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MICROWAVE-ASSISTED SYNTHESIS OF 2-SUBSTITUTED-4H-3, 1-BENZOXAZIN-4-ONES IN TETRAETHYLAMMONIUM CHLORIDE AS AN IONIC LIQUID

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ABSTRACT
A series of 2-substituted 4*H*-3, 1-benzoxazine-4-ones were synthesized from N-acyl anthranilic acid in the presence molten tetraethylammonium chloride as an ionic liquid under microwave irradiation. The advantages of this procedure is the employment of $Mg(HSO_4)_2$, a dehydrating agent as a catalyst instead of acetic anhydride, shorter reaction time, easy workup and high yield of the products.

Keywords: benzoxazine-4-one, ionic liquid, microwave, tetraethyl ammonium chloride

INTRODUCTION
4*H*-3, 1-Benzoxazin-4-ones (acylanthranils) are a class of fused heterocycles of considerable interest owing to their biological activity[i]. The 2-substituted benzoxazin-4-ones are known as mechanism-based inhibitors of standard serine proteases of the chymotrypsin superfamily[ii] and inhibit by formation of an acyl–enzyme complex through attack of the active site serine on the carbonyl group[iii-iv]. Therefore, the 2-substituted benzoxazinones showed bioactivities on human leukocyte elastase[i, v], C1r serine protease of the complement system[vi], cathepsin G[vii] human chymase[v] and tissue factor VIIa[viii]. Furthermore, there is interest that 2-substituted benzoxazin-4-ones could also be virtual protease inhibitors against herpes simplex virus type 1 (HSV-1) protease[viii] and hCMV protease[ix].

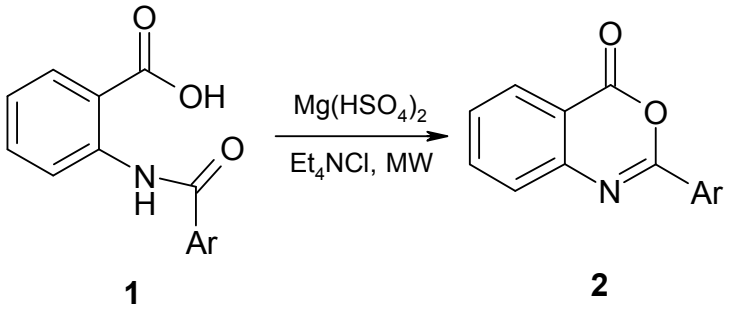
Several methods have been reported for the preparation of 2-substituted-4*H*-3, 1-benzoxazin-4-ones[x]. The most popular synthetic pathways involve the use of anthranilic acid or its derivatives[xi] *N*-acylanthranilic acids[xii] or isatonic anhydride[xiii]. Other synthetic methods such as oxidation of indoles[ixv], [4 + 2] cycloaddition of 1, 2, 3-benzotriazin-4-ones with benzaldehydes[xv], electrochemical cyclization of *o*-trichloroacetylanilides[xvi] and solid-phase synthesis[xvii] were described.

Catalytic reactions using ionic liquids have attracted considerable interests because they possess unique advantages of negligible vapour pressure, excellent thermal stability, and interesting intrinsic physicochemical characteristics. Ionic liquids have been used as effective solvents for clean chemical reactions, namely as replacements for volatile organic and dipolar aprotic

solvents[xviii]. However, high cost of most of the conventional room temperature ionic liquids and apprehension regarding the toxicity of some of them has led to the use of more benign salts in the molten state as practical alternatives. For example molten tetrabutylammonium bromide was used as an efficient ionic liquid in a number of useful synthetic transformations[xix, xx]. In this study we used tetraethylammonium chloride in molten state as the reaction media.

RESULTS AND DISCUSSION

In continuation of our interest in microwave-assisted synthesis[xxi], we wish to report the synthesis of 2-substituted 4*H*-3, 1-benzoxazine-4-ones **2** under microwave conditions (Scheme 1). A Lewis acid such as $Mg(HSO_4)_2$ did catalyze the reaction and as shown in table 1 benzoxazine-4-ones 2 were formed in this reaction.



