Synthesis of *N*-Sulfonyl Arylaldimines Developed by Retesting an Old Process

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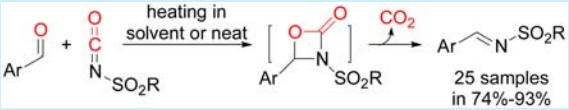
Supporting Information

ABSTRACT: By simply heating the mixture of an arylaldehyde and a sulfonylisocyanate in a solvent or in neat form under catalyst- and additive-free conditions, the desired *N*-sulfonylimine was produced with the release of carbon dioxide. The method is characterized by its unique clean efficiency, convenience, and scalability, but it was reported to fail half a century ago.



Electron-deficient imines are also called activated imines. The most prominent among them are *N*-sulfonylimines, which are not only the most activated imines but also those stable enough to be isolated and stored.[1] As excellent electrophiles, they have been used widely in various organic transformations. As shown in Figure 1,[2−6] *N*-sulfonyl arylaldimines (**1**) are the most popular ones due to their relatively easier preparation.

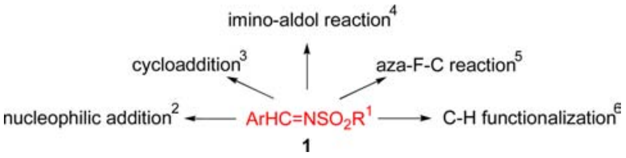
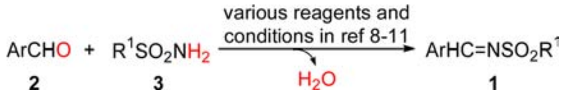


Figure 1. Various organic transformations of **1**.

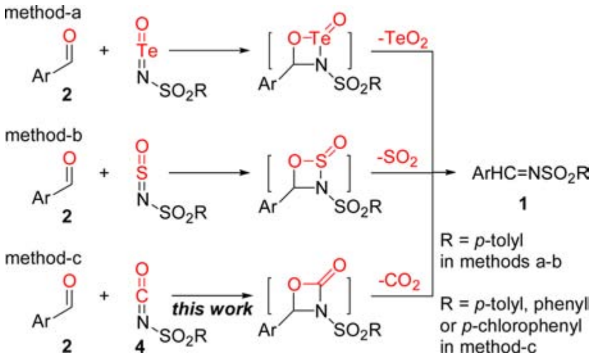
In the literature, a number of methods have been developed for the synthesis of **1**.[7−12] As shown in Scheme 1, the most commonly used methods[8−11] are those based on the dehydration between an arylaldehyde **2** and a sulfonamide **3**. The dehydration theoretically is an ideal pathway, but it is not an easy process to accomplish in practice due to the very low nucleophilicity of **3**. Usually, this problem can be improved by activating the carbonyl group of **2** with Lewis acids,[8] Brønsted acids,[9] or dehydrating reagents.[10] Recently, a novel organocatalytic method was reported,[11] in which the carbonyl group was activated by converting it into an iminium salt in the presence of pyrrolidine (10 mol %) and 4 Å molecular sieves (1 g/mmol). To date, the dehydration methods used often suffer from harsh conditions, tedious workups, and/or the production of large amounts of waste.

Scheme 1. Synthesis of 1 by Dehydration



During this investigation, our attention was drawn to two methods[12] that did not use the dehydration strategy. As shown in Scheme 2, the desired *N*-tosylimine **1** was synthesized efficiently by the reaction of an aldehyde with *N*-tellurinyl tosylamide (TsNTeO, method a)[12a] or with *N*-sulfinyl tosylamide (TsNSO, method b).[12b] Both methods initially carried out a thermal [2 + 2] cycloaddition to form a four-membered ring intermediate. Then, the intermediate underwent a horizontal [2 + 2] cycloreversion to give *N*-tosylimine **1** with the release of TeO_2 or SO_2. Since TeO_2 is an insoluble solid and SO_2 is a gas, the reaction equilibria were irreversibly shifted toward the products, but these methods have been rarely used for this purpose, presumably because of inaccessible reagents, high costs, and unpleasant smells.

Scheme 2. Methods Not Based on Dehydration



Herein, we report a new protocol, method c, for the efficient synthesis of *N*-sulfonylimine **1** that involves simple heating of arylaldehyde **2** with sulfonyl isocyanate **4** in a solvent or neat. Since many sulfonyl isocyanates **4** are commercially available substrates and CO_2 is the only byproduct of method c, the drawbacks associated with methods a and b are overcome completely.

