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A One-Pot Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one Derivatives Catalyzed by Perchloric Acid Supported on Silica ($HClO_4/SiO_2$) in the Absence of Solvent

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1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one derivatives were synthesized in high yields using a facile and one-pot condensation of 2-naphthol, aromatic aldehydes and urea catalyzed by perchloric acid supported on silica under thermal solvent-free conditions.

Keywords: One-pot, $HClO_4$-SiO_2, Heterogeneous catalyst, Naphthoxazine-3-one, Solvent-free reaction

INTRODUCTION

Multicomponent reactions (MCRs) constitute an especially attractive synthetic strategy due to the fact that the products are formed in a single step while diversity can be promoted simply by varying the reacting components [1]. Moreover, multicomponent reactions (MCRs) by virtue of their convergence, productivity, ease of execution and generally high yields of products have attracted considerable attention in the field of combinatorial chemistry [2]. The first MCR was described by Strecker in 1850 for the synthesis of amino acids [3]. However, in the past decade, there have occurred tremendous developments in three- and four-component reactions and great efforts are continually being made to develop new MCRs [4-8].

Solid-phase organic synthesis is a subject of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of potent drug candidates [9]. Moreover, heterogeneous catalysts have attracted special attention in recent years due to economic and environmental considerations. These catalysts are generally inexpensive and easily available. They can conveniently be handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly. The leading contenders for environmentally acceptable processes are supported reagents. The use of silica-supported reagents in one-pot multi-component construction of heterocycles has received considerable attention in organic synthesis [10]. In particular, perchloric acid adsorbed on silica gel ($HClO_4/SiO_2$) [11] has emerged as an extremely useful catalyst in various organic transformations including acylation of alcohols [11], acylation of aldehydes [12], 1,3-dithiolane/dithiane formation [13], tetrahydropyranylation [14], thio-acetalization [14], Ferrier rearrangement [15], Michael addition [16], cleavage of ketals and benzylidene acetals [17], the Hantzsch condensation [18], synthesis of bis-indolylmethanes [19], glycosylation of sugars [20] N-*tert*-butoxycarbonylation of amines [21], synthesis of tetrasubstituted imidazoles [22], synthesis of poly-substituted quinolines [23] and synthesis of benzoxanthenes

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[24].

Aromatic-condensed oxazinone derivatives are an important class of heterocyclic compounds, since many of these heterocyclic systems exhibit biological activities [25]. For example, naphthalene-condensed 1,3-oxazin-3-ones have been reported to act as antibacterial agents [26]. This class of compounds has also been used as precursors in the preparation of phosphinic ligands for asymmetric catalysis [27]. However, to the best of our knowledge, only few experiments on the synthesis of naphthalene-condensed oxazinone derivatives are reported in the literature [26,28]. Recently, some syntheses of naphthalene-condensed 1,3-oxazin-3-ones derivatives have been reported using condensation of amino alkylnaphthols as precursors with phosgene in the presence of triethylamine [29] and carbonyl diimidazol instead of phosgene [30]. However, in these methods, either expensive reagents and solvents are required or the reagents used are highly toxic and hazardous. Furthermore, for the preparation of starting materials such as amino alkylnaphtol, a multi-step reaction using harsh conditions is needed. Therefore, the development of new, simple, green and one-pot methods for the synthesis of naphthoxazinone derivatives are of prime importance.

Recently, Bazgir and co-workers reported a one-pot synthesis of 1,2-dihydro-1-aryl- naphtho[1,2-*e*][1,3]oxazine-3-one derivatives [31] wherein they make use of MW irradiation to achieve good yields, but in thermal conditions no high yields were produced.

In this article, we present a one-pot, three-component method for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives under thermal, solvent-free conditions.

EXPERIMENTAL

General Experimental Procedure

A mixture of an aldehyde (1 mmol), 2-naphtol (1 mmol), urea (1.3 mmol) and $HClO_4$-SiO_2 (40 mg, 0.02 mmol, 2 mol%) was heated at 150 °C with stirring for one hour. After the completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and the reaction mixture was diluted with ethanol (5 ml) and stirred for 5 min at 80 °C. The catalyst was separated by filtration. The residue was kept at room temperature for a while and the solid product was collected by filtration. The product was found to be pure and no further purification was necessary.

The Spectral (IR, ^{1}H NMR, ^{13}C NMR) and Analytical Data of New Compounds

1,2-Dihydro-1-(2-chlorophenyl)naphtho[1,2-e][1,3] oxazine-3-one (4e). IR(KBr): 3237, 3124, 1727, 1396, 1233 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.50 (d, 1H, J = 2.94, CH), 7.18-8.01 (m, 10H, Ar-H), 8.89 (sbr, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 52.46, 114.13, 117.43, 123.58, 124.23, 125.68, 126.32, 128.06, 129.17, 129.32 129.76, 130.13, 130.24, 130.37, 133.09, 143.25, 147.15, 149,08; Calcd. for $C_{18}H_{12}ClNO_2$: C, 70.04; H, 4.04; N, 4.63. Found: C, 69.80; H, 3.90; N, 4.52.

