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COMMUNICATION

Furfuryl Cation Induced Three-Component Reaction to Synthesize Triazole-Substituted Thioesters

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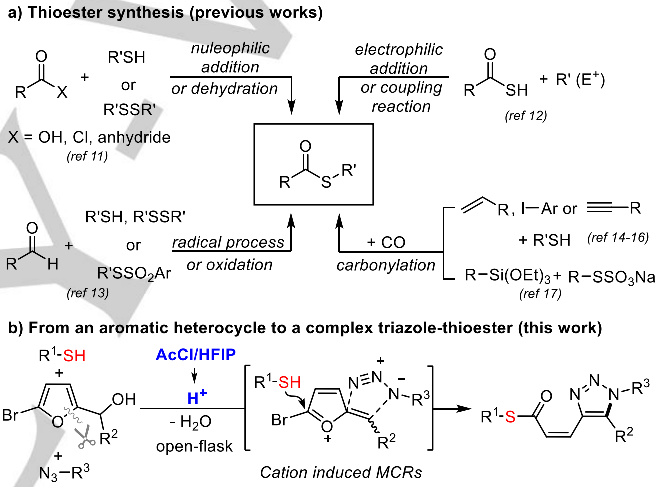
Abstract: A furfuryl cation induced three-component thioesterification reaction between thiols, 5-bromo-2-furylcarbinols and azides is reported. This metal-free method relies on the acetyl chloride/HFIP-mediated cascade formal [3+2] cycloaddition/ring-opening/thioesterification, which allows the efficient construction of a series of complex triazole-thioesters linked with an (*Z*)-olefine. The selenols are also suitable for this strategy. Further derivatization of thioesters highlighted the potential utility of our method.

Because of the weaker orbital overlap relative to esters, [1] thioesters have gained widespread applications as synthetic intermediates for acyl transfer reaction, including native chemical ligation, [2] functional group transformation into an ester, [3] amide, [4] aldehyde [5] or ketone. [5, 6] Also, thioether moieties, including both chain and cyclic forms, are widely found in diverse natural products.[1e] Particular, thioester has been employed as an elegant moiety for asymmetric aldol, [7] Mannich [8] and Michael reactions. [9] In nature, the thioester group plays a pivotal role in metabolism and cellular function regulation. [10]

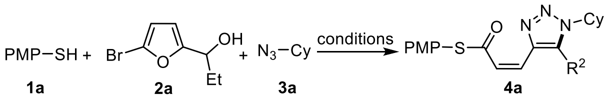
Given the significance of thioesters, some noteworthy methods for synthesizing thioesters have been subsequently developed over the past few decades (Scheme 1a). [1] The traditional methods for thioester formation are the coupling between a thiol or disulfide and an activated carboxylic acid, [11] or the reaction of a thioacid with an electrophile. [12] Several alternative synthetic approaches have been established including the oxidative thioesterification of aldehydes [13] and the thiocarbonylation of alkenes, [14] alkynes [15] or organic halides [16, 4] with CO gas. Jiang and co-workers reported a Pd-catalyzed CO insertion cross-coupling between organosilicon compounds and thiosulfates, that represented an odorless thioesterification method. [17a] An elegant transition-metal-free synthesis of an α-ketothioester via the three-component reaction of an α-hydroxyl ketone, elemental sulfur and a benzyl halide was developed by the same group. [17b] Nonetheless, several limitations have been observed in some approaches including the use of highly reactive oxidants, expensive metal catalysts, long reaction times, harsh reaction conditions, and others. [18] So, the thioesterification reactions under metal-free conditions have attracted the attention of chemists, [19] because they are desired particularly in the pharmaceutical synthesis. Herein, we reported the first thioesterification reaction based on a furan dearomatization strategy, which is carried out via a novel three-component reaction (3-CR) and under mild reaction condition (air tolerant and metal-free). The 3-CR is capable of building up the complex thioesters, featuring a conjugated (*Z*)-α-ene-β-triazole.



