Heterocycles

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Highly Regioselective Migration of the Sulfonyl Group: Easy Access to Functionalized Pyrroles**

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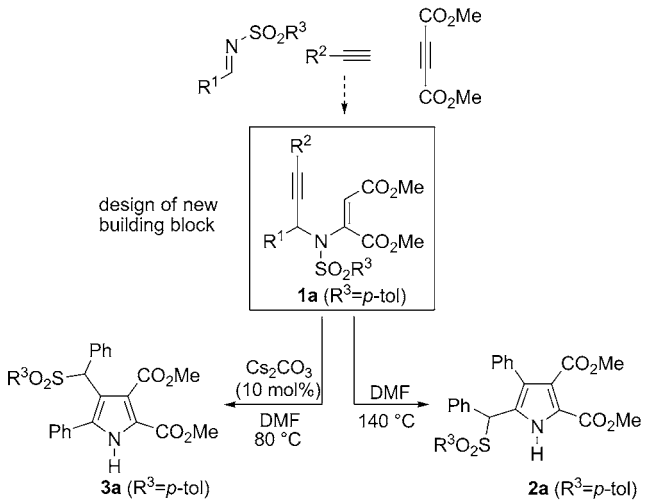
The development of new reactions for the synthesis of diverse molecular frameworks is a challenging task in the field of modern organic chemistry. Chemistry of pyrroles continues to attract the interest of chemists, and new synthetic methods of these compounds occupy an important area of synthetic organic chemistry.[1–3] In search of new routes for the synthesis of pyrroles through the design of new building blocks such as N-sulfonyl-protected azaenyne derivatives **1** (Scheme 1), we



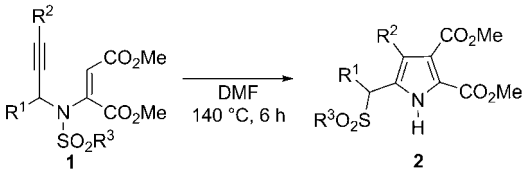
Scheme 1. The new routes for synthesis of functionalized pyrroles. DMF = *N*,*N*-dimethylformamide.

unexpectedly observed a surprising regioselective sulfonyl group migration for **1a** ($R^1 = R^2 = Ph$, $R^3 = p$-Tol), which provides easy access to more valuable functionalized pyrroles in which the N atom is unprotected and the sulfonyl group shifts to being a substituent on the pyrrole. The migration of the sulfonyl group to different positions can be controlled and highly selective formation of both α- and β-(arylsulfonyl)-methyl pyrroles with yields of up to 98 and 97%, respectively, allows the straightforward introduction of sulfonyl groups[4,5] to the pyrrole. To the best of our knowledge, there have been no alternative routes for the synthesis of α- and β-(arylsulfonyl)methyl pyrroles having these substitution patterns so far, thus this is the first example of sulfonyl group migration in pyrrole synthesis. Herein, we describe the preliminary results.

Initially, we chose the N-tosyl-protected 3-aza-1,5-enyne derivative **1a** as model substrate for the synthesis of N-heterocycles. Pyrrole **2a** was formed in 97% yield (Scheme 1) when **1a** was heated to 140°C in DMF for 6 hours. The structure of **2a** was unambiguously confirmed by X-ray crystal diffraction.[6] Interestingly, N–S bond cleavage and C–S bond formation occurred spontaneously in this transformation, and the migration of the sulfonyl group to the α branch of the product **2a** was observed (Scheme 1).

Next, we explored the scope of this interesting transformation. The results are shown in Table 1. Electron-neutral, electron-deficient, and electron-rich aromatic groups (R^1) on **1** were all well tolerated, and the desired products (**2a**–**2g**) were obtained with moderate to good yields (67–98%, entries 1–7). 3-Aza-1,5-enyne **1n** bearing a fused ring was also suitable for this process, albeit with a lower yield (58%, entry 14). Groups (R^2) directly connected to the alkyne moiety containing both aryl (93–98%, entries 8–9) and alkyl (35%, entry 13) substituents were also tolerated. Importantly, the use of the *Z*-isomer **1l** afforded the same product as **1a** (entry 12 verus entry 1), which indicated that the geometry of

Table 1: Scope of synthesis of α-(arylsulfonyl)methyl pyrroles.



