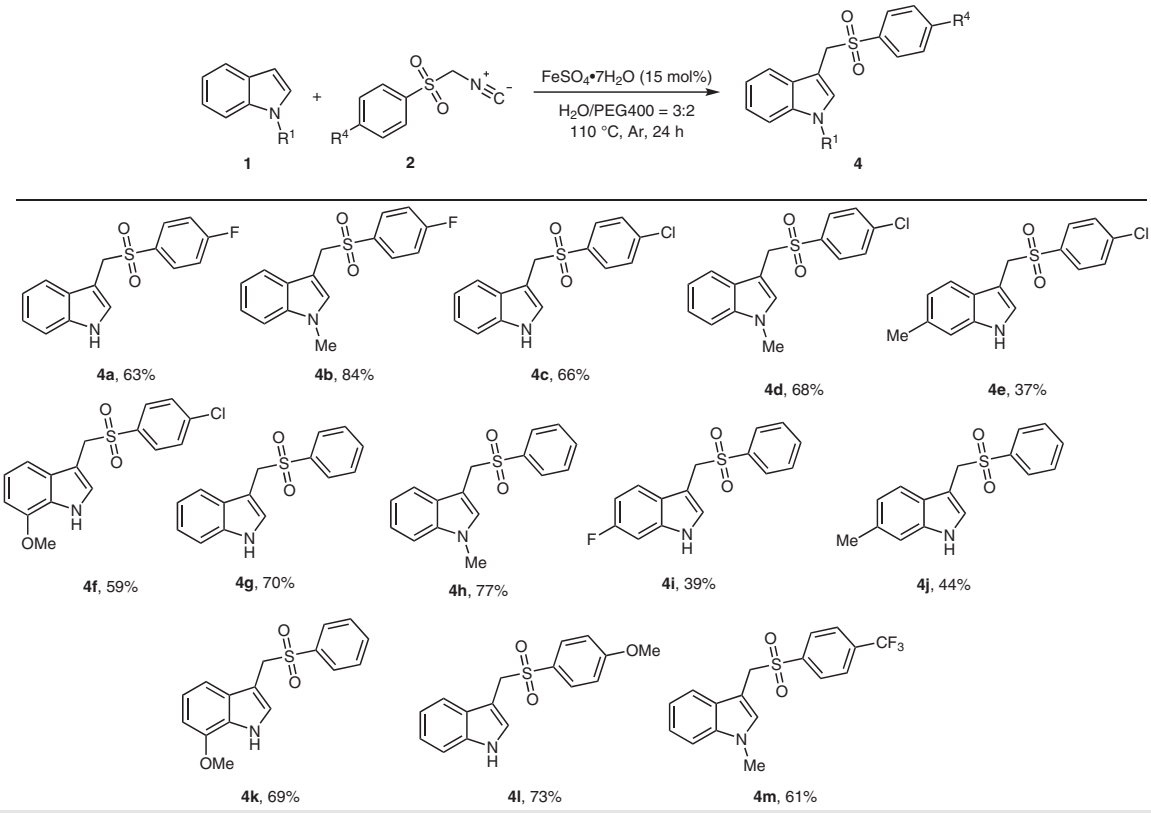
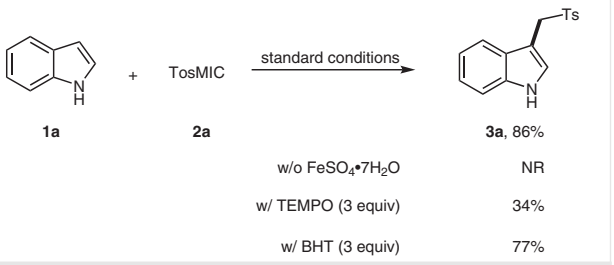


Scheme 3 Substrate scope of the substituted TosMIC. *Reagents and conditions*: **1** (0.1 mmol), **2** (0.3 mmol), $FeSO_4 \cdot 7H_2O$ (15 mol%), H_2O/PEG_{400} = 3:2 (2 mL), under Ar, 110 °C, 24 h.



Scheme 4 Control experiments

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690675.

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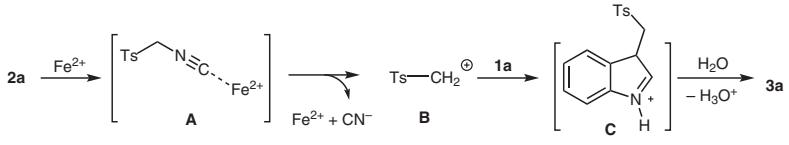

Scheme 5 Proposed reaction mechanism

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(22) **General Procedure for Preparation of Products 3 and 4**

To a 15 mL two-necked Schlenk tube fitted with glass stopper were added indoles **1** (0.1 mmol), TosMIC derivatives **2** (0.3 mmol), and $FeSO_4{\cdot}7H_2O$ (0.015 mmol, 4.2 mg) in a mixed solvent of H_2O and PEG400 (v/v = 3:2, 2 mL) under an Ar atmosphere using the standard Schlenk techniques. The Schlenk tube was capped and heated at 110 °C for 24 h. The reaction mixture was then cooled to room temperature and concentrated directly. After removal of solvent, the residue was purified by preparative thin-layer chromatography (petroleum ether/EtOAc = 1:1) to give the desired product **3** and **4**.

4-Fluoro-3-(tosylmethyl)-1*H*-indole (3b)

Brown solid (28.3 mg, 93%), mp 162–163 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 7.59 (d, *J* = 7.4 Hz, 2 H), 7.18–7.16 (m, 3 H), 7.07–7.06 (m, 1 H), 7.01–6.98 (m, 1 H), 6.60 (t, *J* = 9.2 Hz, 1 H), 4.64 (s, 2 H), 2.36 (s, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ = 156.7 (d, *J* = 244.9 Hz), 144.5, 138.3 (d, *J* = 10.8 Hz), 135.5, 129.2, 128.5, 126.2, 122.8 (d, *J* = 8.0 Hz), 116.0 (d, *J* = 18.8 Hz), 107.6 (d, *J* = 3.6 Hz), 105.2 (d, *J* = 19.2 Hz), 100.6, 54.8, 21.6. ^{19}F NMR (565 MHz, $CDCl_3$): δ = –124.6. HRMS (positive ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{14}FNNaO_2S^+$: 326.0621; found: 326.0621.

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