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Multicomponent Reactions

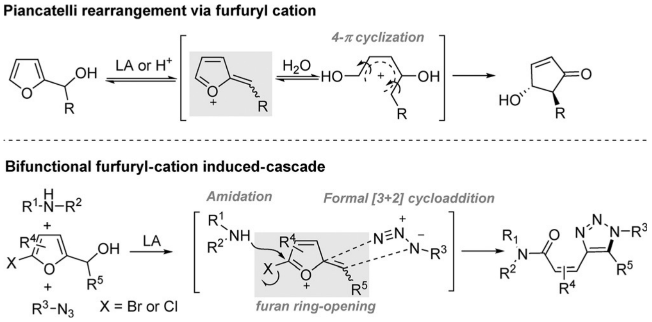
Bifunctional Furfuryl Cations Strategy: Three-Component Synthesis of Enamidyl Triazoles

Hengtuo Yang,[a] Jing Gou,[b] Jiawei Guo,[a] Dongyu Duan,[a] Yu-Ming Zhao,[a] Binxun Yu,*[a] and Ziwei Gao*[a]

Abstract: A new multicomponent synthesis of functionalized enamidyl triazoles starting from simple and readily available starting materials is described. A simple treatment of a dichloromethane solution of an azide, amine, and 5-bromo-2-furylcarbinol with a Lewis acid provides the enamidyl triazole in good to high yield. A triple domino sequence, formal [3+2] cycloaddition/ring-opening/amidation, is involved in this new skeleton-generating reaction.

The synthesis of small polyfunctionalized heterocyclic compounds remains one of the most interesting subjects in the drug discovery process[1] and in isolation and structural identification of biological macromolecules.[2–3] Within this context, development of highly efficient construction of heterocyclic skeletons by combined use of multicomponent reactions (MCRs) and domino processes has been a frequent target for synthetic chemistry efforts.[4] For designing MCRs, a typical guiding principle is to devise a novel multifunctional starting material that is appropriately functionalized, allowing it to be engaged in the subsequent domino process.

Furans play an important role in organic chemistry not only due to their presence as key structural scaffolds in many natural products and in important pharmaceuticals,[5] but they have also been versatile tools in synthetic chemistry and a lot of transformation reactions have been documented for them.[6] The furan ring allows for its facile recyclization reactions into different carbo[7] and heterocycles,[8] particularly furfuryl cations have also served as well-known reactive intermediates. For example, the Piancatelli reaction converts furfuryl carbinols into hydroxycyclopentenones under acidic conditions.[9] This rearrangement process has seen a significant use in complex molecule synthesis. However, the high reactivity and low stability arising from the low resonance energy of the furan ring have rarely been used in MCRs.[10] Herein, we describe our development of a three-component reaction (3-CR) of a 5-halo-furylcarbinol, azide, and amine under Lewis acid conditions (Scheme 1). To the best of our knowledge, the reaction represents the first example of MCRs based on the furfuryl carbinol recyclization, enabling the rapid construction of a diverse set of highly functional enamidyl triazoles.



Scheme 1. Three-component synthesis of functionalized enamidyl triazoles.

The derivatives containing a 1,2,3-triazole conjugated with a α, β-unsaturated amide moiety are of great importance because they have been proven to show significant inhibition activities for matrix metalloproteases (MMPs),[11] histone deacetylase,[12] class I β-lactamase, and so forth.[13] A recent synthetic methodology for the construction of the enamidyl triazole scaffold has been focused primarily on the 1,3-dipolar azide–alkyne cycloaddition (AAC),[14] but tedious multi-step synthesis of precursors limits the further exploitation of its application potential. We have disclosed that the reaction between the furfuryl cation and an azide leads to the (*E*)-stereospecific production of the enonyl triazole.[15] We next wondered about the behavior of the furfuryl cation in the presence of another active functionality on it, to probe if it could perform a bifunctional platform for connecting other two parts in MCRs. We chose 5-halo-2-furylcarbinol as the furfuryl cation source, envisaging that it could achieve a formal [3+2] cycloaddition with an azide, and the resulting α, β-unsaturated acyl halide from furan ring-opening could be trapped with an amine for the construction of the enamidyl triazole.

