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PII: S0040-4039(16)31532-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.064
Reference: TETL 48350

To appear in: *Tetrahedron Letters*

Received Date: 25 October 2016
Revised Date: 12 November 2016
Accepted Date: 15 November 2016

Please cite this article as: Sapegin, A., Reutskaya, E., Smirnov, A., Korsakov, M., Krasavin, M., Facile entry into structurally diverse, privileged, (hetero)arene-fused *N*-alkoxy 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.064

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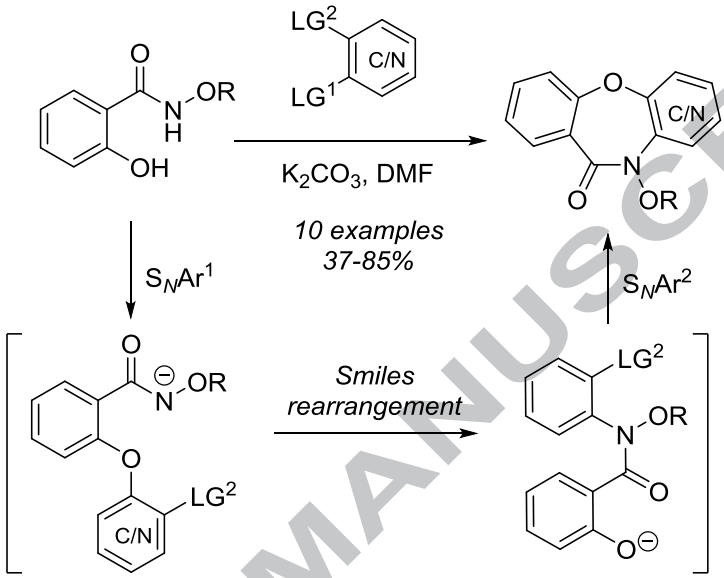

Facile entry into structurally diverse, privileged, (hetero)arene-fused *N*-alkoxy 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones

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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.

Keywords: tandem cyclization, nucleophilic aromatic substitution, Smiles rearrangement, tricyclic scaffolds, benzo[1,4]oxazepines, privileged structures, Lossen rearrangement.

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).

Figure 1. Privileged tricycles for drug design.

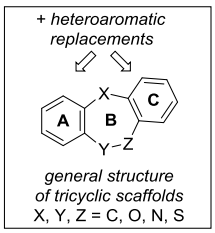
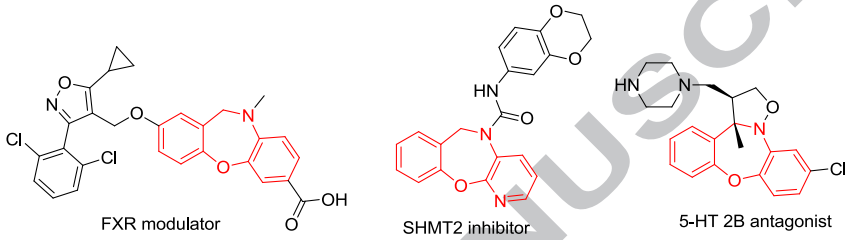
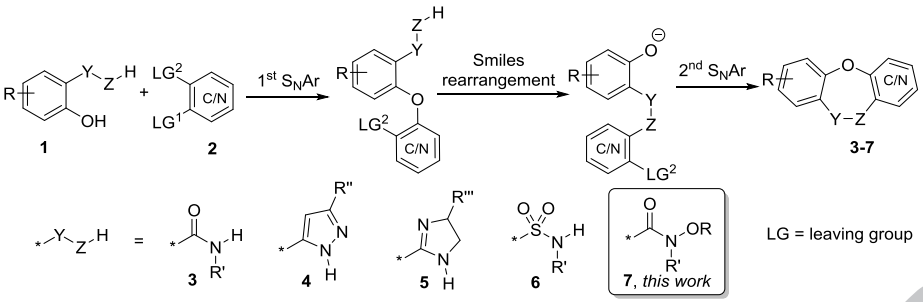


Figure 2. Examples of bioactive tricyclic benzo[1,4]oxazepines from the recent literature.



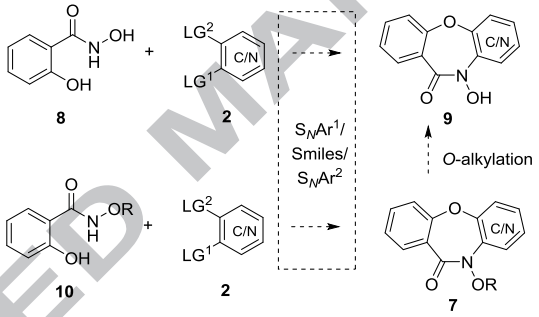
Recently, we have been engaged in developing a unified synthetic methodology toward tricyclic benzo[1,4]oxazepines that represents a facile, modular approach with an opportunity for flexible variation of the fused (hetero)aromatic ring portion of the scaffold. The strategy involves condensation, in the 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).

