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Synthesis of triazolo- and tetrazolo-fused 1,4-benzodiazepines via one-pot Ugi-azide and Cu-free click reactions

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Abstract

A one-pot Ugi-azide reaction followed by intramolecular Cu-free azide-alkyne cycloaddition generates a polycyclic scaffold **7** bearing polycyclic triazole, tetrazole and benzodiazepine rings. This method could be extended for making a more complicated scaffold **8** containing piperazinone ring.

Introduction

Triazole, tetrazole, and benzodiazepine are privileged heterocyclic rings commonly found in drug molecules and functional materials [1 – 5]. For examples, triazole-fused 1,4-benzodiazepins are protease inhibitors [6] and drug molecules alprazolam [7], estazolam [8], and triazolam [9] (Figure 1). Tetrazole-containing functional materials have been developed as photographic sensitizers, diagnostic contrast agents, and high-energy propellants [10 – 18]. Tetrazole could also be found in bioactive compounds [19 – 24], such as tasosartan, alfentanil and cefmenoxime for the treatment of hypertension, anesthesia, and bacterial infections [4].

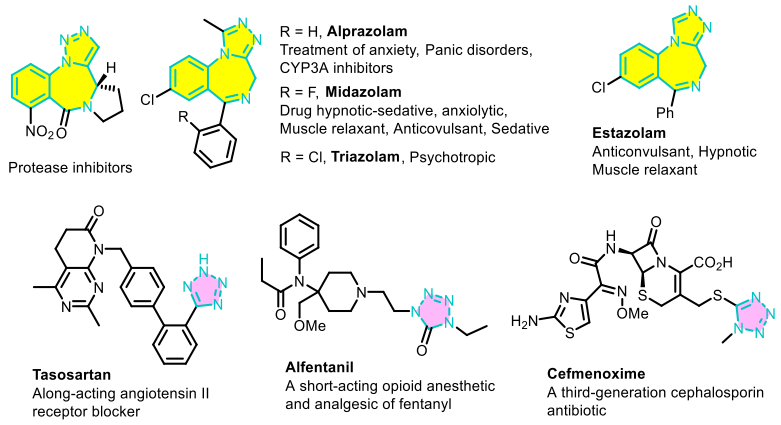
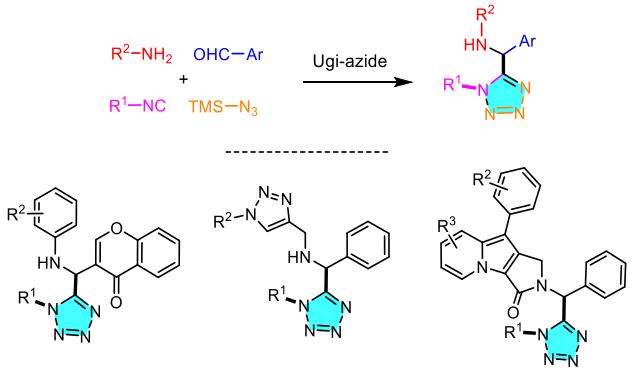


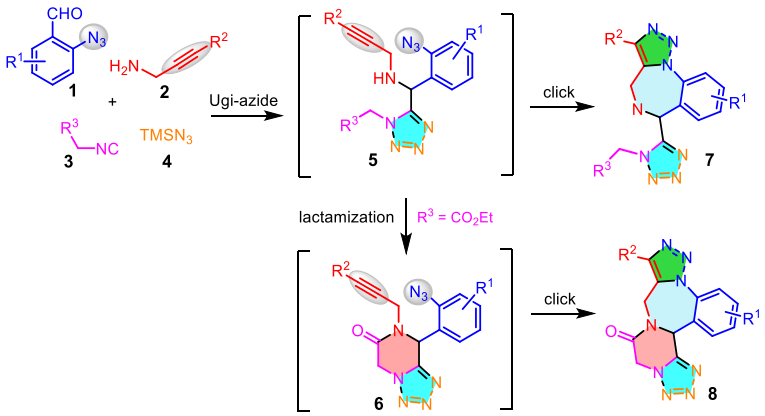
Figure 1. Bioactive molecules bearing triazole, tetrazole and 1,4-benzodiazepin rings.

