Efficient Microwave-Assisted Synthesis of *N*-(*tert*-Butylsulfinyl)imines Catalyzed by Amberlist-15

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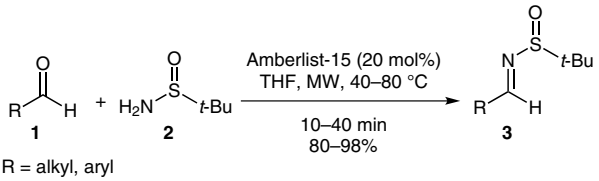
Abstract: A general and efficient methodology is reported for the synthesis of *N*-(*tert*-butylsulfinyl)imines by using the heterogeneous catalyst amberlist-15, under microwave irradiation. Amberlist-15 is easy to handle, safe to use and quickly separable from the reaction mixture. This method offers a number of advantages including operational simplicity, inexpensive catalyst, high yield of products, and broad substrate scope.

Key words: imines, building blocks, microwave, heterogeneous catalyst, aldehydes

N-(*tert*-Butylsulfinyl)imines are important substrates in organic and medicinal chemistry, and a range of amines can be prepared directly from this type of substrate.[1] The traditional method for the synthesis of these substrates is the condensation of 2-methyl-2-propanesulfinamide with a carbonyl compound. To facilitate this transformation, the use of either a carbonyl group activating agent or dehydrating agent has been reported. In most reports, titanium(IV)-based reagents[2] have been used for the preparation of *N*-(*tert*-butylsulfinyl)imines. Other reagents, such as copper(II) sulfate,[2c,3] magnesium sulfate/pyridinium *p*-toluenesulfonate,[4] cesium carbonate,[5] ytterbium(III) triflate,[6] and potassium hydrogen sulfate[7] have also been shown to accomplish this conversion. Although several reagents can achieve this transformation, the development of alternative methods is still needed to enhance the scope of the procedure.

Heterogeneous catalysis has attracted considerable interest due to the many advantages of this approach, including ease of separation of catalyst from reaction mixture and the ability to recycle the catalyst. Amberlist-15 is a heterogeneous resin that is widely used in organic chemistry. It is a macro reticular polystyrene-based ion exchange resin that contains sulfonic acid functionality. Although the versatility of this material is well-known in organic synthesis,[8] to the best of our knowledge, the synthesis of *N*-(*tert*-butylsulfinyl)imine using this catalyst has not been reported. Herein, we wish to disclose a simple and efficient process for the preparation of *N*-(*tert*-butylsulfinyl)imines by using amberlist-15 in a catalytic amount under microwave irradiation (Scheme 1). This clean, high yielding, and scalable method offers many advantages such as operational simplicity and the use of inexpensive catalyst.



Scheme 1 Synthesis of *N*-(*tert*-butylsulfinyl)imines

We began to optimize the methodology by using benzaldehyde (**1a**; Table 1) and 2-methyl-2-propanesulfinamide (**2**) as starting materials. In our preliminary experiments, compound **1a** (1 mmol) was subjected to the reaction conditions with **2** (1.5 mmol) in the absence of amberlist-15 in tetrahydrofuran at room temperature under an inert atmosphere. After 24 h, formation of the desired product **3a** was observed along with unreacted starting materials (reaction analyzed by TLC, LCMS and NMR spectroscopy). The reaction was then repeated under heating (80 °C) for 12 h but no significant progress in the formation of the desired product was noted. With this result in hand, further reactions were conducted by using **1a** and **2** (1:1.5 ratio) in the presence of amberlist-15 (20 mol% by wt) in tetrahydrofuran at ambient temperature for 12 h. In this case, a significant improvement in the yield of the desired product **3a** was observed. Further efforts at optimization focused on reducing the reaction time by increasing the temperature of the reaction. According to a report by Ellman and co-workers, microwave irradiation was useful for the synthesis of *N*-(*tert*-butylsulfinyl)imines at constant temperature.[2a] Recently, Guijarro and co-workers also disclosed a method[2b] for the synthesis of such imines under solvent-free conditions under microwave irradiation. Keeping these observations in mind, we conducted the reaction with a ratio of **1a**/**2** of 1:1.5 at 80 °C under microwave irradiation, and found that the starting aldehyde was consumed in reduced reaction time to provide the product **3a**. We therefore decided to optimize the conditions for this methodology (Scheme 1). During the experiment, the temperature was maintained at 80 °C to get the desired product in maximum yield, since higher temperatures can produce the nitrile compound of the corresponding aldehyde in significant amounts.[9] Thus, a series of aromatic aldehydes **1b**–**k** (Table 1, entries 2–11) were selected for this reaction to study the applicability of the

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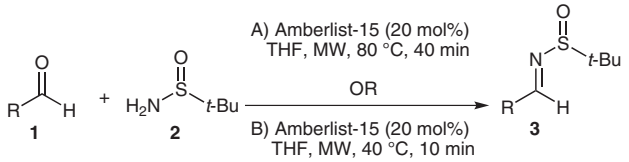
method. In each case, a good to excellent yield of the desired imine **3b**–**k** (Table 1) was obtained under the optimum reaction conditions.[10] The results of all the reactions are summarized in Table 1. The method was tolerant of various aryl halides, including Cl, Br and F. Electron-rich as well as electron-deficient aromatic rings showed similar reactivity under the optimized conditions (see Table 1).

