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Functionalized Orthoesters as Powerful Building Blocks for the Efficient Preparation of Heteroaromatic Bicycles

Gulluzar Bastug, Christophe Eviolitte, and István E. Markó*

Laboratory of Organic and Medicinal Chemistry, Université Catholique de Louvain, Bâtiment Lavoisier, Place Louis Pasteur 1 bte L4.01.02., B-1348 Louvain-la-Neuve, Belgium

istvan.marko@uclouvain.be

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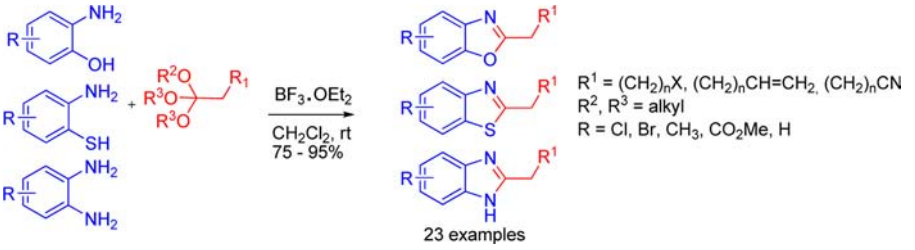
ABSTRACT



By combining substituted anilines with functionalized orthoesters, an efficient and connective methodology for the preparation of benzoxazole, benzothiazole, and benzimidazole derivatives has been established. The versatility of this approach enables the development of new libraries of heterocycles containing multifunctional sites.

Benzoxazoles, benzothiazoles, and benzimidazoles are important fragments in medicinal chemistry because of their wide range of biological activities. For example, mibefradil (**1**),[1] developed by Merck healthcare, contains a benzimidazole core and is active against hypertension. Zopalrestat (**2**),[2] a good representative of benzothiazole-containing drugs, is used for the treatment of diabetic complications and is commercialized by the Takeda Pharmaceutical Co. Calcimycin (**3**),[3] a benzoxazole derivative produced by combinatorx, is employed as an ionophore antibiotic (Figure 1).

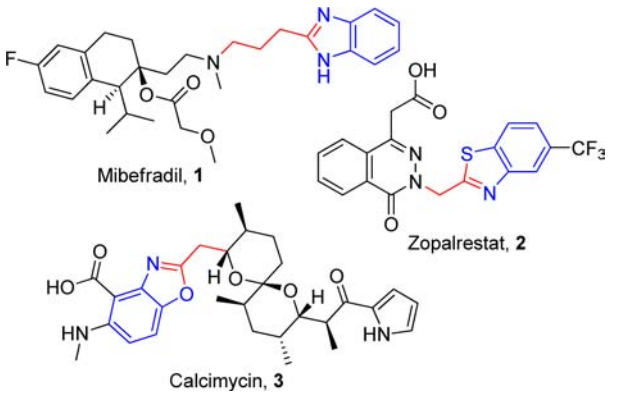


Figure 1. Example of drugs containing heteroaromatic bicycles.

Several methods have been reported for the preparation of these benzofused heterocyclic structures. A general route consists of the condensation of anilines with carboxylic acids,[4] esters,[5] or acid chlorides[6] under strongly acidic conditions, at high temperatures, or under pressure. In a similar

(1) Moreira de Almeida, I. Patent WO2007/93021 A1, 2007.
(2) Murata, T.; Makino, S. Patent EP1876179 A1, 2008.
(3) Jin, X.; Staunton, J.; MacDonald, D.; Dong, H.; Kifle, L. Patent WO2008/133884 A2, 2008.
(4) Soares, A. M. S.; Costa, S. P. G.; Gonalves, M; Sameiro, T. *Tetrahedron* **2010**, *66*, 8189.
(5) Sheng, C.; Che, X.; Wang, W.; Wang, S.; Cao, Y.; Yao, Y.; Miao, Z.; Zhang, W. *Eur. J. Med. Chem.* **2011**, *46*, 1706.
(6) Fukuda, S.; Nakamura, A.; Shimizu, M.; Okada, T.; Oohida, S.; Asahara, T. Patent US2004/14977 A1, 2004.
(7) (a) Khaksar, S.; Heydari, A.; Tajbakhsh, M.; Vahdat, S. M. *J. Fluorine Chem.* **2010**, *131*, 1377. (b) Zhang, Z. H.; Li, T. S.; Li, J. J. *Monatsh. Chem.* **2007**, *138*, 89. (c) Sanjeeva Reddy, C.; Nagaraj, A. *Indian J. Chem.* **2008**, *47*, 1154. (d) Heravi, M. M.; Montazeri, N.; Rahmizadeh, M.; Bakavoli, M.; Ghassemzadehb, M. *J. Chem. Res.* **2000**, *12*, 284. (e) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Catal. Commun.* **2007**, *8*, 1126.