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



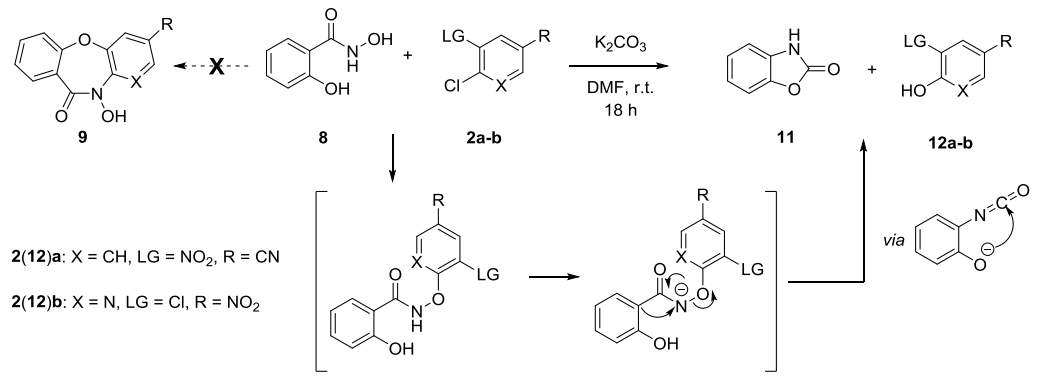
We reasoned that the target *N*-hydroxy and *N*-alkoxy tricyclic benzo[1,4]oxazepines are interrelated and one could either target the *N*-hydroxy version **9** first (using commercially available *N*,2-dihydroxybenzamide, **8**) and then introduce the *O*-alkyl group or prepare various *N*-alkoxy versions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

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



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 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).

Scheme 2. Attempted reaction of hydroxamic acid **8** with bis-electrophilic substrates **2a-b**.



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 ºC, 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**.

Scheme 3. Reaction of (hetero)aromatic substrates **2a-i** with *N*-alkoxy-2-hydroxybenzamides **10a-b**.

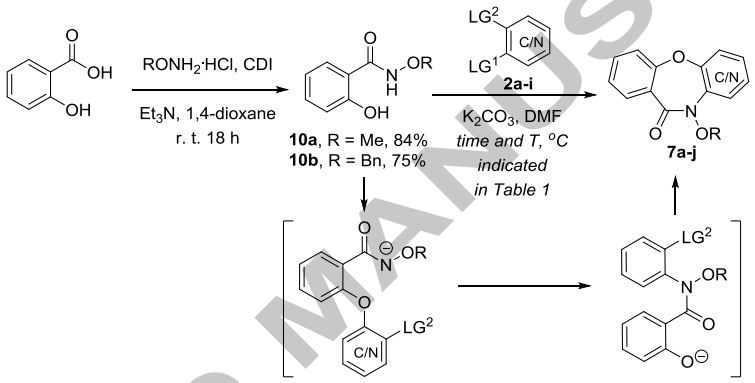
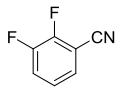
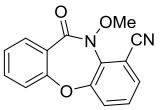
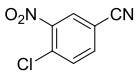
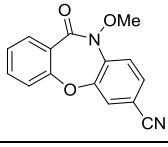
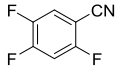
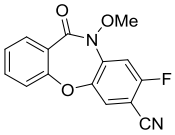
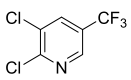
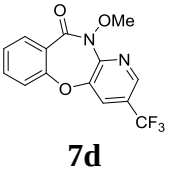
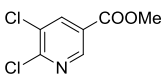
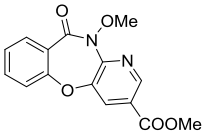
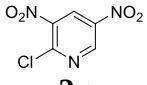
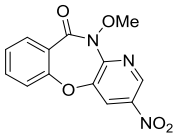
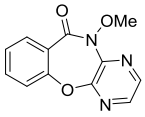
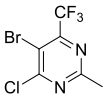
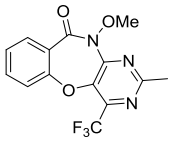
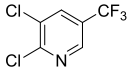
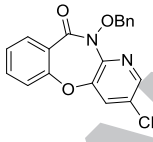
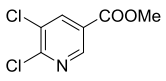
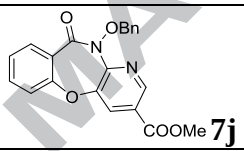


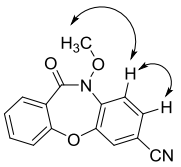
Table 1. *N*-methoxy (**7a-h**) and *N*-benzyloxy (**7i-j**) 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones prepared in this work.

