

Expeditive Access to 2-Substituted 4*H*-Pyrido[1,3]oxazin-4-ones via an Intramolecular O-Arylation

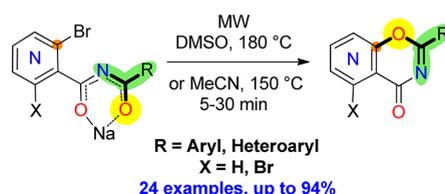
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ABSTRACT



Unreported 2-substituted 4*H*-pyrido[*e*][1,3]oxazin-4-ones are synthesized via an unprecedented intramolecular O-arylation of *N*-aryloxy- and *N*-heteroaryloxy-(iso)nicotinamides under microwave irradiations, in good to excellent yields. The broad applicability was demonstrated by 24 examples with a variety of substituents at the 2-position of the final compounds and 3 possible positions for the nitrogen atom of the pyridine ring. In addition, transformation of one of these compounds into 2-hydroxypyridyl-substituted 1,2,4-triazole and 1,2,4-oxazinone was realized. This approach opens a rapid access to a new bicyclic heteroaromatic chemical series with high potential in medicinal chemistry.

In the past two decades, 2-substituted 4*H*-benzo[*e*][1,3]-oxazin-4-ones have emerged not only as promising medicinal compounds (SCCE and GSK-3 β inhibitors, antiischemics, fluorescent probes)¹ but also as central intermediates for the preparation of 2-hydroxyphenyl-substituted 1,2,4-triazoles,² unsymmetrical 1,3,5-triazines,³ and 1,2,4-oxadiazoles.⁴ The latter find numerous applications in various fields from UV

absorbers to a wide panel of therapeutic indications.⁵ One of the well-known examples is certainly the synthesis of the marketed drug Deferasirox for the treatment of iron overload in blood (Figure 1).⁶

In this context and in the course of our medicinal programs, we were interested in the development of 2-substituted 4*H*-pyrido[*e*][1,3]oxazin-4-ones, which could be considered as aza-analogues of 2-substituted 4*H*-benzo[*e*][1,3]oxazin-4-ones. Such compounds have been recently identified as a new potential source of an original and unreported medicinal

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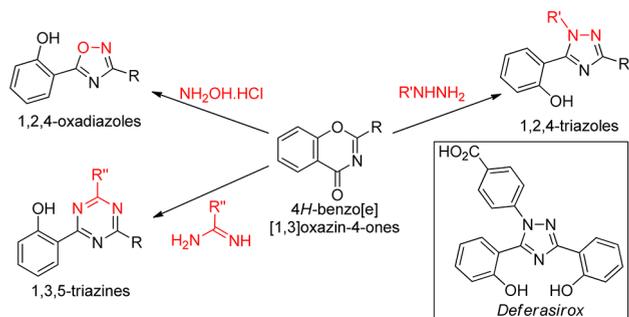


Figure 1. General access to 1,2,4-oxadiazoles, 1,3,5-triazines, and 1,2,4-triazoles from 4*H*-benzo[*e*][1,3]oxazin-4-ones.

chemical series.⁷ They could also lead, following the processes above-mentioned, to hydroxy-pyridinyl substituted triazoles and oxadiazoles which exhibit activities on several biological targets (HIV-1 integrase, PI3K inhibitors, and S1P1 agonists).⁸

Herein, we disclose our study to establish the optimal reaction conditions for the preparation of the 2-phenyl-4*H*-pyrido[4,3-*e*][1,3]oxazin-4-one **3a**, used as a model, the extension of this process to a wide panel of N-oxo-substituted bromonicotinamides, and finally one example of derivatization into triazole and oxadiazole.

Since the initial synthesis of 2-phenyl-4*H*-benzo[*e*][1,3]oxazin-4-one reported by Titherley,⁹ the preparation of 2-(hetero)aryl substituted benzo[*e*][1,3]oxazin-4-ones basically relies on the condensation between a salicylamide and an (hetero)aroyl chloride followed by an intramolecular cyclodehydration.^{1–4,10} Applying this method to 3-hydroxyisonicotinamide **1**, we isolated compound **2**, resulting from the simultaneous esterification of the hydroxy group and the dehydration of the carboxamide into a cyano group (Figure 2a). We then envisioned developing a new approach based on an intramolecular O-arylation step of N-oxo-substituted bromonicotinamides (Figure 2b). To the best of our knowledge, no example of an intramolecular O-arylation on a 3-halogenated position of a pyridine ring with the oxygen atom of an amide or a diamide functional group has been reported so far.