Table 1 Synthesis of *N*-(*tert*-Butylsulfinyl)imines **3a**–**o**[a]



Entry	1	R	3	Yield (%)[b]
1	**1a**	Ph	**3a**	94[2b]
2	**1b**	4-$MeOC_6H_4$	**3b**	90[2b]
3	**1c**	3-$MeOC_6H_4$	**3c**	88
4	**1d**	2-$MeOC_6H_4$	**3d**	95[4b]
5	**1e**	2,4,6-$(MeO)_3C_6H_2$	**3e**	98
6	**1f**	4-$F_3CC_6H_4$	**3f**	88[11]
7	**1g**	4-ClC_6H_4	**3g**	92[2b]
8	**1h**	3,4-$Cl_2C_6H_3$	**3h**	88[12]
9	**1i**	2-FC_6H_4	**3i**	93[4e]
10	**1j**	4-*t*-BuC_6H_4	**3j**	97[13]
11	**1k**	3-indolyl	**3k**	95
12	**1l**	*n*-Pr	**3l**	81[4c]
13	**1m**	*i*-Pr	**3m**	80[2b]
14	**1n**	*t*-Bu	**3n**	85[2b]
15	**1o**	*c*-Hex	**3o**	82[2b]

[a] Compounds **1** and **2** were used in 1:1.5 ratio. For aromatic aldehydes conditions 'A' were applied and conditions 'B' were applied for aliphatic aldehydes.
[b] Yield refers to isolated material. Products were characterized by ^1H and ^{13}C NMR, IR and MS analyses.

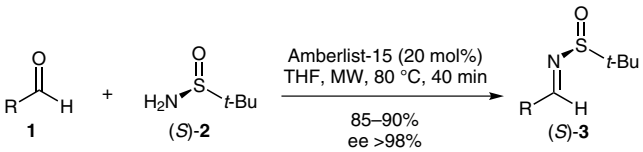
In a separate experiment, the reaction was performed by using benzaldehyde (**1a**; 1 g, 9.4 mmol) and 2-methyl-2-propanesulfinamide (**2**; 1.7 g, 14.2 mmol) under the optimum conditions, from which the desired product (**3a**) was isolated in comparable yield (1.79 g, 91%). From this observation, it was concluded that the process can be applied for the preparation of *N*-(*tert*-butylsulfinyl)imine on a gram scale.

To illustrate the potential of our synthetic procedure, the reaction conditions were also applied to aliphatic aldehydes. Pleasingly, these aldehydes reacted smoothly with **2** at 40 °C in the presence of a catalytic amount (20 mol% by wt.) of amberlist-15 under microwave conditions, thus demonstrating the generality of the methodology. A range of aliphatic aldehydes **1l**–**o** (Table 1, entries 12–15) were subjected to the reaction conditions with **2**, and the desired products **3l**–**o** were obtained in good yields. It is worth noting that at 40 °C, aldehyde functionalities attached to primary, secondary, and tertiary carbon atoms showed similar reactivities with **2**, affording the desired products in high yields (Table 1, entries 12–15).

All products were characterized by NMR, IR and mass spectroscopic analysis. Unfortunately, our efforts toward the synthesis of *N*-(*tert*-butylsulfinyl)imine under the optimum conditions using acetophenone was unsuccessful.

To demonstrate the significance of this method for the synthesis of chiral imines (*S*)-**3**,[14] a number of reactions were performed using (*S*)-2-methyl-2-propanesulfinamide [(*S*)-**2**] and aromatic aldehydes **1a**, **1b** and **1j** under the optimum conditions (Table 2). In each case, the desired product was obtained in good yield with high enantioselectivity (see the Supporting Information for HPLC data).

Table 2 Synthesis of *N*-(*tert*-Butylsulfinyl)imines (*S*)-**3**[a]



Entry	1	R	3	Yield (%)[b]	ee (%)
1	**1a**	Ph	(*S*)-**3a**	90	>99
2	**1b**	4-$MeOC_6H_4$	(*S*)-**3b**	88	>99
3	**1j**	4-*t*-BuC_6H_4	(*S*)-**3j**	85	>99

[a] Compounds **1** and (*S*)-**2** were used in a 1:1.5 ratio.
[b] Yield refers to isolated material. Products were characterized by ^1H and ^{13}C NMR, IR, and MS analyses.

In summary, we have described a general, simple and efficient methodology for the synthesis of *N*-(*tert*-butylsulfinyl)imines by using a heterogeneous polymer-supported catalyst (amberlist-15) under microwave irradiation. This method is useful for the synthesis of *N*-(*tert*-butylsulfinyl)imines (racemic and chiral) from aromatic as well as aliphatic aldehydes. This method can also be applied for the preparation of *N*-(*tert*-butylsulfinyl)imines on a gram scale.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and characterization data of all new compounds.

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(10) **Synthesis of *N*-(*tert*-Butylsulfinyl)imines (3); General Procedure:** To a stirred solution of aldehyde **1** (1 mmol) in THF (1 mL) was added 2-methyl-2-propanesulfinamide (**2**; 1.5 mmol) under inert conditions in a microwave tube. Amberlist-15 (20 mg) was added and the reaction mixture was heated to 80 °C (constant microwave irradiation 1–2 W power and 1–10 psi, with nitrogen gas cooling) under microwave irradiation for 40 min (for aromatic aldehydes and for aliphatic aldehydes all the reactants were mix together in THF and stirred at 40 °C for 10 min). The mixture was cooled to room temperature, then the catalyst was filtered through filter paper and washed with EtOAc. The solvent was evaporated under reduced pressure to obtain a crude mass, which was purified by flash chromatography over silica gel (hexanes–EtOAc) to afford pure **3.**

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(14) For compound (*S*)-**3a** see ref. 4a and for compound (*S*)-**3b** see ref. 7.