1,2-Dihydro-1-(3-bromophenyl)naphtho[1,2-e][1,3] oxazine-3-one (4f). IR(KBr): 3269, 3163, 1746, 1710, 1221 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.25 (d, 1H, J = 2.97, CH), 7.17-8.01 (m, 10H, Ar-H), 8.91 (d, 1H, J = 2.97, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 53.02, 113.29, 116.91, 122.01, 123.05, 125.24, 125.87, 127.57, 128.71, 128.78 129.93, 130.42, 130.55, 130.98, 131.34, 145.35, 147.56, 149,14; Calcd. for $C_{18}H_{12}BrNO_2$: C, 61.04; H, 3.41; N, 3.95. Found: C, 61.66; H, 3.58; N, 4.02.

1,2-Dihydro-1-(3-methoxyphenyl)naphtho[1,2-e][1,3] oxazine-3-one (4i). IR(KBr): 3211, 3135, 1748, 1597, 1263 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.15 (d, 1H, J = 2.96, CH), 6.75-7.99 (m, 10H, Ar-H), 8.85 (d, 1H, J = 2.96, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 53.02, 55.04, 113.29, 116.91, 122.01, 123.05, 125.24, 125.87, 127.57, 128.71, 128.78 129.93, 130.55, 130.98, 131.34, 145.35, 147.56, 149,14, 159.2; Calcd. for $C_{19}H_{15}NO_3$: C, 74.32; H, 4.97; N, 4.50. Found: C, 74.74; H, 4.95; N, 4.59.

1,2-Dihydro-1-(2-thiophen)naphtho[1,2-e][1,3]oxazine-3-one (4k). IR (KBr): 3772, 3266, 1747, 1710, 1516, 1278, 1222, 1178, 806, 728 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.56 (d, 1H, J = 2.92 Hz, CH), 6.92-7.99 (m, 8H, Ar-H), 9.05 (d, 1H, J = 2.92 Hz, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 48.79, 114.52, 116.84, 123.03, 125.20, 125.68, 126.20, 126.96, 127.47, 128.62 128.79, 130.37, 130.43, 146.83, 147.09, 149.49; Calcd. for $C_{16}H_{11}NO_2S$: C, 68.312; H, 3.94; N, 4.98. Found: C, 67.87; H, 3.88; N, 4.87.

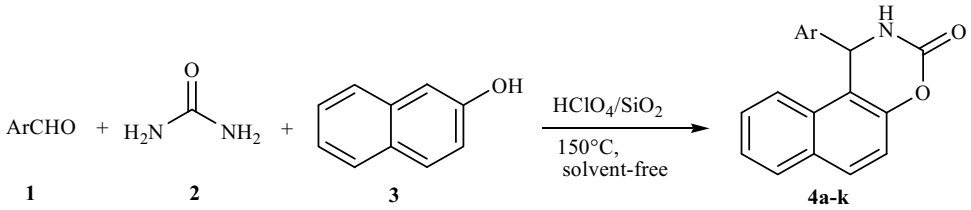
RESULTS AND DISCUSSION

In continuation of our previous work on the synthesis of heterocyclic compounds [24,32-34], herein, we wish to report a novel, one-pot, three-component method for the preparation of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives under thermal, solvent-free conditions (Scheme 1).

Following a typical, general experimental procedure, a solution of an aromatic aldehyde, β-naphtol and urea under neat conditions, in the presence of a catalytic amount of $HClO_4/SiO_2$ (2 mol%), and in the appropriate period of time, the reaction took place. The resulting crude 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones was purified by recrystallization from EtOH to afford the pure product.

To examine the generality of the process, several experimental trials illustrating this method for the synthesis of 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-one derivatives were conducted. The results are summarized in Table 1. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (halide groups) or electron-donating groups (such as hydroxy, alkoxyl groups) were employed which were found to react well to give the corresponding 1,2-dihydro-1-arylnaphtho[1,2-*e*][1,3]oxazine-3-ones in good yields.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. For example, 4-chlorobenzaldehyde reacted with β-naphtol and urea in the presence of 0.5 mol% $HClO_4/SiO_2$ to give the product **4c** in modest yield (45%) under neat conditions after one hour of reaction time. Increasing the molar amounts of the catalyst to 1 mol%, 2 mol% and 3 mol% resulted in increasing the reaction yields to 65%, 89% and 89.2%, respectively. The use of just 2 mol% of $HClO_4/SiO_2$ under solvent-free conditions was sufficient to proceed the reaction. Higher amounts of the



