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Intermolecular Dearomatization Reaction of Pyrroles Promoted by Silica Gel

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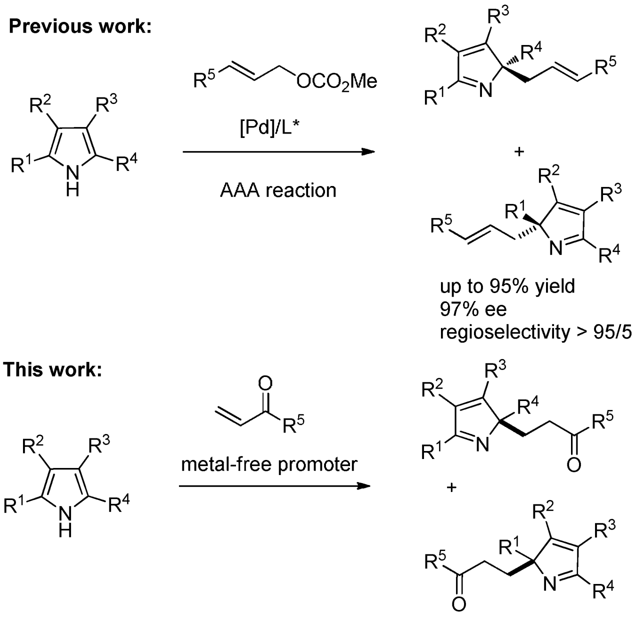
Abstract: An efficient synthesis of polysubstituted 2*H*-pyrrole derivatives *via* a silica gel-promoted intermolecular dearomative Michael addition of pyrroles with α,β-unsaturated ketones has been developed. This transformation features environmentally benign promoter, high efficiency, wide substrate scope and mild reaction conditions.

Keywords: alkylation; dearomatization; Michael addition; pyrroles; silica gel

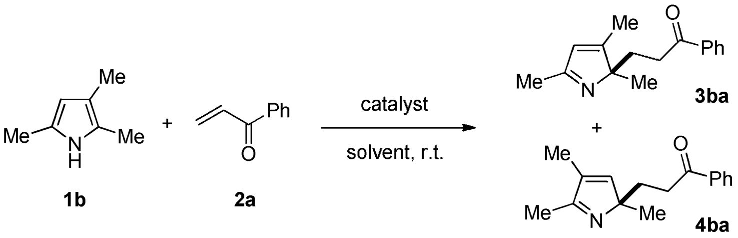
Pyrrole moieties are widely found in numerous biologically active natural products and pharmaceutical agents. Moreover, they are also useful intermediates in organic synthesis. Therefore extensive efforts have been directed at the synthesis and transformation of pyrroles and their derivatives.[1] In the meantime, the dearomatization of aromatic compounds has achieved great progress.[2] Among the substrates, pyrrole and its derivatives can undergo the dearomatization reaction to deliver complex molecules. For instance, in 2007, an elegant [4+3] cyclization of pyrrole with 2-(siloxy)vinyldiazoacetate catalyzed by adamantyl glycine-derived $Rh_2(S\text{-}PTAD)_4$ was reported by Davies and co-workers, offering a promising access to optically active tropanes.[3] Later, the groups of Kuwano and Zhou and Fan reported asymmetric hydrogenative dearomatizations of pyrrole derivatives by chiral Ru and Pd catalysts, respectively.[4,5] Recently, we described a Pd-catalyzed intermolecular allylic dearomatization reaction of pyrroles, providing various chiral polysubstituted 2*H*-pyrroles in excellent enantioselectivity and regioselectivity (Scheme 1, *top*).[6e] To the best of our knowledge, however, there are limited examples of metal-free dearomatization reactions of pyrroles. With our continuing interest in the dearomatization reaction,[6] we envisioned that a dearomatization reaction of pyrroles might be achieved under metal-free conditions by the choice of proper electrophiles and catalyst or promoter (Scheme 1, *bottom*). Herein, we report an intermolecular dearomative Michael addition of pyrroles with α,β-unsaturated ketones promoted by silica gel for the synthesis of polysubstituted 2*H*-pyrroles.

