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CONDENSATION REACTION OF ETHYL 4-OXO-4*H*-BENZO[*d*][1,3]-OXAZINE-2-CARBOXYLATES WITH POTASSIUM CYANATE: 2,4(1*H*,3*H*)-QUINAZOLINEDIONES SYNTHESIS

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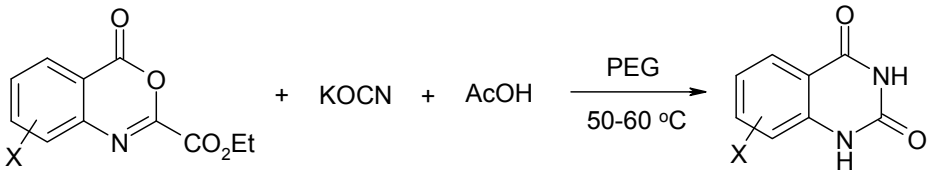
Abstract – The condensation reaction of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates with acidic solution of potassium cyanate offers a novel and expedient route to the synthesis of 2,4(1*H*,3*H*)-quinazolinediones under mild reaction conditions.

4*H*-3,1-Benzoxazin-4-ones are known as important class of heterocycles having significant biological activities. The electronically unsaturated character of 4*H*-3,1-benzoxazinones causes they are active elctrophiles and play a vital role as starting materials for further transformations in design and synthesis of heterocyclic products.[1-5]

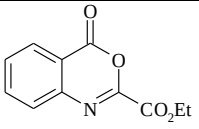
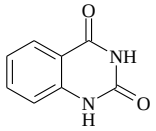
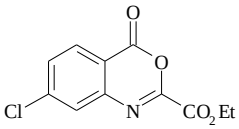
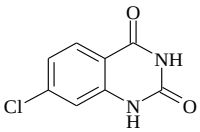
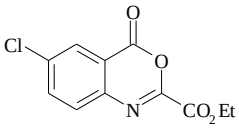
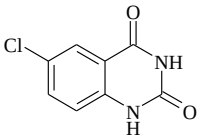
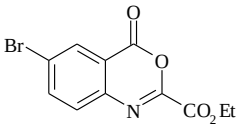
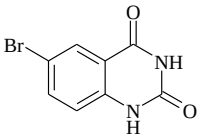
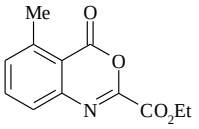
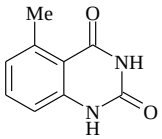
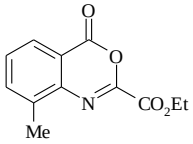
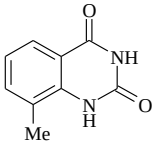
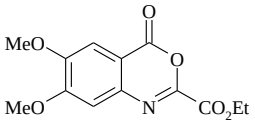
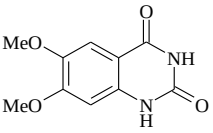
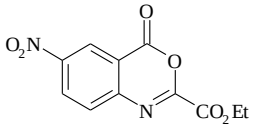
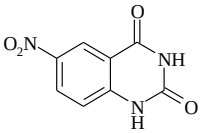
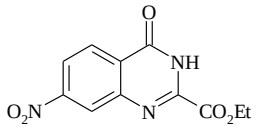
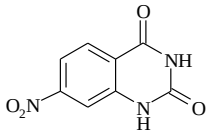
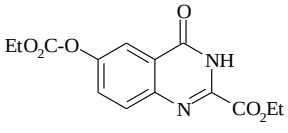
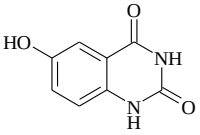
Many biological and pharmacologically active agents incorporate quinazoline-2,4-dione moiety as structural fragment.[6] Although numbers of approaches have been reported for their synthesis,[7] the development of novel and more efficient methods with mild reaction conditions and improved yields is highly desired.

In continuation of our investigation on the synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-one derivatives,[8] we have now focused our attention on the synthesis of biologically active heterocycles using 3,1-benzoxazin-4-ones moiety. The reaction of 4*H*-3,1-benzoxazin-4-one with a number of nitrogen nucleophiles has been reported.[1] They are not satisfactorily stable rings and chemically active functional groups on C-2 position affect on their reactivity. Herein, we have disclosed the condensation reaction of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates **1** with acidic solution of KOCN and preparation of 2,4(1*H*,3*H*)-quinazolinediones (Scheme 1). The reaction conditions are mild and the reaction procedure is simple. Good to high yields of the products are obtained in high purity with simple work-up of the reaction mixture. Also, this method could be utilized for the synthesis of a variety of substituents on aromatic rings. Results are summarized in Table 1.



