Tetrahedron Letters 66 (2021) 152828

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Novel substituted triazolo benzodiazepine scaffolds to explore chemical space

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ARTICLE INFO

Article history:
Received 3 November 2020
Revised 19 December 2020
Accepted 5 January 2021
Available online 26 January 2021

This paper is dedicated to Dale Boger, a long-time friend and colleague, on the occasion of his receiving the Tetrahedron Prize and for his many scientific contributions leading thereto.

Keywords:
Multicomponent assembly process
Reductive amination
Dipolar cycloaddition
Aryl azide
Diversity oriented synthesis
Triazolo-1,4-benzodiazepines

ABSTRACT

Efficient and concise routes to sets of novel triazolo-1,4-benzodiazepine scaffolds that are suitably functionalized for diversification at three positions to explore three-dimensional space with different substituents are described. One approach to these scaffolds features a simplified multicomponent assembly process to give an intermediate azido alkyne that undergoes a facile Huisgen dipolar cycloaddition. The triazolo-1,4-benzodiazepines thus produced may be endowed with aryl halide, secondary amino, alcohol, aldehyde or carboxylic acid groups as functional handles for orthogonal derivatization reactions. Modification of this approach enabled the facile synthesis of the related triazolo-1,4-benzodiazepin-6-ones, also bearing three functional handles. These convenient protocols were used to prepare multi-gram quantities of benzodiazepine analogs as precursors for generating compound libraries for screening campaigns.

Introduction

One of the challenges of modern-day medicinal chemistry and drug discovery is the design and synthesis of molecular frameworks that enable exploration of three-dimensional space with different substituents. The small molecules that are then derived from these scaffolds can not only be used as leads for drug discovery, but they may also serve as chemical probes to study biological pathways relevant to disease. Over the years several useful strategies for creating collections of compounds in which substituents are projected into different regions of chemical space have been developed. These include diversity oriented synthesis (DOS) [1], which typically focuses on designing novel skeletal frameworks or using privileged structures [2] as scaffolds for derivatization, and biology oriented synthesis (BIOS), which employs substructures found in biologically active natural products as templates for creating novel compounds for screening [3].

Our involvement in the NIH Roadmap project led to our development of a platform technology to create functionalized molecules derived from diverse nitrogen heterocycles that featured multicomponent assembly processes (MCAPs) [4]. In these processes three or more reactants are sequentially combined in one pot to deliver key intermediates bearing functional groups that enable multiple cyclizations to generate substituted nitrogen heterocycles that may be further diversified by refunctionalizations or cross-coupling reactions [5]. One such process is exemplified by the synthesis of the substituted triazolobenzodiazepine **2** that features an azide-alkyne 1,3-dipolar cycloaddition (Huisgen cyclization) of the readily available intermediate **1** (Scheme 1) [5d,6]. Notably, the arylaminomethyl subunit found in **1** and **2** as well as the benzodiazepine ring in **2** are privileged structures that are commonly found in compounds comprising screening decks designed to identify bioactive hits for further investigation [2].

Derivatives of 1,4-benzodiazepines have long been of interest in medicinal chemistry because they are β-turn mimetics [7], and they are known to bind to a variety of proteins such as G-protein coupled receptors (GPCRs), enzymes, and ligand-gated-ion channels. Accordingly, it is not surprising that the 1,4-benzodiazepine core is found in many pharmaceutical drugs [8], including Anexate® and Valium® (Figure 1). It did not escape our attention that

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https://doi.org/10.1016/j.tetlet.2021.152828
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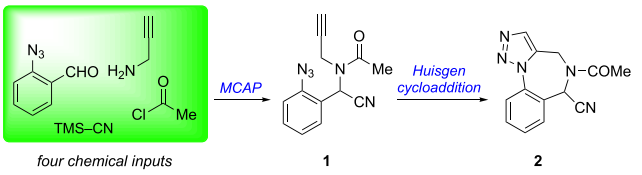


Scheme 1. MCAP approach to creating novel heterocycles exemplified by synthesis of substituted triazolobenzodiazepine **2**.