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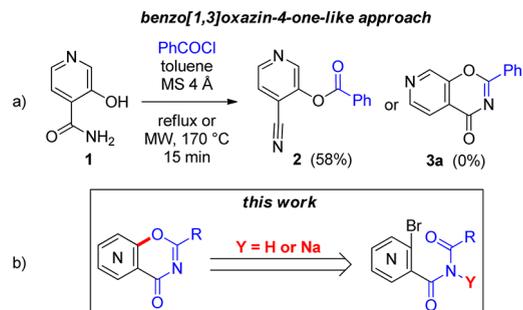
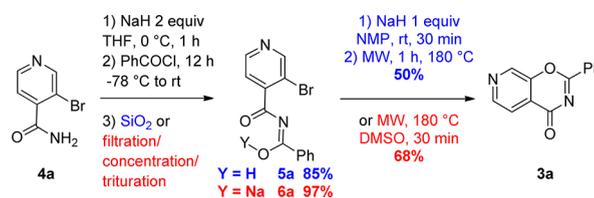


Figure 2. Synthetic approaches to 4*H*-pyrido[*e*][1,3]oxazin-4-ones.

We first explored the reaction conditions to perform the intramolecular O-arylation step able to provide the desired cyclized compound, i.e. 2-phenyl-4*H*-pyrido[4,3-*e*][1,3]oxazin-4-one **3a**, used as a model. Starting from **5a** (obtained by benzylation of **4a**), several protocols reported to perform intramolecular O-arylation at a C-3 halogenated position of a pyridine were tested (see Table 1 in the Supporting Information (SI)).^{11,12} Surprisingly, despite the use of transition metal catalysts or thermal neutral conditions, only the starting material or degradation products were obtained. Moreover, several basic conditions were explored, and only the sequential deprotonation of **5a** using NaH in DMF or NMP, followed by microwave (MW) irradiation, led to the isolation of **3a** in 40% and 50% yield respectively (Scheme 1). During this chemical process, the synthesis of **3a** from **4a** required the use of 3 equiv of sodium hydride. To develop a more expeditive protocol, we decided to isolate the imide sodium salt of **5a** and then to submit it to microwave irradiation in various solvents. Thereby, **6a** was isolated in 97% yield from the benzylation step (from **4a**) by applying a concentration/trituration sequence (Scheme 1).

Scheme 1. Intramolecular O-Arylation of **5a** or **6a** into **3a**



The structure of **6a** was unambiguously confirmed by NMR, IR, mass, and X-ray crystal analysis (Figure 3 and S2 in the SI). It revealed a conformation where the sodium

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atom is positioned at an equal distance between the two oxygen atoms, thus forming a central six-membered ring (Figure 3). Several polar and chelating solvents were then tested under microwave-assisted cyclization conditions to solvate the sodium cation and thereby to allow the rotation of one amide bond in the correct conformation for the O-arylation to proceed. Among all the tested solvents (Table S2 in the SI), the use of DMSO significantly improved the yield of the cyclization up to 68% while NMP or DMF provided **3a** with similar yields to the previous sequential method (Scheme 1).

X-ray crystal analysis of **3a** (Figure 3 and S1 in the SI) definitively confirmed the desired intramolecular O-arylation.

