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An efficient synthesis of highly substituted furans via the electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones

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Abstract

The electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones offers an efficient and straightforward route to highly substituted furans under extremely mild reaction conditions. Iodine, NIS, and PhSeBr have proven successful as electrophiles in this process.

Keywords: Electrophilic cyclization; Furans; Cyclopropanes; Iodine

Furans represent an important class of heterocyclic compounds as they are pivotal skeletons in many biologically active natural products as well as numerous pharmacologically interesting compounds.[1] A variety of compounds with furan units have been used as flavor, fragrance substances, insecticides, and antileukemic agents.[2] Moreover, furans also found wide utility as synthetic intermediates or synthons for numerous functional groups such as carboxylic acids, β-keto-esters, and aromatics.[3] As a result, development of new and efficient methodologies for the synthesis of polysubstituted furans from simple, readily available starting materials remains an important research theme in organic chemistry despite many strategies already existed.[4,5]

Cyclopropanes are key intermediates in many synthetic strategies because of their easy availability and high reactivity.[6] One of the useful reactivities of cyclopropanes is ring opening by nucleophiles when the cyclopropane is activated by one or more electron-withdrawing groups to serve as homo-Michael acceptors.[7] Recently, Schmalz reported an interesting Au(I)-catalyzed cyclization of 1-(1-alkynyl)-cyclopropyl ketones with nucleophiles, leading to substituted furans.[8] The employed Au(I) catalyst is suggested to facilitate the reaction by a dual function as both a Lewis acid and coordination reagent with alkynes. As an alternative to transition metal-catalyzed cyclizations of unsaturated frameworks,[9] electrophilic cyclizations have been frequently utilized to construct a wide range of carbocycles and heterocycles.[10] Noteworthy in these protocols is that the installation of electrophilic groups could facilitate further elaboration of the obtained products. With these considerations in mind and in our ongoing efforts to explore the chemistry of cyclopropane derivatives,[11] herein we wish to present our preliminary results in the electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones **1** using I^+ or $PhSe^+$ as electrophilic species to afford an efficient synthesis of substituted halofurans and chalcogenyl furans, which would be very useful intermediates for access to other furan derivatives since they could be further elaborated to amplify complexity via a variety of carbon–carbon or carbon–heteroatom bond formation reactions (Scheme 1).[12]

We initially examined the electrophile-induced cyclization of 1-phenylethynyl-bicyclo[4.1.0]heptan-2-one **1a** with 1.5 equiv of methanol, 1.1 equiv of I_2, and 1.1 equiv of $NaHCO_3$ in CH_2Cl_2 at room temperature. The reaction

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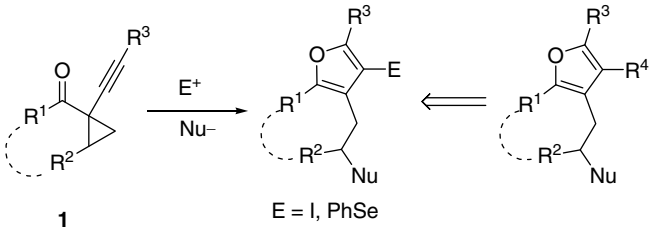

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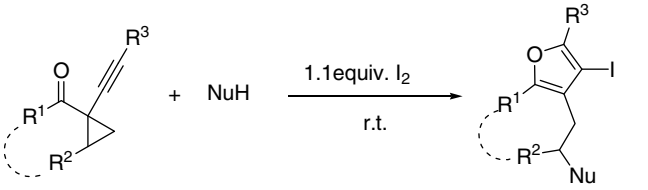
Scheme 1.

proceeded smoothly to give the ring expanded bicyclic cycloheptafuran **2a** in 52% yield along with some **2b** in 20% yield (Table 1, entry 1). It can be inferred that I_2 was served as both an electrophile and a nucleophile in this reaction. Considering the competing reaction between MeOH and I_2, we then tried to use an excess of MeOH to get the desired iodofuran **2a**. Interestingly, when 10.0 equiv of MeOH was utilized and 3.0 equiv of $NaHCO_3$ was employed as a base, the desired product **2a** was isolated in 92% yield, without any of compound **2b** being formed (Table 1, entry 3). NIS as an electrophile was also tested, but gave inferior results (Table 1, entry 7).

