Tetrahedron Letters 57 (2016) 5877–5880

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile entry into structurally diverse, privileged, (hetero)arene-fused *N*-alkoxy 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones

Alexander Sapegin [a], Elena Reutskaya [b], Alexey Smirnov [b], Mikhail Korsakov [b], Mikhail Krasavin [a,*]

[a] *Institute of Chemistry, Saint Petersburg State University, 26 Universitetskii Prospect, Peterhof 198504 Russian Federation*
[b] *The Ushinsky Yaroslavl State Pedagogical University, 108 Respublikanskaya St., Yaroslavl 150000, Russian Federation*

ARTICLE INFO

Article history:
Received 25 October 2016
Revised 12 November 2016
Accepted 15 November 2016
Available online 19 November 2016

Keywords:
Tandem cyclization
Nucleophilic aromatic substitution
Smiles rearrangement
Tricyclic scaffolds
Benzo[1,4]oxazepines
Privileged structures
Lossen rearrangement

ABSTRACT

Rare and highly medicinally relevant *N*-alkoxy-substituted benzo[1,4]oxazepines have been synthesized conveniently *via* the base-promoted S_NAr/Smiles rearrangement/S_NAr tandem cyclization of *N*-alkoxysalicylamides with a range of bis-electrophilic substrates; subsequent de-alkylation gives rise to the respective *N*-hydroxy versions. The compounds reported herein significantly add to the contemporary arsenal of small molecule tools for drug discovery.

Tricyclic (hetero)arene-fused benzo[1,4]oxazepines belong to a broad family of privileged[1] tricyclic systems (Fig. 1) that has delivered numerous biologically active compounds and drugs in diverse disease areas.[2] For example, in 2016 alone, tricyclic benzo[1,4]oxazepine scaffolds have been explored in the context of modulating the nuclear farnesoid X receptor (FXR),[3] serine hydroxymethyltransferase 2 (SHMT2) inhibition,[4] and blocking serotonin receptor 5HT2B activity[5] (Fig. 2).

Recently, we have been engaged in developing a unified synthetic methodology toward tricyclic benzo[1,4]oxazepines that represents a facile, modular approach with an opportunity for flexible variation of the fused (hetero)aromatic ring portion of the scaffold. The strategy involves condensation, in the presence of potassium carbonate, of suitably functionalized phenols **1** with partners **2** containing two leaving groups (1,2-dihalo- or 1-halo-2-nitro (hetero)aromatics). The cyclization is the net result of tandem S_NAr – Smiles rearrangement – S_NAr steps (Scheme 1). It is the interplay of these events that is thought to enable the non-catalyzed ring-forming process which, in many cases, would be difficult to envision taking place without a metal-based catalyst. Depending on the nature of the Y-Z-H moiety in **1** and the structure of the bis-electrophilic partner **2**, numerous novel or known medicinally important ring systems can be accessed in an expedited fashion. To-date, we have reported benzo[1,4]oxazepines containing lactam (**3**)[6] or sultam (**4**)[7] central (seven-membered) rings, as well as pyrazole-(**5**)[8–10] and imidazoline-fused (**6**)[11] scaffolds. *N*-Alkoxy (as well as *N*-hydroxy) benzo[1,4]oxazepin-5-ones **7** are surprisingly scarce in the medicinal chemistry literature In fact, only one example of such compounds (namely, 10-methoxy (hydroxy)dibenzo[*b*,*f*][1,4]oxazepin-11(10*H*)-one) has been described in the context of HIV-1 reverse transcriptase inhibition.[12] In this study, we investigated the applicability of the above unified synthetic strategy toward the synthesis of *N*-alkoxy (hydroxy) tricyclic benzo[1,4]oxazepin-5-ones **7** (Scheme 1).

We reasoned that the target *N*-hydroxy and *N*-alkoxy tricyclic benzo[1,4]oxazepines are interrelated and one could either target the *N*-hydroxy version **9** first (using commercially available *N*,2-dihydroxybenzamide, **8**) and then introduce the *O*-alkyl group or prepare various *N*-alkoxy versions directly and eventually rely on the vast commercially available arsenal of *O*-alkyl hydroxylamines and *N*-alkoxy-2-hydroxybenzamides **10** amenable therefrom (Fig. 3).

However, when hydroxamic acid **8** was treated with bis-electrophilic substrates **2a**–**b** in the presence of K_2CO_3 in DMF, it underwent clean conversion to benzo[*d*]oxazol-2(3*H*)-one **11** while **2a**–**b** were transformed into their hydroxy-substituted

* Corresponding author.
E-mail address: m.krasavin@spbu.ru (M. Krasavin).
URL: http://krasavin-group.org (M. Krasavin).

http://dx.doi.org/10.1016/j.tetlet.2016.11.064
0040-4039/

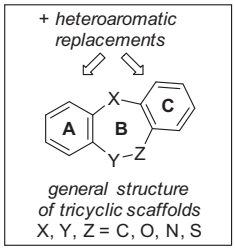


Fig. 1. Privileged tricycles for drug design.

versions **12a**–**b**. Such an outcome, in our view, can be rationalized by the initial *O*-arylation of the hydroxamic acid moiety[13,14] followed by Lossen-type rearrangement[13] (Scheme 2).

