Triarylmethyl chlorides as novel, efficient, and mild organic catalysts for the synthesis of *N*-sulfonyl imines under neutral conditions

Ali Khalafi-Nezhad, Abolfath Parhami, Abdolkarim Zare, Amir Nasrolahi Shirazi, Ahmad Reza Moosavi Zare, and Alireza Hassaninejad

Abstract: A highly efficient procedure for the preparation of *N*-sulfonyl imines via condensation of sulfonamides with aldehydes as well as ketones in the presence of triarylmethyl chlorides as metal-free organo-catalysts at 40 °C is described. The advantages of this class of catalysts over the reported ones are their efficiency and possibility of running reactions in neutral media that makes them suitable for acid-sensitive substrates.

Key words: triarylmethyl chloride, *N*-sulfonyl imine, sulfonamide, aldehyde, ketone.

Résumé : On a développé une méthode très efficace pour préparer des *N*-sulfonylimines par le biais d'une condensation à 40 °C de sulfonamides sur des aldéhydes ou des cétones, en présence de chlorures de triarylméthyles agissant comme catalyseurs organiques sans métaux. Les avantages de cette classe de catalyseurs par rapport d'autres qui ont déjà été utilisés sont leur efficacité et la possibilité d'effectuer les réactions dans des milieux neutres appropriés pour les substrats sensibles aux acides.

Mots-clés : chlorure de triarylméthyle, *N*-sulfonylimine, sulfonamide, aldéhyde, cétone.

[Traduit par la Rédaction]

Introduction

N-Sulfonyl imines are versatile intermediates in organic synthesis (1). They are excellent substrates in aza Diels–Alder reactions (2–3), nucleophilic additions (3), and reductions (4), as well as in radical (5) or ene reactions (6). They have been also used in the synthesis of aziridines (7). So far, several synthetic methods for the preparation of *N*-sulfonyl imines have been reported (8–22). Most of those methods involve the condensation of sulfonamides with aldehydes or ketones in the presence of strong Lewis or protic acids, such as sulfamic acid (22). In many cases, strongly acidic conditions are not compatible with other functionalities present in a given substrate. Some methods need two-step procedures or they are expensive methods and generate toxic by-products. Moreover, several methods require prior preparation of precursors, such as oxime, sulfinylimine, or aziridine. Many methods also need harsh reaction conditions. Because of the limitations of the above methods, development of a new method for the synthesis of *N*-sulfonyl imines under neutral conditions in one-step would be desirable.

Recently, organic Lewis acids, such as NBS, trichlorocyanuric acid, and trichloroisocyanuric acid, have been proved to be useful to chemists in the laboratory and industry because of the good activation of carbonyl compounds, selectivity, and mild reaction conditions (23). The use of organic catalysts instead of inorganic Lewis acids have some advantages, including (*i*) the possibility to perform the reactions for acid sensitive substrates, (*ii*) performing the reactions in milder reaction conditions, and (*iii*) the substrates bearing basic functional groups or electron-donating substituents prone to capture the acidic catalysts do not affect the reaction results. Triarylmethyl chlorides (Ar_3CCl) can be introduced as new organic catalysts that are inexpensive and can be obtained commercially or easily prepared by the known procedures (24). These type of compounds has been extensively studied as bulky protective groups for amino and primary hydroxyl functional groups in multi-step organic synthesis (25). Furthermore, triarylmethyl chlorides in combination with metal salts particularly $SnCl_2$ have been employed in a few organic transformations (26); however, the use of triarylmethyl chlorides in the absence of a co-catalyst is really intriguing. To the best of our knowledge, there is no report for the application of triarylmethyl chlorides as catalyst in organic transformations.

