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Communication

Imine Synthesis

Direct Synthesis of Enolizable *N*-Sulfonyl Ketimines Under Microwave Irradiation

Pablo Ortiz,[a] Juan F. Collados,[a] and Syuzanna R. Harutyunyan*[a]

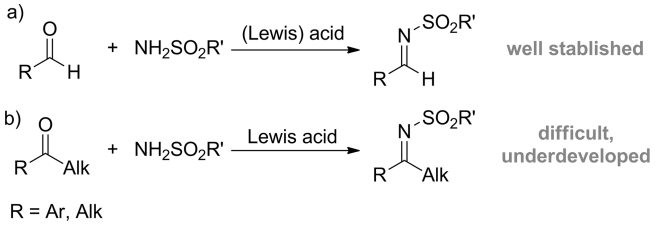
Abstract: *N*-sulfonyl imines are widely used as substrates for a range of transformations. Access to *N*-sulfonyl aldimines is straightforward through direct condensation between the parent aldehyde and the sulfonamide. However, this approach is not efficient for the synthesis of enolizable *N*-sulfonyl ketimines. Herein we report a rapid and facile methodology for obtaining these products using microwave irradiation.

Introduction

The carbonyl group is arguably the most important functional group in synthetic chemistry due to the numerous transformations it can undergo. Its analogue C=N bond is not less relevant, especially considering the widespread applications of imines in organic synthesis. However, contrary to their carbonyl counterparts (aldehydes and ketones), imines are less stable and seldom commercially available, and therefore they usually have to be synthesized.

Among the various types, *N*-sulfonyl imines are the most commonly used because of the strong activating power provided by the sulfonyl moiety.[1] As a consequence, *N*-sulfonyl imines, in particular *N*-tosyl imines, are ubiquitous in organic transformations. To name but a few, they have been used as substrates for cycloadditions,[2–6] aziridines[7] and oxazolines[8] preparations, as well as nucleophilic additions[9–12] and reductions.[13,14]

Due to their widespread use, several methodologies for preparing *N*-sulfonyl imines have been described. There are a myriad of methods reported for the synthesis of *N*-sulfonyl *aldimines* by (Lewis) acid-catalyzed reactions of aldehydes with sulfonamides (Scheme 1, a).[15] These methodologies, however, are generally not efficient when applied to *enolizable ketimines*.[16] The lower electrophilicity of the ketone compared to the aldehyde, together with the relatively low nucleophilic power of sulfonamide, make this transformation difficult (Scheme 1, b).



Scheme 1. Direct synthesis of *N*-sulfonyl imines.

To overcome the reactivity problem, different strategies have been applied. Regarding the ketone partner, its transformation into oximes has allowed successful reactions with both sulfinyl chlorides[17,18] and sulfonyl cyanides[19] to yield *N*-sulfonyl ketimines. Examples of the opposite approach, involving the modification of the nucleophile, have also been reported: sulfinamides, which are more nucleophilic than sulfonamides, have been condensed with the carbonyl group, followed by oxidation to the desired *N*-sulfonyl ketimine.[20,21] This latter method, developed by Ruano et al., is generally considered the most reliable method for the synthesis of *N*-sulfonyl ketimines.[13,14,22–24] Although trustworthy, the method has some significant drawbacks. It involves the handling of peracids and peroxy compounds and is time consuming, since it requires several synthetic operations such as: 1) the preparation of the sulfinamide (only the chiral molecule is commercially available) 2) the condensation with the corresponding ketone, requiring 36 h of reflux, and finally 3) the oxidation of the *N*-sulfinyl imine with MCPBA.[20,21] In fact, Ruano et al. acknowledge that "*In theory, the ideal procedure for obtaining N-sulfonylimines would involve the condensation of carbonyl compounds with sulfonamides.*"[20]

Other routes for the preparation of *N*-sulfonyl ketimines, such as palladium-catalyzed isomerization of *N*-tosyl aziridines[25] or an aza-pinacol rearrangement,[26] have been reported as well. However, these methods are based on starting materials that are not commercially available and require prior synthesis. Another multi-step procedure includes the palladium-catalyzed cross-coupling reaction between organoboronic acids and tosylbenzimidoyl chlorides.[27]

A quick survey of the available methodologies for the synthesis of enolizable *N*-sulfonyl ketimines makes it apparent that this still remains challenging.[28] As part of our ongoing work on nucleophilic additions to *N*-sulfonyl ketimines, we required

