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An Efficient Route to 3-Aryl-Substituted Quinolin-2-one and 1,8-Naphthyridin-2-one Derivatives of Pharmaceutical Interest

Christos A. Mitsos, Alexandros L. Zografos, and Olga Igglessi-Markopoulou*

National Technical University of Athens, School of Chemical Engineering, Laboratory of Organic Chemistry, Zografou Campus, Athens 15773, Greece

ojmark@orfeas.chemeng.ntua.gr

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Abstract: Reaction of arylacetic ester enolates with 2-alkoxy-4*H*-3,1-benzoxazin-4-ones offers a short and versatile synthetic route to 3-aryl-4-hydroxyquinolin-2(1*H*)-ones, through the cyclization of the *β*-ketoesters produced. Similar reactions of 4*H*-pyrido[2,3-*d*][1,3]oxazin-4-ones with ester enolates afford 1-acyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones in a convenient two-step, one-pot procedure.

During the past few years considerable interest has been attracted by the pharmaceutical properties of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones. Antagonistic activity against the glycine site of the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor has been reported for these compounds,[1] as well as for their nonacidic derivatives.[2] The excitation of NMDA receptors is associated with glutamate excitotoxicity, hence such antagonists constitute promising pharmaceutical agents for the treatment of various central nervous system disorders, including global cerebral ischaemia, Parkinson's disease, head injury, epilepsy, and Alzheimer's disease. Recently, 3-aryl-4-hydroxyquinolin-2(1*H*)-ones have been used as precursors of a new class of nonpeptidyl gonadotropine releasing hormone (GnRH) receptor antagonists.[3] Antagonists of this type have been used for the clinical treatment of sex hormone-related conditions.[4] A series of 3-aryl-4-hydroxyquinolin-2(1*H*)-one derivatives, stimulating bone formation, have been synthesized as potent osteoporosis drugs.[5] Furthermore, the structurally similar 3-aryl- and 3-alkyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones have been reported as potent antiallergy agents displaying inhibitory activity against the slow-reacting substance of anaphylaxis (SRS-A).[6] To date 3-aryl-4-hydroxyquinolin-2(1*H*)-ones have been prepared mainly by two methods: (i) the Dieckman reaction of suitable *N*-acylated anthranilate esters[7] and (ii) the condensation of anilines with arylmalonates.[8] In the continuation of our studies on the synthesis of nitrogen-fused heterocycles,[9] we wish to report a new methodology for the synthesis of the 3-aryl-substituted quinolin-2-one and 1,8-naphthyridin-2-one class of compounds.

This new route, illustrated in Scheme 1, is based on the electrophilicity of 2-alkoxy-4*H*-3,1-benzoxazin-4-ones (**1**, X = CH), which constitute activated derivatives of anthranilic acids, analogous to isatoic anhydrides. The nucleophilic ring opening of benzoxazinones **1a** (R^1 = OMe, R^2 = H) and **1b** (R^1 = OEt, R^2 = Cl) by enolates of arylacetic esters **2** (R^3 = Ph, 3-MeOPh, or 4-MeOPh), generated with LDA in THF, proceeded smoothly at −78 °C, affording the *o*-amino-functionalized benzoyl acetates of type **3**. Ketoesters **3**, obtained as oily mixtures with the starting ester **2**, were used for the preparation of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones without further purification. As estimated from the ^{1}H NMR spectra of the crude compounds **3**, when a 2-fold excess of the ester enolate was used the conversion of **1** was nearly quantitative. Deprotection of the amine group of **3** was expected to induce the spontaneous cyclization to the desired quinolinones **4**. Actually, treatment of **3** with excess sodium methoxide in boiling toluene effected this transformation providing 3-aryl-4-hydroxyquinolin-2(1*H*)-ones **4a**−**f** in very good yields (75−93% from **1**, see Table 1).

Having established the feasibility of this approach for the synthesis of quinolinones **4**, the production of 3-aryl -or 3-alkyl-1,8-naphthyridine analogues was a straightforward extension. Incorporation of 4*H*-pyrido[2,3-*d*][1,3]-oxazin-4-ones (**1**, X = N) as acylating agents of esters **2** was expected to result in ketoesters of type **5**, which would be easily transformed to 1,8-naphthyridinones. However, reactions of 2-methyl- and 2-phenyl-4*H*-pyrido-[2,3-*d*][1,3]oxazin-4-ones (**1c** and **1d**) with ethyl phenylacetate (**2a**) and ethyl propionate (**2d**) afforded 1-acyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones **6** as the sole products, instead of the intermediate ketoesters **5**, which

* To whom correspondence should be addressed. Phone: +30 2107723074. Fax: +30 2107723072.