Having the above facts in mind and also in continuation of our previous studies on the preparation of *N*-sulfonyl imines (9*a*, 9*b*) as well as catalysis in organic transformations (27), we describe here the first procedure for the application of triarylmethyl chlorides as catalysts in the synthesis of *N*-

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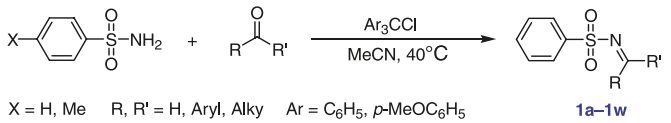
Scheme 1. The condensation of sulfonamides with carbonyl compounds.



sulfonyl imines via the reaction of sulfonamides with aromatic and aliphatic aldehydes as well as ketones under mild and neutral reaction conditions (Scheme 1).

Results and discussions

To optimize the reaction conditions, first we examined the reaction of benzenesulfonamide (2 mmol) with benzaldehyde (2 mmol) as a model in the presence of DMTrCl [Ph(*p*-$MeOC_6H_4)_2CCl$, 0.25 mmol] in MeCN (10 mL) at room temperature. In these conditions, the corresponding *N*-sulfonyl imine **1a** was obtained in 64% yield after 30 min. Increasing the reaction time had no effect on the efficiency of the reaction; however, enhancing the temperature to 40 °C improved the yield to 90%. In another study, the influence of different solvents on the model reaction was investigated. The results are summarized in Table 1. As it can be seen from Table 1, higher yield and shorter reaction time were obtained when MeCN was used. So, MeCN was used as the solvent of choice in all reactions. The reaction of benzenesulfonamide with benzaldehyde was also examined in the absence of solvent in which the product was obtained in 46% within 50 min (Table 1, entry 6). These results indicated the preference of the solvent-phase procedure in comparison with solvent-free conditions. We suggest that it is due to the greater stability of intermediate triphenylcarbonium ions in solvent media.

To select the best triarylmethyl chloride as catalyst, the model reaction was performed using TrCl (Ph_3CCl), MMTrCl (Ph_2(*p*-$MeOC_6H_4$)Cl), and DMTrCl (Ph(*p*-$MeOC_6H_4)_2Cl$) (Table 2). As it is shown in Table 2, there is not a great difference between the catalysts; however; the best yield was obtained using DMTrCl. As expected, the methoxy groups in the catalyst can increase the extent of ionization of triarylcarbenium chloride, thus increasing the amount of Lewis acid in the reaction medium.

To investigate the generality and versatility of the catalyst, the optimized reaction conditions, as described above, were extended to various structurally diverse carbonyl compounds (aldehydes and ketones) and sulfonamides. The results are displayed in Table 3. As Table 3 indicates, the reactions proceeded efficiently, and the desired products were obtained in good to high yields in short reaction times.

In general, higher reaction yields were obtained when benzenesulfonamide was used instead of *p*-toluenesulfonamide. It was observed that the electronic properties of the aromatic ring of aromatic aldehydes can affect the reaction. The results showed that electron-donating substituents improved the reaction yields (Table 3, entries 2, 9, and 10). However, aryl aldehydes possessing electron-withdrawing groups, generally necessitate longer reaction times and decrease the reaction yields (Table 3, entries 3, 11, and 12). Moreover, the presence of a halogen on the aromatic ring of aldehydes slightly decreased the yields and increased the reaction times (Table 3, entries 4, 5, 13, and 14). When the reaction was examined for 4-(dimethylamino)benzaldehyde (Table 3, entry 7), the corresponding bis(indolyl)alkane was obtained in good yield, indicating that the amine function cannot affect the efficiency of the reaction via irreversible complexation with catalyst. *o*-Substituted aromatic aldehydes (Table 3, entry 15) and aliphatic aldehydes (Table 3, entries 18 and 19) needed longer reaction times and afforded lower yields of the products in comparison with the others. The reaction of terphtalaldehyde (2 mmol) with *p*-toluenesulfonamide (4 mmol) afforded the corresponding bis-*N*-sulfonyl imine (Table 3, entry 20) in 51% yield as well as *N*-(4-formylbenzylidene)toluenesulfonamide in 25% yield, which shows the generality and applicability of this method for the synthesis of bis-*N*-sulfonyl imine analogous. Moreover, the reaction of terphtalaldehyde (2 mmol) and *p*-toluenesulfonamide (2 mmol) provided *N*-(4-formylbenzylidene)toluenesulfonamide (Table 3, entry 21) as the product in 76% yield. Generally, aldehydes are more reactive than ketones, since approach of bulky trityl cation is hindered due to the presence of two substituents in ketones. The reaction of ketones with *p*-toluenesulfonamide provided the corresponding *N*-sulfonyl imines in moderate yields (Table 3, entries 22 and 23); however, most of the reported methods were not suitable for the ketones especially enolizable ones.