To explore the alternative approach, we prepared *N*-alkoxy-2-hydroxybenzamides **10a**–**b** using a standard amide coupling approach and introduced them into reaction with a series of bis-electrophilic (hetero)aromatic substrates **2a**–**i** in the presence of K_2CO_3 in DMF. To our delight, the reaction (Scheme 3) proceeded to completion within 2–6 h at 30–70 °C, yielding the target *N*-methoxy (**7a**–**h**) and *N*-benzyloxy (**7i**–**j**) 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones in fair to excellent yields (Table 1).[15] The same approach will likely apply to the preparation of other *O*-substituted analogs of **7a**–**j** *via* the use of numerous other hydroxamic acid esters akin to **10a**–**b**.

For all tandem S_NAr/S_NAr cyclizations leading to tricyclic benzo[1,4]oxazepines reported so far,[6–11] the Smiles rearrangement was consistently observed, as confirmed by single-crystal X-ray analyses and/or conclusive correlations in the NOESY spectra of the respective products, and appeared to be a pre-requisite for successful ring formation.[16] In the present study, we also verified if such a mechanistic picture was maintained for *N*-methoxysalicylamides **10** by correlations observed in the NOESY spectrum of compound **7b** (Fig. 4).

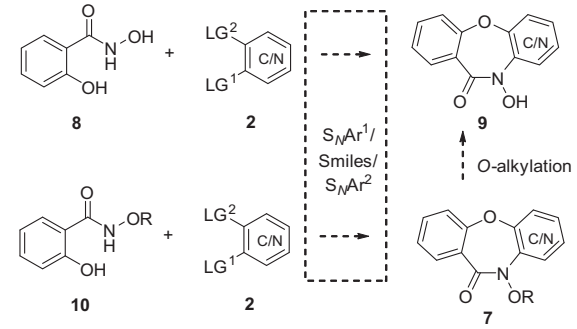


Fig. 3. Possible approaches to *N*-alkoxy tricyclic benzo[1,4]oxazepines **7**.

The rare *N*-alkoxy-substituted tricyclic benzo[1,4]oxazepines **7a**–**j** are of significant interest as novel versions of medicinally important, privileged heterocyclic motifs that have high relevance in diverse biotarget areas (*vide supra*). They can also be viewed as precursors to the respective *N*-hydroxy versions of **7**, which are also exceedingly rare, and potentially attainable by *O*-dealkylation. To demonstrate such a possibility, *O*-dealkylation of representative compound (**7b**) was performed by treatment with BBr_3 to give the respective *N*-hydroxy-substituted compound **13** in moderate yield (Scheme 4).

In conclusion, we have developed a convenient and practically simple method to prepare rare, yet highly medicinally relevant, tricyclic *N*-alkoxy benzo[1,4]oxazepines with a broad diversity of fused (hetero)aromatic rings. The compounds can be viewed as precursors to *N*-hydroxy analogs which cannot be synthesized directly from the respective hydroxamic acid due to the prevailing Lossen rearrangement. The compounds significantly expand the arsenal of small molecule tools for drug discovery and are currently being evaluated as anti-infectives. The results of these studies will be reported on in due course.

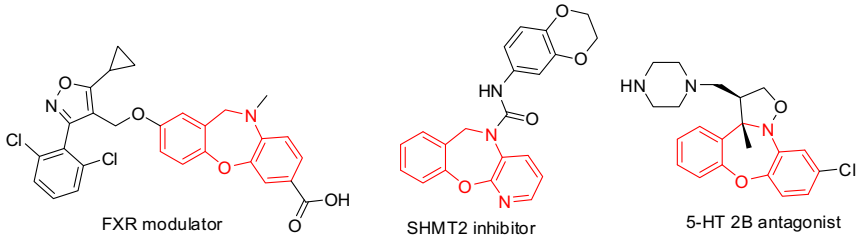
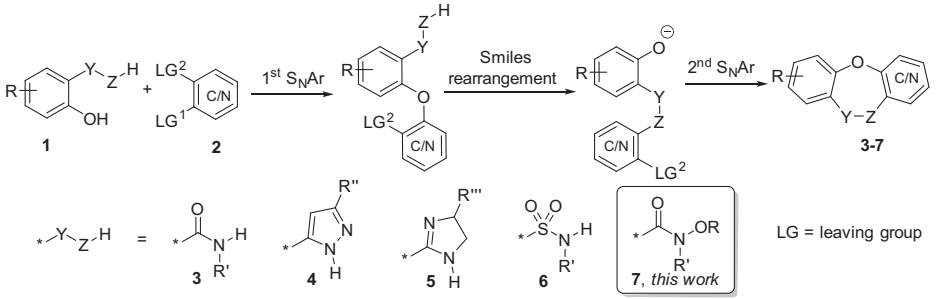


Fig. 2. Examples of bioactive tricyclic benzo[1,4]oxazepines from the recent literature.



Scheme 1. Synthetic strategy toward tricyclic benzo[1,4]oxazepines as previously described by us (**3**–**6**) and pursued in this work (**7**).