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PII: S0040-4039(13)01116-7
DOI: http://dx.doi.org/10.1016/j.tetlet.2013.06.131
Reference: TETL 43184

To appear in: *Tetrahedron Letters*

Received Date: 4 May 2013
Revised Date: 24 June 2013
Accepted Date: 26 June 2013

Please cite this article as: Dar, B.A., Ahmad, S.N., Wagay, M.A., Hussain, A., Ahmad, N., Bhat, K.A., Khuroo, M.A., Sharma, M., Singh, B., Ultrasound promoted expeditious, catalyst-free and solvent-free approach for the synthesis of N,N'-diarylsubstituted formamidines at room temperature, *Tetrahedron Letters* (2013), doi: http://dx.doi.org/10.1016/j.tetlet.2013.06.131

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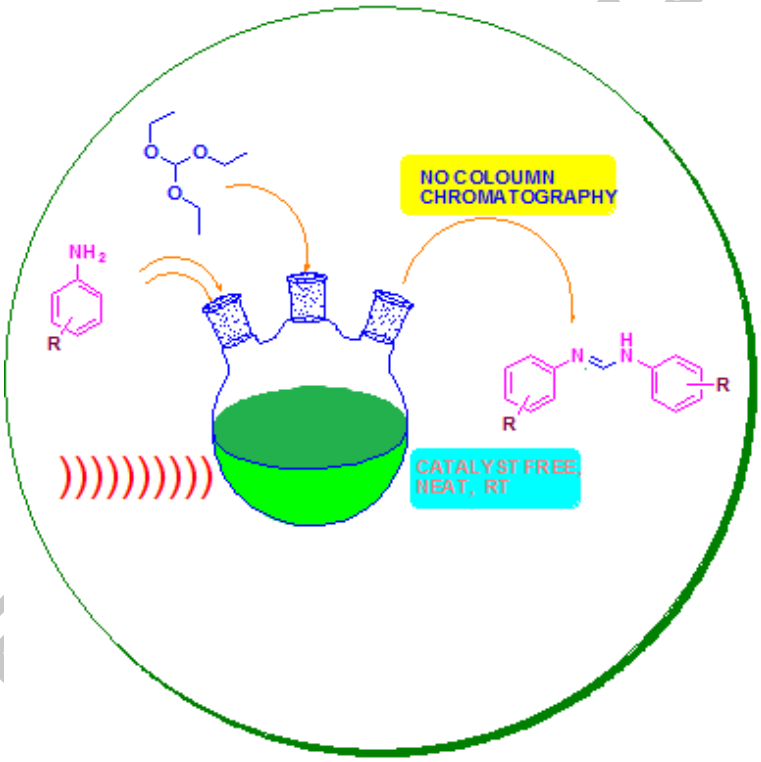

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Abstract

An effortless and efficient protocol was developed for the synthesis of N,N'-diarylsubstituted formamidines under environment-friendly conditions. Ultrasonic energy was employed to obtain the desired products in excellent yields with high purity under solvent-free and catalyst-free conditions. Products were purified by crystallization technique to avoid excess utilization of organic solvents.

Keywords; Formamidines, Ultrasonication, Green chemistry, Crystallization

Introduction

Organic compounds containing formamidine scaffold have been studied extensively because of their significant applications as bioactive molecules,[1] synthons for various chemical transformations,[2] chelating or bridging modes,[3] building blocks in polymer synthesis,[4] ultraviolet light absorbers,[5] bleaching agents for paper,[6] ligands in transition metal catalysts for asymmetric synthesis,[7] protecting groups for primary amines[8] and support linkers in solid phase synthesis.[9] Moreover, formamidines are useful to the physical chemists for dynamic NMR study.[10] Some cryoscopic molecular weight determination experiments have also been reported using the molecular association property of benzene solution of diarylformamidines.[11]