We suggest that complexes of carbonyl compounds and triarylmethyl cation (**I**, **II**, and **III** for benzaldehyde) were formed (Scheme 2). The cationic intermediates **I**, **II**, and **III** were introduced by Oikawa et al. for the first time (31). These complexes act as activated carbonyl compound and then react with *p*-toluenesulfonamide providing **IV**, which converts to **V** by proton transfer. **V** dissociates to form an

Table 1. The effect of various solvents on the reaction of benzenesulfonamide with benzaldehyde in the presence of DMTrCl at 40 °C.

Entry	Solvent	Time (min)	Yield (%)[a]
1	EtOH	60	48
2	EtOAc	100	65
3	DMF	45	51
4	CH_2Cl_2	80	54
5	MeCN	30	90
6	Solvent-free	50	46

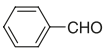
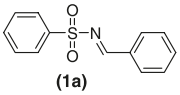
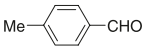
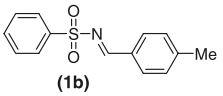
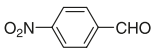
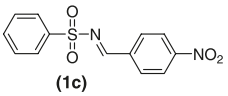
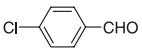
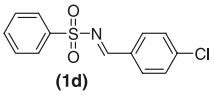
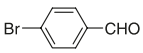
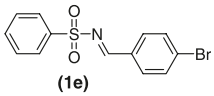
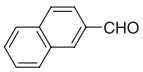
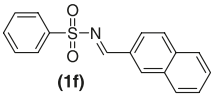
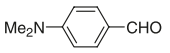
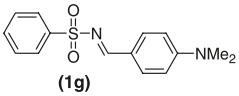
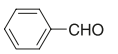
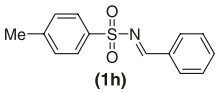
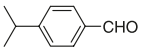
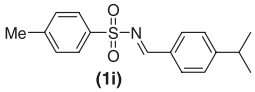
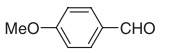
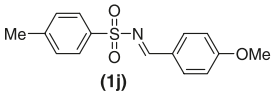
[a]Isolated yield.

Table 2. The influence of different catalysts on the condensation of benzenesulfonamide with benzaldehyde in MeCN at 40 °C.

Entry	Catalyst	Time (min)	Yield (%)[a]
1	TrCl	30	82
2	TrOH	30	12
3	MMTrCl	30	85
4	DMTrCl	30	90

[a]Isolated yield.

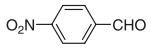
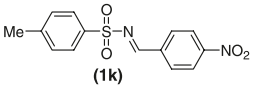
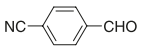
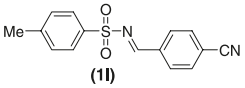
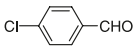
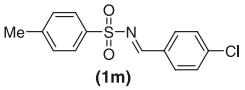
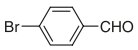
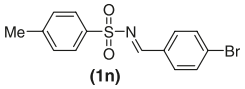
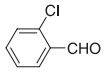
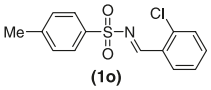
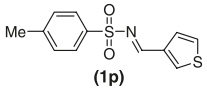
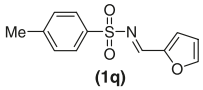
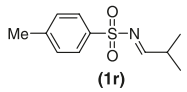
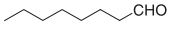
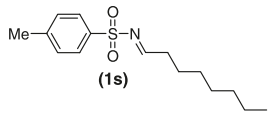
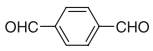
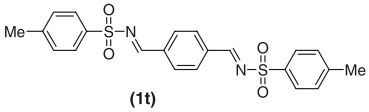
Table 3. Preparation of *N*-sulfonyl imines from sulfonamides and aldehydes as well as ketones in the presence of DMTrCl in MeCN at 40 °C.