Among reported methods for the synthesis of tetrazoles [25 – 28], the Ugi-azide reaction is a good approch for making 1,5-disubstituted-tetrazoles (1,5-DS-T) [29 – 31]. This scaffold could be subsequently link to 1,2,3-triazole [32], 4*H*-chromen-4-one [33], pyrrolo[3,4-*b*]indolizine [34] and others heterocyclic rings in making biologically interested compounds (Scheme 1) [35 – 41].



Scheme 1. Ugi-azide reaction for making 1,5-DS-T-containing heterocycles.

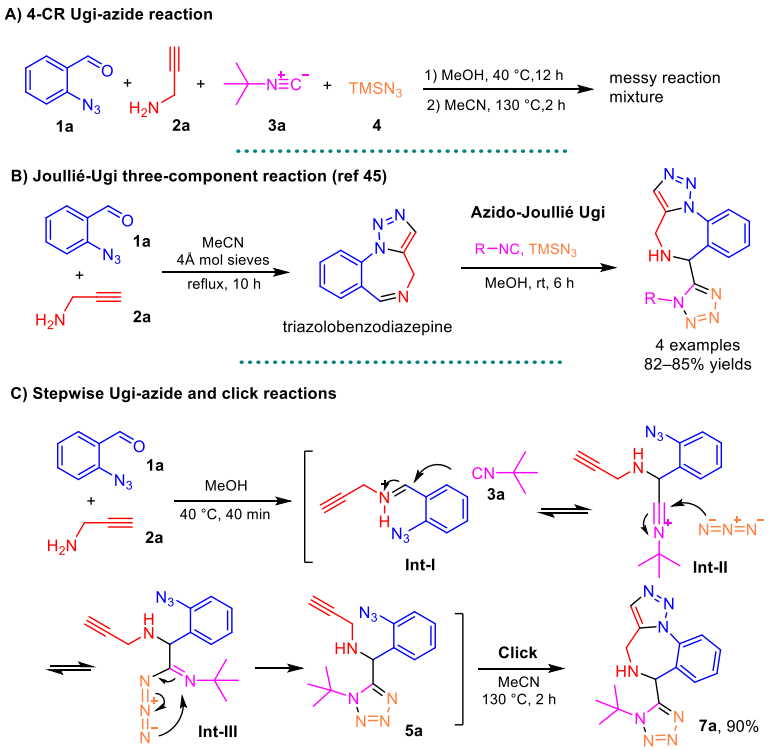
Development of methods for making triazole, tetrazole, piperazinone, and 1,4-benzodiazepine motifs are attractive from both synthetic and medicinal chemistry considerations [42 – 45]. We proposed a one-pot synthesis involving Ugi-azide 4-component (4-CR) reaction followed by lactamization and azide-alkyne cycloaddition for assembling triazole-fused and tetrazole-tethered 1,4-benzodiazepines **7** and triazole-, tetrazole-, and piperazinone-fused 1,4-benzodiazepines **8** (Scheme 2). Functional groups including ester, azido and alkynyl buried in the starting materials are responsible for the post-Ugi transformations.



Scheme 2. Proposed Ugi-azide-initiated synthesis of polyheterocyclic scaffolds **7** and **8**.

