Chemo, Stereo, and Regioselective Addition of α-(2-Methoxyaryl)-*N*-aryl Nitrones to Diarylidineacetone: Synthesis of Novel Isoxazolidines

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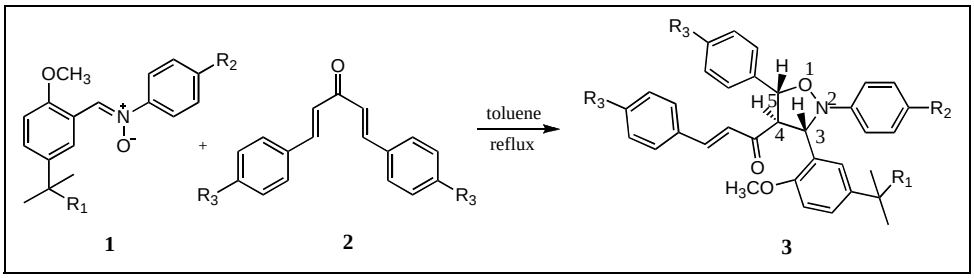

A new set of 2,3,4,5-tetrasubstituted isoxazolidines with an α,β-unsaturated carbonyl function at position 4 has been synthesized. The multicomponent approach and microwave irradiation protocol have also been investigated for the above synthesis.

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INTRODUCTION

1,3-Dipolar cycloaddition reaction is an important and powerful tool for the synthesis of five membered heterocycles [1]. Among all five membered heterocyclic systems, isoxazolidines attracted considerable attention of organic chemists and biochemists due to their potential biological activities [2-5]. In recent years, an enormous number of articles have been published highlighting the synthesis of isoxazolidines *via* 1,3-dipolar cycloaddition reactions [6-10]. These cycloadducts, isoxazolidines have been used as templates to generate β-amino alcohols through reductive cleavage of the N-O bond, which are potential precursors for the synthesis of several natural products such as β-lactam antibiotics and alkaloids [11]. It has also been found that isoxazolidines act as a new class of corrosion inhibitors of mild steel in acidic media [12]. The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical process. Microwave-accelerated reactions under solvent-free conditions are effective protocols in green organic synthesis [13-16]. Parallel to microwave-assisted and solvent-free reactions, multicomponent reactions [MCRs] received considerable attention from synthetic chemists [17-20]. MCRs are used to synthesize interesting complex molecules in fast, efficient and time saving manner. Hence we planned to carry out the cycloaddition reactions of α-(2-methoxyaryl)-N-aryl nitrones to diarylidineacetones not only by conventional method but also under multicomponent and solvent-free microwave conditions. These 1,3-dipolar cycloaddition reactions led to novel isoxazolidines, which are efficient Michael acceptors and potential precursors for bis-heterocyclics.

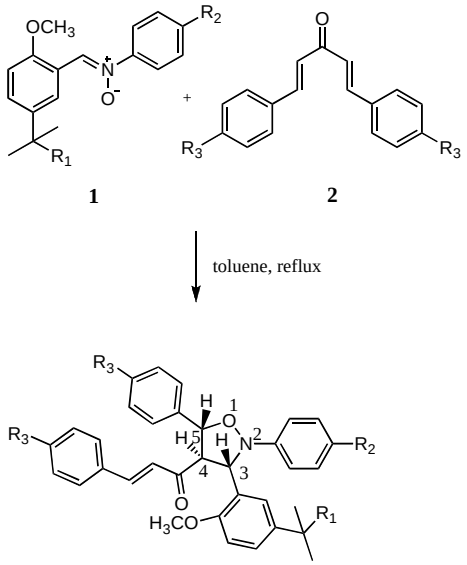
RESULTS AND DISCUSSION

Recently, we have been interested in the synthesis of isoxazolidines *via* 1,3-dipolar cycloaddition reactions and the analysis of the effect of substitutents on the conformation of the central five membered isoxazolidine ring [21-23]. In continuation of this work, we planned to synthesize bis heterocycles with at least one isoxazolidine unit. The synthesis of a set of keto-linked bis heterocyles has been reported recently [24]. But a detailed literature survey revealed that there is no report on the cycloaddition of diaryl nitrones on symmetrical bischalcones. These dipolarophiles, diarylidineacetones (**1**), are interesting as they have two potentially activated double bonds and they can lead to the formation of mono as well as bis type adducts with appropriate amount of the 1,3-dipoles. Thus there is more scope for additional products apart from the normally expected regio and stereoisomers.