With a goal of investigating the proposed three-component reaction, we employed the 5-bromo-furfurylcarbinol (**2a**), aniline (**1a**), and cyclohexyl azide (**3a**) as the standard substrates

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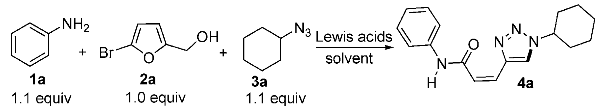
Table 1. Optimization of the reaction conditions.[a]



Entry	Acid [equiv]	Solvent	T [°C]/t [min]	Yield [%][b]
1	$AlCl_3$ (1.1)	CH_2Cl_2	−20 to rt/20	10
2	$FeCl_3$ (1.1)	CH_2Cl_2	−20 to rt/20	5
3	$ZnCl_2$ (1.1)	DCE	rt–reflux/120	trace
4	$InCl_3$ (1.1)	DCE	rt–reflux/120	NR[c]
5	$Sc(OTf)_3$ (0.5)	DCE	rt–reflux/120	ND[d]
6	$Ir(OTf)_3$ (0.5)	DCE	rt–reflux/120	ND[d]
7	$Dy(OTf)_3$ (0.5)	DCE	rt–reflux/120	ND[d]
8	$TiCl_4$ (1.1)/$i$$Pr_2EtN$(1.5)	CH_2Cl_2	−20 to rt/20	66[e]
9	$TiCl_4$ (1.1)/pyridine(1.5)	CH_2Cl_2	−20 to rt/20	59[e]
10	$TiCl_4$ (1.1)/Et_3N(1.5)	CH_2Cl_2	−20 to rt/20	75[e]
11	$TiCl_4$ (0.5)/Et_3N(1.5)	CH_2Cl_2	−20 to rt/20	20[e]

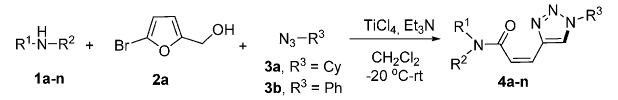
[a] Conditions: 5-bromo-furfurylcarbinol (**2a**; 1.0 mmol), cyclohexyl azide (**3a**; 1.1 mmol), aniline (**1a**; 1.1 mmol), and solvent (5 mL). [b] Isolated yield. [c] NR = no reaction [d] ND = not detected, **2a** was fully consumed but **4a** was not found in the complex mixture. [e] Only the *Z* isomer was observed (as determined by ^{1}H NMR spectroscopy). DCE = 1,2-dichloroethane.

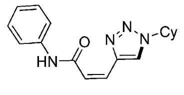
to embark on screening an effective cation-generating reaction conditions (Table 1). Gratifyingly, the optimized conditions were simple, in which stoichiometric $TiCl_4$ in the presence of Et_3N as base at ambient temperature in dichloromethane as solvent were required for the formation of the three-component coupling product **4a** (entry 10). Other bases, such as $i$$Pr_2EtN$ and pyridine, also gave the desired products in similar yields (entries 8 and 9). A low product yield was observed when the reaction was performed with 50 mol% of $TiCl_4$ (entry 11). Of note, only (*Z*)-enamide, which resulted from the furan ring opening, was observed; the (*E*)-isomer was not detected according to the ^{1}H NMR of the crude reaction mixture. We also examined the use of other strong Lewis acids. $AlCl_3$ and $FeCl_3$ (entries 1 and 2) furnished the desired products in 10 and 5% yields, respectively. The relatively weak Lewis acid $ZnCl_2$ gave a trace product in 1,2-dichloroethane at reflux when the reaction time was expanded to 2 h (entry 3). No product was observed with $InCl_3$ condition (entry 4), while the moisture stable rare-earth Lewis acids, such as $Sc(OTf)_3$, $Ir(OTf)_3$, and $Dy(OTf)_3$, were also not suitable for this reaction, and led to a complicated reaction mixture at reflux (entries 5–7).