Entry	1	R^1	R^2	R^3	Yield [%][a]
1	**1a**	C_6H_5	C_6H_5	4-MeC_6H_4	97 (**2a**)
2	**1b**	3-MeC_6H_4	C_6H_5	4-MeC_6H_4	67 (**2b**)
3	**1c**	4-MeC_6H_4	C_6H_5	4-MeC_6H_4	89 (**2c**)
4	**1d**	4-FC_6H_4	C_6H_5	4-MeC_6H_4	97 (**2d**)
5	**1e**	2-$CF_3C_6H_4$	C_6H_5	4-MeC_6H_4	82 (**2e**)
6	**1f**	2-ClC_6H_4	C_6H_5	4-MeC_6H_4	98 (**2f**)
7	**1g**	2-BrC_6H_4	C_6H_5	4-MeC_6H_4	96 (**2g**)
8	**1h**	C_6H_5	4-MeC_6H_4	4-MeC_6H_4	93 (**2h**)
9	**1i**	C_6H_5	4-FC_6H_4	4-MeC_6H_4	96 (**2i**)
10	**1j**	4-FC_6H_4	C_6H_5	C_6H_5	94 (**2j**)
11	**1k**	2-BrC_6H_4	C_6H_5	C_6H_5	95 (**2k**)
12	**1l**[b]	C_6H_5	C_6H_5	4-MeC_6H_4	98 (**2l**)
13	**1m**	C_6H_5	*n*Bu	4-MeC_6H_4	35 (**2m**)
14	**1n**	1-naphthyl	C_6H_5	4-MeC_6H_4	58 (**2n**)

[a] Yields of isolated products. [b] The configuration of the double bond is *Z*.

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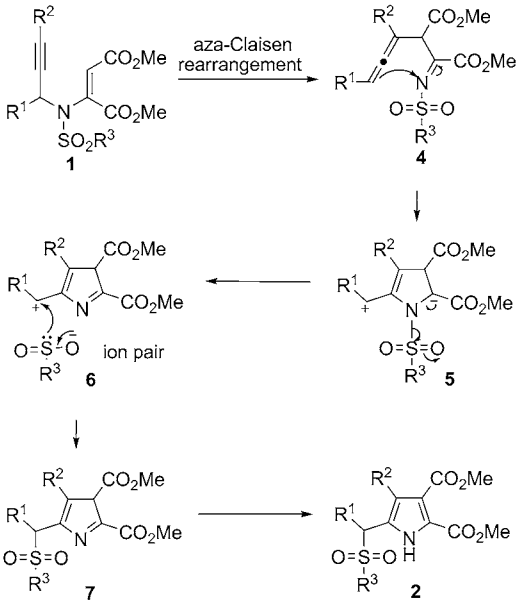
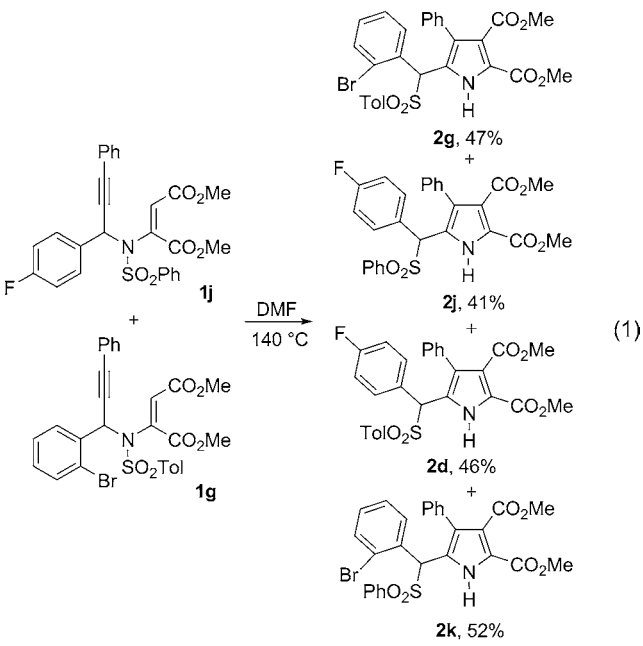
the C=C bond had almost no influence on the yield. It is noted that the electronic properties of the sulfonyl group (R^3) had a slight impact on the yield when the *p*-tolyl group was replaced by a phenyl group (entry 10 versus entry 4, and entry 11 versus entry 7).

The proposed mechanism, which is based on our observations, is depicted in Scheme 2. Reactant **1** was first transformed into intermediate **4** through an aza-Claisen rearrangement. Similar aza-Claisen rearrangements were also proposed in pyrrole synthesis,[7,8] and the synthesis of pyrroles from allene derivatives has also been reported.[9] The nitrogen atom of **4** was electron deficient because of the electron-withdrawing double bond and the sulfonyl group connected to this atom. Therefore, one of the double bonds of the allene moiety of **4** attacked the nitrogen atom and afforded intermediate **5**. The N–S bond was cleaved to yield the ion-pair **6**. To verify the formation of the ion-pair **6**, a crossover experiment was performed. Equimolar amounts of **1j** and **1g** were reacted and yielded the corresponding products **2j** and **2g** in 41 and 47% yields, respectively, and the crossover products **2d** and **2k** in 46 and 52% yields, respectively [Eq. (1)]. The recombination of the cation and the anion of **6** resulted in the formation of the C–S bond of **7**, which then isomerized into pyrrole **2**.



