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Microwave-Assisted Efficient Synthesis of Azlactones Using Zeolite NaY as a Reusable Heterogeneous Catalyst

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ABSTRACT

The efficient preparation of azlactones in the presence of zeolite NaY has been reported. This heterogeneous catalyst was used for efficient synthesis of azlactone derivatives with Ac2O as condensing agent under microwave irradiation and solvent-free conditions. The present method offers advantages of good yields, short reaction time and simple work-up and catalyst reusability, which makes this method mild and eco-friendly.

Keywords

Azlactone, Zeolite NaY, Heterogeneous catalyst, Erlenmeyer synthesis, Microwave irradiation.

1. Introduction

Azlactones, or 2,4-disubstituted oxazolin-5-ones have attracted much interest because of their wide range of biological and pharmaceutical properties.[1,2] They are appropriate building blocks and valuable intermediates for the preparation of diverse biologically active molecules, including amino acids,[3,4] heterocyclic compounds,[5] biosensors and photosensitive devices for proteins.[6] Furthermore, these compounds are pharmaceutically active agent such as anticancer, antitumor, antimicrobial, anti-inflammatory, anti-hypertensive, and inhibitor of central nervous system.[7-10] After primary synthesis report in 1893 by Erlenmeyer,[11] several other dehydrating agent and catalysts such as perchloric acid,[12] polyphosphoric acid,[13] Al_2O_3,[14] supported KF,[15] $Bi(OAc)_3$,[16] $Bi(OTf)_3$,[17] $Yb(OTf)_3$,[18] $Ca(OAc)_2$,[19] organic--inorganic hybrid polyoxometalates,[20] TsCl-DMF,[21] and functionalized magnetic nanocatalyst[22] have been employed in azlactones synthesis. However, some of these procedures have some disadvantageous drawbacks, such as long reaction time, unsatisfactory yields, use of expensive, corrosive and non-reusable catalysts and rigorous work-up procedures. Therefore, the development of a mild, eco-friendly and more convenient method for synthesis of azlactones without using any hazardous solvents and green catalyst is still in demand.

As a consequence of serious pollution problems, the adoption of “cleaner production” methods is an urgent priority. Among the different strategies for achieving this goal, the use of heterogeneous catalysts and solvent-free methods which extremely lead to milder experimental conditions, an easier work-up, reusability of catalysts, has received special attentions.[23,24]

In recent years, Zeolite has received considerable attention as an inexpensive, reusable without any loss of activity, nontoxic, readily available catalyst for various organic transformations under mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity.[25-27]

As a part of our research interest towards the development of efficient one-pot synthetic methodologies in eco-friendly conditions,[22,28,29] herein we wish to explore an efficient microwave-assisted synthesis of azlactone derivatives via the one-pot condensation of carbonyl compounds and hippuric acid under solvent-free conditions using zeolite NaY as an efficient, mild and environmentally benign catalyst (Scheme 1).

2. Experimental

All chemicals and solvents were obtained from commercial sources and used without further purification. All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin layer chromatography (TLC) was performed on UV active precaoted plates of silica gel (TLC Silica gel60 F_{254}).The FT-IR spectrum was recorded on a Unicom Galaxy Series FT-IR 5030 spectrophotometer using KBr discs. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker Avance spectrometer operating at 300 and 75 MHz respectively in DMSO-d_6 or $CDCl_3$ with TMS as an internal standard. Microwave irradiation was carried out in a National Microwave Oven, Model No. NN-K571MF (2450 MHz).

2.1. General procedure for the microwave-assisted synthesis of azlactone derivatives Catalyzed by Zeolite NaY

The appropriate aldehyde or ketone (1 mmol), hippuric acid (1.1 mmol), Ac_2O (1 ml) and catalyst (0.1 g) was mixed in a test tube. Then, the reaction mixture was irradiated using the microwave oven at a power output of 300W for the appropriate time according to Table 2. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. 3 ml cold ethanol/water (1:2) was added and the mixture was stirred for 15 min until a yellow solid precipitated. An aqueous solution of $NaHCO_3$ (10 ml, 20%) was added, the solid products and the catalyst were filtered. The solid materials were dissolved in hot ethanol to remove the catalyst. The solvent was allowed to cool in room temperature to obtain crude products.