An equimolar mixture of α-(2-methoxyaryl)-*N*-aryl nitrone (**1**) and diarylidineacetone (**2**) was refluxed in toluene for 6-8 hours. After working up, it was found that only one product dominates in the reaction mixture as revealed by tlc and the ^{1}H NMR spectrum of the crude reaction mixture. The product (**3**) was nicely crystallized out from petroleum ether and the remaining mass does not

contain any recognizable product apart from the unreacted starting compounds. It is very clear that the cycloaddition has taken place with high diastereoselectivity with 75-85% conversion (Scheme 1).

Scheme 1



Compd	R_1	R_2	R_3	Reaction time (h)	Yield (%)
3a	Me	H	H	6	85
3b	Et	H	H	6	83
3c	Et	H	Me	7	78
3d	Ph	H	H	8	78
3e	Ph	H	Me	8	81
3f	Et	H	Cl	7	84
3g	Ph	Me	H	8	75
3h	Ph	Me	Me	6	80

The product isolated was identified as (*E*)-1-{3-[2-methoxy-5-substitutedphenyl]-2,5-diaryltetrahydro-4-isoxazolyl}-3-aryl-2-propen-1-one (**3**) with *trans* orientation of the substituents between C_4 and C_5 by detailed NMR study.

In order to confirm the assigned stereochemistry, single crystal X-ray analysis was carried out for compound **3b,** (*E*)-1-{3-[2-methoxy-5-(*t*-pentylphenyl]-2,5-diphenyltetrahydro-4-isoxazolyl}-3-phenyl-2-propen-1-one (Figure 1). The central five membered isoxazolidine ring has an envelop conformation with oxygen atom being out of plane as observed in the related isoxazolidine systems [23]. The fact that there is no other regio or stereoisomer was formed during the addition and that one of the double bonds was not attacked by another mole of the 1,3-dipole, clearly indicates the chemo, regio and stereoselectivities associated with the reaction. When the reaction was carried out in 1:2 ratio of dipolarophile and dipole in the expectation of effecting the cycloaddition on both double bonds, it is found that only one product was isolated from the reaction mixture which was shown to be (*E*)-1-{3-[2-methoxy-5-substitutedphenyl]-2,5-diaryltetra-hydro-4-isoxazolyl}-3-aryl-2-propen-1-one (**3**). It is interesting that a second nitrone unit is not undergoing cycloaddition with the other unsaturated system available in **3**, which is probably due to the steric effect.

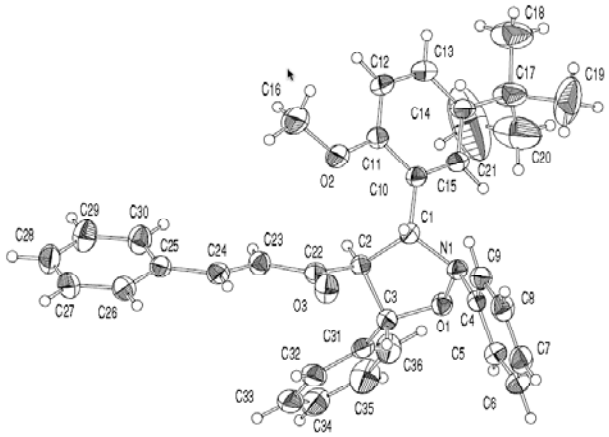


Figure 1. ORTEP diagram of (*E*)-1-{3-[2-methoxy-5-(*t*-pentyl phenyl]-2,5-diphenyl tetrahydro-4-isoxazolyl}-3-phenyl-2-propen-1-one (**3b**).

The role of the 2-methoxy group of the approaching 1,3-dipole in not preventing the cycloaddition and the fact that the substrate **3** itself is reluctant to add with a dipole is shown by the attempted addition of simple C,N-diphenyl nitrone with **3**. A mixture of C,N-diphenyl nitrone and **3** in toluene upon reflux did not undergo any appreciable addition even after 8 hours.