Scheme 1. Representative methods for thioester synthesis in comparison with the present work

The methods to form the structurally more diverse thioesters directly from readily available biomass derivatives has high synthetic value. Biomass-derived furan is a highly crucial synthetic tool because of its low aromaticity. [20] It does not only can serve as masked alkenes, enol ethers, [21] 1,4-diketones, [22] and carboxylic acids, [23] but also usually can allow for facile recyclization reactions into different carbo [24-25, 26] and heterocycles. [27] However, to the best of our knowledge, a direct transformation from furans to thioesters has never been achieved in organic synthesis. Recently, we developed a method for the dearomatized [3+2] cycloaddition of furans with organo azides under the Lewis acid conditions, which enables a convenient and high-efficient synthesis of triazoles. [28] The corresponding three-component reactions (3-CRs) have also been explored by us to afford β-triazole-acrylamides and -acrylates. [28b, c] With the purpose to further dig this strategy, our effort focused on developing a furan-based thioesterification with thiols and azides, which could be initiated by a furfuryl cation induced cascade reaction (Scheme 1b). In our previous furan recyclizations, the stoichiometric Lewis acids, such as $TiCl_4$ or $SnCl_4$ were applied,

Table 1. Acid screen for three-component reaction



Entry [a]	Condition [equiv]	Temp. [°C] / Time [h] /Atmosphere	Yield [%] [b]
1	$SnCl_4$ (1.1), CH_2Cl_2	-20–rt/1.0/N_2	Trace
2	$TiCl_4$ (1.1), CH_2Cl_2	-20–rt/1.0/N_2	Trace
3	$ZnCl_2$ (1.1), CH_2Cl_2	rt–80/1.0//N_2	0
4	$Dy(OTf)_3$ (1.1), CH_2Cl_2	rt–80/5.0/N_2	0
5	$Sc(OTf)_3$ (1.1), CH_2Cl_2	rt–80/5.0/N_2	0
6	AcCl (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/N_2	72 [c] + trace [d]
7	**AcCl (1.5), CH_2Cl_2/HFIP = 1/5**	**-20/1.5/air**	**71 [c] + trace [d]**
8	*p*TsCl (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	39 [c] + 20 [d]
9	$(COCl)_2$ (0.75), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	22 [c] + 18 [d]
10	CCl_3COCl (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	20 [c]+ 14 [d]
11	AcCl (1.5), CH_2Cl_2/IPA = 1/5	-20/1.5/air	Trace
12	4 M HCl in dioxane (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	15 [c] + 25 [d]
13	2 M HCl in EtOAc (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	10 [c] + 30 [d]
14	TfOH (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	20 [c] + 20 [d]
15	CAS (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	16 [c] + 22 [d]
16	*p*TsOH·H_2O (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	18 [c] + 15 [d]
17	TFA (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	Trace
18	$Ca(NTf_2)_2$ (1.1), Bu_4NPF_6 (1.1), CH_2Cl_2	rt–80/5.0/air	0
19	H instead of Et of **2a**, $TiCl_4$ (1.1), CH_2Cl_2	-20–rt/1.0/N_2	Trace
20	H instead of Et of **2a**, AcCl (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.2/air	48 [c] + trace [d]
21	Cl instead of Br of **2a**, AcCl (1.5), CH_2Cl_2/HFIP = 1/5	-20/1.5/air	60 [c] + trace [d]

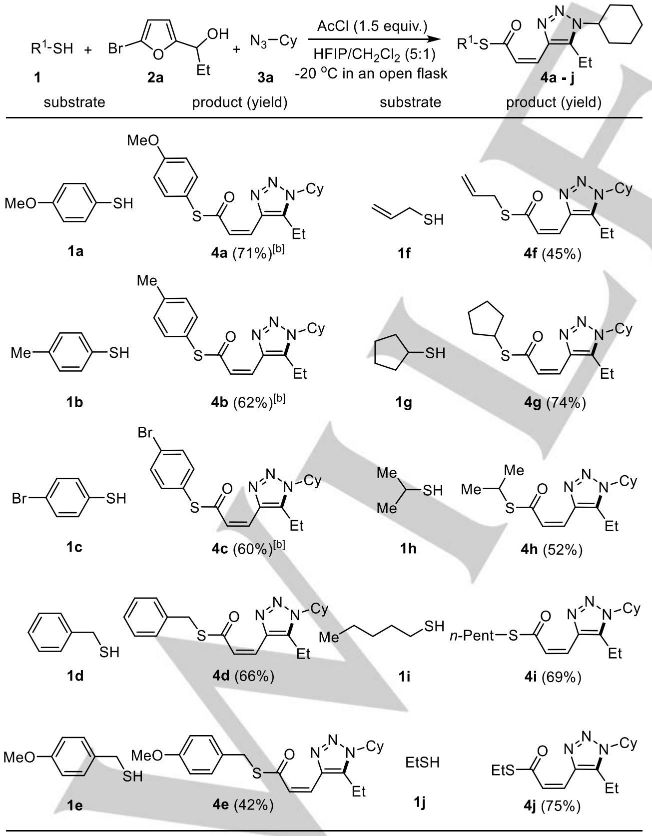
[a] Conditions: 5-bromo-furfurylcarbinol **2a** (0.5 mmol), cyclohexyl azide **3a** (0.7 mmol), *p*-methoxythiophenol **1a** (0.35 mmol), solvent (1.2 mL). [b] Isolated yield. c Only the *Z* isomer of **4a** was observed by ^{1}H NMR. [d] disulfide. Abbreviations: PMP = *p*-methoxyphenyl; Cy = cyclohexyl; HFIP = hexafluoroisopropanol; IPA = isopropyl alcohol; CAS = (±)-camphorsulfonic acid; TFA = trifluoroacetic acid.