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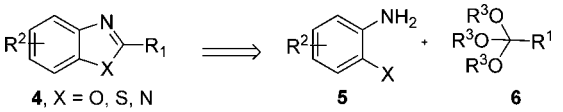
approach, orthoesters can also be used as annelating agents (scheme 1). As reported in the literature, benzimidazoles[7] were prepared from orthoesters in the presence of hexafluoroisopropyl alcohol, aminosulfonic acid, or zirconium oxychloride as catalysts. For the benzothiazoles,[8] silica-supported fluoroboric acid or $Bi(OTf)_3$ can be used in the condensation reaction with orthoesters. Polyphosphoric acid (PPA) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) are also interesting agents for the preparation of benzoxazoles.[9] The main shortcoming of this methodology resides in the limited diversity of the orthoesters employed. Indeed, only three or four commercially available orthoesters are routinely screened.

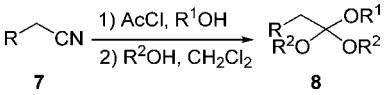
Scheme 1. Preparation of Heteroaromatic Bicycles



The pharmacological potential of these heterocycles, combined with the limited access to high structural complexity, due to the paucity of orthoesters available (typically R_1 = H, Me, Et, Ph), and the harsh conditions used in previously reported condensation reactions, incited us to revisit this ring-forming process.

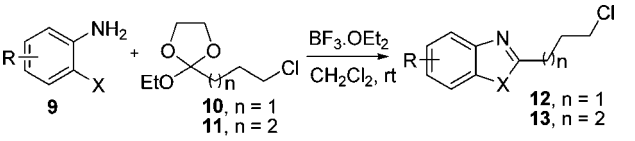
Over the years, our laboratory has prepared a wide range of functionalized orthoesters using the modified Pinner sequence described in Scheme 2.[10] In this method, an imidate salt[11] formed from a nitrile such as **7** is subsequently converted into the corresponding orthoester **8**.

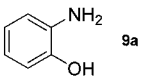
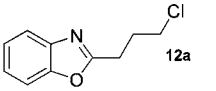
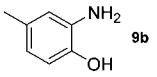
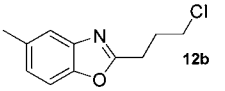
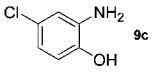
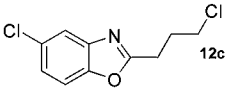
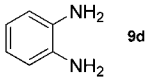
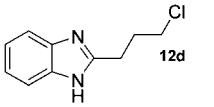
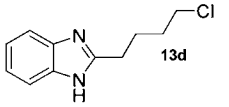
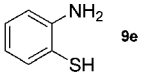
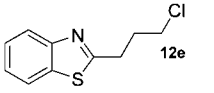
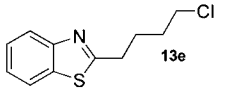
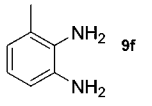
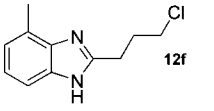
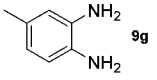
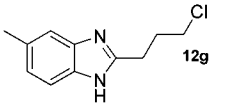
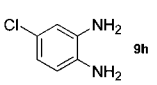
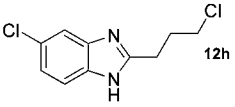
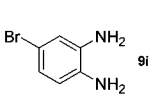
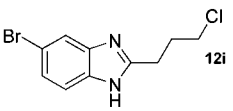
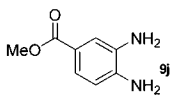
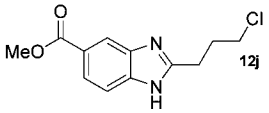
Scheme 2. Modified Pinner Sequence