It was also interesting to investigate this cycloadditon under solvent-free conditions. Though a well ground equimolar mixture of **1** and **2** does not undergo cycloaddition under solventless condition even after considerable time, under microwave irradiation this solid mixture undergoes efficient cycloaddition to give **3** in just five minutes. The same kind of selectivity was observed as in the case of conventional method. A multicomponent approach for the synthesis of the adduct **3** by mixing the aldehyde, aryhydroxylamine and diarylidineacetone in toluene has also been found to be successful, the reaction time being 6-7 hours. In both microwave irradiation and multicomponent conditions, the overall yield was almost similar to that of the conventional method (70-85%).

In order to prove the selectivities associated with the above reaction, the cycloaddition of unsubstituted α,N-diphenyl nitrone with dibenzilidineacetone was carried out (both 1:1 and 1:2 ratio) in toluene under reflux. In both the cases, a complex mixture with at least three products was observed in the crude ^{1}H NMR spectrum in the ratio of 2:1:1. The major compound shows two doublets at 5.2 ppm (J = 9.0 Hz) and 5.3 ppm (J = 7.2 Hz) along with a doublet of doublets at 4.0 ppm (J = 9.0 Hz

and 7.2 Hz). There is one olefinic hydrogen at 6.3 ppm with a coupling constant of 13.2 Hz. From the ^{13}C NMR signals identified to be that of the major component, a carbonyl signal at 194 ppm along with three CH carbons at 84.4, 73.5 and 73.0 ppm have been noticed. The chemical shift positions of hydrogens and carbons of the isoxazolidine ring and the presence of the *trans* coupled olefinic hydrogen clearly suggest that this major compound has a structure similar to **3** with the same stereochemistry, though there is a slight change in one of the vicinal coupling constant. The other minor compounds could not be isolated in pure state from the reaction mixture, preventing correct structural assignments.

EXPERIMENTAL

All chemicals were of reagent grade quality and used without further purification. All melting points were recorded in open capillaries and are uncorrected. The ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 MHz and 75 MHz respectively in $CDCl_3$ using TMS as internal standard. The related 2D NMR spectra were also recorded on the same instrument. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in Hertz. Micro analyses were carried out on a Perkin-Elmer instrument. The single crystal X-ray data set was collected on a Nonius MACH3 Kappa diffractometer with Mo Kappa radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXS-86 and refined by full matrix least squares on F^2 by SHELXL-93. The molecular views were realized by ZORTEP. Crystallographic data (excluding structure factors) for the compound **3b** in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication (CCDC number 251422). All chromatographic separations were performed on 60-120 mesh silica gel using petroleum ether- ethyl acetate as eluent.

General procedure for the preparation of (*E*)-1-{3-[2-methoxy-5-substituted phenyl]-2,5-diaryltetrahydro-4-isoxazolyl}-3-aryl-2-propen-1-one (3). A mixture of α-(5-substituted-2-methoxyphenyl)-N-phenyl nitrone **1** (2 mmol) and diarylidineacetone **2** (2 mmol) was refluxed in toluene (30 mL) for the time period specified in Scheme 1. After completion of the reaction (as indicated by tlc), the solvent was removed under reduced pressure and the product **3** was recrystallised from petroleum ether.

(*E*)-1-(3-(5-*t*-Butyl-2-methoxyphenyl)-2,5-diphenylisoxazolidin-4-yl)-3-phenylprop-2-en-1-one (3a). This compound was obtained as a white crystals (petroleum ether), yield 85%, mp, 148°C; ^{1}H nmr (300 MHz, $CDCl_3$): 1.35 (s, 9H), 3.65 (s, 3H), 3.89 (dd, *J*= 8.7, 5.4 Hz, 1H), 5.30 (d, *J*= 8.7 Hz, 1H), 5.60 (d, *J*= 5.4 Hz, 1H), 6.60 (d, *J*= 16.2 Hz, 1H), 6.80 (d, *J*= 8.7 Hz, 1H), 7.00 (t, *J*= 6.9 Hz 1H), 7.08-7.37 (m, 16H), 8.0 (d, *J*= 2.1Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 31.5, 34.3, 54.9, 70.0, 72.5, 84.1, 109.4, 113.8, 121.2, 124.0, 124.8, 125.6, 127.0, 128.2, 128.6, 128.7, 128.8, 129.0, 129.7, 130.5, 134.1, 137.0, 143.7, 143.8, 151.6, 153.6, 196.2. *Anal.* Calcd. for $C_{35}H_{35}NO_3$: C, 81.21; H, 6.81; N, 2.71%. Found: C, 81.10; H, 6.91; N, 2.68%.

