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Tandem C-2 Functionalization–Intramolecular Azide–Alkyne 1,3-Dipolar Cycloaddition Reaction: A Convenient Route to Highly Diversified 9*H*-Benzo[*b*]pyrrolo[1,2-*g*][1,2,3]triazolo[1,5-*d*][1,4]diazepines

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Supporting Information

ABSTRACT: An efficient diversity-oriented synthetic approach to annulated 9*H*-benzo[*b*]pyrrolo[1,2-*g*][1,2,3]-triazolo[1,5-*d*][1,4]diazepines has been developed using a $Sc(OTf)_3$-catalyzed two-component tandem C-2 functionalization–intramolecular azide–alkyne 1,3-dipolar cycloaddition reaction. The reaction shows high substrate tolerance and provides a library of fused heterocycles that may lead to novel biologically active compounds or drug lead molecules.

Structurally novel and multifarious heterocycles are very useful frameworks for drug discovery because of the high hit rates and the unique pharmacological profiles of their derivatives relative to those of other ring systems.[1] Efficient synthetic transformations that allow the synthesis of highly functionalized molecules from relatively simple substrates by enabling multiple bond forming events to occur in one operation is a major challenge in modern organic synthesis. Such processes avoid time-consuming, costly purification procedures and are instinctively eco-friendly and atom economic.[2,3]

Benzodiazepines (BDZs) are privileged scaffolds in medicinal chemistry and also serve as versatile building blocks for the construction of many bioactive natural products, drugs, and therapeutic leads.[4−6] The interesting biological activities and unprecedented structural features of this scaffold have attracted considerable attention from the synthetic community.[7,8]

An exciting new approach which has recently come into focus is to fuse the benzodiazepine moiety with different heterocycles to enhance their therapeutic potential.[9] While recent synthetic efforts have greatly expanded the diversity of benzodiazepine scaffolds available, newer synthetic routes, particularly ones which can provide direct access to benzodiazepine moiety fused with other important heterocycles, are still extremely desirable. In this context, tandem reactions have emerged as a powerful tool, often enabling a significant streamlining of the synthesis of structurally complex molecular skeletons in a single step without the separation and purification of intermediates.[2b,3c,8d,10]

The renaissance of Huisgen 1,3-dipolar azide–alkyne cycloaddition in synthetic chemistry has found widespread application in many fields such as polymer chemistry,[11] chemical biology,[12] and medicinal chemistry.[13] Lewis acid catalyzed propargylation or nucleophilic substitution of activated/inactivated propargyl alcohols with electron rich arenes to give functionalized alkynes and their subsequent application in the synthesis of bioactive heterocyclic molecules has gained much importance.[14] With these observations, we report a concise and atom-economical diversity oriented synthesis (DOS) that allows rapid access to highly diversified benzodiazepines with the concurrent formation of two new annulated five- and seven-membered heterocyclic rings in a single step. The method involves a two-component tandem C-2 functionalization–intramolecular azide–alkyne 1,3-dipolar cycloaddition reaction. To the best of our knowledge, this is a novel approach for the synthesis of structurally diverse and annulated heterocycles with an embedded benzodiazepine motif by using bifunctional substrates to strategically provide libraries of structurally diverse benzodiazepines that will help in the search of new biologically active compounds or drug lead molecules.

Using the disconnection approach, we envisaged access to product **5** via the C-2 functionalization of 1-(2-azidoaryl)-1*H*-pyrroles **3** and subsequent intramolecular 1,3-dipolar cycloaddition with 1,3-substiuted propargyl alcohols **4** (Scheme 1). Among the various literature methods reported for propargylation, we preferred to use a Lewis acid catalyzed method for the C-2 functionalization of pyrroles (**3**) which were synthesized by a Paal–Knorr reaction of 2-azidoanilines (**1**) and 2,5-dimethoxytetrahydrofuran (**2**).