Several methods have been reported for the synthesis of formamidines but most of them involve multi-step procedures and longer reaction times.[12] Reduction of carbodiimides with sodium borohydride to the corresponding formamidines was reported as a suitable synthetic method,[13] but exercise of toxic organic solvents (iso-propanol) could not be avoided in conducting the reaction or working-up the product. One of the most popular methods for the synthesis of symmetrical and unsymmetrical formamidines is the exchange of N,N-

dimethylformamidines or acetamidines by different amines.[14] The negative aspect of this protocol remains in the utilization of protic organic solvents and high temperature.[15] Other methods involve use of acid chlorides,[16] aldehydes,[17] o-dinitrobenzene,[18] Gold's reagent[19] and 2-nitroanilines[20] as the starting materials. Taylor *et al*.,[13] have reported a general synthetic method for the synthesis of formamidines by the reaction of triethylorthoformate or orthoacetate with a number of aliphatic and aromatic amines in acetic acid under reflux at 140°C - 150°C. For the advancement of this protocol different catalytic systems like $FeCl_3$,[21] β-Cyclodextrin,[22] sulfated zirconia,[23] cerric ammonium nitrate [24] and fluorinated solvent [25] etc have been investigated. The beneficial effect of base in non-protic solvents for these transformations has also been reported.[26] Unfortunately, these protocols have suffered from several problems such as the use of toxic organic solvents (either in conducting of reaction or working-up of product), high temperatures, low reaction rate, strong acidic conditions, low yields of the products, tedious work-up and application of excess amounts of reagents. Therefore, highly efficient and environmentally benign procedure to prepare N,N-diarylformamidines is still demanded.

Application of ultrasonic energy in chemical transformation is an attractive and effective approach to solve the problem of poor reaction rate.[27]The main cause of low reaction rate is due to poor contact between the reactants and poor mass transfer. Subjecting reaction mixture to the ultrasound irradiation coerces the fluids to generate huge number of cavitation bubbles which grow rapidly and subsequently undergo violent collapse. These vigorous collapses result in the creation of micro-jets that can produce fine emulsion between the reactants. Moreover, these collapses also lead to the amplification in the local temperature within the reaction mixture.[28]Many chemical reactions can be conducted smoothly by sonication to afford improved yields and increased selectivity. Thus, the ultrasound irradiation has been

established as an important technique in organic synthesis.[29] In continuation of our interest in ultrasound assisted organic reactions, [30] we herein describe the ultrasound promoted procedure for the synthesis of N,N'-diarylsubstituted formamidines with different species of aryl amines, in catalyst-free and solvent-free conditions (Scheme 1). The rapid kinetics under mild conditions, simple work-up and easy purification are added advantages of this protocol.

Scheme 1

In a preliminary experiment, we attempted one pot coupling of 4- methoxyaniline (2 mmol), triethylorthoformate (1mmol) as the model reaction to optimize the reaction conditions. The reaction proceeded efficiently with 100% conversion to afford the corresponding diarylformamidines (98% yields) within short time (50 min) at room temperature (Scheme 1). No chromatographic technique was used for product purification; the desired products were purified through crystallization to avoid the excess use of volatile organic solvents. Moreover this method avoids the exposure of silica gel which is responsible for the decomposion of formamidines to the corresponding amines.[31]

Performing the model reaction under stirring conditions at room temperature without ultrasonic radiation furnished traces of the product even after 24 h, both with and without solvent (Table 1, entry 1–2). Increasing temperature up to 100 ^{o}C under stirring conditions in the absence of ultrasound radiations could yield only 41% after 24 h reaction time under solvent-free conditions. Stirring the reaction mixture at 100 ^{o}C using DMSO as solvent yielded 46% of the

desired product in 24 h reaction time (Table 1, entry 5–6). The ultrasonic energy thus might be the major reason for the high efficiency of the one-pot and solvent-free reactions.