(*E*)-1-(3-(5-*t*-Pentyl-2-methoxyphenyl)-2,5-diphenylisoxazolidin-4-yl)-3-phenylprop-2-en-1-one (3b). This compound was obtained as a white crystals (petroleum ether), yield 83%, mp, 138°C; ^{1}H nmr (300 MHz, $CDCl_3$): 0.75 (t, *J*=7.2 Hz, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.65 (q, *J*= 7.2 Hz, 2H), 3.65 (s, 3H), 3.89 (dd, *J*= 8.7, 5.1 Hz, 1H), 5.35 (d, *J*= 8.7 Hz, 1H), 5.60 (d, *J*= 5.1 Hz, 1H), 6.56 (d, *J*= 16.2 Hz 1H), 6.80 (d, *J*= 8.7 Hz 1H), 6.95 (t, *J*= 7.2 Hz, 1H), 7.04-7.39 (m, 16H), 7.90 (d, *J*= 2.1Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 9.6, 29.1, 37.3, 38.0, 55.3, 70.4, 72.5, 84.7, 109.8, 114.4, 121.7, 125.1, 126.0, 126.1, 127.5, 128.7, 129.0, 129.1, 129.3, 129.5, 130.1, 131.0, 134.6, 137.7, 142.4, 144.3, 151.9, 154.0, 196.7. *Anal.* Calcd. for $C_{36}H_{37}NO_3$: C, 81.32; H, 7.01; N, 2.63%. Found: C, 81.42; H, 6.92; N, 2.61%.

(*E*)-1-(3-(5-*t*-Pentyl-2-methoxyphenyl)-2-phenyl-5-*p*-tolylisoxazolidin-4-yl)-3-*p*-tolylprop-2-en-1-one (3c). This compound was obtained as a white crystals (petroleum ether), yield 78%, mp, 149°C; ^{1}H nmr (300 MHz, $CDCl_3$): 0.72 (t, *J*=7.2 Hz, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.70 (q, *J*= 7.2 Hz, 2H), 2.32 (s, 3H), 2.33 (s, 3H), 3.65 (s, 3H), 3.85 (dd, *J*= 8.7, 5.4 Hz, 1H), 5.31 (d, *J*= 8.7 Hz, 1H), 5.65 (d, *J*= 5.1 Hz, 1H), 6.65 (d, *J*= 15.9 Hz 1H), 6.79 (d, *J*= 8.4 Hz 1H), 6.95 (t, *J*= 7.7 Hz, 1H), 7.08-7.35 (m, 14H), 7.90 (d, *J*= 1.8Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 9.2, 21.1, 21.4, 28.6, 28.7, 36.9, 37.5, 54.8, 69.9, 71.9, 84.2, 109.3, 113.9, 121.1, 124.6, 124.7, 125.5, 127.0, 128.2, 129.0, 129.3, 129.5, 129.8, 131.5, 134.1, 138.4, 141.0, 141.9, 143.8, 151.6, 153.6, 196.3. *Anal.* Calcd. for $C_{38}H_{41}NO_3$: C, 81.54; H, 7.38; N, 2.50%. Found: C, 81.65; H, 7.29; N, 2.58%.

