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Facile One-Pot Assembly of Imidazotriazolobenzodiazepines via Indium(III)-Catalyzed Multicomponent Reactions

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ABSTRACT

An operationally simple, one-pot multicomponent reaction has been developed for the assembly of 9*H*-benzo[*f*]imidazo[1,2-*d*][1,2,3]triazolo[1,5-*a*][1,4]diazepines adorned with three diversification points via an atom-economical transformation incorporating α-diketones, *o*-azidobenzaldehydes, propargylic amines, and ammonium acetate. This process involves tandem $InCl_3$-catalyzed cyclocondensation and intramolecular azide−alkyne 1,3-dipolar cycloaddition reactions; optimization data, substrate scope, and mechanistic insights are discussed.

Imidazoles, triazoles, and benzodiazepines are privileged heterocyclic structures present in various natural products and synthetic pharmaceuticals. The imidazole scaffold is widely found in bioactive compounds possessing anti-inflammatory, anticancer, anti-HIV, and antituberculosis activities.[1] 1,2,3-Triazole-derived molecules are, for example, reported to have antiprotozoal and antiviral properties.[2] The 1,4-benzodiazepine core is a ubiquitous motif found in numerous psychoactive pharmaceutical agents, for instance, diazepam (Valium).[3a]

Furthermore, fused-ring systems embodying benzodiazepine and imidazole and/or triazole substructures have attracted considerable attention due to their highly potent biological activities. Two of these pharmaceutically important imidazobenzodiazepines are Bretazenil (**1**)[3b] and Midazolam (**2**),[3c] which are currently used in the treatment of anxiety, seizure, and insomnia (Figure 1). Derived from the triazolodiazepinone skeleton, the synthetic molecule **3** is found to show good serine protease inhibition activity.[4]

Due to the pharmacological significance of the aforementioned cores, a number of synthetic methods have recently

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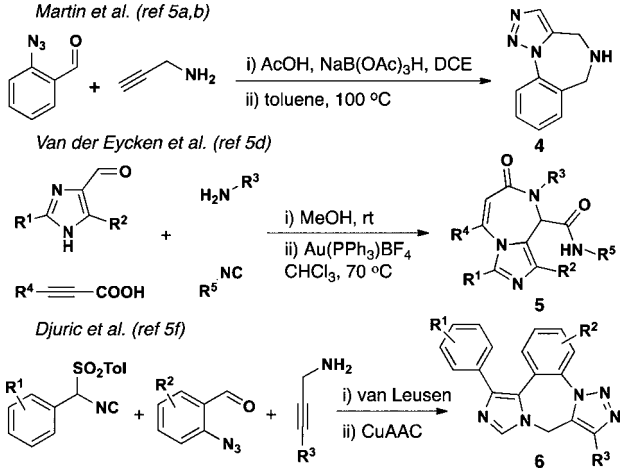
Figure 1. Pharmaceutical examples exploiting bioactive imidazole, triazole, and benzodiazepine.

Scheme 1. Previous Work on Imidazole/Triazole/Diazepine-fused Skeletons

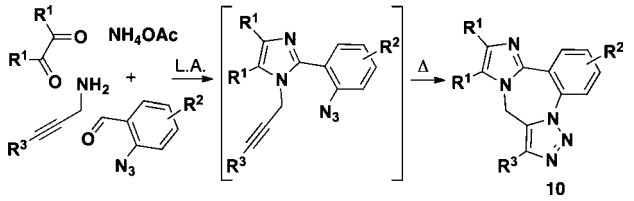


CuAAC = copper-catalyzed azide−alkyne cycloaddition.

been developed for the construction of imidazole/triazole/diazepine-fused skeletons. Martin[5a,b] and co-workers reported an effective route to 1,2,3-triazole-fused 1,4-benzodiazepines (**4**) via cascade reductive amination and intramolecular Huisgen cycloaddition reactions[5c] (Scheme 1). In addition, the atom economy, ease of diversification, and operational simplicity of multicomponent reactions (MCRs) have been extensively exploited to provide ready accesses to these complex annulated ring systems from simple building blocks. In that context, Van der Eycken has reported an expedient post-Ugi intramolecular heteroannulation approach for the synthesis of imidazo[1,4]diazepin-7-ones, (**5**; Scheme 1)[5d,e] and Djuric has demonstrated an interesting postmodification of the van Leusen imidazole synthesis using an intramolecular azide−alkyne cycloaddition to construct **6**, which incorporates imidazole, triazole, and diazepine rings in one scaffold.[5f]

Prompted by the synthetic interest and applications of imidazole/triazole/diazepine-fused skeletons and encouraged by recently reported MCRs of these scaffolds, we report herein a facile route to the novel imidazo-[1,2,3]triazolo[1,4]benzodiazepines via the Lewis acid-catalyzed multicomponent reaction of symmetrical α-diketones, *o*-azidobenzaldehydes, propargylic amines,