The study was commenced by employing a stoichiometric amount of molecular iodine as a Lewis acid catalyst to react 1-(2-azidophenyl)-1*H*-pyrrole (**3a**) with 1,3-diphenylprop-2-yn-

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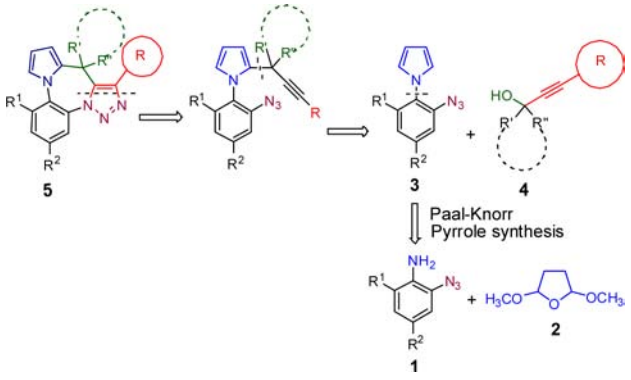
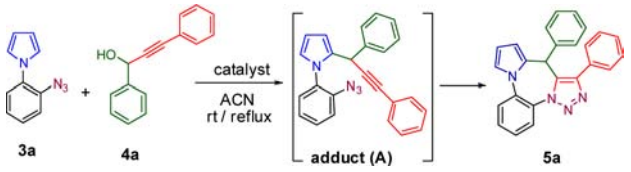
Scheme 1. Retrosynthetic Analysis: Tandem C-2 Functionalization−Intramolecular Huisgen 1,3-Dipolar Cycloaddition



1-ol (**4a**) in acetonitrile at room temperature. Within 1 h, the reaction showed a complex mixture on TLC with complete consumption of both the reactants (entry1, Table 1). Our attempt to purify or isolate the desired product by column chromatography was unsuccessful. Presumably, high instability of the initially formed adduct (**A**) with reactive azide−alkyne functionalities and failure to cyclize under mild reaction conditions may be the reason for the formation of a complex mixture. It was therefore thought that if the reaction is carried out under reflux conditions, thermal activation may lead to intramolecular cyclization and afford the target compound. Consequently, under heating, the reaction was complete within 30−40 min; however, we were successful in isolating the target compound **5a** only in very low yields (12%, entry 2). Spectral analysis by $^{1}H/^{13}C$ NMR and ESI-HRMS confirmed the structure as that of the target molecule **5a** arising from C-2 functionalization of the pyrrole and azide−alkyne intramolecular 1, 3-dipolar cycloaddition.

Table 1. Optimization of Reaction Conditions



entry	catalyst	mol %	time(h)[a]/ temp[b]	solvent	yield (%)[c]
1	I_2	200	1/rt	ACN	cm[d]
2	I_2	200	0.5/80	ACN	12
3	$AlCl_3$	5	2/80	ACN	20
4	$FeCl_3$	5	2/80	ACN	25
5	$ZnCl_2$	5	3/80	ACN	15
6	$CuCl_2$	5	3/80	ACN	18
7	$Yb(OTf)_3$	5	3/80	ACN	46
8	$Al(OTf)_3$	5	3/80	ACN	50
9	$Cu(OTf)_2$	5	3/80	ACN	48
10	$Zn(OTf)_2$	5	3/80	ACN	40
11	Ag(OTf)	5	3/80	ACN	32
12	$Fe(OTf)_3$	5	3/80	ACN	43
13	$Sc(OTf)_3$	5	3/80	ACN	65
14	$Sc(OTf)_3$	10	3/80	ACN	53
15	**$Sc(OTf)_3$**	**3**	**3/80**	**ACN**	**72**
16	$Sc(OTf)_3$	2	3/80	ACN	58

[a]Time in hours. [b]Temperature in °C. [c]Isolated yields after column chromatography. [d]Complex mixture.