Results and Discussion

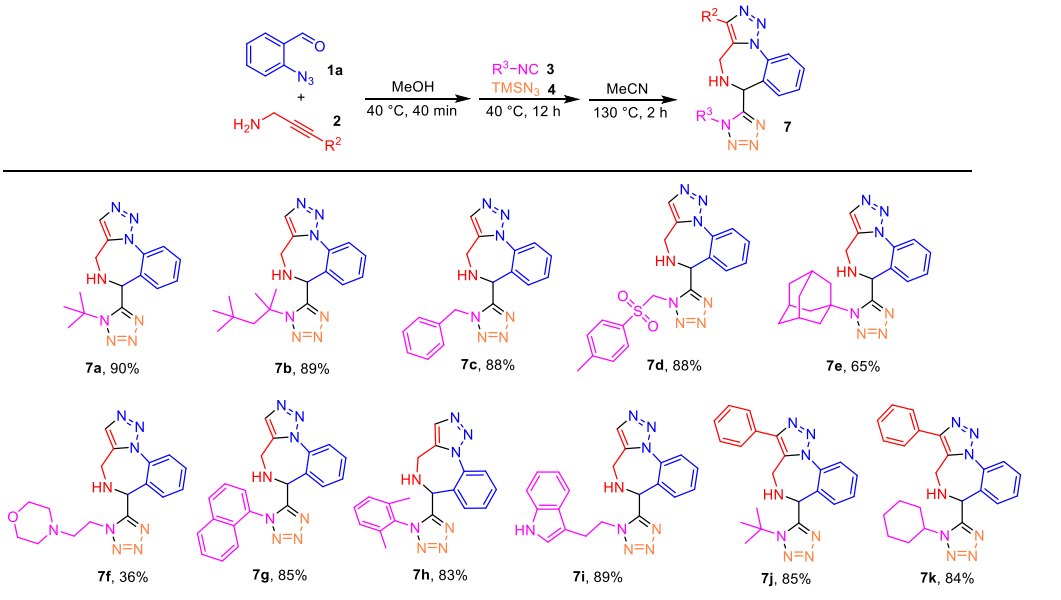
We first carried out the Ugi-azide 4-CR at 0.2 mmol scale with equal molar amount of 2-azidobenzaldehyde **1a**, propargylamine **2a**, tert-butyl isocyanide **3a**, and $TMSN_3$ **4** in 2 mL of MeOH. After heating the reaction mixture at 40 ° C for 12 h, the solvent was removed and changed to 2 mL of MeCN and heated at 130 ° C for 2 h (Scheme 3A). However, no product was detected from the reaction mixture. The functional groups in four starting materials may not be compatible under the 4-CR conditions, in which propargyl amine may have competitive reaction with 2-azidobenzaldehyde **1a** and $TMSN_3$ **4**. Literature search indicated that Shaabani's group has reported a reaction of 2-azidobenzaldehyde **1a** and propargylamine **2a** for making triazolobenzodiazepine which can serve as a cyclic imine for modified Joullié-Ugi 3-CR with isocyanide and trimethylsilyl azide ($TMSN_3$) in the synthesis of tetrazole-tethered triazolobenzodiazepines (Scheme 3B). Thus, we changed the reaction condition by first reacting 0.2 mmol each of **1a** and **2a** in 2 mL MeOH at 40 ° C for 40 min to form Schiff base **Int-I** followed by addition of 0.2 mmol each of **3a** and $TMSN_3$ **4** to make 1,5-DS-T as Ugi-azide adduct **5a**. After evaporation of MeOH solvent, the reaction mixture was redissolved in 2 mL of MeCN and heated at 130 ° C for 2 h in a sealed vial for Cu-free intramolecular click reaction to give product **7a** in 90% yield after purification (Scheme 3C) [46].



Scheme 3. 4-CR vs stepwise Ugi-azide reactions for the synthesis of **7a**.

After establishing the reaction conditions for Ugi-azide and click reactions to make triazole-fused and tetrazole-tethered benzodiazepine **7a**, we made more analogs by conducting reactions 2-azidobenzaldehyde **1a** with ten different isocyanides **3**, two 2-yn-1-amines (propargylamine **2a**, 3-phenylprop-2-yn-1-amine **2b**), and $TMSN_3$ to give products **7a** – **k** in 36 – 90% yields (Table 1).