2.2. Spectral data for selected compounds

*4-benzylidene-2-phenyloxazol-5(4H)-one (**3a**):*

IR (KBr): ν_{max} = 3070, 1789, 1651, 1552, 1450, 1305, 1158, 760, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 1 H), 7.42--7.63 (m, 6 H), 8.18--8.21 (m, 4H). Anal Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.31; H, 4.53; N, 5.58.

*4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-one (**3b**)*:

IR (KBr): ν_{max} = 3065, 1796, 1653, 1607, 1557, 1491, 1298, 1161, 1001, 889, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.21--7.34 (m, 3 H), 7.50--7.62 (m, 3H), 8.11--8.19

(m, 4H). Anal Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.69; H, 5.08; N, 5.41.

*4-(3,4-dimethoxybenzylidene)-2-phenyloxazol-5(4H)-one (**3g**):*

IR (KBr): ν_{max} = 3090, 3001, 2961, 2836, 1784, 1649, 1595, 1452, 1329, 1244, 1140, 1018, 866, 627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 7.49-7.62 (m, 5H), 7.19 (s, 1H), 6.94 (d, J = 8.3 Hz, 1H) 4.03 (s, 3H), 3.96 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 167.4, 161.9, 151.8, 148.8, 132.7, 131.6, 130.8, 128.7, 127.7, 127.6, 126.7, 125.6, 110.6, 55.7, 55.6; Anal Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.84; H, 4.93; N, 4.61.

*2-phenyl-4-(3,4,5-trimethoxybenzylidene)oxazol-5(4H)-one (**3h**):*

IR (KBr): ν_{max} = 2999, 2942, 2841, 1784, 1761, 1655, 1578, 1506, 1452, 1329, 1256, 1126, 1003, 966, 851, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, J = 7.8 Hz, 2H), 7.55-7.57 (m, 5H), 7.18 (s, 1H), 3.99 (s, 6H), 3.96 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 167.3, 162.9, 153.0, 141.1, 133.1, 132.2, 131.5, 128.9, 128.8, 128.0, 125.5, 109.7, 60.9, 56.0; Anal Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.34; H, 5.10; N, 4.19.

*4-(2,6-dichlorobenzylidene)-2-phenyloxazol-5(4H)-one (**3j**):*

IR (KBr): ν_{max} = 3084, 1797, 1759, 1672, 1564, 1427, 1321, 1165, 981, 866, 777, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 7.9 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.37 (s, 1H), 7.33(t, J = 7.5 Hz, 1H);^{13}C NMR(75 MHz,

$CDCl_3$): δ = 165.8, 164.5, 137.8, 135.1, 133.7, 131.3, 130.4, 128.8, 128.6, 128.2, 126.4, 125.3; Anal Calcd for $C_{16}H_9Cl_2NO_2$: C, 60.40; H, 2.85; N, 4.40. Found: C, 60.51; H, 2.91; N, 4.37.

*N-acetyl-N-(1,3-dioxo-1,3-dihydrobenzo[c]oxepin-4-yl)benzamide (**3n**):*

IR (KBr): ν_{max} = 3080, 1811, 1772, 1682, 1651, 1604, 1410, 1309, 1197, 1089, 995, 1028, 995, 763, 686 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 8.20 (d, J = 8.0, 1H), 8.07 (d, J = 7.8, 1H), 7.93 (t, J = 8.0, 1H), 7.87 (s, 1H), 7.70-7.77 (m, 3H), 7.48-7.53 (m, 3H), 2.27 (s, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 168.2, 160.1, 157.6, 135.8, 133.6, 133.4, 130.7, 130.0, 128.9, 128.6, 128.5, 128.2, 126.0, 125.8, 108.0, 21.7; Anal Calcd for $C_{19}H_{13}NO_5$: C, 68.06; H, 3.91; N, 4.18. Found: C, 68.15; H, 3.97; N, 4.27.