Entry	R(CO)R'	Product	Time (min)	Yield[a] (%)	Ref.
1		 **(1a)**	30	90	19
2		 **(1b)**	30	94	16
3		 **(1c)**	45	80	21*a*
4		 **(1d)**	45	84	16
5		 **(1e)**	45	85	10*b*
6		 **(1f)**	30	87	18
7		 **(1g)**	30	83	10*c*
8		 **(1h)**	45	85	17
9		 **(1i)**	30	90	10*b*
10		 **(1j)**	30	91	9

equilibrating mixture of cations as is shown in Scheme 2. The **VI** eliminates a proton to give the sulfonylimine product, and simultaneously the triarylmethanol is converted to triarylmethyl chloride. The suggested mechanism is confirmed, since the catalyst was completely recovered unchanged, and no triarylmethanol could be identified after the completion of the reaction as it could be observed on TLC by comparison with pure authentic samples. If a base, such as triethylamine or pyridine (in equimolar amount relative to DMTrCl), was added to the model reaction preceding to the addition of DMTrCl, the yield would decrease greatly (9%); moreover, the DMTrCl was not regenerated and DMTrOH was obtained instead. We suggest that this is owing to the ability of base to interfere with the protonation and proton transfer steps in the mechanism. Increasing the amounts of base and DMTrCl had negligible effect on the yield. In another experiment, to examine the applicability of another organo-catalyst for the synthesis of *N*-sulfonyl imines, the reaction was performed using the same amount of 2,4,6-trichloro-1,3,5-triazine instead of DMTrCl and in DMF as the solvent. The results showed that this catalyst is also able to perform the reaction (30% yield in 60 min) and emphasize the role of organo-catalysts for activation carbonyl groups.

In conclusion, this new strategy offers several advantages, including neutral and mild reaction conditions, short reaction times, high yields of products, low catalyst loading as well as simple experimental and isolation procedures, which make it useful for the synthesis of *N*-sulfonyl imines. The

Table 3 (*continued*).

Entry	R(CO)R'	Product	Time (min)	Yield[a] (%)	Ref.
11		 (1k)	50	74	21*b*
12		 (1l)	50	77	10*a*
13		 (1m)	50	80	9
14		 (1n)	50	82	19
15		 (1o)	50	71	10*a*
16		 (1p)	40	86	10*a*
17		 (1q)	40	83	10
18		 (1r)	50	68	28
19		 (1s)	50	74	29
20		 (1t)	60	51[b]	32

selected catalyst is found to be highly efficient, easily available, economical, and recyclable.

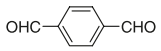
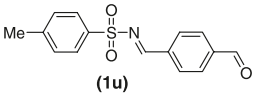
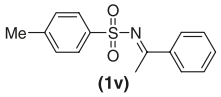
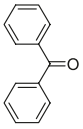
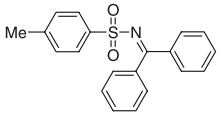
Experimental

All chemicals were purchased from Merck or Fluka chemical companies. All known compounds were identified by comparison of their melting points, ^{1}H NMR, and ^{13}C NMR data with the authentic samples. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avance DPX-250 FTNMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a PerkinElmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the synthesis of *N*-sulfonyl imines