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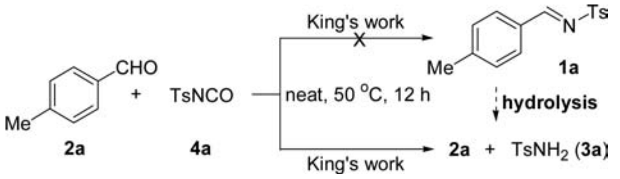
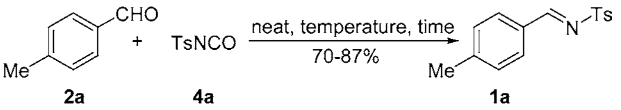
After understanding the pathway of methods a and b, we realized that their drawbacks might be overcome by using tosylisocyanates **4a** (TsNCO) as an alternative to TsNTeO or TsNSO. Disappointingly, the investigation showed that the reaction between 4-methylbenzaldehyde (**2a**) and **4a** had been reported by King[13] in 1960, but it failed to give the desired product *N*-tosylimine **1a**. As shown in Scheme 3, this failure was attributed to the poor hydrolytic stability of **1a** because only the hydrolytic products **2a** and tosylamide (**3a**) were isolated from the reaction. Since then, no such methodology study has been reported in the literature for over half a century.

Scheme 3. King's Original Work



However, we know now that **1a** is a quite stable compound that can be prepared by different methods and purified by recrystallization[8b,9e,f] or chromatography.[7a,c,e,10e] Therefore, we believed that King's experiment and conclusion were incorrect and needed to be retested. As shown in Table 1, when King's experiment was repeated by heating the neat mixture of **2a** and **4a** at 50 °C for 12 h (entry 1), two important phenomena were observed: (a) CO_2 was slowly released, and (b) the reaction mixture had solidified completely within 4 h. To our delight, the desired **1a** was obtained in 70% yield after workup. We hypothesized that a reduction in the yield of **1a** might be caused by a solidification of the reaction system, wherein further release of CO_2 was being blocked off and some unreacted substrates were trapped within. Thus, the reaction temperature was gradually elevated, and the yield of **1a** was increased by the increase of the reaction time and temperature (entries 2 and 3). Eventually, we found that when the reaction was conducted at 120 °C (entry 4), no solidification occurred (the melting point of **1a** is 111–112 °C), and **1a** was obtained in 90% yield within 3 h. These results were in full agreement with our hypothesis.

Table 1. Effect of Temperature on the Neat Reaction of 2a and 4a[a]

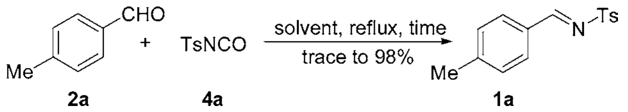


entry	temp (°C)	reaction time (solidification time)	yield of **1a**[b] (%)
1	50	12 h (~4 h)	70
2	70	12 h (~6 h)	76
3	90	12 h (~7 h)	84
4[c]	120	3 h (N/A)	90

[a] The neat mixture of **2a** (5 mmol) and **4a** (5 mmol) was heated at different temperature. [b] Isolated yield was obtained by recrystallization. [c] Substrate **2a** was exhausted.

Encouraged by these exciting results, we tested the same reaction in different solvents. As shown in Table 2, this reaction tolerated a wide range of solvents, and the best results were obtained in DCE at reflux, whereupon **1a** was obtained in 93% yield within 40 min. The higher efficiency might be due to the more facile release of CO_2 in solution.

Table 2. Effect of Solvent on the Reaction of 2a and 4a[a]

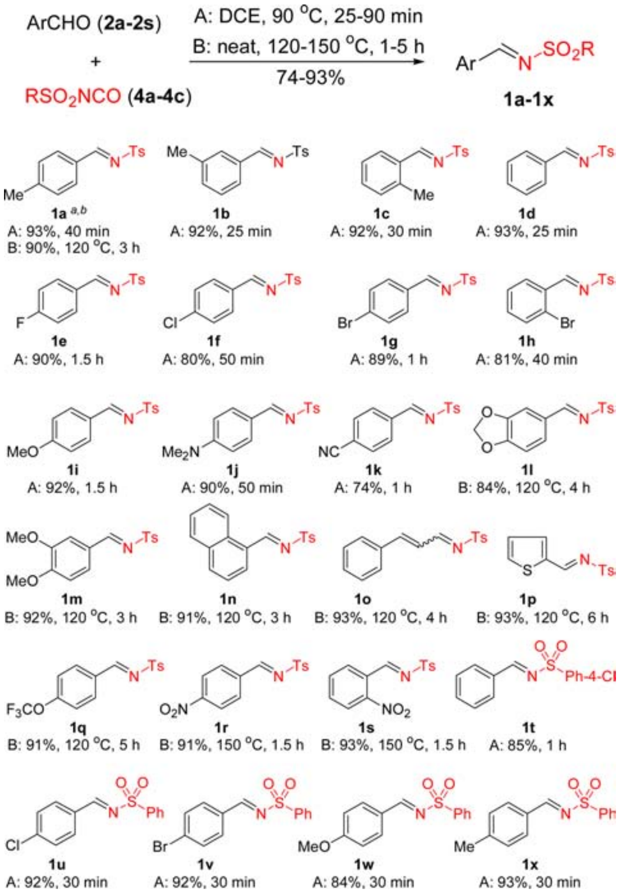


entry	solvent	temp (°C)	time (min)	yield of **1a**[b] (%)
1	THF	70	60	trace
2	DME	120	60	50
3	dioxane	100	60	58
4	C_6H_5Me	110	60	65
5	C_6H_5Cl	130	60	70
6	DCE	90	60	93
7	DCE	90	40	93
8	DCE	60	60	83

[a] The solution of **2a** (5 mmol) and **4a** (5 mmol) in different solvent (5 mL) was refluxed. [b] Isolated yield was obtained by recrystallization.