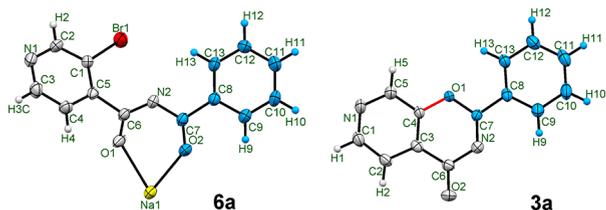


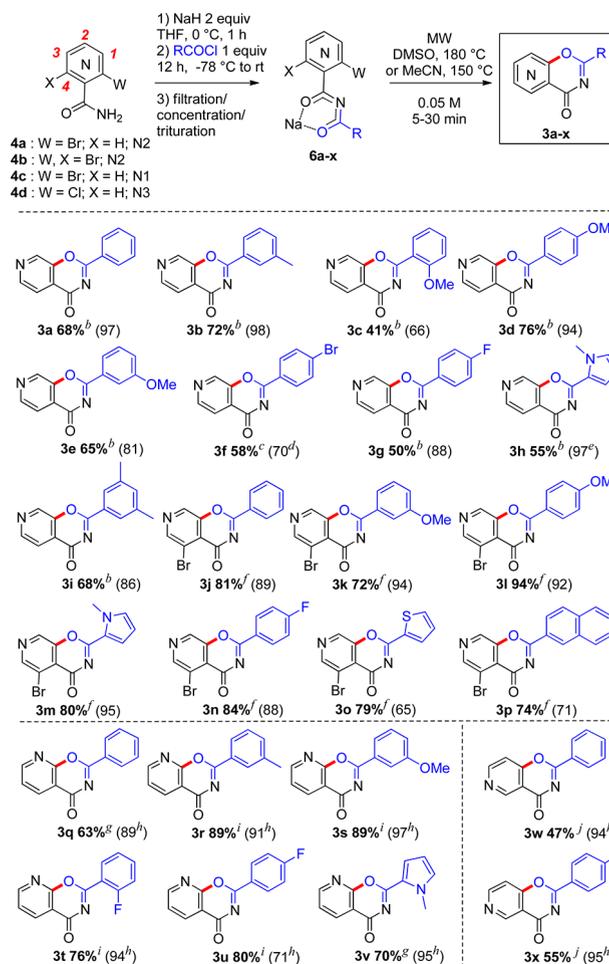
Figure 3. ORTEP diagrams of compounds **6a** and **3a** with thermal ellipsoids at 50% probability.

Extension of this synthetic process was carried out with several substituted benzoyl chlorides and heteroaryl chlorides with four different bromonicotinamides (Scheme 2). The imide sodium salts **6a–x** were obtained in good to excellent yields from **4a–d** (yields in parentheses, Scheme 2).¹³

In terms of limitations, the use of alkyl chlorides was unable to generate the corresponding imide sodium salt ($R = \text{Me}$), or led to degradation during the cyclization process ($R = t\text{-Bu}$). Similarly, starting from 3-bromopyridinamide (compound **4**, Scheme 2, with $W = \text{Br}$, no X and $N4$), the generation of the corresponding imide sodium salt ($R = \text{Ph}$) failed or the cyclization of the corresponding imide sodium salts ($R = p\text{-MeO-Ph}$) led to the complete degradation of the cyclization precursor (Table S3 in the SI). Although a 3-halogenated pyridine ring is not the most reactive substrate toward nucleophilic aromatic substitutions, compounds **3a–i** were obtained in moderate to good yields. The yield dropped dramatically for the ortho-substituted example **3c** (compared to **3d** and **3e**). This could be explained by an unfavorable stereoelectronic 1,3-interaction between the methoxy group and the nitrogen or oxygen atom of the oxazinone ring. This interaction would lead to the rotation of the phenyl substituent. Accordingly, the resulting nonplanar structure would present less steric interactions while losing the stabilizing electronic resonance between the bicyclic core and the phenyl substituent (see X-ray structure of **3c**, Figure S3 in the SI). Besides, a meta disubstituted phenyl

(13) Compounds **4a**, **c**, **d** are commercially available. **4b** was easily prepared in one step from commercially available 3,5-dibromo-4-cyanopyridine (see Supporting Information).