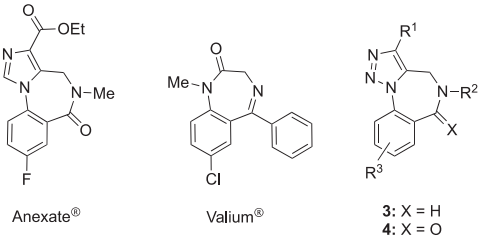


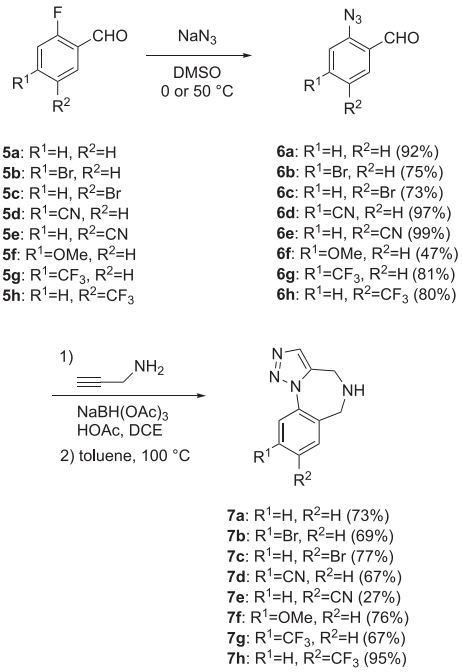
Fig. 1. Exemplary 1,4-benzodiazepine drugs Anexate® and Valium® have structural characteristics similar to the 1,2,3-triazolo-1,4-benzodiazepines **3** and **4**.

congeners of **2** such as the substituted triazolobenzodiazepines **3** and **4** might exhibit interesting properties. For example, such compounds have been reported to bind to cell surface GABA receptor/chloride ion channel complex [9] and inhibit serine proteases [10]. Moreover, it is also notable that scaffolds like **3** and **4** comprise medium-ring nitrogen heterocycles, which are underrepresented among new chemical entities found in compound libraries used for biological screening [11]. With this as background, we embarked on a series of studies directed toward the synthesis of several heterocyclic scaffolds related to **3** and **4** that were suitably substituted for further derivatization [12]. Although other triazolobenzodiazepines are known, compounds **3** and **4** represent unique opportunities for lead discovery because they are the first members of this class to possess functional handles that enable diversification of substituents on both the triazole and the aryl rings.

Discussion and results

Our approach to access a series of 1,2,3-triazolo-1,4-benzodiazepines **3** (R^1 = H) is related to the MCAP depicted in Scheme 1 and features the reductive amination of a series of 2-azidobenzaldehydes with a propargylamine followed by a Huisgen cycloaddition (Scheme 2). The requisite 4- and 5-substituted (*i.e.,* Br, CN, OMe and CF_3) 2-azidobenzaldehydes **6b**–**h** were prepared in 47–99% yield *via* the S_NAr reaction of the corresponding 2-fluorobenzaldehydes **5b**–**h** with sodium azide in DMSO [13], whereas 2-azidobenzaldehyde (**6a**) was prepared *via* S_NAr reaction of 2-nitrobenzaldehyde with sodium azide in HMPA at room temperature (92%) (Scheme 2) [14]. Although reactions of **5b**–**f** proceeded well at 50 °C, poor yields were observed when the CF_3-substituted aldehydes **6g** and **6f** were prepared at 50 °C, so those reactions were conducted at 0 °C. These reactions were readily scalable, and the products could be easily purified *via* recrystallization from *i*-PrOH. Reductive amination of **6a**–**h** with propargylamine in the presence of $NaBH(OAc)_3$ followed by heating the intermediate crude amine at 100 °C gave the 1,2,3-triazolo-1,4-benzodiazepines **7a**–**h**, typically in good overall yields.

We have previously shown that the secondary amine in compounds such as **7a**–**h** can be further diversified by arylation, urea formation, reductive *N*-alkylation, *N*-acylation, or sulfonylation

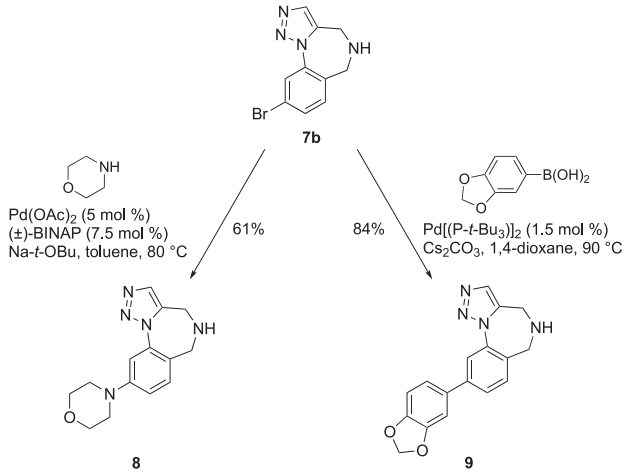


Scheme 2. Synthesis of triazolo-1,4-benzodiazepines.