To generalize this novel method, the scope of substrates was tested initially under conditions A (at reflux in DCE). As shown in Scheme 4, when **4a** was fixed, most electron-donating group (EDG)-substituted aldehydes (**2a–2j**) reacted smoothly to give excellent yields of products **1a–1j**. To our surprise, the EDG-substituted aldehydes **2l–2m** did not give satisfactory yields of **1l–1m**. However, these problems were easily resolved by treating them under conditions B (by heating neat). In fact, conditions B proved to be an essential choice for the synthesis of

Scheme 4. Scope of the Method



[a] A: The reaction was boiled in DCE. [b] B: The reaction was heated in neat.

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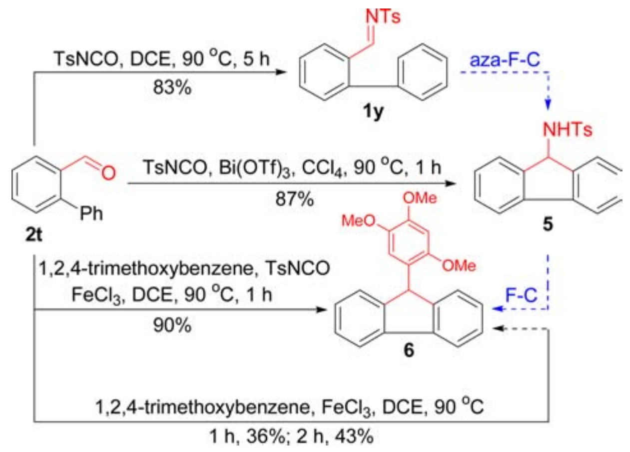
1n−**1s**. Although **1n**−**1q** could be obtained in excellent yields at 120 °C, 150 °C had to be used to obtain an excellent yield of **1r**−**1s**. Very similar to **4a**, the commercially available sulfonylisocyanates **4b** and **4c** worked well in the syntheses of **1t**−**1x**. Under conditions A and B, **1a** was prepared on a 50 g scale in 95 and 91% yields, respectively. As expected, alkylaldehydes (as enolizable aldehydes) were not suitable substrates for this method.

Since the aza-Friedel−Crafts reaction is a typical application[5] of *N*-tosyl arylaldimine **1** and its product easily undergoes further electrophilic reaction,[5d,14] tandem reactions were expected by using 2-formyl biphenyl (**2t**) as a substrate. As shown in Scheme 5, the desired tosylimine **1y** was obtained in 83% yield by heating a mixture of **2t** and TsNCO together. The same reaction gave 9-tosylaminofluorene **5** in 87% yield in the presence of $Bi(OTf)_3$ (10 mol %). When the same reaction was treated by $FeCl_3$ (10 mol %) in the presence of 1,2,4-trimethoxybenzene, 9-arylfluorene **6** was obtained in 90% yield. Further conditional experiment showed that **6** was obtained in very low yield in the absence of TsNCO. The higher yields of **5** and **6** (compared to that of **1y**) may derive from the fact that **1y** was not isolated and purified in these tandem reactions. In fact, most products of **1a**−**1x** were synthesized in quantitative yield. Their isolated yields were decreased by purification, especially by SiO_2 flash chromatography, because they are sensitive to hydrolysis. That was the reason that **1a**−**1y** were purified by a standard recrystallization procedure: **1**/EtOAc/petroleum ether (60−90 °C) = 5 mmol/2 mL/12 mL.

Scheme 5. Tandem Synthesis of Fluorenes 5 and 6



The shorter reaction times in the syntheses of **5** and **6** (compared to that of **1y**) proved that the synthesis of **1y** was catalyzed by Lewis acids. However, this idea was not used in the synthesis of **1a**−**1x** because these products can be decomposed by Lewis acids. We believe that the success for the tandem syntheses of **5** and **6** mainly stems from the fact that our method has two specific advantages compared to the other existing methods: the synthesis of **1y** proceeded under catalyst-/additive-free conditions and without the formation of H_2O, following which Friedel−Crafts reactions and their catalysts were not disturbed at all.

In conclusion, four items have been included in this article. First, we found that King's experiment and explanation in 1960 was wrong. Second, King's experiment was retested, and its problems were revealed. Third, the first practical method for the prparation of *N*-sulfonylimines under catalyst-, additive-, and water-free conditions was developed and was characterized by its unprecedented cleanliness, efficiency, convenience, and scalability. Finally, the method was successfully applied in two tandem syntheses of fluorenes. It may be expected that this method will not only change the synthesis of *N*-sulfonyl arylaldimines but also change their synthetic transformations subsequently.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03686.

Experiments, characterization, ^1H and ^{13}C NMR spectra for all products **1a**−**1y**, **5**, and **6** (PDF)

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Notes

The authors declare no competing financial interest.

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