At the beginning, we chose 2,3,4-trimethylpyrrole (**1b**) and 1-phenyl-2-propen-1-one (**2a**) as the model substrates to test the dearomatization reaction. In the presence of $TsOH \cdot H_2O$ (10 mol%), the Friedel–Crafts type[7] dearomatization reaction proceeded smoothly in DCM to afford 2*H*-pyrrole **3ba** along with **4ba** in less than 40% yield after 10 h (Table 1, entry 1). To



Scheme 1. Intermolecular dearomatization reactions of pyrroles.

Table 1. Investigation of the reaction conditions.[a]

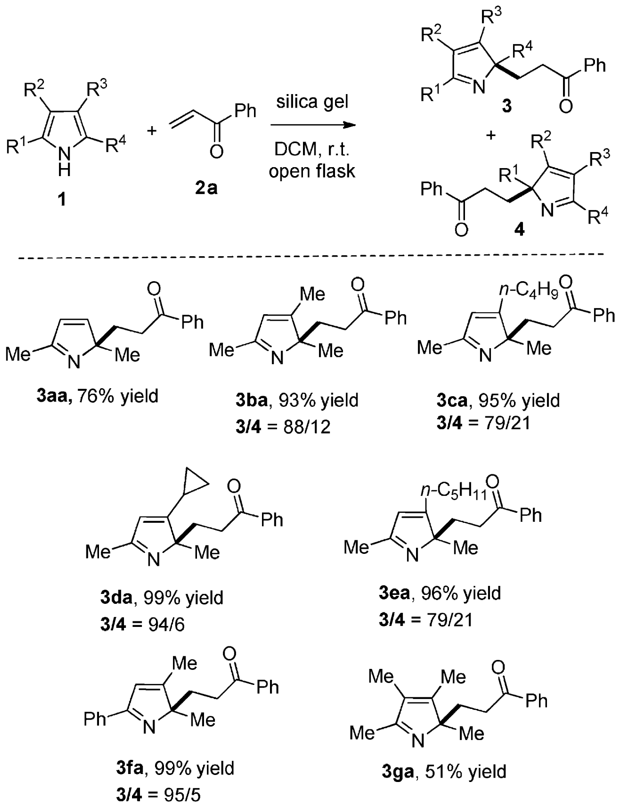


Entry	Catalyst	Solvent	Time	Yield[b] [%]	**3/4**[b]
1	TsOH·H$_2$O (10 mol%)	DCM	10 h	<40	–
2	TsOH·H$_2$O (10 mol%)	DCM	16 h	>95	83/17
3	silica gel I (50 mg)[c]	DCM	10 min	>95	88/12
4	silica gel II (50 mg)[d]	DCM	10 min	>95	88/12
5	slica gel III (50 mg)[e]	DCM	10 min	>95	86/14
6	silica gel II (50 mg)[f]	DCM	20 min	>95	88/12
7	silica gel I (30 mg)	DCM	10 min	89	87/13
8	silica gel I (10 mg)	DCM	10 min	74	87/13
9	none	DCM	60 min	trace	–
10	silica gel I (50 mg)	toluene	10 min	90	85/15
11	silica gel I (50 mg)	Et$_2$O	10 min	85	83/17
12	silica gel I (50 mg)	THF	10 min	46	81/19
13	silica gel I (50 mg)	CH$_3$CN	10 min	84	86/14
14	silica gel I (50 mg)	hexane	10 min	>95	85/15

[a] *Reaction conditions:* 0.3 mmol of **1b**, 0.45 mmol of **2a** in 2.0 mL of solvent at room temperature.
[b] Determined by ^{1}H NMR.
[c] Supplied by Silicycle, Quebec city, Canada (230–400 mesh).
[d] Supplied by Jiangyou silicone Co., Ltd., Yantai, Shangdong province (100–200 mesh).
[e] Supplied by Jiangyou silicone Co., Ltd., Yantai, Shangdong province (300–400 mesh).
[f] Pretreated with Et$_3$N.