Scheme 2. Our Synthetic Strategy toward Imidazo-[1,2,3]triazolo[1,4]benzodiazepines



and ammonium acetate (Scheme 2). Indeed, there are numerous procedures for the synthesis of imidazoles.[6] Among these, we were especially interested in cyclocondensations of α-diketone, aldehyde, 1°-amine, and ammonia reactants; conventionally catalyzed by a variety of Brønsted/Lewis acids to promote imine formation and subsequent heterocyclization.[7] Our rationale is based on the idea of assembling a highly substituted imidazole ring from an α-diketone, an aldehyde substrate bearing azide functional group, and a 1°-amine substrate bearing an alkyne functional group. We envisioned that the resulting post-cyclocondensation system would preorganize the azide and alkyne moieties for a subsequent thermally driven intramolecular 1,3-dipolar cycloaddition.[5a,8] The result of this one-pot, tandem, multicomponent reaction would be the tetracyclic core of **10** adorned with three diversification points (Scheme 2).[9]

Initial investigations centered on the cyclocondensation of benzil (**7d**; 1.1 equiv), *o*-azidobenzaldehyde (**8a**; 1 equiv), propargylamine (**9a**; 1.1 equiv), and ammonium acetate (1.1 equiv). Lewis acid screening began with molecular iodine since it is known to be an efficient catalyst for the rapid, one-pot formation of 1,2,4,5-tetra-substituted imidazoles in excellent yields.[7e] Subjecting the starting materials and a catalytic amount of I_2 (15 mol %) to stirring in MeOH at 80 °C in a sealed microwave vial for 24 h furnished the desired imidazotriazolobenzodiazepine

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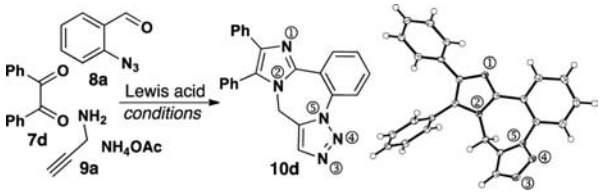
Table 1. Optimization Data: Multicomponent Assembly of **10d**[a]



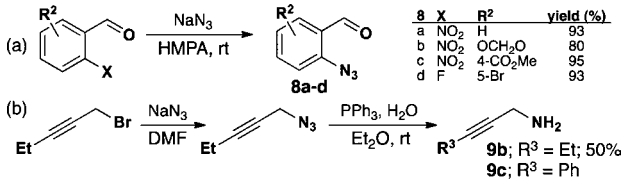
entry	Lewis acid (mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	I_2 (15)	MeOH	80	24	45
2	I_2 (15)	toluene	80	24	trace
3	I_2 (15)	DMF	80	48	trace
4	I_2 (1 equiv)	EtOH	100	72	30
5	I_2 (1 equiv)	EtOH	100	72	31[c]
6	$Cu(OAc)_2$ (20)	MeOH	80	24	0
7	$FeCl_3$ (10)	MeOH	100	72	51
8	$Zn(ClO_4)_2$ (10)	MeOH	100	72	58
9	$Sc(OTf)_3$ (10)	MeOH	100	48	57
10	$CeCl_3$ (10)	MeOH	100	72	67
11	$InBr_3$ (10)	MeOH	100	72	52
12	$InCl_3$ (10)	MeOH	100	48	71
13	$InCl_3$ (5)	MeOH	100	48	65
14	$InCl_3$ (5)	MeOH	80	72	51
15	$InCl_3$ (20)	MeOH	100	48	70
16	$InCl_3$ (10)	EtOH	100	48	46
17	$InCl_3$ (10)	MeCN	100	48	25

[a] Optimal reaction condition: benzil (1.1 equiv), *o*-azidobenzaldehyde (1 equiv), propargylamine (1.1 equiv), ammonium acetate (1.1 equiv), $InCl_3$ (10 mol %), MeOH (0.1 M), 100 °C in a sealed microwave vial. [b] Isolated yields. [c] Additives: $CuSO_4 \cdot 5H_2O$ (10 mol %), sodium ascorbate (20 mol %). Tf = trifluoromethanesulfonyl.

