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Eco-friendly and efficient catalyst-free synthesis of *N*-sulfonylimines from sulfonamides and aldehydes: crucial role of Al₂O₃ as a reusable dehydrating agent†

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A green synthetic method for the synthesis of *N*-sulfonylimines was developed involving the straightforward condensation of sulfonamides with aldehydes under green and catalyst-free conditions, mediated by neutral Al₂O₃ as an efficient and reusable dehydrating agent. *N*-Sulfonylimines were produced in high yields and purity under simple experimental procedures.

Imines containing electron-withdrawing *N*-substituents are well-recognized intermediates toward molecules with synthetic and biological interest.[1] Especially, *N*-sulfonylimines are the most widely studied derivatives due to their unique characteristics that are not easily found in other electron-deficient imines. *N*-Sulfonylimines demonstrate a good compromise between being sufficiently stable imines but also reactive enough to be versatile substrates in many transformations as well. In addition, they have been extensively explored as excellent activated electrophiles in hetero-Diels–Alder reactions,[2] nucleophilic additions to afford chiral amines,[3] imino-aldol reactions,[4] reductions,[5] aza-Friedel–Crafts,[6] ene-reactions,[7] as well as in the asymmetric synthesis of β-amino acid derivatives.[8] They have also been applied as important precursors in the preparation of a variety of heterocyclic compounds such as oxaziridines,[9] imidazolines,[10] and aziridines.[11]

So far, with the increasing demand for *N*-sulfonylimines, numerous methods to prepare these compounds have been reported. Most of them involve the direct condensation of sulfonamides with aldehydes and are mediated by: (i) strong Lewis acid catalysts, including FeCl₃,[12] WCl₆,[13] ZnCl₂/SiO₂,[14] TiCl₄/Et₃N,[15] and AlCl₃,[16] (ii) Brønsted acid catalysts, such as Amberlyst 15/molecular sieves,[17] HY9 zeolite,[18] and sulfamic acid (NH₂SO₃H),[19] (iii) organocatalysts, such as pyrrolidine/molecular sieves,[20] and Ar₃CCl,[21] and (iv) activating reagents, *i.e.* Si(OEt)₄,[22] TFAA,[23] Silphox [POCl₃₋ₙ(SiO₂)ₙ],[24] and silica chloride (SiO₂–Cl).[25] Some methods are multi-step procedures, such as the reaction of aldehydes with isocyanates analogues,[26]

oxidation of *N*-sulfinimines,[27] rearrangement of oxime *O*-sulfinates,[28] and condensation of benzyl alcohols with chloramine-T or sulfonamides.[29] It should be mentioned that most of these methods have one or more of the following disadvantages: harsh reaction conditions, unsatisfactory yields, use of hazardous reagents and toxic solvents, expensive and non-recyclable catalysts, generation of toxic waste, and tedious work-up.

The ideal synthetic route for the *N*-sulfonylimines formation is the direct condensation of sulfonamides with aldehydes. However, it is worth mentioning that the conversion rate may be limited due to the unfavorable thermodynamics because of water generated in the reaction medium as a by-product (Scheme 1), and by the weak nucleophilicity of sulfonamides, which usually required elevated temperatures and strong acidic conditions to achieve carbonyl activation. Nevertheless, these conditions are generally incompatible with acid-sensitive substrates and the limited stability of the resulting imines in the medium.

From a green chemistry perspective, catalyst-free procedures have many advantages, due to the simple experimental procedure, low cost, and importantly the compatibility for acid or base sensitive substrates. To our knowledge, there is no efficient catalyst-free procedure for the synthesis of *N*-sulfonylimines from aldehydes and sulfonamides described in the literature. Poisson *et al.* have reported the condensation of *p*-tosylamide with benzaldehyde under catalyst-free conditions, and the conversion was reported not to exceed 75% under microwave

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Scheme 1 One-pot synthesis of *N*-sulfonylaldimines from sulfonamides and aldehydes.

irradiation, even when heating up to 180 °C.[30] Therefore, these authors replaced this reaction by the condensation of sulfonamides with benzaldehyde dimethylacetal instead of benzaldehyde to achieve full conversions into the sulfonylimines.