Using the standard conditions, we explored the scope of the present three-component reaction. First, we focused on the variation of the most readily available component, the amine (Table 2). Various aromatic and aliphatic amines participated in the reaction with **2a** and **3a** to afford the corresponding *Z*-enamidyl triazoles **4a**–**4l** in moderate to high yields. Electron-poor aromatic amines, which are more reactive than aliphatic amines, afforded the desired products **4g**, **4j**, and **4m** in high yields. This could be ascribed to the fact that more basic aliphatic amines may be able to interfere in trapping of the acidic byproducts with Et_3N. A comparison of the yields of primary with secondary amines indicated that the basicity is more important than steric factors; for example, although the steric profile is evidently increased from *n*-butyl, to isobutyl to *tert*-butyl amine, the products showed similar yields (**4b**, **4e**, and **4h**). Meanwhile, cyclic and more basic amines, such as azetidine, pyrrolidine and morpholine, generated the corresponding products in relatively low yields (**4i**, **4k**, and **4l**). The yield of compound **4c** also supports this trend. The terminal alkyne substrate was well tolerated (**4f**). The structure of **4m** was determined by single-crystal X-ray diffraction analysis.[16] The *cis*-stereospecificity of double bonds for the other products was assigned by analogy to **4m** and also with ^{1}H NMR spectroscopy.

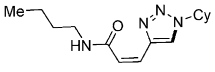
We next examined various azides using **2a** and phenyl amine (**1a**) or *n*-butyl amine (**1b**) as the reaction partners (Table 3). Aromatic azides smoothly participated in the three-component coupling reaction to afford the corresponding products **4n** and **4q** in moderate yields. The *n*-butyl azide underwent [3+2] cycloaddition with **2a**, followed by amidation

Table 2. Reaction scope of amines.[a]

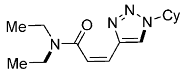




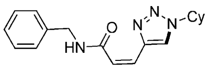
4a: 75%



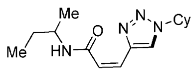
4b: 63%



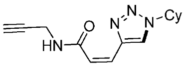
4c: 56%



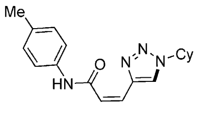
4d: 71%



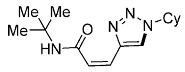
4e: 69%



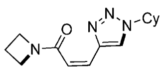
4f: 67%



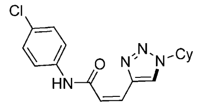
4g: 86%



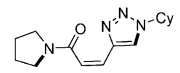
4h: 74%



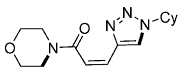
4i: 53%



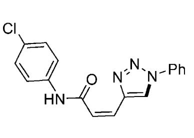
4j: 77%



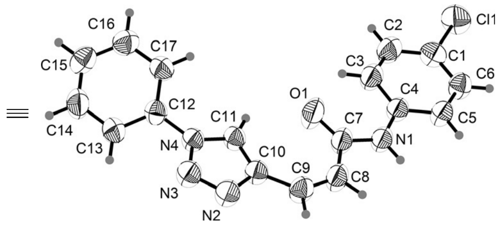
4k: 61%



4l: 59%

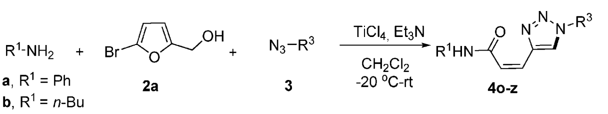


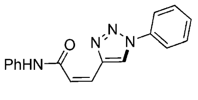
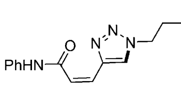
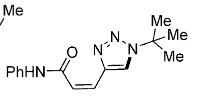
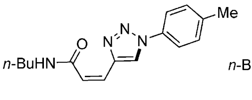
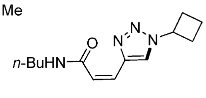
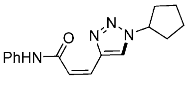
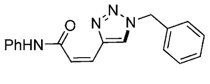
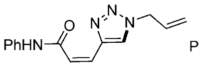
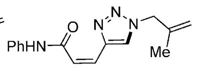
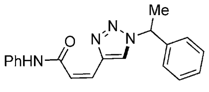
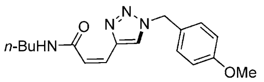
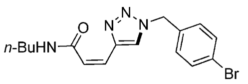
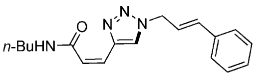
4m: 65%[b]



[a] Conditions: **2a** (1.0 mmol), **3a** (1.1 mmol), amine **1** (1.1 mmol), $TiCl_4$ (1.1 mmol), Et_3N(1.5 mmol), and CH_2Cl_2 (5 mL) at −20 °C to rt; yields given are average isolated yields of at least two runs; in all cases only *Z* isomer was determined by ^{1}H NMR spectroscopy. [b] **3b** was used instead of **3a**. Cy = cyclohexyl.