10d in 45% yield together with a small amount of a free-azide–alkyne-tethered intermediate as the main side product (Table 1, entry 1). However, switching to toluene or DMF as solvent under the same conditions failed to deliver product (entries 2–3). Next, we reasoned that increased catalyst loading as well as reaction temperature would enhance the yield of **10d** by increasing the rate of both the cyclocondensation and cycloaddition steps. Interestingly, the presence of one equivalent of I_2 in EtOH/100 °C/72 h reduced the yield of **10d** (45 → 30%; entries 1 vs 4) even when azide–alkyne cycloaddition catalysts such as $CuSO_4$ and sodium ascorbate were added (entry 5).[10] On the basis of these results, we examined a series of transition metal Lewis acids [$Cu(OAc)_2$, $FeCl_3$, $Zn(ClO_4)_2$, $Sc(OTf)_3$, $CeCl_3$, $InCl_3$, $InBr_3$] for their ability to activate 1,2-dicarbonyl electrophiles (entries 6–12). While most of these Lewis acids showed better efficacy than I_2, the $InCl_3$ reaction proceeded best and afforded a significant improvement in product yield (45 → 71%) (entry 12) with complete conversion of the precycloaddition intermediate to **10d** (as monitored by LC/MS). Further screening established the optimal catalyst loading as 10 mol %; lower or higher loadings slightly decreased the yield (entries 13–15). MeOH proved to be better than EtOH and MeCN (entries 16–17) as solvent. Finally, the structure of **10d** was unambiguously established by X-ray crystallography (Table 1).[11]

With these optimal conditions in hand, we set out to explore a method for the preparation and diversification of the α-diketone, aldehyde, and amine components. Indeed, each component for this MCR can be accessed via simple transformations. We utilized a variety of commercial symmetrical α-diketones: glyoxal (**7a**), 2,3-butanedione (**7b,c**), and benzil derivatives (**7d,e/k–n**: R^1 = Ph; **7f**: R^1 = *o*-ClC_6H_4; **7g**: R^1 = *p*-BrC_6H_4; **7h**: R^1 = *p*-$MeOC_6H_4$; **7i,j**: R^1 = *p*-MeC_6H_4). The requisite *o*-azidobenzaldehyde and derivatives (**8a–d**; Scheme 3a) were synthesized in excellent yields (80–95%) by nucleophilic aromatic substitution on commercially available *o*-nitrobenzaldehyde or *o*-fluorobenzaldehyde derivatives in HMPA (method by Driver).[12a] The propargylamine component was obtained from the corresponding propargyl halide in two steps (Scheme 3b); e.g., S_N2 displacement of bromide from 1-bromopent-2-yne by sodium azide in DMF yielded the alkyl azide and subsequent in situ Staudinger reduction[12b] delivered **9b**.

Scheme 3. Preparation of *o*-Azidobenzaldehyde **8** and Pent-2-yn-1-amine **9b**



Next, we examined the substrate scope of this MCR by subjecting α-diketones **7a–n**, aldehydes **8a–d**, amines **9a–c**, and ammonium acetate to our optimized conditions. In all cases, these four components were successfully assembled into the corresponding imidazotriazolobenzodiazepines **10a–n** (Scheme 4). The electronic effects of substituents on each component have a significant impact on the product yields; that said, trends were not uniform. For example, when R^1 on **7** is phenyl (**7d** → **10d**), the yield is higher than when R^1 is H (**7a** → **10a**) or Me (**7b** → **10b**). Surprisingly, the presence of either e-donating or e-withdrawing groups on R^1 aryls (**7f–h** → **10f–h**) generally suppressed the yield [except for the case of R^1 = *p*-MeC_6H_4 (**7i** → **10i**; 72%)]. Similarly, when R^2 is an e-donating substituent (dioxole; **8b** → **10j**), the yield is slightly improved compared to an e-withdrawing substituent (R^2 = CO_2Me; **8c** → **10e**). That said, ester moieties in **10c/e/m** were tolerated with no transamination detected.

(10) Iodine might have an adverse effect on the intramolecular azide–alkyne cycloaddition, as monitoring by LC/MS showed an unchanged ratio between product **10d** and its pre-cycloaddition intermediate.

(11) Compound **10d** crystallized in the monoclinic space group $P2_1/n$ with a final R_1 value of 3.40% for all reflections $> 2\sigma$.

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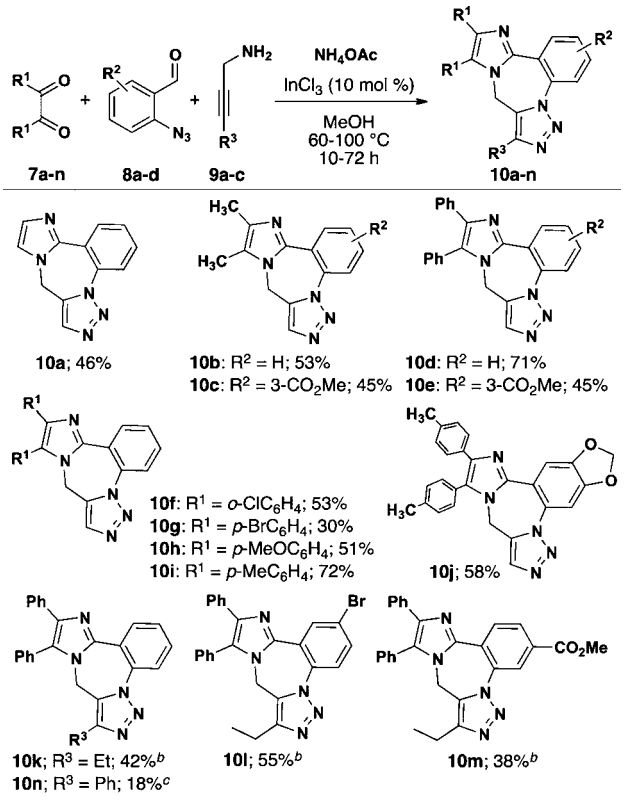
Scheme 4. Examples of Imidazotriazolobenzodiazepines[a]