With the optimized conditions in hand, we next investigated the annulation reaction of various cyclopropyl ketones **1**.[13] The results are summarized in Table 2. Treatment of **1a** with secondary alcohol *i*-PrOH under the optimized conditions gave the product **2c** in 88% yield (Table 2, entry 3). However, in the case of *tert*-butyl alcohol the reaction could not proceed as expected, indicating that tertiary alcohols are not suitable nucleophiles in this reaction (Table 2, entry 4). Employing NIS as an electrophile, the reaction of propargylic alcohol with **1a** proceeded smoothly to afford product **2e** in 67% yield (Table 2, entry 5). When the reaction was carried out without any MeOH,

Table 2
Iodocyclization of 1-(1-alkynyl)-cyclopropyl ketones[a]



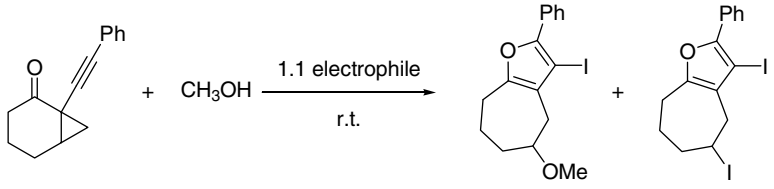
1 2

Entry	R^1/R^2	R^3	NuH	**2**, Yields[b] (%)
1	$-(CH_2)_3-$	C_6H_5	MeOH	**2a**, 92
2	$-(CH_2)_3-$	C_6H_5	I_2	**2b**, 74
3	$-(CH_2)_3-$	C_6H_5	*i*-PrOH	**2c**, 88
4	$-(CH_2)_3-$	C_6H_5	*t*-BuOH	**2d**, 0
5	$-(CH_2)_3-$	C_6H_5		**2e**, 67[c]
6	$-(CH_2)_3-$	C_4H_9	MeOH	**2f**, 78
7	C_6H_5/H	C_6H_5	I_2	**2g**, 86
8	$4\text{-}CH_3OC_6H_4/H$	C_6H_5	I_2	**2h**, 90
9	$n\text{-}C_3H_7/H$	C_6H_5	I_2	**2i**, 81
10	$2\text{-}CH_3OC_6H_4/H$	C_6H_5	I_2	**2j**, 85

[a] Unless noted, all of the reaction was carried out using I_2 (1.1 equiv), nucleophile (10 equiv) and $NaHCO_3$ (3 equiv) at room temperature for 2 h.
[b] Isolated yields.
[c] NIS was used.

compound **2b** was isolated in 74% yield (Table 2, entry 2). The methodology worked well with substrates bearing an alkyl substituent at the end of alkyne moiety to produce the cyclization products (Table 2, entry 6). For the monocyclic 1-(1-alkynyl)-cyclopropyl ketones, unfortunately, alcohols could not serve as nucleophiles in these reactions and the products, which are obviously formed by nucleophilic attack of iodide were obtained in good yields (Table 2, entries 7–10).

Table 1
Electrophile-induced cyclization of 1[a]

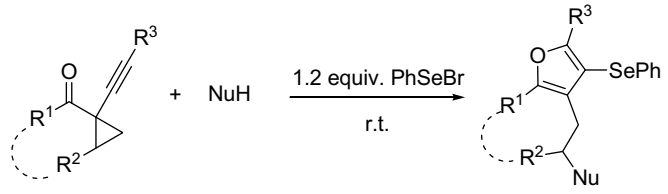


1a 2a 2b

Entry	Electrophile	Nucleophile	Solvent	Yield of **2a**[b] (%)
1	I_2	1.5 CH_3OH	CH_2Cl_2	52
2	I_2	3.0 CH_3OH	CH_2Cl_2	73
3	I_2	10.0 CH_3OH	CH_2Cl_2	92
4	I_2	CH_3OH	CH_3OH	85
5	I_2	10.0 CH_3OH	CH_2Cl_2	83[c]
6	I_2	10.0 CH_3OH	CH_3CN	67
7	NIS	10.0 CH_3OH	CH_2Cl_2	71

[a] Reaction conditions: a solution of 0.5 mmol of **1a**, 1.1 equiv of electrophile, the nucleophile indicated and 3.0 equiv of $NaHCO_3$ in 5 mL of solvent was stirred at room temperature for 2 h.
[b] Isolated yield.
[c] 3.0 equiv of Na_2CO_3 was used.

Table 3
Reaction of 1-(1-alkynyl)-cyclopropyl ketones with PhSeBr[a]