These orthoesters are particulary interesting since their substituents can be converted into a wide variety of functionalities suitable for the preparation of libraries in medicinal chemistry oriented synthesis.[12] At the onset of our study, the chlorine-containing orthoesters **10** and **11** and their unsaturated analogues **14** and **15** were prepared

Table 1. Condensation of Anilines and Chlorinated Orthoesters



entry	aniline	product	yield[a]
1			82%
2			80%
3			95%
4			73%
5			83%
6			91%
7			90%
8			92%
9			91%
10			85%
11			84%
12			85%

[a] Isolated yields after column chromatography on silica gel or recrystallization.

(8) (a) Patil, A. V.; Lee, S. H.; Bandgar, B. P. *Bull. Korean Chem. Soc.* **2010**, *31*, 1719. (b) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatsh. Chem.* **2007**, *138*, 663. (c) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Catal. Commun.* **2007**, *8*, 1865.

(9) (a) Jared, F. M.; Andrew, J. M.; El-Malika, J. *Org. Lett.* **2008**, *10*, 4915. (b) Hojati, S. F.; Maleki, B.; Beykzadeh, Z. *Monatsh. Chem.* **2011**, *142*, 87. (c) Mylari, B. L.; Scott, P. J.; Zembrowski, W. J. *Synth. Commun.* **1989**, *19*, 2921. (d) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Zolfigol, M. A.; Hojati, S. F. *J. Iran Chem. Soc.* **2008**, *5*, S65.

(10) (a) Markó, I. E.; Ates, A. *Synlett* **1999**, 1033. (b) Markó, I. E.; Vanherck, J.-C.; Ates, A.; Tinant, B.; Declercq, J.-P. *Tetrahedron Lett.* **2003**, *44*, 3333. (c) Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962. (d) Maulide, N.; Markó, I. E. *Chem. Commun.* **2006**, *11*, 1200. (e) Maulide, N.; Markó, I. E. *Org. Lett.* **2006**, *8*, 3705. (f) Maulide, N.; Markó, I. E. *Org. Lett.* **2007**, *19*, 3757. (g) De Bo, G.; Markó, I. E. *Eur. J. Org. Chem.* **2011**, 1859.

(11) Yadav, V. K.; Babu, K. G. *Eur. J. Org. Chem.* **2005**, 452.

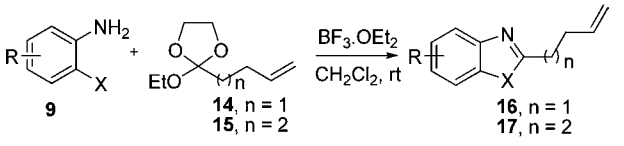
(12) Wermuth, C. G. *The practice of medicinal chemistry*, Elsevier, 2008.

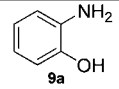
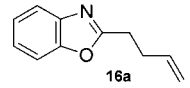
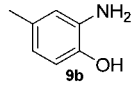
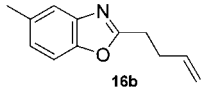
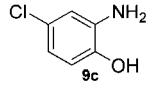
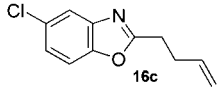
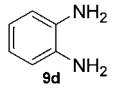
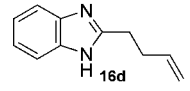
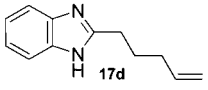
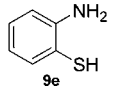
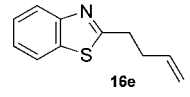
in large scale (> 10 g) and in high yield by the modified Pinner sequence.

The starting materials **10** and **11** were condensed with a variety of substituted anilines (Table 1), leading to the corresponding fused heterocycles in good to excellent yields. The condensations were carried out at room temperature in the presence of 1 equiv of $BF_3 \cdot OEt_2$ and were complete within 3 h. As can be seen in Table 1, the reaction occurs efficiently with both electron-donating and electron-withdrawing groups on the aromatic ring (entries 1–12). Benzoxazoles, benzothiazoles, and benzimidazoles, bearing a functionalized alkyl side chain, can thus be generated efficiently.