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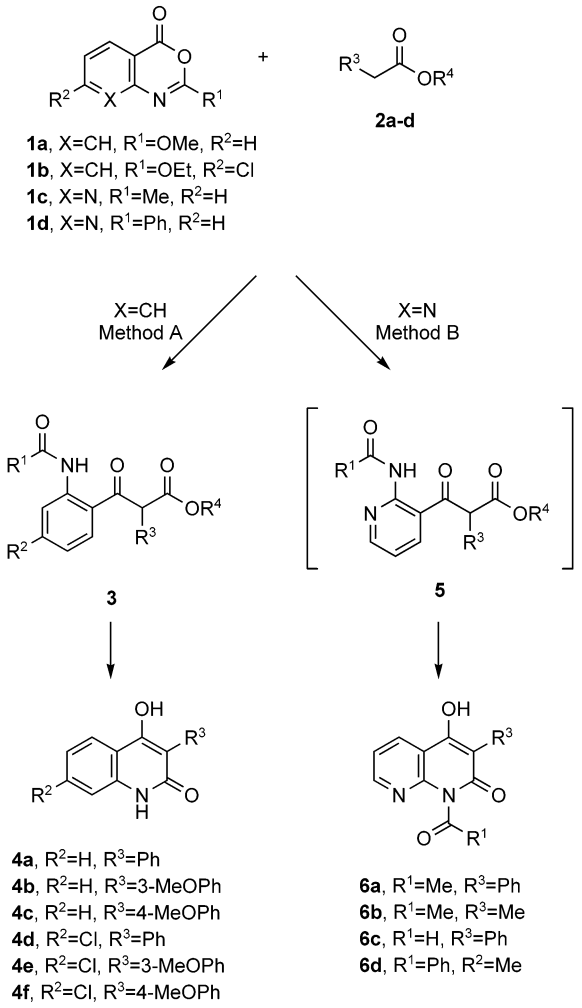
SCHEME 1[a]



[a] Method A: (i) LDA, THF, −78 °C, (ii) MeONa, toluene, reflux. Method B: LDA, THF, −78 °C.

TABLE 1. 4-Hydroxyquinolin-2(1*H*)-ones 4 and 1-Acyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones 6 Obtained

product	method	yield (%)	product	method	yield (%)
4a	A	89	**6b**	B	14
4b	A	75	**6b**[a]	C	38
4c	A	79	**6b**[b]	C	41
4d	A	83	**6c**	B	41
4e	A	87	**6d**	B	13
4f	A	93	**6e**	C	27
6a	B	57			

[a] From diethyl methylmalonate. [b] From methyl 2-methylacetoacetate. [c] From diethyl butylmalonate.

undergo spontaneous cyclization under the conditions employed. This remarkable transformation of the amide functionality in **5** into the imide one in **6** has been observed previously and was ascribed to the formation of a reactive ketene intermediate.[10] This route represents an attractive one-pot procedure for the preparation of 4-hydroxy-1,8-naphthyridin-2(1*H*)-ones, although very low yields were obtained in the case of 3-alkyl naphthyridinones **6b** and **6d** (see Table 1).

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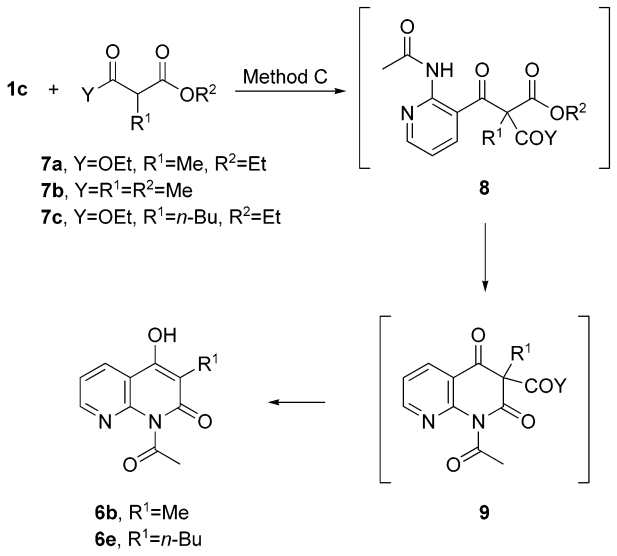
SCHEME 2[a]



[a] Method C: NaH, THF, rt.