Scheme 1

Table 1. Reaction of β-Naphthol with Aldehydes and Urea under Thermal Solvent-Free Conditions

Entry	Ar	Product	Yield (%)	M.p. (°C)	Reported M.p. (°C)
1	C_6H_5	4a	85	218-220	218-220
2	4-FC_6H_4	4b	90	206-207	202-204
3	4-ClC_6H_4	4c	88	212-214	208-210
4	4-BrC_6H_4	4d	92	218-220	220-223
5	2-ClC_6H_4	4e	90	250-252	-
6	3-BrC_6H_4	4f	89	232-235	-
7	4-MeC_6H_4	4g	85	169-171	166-168
8	4-$MeOC_6H_4$	4h	85	191-193	185-188
9	3-$MeOC_6H_4$	4i	84	202-204	-
10	4-OHC_6H_4	4j	75	185(dec.)	180(dec.)
11	2-Thiophen	4k	92	208-210	-

catalyst did not improve the results of the reaction to a noticeable extent. The yields were in general high, regardless of the structural variations in aromatic aldehydes. Under the identical conditions, the rate of the reaction was affected by the presence of $HClO_4/SiO_2$ and the yields were 70%, 89% and 89.5% after different time intervals of 0.5 h, 1 h, 2 h, respectively. Thus, 2 mol% of $HClO_4/SiO_2$ was chosen as the suitable amount of the catalyst for these reactions. The catalyst could be reused 5 times for the synthesis of **4c** without significant loss of its activity. This reaction was also examined in the presence of SiO_2 at 150 °C. As we noticed earlier, the reaction failed under this condition.

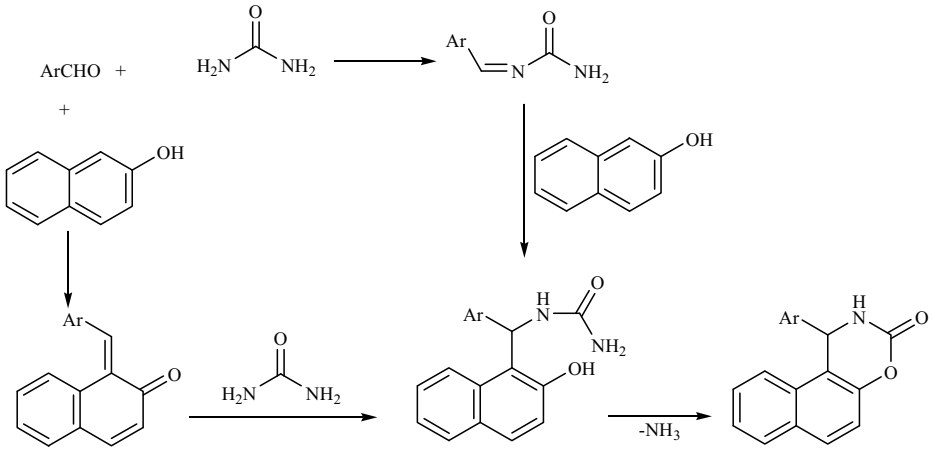
We further examined the effect of the solvents upon the reaction of 4-chlorobenzaldehyde with β-naphtol and urea catalyzed by $HClO_4/SiO_2$ (2 mol%) in various solvents the results of which are summarized in Table 2. The yields refer to the isolated products. The results show that the solvent-free condition is a more suitable one for the reactions.

We propose the following possible mechanism to account for the reaction. The reaction could be mechanistically considered to proceed through the acylimine intermediate (formed *in situ* by reaction of the aldehyde with urea) [35] or *ortho*-quinone methides (O-QMs) intermediate (formed *in situ* by reaction of the aldehyde with β-naphtol) [36]. The subsequent addition of the β-naphtol to the acylimine or addition of the urea to the O-QMs, followed by cyclization affords the corresponding products 4a-k and ammonia (Scheme 2). The structures of the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analyses. Replacement of β-naphtol with α-naphtol under these conditions produced no product.

Table 2. The Reaction of 4-Chlorobenzaldehyde with β-Naphthol and Urea Catalyzed by $HClO_4/SiO_2$ at Reflux Conditions

Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	2	0
2	DMF	2	10
3	CH_3CN	2	0
4	Water	2	0
5	$CHCl_3$	2	0
6	Solvent-free	1	88

In conclusion, we have described a highly efficient one-pot synthesis for the preparation of naphthoxazine-3-one derivatives in three-component cyclo-condensation reaction of β-naphtol, aromatic aldehydes and urea under solvent-free thermal conditions. Easy work-up, low cost, ready availability of the catalyst make the procedure an attractive alternative to the existing methods for the synthesis of naphthoxazine-3-one derivatives.



Scheme 2

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