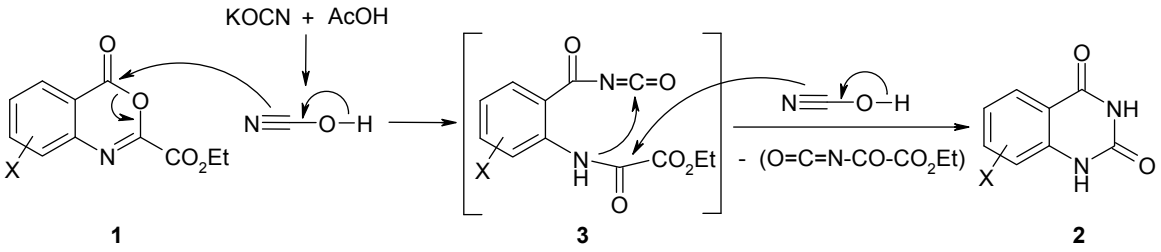
Scheme 1

Table 1. Reaction of benzoxazin-4-ones **1** with acidic solution of KOCN in PEG-400 at 50-60 °C.

Entry	**1**	**2**	Time/min	Yield **2** /% [a,b]	Mp/°C (lit.)
1			25	92	>350 (9)
2			20	90	290-292 (9)
3			45	82	320-323 (9)
4			50	85	318-323 (7a)
5			135	74	297-300 (9)
6			120	75	297-300 (10)
7			155	80	321-324 (9)
8			15	85	336-338 (9)
9			30	80	>350 (11)
10			90	78	309-312 (12)

[a] All the products were identified and characterized by comparison of their physical and spectral data with those of authentic samples. [b] Isolated yield.

Electron-withdrawing effect of the ethyl carboxylate group on C-2 position of 4*H*-3,1-benzoxazinones **1** causes the easily influence of C-4 carbonyl against nucleophilic attacks probably because they increase the electrophilic strength of C-4 carbonyl. Also, as it is observed in Table 1, electron-withdrawing groups on benzene ring increase the reaction rate; however, electron-donating substituents decrease the coupling reaction rate. The plausible mechanism is proposed in Scheme 2. Although we have made no attempts to characterize the produced intermediates, it seems that the reaction begins by nucleophilic attack of the cyanic acid to the C-4 carbonyl of benzoxazin-4-ones **1**. The subsequent nucleophilic attack of another molecule of cyanic acid to the intermediate **3** following with fast cyclization of the produced adduct, leads to the desired compounds **2**.



Scheme 2

The reactions were carried out in PEG as an excellent green polar solvent. It easily dissolves the polar starting materials. Also, it is miscible with water; therefore, it is simple to remove the solvent and the residual KOCN in work-up process by washing of the reaction mixture with water.

In conclusion, condensation reaction of ethyl 4-oxo-4*H*-benzo[*d*][1,3]oxazine-2-carboxylates with acidic solution of potassium cyanate under mild conditions, proposes a novel approach for 4*H*-3,1-benzoxazinones as starting material in design and synthesis of 2,4(1*H*,3*H*)-quinazolinediones. The reactions procedure is simple and can be used for a variety of substituents on aromatic ring. Good to high yields of the products obtain in high purity with simple work-up.

EXPERIMENTAL

Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. PEG with molecular weight 400 was used in reactions. The synthesis of the benzoxazin-4-ones **1** was achieved by using the recent published methods.[8]

General reaction procedure: A mixture of a 4*H*-3,1-benzoxazin-4-one derivative **1** (1 mmol) was dissolved in PEG (0.5 mL), then, KOCN (2.1 mmol, 0.18 g) and AcOH (2.2 mmol, 0.12 mL) were added to the mixture (in the case of entry 10, 3 mmol KOCN and 3.2 mmol AcOH were used) and heated for the times as indicated in Table 1. After completion of the reaction, the precipitate was washed with cold water (three times) to remove the residual of KOCN, AcOH and PEG. The raw products were recrystallized from EtOH, or EtOH/AcOH.

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