1 **2**

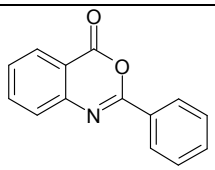
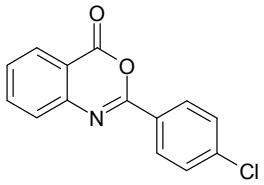
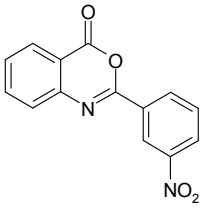
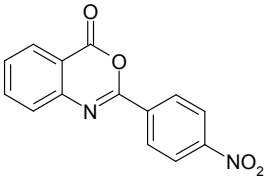
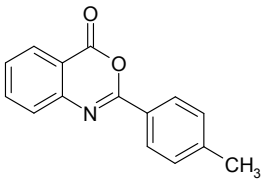
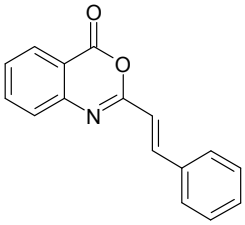
Scheme1

We initiated the cyclodehydration reaction of N-benzoyl anthranilic acid under microwave conditions by using different quantities of $Mg(HSO_4)_2$ and Et_4NCl. 10 mol% of $Mg(HSO_4)_2$ was found the best to catalyze the N-acyl anthranilic acid reaction in the presence of 1 eq of Et_4NCl at 900 W microwave power after 4 min.

In order to explore the generality of this process various aryl aldehydes were treated with electron donating and electron withdrawing substituents on the benzene ring.

Having established the optimized reaction conditions, several 2-substituted-4*H*-3, 1-benzoxazine-4-ones were synthesized in excellent yields by cyclization of different N-acyl anthranilic acid derivatives. The results are summarized in Table 1. In all cases, 2-substituted-4*H*-3, 1-benzoxazine-4-ones were exclusively formed and the by product was water which can be easily separated from the reaction mixture and in addition is not harmful to the environment.

Table 1. Microwave-assisted $Mg(HSO_4)_2$ catalyzed synthesis of 2-substituted 4*H*-3, 1-benzoxazine-4-ones

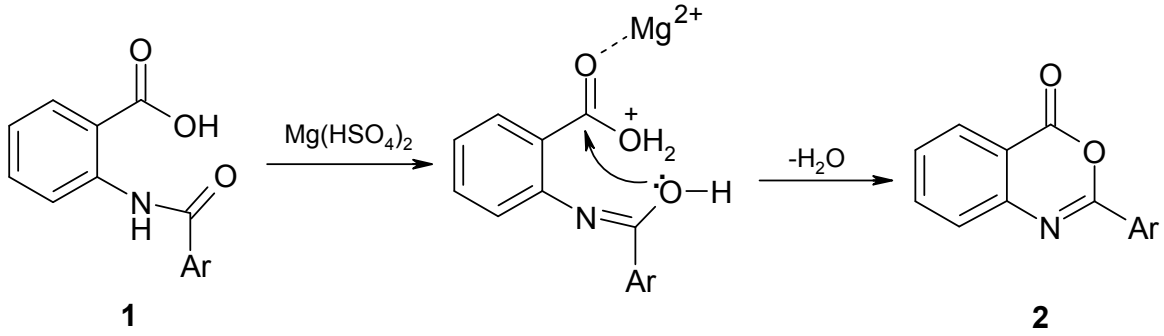
Entry	Product	Yield(%)	References to known compounds
2a		90	xxii
2b		86	xxiii
2c		95	xxiv
2d		90	xxiv
2e		94	xxiii
2f		80	xxii

We next turned our attention to the acetic anhydride and $CCl_4/PPh_3/Et_3N$ in the synthesis of 2a. The results are given in table 2. We anticipated that under these conditions the synthesis required prolonged reaction times and slightly lower yields. The results of table 2 suggested that a small amounts of $Mg(HSO_4)_2$ was an important factor in catalyzing to complete the reaction in a short period of time .

Table 2. Comparison the results of synthesis of **2a** in various conditions.

Entry	Reagent	Molar Ratio of Reagent	Condition	Time (min)	Yield (%)
1	$Mg(HSO_4)_2$	10 mol%	microwave	4	90
2	Ac_2O	10 eq	microwave	20	92
3	$CCl_4/PPh_3/Et_3N$	50/1/1 eq	Reflux	120	85

The cyclodehydration reaction appears to proceed via protonation of (**1**) by $Mg(HSO_4)_2$ and attack of enol form of amide moiety to carbonyl group of carboxylic group.



Scheme 2

In summary, th utility of $Mg(HSO_4)_2$ catalyst which is experimentally simple and inexpensive catalyzes the formation 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives by cyclodehydration of N-acyl anthranilic acids in the presence molten tetraethyl ammonium chloride and under microwave irradiation. The present methodology is a versatile synthetic approach for synthesis of 2-substituted-4*H*-3, 1-benzoxazin-4-ones in comparison to the other methods that use toxic reagents such as acetic anhydride and long reaction times.

