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Tetrahedron Letters 48 (2007) 1845–1848
Tetrahedron Letters

Eco-friendly synthesis of imines by ultrasound irradiation

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Received 16 October 2006; revised 15 December 2006; accepted 3 January 2007
Available online 7 January 2007

Abstract—A series of imines was synthesized by an ultrasound-assisted reaction of aldehydes and primary amines using silica as the promoter. Products were obtained in high yields even in large scale synthesis.

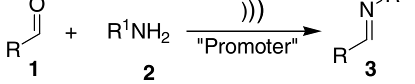
The nitrogen atom is present in most natural products, biologically important molecules, pharmaceuticals, and dyes.[1] Imines and their derivatives are useful intermediates in organic synthesis,[2] in particular for the preparation of heterocycles and non-natural β-aminoacids.[3]

Several methods for the synthesis of imines are described in the literature; they can be obtained from aldehydes,[4] *gem*-dibromomethylaryl derivates,[5] formamides,[6] palladium catalyzed amination[7] as well as by polymer-supported.[8] However, these methodologies often require complex procedures, long reaction times, and large quantities of aromatic solvents. This conventional phase solution chemistry typically involves distillation under reduced pressure or azeotropic removal of water by a Dean–Stark apparatus. Solvent-free synthesis of imines and enamines under microwave irradiation has been described.[9] However, this method was applied for a limited number of compounds and the possibility of scaling up the synthesis was not evaluated. More recently, Chakraborti et al. reported the synthesis of imines using magnesium perchlorate as the catalyst with reaction times ranging from 15 to 480 min.[10]

It is well known that many organic reactions are accelerated by ultrasound irradiation.[11] Compared with traditional methods, this technique is more convenient taking green chemistry concepts into account. Sonochemistry is considered a processing aid (or auxiliary) in terms of energy conservation and waste minimization.[12] Recently we have developed general methods for the synthesis of numerous useful organic compounds under ultrasound irradiation, for example, aryl acetylenes[13] and heterocycles.[14] Moreover, we have used sonochemistry to accelerate Suzuki–Miyaura reactions.[15]

As a part of our growing interest in sonochemistry, with the aim of improving the synthesis of imines, we decided to undertake a systematic study of the preparation of imines using this alternative energy source (Scheme 1).

First of all, we screened a wide variety of promoter to the imines synthesis (Table 1) using benzaldehyde (**1a**) and *p*-methoxyaniline (**2a**) in ethanol under ultrasound irradiation as a standard reaction. Looking for cleaner approaches to classical syntheses, we chose some solid supported catalysts, for example, clay, silica or resin due to their low impact in the environment, possibilities to recycle them and in some cases their high availability from nature. As can be seen in Table 1, the best results were reached with alumina and silica (Table 1, entries 2 and 6) 83% and >99% yields, respectively. When no promoter (Table 1, entry 1) was used the desired product **3a** (*N*-benzylidene-4-methoxybenzenamine) was obtained in a 57% yield. The resins DOWEX® and Amberlyst®



Scheme 1. General systematic study.

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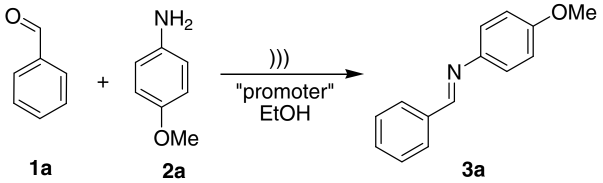
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2007.01.014

Table 1. Choose of promoter



Entry	Catalyst	Yield[a] (%)
1	Absence	57
2	Alumina	83
3	DOWEX®	39
4	Amberlyst®	26
5	Celite®	73
6	Silica	>99

[a] Isolated yields.

(Table 1, entries 3 and 4) were employed also as a promoters, but very low yields were obtained. When Celite® (Table 1, entry 5) was used the product (**3a**) was obtained in a good yield, 73%.

We also tested the appropriate quantities of silica necessary to perform the synthesis of imines under ultrasound irradiation (Table 2). These experiments led us to conclude that 5 equiv of silica furnishes the respective product in a quantitative yield (Table 2, entry 3).

We also analyzed the effect of the reaction solvent. In addition to ethanol we tested ethyl acetate, dichloromethane and THF (Table 2, entries 4–6). As can be seen a similar result was obtained when dichloromethane was used (Table 2, entry 5), but we chose ethanol due to several advantages. Among them ethanol is an inexpensive solvent, derivated from a renewable source and very much available all over the world.

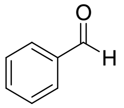
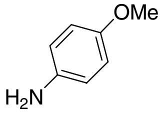
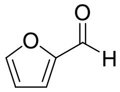
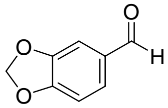
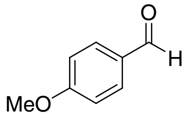
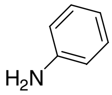
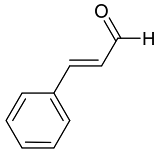
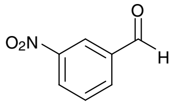
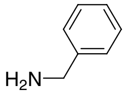
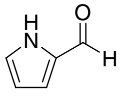
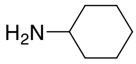
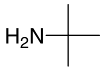
The scope and generality of this process are illustrated by a series of 20 imines as can be seen in Table 3. A wide range of aromatic and heteroaromatic aldehydes were employed and all imines were obtained in excellent yields (Table 3, entries 1–16), and was observed that is a general method that tolerates both electron-withdrawing and electron-donating substituents. An α,β-unsaturated aldehyde (cinnamaldehyde **1h**) was also used and the yields were excellent (Table 3, entries 7, 9, 17 and 19).

