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GUANIDINE HYDROCHLORIDE CATALYZED, RAPID AND EFFICIENT ONE-POT SYNTHESIS OF NAPHTHOXAZINONES UNDER SOLVENT-FREE CONDITIONS

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A novel method for the synthesis of 1-aryl-1,2-dihydro-3H-naphtho[1,2-e][1,3]oxazin-3-one derivatives employing one-pot three-component reaction of β-naphthol, aromatic aldehydes, and urea using a catalytic amount of guanidine hydrochloride under solvent-free thermal conditions is described. This method provides several advantages like clean and environmentally benign reaction, simple work-up procedure, low cost, easy product separation without need of further purification with column chromatography, shorter reaction times, and high yields.

Keywords: aldehyde, guanidine hydrochloride, naphthol, naphthoxazinone, solvent-free reaction.

Aromatic condensed oxazinone derivatives have received considerable attention due to the attractive pharmacological properties associated with their heterocyclic scaffold, such as herpes virus protease inhibition [1] and antimicrobial activity [2]. Despite their high potential, there are only few reports that describe the synthesis of naphthalene-condensed oxazinone derivatives.

Recently, some syntheses of naphthalene-condensed 1,3-oxazin-3-one derivatives have been reported using condensation of aminoalkylnaphthols as precursors with phosgene in the presence of triethylamine [3]. Condensation of naphthol with aldehydes and urea for the synthesis of naphthoxazinones has been explored using different catalysts such as copper nanoparticles in PEG-400 [4], silica-supported perchloric acid [5], phosphomolybdic acid [6], pTSA [7], I_2 [8], acetic acid [9], TMSCl/NaI [10], and zinc triflate [11]. However, in these methods, either expensive reagents are required or the reagents used are highly toxic and hazardous. Therefore, the development of new, simple, green one-pot methods for the synthesis of naphthoxazinone derivatives is of prime importance.

Organocatalysts have been used widely in many reactions as mono- and bifunctional catalysts due to economic and environmental considerations. Among many organocatalysts, hydrogen-bonding compounds such as guanidine derivatives are becoming powerful tools for activation of the carbonyl functionality in organic transformations. Recently, guanidinium salts have been successfully employed as novel chiral phase-transfer catalyst in the conjugate addition of nitroalkanes with enones [12]. Moreover, these organocatalysts provide an

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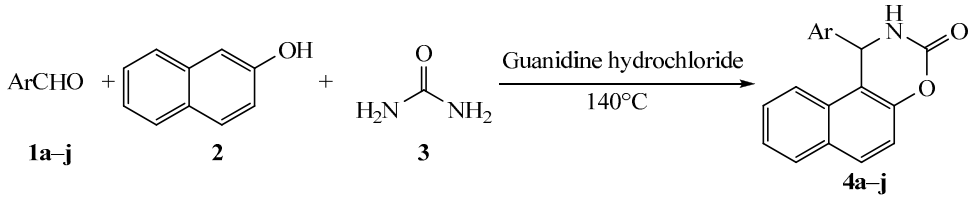
environment to the process of activating the nucleophile, the electrophile, or both reactants through weak interactions, such as hydrogen bonding or ion pairing, or much stronger interactions, such as covalent bonding.

Due to our interest in developing solvent-free multicomponent reactions [13-16], we report here, a simple and facile protocol for the synthesis of a series of 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives from aldehydes **1a-j**, 2-naphthol (**2**), and urea (**3**) using guanidine hydrochloride as an organocatalyst under solvent-free conditions. To the best of our knowledge, in the open literature, one-pot synthesis of naphthoxazinones catalyzed by guanidine hydrochloride has not been previously reported.

In our initial experiments, the interaction of equimolar quantities of 2-naphthol, benzaldehyde, and urea was selected as a model reaction, and its behavior was studied in the presence of 10 mol% of guanidine hydrochloride under solvent-free conditions. Moreover, to optimize the reaction temperature, we have carried out the same model study at various temperatures (100-180°C). Our investigation demonstrated that 140°C is an effective temperature in terms of reaction time and yield obtained. Then we screened the effect of catalyst concentration on the model reaction at this temperature. We have varied the concentration of catalyst at 2, 5, 7, 10, and 15 mol%. The results indicated that when the reaction was carried out in the presence of 10 mol% of catalyst, it gave excellent product yield. Increase of the catalyst concentration to 15 mol% failed to improve the yield.

To show the generality of this method, the optimized system was used for the synthesis of other 1-aryl-1,2-dihydronaphtho[1,2-*e*][1,3]oxazin-3-one derivatives by condensation of 2-naphthol (**2**) with a wide range of aromatic aldehydes **1a-j** and urea (**3**) utilizing guanidine hydrochloride as organocatalyst under solvent-free conditions at 140°C. In all cases, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted efficiently, leading to the corresponding naphthoxazinones **4a-j** as observed in short reaction times (60-75 min) with high to excellent yields (Table 1).