Orthoesters **14** and **15**, interesting annelating agents possessing a terminal alkene, were coupled with various aniline derivatives under identical conditions. Again, the desired compounds could be isolated in high yields (Table 2). It is noteworthy that the substituents on the aromatic ring have little or no effect on the outcome of this reaction (entries 1–3). Moreover, the presence of the alkene moiety enables an even wider range of modifications to be performed on adducts **16** and **17** (vide infra).

Table 2. Condensation of Anilines and γ,δ-Unsaturated Orthoesters

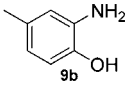
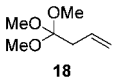
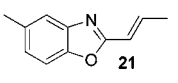
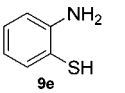
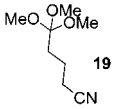
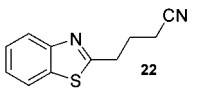
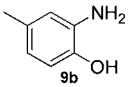
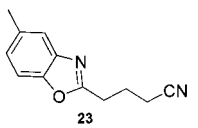
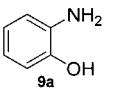
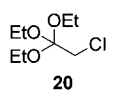
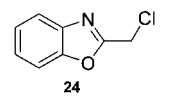
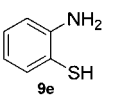
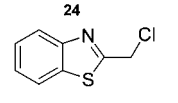


entry	aniline	product	yield[a]
1	 9a	 16a	95%
2	 9b	 16b	80%
3	 9c	 16c	88%
4	 9d	 16d	75%
5		 17d	75%
6	 9e	 16e	95%

[a] Isolated yields after column chromatography on silica gel or recrystallization.

At this stage, several new orthoesters were prepared by electrochemistry and submitted to the conditions described above, providing a wide variety of fused hetero aromatic bicycles (table 3).[13] These orthoesters differ by the nature of the alkyl side chain and the alkoxy groups. Gratifyingly, these modifications do not affect the results of the annelating reaction. As can be seen in Table 3, the desired adducts are obtained in good to excellent yields. It should be noted that the β,γ-unsaturated orthoester **18** undergoes migration of the alkene moiety during the condensation reaction, affording solely the α,β-unsaturated benzoxazole **21** (Table 3, entry 1). Moreover, it is important to highlight that neither **18** nor **19** could be prepared via the Pinner methodology.[14]

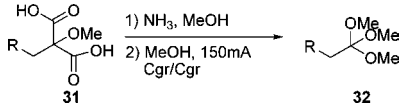
Table 3. Condensation of Anilines and Functionalized Orthoesters

entry	aniline	orthoester	product	yield[a]
1	 9b	 18	 21	80%
2	 9e	 19	 22	95%
3	 9b		 23	75%
4	 9a	 20	 24	85%
5	 9e		 25	94%

[a] Isolated yields after column chromatography on silica gel or recrystallization.

To illustrate the synthetic potential of these easily assembled and functionalized heteroaromatic rings, we prepared some tricyclic compounds. Indeed, simple treatment of the chlorinated heterocycle **12d** with NaH in THF afforded the desired product **26a** in 93% yield (scheme 3).[15] When benzimidazole **13d** was used in the cyclization reaction, the 4,5,5-tricycle was generated in 95% of yield. With the substituted benzimidazole **12h**, the two regioisomers

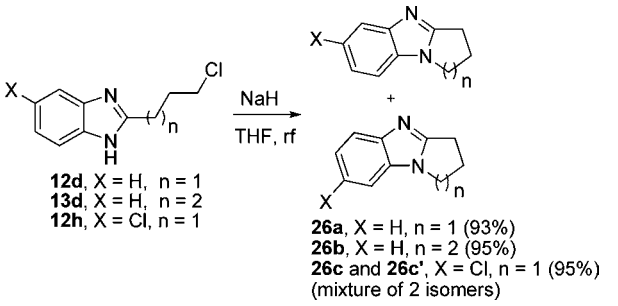
(13) Recently, our laboratory has developed a novel method for the synthesis of orthoesters that cannot be obtained by the Pinner protocol. It involves the electrolysis of the bis-ammonium salt derived from the corresponding diacid **31**. An example is decribed in the Supporting Information.Mathot, C.; Lam, K.; Lucaccioni F.; Markó, I. E. Unpublished work.