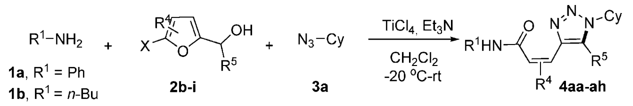
Table 3. Reaction scope of azides.[a]

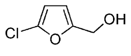
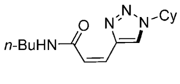
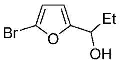
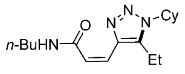
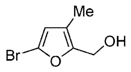
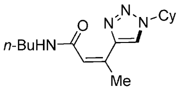
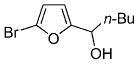
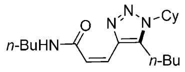
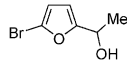
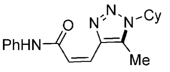
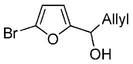
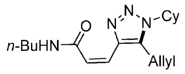


 **4n**: 58%	 **4o**: 76%	 **4p**: 59%
 **4q**: 64%[b]	 **4r**: 65%[b]	 **4s**: 70%
 **4t**: 62%	 **4u**: 72%	 **4v**: 67%
 **4w**: 58%	 **4x**: 52%[b]	
 **4y**: 55%[b]	 **4z**: 37%[b]	

[a] Conditions: **2a** (1.0 mmol), **3a** (1.1 mmol), **1** (1.1 mmol), TiCl$_4$ (1.1 mmol), Et$_3$N(1.5 mmol), and CH$_2$Cl$_2$ (5 mL) at $-20\,^{\circ}$C to rt; yields given are average isolated yields of at least two runs; in all cases only *Z* isomer was determined by ^{1}H NMR spectroscopy. [b] **1b** was used instead of **1a**.

Table 4. Reaction scope of furfuryl alcohols.[a]



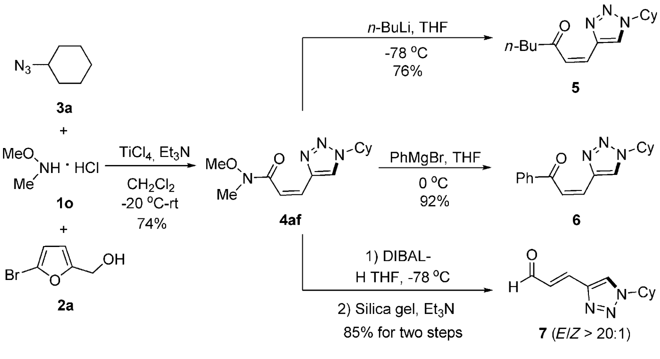
Substrate	Product[b]:Yield[c]	Substrate	Product[b]:Yield[c]
 **2b**	 **4c**: 55%	 **2e**	 **4ac**: 73%
 **2c**	 **4aa**: 69%	 **2f**	 **4ad**: 70%
 **2d**	 **4ab**: 77%[d]	 **2g**	 **4ae**: 51%

[a] Conditions: **2** (1.0 mmol), **3a** (1.1 mmol), **1** (1.1 mmol), TiCl$_4$ (1.1 mmol), Et$_3$N(1.5 mmol), and CH$_2$Cl$_2$ (5 mL) at $-20\,^{\circ}$C to rt. [b] In all cases only *Z* isomer was determined by ^{1}H NMR spectroscopy. [c] Yields given are average isolated yields of at least two runs. Cy = cyclohexyl. [d] **1b** was used instead of **1a**.

in one pot, leading to **4o** in good yield. Cyclic and benzyl secondary azides also afforded the desired 3-CR products in moderate yields (**4r**, **4s**, and **4w**). A tertiary azide was also reacted with 5-bromo-furfurylcarbinol and the corresponding **4p** was obtained in a moderate yield, although prolonged reaction time was required, presumably due to the more steric bulkiness of the substrate. The aromatic ring of benzyl azides bearing an electron-donating (-OMe) or -withdrawing (-Br) group were all compatible, furnishing the corresponding enamides **4x** and **4y** in 52 and 55% yields, respectively. The double bonds on allylic or cinnamyl substrates, which are usually considered as Lewis acid sensitive groups, had little influence on the reaction outcome (**4u**, **4v**, and **4z**).

