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Synthesis of dipyrrolo-diazepine derivatives via intramolecular alkyne cyclization

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ABSTRACT

A regioselective approach was developed for the synthesis of dipyrrolo-diazepine derivatives. The synthetic route to dipyrrolo-diazepines first involves the synthesis of dipyrromethanes, followed by reaction of propargyl bromide in the presence of NaH to attach one alkyne functionality to the pyrrole nitrogen atom. Intramolecular heterocyclization with NaH in DMF between the alkyne functionality and pyrrole nitrogen atom gave the desired structures in good yields.

1. Introduction

Diazepines are a well-known class of heterocyclic compounds demonstrating a range of clinically important properties such as anxiolytic, hypnotic, sedative, anticonvulsant, skeletal, amnestic and muscle relaxant properties [1–5]. In particular, benzodiazepines are used to treat anxiety disorders. They act on the central nervous system to produce a calming effect [6–8].

Clozapine (**1**) containing a benzodiazepine structure [9] is a drug effective in decreasing psychopathology, improving some aspects of cognition, improving quality of life, decreasing hospitalization, and decreasing suicide attempts and completions [10,11]. Lorazepam (**2**) is a benzodiazepine used to treat irritable bowel syndrome, epilepsy, and insomnia and to control tension caused by alcohol withdrawal. The compound causes a slowing of activity in the brain and allows relaxation [12]. Diazepam (**3**), also containing a benzodiazepine structure, is used to treat anxiety, acute alcohol withdrawal, and seizures. It is also used to relieve muscle spasms (Fig. 1) [12,13].

Various diazepinone derivatives have been synthesized in which the benzene ring is replaced by heterocycles such as indole, pyrrole, pyridine, and quinolone, and their activities have been studied [14]. Thiophene is an isostere of the benzene ring. Clotiazepam (**4**) [15,16] differs from benzodiazepines in that the benzene ring has been replaced by a thiophene ring. It is a marketed drug and possesses anxiolytic, sedative, and muscle relaxant properties. However, furan- and pyrrole-fused diazepinone derivatives are not common in the literature. De Meijere and coworkers [17] described the synthesis of new types of pyrrolo- and furo-condensed perhydro[1,4]diazepine-2,5-diones **5** starting from spiro seven-membered ring compounds. Very recently, we reported the first synthesis of furo- and thieno-fused 1,3-diazepine-4,6-dione derivatives **6** starting from ethyl 2-(2-methoxy-2-oxoethyl)-3-furancarboxylate and 2-(2-methoxy-2-oxoethyl)-3-thiophencarboxylate (Fig. 2) [18].

As a continuation of that work, we decided to synthesize pyrrole-fused diazepinone derivatives. Synthesis of compound **7** was performed with the reaction of 1*H*-pyrrole-2-carbaldehyde and propargyl bromide [19]. The reaction of **7** with hydrazine monohydrate resulted in the formation of 5*H*-pyrrolo[2,1-d][1,2,5]-triazepine (**9**) (Scheme 1) [19]. Unfortunately, the oxidation reactions to introduce a carbonyl group into the molecule **9** failed. Therefore, we turned our attention to the construction of the desired heterocyclic scaffold by intramolecular cyclization reaction of a *N*-propynyl methyl ester **11** [19,20]. with hydrazine monohydrate. Unfortunately, the desired compound **13** was formed in

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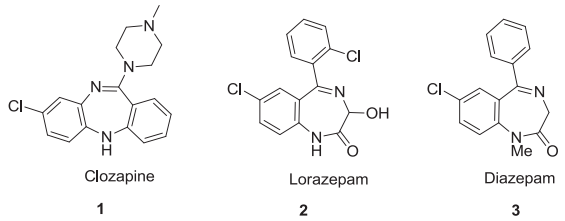


Fig. 1. Structures of some diazepine drugs.

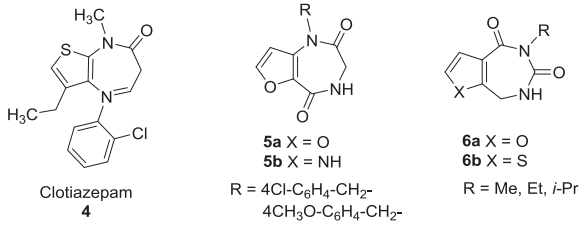
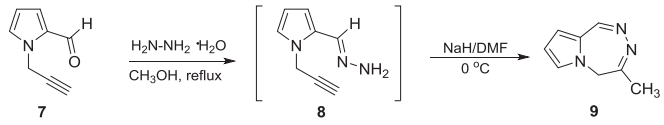
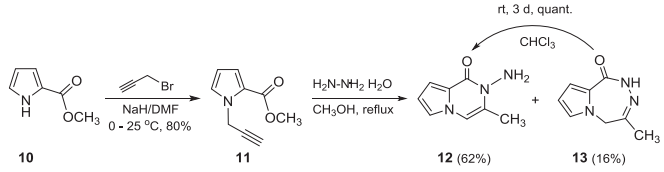


Fig. 2. Furan- and thiophene-fused diazepinone derivatives.



Scheme 1. Reaction of *N*-propynyl carbaldehyde **7** with hydrazine hydrate.