With the product in hand, we then approached the reaction using metal halides such as $AlCl_3$, $FeCl_3$, $ZnCl_2$, and $CuCl_2$ (5 mol %) as Lewis acids, under reflux conditions. Interestingly, in each case the reaction was complete within 2−3 h, but again the yield of cyclized product **5a** was quite low (entries 3−6). For further enhancement of the yield, we next focused our attention using metal triflates as environmentally friendly Lewis catalysts that are also known to catalyze many useful organic transformations.[15] Gratifyingly, the use of 5 mol % of $Yb(OTf)_3$ in acetonitrile under reflux conditions (entry 7) provided the desired compound in 46% yield in 3 h. This experiment confirmed that with the optimization of catalyst and its loading, the desired benzodiazepines could be prepared in good yields. With this hope, we examined the feasibility of other triflates such as $Al(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, Ag(OTf), and $Fe(OTf)_3$ (entries 8, 9, 10, 11, and 12), but no significant improvement in the reaction was observed. However, when 5 mol % of $Sc(OTf)_3$ was used as catalyst, we were pleased to observe a clean reaction with an isolable yield of 65% of the corresponding cyclized compound (entry13). Increasing the catalyst loading to 10 mol % caused a substantial decrease in yield (53%, entry 14), but to our surprise, lowering the catalyst loading to 3 mol % enhanced the yield to 72% (entry 15). Further lowering of the catalyst loading was found to be detrimental, both to the rate and yield of the reaction (entry 16, Table 1). From these set of experiments, it was observed that the use of 3 mol % of $Sc(OTf)_3$ as catalyst in acetonitrile under reflux conditions gave the best results in one pot. The reaction rate was found to be sluggish on changing from acetonitrile to toluene.

With a productive one-step optimized protocol in hand, we investigated the substrate scope of the reaction with respect to a variety of propargyl alcohols comprising aryl, heteroaryl and aliphatic substrates, all providing the annulated benzodiazepines in good to high yields. Substrates with electron-donating substituents at the para position of aromatic ring of alkynyl (**5b−g**) and propargylic positions (**5i−j**) enhanced both the reactivity and yield of the product (Scheme 2).This was also confirmed by replacing the aromatic ring with electron rich furan and thiophene heterocycles, wherein the products were isolated in high yields (**5k−q**). When the terminal aromatic ring of the alkyne was replaced by an aliphatic cyclopropyl substituent, the yield of the benzodiazepines was again found to be excellent (**5u** and **5v**). On the other hand, incorporation of a chloro substituent at the para position of the aromatic ring of propargyl alcohol reduced the yield (**5s** and **5t**). Furthermore, a slight decrease in yield was also observed when phenyl and methyl substituents were present at the ortho position of phenyl ring (**5h** and **5r**), probably due to steric hindrance. The structure of one of the newly synthesized benzodiazepine molecule **5l** was also confirmed by its single crystal X-ray analysis.[16]

Sterically hindered propargyl alcohols with *gem*-dimethyl groups at the propargylic position (**4p−s**) also underwent a smooth reaction with aryl azides **3a** and **3b**. The reactivity of the substrates and yield of the annulated products (**6a−h**) were found to be comparable to those of 1,3-diaryl propargyl alcohols (Scheme 3). The presence of a methoxy group at the para position of the aromatic ring at the terminal alkyne position (**6b** and **6e**) enhanced the yield of the benzodiaze-