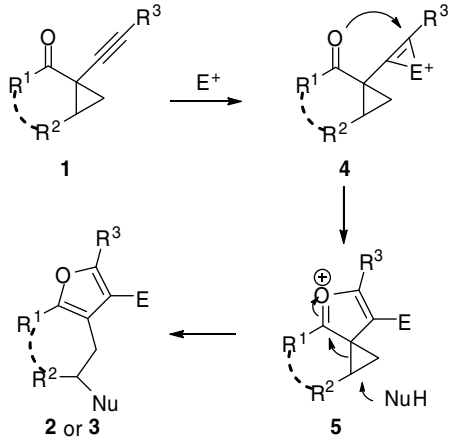


Entry	R^1/R^2	R^3	NuH	**3**, Yields[b] (%)
1[c]	$-(CH_2)_3-$	C_6H_5	MeOH	**3a**, 41
2	$-(CH_2)_3-$	C_6H_5	Br	**3b**, 78
3	$-(CH_2)_3-$	C_4H_9	Br	**3c**, 75
4	C_6H_5/H	C_6H_5	Br	**3d**, 67
5	4-$CH_3OC_6H_4$/H	C_6H_5	Br	**3e**, 82
6	*n*-C_3H_7/H	C_6H_5	Br	**3f**, 70
7	2-$CH_3OC_6H_4$/H	C_6H_5	Br	**3g**, 81

[a] Unless noted, all of the reaction was carried out using PhSeBr (1.2 equiv) at room temperature for 1 h.
[b] Isolated yields.
[c] 10.0 equiv of MeOH was used.

Moreover, we also examined a similar electrophilic cyclization reaction of cyclopropyl ketones **1** with PhSeBr.[14] The results are summarized in Table 3. Treatment of **1a** with 10.0 equiv of methanol, 1.2 equiv of PhSeBr, and 3.0 equiv of $NaHCO_3$ in CH_2Cl_2 at room temperature gave the desired tetrasubstituted furan **3a** in 41% yield along with some **3b** in 35% yield (Table 3, entry 1). When the reaction was carried out without any bases, the product **3b** was isolated in 78% yield without any of tetrasubstituted furan **3a** being formed (Table 3, entry 2). For other cyclopropyl ketones, the reaction with bromine anion serving as a nucleophile proceeded efficiently to give the cyclization products in good yields (Table 3, entries 3–7).

On the basis of the results obtained above, a plausible reaction mechanism is depicted in Scheme 2. The addition of I^+ or $PhSe^+$ to the triple bond of **1** would form the bridged intermediate cation **4**. The anti attack of the oxygen onto the cation **4** led to the formation of intermediate **5**, which could be attacked by the nucleophile in a regioselective homo-Michael-type addition to afford furan derivative **2** or **3**.



Scheme 2.

In summary, we have demonstrated that electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones affords highly substituted furans in good to excellent yields under mild conditions. The iodo or phenylselenenyl derivatives are potential synthetic intermediates. Further investigation on the scope and limitations of this electrophilic cyclization is underway.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.081.

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13. *Typical procedure for the synthesis of* **2**: To a solution of 1-(1-alkynyl)-cyclopropyl ketones **1** (0.5 mmol) in 5 mL of CH_2Cl_2 was added MeOH (5 mmol), $NaHCO_3$ (1.5 mmol), and I_2 (0.55 mmol). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with ether, washed with saturated $Na_2S_2O_3$ and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel. Compound **2a**. IR (neat): 2928, 1094, 951, 763 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.96–7.99 (m, 2H), 7.39–7.43 (m, 2H), 7.29–7.33 (m, 1H), 3.42 (s, 3H), 3.33–3.37 (m, 1H), 2.78–2.90 (m, 3H), 2.55–2.60 (m, 1H), 2.15–2.17 (m, 1H), 1.97–1.99 (m, 1H), 1.78–1.82 (m, 1H), 1.61–1.65 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 152.5, 148.5, 130.4, 128.1, 127.5, 125.8, 119.5, 78.7, 70.5, 56.1, 35.3, 31.7, 28.1, 22.1. MS (70 eV): m/z (%) = 368 (100) [M^+]. Anal. Calcd for $C_{16}H_{17}IO_2$: C, 52.19; H, 4.65. Found: C, 52.37; H, 4.79.
14. *Typical procedure for the synthesis of* **3**: To a solution of 1-(1-alkynyl)-cyclopropyl ketones **1** (0.5 mmol) in 5 mL of CH_2Cl_2 was added PhSeBr (0.6 mmol). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel. Compound **3b**. IR (neat): 2928, 1601, 1439, 735, 688 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 7.97–7.99 (m, 2H), 7.14–7.38 (m, 8H), 4.21–4.26 (m, 1H), 3.24–3.25 (m, 1H), 2.86–3.00 (m, 3H), 2.49–2.52 (m, 1H), 2.21–2.25 (m, 1H), 2.01–2.06 (m, 1H), 1.71–1.74 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): 153.4, 152.9, 132.3, 130.5, 129.3, 128.7, 128.3, 127.9, 126.2, 126.0, 122.2, 106.0, 52.2, 41.7, 35.5, 28.2, 25.2. MS (70 eV): m/z (%) = 446 (100) [M^+]. Anal. Calcd for $C_{21}H_{19}BrOSe$: C, 56.52; H, 4.29. Found: C, 56.22; H, 4.40.