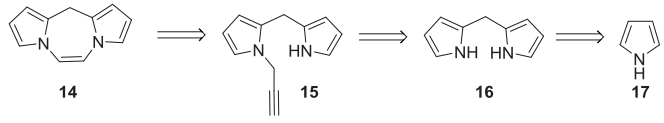
Scheme 2. Reaction of *N*-propynyl carbaldehyde **7** and ester **10** with hydrazine hydrate.

only 16% yield (Scheme 2). Furthermore, triazepinone derivate **13** was smoothly rearranged to the six-membered ring isomer **12** in quantitative yield upon standing at room temperature in chloroform. Finally, we decided to synthesize diazepine derivatives fused to pyrrole rings.

2. Results and discussion

Our planned approach to **14** involved metal-free cyclization of propargylated dipyrromethane derivatives **15** synthesized by the reaction of pyrrole with aldehydes, followed by the reaction with propargyl bromide of dipyrromethane **16**. The retrosynthesis is summarized in Scheme 3.

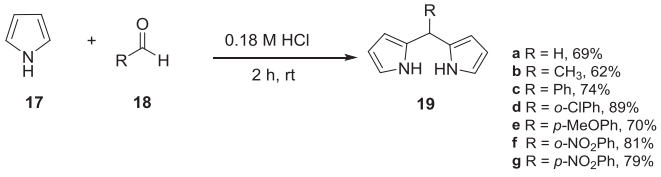
Many procedures are reported in the literature for the synthesis of *meso*-substituted dipyrromethanes. Trifluoroacetic acid or $BF_3 \cdot O(Et)_2$ catalyzed reaction of aldehydes with excess pyrrole afforded *meso*-substituted dipyrromethanes [21]. Temelli and Unaleroglu reported a new procedure for *meso*-substituted dipyrromethanes by the reaction of *N*-tosyl imines with excess pyrrole in the presence of metal triflates [22]. Singh et al. used Amberlyst 15 as an efficient catalyst for condensation of electron-rich heterocycles with a variety of aldehydes to give dipyrromethanes [23]. However, Sobral et al [24]. described an efficient synthesis of dipyrromethanes in water. We also used 0.18 M HCl for the reaction of freshly distilled excess pyrrole with benzaldehyde in water at room temperature to give 2,2'-(phenylmethylene)bis(1*H*-pyrrole) (**19c**) in 74% yield. Then, for testing the scope of further reactions, additional derivatives **19a-g** were synthesized (Scheme 4).



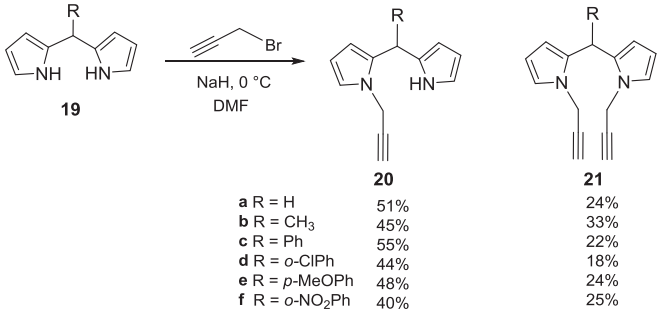
Scheme 3. Retrosynthesis of dipyrrolo-diazepine derivatives.

After synthesis of *meso*-substituted dipyrromethanes, the next step was the incorporation of propargyl groups into the molecule which are the key functional groups for final cyclization reactions. According to the common literature procedures [19,25a,b,c] **19c** was first reacted with NaH in DMF, followed by dropwise addition of a solution of propargyl bromide in dry DMF at 0 °C. Unfortunately, double propargylated dipyrromethane derivatives **21a-f** were formed as the major products. For example, **20c** and **21c** were formed in yields of 16% and 45%, respectively. To increase the yield of the mono-propargylated compounds **20**, NaH was added portionwise to a mixture of dipyrromethanes and propargyl bromide. The yield of **20c** was increased up to 55% (Scheme 5).

Characterization of compounds **20c** and **21c** was achieved by using ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of compounds **20c** the NH proton of the pyrrole unit resonates at 7.91 ppm as a broad singlet and the terminal alkyne proton resonates at 2.36 ppm as a triplet ($J = 2.5$ Hz) due to coupling with methylene protons. The methylene protons appear as a doublet. Furthermore, the presence of two unequal pyrrole rings clearly indicates mono-substitution. On the other hand, the absence of NH proton resonance in the spectra of **21c** and the observed symmetry in the ^{1}H- as well as in the ^{13}C NMR spectra also support the symmetrical structure. The methylene protons are diastereotopic [26], and they give rise to an AB-system with further splitting with the alkyne proton ($^4J = 2.5$ Hz). The A-part of the AB-system resonates at 4.37 ppm, whereas the B-part of the AB-system appears at 4.30 ppm. The main coupling of the AB-system was measured as $J = 14.0$ Hz which is within the expected range [26].



Scheme 4. Synthesis of dipyrromethanes (**19a-g**).



Scheme 5. Synthesis mono- and dipropargylated dipyrromethanes **20a-f** and **21a-f**.