Considering these precedents and in the context of our interest in the design and development of a green synthetic methodology,[9,31] we think that the development of a new straightforward strategy for the *N*-sulfonylimine synthesis under mild and catalyst-free conditions would be highly desirable. For this reason, we carried out a systematic study in which we examined the influence of the solvent, temperature, and dehydrating agent on the condensation of sulfonamides with aldehydes. This study aims at finding the optimal conditions for an efficient synthesis of the corresponding *N*-sulfonylimines under green conditions. In this work, we used a pressure tube as an efficient and environmentally benign heating technique which received considerable attention as a preferable and practical alternative in many organic transformations. This technique meets with green chemistry protocols by affording a cleaner reaction profile in a shorter reaction time, energy saving, preventing the use of high temperature, excess of solvents, and release of toxic gas.[20,31,32]
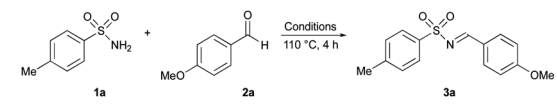
Herein, we disclose a successful demonstration of the catalyst-free direct condensation of *N*-sulfonamides with aldehydes mediated by neutral Al_2O_3, as an efficient and reusable dehydrating agent, under simple and eco-friendly conditions. To investigate the optimum conditions for the direct synthesis of *N*-sulfonylimines under catalyst-free conditions, we chose *p*-tosylamide **1a** and *p*-anisaldehyde **2a** as the model substrates. The results of the optimization study are summarized in

Table 1 Optimization of the reaction conditions[a]

Entry	Additive	Solvent	Conv.[b] (%)
1	—	—	45
2	—	—	58[c]
3	—	DMC	38
4	Al_2O_3	—	97
5	Al_2O_3	—	100[d]
6	Al_2O_3	DMC	**100**
7	Al_2O_3	DMC	80[f]
8	MgO	DMC	50
9	MS (4 Å)	DMC	16
10	Na_2CO_3	DMC	31
11	Al_2O_3	PC[e]	96
12	Al_2O_3	AcOEt	47
13	Al_2O_3	EtOH	0
14	Al_2O_3	Toluene	61
15	Al_2O_3	CH_2Cl_2	39

[a] Reaction conditions: *p*-tosylamide **1a** (1.2 mmol), *p*-anisaldehyde **2a** (1 mmol), additive (2 equiv.), solvent (1 mL). The mixture was stirred in a pressure tube. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Conversion after 12 h. [d] Full conversion (100%) after 6 h. [e] Propylene carbonate. [f] Reaction performed at 90 °C.

Table 1. We first examined the reaction at 110 °C (Table 1, entries 1–3) to evaluate the ability of sulfonamide **1a** and aldehyde **2a** to undergo condensation without any additive. We noticed that 58% of the corresponding imine **3a** was formed under solvent-free conditions after 12 h of reaction time; 38% of **3a** was formed after 4 h when anhydrous DMC (dimethyl carbonate) was used as the solvent of the reaction. In line with these promising results, it appeared that the reaction worked equally well in the absence of a catalyst (Table 1, entry 2). The incomplete conversion was unsurprisingly attained due to the water generation in the reaction media, leading to the hydrolysis of **3a** and decreased the yield of the imine. This problem motivated us to study the effect of water scavenger additives on the *N*-sulfonylimine production as an alternative process for the removal of water produced during the reaction. Various common activated neutral and basic dehydrating agents such as 4 Å molecular sieves, neutral Al_2O_3, MgO, and Na_2CO_3 have been investigated to test their performance (Table 1, entries 6 and 8–10). Lower temperature (Table 1, entry 7) led to lower conversion (no conversion was observed at rt). The best results were obtained when neutral Al_2O_3 was used as the dehydrating agent at 110 °C and in the presence of anhydrous DMC as the solvent of the reaction (Table 1, entry 6). In this case, a total conversion of **1a** and **2a** into the imine **3a** was observed after 4 h. The influence of the solvent on the reaction efficiency was also studied (Table 1, entries 6 and 11–15) which led to total conversion of **1a** and **2a** into the corresponding imine **3a** in 4 h when DMC was used as the solvent, and after 6 h under solvent-free conditions.