[a] *Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands*
E-mail: s.harutyunyan@rug.nl
http://www.sr-harutyunyan.com/

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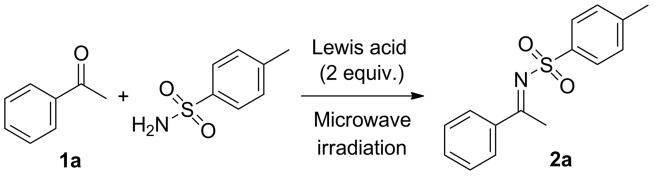
a reliable and quick procedure for their preparation. Direct condensation of sulfonamides with ketones requires acid catalysis and long reaction times under reflux, due to the overall low reactivity of the reagents. Moreover, this approach generally results in low yields, owing to the kinetic instability and ease of enolization of *N*-sulfonyl ketimines under harsh reaction conditions. We reasoned that microwave irradiation (MWI) could be an alternative strategy to address the issues related to the reactivity of the reagents and the low yields. MWI has previously been used for the synthesis of *N*-sulfinyl imines,[29,30] using the relatively more nucleophilic sulfinamides. MWI has also been used for the synthesis of *N*-sulfonyl aldimines starting from the more reactive aldehydes.[31,32]

Results and Discussion

We began our investigation on a model reaction, namely the condensation between acetophenone **1a** and *p*-toluenesulfonamide (Ts-NH_2), using $Ti(OEt)_4$ as both Lewis acid and drying agent. Titanium ethoxide was chosen rather than the commonly used chlorides in order to avoid the HCl formed upon quenching, which can catalyze imine hydrolysis. Some of the reported microwave-assisted methods for the synthesis of *N*-sulfonyl aldimines are run solvent free,[29,31,32] and so was our first attempt (Table 1, entry 1). In this case the reaction crude was highly viscous and revealed less than 50 % conversion to the desired *N*-sulfonyl imine **2a**. Therefore we decided to run the reaction with a solvent (Table 1, entries 2–4). Results were slightly better with dicholoroethane (DCE) than with toluene. However, the environmental impact outweighed the benefits, so the latter was chosen as the reaction solvent for the subsequent studies.

Table 1. Optimization of reaction conditions.[a]



Entry	Equiv. Ts-NH_2	Time [min]	Temp. [°C]	Lewis acid (2 equiv.)	Solvent	Conv. [%][b]
1	1	120	100	$Ti(OEt)_4$	–	49
2	1	120	100	$Ti(OEt)_4$	toluene	59
3	1	120	100	$Ti(OEt)_4$	DCE	61
4	1	120	100	$Ti(OEt)_4$	DCM	49
5	2	120	100	$Ti(OEt)_4$	toluene	64
6	1.2	120	100	$Ti(OEt)_4$	toluene	64
7	1.2	120	125	$Ti(OEt)_4$	toluene	80
8	1.2	120	150	$Ti(OEt)_4$	toluene	92
9	1.2	240	150	$Ti(OEt)_4$	toluene	94
10	1.2	60	150	$Ti(OEt)_4$	toluene	93
11	1.2	30	150	$Ti(OEt)_4$	toluene	89
12	1.2	120	150	$Ti(OiPr)_4$	toluene	50
13	1.2	120	150	B, Al, Zn[c]	toluene	0
14[d]	1.2	60	150	$Ti(OEt)_4$	toluene	93
15[e]	1.2	60	150	$Ti(OEt)_4$	toluene	93

[a] Reaction conditions: **1a** (1 mmol), *p*-toluenesulfonamide, dry solvent (0.5 mL) and Lewis acid (2 equiv.), stirred under microwave irradiation (60 W). [b] Conversion was estimated by ^1H NMR spectroscopy. [c] $BF_3{\cdot}OEt_2$, $AlCl_3$ and $ZnCl_2$ were independently tested. [d] $MgSO_4$ was added. [e] 1 equiv. of $Ti(OEt)_4$ was used.