Entry	**10**	**2**	**7**	Time (h)	T (^{o}C)	Yield (%)
1	**10a**	 **2c**	 **7a**	6	60	81
2	**10a**	 **2b**	 **7b**	5	60	74
3	**10a**	 **2d**	 **7c**	3	40	63
4	**10a**	 **2e**	 **7d**	3	50	76

5	**10a**	 **2f**	 **7e**	5	60	62
6	**10a**	 **2g**	 **7f**	2	30	85
7	**10a**	 **2h**	 **7g**	5	70	77
8	**10a**	 **2i**	 **7h**	3	30	69
9	**10b**	 **2j**	 **7i**	3	50	41
10	**10b**	 **2k**	 **7j**	5	60	37

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).

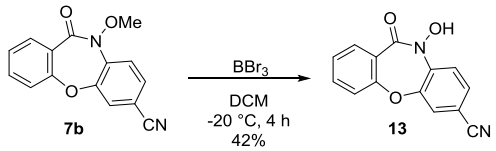
Figure 4. Through-space correlations observed in the NOESY spectrum of compound **7b**.



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).

Scheme 4. *O*-Demethylation of compound **7b**.



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.

Acknowledgements

We gratefully acknowledge support from the Russian Scientific Fund (Project Grant 14-50-00069). NMR studies were performed at the Research Centre for Magnetic Resonance of Saint Petersburg State University Research Park.

Supplementary data

The supplementary data containing NMR spectra of the reaction products is available on http://www.sciencedirect.com.

References and notes

1. Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 1-15.
2. Fedi, V.; Guidi, A.; Altamura, M. *Mini-Rev. Med. Chem.* **2008**, *8*, 1464-1484.
3. Wang, X.; Yang, X.; Pan, S.; Guo, R.; Wu, J.; Zhang, Y.; Cheng, C. Int. Patent Appl. WO 2016127924A1; Chem. Abstr. 2016, 165, 286979.
4. Neamati, N.; Xu, S.; Tamura, S. Int. Patent Appl. WO 2016085990A1; Chem. Abstr. 2016, 165, 62459.
5. Zhou, Y.; Ma, J.; Lin, X.; Huang, X.-P.; Wu, K.; Huang, N. *J. Med. Chem.* **2016**, *59*, 707-720.
6. Sapegin, A. V.; Sakharov, V. N.; Kalandadze, L. S.; Smirnov, A. V.; Khristolyubova, T. A.; Plakhtinskii, V. V.; Ivashchenko, A. V. *Mendeleev Commun.* **2008**, *18*, 281.

7. Sapegin, A.; Panova, V.; Reutskaya, E.; Smirnov, A. V.; Krasavin, M. *Tetrahedron* **2016**, *72*, 7570-7578.
8. Sapegin, A. V.; Kalinin, S. A.; Smirnov, A. V.; Dorogov, M. V.; Krasavin, M. *Synthesis* **2012**, *44*, 2401-2407.
9. Sapegin, A.V.; Kalinin, S. A.; Smirnov, A. V.; Dorogov, M. V.; Krasavin, M. *Tetrahedron* **2014**, *70*, 1077-1083.
10. Sapegin, A.V.; Kalinin, S. A.; Smirnov, A. V.; Dorogov, M. V.; Krasavin, M. *Eur. J. Org. Chem.* **2015**, 1333-1340.
11. Karamysheva, K.; Reutskaya, E.; Sapegin, A.; Dorogov, M.; Krasavin, M. *Tetrahedron Lett.* **2015**, *56*, 5632-5636.
12. Klunder, J. M.; Hargrave, K. D.; West, M.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C.; Adams, J. *J. Med. Chem.* **1992**, *35*, 1887-1897.
13. Yu, W.; Bulger, P. G.; Maloney, K. M. *Green Chem.* **2016**, *18*, 4941-4946.
14. Ishiguro, M.; Ishida, T.; Tomino, I. PCT Int. Appl. WO9518106A1; *Chem. Abstr.* **1995**, *123*, 228002.
15. General procedure for the preparation of compounds **7a-j**: the respective *N*-alkoxysalicylamide **10** (2 mmol) and 1,2-dihaloarene (1-halo-2-nitroarene) partner **2** (2 mmol) were combined in anhydrous DMF (7 mL) with freshly calcinated K_2CO_3 (829 mg, 6 mmol). The mixture was stirred at the temperature and time period indicated in Table 2. DMF was removed *in vacuo* and the residue treated with water (10 mL), which caused the viscous oil to separate. This was extracted with CH_2Cl_2 (5 mL) and the organic layer separated, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using an appropriate gradient of CH_2Cl_2 in hexanes as eluent.
16. In cases when the potential Smiles rearrangement was suppressed by unfavorable electronic effects in the substrates, the process halts after the first S_NAr and the cyclization does not occur (Sapegin, A.; Krasavin, M. Unpublished results).

Highlights

- Rare tricyclic *N*-alkoxy benzo[1,4]oxazepines synthesized *via* a novel strategy
- Involves a tandem S_NAr – Smiles rearrangement - S_NAr process
- *O*-Alkyl hydroxamic acids react with bis-electrophilic (hetero)aromatic compounds
- *N*-Hydroxy compounds can be obtained by *O*-dealkylation
- Free hydroxamic acids do not react in the same way and undergo Lossen rearrangement