Table 1

Reaction of 4-methylaniline with triethylorthofornate under different reaction conditions

Entry	Condition	Solvent	**Time**	**Yield[a](%)**
1	Stirring at 30 ^{o}C	DMSO	24 h	Traces
2	Stirring at 30 ^{o}C	No solvent	24 h	Traces
3	Sonication at 30 ^{o}C	No solvent	50 min	98
4	Sonication at 30 ^{o}C	DMSO	90 min	91
5	Stirring at 100 ^{o}C	No solvent	12 h	21
6	Stirring at 100 ^{o}C	DMSO	12 h	27

a = HPLC Yield calculated based on the integration of the analytical HPLC signals

Screening of different solvents such as water, ethanol, methanol, dichloromethane, N,N-diethylformamide, toluene, hexane, acetonitrile for this reaction and their comparison with the solvent-free approach proved that better results are obtained in solvent-free conditions (Table 2, entry 1–12).

Table 2.

Effect of solvents on the reaction of 4- methoxyaniline and triethylorthoformate under ultrasonication.

Entry	Solvent	Time(min)	Yield[a](%)
1	Solvent-free	50	98
2	Hexane	90	72
3	Dimethylsulfoxide	90	91
4	Tetrahydrofuran (THF)	100	75
5	Dimethylformamide	100	84
6	Acetone	120	71
7	Acetonitrile	100	88
8	Methanol	90	75
9	Toluene	120	72
10	Dichloromethane	120	69
11	Ethanol	90	66
12	Water	120	49

a = HPLC Yield calculated based on the integration of the analytical HPLC signals

Having optimized reaction conditions in hand we attempted to study the scope and the limitations of this novel method, we investigated the reaction using several electron-donating and electron-withdrawing substituted anilines with triethylorthoformate under solvent-free

conditions. The reaction was found compatible with various functional groups such as F, Cl, Br, I, OMe, NO_2, CF_3 and CN with excellent chemoselectivity (Table 3, entries 3-8 & 12-14). All the respective products were formed very easily. Anilines substituted with electron donating groups were observed to require lesser time than the anilines substituted with electron withdrawing groups. No significant improvement in the yield of the products was observed for low yielding reactions (e.g., Table 3, entry 5), (Fig. 1) even after longer reaction times. Upon conducting these reactions under conventional stirring, very low product yields were obtained even after 12-18 h. So it is clear that the reaction times are reduced to a great extent and the yield of the products is increased under ultrasonic irradiation without using any catalyst in all the cases. Based on the results of this study, it seems that the ultrasound radiations are sufficient to drive this reaction in the absence of any catalyst with decreased reaction times and improved yields of desired products.

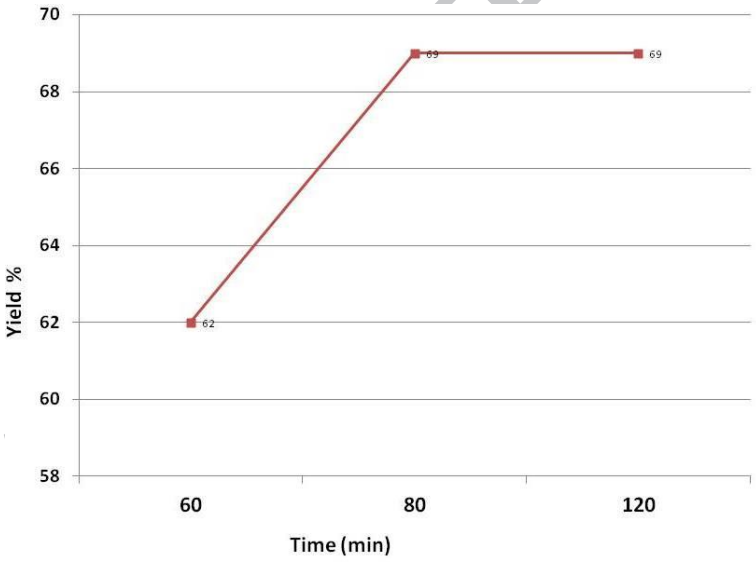
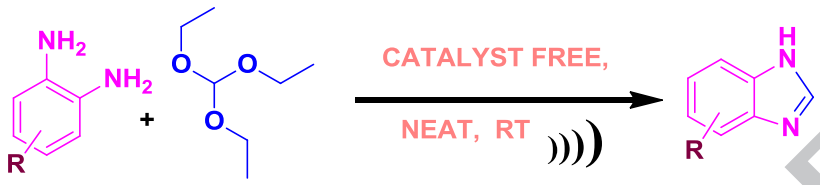


Figure 1. Effect of reaction time on the yield.