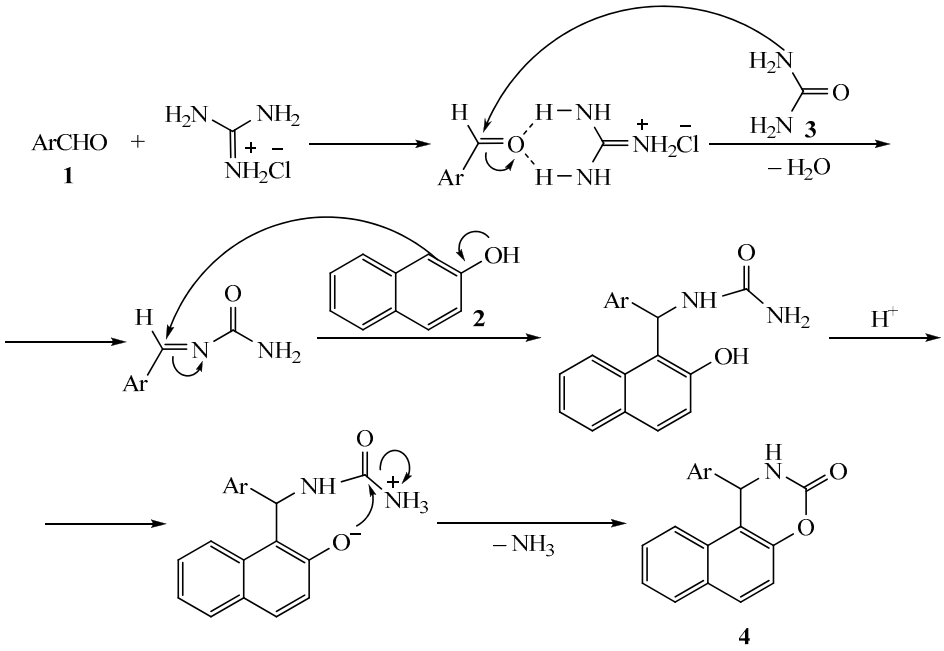


1a–j **2** **3** **4a–j**

TABLE 1.

Compound	R	Reaction time, min	Yield, %	Mp, °C
4a	Ph	70	88	215-216 (218-220 [7])
4b	4-ClC_6H_4	60	85	210-212 (208-210 [7])
4c	4-$MeOC_6H_4$	65	88	184-185 (185-188 [7])
4d	2-ClC_6H_4	60	90	248-250 (250-252 [5])
4e	4-$(Me_2N)C_6H_4$	60	88	220-221 (218-219 [17])
4f	3,4,5-$(MeO)_3C_6H_2$	60	87	225-226 (228-230 [11])
4g	3-$O_2NC_6H_4$	75	90	258-260 (260-262 [18])
4h	4-Cl-3-$O_2NC_6H_3$	60	86	199-200
4i	2-$(PhCH_2O)C_6H_4$	75	89	238-240
4j	4-HO-3-$MeOC_6H_3$	70	90	188-190

Concerning the reaction mechanism, we propose that guanidine hydrochloride initially acts as a hydrogen bond donor to activate the aldehyde molecule by formation of six-membered ring with the aldehyde oxygen. Then, the reaction proceeds through the *in situ* formation of acylimine intermediate by the nucleophilic addition of urea to aldehyde. Subsequently, the resulting acylimine intermediate undergoes cyclization with 2-naphthol (**2**), affording the corresponding products with removal of ammonia in the presence of guanidine hydrochloride as the proton donor. It should be noted that no naphthoxazinethione derivatives **4** were obtained when urea was replaced with thiourea even after 5 h of vigorous stirring and the reactants could be recovered as a sticky mixture. Likewise, the replacement of 2-naphthol (**2**) with 1-naphthol under the same conditions did not yield any product.



All obtained products were well characterized by ^{1}H NMR, ^{13}C NMR, FTIR, mass spectra, elemental analyses, and melting points. To the best of our knowledge, the synthesis of compounds **4h-j** has not been previously reported in the literature. The IR spectra of the compounds showed a sharp absorption peak due to the stretching vibrations of the carbonyl at about 1730 cm^{-1}. The ^{1}H NMR spectra of compounds **4h-j** show a doublet for the methine protons in the range of 6.00-6.40 ppm. The NH proton signal appeared as a doublet at about 8.50-8.70 ppm, and that of aromatic protons – in the region of 6.60-8.90 ppm. The ^{13}C NMR, mass spectra, and elemental analyses confirmed the structures of the synthesized compounds.

In conclusion, a novel method for the synthesis of condensed naphthoxazinone derivatives from 2-naphthol, aromatic aldehydes, and urea in the presence of guanidine hydrochloride has been developed that is simple, green, and efficient. The method employs an easy work-up procedure and avoids the use of expensive reagents while featuring high product yields. Both donor and acceptor substituents in the aldehyde reactant, as well as the hydroxy group, are compatible with the reaction conditions.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu 4300 spectrophotometer in KBr. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 and Bruker Avance 300 spectrometers with TMS as internal standard. Mass spectra were obtained with an HP (Agilent technologies) 5937 mass selective detector. Elemental analyses were carried out on a CHN–O–Rapid Heraeus elemental analyzer. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. All commercially available chemicals and reagents were used without further purification.