*4-cyclopentylidene-2-phenyloxazol-5(4H)-one (**3p**):*

IR (KBr): ν_{max} = 3054, 2962, 2874, 1778, 1676, 1568, 1450, 1323, 1249, 1147, 881, 777, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.6 Hz, 2H), 7.46-7.56 (m, 3H), 2.96(t, J = 7.2 Hz, 4H), 1.86-1.93 (quin, J = 5.6 Hz, 4H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 165.5, 164.8, 160.0, 132.4, 128.8, 128.5, 127.6, 126.1, 34.0, 32.5, 26.5, 25.6; Anal Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.08; H, 5.83; N, 6.11.

*4-(4-(tert-butyl)cyclohexylidene)-2-phenyloxazol-5(4H)-one (**3r**):*

IR (KBr): ν_{max} = 3051, 2970, 2945, 2866, 1786, 1755, 1660, 1572, 1450, 1321, 1151, 977, 883, 781, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 8.2 Hz, 2H), 7.46-7.58 (m, 3H), 4.05 and 3.59 (AB system, J = 12.5 Hz, 2H), 2.07-2.20 (m, 4H), 1.24-1.41 (m, 3H), 0.91 (s, 9H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 165.5, 161.2, 159.2, 132.3, 128.75, 128.72, 127.6, 126.1, 47.4,

32.5, 31.9, 28.9, 27.5; Anal Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.85; H, 7.85; N, 4.70.

3. Results and discussion

Initially, as a model, the condensation reaction of benzaldehyde, hippuric acid and acetic anhydride was examined in the presence of zeolite NaY in different solvents and solvent-free condition under microwave irradiation (Table 1). As shown in Table 1, it was found that microwave-assisted solvent-free condition is a more efficient (Table 1, entry 5) over the organic solvents. When the reaction was carried out in the presence of different amounts of catalyst, the highest yield was obtained with 0.1g of catalyst under microwave-assisted solvent-free condition after 10 minutes. Increasing the amount of catalyst to 0.2g did not affect the product yield (Table 1, entry 7). Moreover, the catalyst is essential and in the absence of the catalyst, only 20% of the corresponding azlactone was produced (Table 1, entry 8). The recyclability of zeolite NaY was investigated. The catalyst was recovered easily by simple filtration, washed with hot ethanol and dried under vacuum and reused in a subsequent reaction. As seen in Table 1, entry 6, the catalyst showed no substantial reduction in the activity even after four runs.

After optimization of condition for azlactones synthesis and in order to investigate the generality of this procedure, a variety of aromatic aldehydes bearing electron-withdrawing and electron-donating groups and heterocyclic aldehydes were reacted with hippuric acid and Ac_2O in the presence of zeolite NaY under microwave-assisted solvent-free conditions. The results (Table 2) indicated that the corresponding azlactones were synthesized in 70-92% isolated yield in 10-15 min. In order to further expand the scope of this catalytic system, cyclic ketones such as

cyclopentanone, cyclohexanone and 4-(t-Bu)-cyclohexanone were used and successfully converted to their corresponding azlactone derivatives with moderate yields (Table 2, entries 15-17). Aliphatic aldehydes and ketones were also examined under the same conditions, but the corresponding products were not isolated.

A proposed mechanism for the formation of azlactones catalyzed by zeolite NaY depicted in Scheme 3. We assumed that the reaction proceeds via the initial activation of the carbonyl group of acetic anhydride, followed by nucleophilic addition of hippuric acid and cyclization at the oxygen center, with eliminaton of acetic acid and water, to form 2-phenyl-5-oxazolone intermediate. Then zeolite-assisted deprotonation of intermediate, produce oxazolone anion which adds to the activated carbonyl compounds and form the corresponding product. It seems that microwave irradiation accelerates the intermediates formation and therefore, accelerates the reaction accordingly.

It is noteworthy that, the condensation of 2-formylbenzoic acid and hippuric acid under optimized reaction conditions was produced benzo[c]oxepine-1,3-dione derivative as an unexpected product (Table 1, entry 14). Possible route for the formation of this product proposed previously,[22] and illustrated in the Scheme 4. Condensation of the 2-formylbenzoic acid and hippuric acid in the presence of the catalyst affords the corresponding azlactone as an intermediate. The possible re-cyclization of azalactone ring by carboxylic acid group and formation of the fused oxepine ring, followed by acetylation of NH group produce a novel product. The structure of this compound was confirmed with FT-IR, ^{1}H-NMR and ^{13}C-NMR specteroscopy.