which might not be suitable for using thiol due to its strong coordination. Herein, searching a stable and readily available furfuryl cation promoter and avoiding the using of metal reagent would be our major concerned issue in this 3-CR. Moreover, we expect the reaction cannot only be realized under a mild air atmosphere, but also avoiding homocoupling of thiol to disulfide prior to the thioesterification.

As a model reaction for furan thioesterification, we examined the reaction of *p*-methoxythiophenol **1a**, 5-bromo-furfurylcarbinol **2a** and cyclohexyl azide **3a** in the presence of several furfuryl cation promoters (Table 1). The use of strong Lewis acids such as $SnCl_4$ and $TiCl_4$, which were used for previous furan dearomatized triazole synthesis, only gave a trace amount of thioester **4a** along with complex unidentified byproducts (entries 1 and 2). Other Lewis acids that exist relatively weak coordination with thiophenol such as $ZnCl_2$, $Dy(OTf)_3$ and $Sc(OTf)_3$ failed to afford the desired product, even were heated to 80 °C in a sealed tube and the reaction time was expanded to 5h (entries 3−5). The seminal work by the group of Aubé showed that the intramolecular Schmidt reaction of alkyl azides and ketones could be achieved by HCl, that *in situ* formation from the reaction of acyl chloride with hexafluoroisopropanol (HFIP). [29] A buffering effect of HCl/HFIP solutions also is presented, which can lead to lower acidity than the $TiCl_4$ system. Inspired by Aubé's work, we prefer to use AcCl-generated HCl due to AcCl is generally easier to handle and more resistant to hydrolysis in air. Furthermore, the inferiority for the coordination of thiols with Lewis acids could be ruled out if AcCl/HFIP was used, because of 1 equivalent AcCl could only induce the formation of furfuryl cation before the addition of thiols. To our delight, the combination of AcCl/CH_2Cl_2/HFIP was shown to be a sufficiently mild condition to afford the desired thioester product **4a** in high yield (entry 6). Interestingly, the nearly identical yield was obtained when the same condition was set up in an open-flask without N_2 protection. However, a trace disulfide was observed (entry 7). The double bond between thioester and triazole was determined as a *Z*-configuration with ^{1}H NMR. The more reactive acid chlorides, such as *p*TsCl, Cl_3CCOCl and $(COCl)_2$, could afford **4a** in meager yields along with the formation of an amount of disulfide (entries 8−10). Instead of HFIP, isopropanol was used and the reaction hardly proceeded (entry 11). Direct using HCl in dioxane or EtOAc solutions was found to give the worse results with 15% or 10% yields of **4a** (entries 12 and 13). The low product yields were observed in the presence of the other Brønsted acids such as TfOH, CAS and *p*TsOH·H_2O (entries 14−16). A trace of desired product was obtained when using TFA condition (entry 17). Air and moisture-stable $Ca(NTf_2)_2/Bu_4NPF_6$ could not promote the 3-CR reaction (entry 18).[30] Next, we investigated the primary furfuryl alcohol for the reaction using AcCl/HFIP as the initiator, which gave the thioesters in 48% yield (entry 20). Finally, The substrate that contains a chlorine instead of bromine on the 5-position of the furan was also suitable for this conversion and offered the product **4a** in 60% yield (entry 21).

