Microwave Assisted Solvent Free Synthesis of Azomethines from Aryl Aldehydes on Melamin Formaldehyde as Solid Support

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Received 29 October 2010; Accepted 20 January 2011

Abstract: Various aryl aldehydes underwent prompt one pot conversion into the corresponding azomethines in high yields by reacting with hydroxylamine hydrochloride supported on melamine formaldehyde under microwave irradiation.

Keywords: Microwave, Solvent free, Melamin formaldehyde, Aryl aldehyde, Azomethine, One pot

Introduction

Azomethines are important building blocks in enantioselective oxidations (chiral oxaziridines)¹, cycloadditions² and cyclizations³. The synthesis of azomethines³ from anilines and aromatic aldehydes is usually carried out in solution by acid catalysis and removal of the water formed in the reaction. Yields are rarely reported but may reach 80-90% after workup including neutralization and crystallization.

Azomethine compounds are widely studied and used as attracting complexation agents^{4,5}. The traditional syntheses of such compounds are still commonplace alongside modern synthetic protocols⁴. Typically, the synthesis employs the use of a high boiling point volatile organic solvent such as toluene, followed by extensive recrystallisation and/or chromatography. In embracing the principles of green chemistry⁶, azomethine (Figure 1) are intermediates in many reaction of both enzymatic and pharmaceutical insert. Traditional synthesis often involve the use of toxic solvent such as methylene chloride⁷ or refluxing in petroleum-based solvents such as toluene as azeotroping agents⁸. Some recent imine syntheses have successfully used more benign solvents or conditions but still require recrystallization or other work up procedures, which negate some of the benefits of the green

synthesis itself⁹⁻¹⁴. Here we describe a greener synthesis of aryl aldimines using ethyl *L*-lactate as the solvent. Water was used as a cosolvent to optimize solvent polarity and induce rapid formation of product. The imines crystallized directly out of solution in high purity and yield, requiring no further purification.

However, most of these reported methods are associated with significant drawbacks such as low yields, long reaction time, toxic and non-available reagents and harsh reaction conditions. Recently we have developed a more advantageous method for the solvent free conversion of aldehydes into azomethines under solvent free and microwave irradiation conditions using melamine formaldehyde(M.F) resin as solid support (Figure 1, Table1).

Experimental

Benzaldehyde derivatives, aniline derivatives, melamine formaldehyde (Merck) were used without further purification. Silica gel Aldrich, - 150 mesh (Aldrich) and TLC plates (Merck) were used. Solvents were purified by standard methods. Infrared spectra were recorded as KBr disks on a Shimadzu model 420 spectrophotometer. The UV/vis measurements were made on an Uvicon model 922 spectrometer. ¹H, ¹³C-NMR spectra, were carried out on a Bruker AVANCE DRX 300 spectrometer. All the chemical shifts are quoted in ppm using the high-frequency positive convention; the ¹H and ¹³C-NMR spectra were referenced to external SiMe₄. Experiments were carried out in closed vessel multi mode microsynth milstone laboratory microwave oven using a 900 watts westpointe microwave operating at 3.67 GHz with an internal volume of 0.9 m². All experiments had good reproducibility by repeating the experiments in same conditions. All compounds have a well known structures¹⁷.

General procedure

Benzaldehyde (1 mmol), aniline (1 mL) and melamine formaldehyde (2 g) were mixed thoroughly with mechanical mixer. This mixture then irradiated in microwave oven (800 w) (approximately 5 min). The progress of the reaction was monitored for the period of 30 s by TLC (EtOAc/Hexane, 20:1). On the completion of the reaction (monitored by TLC), CH₂Cl₂ was added priory (2×10 mL). The melamine formaldehyde was removed by simple filtration and the organic layer was separated. The solvent was removed by a rotary evaporator and the resulting precipitate was purified by recrystallization with methanol. The residue then washed with ethanol and dried in electrical oven to give benzonitrile in good to high yields (Table 1). Recyclization of melamine formaldehyde resin was carried out with CCl₄. For other benzaldehyde derivatives, procedure was the same as benzaldehyde (Figure 1).