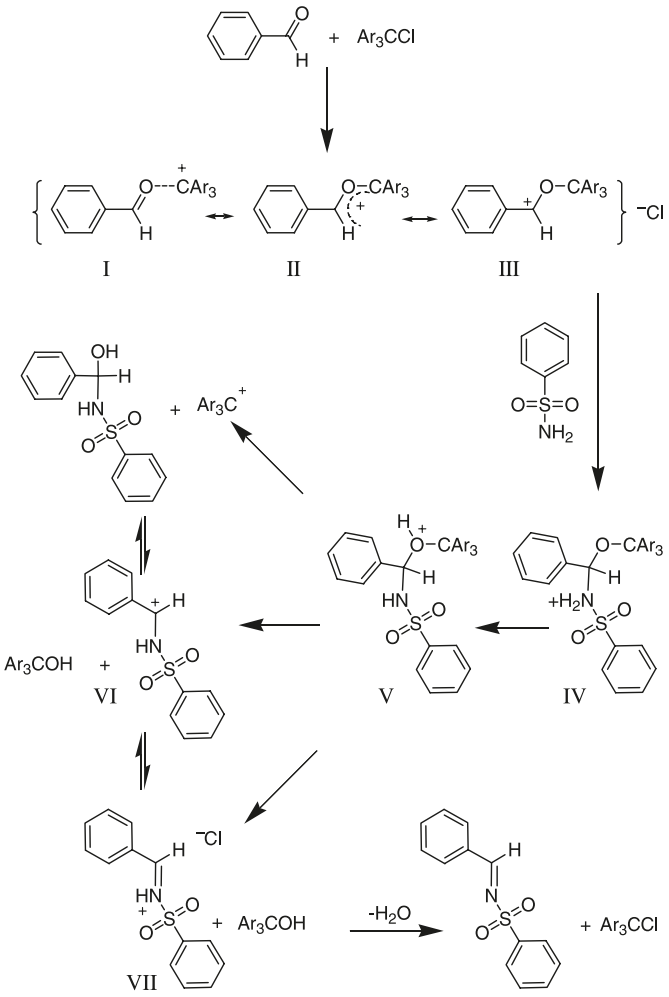
To a mixture of sulfonamide (2 mmol), carbonyl compound (2 mmol), and MeCN (10 mL) in a 25 mL round-bottomed flask connected to a reflux condenser was added DMTrCl (0.25 mmol), and the resulting mixture was stirred at 40 °C for the times indicated in Table 3. Subsequently, the solvent was evaporated and to it was added EtOAc (50 mL) and extracted with saturated solution of $NaHSO_3$ (2 × 50 mL) to remove the unreacted carbonyl compound. The organic layer was dried with $MgSO_4$ and concentrated to 5 mL and to it was added gradually *n*-hexane (20–30 mL) and allowed to stand at room temperature until crystals were formed, which then was collected by filtration, washed with *n*-hexane, and dried. The catalyst was recovered by evaporation of the filtrate and subsequent recrystalization in *n*-hexane.

Table 3 (*concluded*).

Entry	R(CO)R'	Product	Time (min)	Yield[a] (%)	Ref.
21		 (1u)	50	76[c]	33
22		 (1v)	60	59	30
23		 (1w)	70	42	30

[a]Isolated yield.
[b]Molar ratio of $TsNH_2$/terphtalaldehyde is 2:1.
[c]Molar ratio of $TsNH_2$/terphtalaldehyde is 1:1.

Scheme 2. The proposed mechanism for the condensation of sulfonamides with carbonyl compounds.



Acknowledgements

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32. Spectral data for unknown compound, 4-methyl-*N*-{(*E*)-[4-((*E*){[(4-methylphenyl)sulfonyl]imino}methyl)phenyl]methylidene}benzenesulfonamide (**1t**): Pale yellow crystals, mp 109–110 °C. ^{1}H NMR (DMSO-d_6, ppm) δ: 2.36 (s, 6H), 7.28 (d, 4H, J = 7.5 Hz), 7.76 (d, 4H), 8.01 (d, 4H, J = 7.5 Hz), 9.31 (s, 2H). ^{13}C NMR (DMSO-d_6) δ: 21.8, 124.7, 128.7, 137.9, 140.2, 141.6, 145.7, 172.5. MS *m/z*: 349 [M^+ – $CH_3C_6H_4$]. Anal. calcd. for $C_{22}H_{20}N_2O_4S_2$: C, 59.98; H, 4.58; N, 6.36. Found: C, 60.17; H, 4.35; N, 6.58.
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