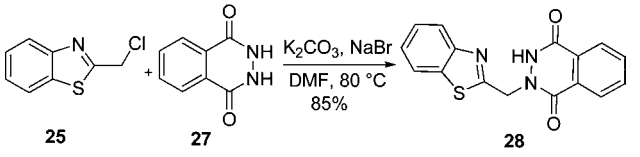
(14) In the case of the orthoester **19**, it is likely that the starting material (propane-1,3-dinitrile) will undergo a double Pinner reaction. This example highlights the complementarity between our novel electrochemically based synthesis of orthoesters and the Pinner protocol.

(15) Haque, R.; Rasmussen, M. *Tetrahedron* **1997**, *53*, 6937.

Scheme 3. Cyclization Reactions



Scheme 4. Alkylation of Chlorinated Heterocycle



26c and **26c′** were obtained in a 1:1 ratio. Unfortunatly, they could not be separated.

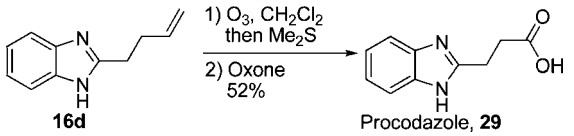
To illustrate further the potential of the products synthesized through our method, the substituted benzothiazole **25** was coupled with the phthalhydrazide **27** to afford compound **28** (Scheme 4).[16] This adduct is an advanced intermediate for the synthesis of zopalrestat analogues.

Oxidation of the alkene moiety present in imidazole **16d** enables the preparation of the corresponding acid, procodazole (**29**) (Scheme 5). Starting from orthoester **14** and phenyldiamine **9d**, procodazole (**29**) could thus be assembled in three steps (condensation, ozonolysis and oxidation) in 39% overall yield and under mild conditions.[17]

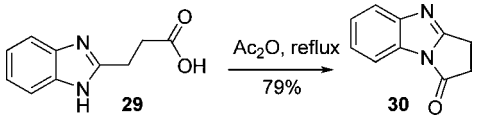
(16) Kotani, T.; Nagaki, Y.; Ishii, A.; Konishi, Y.; Yago, H.; Suehiro, S.; Okukado, N.; Okamoto, K. *J. Med. Chem.* **1997**, *40*, 684.

(17) (a) Meyer, R.; Maier, J. *Liebigs Ann. Chem.* **1903**, *327*, 41. (b) Chatterjee, B. *J. Chem. Soc.* **1929**, 2967. (c) Guenes, H. S.; Cosar, G. *Arzneim.-Forsch.* **1992**, *42*, 1045. (d) Tewari, A. K; Mishra, A. *Indian J. Chem. Sect. B* **2006**, *45*, 489. (e) Yao, M.-X.; Zeng, M.-H.; Zou, H.-H.; Zhou, Y.-L.; Liang, H. *Dalton Trans.* **2008**, *18*, 2428. (f) Maras, M.; Kocevar, M. *Helv. Chim. Acta* **2011**, *94*, 1860. (g) Phillips, M. A. *J. Chem. Soc.* **1928**, 2395.

Scheme 5. Synthesis of Procodazole **29**



Scheme 6. Lactam Formation



Futhermore, procodazole (**29**) can undergo a subsequent ring closure by treatment with acetic anhydride to provide the tricyclic lactam **30**, as described by Staněk and Wollrab, in 79% yield (Scheme 6).[18]

In summary, our methodology enables the convenient, flexible, connective, and efficient preparation of functionalized benzoxazole, benzothiazole, and benzimidazole derivatives in good to excellent yields under mild conditions. The rapid and easy access to a large variety of substituted orthoesters enabled us to widen the scope of this condensation, hence opening new avenues for its application in medicinal chemistry.

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Supporting Information Available. Full experimental and characterization details for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) Staněk, J.; Wollrab, V. *Monatsh. Chem.* **1960**, *91*, 1064.

The authors declare no competing financial interest.