Scheme 2. Proposed mechanism for the synthesis of α-(arylsulfonyl)-methyl pyrroles through sulfonyl group migration.

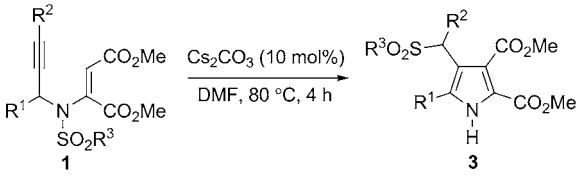
In the presence of a base, the propargyl moiety of **1** may transform into the allene moiety of **9** (see Scheme 3 for structure), and the newly formed compound may also subsequently form heterocycles under the proper reaction conditions. With this hypothesis in mind, 10 mol% of Cs_2CO_3 was added to a solution of **1a** in DMF. A different type of pyrrole (**3a**; see Scheme 1 for structure) was obtained. The structure of **3a** was also confirmed by an X-ray crystal diffraction study.[10] A similar sulfonyl group migration occurred, with the sulfonyl group selectively migrating to the β substituted pyrrole **3a**.



Given the information above, we selected Cs_2CO_3 as the base, DMF as the solvent, 80 °C as the temperature and 4 hours as the reaction time to test the scope of the reaction.[11] In general, moderate to good yields (84–97%) were obtained for this process regardless of the electronic properties of the phenyl rings of R^1, R^2, and R^3, as shown in Table 2. The *Z* isomer of **1a** afforded the same product (entry 12) as the *E* isomer, although the yield obtained from the *Z* isomer is lower than that obtained with the *E* isomer.

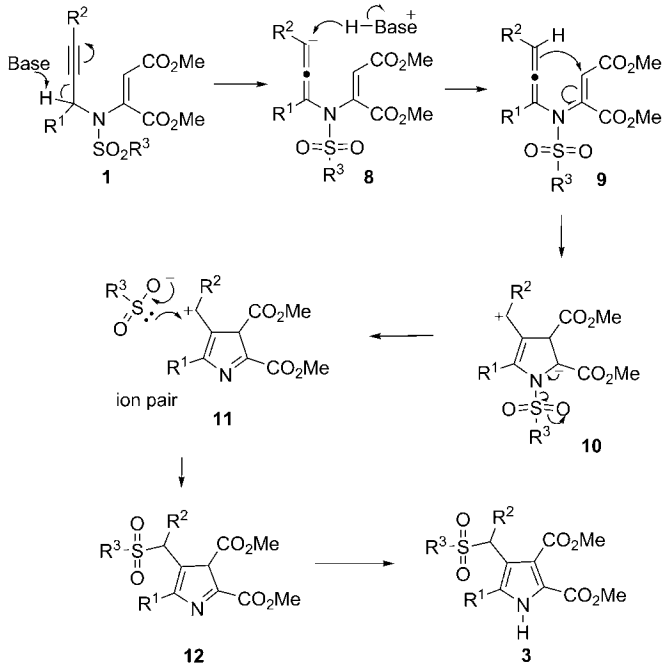
To account for these observations, another proposed mechanism is depicted in Scheme 3. In the presence of base,

Table 2: Scope of the synthesis of β-(arylsulfonyl)methyl pyrroles.



Entry	1	R^1	R^2	R^3	Yield [%][a]
1	**1a**	C_6H_5	C_6H_5	4-MeC_6H_4	97 (**3a**)
2	**1b**	3-MeC_6H_4	C_6H_5	4-MeC_6H_4	82 (**3b**)
3	**1c**	4-MeC_6H_4	C_6H_5	4-MeC_6H_4	95 (**3c**)
4	**1d**	4-FC_6H_4	C_6H_5	4-MeC_6H_4	94 (**3d**)
5	**1e**	2-$CF_3C_6H_4$	C_6H_5	4-MeC_6H_4	94 (**3e**)
6	**1f**	2-ClC_6H_4	C_6H_5	4-MeC_6H_4	93 (**3f**)
7	**1g**	2-BrC_6H_4	C_6H_5	4-MeC_6H_4	90 (**3g**)
8	**1h**	C_6H_5	4-MeC_6H_4	4-MeC_6H_4	92 (**3h**)
9	**1i**	C_6H_5	4-FC_6H_4	4-MeC_6H_4	94 (**3i**)
10	**1j**	4-FC_6H_4	C_6H_5	C_6H_5	95 (**3j**)
11	**1k**	2-BrC_6H_4	C_6H_5	C_6H_5	88 (**3k**)
12	**1l**[b]	C_6H_5	C_6H_5	4-MeC_6H_4	84 (**3l**)

[a] Yields of isolated products. [b] The configuration of the double bond is Z.