4. Conclusions

The Zeolite NaY catalyst has been successfully used for microwave-assisted synthesis of azlactone derivatives via the condensation of hippuric acid with a wide variety of aromatic, heteroaromatic and cyclic ketones under solvent-free conditions. Short reaction times, removal of the solvent, the simple experimental and work-up procedure combined with the reusability of catalyst, generality and good yields make this method as a mild and eco-friendly protocol for azlactones synthesis.

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Table 1: Optimization of reaction conditions for synthesis of 4-benzylidene-2-phenyloxazol-5(4*H*)-one (Table 2, entry 1)[a].

Entry	**Catalyst (mg)**	**Solvent**	**Condition**	**Time (min)**	**Yield (%)[b]**
1	Zolite NaY	$CHCl_3$	Reflux	100	38
2	Zolite NaY	DMF	Reflux	85	53
3	Zolite NaY	THF	Reflux	100	49
4	Zolite NaY (0.05)	-	MW	10	60
5	Zolite NaY (0.1)	-	MW	10	86
6	Zolite NaY (0.1)	-	MW	10	86, 87, 83, 82[c]
7	Zolite NaY (0.2)	-	MW	10	87
8	-	-	MW	10	25

[a]Benzaldehyde (1 mmol), hippuric acid (1.1 mmol), Ac_2O (1 ml).

[b]Isolated yields.

[C]Catalyst reused in four consecutive reactions.

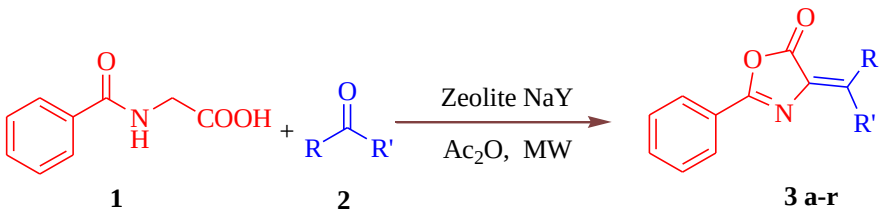
Table 2: Synthesis of azlactone derivatives catalyzed by zeolite NaY under microwave irradiation.

Entry	Aldehydeor Ketone (R, R')	Time(min)	Yield (%)[a]	Product	M.P. (°C)	
					Found[b]	Reported [Lit.]
1	C_6H_5CHO	10	86	**3a**	165-166	167-168 [14]
2	4-MeC_6H_4CHO	15	87	**3b**	140-143	143-144 [14]
3	4-ClC_6H_4CHO	12	83	**3c**	192-194	188-189 [22]
4	3-$NO_2C_6H_4CHO$	12	92	**3d**	171-173	171-172 [22]
5	4-BrC_6H_4CHO	15	82	**3e**	194-195	197-199 [22]
6	3-$MeOC_6H_4CHO$	15	81	**3f**	103-105	99-102 [14]
7	3,4-$(MeO)_2C_6H_3CHO$	10	76	**3g**	152-154	150-152 [19]
8	3,4,5-$(MeO)_3C_6H_2CHO$	12	70	**3h**	199-202	203-204 [22]
9	4-$N(Me)_2C_6H_4CHO$	10	85	**3i**	216-218	212-214 [21]
10	2,6-$Cl_2C_6H_4CHO$	12	80	**3j**	159-160	153-155 [22]
11	Pyridine-2-CHO	12	85	**3k**	163-165	168-169 [14]
12	Thiophene-2-CHO	10	88	**3l**	167-169	170-171 [22]
13	5-(Me)-Thiophene-2-CHO	12	90	**3m**	152-155	145-147 [15]
14	2-Formylbenzoic acid[c]	10	89	**3n**	195-197	198-199 [22]
15	Cyclohexanone	15	42	**3o**	137-140	128 [15]
16	Cyclopentanone	15	48	**3p**	113-116	116 [22]
17	4-(t-Bu)-Cyclohexanone	15	40	**3r**	126-128	124-125 [22]

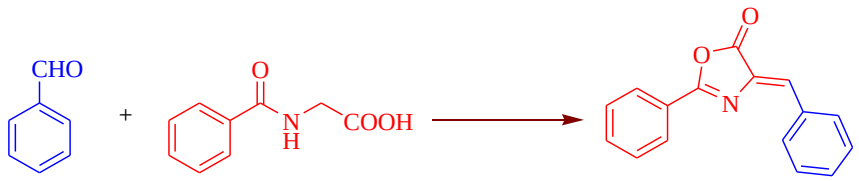
[a]Isolated yields.

