Communication

One-Pot Synthesis of Triazolobenzodiazepines Through Decarboxylative [3 + 2] Cycloaddition of Nonstabilized Azomethine Ylides and Cu-Free Click Reactions

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Abstract: A one-pot synthesis of triazolobenzodiazepine-containing polycyclic compounds is introduced. The reaction process involves a decarboxylative three-component [3 + 2] cycloaddition of nonstabilized azomethine ylides, N-propargylation, and intramolecular click reactions.

Keywords: one-pot synthesis; decarboxylative [3 + 2] cycloaddition; nonstabilized azomethine ylides; click reaction

1. Introduction

Triazolobenzodiazepines and related scaffolds are privileged heterocyclic systems for biologically active molecules, such as benzodiazepine-bearing bretazenil [1], midazolam [2]; protease inhibitors [3], alprazolam [4], estazolam [5], and triazolam [6] (Figure 1). Due to their medicinal significance, the development of synthetic methods for triazolobenzodiazepine-bearing compounds continuously attracts the attention of organic and medicinal chemists [7–9].

![Figure 1. Biologically active triazolobenzodiazepine-related molecules.](image-url)

Highly efficient and atom economic synthesis such as one-pot reactions and multicomponent reactions (MCRs) have gained increasing popularity in the synthesizing of complex molecules including triazolobenzodiazepine-type compounds [10–15]. For example, the Martin group reported a cascade reductive amination and intramolecular [3 + 2] cycloaddition reaction sequence for triazole-fused 1,4-benzodiazepines (Scheme 1A) [10,11]. The Djuric group modified the van Leusen imidazole synthesis to develop an intramolecular azide-alkyne cycloaddition for imidazole- and triazole-fused benzodiazepine compounds (Scheme 1B) [12]. The Kurth group reported a Lewis acid-catalyzed...
MCR for imidazole- and triazole-fused benzodiazepines through sequential [3 + 2] cycloaddition and cycloaddition reactions (Scheme 1C) [13]. Introduced in this paper is a new sequence involving decarboxylative intermolecular [3 + 2] cycloaddition of nonstabilized azomethine ylides followed by N-propargylation and intramolecular [3 + 2] cycloaddition for triazolobenzodiazepines (Scheme 1D).

A. Martin’s work

B. Djuric’s work

C. Kurth’s work

D. This work (one-pot)

Scheme 1. Atom economic synthesis of triazolobenzodiazepines.

1,3-Dipolar cycloaddition of primary amino esters, aldehydes, and activated alkenes is a well-established three-component reaction [16–21]. The azomethine ylides derived from deprotonation of iminium ions are CO₂R-stabilized ylides A (Figure 2A) [22–30]. In recent years, our lab has reported a series of azomethine ylides A-based [3 + 2] cycloadditions for diverse heterocyclic scaffolds [31–35], including one-pot [3 + 2] and click reactions for triazolobenzodiazepines [32]. Compared to the reactions of stabilized ylides A, cycloadditions of nonstabilized ylides B are less explored (Figure 2B) [36–42]. We have recently reported the synthesis of α-trifluoromethyl pyrrolidines through decarboxylative [3 + 2] cycloaddition of nonstabilized azomethine ylides B derived from α-amino acids [43]. Presented in this paper is a new application of nonstabilized azomethine ylides in the one-pot [3 + 2] and click reactions for triazolobenzodiazepines.

2. Results and Discussions

Reaction conditions for the synthesis of proline 4a through one-pot [3 + 2] cycloaddition were developed using 1:1:2:1 of 2-azidebenzaldehyde 1a, 2-aminoisobutyric acid 2a, and N-ethylmaleimide 3a in the presence of 0.3 equiv. of AcOH for decarboxylation [43] (Table 1). After screening
solvents including 2-methyltetrahydrofuran, toluene, EtOH and CH$_3$CN as well as reaction time and temperature, it was found that a reaction using CH$_3$CN as a solvent at 110 °C for 6 h afforded 4a in 93% LC (liquid chromatography) yield with a dr (diastereomer) of 6:1 (Table 1, entry 6). The stereochemistry of 4a was determined according to the literature report [38].