(*E*)-1-(3-(2-Methoxy-5-(2-phenylpropan-2-yl)phenyl)-2,5-diphenylisoxazolidin-4-yl)-3-phenylprop-2-en-1-one (3d). This compound was obtained as a white crystals (petroleum ether), yield 78%, mp, 140°C; ^{1}H nmr (300 MHz, $CDCl_3$): 1.71 (s, 3H), 1.72 (s, 3H), 3.65 (s, 3H), 3.85 (dd, *J*= 8.7, 5.1 Hz, 1H), 5.30 (d, *J*= 8.7 Hz, 1H), 5.60 (d, *J*= 5.1 Hz, 1H), 6.65 (d, *J*= 16.2 Hz, 1H), 6.75 (d, *J*= 8.7 Hz, 1H), 6.95 (t, *J*= 7. 5 Hz, 1H), 7.08-7.36 (m, 21H), 7.90 (d, *J*= 1.8Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 30.8, 30.9, 42.5, 54.9, 69.6, 72.0, 84.1, 109.5, 113.9, 121.2, 125.2, 125.4, 125.5, 126.6, 126.8, 127.0, 127.9, 128.2, 128.5, 128.6, 128.8, 129.0, 129.7, 130.5, 134.1, 137.1, 143.2, 143.8, 150.8, 151.4, 153.8, 196.2. *Anal.* Calcd. for $C_{40}H_{37}NO_3$: C, 82.87; H, 6.43; N, 2.42%. Found: C, 82.80; H, 6.51; N, 2.40%.

(*E*)-1-(3-(2-Methoxy-5-(2-phenylpropan-2-yl)phenyl)-2-phenyl-5-*p*-tolylisoxazolidin-4-yl)-3-*p*-tolylprop-2-en-1-one (3e). This compound was obtained as a white crystals (petroleum ether), yield 81%, mp, 138°C; ^{1}H nmr (300 MHz, $CDCl_3$): 1.97 (s, 6H), 2.34 (s, 3H), 2.37 (s, 3H), 3.35 (s, 3H), 3.80 (dd, *J*= 8.7, 5.1 Hz, 1H), 5.26 (d, *J*= 8.7 Hz, 1H), 5.60 (d, *J*= 5.1 Hz, 1H), 6.50 (d, *J*= 16.1 Hz, 1H), 6.70 (d, *J*= 8.4 Hz, 1H), 1H), 6.80-7.51 (m, 20H), 7.90 (d, *J*= 2.1Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 21.2, 21.4, 30.9, 42.5, 54.8, 66.1, 72.0, 82.7, 109.7, 114.2, 121.2, 124.6, 125.4, 125.8, 126.6, 127.1, 127.6, 127.9, 128.3, 128.9, 129.0, 129.3, 129.6, 129.8, 133.9, 135.9, 138.0, 142.1, 143.0, 150.0, 150.9, 153.7, 196.3. *Anal.* Calcd. for $C_{42}H_{41}NO_3$: C, 83.00; H, 6.80; N, 2.30%. Found: C, 83.16; H, 6.85; N, 2.22%.

(*E*)-1-(3-(5-*t*-Pentyl-2-methoxyphenyl)-5-(4-chloro phenyl)-2-phenylisoxazolidin-4-yl)-3-(4-chloro phenyl) prop-2-en-1-one (3f). This compound was obtained as a white crystals (petroleum ether), yield 84%, mp, 137°C; ^{1}H nmr (300 MHz, $CDCl_3$): 0.75 (t, *J*=7.5 Hz, 3H), 1.30 (s, 3H), 1.31 (s, 3H), 1.65 (q, *J*= 7.2 Hz, 2H), 3.66 (s, 3H), 2.33 (s, 3H), 3.75 (s, 3H), 3.75 (dd, *J*= 8.4, 5.1 Hz, 1H), 5.34 (d, *J*= 8.4 Hz, 1H), 5.56 (d, *J*= 5.1 Hz, 1H), 6.54 (d, *J*= 16.2 Hz, 1H), 6.78 (d, *J*= 8.4 Hz 1H),

6.98 (t, *J*= 6.9 Hz, 1H), 7.01-7.40 (m, 14H), 7.83 (d, *J*= 2.1Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 9.1, 28.6, 28.7, 36.8, 37.5, 54.9, 69.8, 72.1, 83.1, 109.5, 113.9, 121.5, 124.6, 125.5, 125.8, 128.3, 128.8, 129.1, 129.2, 129.3, 129.4, 132.5, 134.4, 135.9, 136.6, 142.1, 142.4, 151.3, 153.5, 195.8. *Anal*. Calcd. for $C_{36}H_{35}NO_3$: C, 72.00; H, 5.87; N, 2.33%. Found: C, 72.10; H, 5.78; N, 2.30%.