Figure 1. Preparation of azomethin compounds in microwave irradiation on melamin formaldehyde as solid support

All azomethine compounds were compared with the same compounds and the structure of all compounds were proved^{3-5,18} (Table 1).

Table 1. Solvent free synthesis of azomethine derivatives under microwave irradiation

R ₁	R ₂	Time, min	m.p.°C	Yield, %
H	H	5	48-50	86
<i>p</i> -Cl	H	6	60-61	88
<i>p</i> -Me	H	5	37-38	90
<i>p</i> -NO ₂	H	4	76-78	92
<i>p</i> -DiMe	H	4	81-82	89
2,4-DiChloro	H	8	78-80	85
2,6-DiChloro	H	4.5	46-48	89
2-Cl,6-F	H	4	---	90
3-NO ₂	H	5	65-67	93
H	3-Cl,4-Me	3.5	54-55	91
H	5-Cl,2-Me	3.5	86-88	91
3-NO ₂	3-Cl,4-Me	3	94-96	92
3-NO ₂	5-Cl,2-Me	3	86-87	93
2,6-DiChloro	3-Cl,4-Me	2.5	90-92	94
2,6-DiChloro	5-Cl,2-Me	2	88-89	96

Results and Discussion

The lack of control in domestic microwave ovens when performing microwave assisted syntheses has led to a vast number of incidents, including explosions, being reported. One method for avoiding the problem, has been the omit the solvent from the reaction and perform the reactions on solid supports such as various clays, aluminum oxides and silica. A number of very interesting syntheses have been performed using this techniques and a majority of the publications contain work conducted in this manner^{15,16}. The solvent free technique has been claimed to be particularly environmentally friendly, since it avoids the use of solvents and offers a simpler method for workup.

As shown in the Table 1, the reaction could be easily applied to structurally diverse aldehydes and amines to give the corresponding azomethines in excellent yields. This protocol was compatible with reactive benzaldehydes containing different electron-withdrawing and electron-donating substituents. The variation of electron-donating and withdrawing substituents to the aromatic rings have no significant effects on the reaction rates and yields. The present method probably proceeds *via* initial formation of *O*-acetylaldehyde intermediates, formed *in situ* by dehydration reaction of aldol intermediates with followed by its decomposition under microwave irradiation conditions.

In these reactions, arylaldehydes bearing both electron-donating and electron-withdrawing substituents, are rapidly converted into nitriles in good yields (48-96%) with melamine formaldehyde coupled with MW irradiation under solvent free condition.

The procedure in its entirety involves admixing aldehydes with melamine formaldehyde and subjecting the solid reaction mixture to microwave irradiation in an unmodified laboratory MW oven at its full power (900 Watts) for 2-8 min. A variety of aldehydes undergo facile conversion in the presence of hydroxylamine hydrochloride 'doped' melamine formaldehyde to afford high yield of imines within a short time of irradiation (Figure 1).

In the case of aliphatic aldehydes, however, only poor yields of imines (10-15%) are obtained with complex by-product formation that was not included in Table 1. It was shown in Table 1 that withdrawing groups on benzaldehyde derivatives such as Cl, NO₂ decrease the time of the reaction probably due to increasing the positive property of carbonyl group, but was not case sensitive for yield of products. As a model compound, we were examined the reaction with various aniline derivatives. Best results are obtained with derivatives involving electron donating groups.

Conclusion

It can be concluded that the melamine formaldehyde as a solid support, can be used as an efficient, excellent, readily available and cheap catalyst in conversion of aldehydes to imines under microwave irradiation. Furthermore, the reaction is a green process and the catalyst is recyclable for several uses. The advantages of the present method in terms of facile manipulation, fast reaction rates and formation of cleaner products under neat reaction conditions should make this protocol as a valuable alternative to the existing methods.

Acknowledgment

We gratefully thank the chemical research center of Islamic Azad University, Firoozabad Branch for their financial support of this work.

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