In this study, we emphasize that dialkyl carbonates, such as DMC and PC (propylene carbonate), have been found to be far better solvents than the other ones (Table 1, entries 6 and 8). In fact, DMC and PC are highly recommended as green and sustainable alternative solvents for chemical transformations, owing to their low toxicity, non-corrosive, high biodegradability, economical manufacturing, and the use of abundant and renewable sources such as CO_2 in their production.[9,31,33]
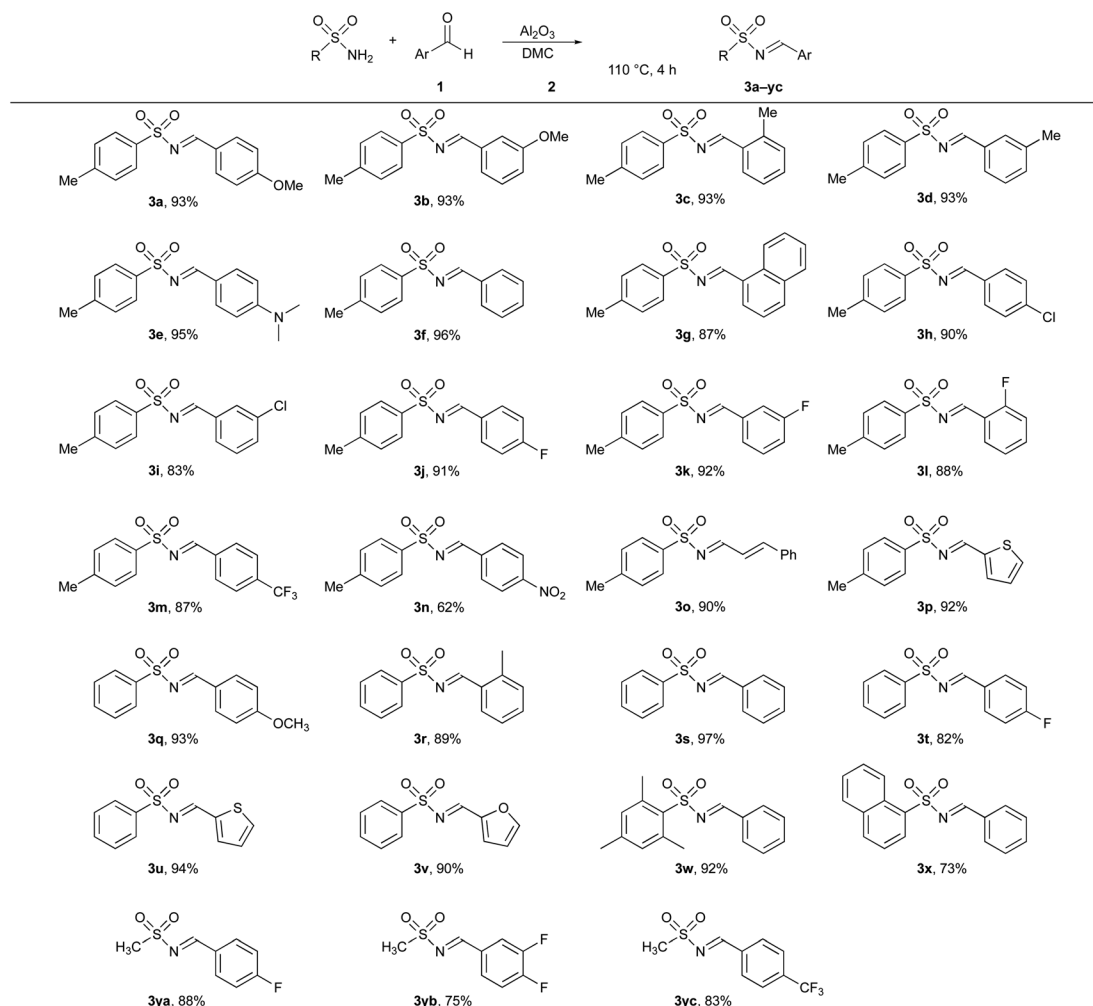
Thus, the optimized reaction conditions obtained for the synthesis of *N*-sulfonylimine **3a** were achieved by stirring a mixture of *N*-tosylamide **1a**, aldehyde **2a**, and neutral Al_2O_3 in dry DMC for 4 h at 110 °C. Pure product was obtained by filtration of the insoluble Al_2O_3 and purifying the crude by simple recrystallization. In order to demonstrate the feasibility, as well as the generality of the method, a wide variety of aryl aldehydes and sulfonamides were investigated under the optimized conditions (Table 2), and the corresponding *N*-sulfonylimines **3a–yc** were successfully obtained in good to excellent yields. It is worth noting that the presence of electron-donating substituents, as well as electron-withdrawing substituents, on the aromatic ring of aldehydes had no significant influence on the efficiency of the process. Unsurprisingly, all *N*-sulfonylimines **3a–yc** were obtained exclusively in the *E*-isomer form. Indeed, the less stable *Z*-isomer is thermodynamically unfavoured. These stereochemical results are in line with the ones obtained in other procedures described in the literature.[12–29] Interestingly, when a carboxylic amide was used instead of

Table 2 Preparation of N-sulfonylimines **3a–yc** from sulfonamides **1** and aldehydes **2**[a]