(*E*)-1-(3-(2-Methoxy-5-(2-phenylpropan-2-yl)phenyl)-5-phenyl-2-*p*-tolylisoxazolidin-4-yl)-3-phenylprop-2-en-1-one (3g). This compound was obtained as a white crystals (petroleum ether), yield 75%, mp, 162 °C; ^{1}H nmr (300 MHz, $CDCl_3$): 1.62 (s, 6H), 2.27 (s, 3H), 3.23 (s, 3H), 3.65 (dd, *J*= 8.7, 5.4 Hz, 1H), 5.10 (d, *J*= 8.7 Hz, 1H), 5.31 (d, *J*= 5.4 Hz, 1H), 6.60 (d, *J*= 15.8 Hz, 1H), 6.60 (d, *J*= 15.8 Hz, 1H), 6.75-7.55 (m, 22H), 7.85 (d, *J*= 2.1Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$): 21.0, 31.1, 31.2, 42.7, 54.9, 66.7, 72.5, 82.8, 109.9, 114.7, 124.9, 125.7, 125.9, 127.0, 127.1, 127.4, 128.3, 128.4, 128.6, 128.7, 128.9, 129.8, 129.9, 130.1, 131.0, 134.6, 137.6, 141.5, 143.3, 148.5, 151.3, 154.2, 196.9. *Anal*. Calcd. for $C_{41}H_{39}NO_3$: C, 82.94; H, 6.62; N, 2.36%. Found: C, 82.81; H, 6.52; N, 2.25%.

(*E*)-1-(3-(2-Methoxy-5-(2-phenylpropan-2-yl)phenyl)-2,5-diptolylisoxazolidin-4-yl)-3-*p*-tolylprop-2-en-1-one (3h). This compound was obtained as a white crystals (Petroleum ether), yield 80%, mp, 160 °C; ^{1}H nmr (300 MHz, $CDCl_3$): 1.71 (s, 3H), 1.72 (s, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 3.64 (s, 3H), 3.79 (dd, *J*= 8.7, 5.1 Hz, 1H), 5.26 (d, *J*= 8.7 Hz, 1H), 5.57 (d, *J*= 5.1 Hz, 1H), 6.50 (d, *J*= 15.9 Hz, 1H), 6.73 (d, *J*= 8.7Hz, 1H), 1H), 7.05-7.37 (m, 17H), 7.90 (d, *J*= 2.4Hz, 1H); ^{13}C nmr (75 MHz, $CDCl_3$)*: 21.0, 21.6, 21.8, 31.2, 31.3, 42.9, 55.4, 70.2, 72.5, 84.4, 109.9, 114.5, 124.9, 125.7, 125.9, 127.1, 127.2, 127.4, 128.3, 128.7, 129.7, 129.9, 130.4, 130.9, 131.9, 134.6, 138.7, 141.5, 143.5, 144.2, 149.6, 151.3, 154.2, 196.9. [*one aromatic carbon was merged with others]. *Anal*. Calcd. for $C_{43}H_{43}NO_3$: C, 83.06; H, 6.97; N, 2.25%. Found: C, 83.20; H, 7.01; N, 2.31%.

Under microwave irradiation. An equimolar mixture (1 mmol) of α-(5-substituted-2-methoxyphenyl)-N-phenyl nitrone (**1**) and diarylidineacetone (**2**) without solvent was irradiated in a microwave oven at 540 W power for 5 minutes. The progress of the reaction was monitored by tlc. After completion of the reaction, pure product (**3**) was crystallized in petroleum ether.

Yields: **3a**, 84%; **3b**, 86%; **3c**, 78%; **3d**, 80%; **3e**, 84%; **3f**, 86%; **3g**, 78%; **3h**, 84%.

Under multicomponent condition. A mixture of 2-hydroxy-5-substituted benzaldehyde (2 mmol), arylhydroxylamine (2 mmol) and diarylidineacetone **1** (2 mmol) was refluxed in toluene (30 mL) for 6-7 hours. After completion of the reaction, the product was separated as mentioned in the conventional method.

Reaction times: **3a**, 6h; **3b**, 6h; **3c**, 7h; **3d**, 7h; **3e**, 6h; **3f**, 6h; **3g**, 7h; **3h**, 6h. Yields: **3a**, 80%; **3b**, 83%; **3c**, 78%; **3d**, 82%; **3e**, 86%; **3f**, 81%; **3g**, 81%; **3h**, 80%.

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