[b]Melting points are not corrected.

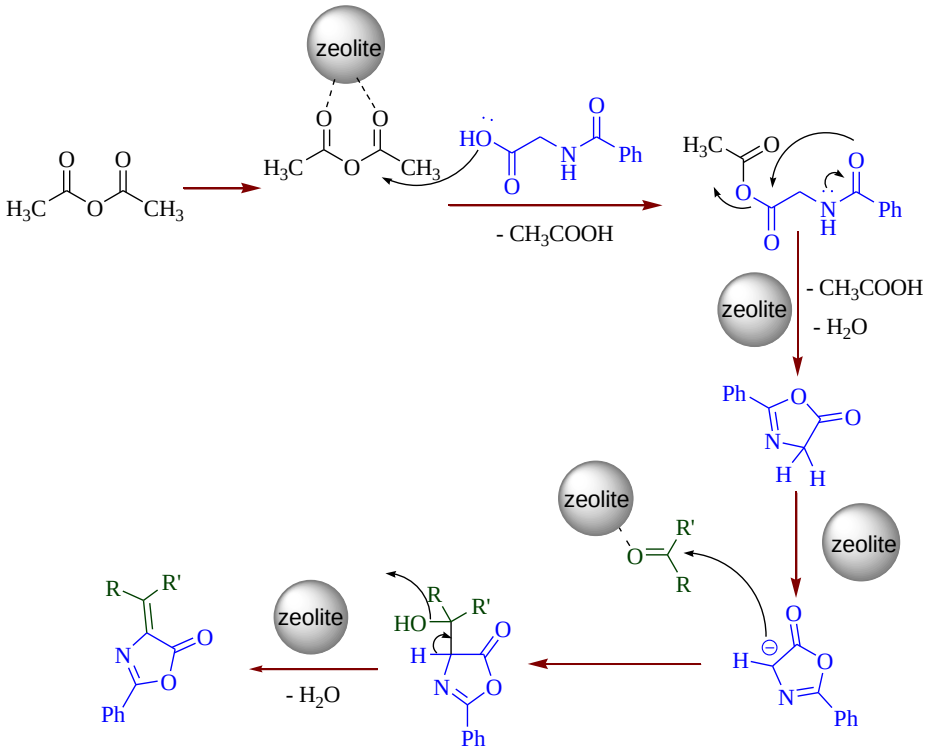
[c]Scheme 4.



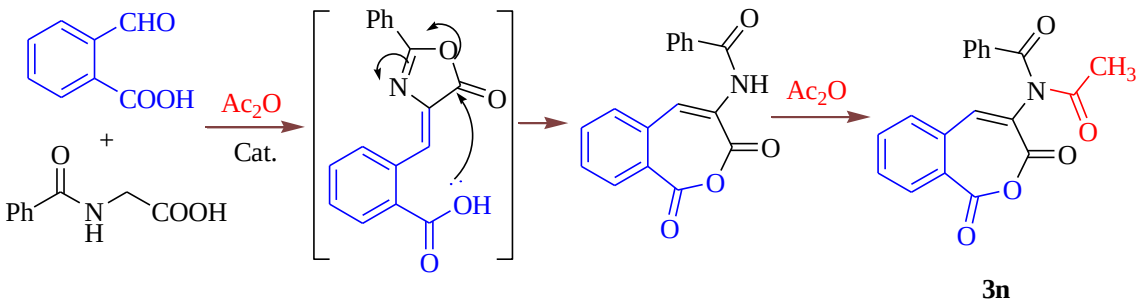
Scheme 1: The Zeolite NaY catalyzed Erlenmeyer azlactones synthesis.



Scheme 2: Optimization of reaction condition.



Scheme 3: Plausible mechanism for azlactone formation in the presence of zeolite NaY.



3n

Scheme 4: Proposed route for condensation of hippuric acid and 2-formylbenzoic acid.