Table 2. Loading of silica

Entry	Silica ratio (equiv)	Solvent	Yield[a] (%)
1	1	EtOH	87
2	2.5	EtOH	93
3	5	EtOH	>99
4	5	AcOEt	60
5	5	Dichloromethane	98
6	5	THF	75

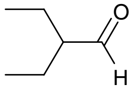
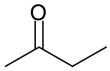
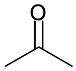
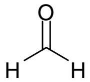
[a] Isolated yields.

Table 3. Synthesis of imines under ultrasound irradiation using silica

Entry	Aldehyde (**1**)	Amine (**2**)	Imine (**3**)	Yield[a] (%)
1	 **1a**	 **2a**	**3a**	>99 (96)[b]
2	 **1b**	**2a**	**3b**	85
3	 **1c**	**2a**	**3c**	>99 (91)[b]
4	 **1d**	**2a**	**3d**	>99
5	**1a**	 **2b**	**3e**	>99 (90)[b]
6	**1c**	**2b**	**3f**	90
7	 **1e**	**2b**	**3g**	85
8	 **1f**	**2b**	**3h**	86
9	**1e**	 **2c**	**3i**	88
10	**1f**	**2c**	**3j**	96 (93)[b]
11	**1b**	**2c**	**3k**	87
12	**1c**	**2c**	**3l**	98
13	**1d**	**2c**	**3m**	90
14	 **1g**	 **2d**	**3n**	93 (90)[b]
15	**1a**	**2d**	**3o**	86
16	**1c**	**2d**	**3p**	90
17	**1e**	**2d**	**3q**	88
18	**1a**	 **2e**	**3r**	95

The reaction worked very well with 2-ethyl butyraldehyde **1h**, an aliphatic aldehyde (Table 3, entries 20–23), but when formaldehyde was used no reaction was

Table 3 (*continued*)

Entry	Aldehyde (**1**)	Amine (**2**)	Imine (**3**)	Yield[a] (%)
19	**1e**	**2e**	**3s**	96 (90)[b]
20	 **1h**	**2a**	**3t**	88
21	**1h**	**2b**	**3u**	99
22	**1h**	**2c**	**3v**	94
23	**1h**	**2d**	**3w**	95
24	 **1i**	**2a**	**3x**	nr
25	 **1j**	**2a**	**3y**	nr
26	 **1k**	**2a**	**3z**	nr

[a] Isolated yields.

[b] Scale-up of 50 mmol.

observed (Table 3, entry 26). Ketones were tested (Table 3, entries 24 and 25), but no reaction was observed too.

About primary amines **2**, we used aromatic amines as well as benzylic and aliphatic amines and as can be seen in Table 3 no difference in the reactivity was observed. All imines were obtained in a very high yield and in some cases quantitatives yields were reached.

In addition, the synthesis of imines on a large-scale (50 mmol) was tested. The reaction demonstrated to be very efficient on this scale and the products **3a**, **3b**, **3e**, **3j**, **3n** and **3s** were obtained in excellent yields (90–96%) using the same reaction conditions (Table 3).

The reusability of the promoter was checked over several cycles. The reactivation of the catalyst was given only by heating in a oven for 4 h. As can be seen in the Figure 1 a slight decrease was observed in the second and third utilization and in the fifth the yield decayed by half.

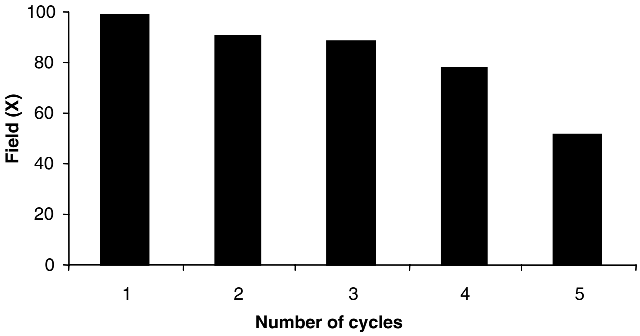


Figure 1. Reusability of the promoter.

In conclusion, we have developed a mild, convenient and improved protocol for the preparation of imines by ultrasound irradiation. Among the advantages of the method we can mention: (i) the reaction is simple to execute; (ii) the yields are excellent (85–>99%); (iii) a very simple work-up; and (iv) short reaction time (10 min).

Moreover, this protocol can be included in some green chemistry concepts as (i) atom economic; (ii) waste minimization; and (iii) energy conservation.

Acknowledgments

The authors wish to thank FAPESP (Grant 03/01751-8 and the Scholarship 03/13475-5-CMPP, 03-13897-7-RC), and CNPq agencies for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.014.

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