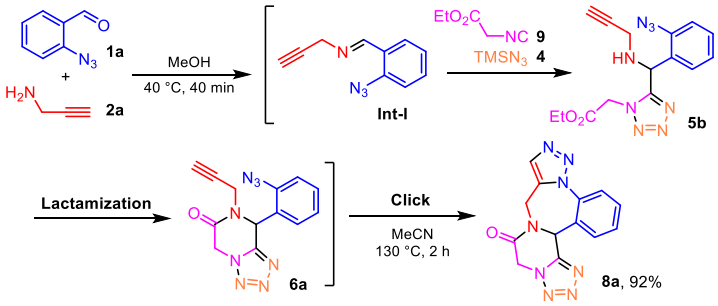
Table 1. Synthesis of benzodiazepines **7**.



Reaction conditions: 1) 0.2 mmol each of 2-azidobenzaldehyde **1a** and 2-yn-1-amines **2** in MeOH (2 mL), 40 ° C for 40 min; then add 0.2 mmol each of isocyanides **3** and $TMSN_3$ **4**, 40 ° C for 12 h; 2) change solvent to MeCN (2 mL), 130 ° C for 2 h.

As shown in Scheme 2, we also proposed the synthesis of triazole-, tetrazole-, and piperazinone-

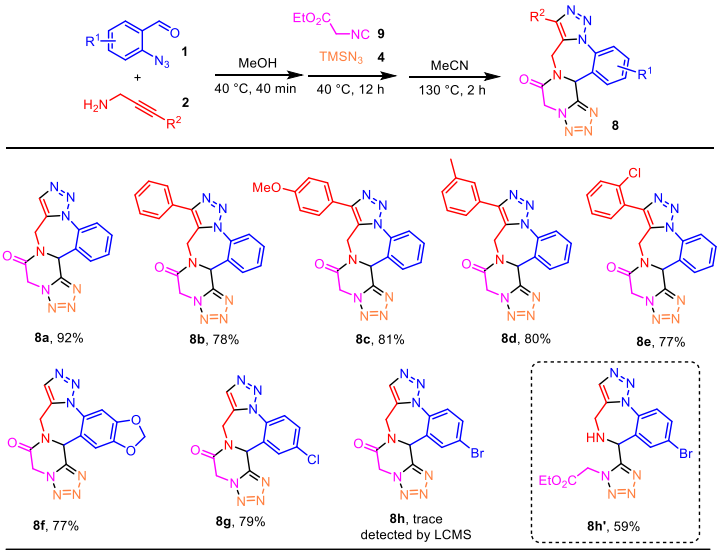
fused 1,4-benzodiazepines **8**. For the synthesis of this unique polycyclic scaffold, 2-isocyanoacetate **9** plays a critical role in the formation of piperazinone ring. Thus, the reaction of 0.2 mmol each of **1a** and **2a** led to the formation of **Int-I** which then reacted with 0.2 mmol each of **9** and **4** to form 1,5-DS-T **5b** which consequently underwent lactamization to form **6a** followed by intramolecular click reaction to afford highly condensed polycyclic product **8a** in 92% isolated yield (Scheme 4).



Scheme 4. Synthesis of polycyclic compound **8a**.

The reaction scope was explored in making products analogs **8a** – **h** by the reaction of four different 2-azidobenzaldehydes **1** and five different 2-yn-1-amines **2** with 2-isocyanoacetate **9** and $TMSN_3$ **4** (Table 2). The reaction of five different 2-yn-1-amines **2** yielded products **8a** – **e** in 77 – 92% yields,

Table 2. Synthesis of product analogs **8**.