Next, the effect of different ratios of the reagents on the reaction conversion was tested. Using two equivalents of Ts-NH_2 had only a slight, positive impact on the conversion, (Table 1, entry 5) and further optimization revealed 1.2 equiv. as the optimal excess of the reagent. On the other hand, an excess of **1a** had no effect on the conversion. As expected, the reaction outcome was strongly dependent on the temperature at which it was carried out. The conversion rose from to 64 % to 80 %, and peaked at 92 % when running the reaction at 100, 125 and 150 °C, respectively (Table 1, entries 6, 7 and 8, respectively). It is worth noting that it takes less than two minutes to reach 150 °C, which is not possible with a standard reflux system, and the power required for this corresponds to that needed for an office light bulb (60 W). Higher temperatures were also tested in an attempt to reach full conversion, but side products became predominant due to decomposition. Extending the reaction time from the standard 2–4 h was not beneficial either. Further optimization indicated that even one hour is sufficient to reach the maximum conversion (Table 1, entries 9 and 10 respectively), but shortening it further had a deleterious effect (Table 1, entry 11).

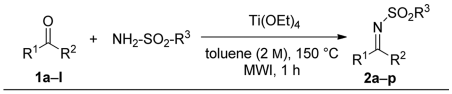
Finally, we investigated the last reaction parameter remaining, the Lewis acid. The crucial role of $Ti(OEt)_4$ was exemplified when $Ti(OiPr)_4$ was used instead, as it resulted in significantly reduced conversion (50 vs. 92 %, Table 1, entries 12 and 8). Significantly, with Lewis acids derived from other metals, such as BF_3, $AlCl_3$ or $ZnCl_2$, only starting material was recovered (Table 1, entry 13). Adding extra dehydrating agent ($MgSO_4$) did not have any influence on the conversion. Importantly, we could lower the number of equivalents of $Ti(OEt)_4$ from 2 to 1 without any impact on the conversion (Table 1, entry 15).

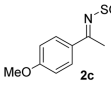
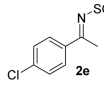
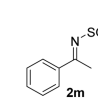
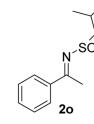
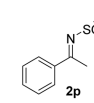
Having solved one of the major issues in the synthesis of enolizable ketimines, namely the conversion, we moved to the next problem: product isolation. The kinetic instability of imines often causes low isolated yields even when the conversion is high.[21,33] Purification by column chromatography using either silica or neutral aluminum oxide as well as their passivated analogues led to partial hydrolysis of the ketimine product. To overcome this problem we attempted crystallization. Unfortunately, the traces of remaining Ts-NH_2 prevented selective product crystallization. Despite these difficulties encountered in the purification, the acetophenone-derived *N*-tosyl imine **2a** could be obtained with 75 % yield after fast column chromatography (Table 2, entry 1).

Next we investigated the scope of the reaction. In order to compare our method with those previously reported, both yields are presented in Table 2. It should be noted that, unfortunately, many of the reports using ketimines do not report the actual yields for their synthesis. We compare our methodology against the reported direct condensation yields (one-step reaction between the ketone and the sulfonamide) as well as against multi-step synthesis protocols, most of which can be attributed to Ruano's method.[20]

The initial substrate scope involved the synthesis of aryl alkyl ketimines. The presence of electron-donating groups (EDG) in

Table 2. Substrate scope.



Entry	Product **2**	Yield (conv.) (%)[a]	Yield (%) of direct condensation[b]	Yield (%) of multistep synthesis
1	 **2a**	75 (93)	15–65[15,32,34–37]	75[20]
2	 **2b**	67 (82)	–	–
3	 **2c**	62 (82)	–	61[20]
4	 **2d**	70 (87)	–	–
5	 **2e**	44 (78)	–	–
6	 **2f**	62 (79)	–[c]	–[c]
7	 **2g**	35 (57)	–[c]	–[c]
8	 **2h**	–[d]	–[e]	–[e]
9	 **2i**	42 (56)[f]	–	45[27]
10	 **2j**	54 (74)	–	58[20]
11	 **2k**	60 (84)	–	43,[20] 51[26]
12	 **2l**	84 (91)	42–83[16,35,37,38]	69[20]
13	 **2m**	54 (68)	–	63[20]
14	 **2n**	37 (79)	–[c]	–[c]
15	 **2o**	27 (61)	18[12]	–
16	 **2p**	–	–[e]	–[e]

the aromatic ring resulted in relatively lower yields of the imine, due to ketone deactivation. Hence, imines **2b** and **2c** with *p*-Me and *p*-OMe substituents, respectively, were isolated in 67 % and 62 % yield (Table 2, entries 2 and 3 respectively). *N*-tosyl imine **2d** with a more electron-rich aromatic ring, such as thiophene, was isolated in a good 70 % yield (Table 2, entry 4). Surprisingly, introducing an electron-withdrawing group in the aromatic ring did not enhance the conversion. In fact, product **2e** was obtained with slightly lower conversion (78 %) than in the case of ketones with EDG (Table 2, entry 5). An additional drawback of the activated substrate was more rapid hydrolysis of the corresponding ketimine, leading to only 44 % of isolated yield.