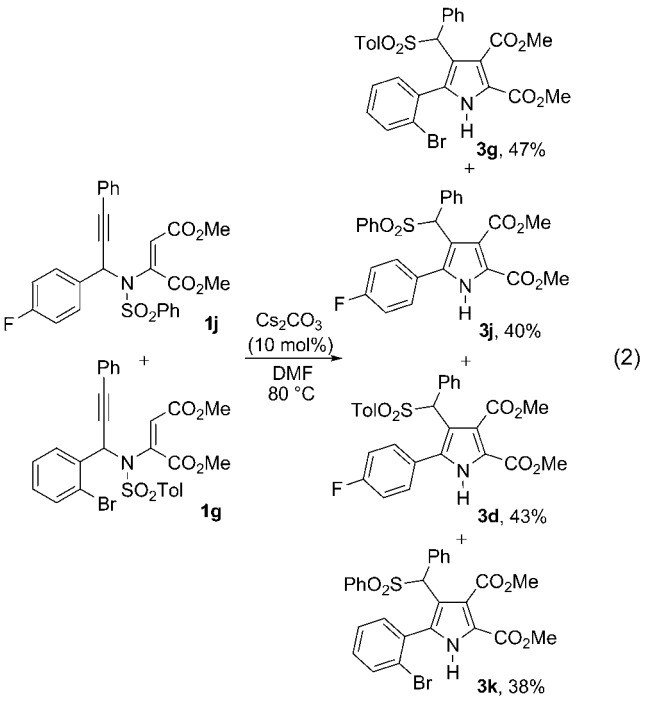


Scheme 3. Proposed mechanism for the synthesis of β-(arylsulfonyl)-methyl pyrroles.

the propargyl moiety of **1** is transformed into the allene intermediate **9**. One of the double bonds of the allene moiety of **9** attacked the carbon atom of the olefin moiety to afford the intermediate **10**. The N–S bond cleaved to form the ion-pair **11**, which recombined to form the C–S bond, and then **12** aromatized to deliver the pyrroles **3**.

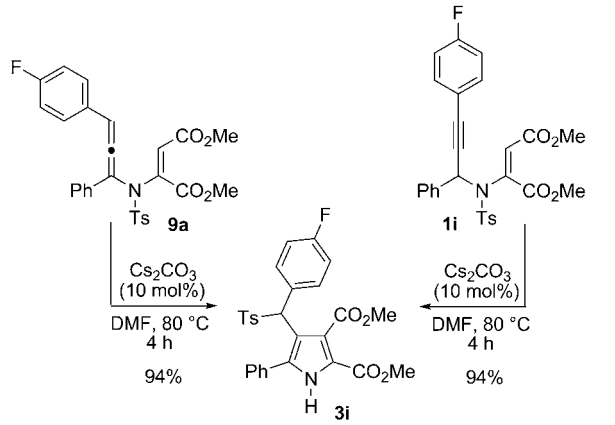
To support the proposed mechanism, many experiments were performed. To verify the existence of the allene intermediate **9**, we treated the isolated compound **9a** as the starting material and subjected it to the same reaction conditions as used for **1i** (Scheme 4). As expected, the same product, **3i**, was obtained in the same yield. This result confirmed that the reaction proceeded via the intermediate **9**.

To verify the nature of ion-pair **11** (Scheme 3), one crossover experiment was performed. A 1:1 mixture of **1j** and **1g** under basic conditions afforded the products **3j** and **3g** in 40 and 47% yields, respectively, and the crossover products **3d** and **3k** in 43 and 38% yields, respectively [Eq. (2)].