We then investigated the generality of this thioesterification of **2a** with various thiols using cyclohexyl azide **3a** as reaction partner and AcCl/HFIP in an open-flask as the most effective condition. These results are summarized in Table 2. The aryl thiols **1a−c** smoothly reacted with **2a** and **3a** in one pot, giving the corresponding triazole-thioesters **4a−c** in satisfying yields. Electron-rich thiophenol **1a** is more reactive and afforded relatively high yield. However, a trace amount of homocoupling products still can be observed in these reaction systems. Similarly, various aliphatic thiols **1d−j** were investigated for this 3-CR. Benzylic thiols **1d** and **1e** smoothly reacted. The latter is not stable enough under the acidic condition and gave the corresponding product **4e** in 42% yield, which might be caused by the electron-donating effect of -OMe on the phenyl ring. Allylic thiol **1f** is compatible in this cascade reaction. When secondary and primary thiols **1g−i** were employed, the alkyl thioesters **4g−i** were obtained in 52−74% yields. A similar result was obtained when EtSH was used. Significantly, the generation of disulfide for the alkanethiol system was not detected. Because aryl thiols have a lower bond dissociation energy (S−H) than alkanethiols, resulting in the more facile formation of homocoupling products.

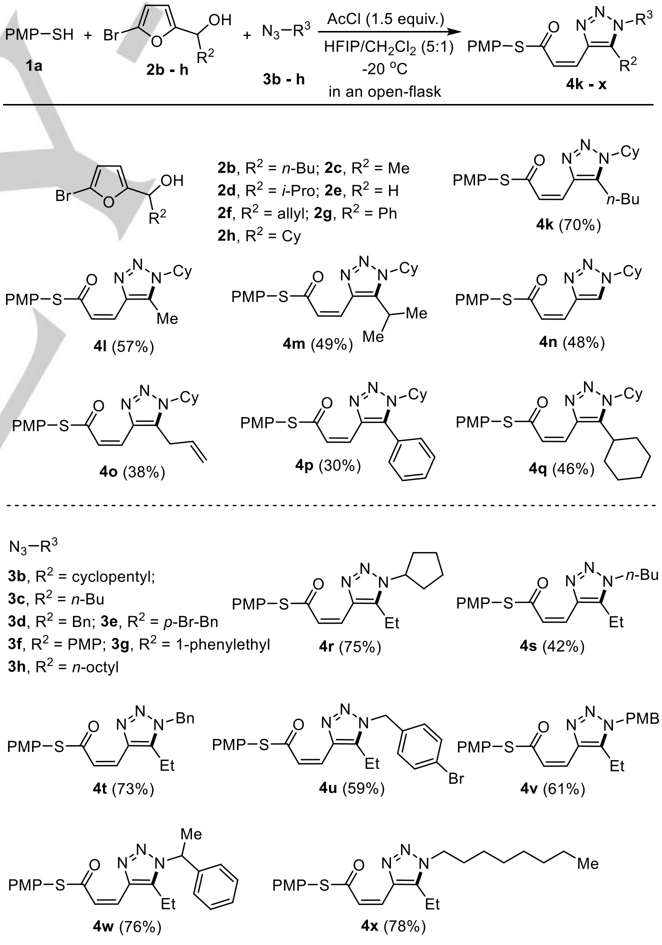
Table 2. Thiol scope of AcCl/HFIP promoted 3-CR [a]



[a] Conditions: 5-bromo-furfurylcarbinol **2a** (0.5 mmol), cyclohexyl azide **3a** (0.7 mmol), thiol **1** (0.35 mmol), AcCl (0.5 mmol), HFIP (1.0 mL) and CH_2Cl_2 (0.2 mL), -20 °C; only the *Z*-isomer was observed by ^1H NMR in each example; isolated purified yield. [b] trace of disulfide was observed.

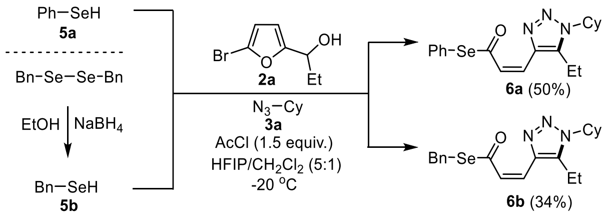
We then used this one-pot protocol to test a range of different 2-furfurylcarbinol **2** and azides **3** under the optimal conditions with *p*-methoxythiophenol **1a** (Table 3). Secondary 5-bromo-furfuryl alcohols with a wide variety of side chains, including *n*-butyl, methyl, isopropyl and allyl are capable of reacting with cyclohexyl azide **2a** to furnish the corresponding triazole **4k−m** and **4o** in moderate yields. Although benzylic adducts usually could generate the more reactive furfuryl cations and gave the satisfying yields in our previous works, the thioesterification of **4p** only afforded a 30% yield. Albeit cyclohexyl substituted substrate **2h** exists more steric hindrance effects when approaching with another cyclohexyl azide **3a**, the reaction still can produce the desired triazole-thioester **4q** in 46% yield. Subjecting alkyl azides **3b** and **3c** to optimized 3-CR conditions generated thioesters **4r** and **4s** in good yield. A series of acidic sensitive benzylic azides was studied, leading to the desired product 4**t−w** in good yield. A more flexible *n*-octyl azide did not interrupt the reactivity and gave a long tail product **4x** in 78% yield.