our delight, the yield of product **3ba** and **4ba** can be further enhanced to 95% after 16 h in a ratio of 85:15 (Table 1, entry 2). Interestingly, we found that the silica gel alone could promote this reaction and display high efficiency. In the presence of silica gel I (50 mg), this intermolecular reaction (0.3 mmol scale) proceeded to completion in 10 min (Table 1, entry 3). As silica gel is inexpensive, readily available and nontoxic, such a reaction is an environmentally benign and highly desirable process.[8] Encouraged by this preliminary result, we investigated various silica gels and other reaction parameters. The results are summarized in Table 1. We found that silica gels from different suppliers with varying sizes all efficiently promoted this reaction, resulting in nearly the same yield and regioselectivity (Table 1, entries 3–5). A silica gel pretreated with Et$_3$N gave identical results although a slightly longer reaction time was required (Table 1, entry 6). Notably, only a trace amount of the desired product was detected in the absence of silica gel, which ruled out the background reaction (Table 1, entry 9). Next, we further examined the solvent effects. A variety of solvents such as toluene, Et$_2$O, CH$_3$CN and hexane could be employed in the reaction to afford the desired product in good yields and regioselectivity except for THF, in which only 46% yield was obtained (Table 1, entries 10–14). DCM was found to be the optimal solvent (>95% yield, Table 1, entry 3). Thus the optimized conditions were obtained as follows: 50 mg silica gel (0.3 mmol substrate scale), 1.5 equivalents of **2** in DCM at room temperature.

Under the optimized reaction conditions, the substrate scope was then examined. Firstly, various pyrrole derivatives **1** were tested. The results are summarized in Scheme 2. When symmetrical 2,5-dimethylpyrrole (**1a**) was used, the dearomatization process proceeded well, giving the desired product **3aa** in 76% yield (Scheme 2, **3aa**). When the methyl group at the C-3 position was replaced by *n*-butyl (**1c**), cyclopropyl (**1d**) or *n*-pentyl (**1e**), the dearomatization reaction also occurred smoothly, affording the dearomatization products in excellent yields and good regioselectivity (Scheme 2, 95–99% yields). In addition, 2,3-dimethyl-5-phenylpyrrole (**1f**) was also a suitable substrate in this reaction, dearomative product was obtained in 99% yield with 95/5 regioselectivity in favour of **3fa** (Scheme 2). Notably, the reaction