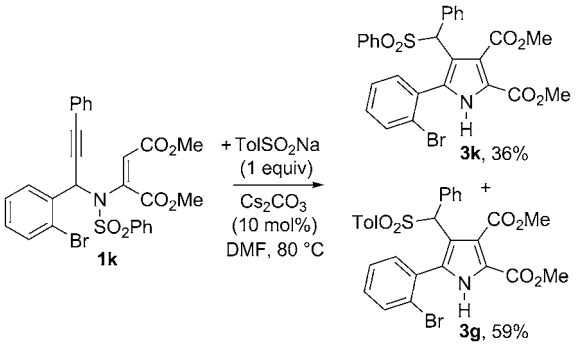


(2)

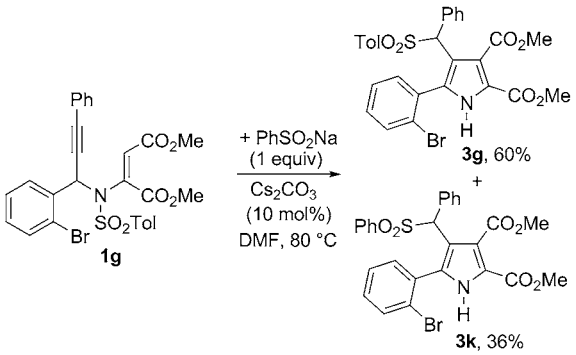
To additionally verify the formation of the ion-pair **11**, wherein the sulfinyl group was negatively charged and the relational group was positively charged, two competition experiments were performed [Eqs. (3) and (4)]. We intentionally added the sulfinyl anion, which is similar to the sulfonyl group of the reactant in the reaction system. Thus, if the reaction generated the sulfinyl anion, the external sulfinyl anion could compete with the sulfinyl anion generated in situ, and the competitive product would be obtained. One equivalent of sodium *p*-tolyl sulfinate was added to the reactant **1k**, which has a phenyl group, and afforded the corresponding product **3k** in 36% yield and the competitive product **3g** in 59% yield in the presence of base [Eq. (3)]. In addition, one equivalent of sodium phenyl sulfinate was added to the reactant **1g**, which has a *p*-tolyl group, thus yielding the corresponding product **3g** in 60% yield and the competitive product **3k** in 36% yield [Eq. (4)]. These two experiments verified the formation of the ion pair and confirmed that the original sulfinyl anions can be displaced by the external ions. Interestingly, the yield of the product **3g**, which contains the *p*-tolyl sulfonyl group, was greater than that of the product containing the phenylsolfonyl group (**3k**) regardless of whether the tosyl group was original or external. This result indicates that the *p*-tolyl sulfinyl group is more reactive than the phenylsolfinyl group in this process, and additionally illustrates that the sulfinyl moiety of the ion pair is negatively charged. The ability of the *p*-tolyl group to stabilize the anion is weaker than that of the phenyl group, therefore the *p*-tolyl sulfinyl anion is more likely to form the C–S bond.



Scheme 4. Synthesis of β-(arylsulfonyl)methyl pyrrole from allene derivative. Ts = 4-toluenesulfonyl.



(3)



(4)

The proposed mechanisms depicted in Schemes 2 and 3 indicate that the two pathways for the generation of the pyrroles **2** and **3** proceed via allene intermediates (**4** and **8**), and the generation of ion-pair intermediates (**6** and **11**).

In summary, highly regioselective sulfonyl group migrations in the synthesis of functionalized pyrroles have been successfully developed. The migration of the sulfonyl group to different positions can be controlled with high selectivity for the formation of both α- and β-(arylsulfonyl)methyl pyrroles. These reactions benefit from allowing the straightforward introduction of sulfonyl groups to the pyrroles. Crossover and competition experiments indicated that both reactions proceed through ion-pair intermediates. Additional investigations on the application of the developed strategy and detailed mechanistic studies are currently ongoing in our laboratory.

Experimental Section

Procedure for the synthesis of pyrrole **2**: Starting material **1** (0.2 mmol) in DMF (1 mL) was stirred at 140 °C for 6 h under argon atmosphere. The solvent was evaporated and the crude reaction mixture was directly purified by silica gel flash column chromatography (eluent: petroleum ether/ethyl acetate 5:1) to give the desired pyrroles **2**.

Procedure for the synthesis of pyrrole **3**: Starting material **1** (0.2 mmol) was placed in a dried Schlenk tube. Subsequenly, 1 mL distilled DMF and Cs_2CO_3 (6.5 mg, 0.02 mol) were added. The resulting mixture was stirred at 80 °C for 4 h under argon atmosphere. The solvent was evaporated and the crude reaction mixture was directly purified by silica gel flash column chromatography (eluent: petroleum ether/ethyl acetate 5:1) to give the desired pyrroles **3**.

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Keywords: heterocycles · reaction mechanisms · rearrangement · regioselectivity · synthetic methods

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[10] CCDC 837830 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[11] For details of the screening of reaction temperature and reaction time, please see the Supporting Information.