Table 3. Azide and 5-bromo-2-furfurylcarbinol scopes of 3-CR [a, b]



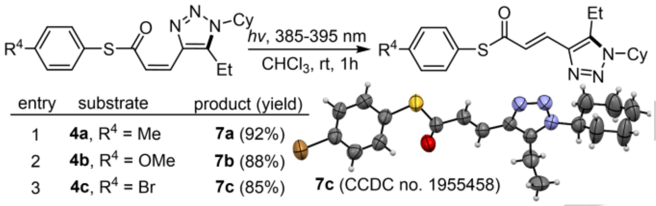
[a] Condition: 5-bromo-furfurylcarbinol **2** (0.5 mmol), azide **3** (0.7 mmol), *p*-methoxythiophenol **1a** (0.35 mmol), AcCl (0.5 mmol), HFIP (1.0 mL) and CH_2Cl_2 (0.2 mL), -20 °C; only the *Z*-isomer was observed by ^1H NMR in each example; isolated purified yield. [b] trace of disulfide was observed.

Selenol ester is also an essential structural motif that can be widely applied as building blocks of heterocycles and precursors of acyl radicals and anions, etc. [1c] To our delight, treatment of 5-bromo-furylcarbinols **2a** and azide **3a** with phenyl and benzylic selenols under the same reaction condition can afford triazole-selenoesters **6a** and **6b** in 50% and 34% yields (Scheme 2). Far as we knew, this also could be the first example for synthesizing a selenoester starting from an aromatic heterocycle.



Scheme 2. Selenol ester synthesis via 3-CR

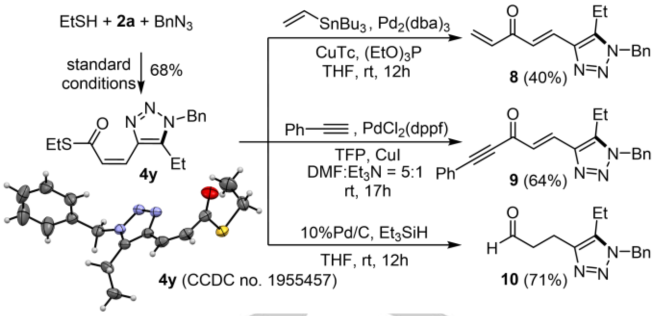
Usually, aryl thioester is an active acyl radical precursor under a UV irradiation. [31] A brief investigation into the olefin-isomerization of α, β-unsaturated thiophenolesters indicated that a UV light source (50W LED, 385−395 nm) could lead a remarkable transformation from *Z* to *E* configuration (Scheme 3). [28c] The latter is thermodynamically more favored. Importantly, the aryl thioester group is undisrupted in this single-step conversion.



entry	substrate	product (yield)
1	**4a**, R^4 = Me	**7a** (92%)
2	**4b**, R^4 = OMe	**7b** (88%)
3	**4c**, R^4 = Br	**7c** (85%)

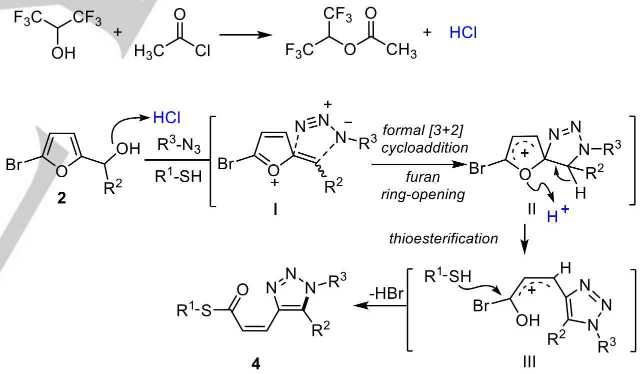
Scheme 3. Photoisomerization of thiol ester