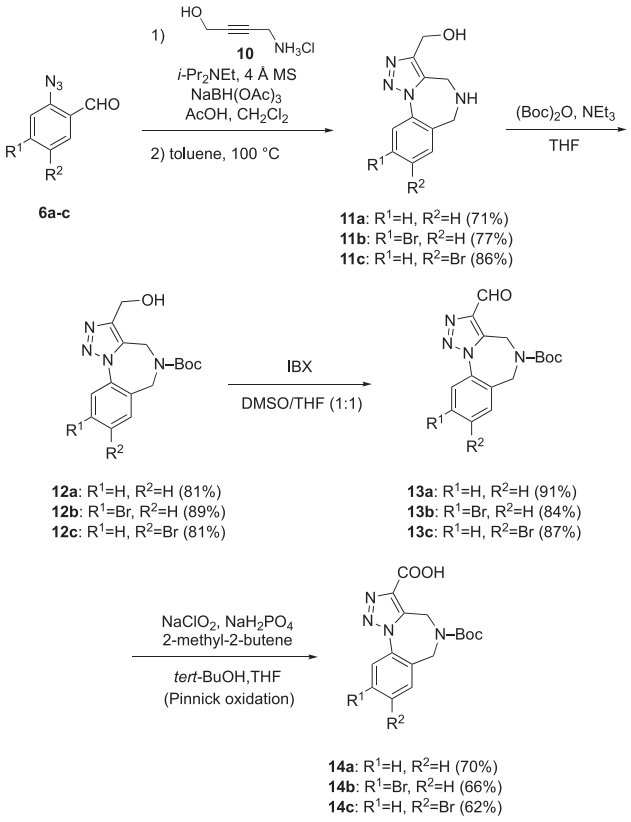
reactions [6]. To exemplify possible ways in which different aryl substituents may be introduced, Buchwald coupling of aryl bromide **7b** with morpholine gave **8** in 61% yield, and Suzuki coupling of **7b** with 3,4-methylenedioxyphenylboronic acid gave the biaryl **9** in 84% yield (Scheme 3). Other possibilities include conversion of the aryl nitrile moiety in **7d,e** into benzylic amines, aldehydes or carboxylic acids, each of which can in turn be diversified further. Demethylation of **7f** would provide a phenol that can be alkylated. Hence, there is considerable opportunity to generate collections of novel compounds.

Inasmuch as there are only two points of diversification on compounds like **7b–f**, there are limitations to the regions of chemical space that can be explored, so we turned our attention to analogs of **3** having an additional functional handle (*e.g.,* R^1 = CH_2OH, CHO, CO_2H, etc.) on the triazole ring. For example, a primary alcohol, R^1 = CH_2OH, could be modified by *O*-alkylation, a formyl group, R^1 = CHO, could be elaborated by reductive amination, and a carboxylic acid, R^1 = CO_2H, might be derivatized by amidation. Preparation of such compounds would simply require straightforward modification of the reactions in Scheme 2.

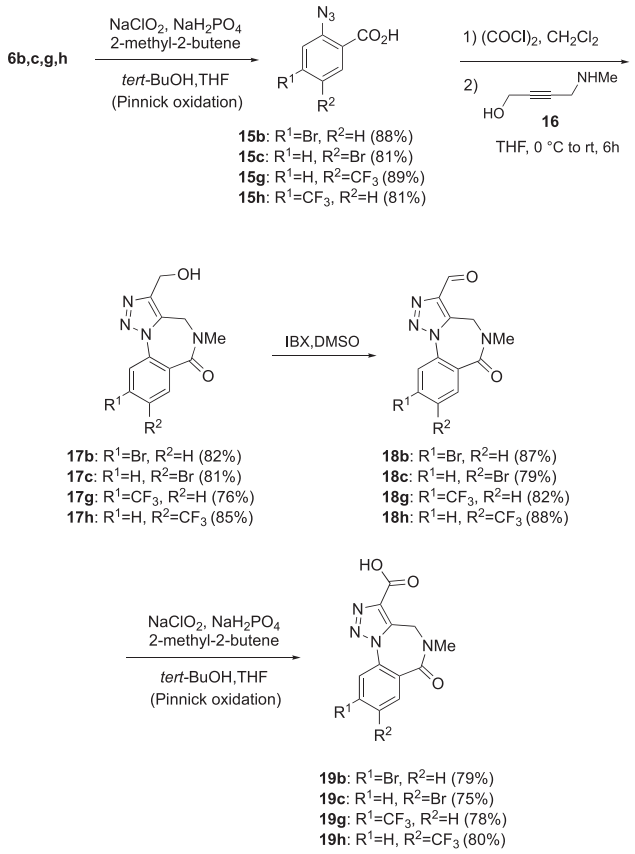
To reduce this plan to practice, azidobenzaldehydes **6a**–**c** were reductively aminated with the hydrochloride salt of 4-aminobut-2-yn-1-ol (**10**) [15] in the presence of Hünig's base and $NaBH(OAc)_3$, and the intermediate amines were heated at 100 °C to induce the azide-alkyne cycloaddition to furnish the triazolobenzodiazepines **11a**–**c** in 71–86% overall yields (Scheme 4). Although derivatization of the secondary amine group in **11a**–**c** is a possibility, we elected to protect the amine by reaction with $(Boc)_2O$ in the presence of Et_3N to give the carbamates **12a**–**c** (81–89%). The hydroxymethyl group in **12a**–**c** may now be elaborated by *O*-alkylations to generate a set of ether analogs. To further increase the possibilities for diversification, alcohols **12a-c** were oxidized with IBX using THF as a cosolvent to enhance the solubility of the alcohols and provide the corresponding aldehydes **13a**–**c** (84–91%) [16,17]. Finally, Pinnick oxidation of **13a**–**c** delivered the carboxylic acids **14a**–**c** in 62–70% yields [18,19]. We briefly explored several methods (*e.g.,* $KMnO_4$ and TPAP/NMP) to directly oxidize **12a**–**c** to the acids **14a**–**c**, but these procedures failed to give good yields.