Scheme 2. Synthesis of 2-Substituted 4*H*-Pyrido[*e*][1,3]oxazin-4-ones via MW-Assisted Intramolecular O-Arylation^a

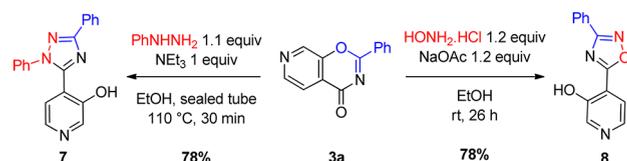


^a Isolated yield of **3a–x** from the intramolecular O-arylation of the corresponding precursor **6a–x**. In parentheses: isolated yields for the preparation of **6a–x**. ^b Reaction was run for 30 min at 180 °C in DMSO. ^c Reaction was run for 1 h at 180 °C in DMSO. ^d For the preparation of **6f**, 4-bromobenzoyl chloride was added at 0 °C. ^e To satisfy purity, **6h** was prepared from the corresponding purified diamide (NH) **5h** with 1 equiv of NaH in THF at 0 °C for 1 h. ^f Reaction was run for 20 min at 180 °C in DMSO. ^g Reaction was run either for 30 min at 180 °C in DMSO or for 15 min at 150 °C in MeCN (**3q** isolated respectively in 63 and 56% yield). ^h Yields of the crude **6q–x** which were immediately engaged in the cyclization process due to their instability. ⁱ Reaction was run for 15 min at 150 °C in MeCN. ^j Reaction was run for 5 min at 180 °C in DMSO.

substituent is well-tolerated (**3i** isolated in 68% yield) as well as a heteroaromatic substituent (**3h**). The presence of an additional electron-withdrawing bromine atom at the C-5 position of the pyridine ring significantly improved the yield of the final cyclized compounds (**3j–n** vs **3a, d, e, g, h**). For these examples, good to excellent yields were obtained, from 72% (**3k**) to 94% (**3l**). Moreover, the presence of a bromine in the pyridine ring of the final products introduces a potential site for further functionalizations. Next, starting from **4c** and **4d**, the thus generated imide sodium salts **6q–x** exhibit a halogen atom respectively at the C-2 and C-4 positions of the pyridine, which is known to be

more reactive toward nucleophilic aromatic substitution.¹⁴ Surprisingly, they appeared to degrade rapidly, which was more pronounced for **6w**, **x** either in the presence of a bromine or a chlorine atom. Consequently, **6q–x** have been freshly prepared and immediately engaged in the cyclization process. The corresponding cyclized products **3q–v** were isolated mainly in good to excellent yields using relatively milder reaction conditions (150 °C, 15 min) in acetonitrile. Cyclizations of **6w**, **x** were successful in DMSO at 180 °C for 5 min leading to **3w**, **x** in respectively 47% and 55% yield.

Scheme 3. Preparation of 1,2,4-Triazole **7** and 1,2,4-Oxadiazole **8** from **3a**



Finally, we explored the chemical potential of these 4*H*-pyrido[*e*][1,3]oxazin-4-ones. Exposure of **3a** to phenyl hydrazine¹⁵ or hydroxylamine^{4b} led respectively to the corresponding hydroxypyridine substituted 1,2,4-triazole **7** and 1,2,4-oxadiazole **8** in 78% yield each (Scheme 3).

These derivatization examples enhance the medicinal potential of the 4*H*-pyrido[*e*][1,3]oxazin-4-ones, by using them as intermediates, and provide a rapid and

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complementary alternative for the preparation of hydroxy-pyridine substituted 1,2,4-triazoles and 1,2,4-oxadiazoles.

In conclusion, we have developed a two-step synthesis of unreported 2-substituted 4*H*-pyrido[1,3]oxazin-4-ones. Notably, we isolated the sodium salt of *N*-aroyl- and *N*-heteroaroyl-bromo(iso)nicotinamides in good to excellent yields. Engaged in an undescribed microwave-assisted intramolecular *O*-arylation reaction, these sodium salts provided the desired bicyclic pyrido-oxazinones in yields up to 94%. This process was successfully applied to a wide panel of aryl and heteroaryl substituents and with three possible positions for the nitrogen atom in the pyridine ring. One-step derivatization into 1,2,4-triazole and 1,2,4-oxadiazole was performed with good yields on a model compound, illustrating the chemical potential of these structures used as intermediates. Importantly, this synthetic pathway opens an efficient, metal-free, and rapid route to 2-substituted 4*H*-pyrido[*e*][1,3]oxazin-4-ones, as a new heteroaromatic bicyclic chemical series with high medicinal potential.

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Supporting Information Available. Experimental procedures, Tables S1 and S2, characterization data for all compounds described, crystallographic data for compounds **3a**, **3c**, and **6a** and CIFs. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.