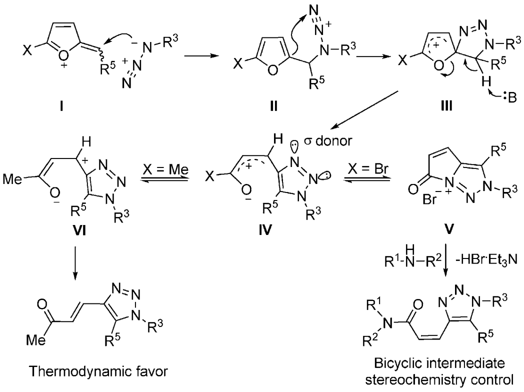
By varying the 5-halo-furylcarbinol component using the readily attained starting materials **2b**–**2g**, six further examples of enamidyl triazole compounds **4c**–**4ae** were synthesized (Table 4). The reaction of substrate **2b**, which had a chlorine group instead of bromine on the 5-position of the furan ring, produced the product **4c** in a lower yield (55%), indicating the more electron-withdrawing Br group, as an amidation evocator, strongly increases the substrate reactivity in this type of 3-CR. 3-Methyl-substituted furan **2c** was found to be effective to generate the corresponding trisubstituted olefin **4aa**. The carbonyl group and triazole were individually located at the *cis* position to the double bond. Secondary alcohols with a side chain, like methyl, ethyl, and *n*-butyl, generated the corresponding products in similar yields compared with primary alcohols (**4ab**, **4ac**, and **4ad**). Homoallylic alcohol **2g** was well tolerated during the reaction, affording **4ae** in 51% yield.

To further demonstrate the synthetic utility of this reaction, the Weinreb amide **4af** was synthesized by the optimal reaction conditions (Scheme 2).[17] It was easily transformed into alkyl or aryl ketones with organolithium or Grignard reagents in high yields. Surprisingly, the aldehyde **7**, which was obtained with DIBAL-H reduction of **4af**, was not quite stable. It could easily change into the *trans* isomer after being passed through an Et$_3$N/SiO$_2$ column. This could be attributed to a reversible Michael reaction, which may favorably react between more reactive α,β-unsaturated aldehyde and a tertiary amine, affording a thermodynamic more stable (*E*)-enealdehyde.



Scheme 2. Subsequent transformations of Weinreb amides.

The mechanism of this 3-CR transformation is proposed in Scheme 3. The regioselective [3+2] cycloaddition between oxocarbenium **I** and the azide could give spiro-dihydrofuran cation **III**, which is configured to aromatize to triazole by β-H elimination in the vicinity of oxygen, followed by ring-opening of the furan to deliver the delocalized zwitterion **IV**. The (*Z*)-stereochemistry is entirely opposite to the recent results we reported with the 5-methyl-furfurylcarbinol as the substrate.[15] This may be ascribed to the strong σ donor property of the nitrogen atom on triazole, which could transform **IV** into the more electrophilic bicyclic intermediate **V** with high (*Z*)-stereochemistry control. Finally, the aminidation of **V** with an amine affords the enamidyl triazole.



Scheme 3. Proposed reaction pathway.

In conclusion, a 3-CR based on a furan platform strategy was accomplished under the Lewis acid promotion consisting of an azide, amine, and 5-halo-2-furylcarbinol. This one-pot protocol is realized by a tandem reaction, which is composed of a formal [3+2] cycloaddition of the azide with a bifunctional furfuryl cation to generate the triazole, ring-opening of a furan, and the subsequent amidation to afford the (*Z*)-enamidyl triazole. Further studies toward synthetic applications of this method are under investigation.

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Keywords: azides · cyclization · cycloaddition · heterocycles · ring opening · synthetic methods

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