Next, we examined the derivatization of the triazole-thioester, as summarized in Scheme 4. A Stille coupling of **4y** with tri(*n*-butyl)vinylstannane under the Liebeskind conditions afforded dienone **8**. [6f] A Sonogashira type coupling of **4y** with phenylacetylene delivered ynone **9** in 64% yield. [5a] Interestingly, the *cis* double-bonds were converted into *trans* simultaneously by the conditions of overnight at room temperature. Perhaps the highly conjugated system could facilitate the isomerization of olefin. By comparison, the organolithium or Grignard reagents could be utilized to convert *cis*-enamidyl triazoles into *cis*-ketones in our previous studies. [28b] So, these Pd-catalysed transformations could be the complementary derivatization methods for the furan-based triazole synthesis. Reduction of **4y** under the Fukuyama conditions (Et_3SiH, 10% Pd/C) [5a] gave aldehyde **10** in 71% yield, that the double-bond can be hydrogenated as well. These conversions also further proved that oxidation−addition of Pd complexes with thioester is effortless and triazole under Pd(0) conditions is compatible. The structure of **4y** and **7c** were determined by single crystal X-ray diffraction analysis (CCDC no. 1955457 and 1955458). The configuration of olefins for the other products was assigned by analogy to **4y** and **7c**, and also with ^1H NMR.



Scheme 4. Further transformations. Abbreviations: CuTc = copper(I) thiophene-2-carboxylate; TFP = tri(2-furyl)phosphine.

A plausible mechanism is proposed in Scheme 5. Aubé's group has demonstrated the combination of AcCl with HFIP could generate the HCl *in situ.* We also found that direct using HCl in dioxane or EtOAc could achieve this transformation, although the desired product was observed in low yields (Table 1, entries 12 and 13). So, as a superior acidic species, HCl could induce the dehydroxylation of furylcarbinols in our 3-CR. A formal [3+2] cycloaddition occurs between the resulting oxocarbenium **I** and the azides. The aromatization of triazole and the subsequently ring-opening of furan deliver the delocalized enolate cation **III**. The critical step is the trapping of this intermediate by thiols, and stereospecifically yield the desired (*Z*)-β-triazole-thioacrylates. Further studies are underway to help elucidate the mechanism of this cascade transformation.



Scheme 5. Proposed reaction mechanism

In summary, we have developed a mild and efficient thioesterification of 5-bromo-2-furylcarbinols, promoting by a latent Brønsted acid condition of low-cost AcCl in HFIP. This cascade reaction is sturdy with a broad diversity of thiols and azides, that could synthesize a variety of complex thioesters with a triazole moiety and connected by a (*Z*)-olefin. The synthetic versatility of the resulting products due to the unique reactivity of the thioester group are additional benefits of our methodology. Work on further applications and its mechanism studies is currently underway in our laboratory.

Experimental Section

Typical Procedure for Three-Component Reaction.

To a solution of azide **3** (0.7 mmol) in HFIP (1 mL) was added acetyl chloride (0.5 mmol) at -20 °C in an open flask. Thiol **1** (0.35 mmol) and a solution of **2** (0.5 mmol) in DCM (0.2 mL) were subsequently added into the mixture. The resulting solution was stirred for 1.5 hours at -20 °C and then quenched with saturated $NaHCO_3$ (5 mL). The mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. The solution was concentrated by rotary evaporator under reduced pressure gave a residue, which was purified by using flash column chromatography with petroleum ether/ethyl acetate as eluent to afford the product **4.**

Acknowledgements

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Keywords: thioester • furan • dearomatization • triazole • multi-component reactions

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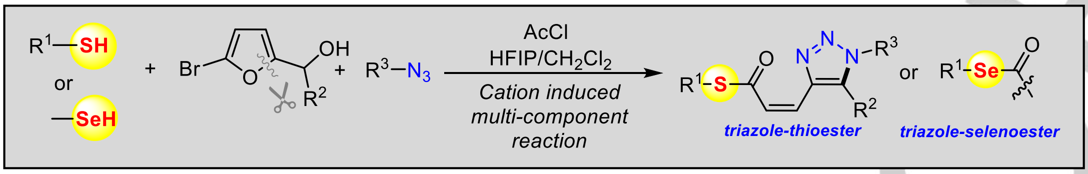
Key Topic: Furan Chemistry

Furfuryl Cation Induced Three-Component Reaction to Synthesize Triazole-Substituted Thioesters



A metal-free three-component thioesterification between thiols, 5-bromo-2-furylcarbinols and azides that provides rapid access to thioesters bearing a triazole moiety, highlighted by the cascade [3+2] cycloaddition/furan ring-opening/thioesterification, is disclosed. The selenols are also suitable for this reaction. The new reaction features simple reaction conditions of AcCl/HFIP and a general substrate scope.