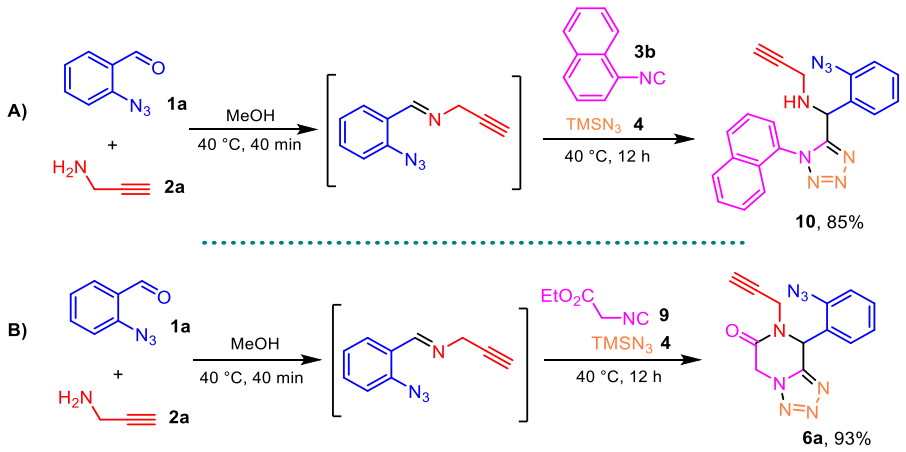


Reaction conditions: 1) 0.2 mmol each of 2-azidobenzaldehyde **1a** and 2-yn-1-amines **2** in MeOH (2 mL), 40 ° C for 40 min; then addition of 0.2 mmol each of 2-isocyanoacetate **9** and $TMSN_3$ **4**, 40 ° C for 12 h; 2) changing solvent to MeCN (2 mL), 130 ° C for 2 h.

which demonstrates a good substitution tolerance of R^2 on 2-yn-1-amines **2**. The reaction of 6-azidobenzo[*d*][1,3]dioxole-5-carbaldehyde **1b** with propargylamine **2a**, 2-isocyanoacetate **9**, and

$TMSN_3$ **4** gave product **8f** in a 77% yield. Azidobenzaldehydes bearing a Cl group could give product **8g** in 79% yield. However, the reaction of 2-azido-5-bromobenzaldehyde **1d** gave a trace amount of product **8h**. The compound **8h'** in 59% yield is an intermediate without lactamization. It is likely that the bromo group on the phenyl ring interfered with the lactamization process.

Two control reactions were conducted to study the reaction process. The reaction of **1a**, **2a**, **3b** and **4** at 40 °C afforded Ugi-azide product **10** in 85% yield without formation of triazole ring, which indicates that intramolecular click reaction needs a higher temperature (Scheme 5A). The reaction involving the lactamization step was carried out using 2-isocyanoacetate **9** which gave tetrazole-fused piperazinone **6a** in 93% yield, which also indicates that at this reaction temperature, lactamization could happen prior to the click reaction (Scheme 5B).



Scheme 5. Control reactions to trap the Ugi-azide adduct.

Compounds **6a** and **8a** have same molecular weights, but their ^{1}H-NMR spectra are different (Figure 3). It is evidenced by the disappearance of alkyne H at 2.36 ppm from **6a** and the appearance of 8.14 ppm peak of H on triazole ring of **8a**. The aromatic Hs in **8a** shown as two distinct doublets and two triplets with a slightly downfield shifted as compared to the aromatic Hs in **6a**. This observation reflects a rigid conformation of aromatic Hs after forming a 7-membered piperazinone ring in **8a**.