Table 1. Three-component decarboxylative [3 + 2] cycloaddition $^a$.

| Entry | Solvent | T ($^\circ$C) | t (h) | 4a (%) $^b$ | dr (%) $^c$ |
|-------|---------|---------------|-------|-------------|-------------|
| 1     | 2-Me THF | 80            | 4     | trace       | —           |
| 2     | MePh    | 110           | 4     | 82          | 5:1         |
| 3     | EtOH    | 80            | 4     | 93          | 6:1         |
| 4     | EtOH    | 110           | 6     | 92          | 6:1         |
| 5     | CH$_3$CN| 110           | 4     | 93          | 6:1         |
| 6     | CH$_3$CN| 110           | 6     | 88          | 6:1         |
| 7     | CH$_3$CN| 125           | 12    |             |             |

$^a$ Reaction conditions: 1:1.2:1 1a:2a:3a for [3 + 2] cycloaddition. $^b$ Detected by LC-MS. $^c$ Determined by $^1$H NMR.

Decarboxylative [3 + 2] cycloaddition product 4a was then used for the development of conditions for the N-propargylation and sequential click reaction for the synthesis of triazolobenzodiazepine 6a. In the presence of K$_2$CO$_3$, 4a reacted with propargyl bromide in CH$_3$CN at 80 °C for 2 h to give 5a in 94% LC yield (Table 2, entries 2–5). Without separation, the reaction mixture was used for intramolecular click reaction at 100 °C under the catalysis of Cu salts (Table 2, entries 2–4). The CuI-catalyzed click reaction gave 6a in 89% LC yield, which is better than the reactions catalyzed with CuCl or CuBr. In our previous work, the intramolecular click reaction was accomplished under microwave heating and Cu-free conditions [32]. In this work, N-propargylation compound 5a generated under the microwave heating was continuously heated at 150 °C for 1 h to give 6a in 88% LC yield without CuI catalyst (Table 2, entry 6). A Cu-free control reaction of 5a under conventional heating at 100 °C for 3 h only gave 5% of 6a (Table 2, entry 5).

Table 2. One-pot N-propargylation and click reaction $^a$.

| Entry | Solvent | T$_1$ ($^\circ$C) | t$_1$ (h) | 5a (%) $^b$ | Cat. | T$_2$ ($^\circ$C) | t$_2$ (h) | 6a (%) $^b$ |
|-------|---------|-----------------|-----------|-------------|------|-----------------|-----------|-------------|
| 1     | EtOH    | 80              | 2         | trace       |      |                 |           |             |
| 2     | CH$_3$CN| 80              | 2         | 94          | CuCl | 100             | 3         | 35          |
| 3     | CH$_3$CN| 80              | 2         | 94          | CuBr | 100             | 3         | 60          |
| 4     | CH$_3$CN| 80              | 2         | 94          | CuI  | 100             | 3         | 89          |
| 5     | CH$_3$CN| 80              | 2         | 94          | —    | 100             | 3         | 5           |
| 6 $^c$| CH$_3$CN| 110             | 0.5       | 93          |      | 150             | 1         | 88 (dr 6:1)|

$^a$ Reaction conditions: K$_2$CO$_3$ (2.5 equiv.) and propargyl bromide (5.0 equiv.) under conventional or microwave heating. $^b$ Detected by LC-MS. $^c$ Microwave heating for both N-propargylation and click reactions.

After establishing the three-component [3 + 2] cycloaddition, N-propargylation, and sequential click reactions for 6a shown in Tables 1 and 2, we then aimed to combine these three reactions in one pot. After modification of the conditions shown in Tables 1 and 2, the best conditions for the one-pot
One of the main objectives of this work, however, is to introduce a caveat for the interpretation of gene expression of acute-phase cytokines, and demonstrated that Kupffer cells are involved in this process [22]. Zymosan is known to trigger an inflammatory response through the activation of Kupffer cells at 3 h (Figure 3B,D), for [3 + 2] cycloaddition of nonstabilized azomethine ylides, followed by N-propargylation and a Cu-free intramolecular click reaction using CuI as a catalyst for the click reaction didn’t give a better yield (Table 3, entry 4).