EXPERIMENTAL SECTION

All compounds were identified by comparison of their spectral data and physical properties with those of the authentic samples. ^1H NMR and ^{13}C NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using $CDCl_3$ as a solvent. IR spectra were recorded on Mattson 1000 FT-IR spectrometer using KBr pellets. Melting points were recorded on a Gallenkamp melting point apparatus and were uncorrected. Anthranilic acid, acid chlorides and tetraethylammonium chloride were purchased from Merck chemical company and were used without further purification.

General procedure for the preparation of 2-substituted 4*H*-3, 1-benzoxazine-4-ones:

Appropriate N-acyl anthranilic acid (1 mmol), Et_4NCl (1 mmol) and $Mg(HSO_4)_2$ (10 mol%) were mixed in an open vessel and irradiated in an microwave oven (Butane) at 900 W for 4 minutes. The mixture was dissolved in 5 mL ethanol and poured into 50 mL saturated solution of $NaHCO_3$. The resulting precipitate was filtered off and washed thoroughly by water to give pure 2-substituted 4H-3, 1-benzoxazine-4-ones in good yield.

2-Phenyl 4*H*-3, 1-benzoxazine-4-one (2a): IR (KBr): 3100, 1765, 1617 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 7.17 (t, J = 7.5 Hz, 1H), 7.55-7.66 (m, 4H), 8.10 (d, J = 7.1 Hz, 2H), 8.15 (d, J = 7.7 Hz, 1H), 8.98 (d, J = 8.4 Hz, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 115.90, 120.89, 122.98, 127.82, 129.23, 131.36, 132.34, 135.13, 135.38, 142.33, 166.15, 169.07.

2-(4-Chloro-phenyl) 4*H*-3, 1-benzoxazine-4-one (2b): IR (KBr): 3120, 1773, 1625 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 7.01 (t, J = 7.5 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.46 (t, 7.8 Hz, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 7.9 Hz, 1H), 8.72 (d, J = 8.4 Hz, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 115.78, 120.54, 123.13, 129.10, 129.34, 131.32, 133.63, 134.96, 138.43, 141.88, 164.72, 168.92.

2-(3-Nitro-phenyl) 4*H*-3, 1-benzoxazine-4-one (2c): IR (KBr): 3085, 1766, 1625, 1535, 1354 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 7.62 (t, J = 7.6 Hz, 1H), 7.74-7.79 (m, 2H), 7.92 (t, J = 7.4 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 8.45 (d, J = 7.0 Hz, 1H), 8.65 (d, J = 7.8 Hz, 1H), 9.19 (s, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 117.54, 123.74, 127.26, 127.97, 129.24, 129.56, 13.38, 130.61, 132.58, 134.06, 137.34, 146.71, 149.08, 155.25, 159.16.

2-(4-Nitro-phenyl) 4*H*-3, 1-benzoxazine-4-one (2d): IR (KBr): 3074, 1770, 1670, 1600, 1525, 1330 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 7.63-7.68 (m, 2H), 7.93 (t, J = 7.2 Hz, 1H), 8.25 (d, J = 8.8 Hz, 2H), 8.54 (d, J = 8.8 Hz, 2H), 8.93 (d, J = 8.4 Hz, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 117.56, 123.75, 124.31, 128.09, 128.98, 129.69, 131.49, 135.33, 137.32, 163.82, 169.24.

2-(4-Methyl-phenyl) 4*H*-3, 1-benzoxazine-4-one (2e): IR (KBr): 3031, 2937, 1765, 1617 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 2.48 (s, 3H), 7.35 (d, J = 8.1 Hz, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 7.1 Hz, 1H), 8.24 (d, J = 8.1 Hz, 2H), 8.27 (d, J = 7.1 Hz, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 21.94, 117.39, 127.53, 128.41, 128.99, 129.90, 135.09, 136.92, 166.15, 169.05.

2-Styryl 4*H*-3, 1-benzoxazine-4-one (2f): IR (KBr): 3081, 1765, 1647, 1602 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ(ppm) 6.80 (d, J = 16.1Hz, 1H), 7.40-7.44 (m, 3H), 7.50 (t, J = 7.5 Hz, 1H), 7.58-7.62 (m, 3H), 7.80 (t, J = 7.5 Hz, 1H), 7.86 (d, J = 16.1 Hz, 1H), 8.22 (d, J = 6.8 Hz, 1H); ^{13}CNMR ($CDCl_3$): δ(ppm) 116.89, 118.79, 126.85, 127.95, 128.12, 128.58, 128.95, 130.26, 134.60, 136.49, 141.98, 147.07, 157.28, 159.24.

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