Iranian Journal of Organic Chemistry 1 (2008) 43-45

Solvent-Free Synthesis of Benzoxazin-4-ones from N-Acyl Anthranilic Acid Derivatives

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Abstract: We have developed an efficient methodology for the preparation of 2-aryl-4*H*-3, 1-benzoxazine-4-one from an opportune N-acyl anthranilic acid derivative, under solvent free conditions, recyclable and eco-friendly catalyst and shorten experimental time, and good to excellent yields.

Keywords: Benzoxazin-4-one, Anthranilic acid, Solvent free, Eco-friendly, Bentonite.

Introduction:

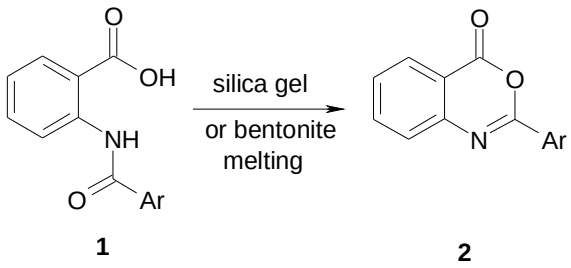
4*H*-3, 1-Benzoxazin-4-ones are a class of fused heterocyclic compounds of considerable interest owing to their biological activities. Some of these compounds act as inhibitors of human leukocyte elastase [1, 2], and serin protease [3, 4]. Moreover, 2- substituted 4*H*-3, 1-benzoxazin-4-ones, were reported to be used as precursors for the preparation of a wide variety of heterocyclic compounds such as quinazolinones [5, 6] and quinolines [7]. Several methods have been reported for the preparation of 2-substituted-4*H*-3, 1-benaoxazin-4-ones. The most popular synthetic pathways involve the use of anthranilic acid or its derivatives, N-acyl anthranilic acids [8] or isotonic anhydride [9]. Other synthetic methods such as [4+2] cycloaddition of 1, 2, 3-benzotriazin-4-ones with benzaldehydes [10], electrochemical cyclization of o-trichloroacetyl anilides [11], and palladium catalyzed carbonylation of o-iodoanilines [12] have also been reported.

Results and Discussion:

In recent decade, using applicable catalysts that are eco-friendly, green and simply recyclable in the reaction mixture has been under attention [13].

In this investigation we looked at a recycled powdered, a dehydrating agent such as silica gel, mineral clay bentonite [14], instead of common chemical dehydrating compounds which these dehydrating chemicals could not be reused. Precisely how these catalysts effect benzoxazin formation is not known at the moment. The reaction was performed in the absence of organic solvents which most of these solvents are deleterious to the environment. No cumbersome apparatus or difficult conditions are needed as some known methods are required [16], the experimental time is short and the yield is good.

Thus, in this method readily available N-acyl anthranilic acid derivatives (**1a-h**) dissolved in small amounts of chloroform and mixed with silica gel, bentonite and after melting the reaction mixture for a few minutes, the mixture converts to benzoxazinone derivatives (**2a-h**) (Scheme 1), and were further purified.



1 **2**

Scheme 1

In order to explore the generality of this process various N-acyl anthranilic acid derivatives were treated with electron donating and electron withdrawing substituents on the benzene ring.

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 no by product was formed.

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.

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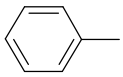
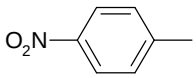
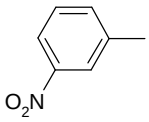
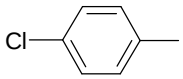
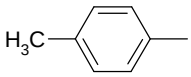
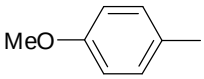
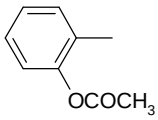
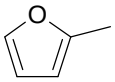
Table 1. Synthesis of 2-substituted benzoxazin-4-ones

Entry	Ar	Yield (%)[a]	Yield (%)[b]	mp (°C)	lit. mp [ref]
2a		85	88	120	123 [15]
2b		74	77	205	208 [15]
2c		77	80	166	170 [15]
2d		70	72	189	190 [16]
2e		80	79	152	155 [16]
2f		76	78	150	148 [16]
2g		60	66	148	150 [17]
2h		70	75	98	102 [16]

[a]Yields in the presence of silica gel as dehydrating agent
[b]Yields in the presence of bentonite as dehydrating agent

The IR spectral data are summarized in Table 2.

Table 2. IR data of benzoxazinones

	(KBr) $\nu_{max}(cm^{-1})$
2a	3081, 1770(C=O), 1620(C=N), 1570, 1250
2b	3096, 1769(C=O), 1630(C=N), 1610, 1530, 1350, 1240
2c	3090, 1766(C=O), 1625(C=N), 1605, 1535, 1354, 1230
2d	3100,1773(C=O), 1625(C=N), 1605, 1260
2e	3031, 2937, 1765(C=O), 1617(C=N), 1370, 1250
2f	3060, 2950, 1760(C=O), 1620(C=N), 1380, 1230
2g	3050, 2930, 1765(C=O), 1755(C=O), 1625(C=N), 1380, 1240
2h	3080, 1765(C=O), 1620(C=N), 1230

Experimental section:

General: All chemical reagents were purchased from Merck Chemical Co. and were used without further purification. N-acylanthranilic acid derivatives were prepared according to the literature methods [15-17]. Melting points were recorded on a Gallenkamp (UK) melting point apparatus and are uncorrected. The IR spectra were measured on a Mattson 1000 FT-IR spectrometer.

General procedure for the preparation of (2a-h): 1mmol of N-acyl anthranilic acid **(1a-h)** was dissolved in a small amount of chloroform then were mixed with 1 g of silica gel or bentonite and let it dry, and then the mixture was heated to the melting point of the corresponding N-acyl anthranilic acid about 4 minutes. The resulting mixture was poured in to 20 ml of ethanol and boiled for 5 minutes, filtered. The filtration was added to 30 ml

concentrated solution of sodium bicarbonate, then the resulted precipitate was filtered and washed with 20 ml water, dried, and further characterized.

Acknowledgements:

The authors express appreciation to the Shahid Bahonar University of Kerman Faculty Research Committee for its support of this investigation.

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