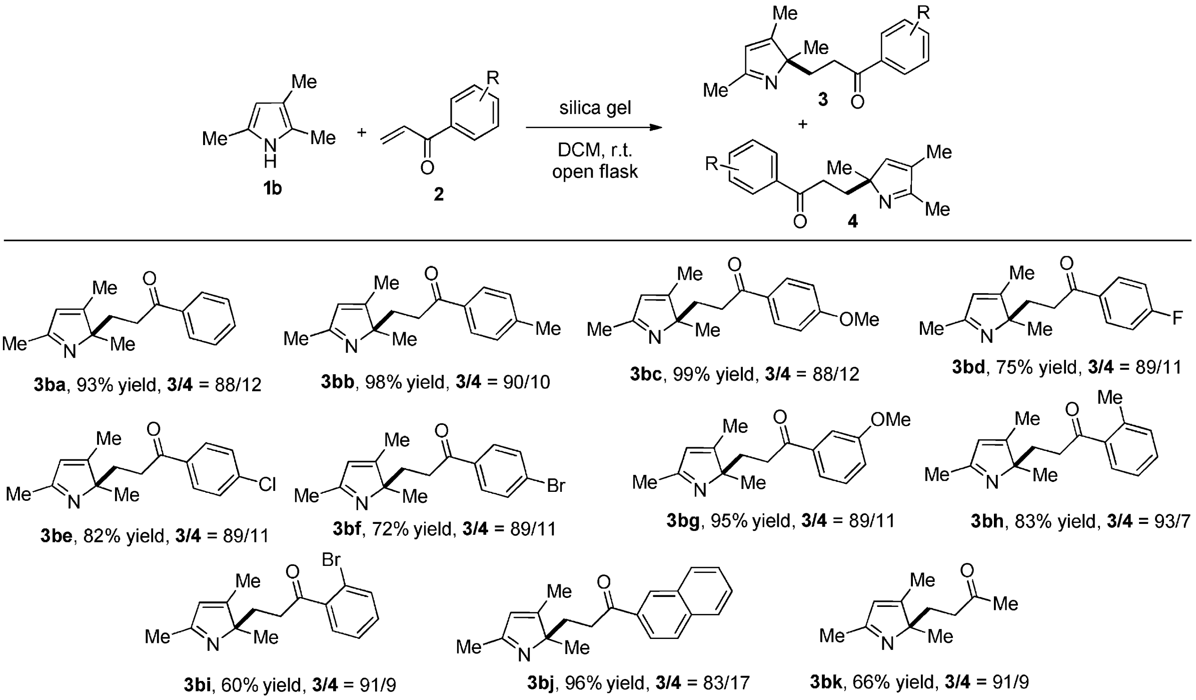


Scheme 2. Reaction substrate scope: pyrroles. *Reaction conditions:* silica gel (50 mg), **1** (0.3 mmol) and **2a** (0.45 mmol) in DCM (2.0 mL) at room temperature for 20 min. Isolated yields of **3** and **4** were reported. The ratio of **3**/**4** was determined by ^{1}H NMR analysis of the crude reaction mixture.

occurs preferentially at that position of the pyrroles where the HOMO of the molecule distributes most significantly.[6f] Moreover, when substrate **1g** bearing 2,3,4,5-tetramethyl groups was employed, the desired product was obtained in 51% yield (Scheme 2, **3ga**). The structures of the major regioisomers (**3ba**, **3da** and **3fa**) were further confirmed unambiguously by 2D-NOESY analysis.[9]

In addition, the reactions of various enones **2** with 2,3,5-trimethylpyrrole were also investigated. As seen from the results in Scheme 3, enones **2** bearing either an electron-donating group (4-Me, 4-MeO, 3-MeO, 2-Me) or electron-withdrawing group (4-F, 4-Cl, 4-Br, 2-Br) on the phenyl ring were well tolerated, and the corresponding products were obtained in good to excellent yields and regioselectivity (Scheme 3, **3bb**–**3bi**, 60–99% yields). It is worth noting that the reaction conditions are also compatible for both a naphthylenone (**2j**) and an aliphatic enone (**2k**) (Scheme 3, 96% and 66% yields, respectively). Unfortunately, the reaction of 2,5-dimethylpyrrole (**1a**) with an α,β-disubstituted enone such as chalcone only gave a trace amount of product under the optimized reaction conditions.

In summary, we have developed a highly efficient synthesis of polysubstituted 2*H*-pyrrole derivatives *via* silica gel-promoted intermolecular dearomative addition of pyrroles and α,β-unsaturated enones. With commercially available silica gel, the dearomatized products were obtained with up to 99% yield under mild reaction conditions. Further studies on the enan-



Scheme 3. Reaction substrate scope: enones. *Reaction conditions:* silica gel (50 mg), **1b** (0.3 mmol) and **2** (0.45 mmol) in DCM (2.0 mL) at room temperature for 20 min. Isolated yields of **3** and **4** are reported. The ratio of **3**/**4** was determined by ^{1}H NMR analysis of the crude reaction mixture.

tioselective control and new metal-free dearomatization reactions are currently underway in our laboratory.

Experimental Section

General Procedure for the Intermolecular Dearomatization Reaction of Pyrroles Promoted by Silica Gel

A flame-dried Schlenk tube was cooled to room temperature. To a solution of substituted pyrrole **1** (0.30 mmol, 1.0 equiv.) in dichloromethane (2 mL) in this tube was added enone **2** (0.45 mmol, 1.5 equiv.), then silica gel (50 mg, $0.17\ \mathrm{g\,mmol^{-1}}$) was added in one portion. The reaction mixture was stirred at room temperature. After the reaction was complete, the mixture was purified by silica gel column chromatography (PE/acetone = 3/1–1/1) to afford the desired product.

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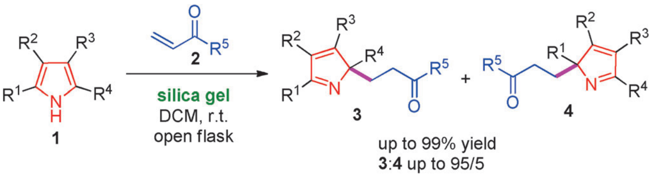
[9] For details, see the Supporting Information.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up to 99% yield
3:4 up to 95/5