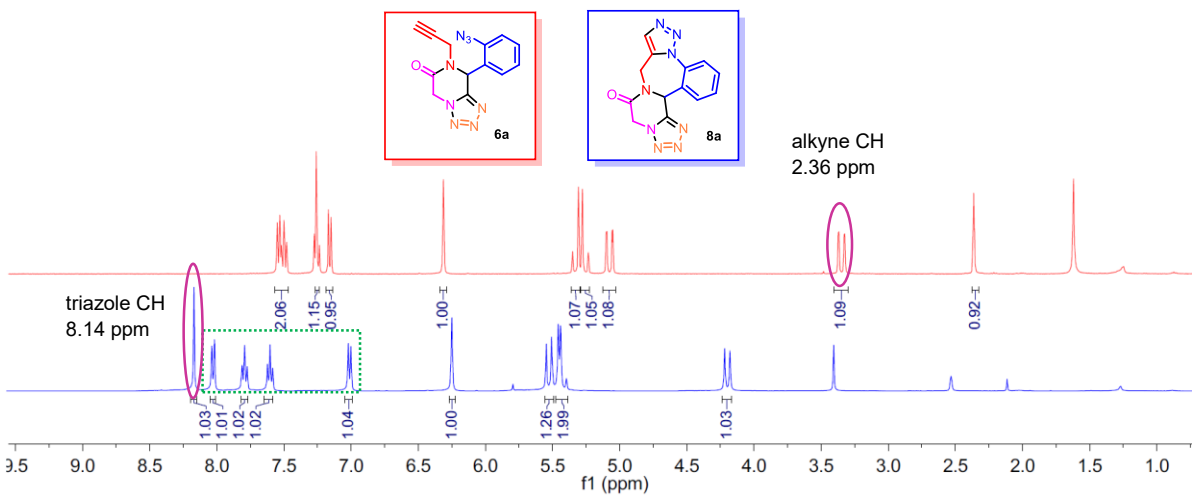
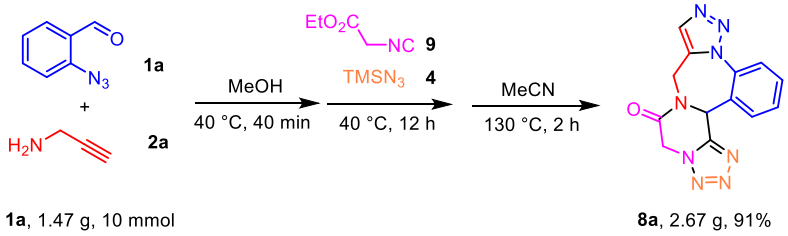


Figure 3. ^{1}H NMR spectra of compounds **6a** (red) and **8a** (blue).

To evaluate the scalability of this protocol, we performed the synthesis of tetracyclic tetrazolo-pyrazino[2,1-*a*]isoquinolin-6(5*H*)-one **6c** in gram quantity of **1a** which led to the formation of product **6c** in a satisfactory yield of 77% (Scheme 7).



Scheme 7: Gram-scale one-pot synthesis of **8a**.

Conclusion

We have developed a new synthetic method to access triazole-fused and tetrazole-tethered benzodiazepines **7** *via* Ugi-azide/intramolecular click reaction under Cu-catalyst-free conditions. The 4-CR Ugi-azide reaction was modified to be a one-pot two-step reaction process to address functional group compatibility issues. By using 2-isocyanoacetate, the Ugi-azide adducts could undergo lactamization and lead to the formation of highly condensed 1,4-benzodiazepines **8** fused with triazole, tetrazole, and piperazinone rings. This is a new example of combining MCR and post-condensation modification as a one-pot synthesis to access novel heterocyclic scaffolds in a highly efficient manner.

Experimental

General procedure for synthesis of analogs **7** and **8**

A solution of 2-azidobenzaldehyde **1** (0.2 mmol, 1 equiv) and propargylamine **2** (0.2 mmol, 1 equiv) in MeOH (2 mL) was heated at 40 °C for 40 min in a metal bath, then followed by the addition of isocyanides **3** (0.2 mmol, 1 equiv) and $TMSN_3$ **4** (0.2 mmol, 1 equiv), and stirred at 40 °C for 12 h. Next, the reaction mixture was evaporated to remove MeOH solvent and redissolved in MeCN (2 mL) in a sealed vial at 130 °C for 2 h. After the reaction had reached completion as monitored by TLC, the reaction mixture was concentrated in vacuo, and isolated by chromatography column on silica gel to afford products **7a–k** in 36–90% yields, **8a–g** in 77–92% yields.

Notes: When 2-yn-1-amine hydrocholoride **2b−e** were employed into this one-pot reaction, Et_3N (0.3 mol, 1.5 equiv) was added into the vessel at the initiate stage.

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