To overcome this drawback, a modification of the methodology was attempted targeting the synthesis of a nonenolizable analogue of intermediate **5**, which we hoped could be isolated. As a preliminary attempt in this direction, pyridoxazinone **1c** was employed as an acylating agent of a substituted malonate or acetoacetate **7**, as shown in Scheme 2. Despite our expectations, this procedure resulted in the direct formation of 3-alkyl naphthyridinones **6b** and **6e** instead of the intermediate ketoesters **8**. Apparently, this transformation involves cyclization of **8** toward the 3,3-disubstituted 1,8-naphthyridinones **9**, which undergo decarboxylation or deacetylation during the aqueous workup to afford naphthyridinones **6**.

In conclusion, an efficient method for the synthesis of 3-aryl-4-hydroxyquinolin-2(1*H*)-ones and its extension to similar 1,8-naphthyridine derivatives have been developed. Further investigations concerning the application of substituted malonate carbanions as alternative nucleophiles in this sequence are currently under way.

Experimental Section

Preparation of Benzoxazinones 1a,b and Pyridoxazinones 1c,d. Compounds **1a**−**d** were prepared according to literature procedures.[9]

General Procedure for the Preparation of 3-Aryl-4-hydroxyquinolin-2(1*H*)-ones 4 (Method A). A solution of the appropriate arylacetic ester **2** (4.0 mmol) in anhydrous THF (10 mL) was added dropwise, under argon, to a solution of LDA (2.0 M solution in THF/ethylbenzene/heptane; 4.0 mmol, 2.0 mL) in anhydrous THF (20 mL), at −78 °C. The addition was completed in 20 min, the mixture stirred at −78 °C for 10 min, and then a solution of benzoxazinone **1a** (or **1b**) (2.0 mmol) in anhydrous THF (20 mL) was added dropwise over 30 min and the mixture stirred at −78 °C for 30−40 min. After being quenched with 10% hydrochloric acid (10 mL) the mixture was diluted with diethyl ether (15 mL), the organic phase was separated, and the aqueous layer was extracted further with diethyl ether (15 mL). The mixture of the organic extracts was diluted with light petroleum (20 mL), the water was separated and removed, and the organic phase was dried over sodium sulfate and concentrated in vacuo to afford the crude acylated arylacetic ester **3** as a viscous oil. A solution of crude compound **3** in anhydrous toluene (5 mL) was

added to a suspension of sodium methoxide [generated by the addition of methanol to a suspension of sodium hydride (60% in oil; 4.5 mmol, 0.18 g) in anhydrous toluene (20 mL)] and the mixture was heated at reflux for 3 h. The insoluble salt was dissolved by the addition of water (ca. 40 mL), the aqueous layer separated, and the organic phase extracted further with water (10 mL). After being washed with a small amount of light petroleum the mixture of aqueous extracts was acidified with 10% hydrochloric acid under cooling at 0 °C and the fine precipitate formed was filtered and washed with ice-cold water.

General Procedure for the Preparation of 1-Acyl-4-hydroxy-1,8-naphthyridin-2(1*H*)-ones 6 (Method B). The appropriate ester **2** (3.0 mmol) was added dropwise, under argon, to a stirred solution of LDA (2.0 M solution in THF/ethylbenzene/heptane; 3.0 mmol, 1.5 mL) in anhydrous THF (10 mL), at −78 °C, and the mixture was stirred for 30 min. A solution of pyridoxazinone **1c** (or **1d**) (2.2 mmol) in anhydrous THF (10 mL) was added dropwise over 15 min and the mixture was stirred at −78 °C for 1 h, then allowed to reach rt and stirred for an additional 1 h. The solvent was evaporated in vacuo, the residue dissolved in water, and the aqueous mixture washed with diethyl ether. The aqueous solution was acidified with 10% hydrochloric acid and the precipitated solid collected by filtration.

General Procedure for the Reactions of Pyridoxazinone 1c with Alkyl-Substituted *β*-Dicarbonyl Compounds 7 (Method C). The appropriate malonate or acetoacetate **7** was added dropwise to a suspension of sodium hydride (55−60% in oil; 22 mmol, 0.88 g) in anhydrous THF (20 mL) and the mixture was stirred at room temperature for 30 min. Pyridoxazinone **1c** (5.5 mmol, 0.89 g) was added, the mixture stirred at room temperature for 3 h, and the solvent evaporated in vacuo. The residue was dissolved in water and the aqueous mixture was washed with diethyl ether and acidified with 10% hydrochloric acid. The acidified mixture was extracted with dichloromethane and the mixture of the extracts was dried over anhydrous sodium sulfate and evaporated in vacuo. The oily residue was treated with diethyl ether and the solid formed collected by filtration.

Supporting Information Available: Experimental details and spectroscopic data for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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