Further we extended this methodology for the synthesis of ~~bB~~benzimidazoles and the experiments revealed that a similar procedure is also applicable for the preparation of a wide range of benzimidazole analogous (Scheme 2).

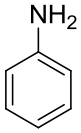
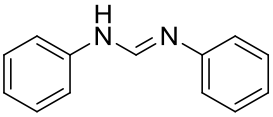
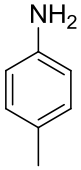
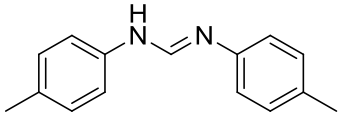
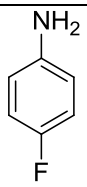
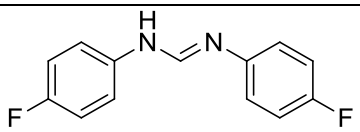
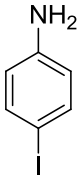
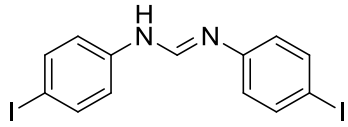
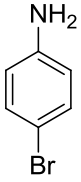
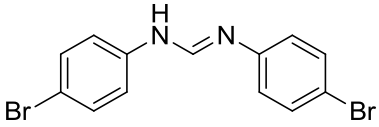
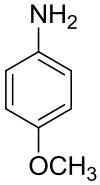
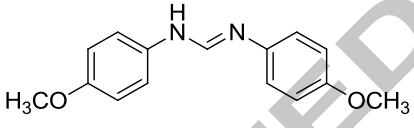
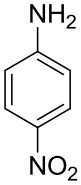
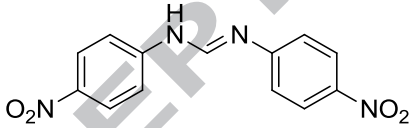
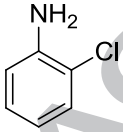
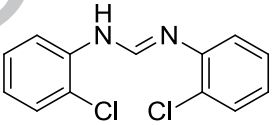
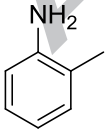
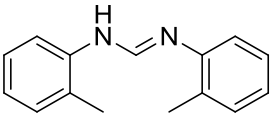


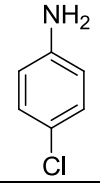
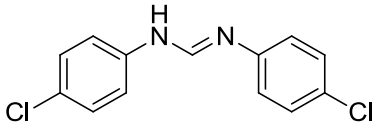
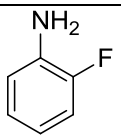
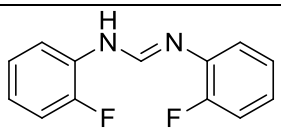
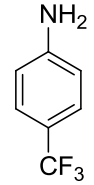
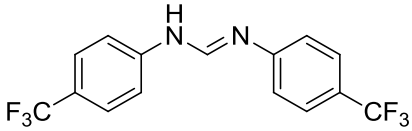
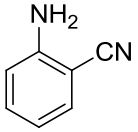
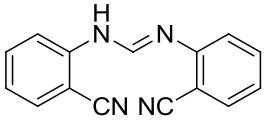
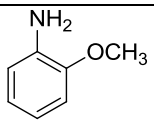
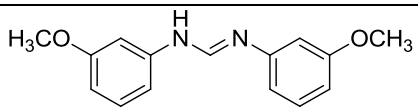
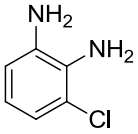
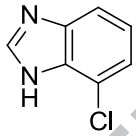
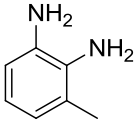
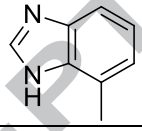
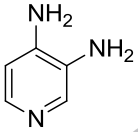
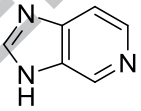
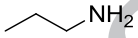
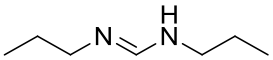
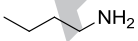
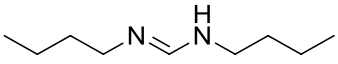
Scheme 2