To examine the role of sterics, both substrates with *ortho* substituents in the aromatic ring as well as substrates with bulky alkyl groups, were tested. A methyl group in *ortho* position was tolerated, providing product **2f** with 62 % of isolated yield (Table 2, entry 6). The bulkiness of the alkyl moiety had a stronger impact on the reaction outcome. The imine **2g**, with a *tert*-butyl group instead of the methyl of the benchmark acetophenone-derived **2a**, was formed in 57 % conversion (Table 2, entry 7). Interestingly, isopropyl bearing imine **2h** could not be obtained, due to complete tautomerisation to the enamine product. The trend towards enamine formation was also observed when the R^2 was Et. The enamine product (15 %) was formed next to the desired product **2i**, which was obtained with 42 % isolated yield (Table 2, entry 9).

Next we applied the methodology to the synthesis of dialkyl ketimines. *N*-Tosyl imine **2j** was obtained in 54 % isolated yield (Table 2, entry 10). The product **2k** with the bulkier *tert*-butyl group was obtained in higher yield, 60 %, probably due to the less pronounced enolization pathway (Table 2, entry 11). The synthesis of a diaryl ketimine was also attempted. *N*-tosyl imine **2l**, derived from benzophenone, was obtained with an excellent yield of 84 % (Table 2, entry 12).

Finally, to assess the viability of the method for the synthesis of other *N*-sulfonyl imine derivatives, the influence of the substituent in the sulfonamide (R^3) moiety was investigated. Replacing the aryl with an alkyl group in the sulfonamide decreased the reactivity of the corresponding Ts-NH_2, and the acetophenone-derived *tert*-butyl *N*-sulfonyl imine **2m**, as well as methyl *N*-sulfonyl imine **2n**, were obtained in 54 % and 37 % yields, respectively (Table 2, entries 13 and 14). As expected, the synthesis of *N*-sulfonylmesityl imine **2o** provided the product with a modest 27 % yield, but this is nevertheless significantly higher than what is possible with the previously reported method (Table 2, entry 15).[12] Most yields lie in the moderate to good range, but it should be noted that these surpass the yields of all previous methods based on direct condensations. When compared to Ruano's[20] and other multistep syntheses,[26,27] this one-step synthesis provides similar yields, using an operationally far simpler procedure, reduced amounts of reagents, and remarkably shorter reaction times. To further prove the synthetic utility of the methodology we scaled up the synthesis to 6.5 mmol of acetophenone **1a**. *N*-Tosyl imine product **2a** was obtained in 1.2 g (66% yield, see Supporting Information for details).

Conclusions

In summary, we have developed a simple and rapid method for the synthesis of *N*-sulfonyl ketimines, via direct condensation of ketones and sulfonamides, assisted by MWI. Microwave-assisted synthesis of imines from the commercially available ketones and sulfonamides allows completing the transformation in one hour, with minimal environmental impact, both in terms of energy and solvent use: no chlorinated solvents and no reflux setup. The formation of *N*-sulfonyl ketimines reported here represents the first alternative to multistep procedures based on the formation of *N*-sulfinyl imines, furnishing the products in similar yields, with the additional advantages of using commercially available reagents, a one-step procedure, lower energy consumption and shorter reaction times.

Experimental Section

Procedure for the Synthesis of *N*-Sulfonyl Imines: A 10 mL microwave vial equipped with a stirrer was charged with the ketone (1 mmol), the sulfonamide (1.2 mmol), dry toluene (0.5 mL) and $Ti(OEt)_4$ (1 mmol). The vial was closed and heated at 150 °C for 1 h using microwave irradiation. After completion, it was let to cool down to room temperature, diluted with 5 mL of AcOEt, quenched with 1 mL of $NaHCO_3$, and filtered through a pad of celite. The solvent was evaporated in vacuo and the crude was analysed by ^1H NMR spectroscopy. Conversion was estimated by comparing the integration of signals corresponding to the product and to the unreacted ketone. In the case of volatile ketones the comparison was done against the remaining *p*-toluenesulfonamide. The crude product was purified by flash chromatography on silica gel using mixtures of *n*-pentane and AcOEt as the eluent.

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Keywords: Microwave chemistry · Imines · Ketimines · Condensation reactions

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