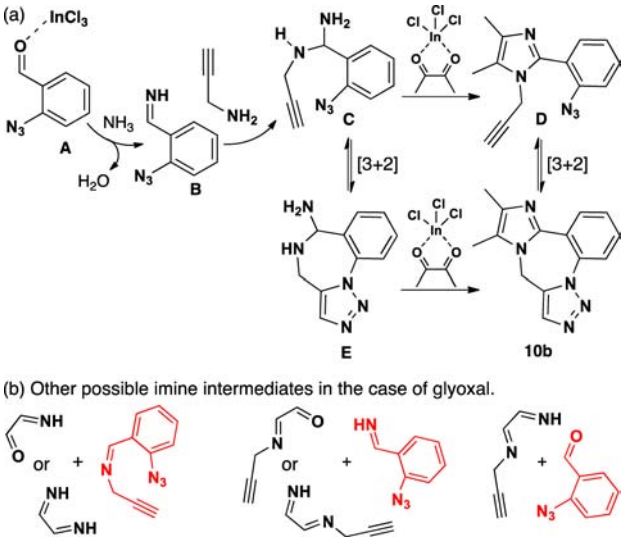


[a] Reaction condition: α-diketone (1.1 equiv), aldehyde (1 equiv), amine (1.1 equiv), ammonium acetate (1.1 equiv), $InCl_3$ (10 mol %), MeOH (0.1 M), 60−100 °C in sealed microwave vials. Isolated yields. [b] Reactions were performed at 80 °C. [c] Reaction performed at 60 °C.

Employing internal alkynylamines (**9b** → **10k**−**m**; **9c** → **10n**) in place of propargylamine resulted in somewhat lower yields (cf., **10e** in 45% vs **10m** in 38%), and the increased formation of unidentified side products complicated purification. With targets **10k**−**n**, lowering the reaction temperature improved product yields (cf., **10k** in 42% at 80 °C vs 30% at 100 °C). Finally, we note that the aryl halide moieties in **10f/g/l** and the ester moieties in **10c/e/m** set the stage for subsequent synthetic modification; for example, Suzuki−Miyaura cross-coupling[13] or Buchwald−Hartwig aminations[9a] and amide coupling reactions, respectively.

While a number of mechanisms can be envisioned for this indium(III)-catalyzed MCR, the sequence presented in Scheme 5a for formation of **10b** is illustrative. Here, the tandem process ensues by initial $InCl_3$-catalyzed imine formation (**A** → **B**) followed by nucleophilic addition of propargylamine to the resulting imine (**B** → **C**). From intermediate **C**, there are two feasible pathways to **10b** with the difference being the order in which the steps occur: **C** → **D** → **10b** proceeds with imidazole formation first, while **C** → **E** → **10b** proceeds with triazole formation first. In the case of the less hindered dicarbonyl glyoxal (and, to a lesser extent, the diketo reactants), it is conceivable that α-diimine or α-ketoimine intermediates (Scheme 5b) may compete with the formation of **C**. These added options might explain the somewhat lower yield of glyoxal-derived **10a**.

Scheme 5. Proposed Mechanism for the Formation of **10b**[a]



[a] As judged by LC/MS, the formation of intermediate **D** is somewhat accelerated under microwave irradiation compared to that under thermal heating. However, the overall time required for the reaction is comparable in both methods.

In summary, we have developed a versatile MCR for the synthesis of substituted imidazotriazolobenzodiazepines that proceed by tandem $InCl_3$-catalyzed cyclocondensation and intramolecular Huisgen 1,3-dipolar cycloaddition reactions. This method incorporates two-step cascade reactions in an operationally simple, one-pot procedure that affords a highly atom-economical transformation engaging four starting materials, allowing for easy diversification of the final products. This method accommodates a wide scope of α-diketones, various substituted *o*-azidobenzaldehydes, as well as modification of the propargylic amine and affords good functional group tolerance.

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Supporting Information Available. Full experimental details and characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS, and mp) of all novel compounds; X-ray crystal data for compound **10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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