This method is equally effective with the substrates bearing electron withdrawing as well as electron donating groups on the aromatic ring (Table 3, entry 15-17). Benzimidazole heterocycles are very important bioactive compounds which are known to show antiviral, antihypertension, anticancer properties.[32] A typical procedure for one-pot synthesis of N,N'-diarylsubstituted formamidines is given in refrences section.[33]

Table 3. Synthesis of N,N'-diarylformamidines.

Entry	**Aniline**	**Product**	**Time**		**Yield[a] %**	
			Stirring at 100 ^{o}C	Sonication at R.T.	Stirring	Sonication

1			12 h	50 min	21	98
2			12 h	50 min	27	98
3			12 h	70 min	9	81
4			15 h	70 min	10	78
5			15 h	80 min	10	69
6			12 h	50 min	27	98
7			16 h	90 min	6	64
8			16 h	90 min	7	67
9			12 h	50 min	18	96

10			16 h	100 min	9	72
11			16 h	100 min	11	84
12			15 h	80 min	12	86
13			12 h	80 min	14	78
14			12 h	50 min	24	95
15			18 h	120 min	9	66
16			18 h	120 min	12	67
17			18 h	120 min	8	62
18			18 h			
19			18 h			

Conditions: a= HPLC Yield calculated based on the integration of the analytical HPLC signals.

Under conventional stirring the reactions were carried out in DMSO medium.

In conclusion, we have developed a mild and efficient method for the synthesis of formamidine and benzimidazole derivatives using various electronically and structurally divergent amines in good to excellent isolated yields. In comparison to the methods using potentially hazardous catalysts or additives, this method is inexpensive, easy to handle, requires short reaction times, avoids the use of any base, metal/acid catalyst with no side reaction, provides easy product purification by non-aqueous work-up. Further studies and efforts to extend the scope of this method for other useful reactions are currently underway.

^{1}H, ^{13}C NMR of some representative compounds is provided in supplementary information.

Acknowledgments

B. A. D. thanks CSIR, New Delhi for awarding the senior research fellowships.

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33 Typical procedure for one-pot synthesis of N,N'-diarylsubstituted formamidines:

A mixture of trimethyl orthoformate (1 mmol), amine (2 mmol) (Scheme 1) or O-phenylenediamine (1.3 mmol) (Scheme 2) was taken in a 5 ml glass test tube with total reaction volume 0.4– 0.5 ml approximately. The reaction mixture was placed at room temperature for specified time under ultrasonic irradiation, performed in a Bandelin Sonorex Super RK 510 H ultrasonic bath with inner tank dimensions; l x w x d: 300 x 240 x150 mm, Exterior dimensions; l x w x h: 325 x 265 x 305 mm, Frequency: 35 kHz and Ultrasonic peak output: 640W⁄. Progress of the reaction was monitored by TLC (silica gel). After completion of the reaction the mixture concentrated under reduced pressure. To calculate the reaction yield an aliquot (1 mg) of the reaction mixture was dissolved in methanol (1 ml) and subjected to HPLC analysis (Agilent 1100

series, mobile phase- water containing 0.5%acetic acid and acetonitrile in gradient system, flow rate-0.7 ml/min, column-RP-18, column temp.-30^0, wavelength-254nm) and percentage yield of compound was obtained based on calculated peak area. The crude product thus obtained was purified by the process of crystallization to afford the corresponding pure N,N'-diarylsubstituted formamidines or respectively the benzimidazole in good to excellent yields. The physical data (^{1}H, ^{13}C NMR, HRMS and IR) of these known compounds were found to be identical with those reported in the literature.