Scheme 3. Exemplary pathways for diversification of **7b**.



Scheme 4. Synthesis of novel triazolo-1,4-benzodiazepine alcohols, aldehydes and carboxylic acids.



Scheme 5. Synthesis of novel triazolo-1,4-benzodiazepin-6-one alcohols, aldehydes and carboxylic acids.

Nevertheless, the aldehydes **13a–c** and the carboxylic acids **14a–c** are well suited for further diversification of the substituent on the triazole ring. Additional opportunities to create novel composition of matter involve manipulations of the Br group as outlined previously. Application of this synthetic sequence to aldehydes **6d–h** opens the door to even more possibilities.

We then focused upon the synthesis of analogs of the lactam **4** having a functional handle (*e.g.,* R^1 = CH_2OH, CHO, CO_2H, etc) on the triazole ring, and we envisioned a simple variant of the plan set forth in Scheme 4 in which substituted 2-azidobenzamides would serve as the key intermediates as outlined in Scheme 5. Accordingly, aldehydes **6b,c,g,h** were first converted into their respective benzoic acids **15b,c,g,h** in 81–89% yield *via* a Pinnick oxidation as before. These acids were then transformed by reaction with oxalyl chloride into the corresponding acid chlorides that were not purified but rather allowed to react with the known amine **16** [20]. The intermediate amides thus produced underwent spontaneous intramolecular Huisgen cycloaddition at room temperature to deliver the hydroxymethyl-substituted triazolo-1,4-benzodiazepine lactams **17b,c,g,h** in 76–85% overall yield from **15b,c,g,h**. We also prepared the corresponding aldehydes **18b,c,g,h** and carboxylic acids **19b,c,g,h** by sequential IBX (79–88%) and modified Pinnick (75–80%) oxidations. As before, the hydroxymethyl, formyl, and carboxylic acid functional groups in these sets of triazolo-1,4-benzodiazepinones provide multiple opportunities for creating diverse collections of analogs.

Summary

Given their diverse pharmacology and widespread clinical use, synthetic approaches that enable access to substituted benzodiazepines are of great value. Toward creating sets of such compounds, we have developed a concise and easily scalable approach to prepare novel triazolo-1,4-benzodiazepine scaffolds having the general structures **3** and **4**. Each of these cores has several distinct functional handles that can be readily derivatized to generate collections of small molecules for screening. Substituted triazolo-1,4-benzodiazepines derived from these scaffolds offer unique opportunities for lead discovery because they are the first members of this class of privileged structures to possess orthogo-

nal functionality on both the triazole and the aryl rings. Moreover, members of compound libraries derived from these heterocyclic cores can be strategically substituted to explore three-dimensional space in multiple directions to optimize opportunities for identifying novel hits in screening campaigns.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank the Robert A. Welch Foundation (F-0652) and Dart Neuroscience, LLC for financial support. We also thank the UT Austin Mass Spectrometry Facility for high-resolution mass spectral data and the NIH (Grant Number 1 S10 OD021508-01) for funding the Bruker AVANCE III 500 NMR spectrometer used to characterize new compounds. We also thank Drs. Guy Breitenbucher and Edwin Schweiger for helpful discussions.

Appendix A. Supplementary data

Supplementary data (experimental procedures and characterization data for repre-sentative new compounds) to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152828.

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