3a, 93%   3b, 93%   3c, 93%   3d, 93%

3e, 95%   3f, 96%   3g, 87%   3h, 90%

3i, 83%   3j, 91%   3k, 92%   3l, 88%

3m, 87%   3n, 62%   3o, 90%   3p, 92%

3q, 93%   3r, 89%   3s, 97%   3t, 82%

3u, 94%   3v, 90%   3w, 92%   3x, 73%

3ya, 88%   3yb, 75%   3yc, 83%

[a] Reaction conditions: N-sulfonamide (1.2 mmol), aldehyde (1 mmol), Al_2O_3 (2 mmol), DMC (1 mL), the reaction was heated at 110 °C in a pressure tube for 4 h (reaction monitored by TLC).
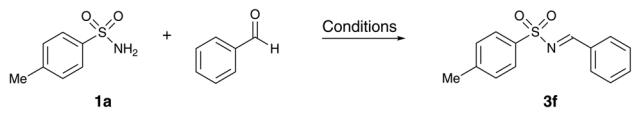
a sulfonyl amide, the corresponding acyl imine was not formed.[34]

The catalyst-free approach for the synthesis of N-sulfonylimines was successfully demonstrated. In fact, it is worth pointing out the crucial role of the dehydration played by aluminium oxide in the described reaction. Al_2O_3 is well known for its high adsorption capacity when exposed to moist air or wet solution and has proved to be one of the most effective adsorbents applied for removing traces or bulk of water from fluids (gas, liquid).[35] In addition, it is characterized by its wide surface area, high stability, and mechanical strength, also, it can be highlighted as inexpensive, reusable, and commercially available. The unique physical and chemical proprieties as well as the non-toxic and environmentally nature of Al_2O_3 make it a promising material for the application in the laboratory and in diverse areas of industry.[36] Furthermore, from a practical point of view, this inorganic compound provides a significant solution to known synthetic drawbacks while using N-

sulfonylimines. Interestingly, Al_2O_3 (i) is able to capture a large quantity of water from the reaction medium, consequently pushing the equilibrium toward the formation of N-sulfonylimines without the need of addition of a catalyst; (ii) does not react with the product, whereas conventional routes commonly involve harsh acidic conditions which make them unsuitable for acid-sensitive substrates, and (iii) can be easily separated from the reaction medium and be reused after simple washing with DMC. Indeed, it was found that the use of Al_2O_3 in the preparation of imine **3f** afforded the same efficiency in the 2nd, 3rd, 4th, and 5th runs (100% conversions, 92–96% yields) as in the first run.

A comparison of the efficiency of our method with some previously reported methods for the preparation of N-sulfonylimine **3f** was highlighted in Table 3. The only catalyst-free approach described for the direct synthesis of N-sulfonylimines showed a conversion of 75% when molecular sieves were used as dehydrating agent.[30] However, the present method

Table 3 The comparative synthesis of the *N*-sulfonylimine **3f** using the present work *vs.* previous methods

Conditions	Additive	Catalyst	Yield **3f** (%)
DMC, 110 °C, 4 h	**Al₂O₃**	—	**96**
MW, 180 °C, 0.5 h	3 Å + 4 Å MS	—	75 (conv.)[30]
CH₂Cl₂, 0 °C, 0.5 h	—	TiCl₄, Et₃N	58 (ref. 15)
CH₂Cl₂, 60 °C, 24 h	4 Å MS	Pyrrolidine (10%)	99 (ref. 20)
PhMe, 110 °C, 16 h	5 Å MS	Amberlyst 15	90 (ref. 36)
EtOH, rt, 1 h	—	FeCl₃ (4%)	92 (ref. 12)
160 °C, 6 h	—	Si(OEt)₄	68 (ref. 22)

furnished higher yields and similar efficiency as the reported methodologies mediated by catalysts. Noteworthily, the combination of an inexpensive dehydrating agent with the use of green and recyclable solvent (DMC) without the use of a catalyst makes this strategy a suitable alternative for the synthesis of *N*-sulfonylimines.

To sum up, we have developed herein an efficient catalyst-free one-pot synthesis of *N*-sulfonylaldimines by condensation of *N*-sulfonamides with aldehydes, in the presence of neutral Al₂O₃ as the dehydrating agent and DMC as a green and recyclable solvent. Al₂O₃ was found to be a highly effective, commercially available, inexpensive, and heterogeneous dehydrating additive. This new strategy appears to provide one of the most practical and environmentally benign routes to *N*-sulfonylimines. The method uses catalyst-free conditions, simple experimental procedures, and green chemistry protocols to afford *N*-sulfonylaldimines in high yield and low cost.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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