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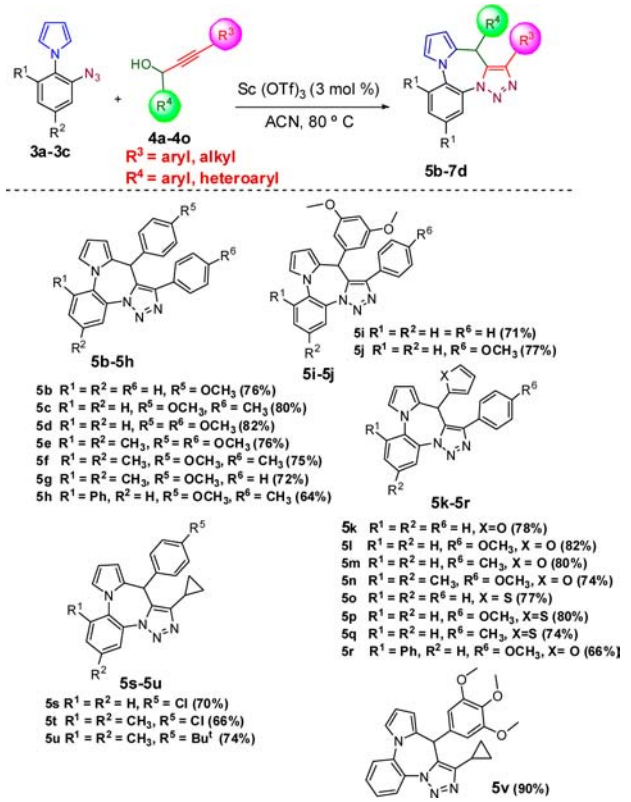
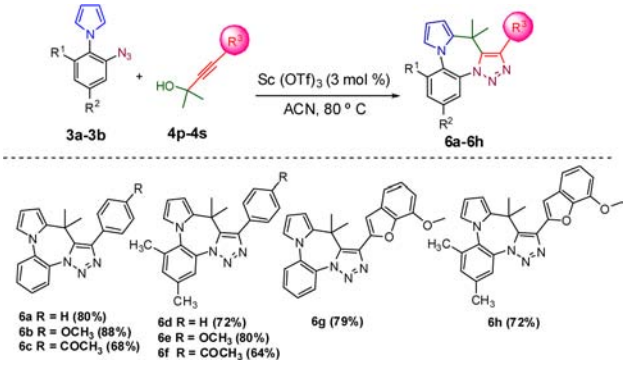
Scheme 2. Exploring the Scope of Various Substituents at R^3 and R^4: Synthesis of 8,9-Substituted 9*H*-Benzo[*b*]pyrrolo[1,2-*g*][1,2,3]triazolo[1,5-*d*][1,4]diazepines (5b–v)



Scheme 3. Tandem Synthesis of 9,9-Dimethyl-8-aryl-9*H*-benzo[*b*]pyrrolo[1,2-*g*][1,2,3]triazolo[1,5-*d*][1,4]diazepines

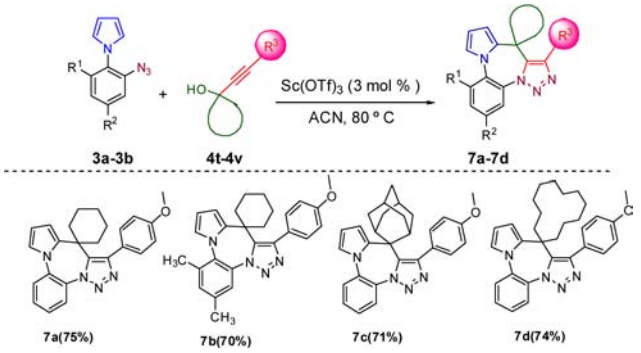


pines, whereas electron-withdrawing acetyl group (**6c** and **6f**) decreased the yield.

The tandem C-2 functionalization–1,3-dipolar Huisgen cycloaddition was not limited to the formation of annulated tetracyclic benzodiazepines as annulated spirocyclic benzodiazepine derivatives (**7a–d**) were also prepared in good yields by the reaction of cyclohexanone-, adamantanone-, and cyclododecanone-derived propargyl alcohols (**4t–v**) with aryl azides **3a** and **3b** under the same optimized conditions (Scheme 4).

In summary, we have successfully developed an interesting protocol for the synthesis of structurally complex and annulated 9*H*-benzo[*b*]pyrrolo[1,2-*g*][1,2,3]triazolo[1,5-*d*][1,4]-diazepines via a $Sc(OTf)_3$-catalyzed two component tandem reaction. The reaction shows high generality and functional

Scheme 4. Synthesis of Spirocyclic Annulated Benzodiazepines



group tolerance. It provides a direct approach for the generation of a library of diverse and fused annulated benzodiazepines which may be of biological interest.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, spectroscopic data (copies of ^1H and ^{13}C NMR spectra) of all new compounds; ORTEP diagram, X-ray crystal data, and CIF file of compound **5l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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