1-Aryl-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-ones 4a-j (General Method). Guanidine hydrochloride (9.5 mg, 10 mol %) was added to a mixture of 2-naphthol (**2**) (144 mg, 1 mmol), urea (**3**) (60 mg, 1 mmol), and an aldehyde **1a-j** (1 mmol), and the mixture was heated in contact with air at 140°C for the appropriate amount of time as indicated in Table 1. The progress of the reaction was monitored by thin-layer chromatography on silica gel, using EtOAc–hexane, 2:1, as eluent. After completion, the reaction mixture was cooled to room temperature and EtOH (5 ml) was added until white solid products precipitated. The crude product was stirred for 5 min in boiling EtOH and, after cooling, the resulting white precipitate was filtered. The obtained products were found to be pure upon TLC examination.

1-(4-Chloro-3-nitrophenyl)-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-one (4h). IR spectrum, ν, cm^{-1}: 3381 (NH), 3060, 1725 (C=O), 1532, 1224, 1179. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 6.40 (1H, d, *J* = 3.0, 1-CH); 7.39 (1H, d, *J* = 9.0, H Ar); 7.46-7.53 (3H, m, H Ar); 7.72 (1H, d, *J* = 8.5, H Ar); 7.81 (1H, d, *J* = 8.5, H Ar); 7.98 (1H, d, *J* = 7.8, H Ar); 8.03 (1H, d, *J* = 9.0, H Ar); 8.16 (1H, d, *J* = 2.0, H Ar); 8.97 (1H, d, *J* = 3.0, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 52.8; 112.7; 117.4; 123.3; 124.9; 125.1; 125.8; 128.2; 129.1; 129.2; 130.9; 131.3; 132.7; 132.9; 143.9; 147.9; 148.1; 149.2. Mass spectrum, *m*/*z* (I_{rel}, %): 356 $[M (^{37}Cl)]^+$ (24), 354 $[M (^{35}Cl)]^+$ (75), 310 (85), 294 (42), 276 (100), 264 (88), 230 (51), 202 (87), 189 (42), 127 (36), 100 (47). Found, %: C 61.12; H 3.13; N 7.87. $C_{18}H_{11}ClN_2O_4$. Calculated, %: C 60.94; H 3.13; N 7.90.

1-(2-Benzyloxyphenyl)-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-one (4i). IR spectrum, ν, cm^{-1}: 3142 (NH), 3054, 1737 (C=O), 1596, 1387, 1224, 1180. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 5.19 (1H, d, *J* = 12.4) and 5.22 (1H, d, *J* = 12.4, CH_2); 6.39 (1H, d, *J* = 2.6, 1-CH); 6.88 (1H, t, *J* = 4.9, H Ar); 7.07 (1H, d, *J* = 8.1, H Ar); 7.19-7.42 (10H, m, H Ar); 7.72-7.74 (1H, m, H Ar); 7.91-7.95 (2H, m, H Ar); 8.57 (1H, d, *J* = 2.6, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 50.1; 69.9; 113.3; 113.7; 117.2; 121.4; 123.0; 125.2; 127.6; 128.1; 128.2; 128.8; 129.1; 129.4; 129.4; 129.9; 130.3; 130.7; 131.0; 137.2; 148.0; 149.8; 155.4. Mass spectrum, *m*/*z* (I_{rel}, %): 381 $[M]^+$ (35), 290 (88), 247 (29), 231 (100), 189 (25), 165 (8), 91 (87). Found, %: C 78.68; H 5.05; N 3.70. $C_{25}H_{19}NO_3$. Calculated, %: C 78.72; H 5.02; N 3.67.

1-(2-Hydroxy-3-methoxyphenyl)-1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-one (4j). IR spectrum, ν, cm^{-1}: 3220 (NH), 3150, 1736 (C=O), 1512, 1220. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.75 (3H, s, OCH_3); 6.04 (1H, d, *J* = 3.5, 1-CH); 6.22 (1H, br. s, NH); 6.82 (2H, m, H Ar); 7.18-7.58 (6H, m, H Ar, OH); 7.82-7.87 (2H, m, H Ar). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ, ppm: 55.2; 55.5; 112.7; 114.6; 117.0; 122.8; 125.1; 127.4; 128.2; 128.8; 129.3; 130.4; 130.9; 134.0; 147.4; 150.3; 152.2; 153.1; 159.6. Mass spectrum, *m*/*z* (I_{rel}, %): 321 $[M]^+$ (5), 313 (14), 281 (18), 261 (100), 246 (47), 218 (71), 202 (16), 189 (42), 177 (18), 144 (14), 115 (25). Found, %: C 71.12; H 4.61; N 4.41. $C_{19}H_{15}NO_4$. Calculated, %: C 71.02; H 4.71; N 4.36.

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