Under the optimized conditions for the one-pot synthesis [44], 13 analogues of triazolobenzodiazepines 6a–m were synthesized using different sets of azidobenzaldehydes 1 (R₁ = H, CF₃, Br, Cl, NO₂), amino acids 2 (R² = H, Me; R³ = Me, Ph, i-Pr), and maleimides 3 (R⁴ = Me, Et, Ph, Bn, 4-Br-Ph) (Table 4). The reactions of five different maleimides with 2-aminoisobutyric acids and 2-azidobenzaldehyde gave 6a–e in 55–65% isolated yields. The substitution groups on the benzaldehydes had some influence on the product yield. For example, the azidobenzaldehydes bearing electron-withdrawing groups, such as Br and CF₃, gave 6f and 6g in lower yields (59% and 35%), while the azidobenzaldehyde with the strong electron-withdrawing group NO₂ gave no product of 6m. The reactions of glycine and leucine with azidobenzaldehydes (R₁ = H, Br, Cl) and maleimides (R⁴ = Me, Et) gave 6h–l in 44–55% yields. The stereochemistry of product 6 was established during the step of the decarboxylative [3 + 2] cycloaddition, which was determined according to the literature report [38].

| Entry | T₁ (°C) | t₁ (h) | Cat. | T₂ (°C) | t₂ (h) | 6a (%) b |
|-------|---------|--------|------|---------|--------|----------|
| 1     | 110     | 0.5    | —    | 150     | 1      | 75       |
| 2     | 150     | 0.5    | —    | 150     | 1      | 51       |
| 3     | 150     | 1      | —    | 150     | 1      | 76 (dr 6:1) |
| 4     | 110     | 0.5    | Cul  | 110     | 1      | 70       |

a Reaction conditions: 1:1.2:1 1a:2a:3a, K₂CO₃ (2.5 equiv.), propargyl bromide (5 equiv.). b Detected by LC-MS, 6:1 dr.

One-pot synthesis of triazolobenzodiazepines 6 a.

| 6a, 65%, dr 6:1 | 6b, 55%, dr 7:1 | 6c, 57%, dr 7:1 | 6d, 60%, dr 7:1 | 6e, 63%, dr 6:1 | 6f, 59%, dr 5:1 | 6g, 35%, dr 4:1 | 6h, 52%, dr 4:1 | 6i, 44%, dr 4:1 | 6j, 47%, dr 4:1 | 6k, 55%, dr 3:1 | 6l, 52%, dr 2:1 | 6m, 0% |

a Reaction conditions, see [44]. b Isolated yield.
The proposed mechanism for the synthesis of product 6a is outlined in Scheme 2. The condensation of 2-azidebenzaldehyde 1a and 2-aminosobutyric acid 2a give oxazolidin-5-one I. It then underwent decarboxylation to form the nonstabilized azomethine ylide II for [3 + 2] cycloaddition with 3a to form 4a. Formation of 5a through propargylation followed by continuous heating for intramolecular click reaction affords product 6a. There are several reports in literature which demonstrated that intramolecular click reactions in one-pot synthesis could be achieved under Cu-free conditions [10,15,32,45,46].

Scheme 2. Mechanism for one-pot synthesis of 6a.

3. Summary

A one-pot synthesis of fused-triazolobenzodiazepines was developed using readily available amino acids, maleimides, and 2-azidebenzaldehydes for decarboxylative [3 + 2] cycloaddition of nonstabilized azomethine ylides, followed by N-propargylation and a Cu-free intramolecular click reaction. This is a highly efficient and operational simple reaction process for fused-triazolobenzodiazepines, and only CO₂ and H₂O were generated as byproducts.

Supplementary Materials: The following are available online. ¹H-NMR, ¹³C-NMR, and ¹⁹F-NMR spectra of final products.

Author Contributions: X.M. and X.F. developed above reactions; W.Q., W.Z., and B.W. expanded the substrates scope; X.F. and W.Z. conceived the project; W.Z. supervised the project and revised the manuscript.

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**Sample Availability:** Samples of the compounds are available from the authors.