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Bi(OTf)$_3$-Mediated Cycloisomerization of γ-Alkynyl Arylketones: Application to the Synthesis of Substituted Furans

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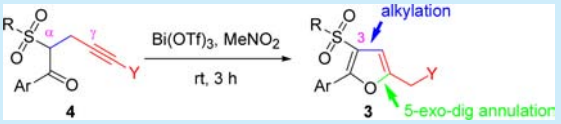
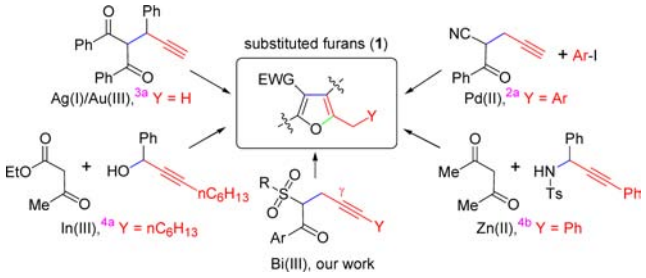
Supporting Information

ABSTRACT: A novel Bi(OTf)$_3$-mediated cycloisomerization of γ-alkynyl arylketones **4**, **7**, or **10** with molecular sieve (MS) in $MeNO_2$ affords 3-substituted furans **3**, **8**, or **11** at rt for 3 h in moderate to good yields. The method provides mild, less-toxic, atom-economic and efficient conditions. The mechanism has been studied and proposed. Moreover, this route can be enlarged to gram scale.



Functionalized furan is a versatile synthetic building block in numerous biologically active molecules, pharmaceuticals, and natural products.[1] Development of new routes to substituted furans (**1**) from readily available starting materials still represents a continuing need in the organic synthetic field. Among these protocols, transition metals (Pd^{2+}, Ag^{+}/Au^{3+}, In^{3+}, or Zn^{2+}) promoting cycloisomerization of diversified γ-alkynones (or in situ generated from coupling of alkynes and 1,3-dicarbonyl synthons) is a major pathway (see Scheme 1).[2−4] Routes to base

Scheme 1. Metal-Mediated Syntheses of Substituted Furans (1)



(DBU or NaH) mediated cyclization of γ-alkynones have been documented.[5] However, the preparation of furan derivatives often presents drawbacks (e.g., multistep operations and harsh conditions), and this has encouraged organic researchers to explore more efficient synthetic protocols. To the best of our knowledge, for the synthesis of furans, no literature on Bi(III)-mediated annulation of γ-alkynones has been reported. Bi(III) compounds with nontoxic and environmentally friendly properties has been documented for a wide variety of organic reactions.[6,7] Bi(III)-promoted reactions of γ-alkenyl,[7a,b] γ-allenyl,[7c] or γ-alkynyl[7d] carbonyl synthons provide diversified skeletons.

In continuation of our investigation of the application of α-sulfonyl ketones **2**,[8] an easy and atom-economic Bi(OTf)$_3$-mediated intramolecular 5-*exo*-*dig* cycloisomerization of α-sulfonyl-γ-alkynyl arylketones **4** (derived from alkylation of **2** with propargylic bromides) is employed to construct the structure of 3-sufonyl furans **3**, as shown in Scheme 2. A number of articles have highlighted fascinating developments based on

Scheme 2. Synthetic Route to 3-Sulfonyl Furans 3

the skeleton of α-sulfonyl ketones (β-ketosulfones)[9] and γ-alkynones are important intermediates in organic transformations, which can be easily constructed to the other functionalized frameworks such as dihydropyrroles or dihydrofurans.[10] Sulfonyl furans exhibit some potent biological activities, such as an endothelial lipase inhibitor or EP1 receptor antagonist.[11]

After further comparison of literature on the metal-catalyzed benzannulation of γ-alkynones, we chose model substrate **4a** (R = Tol, Ar = Ph, Y = H) to initiate our studies with the screening of metal triflate-mediated reaction conditions. Alkylation of **2a** with propargyl bromide afforded **4a** in a 90% yield in boiling acetone for 8 h. Initially, the use of various metal triflates as catalysts was investigated for the formation of the 3-sulfonyl furan **3a**. Catalytic amounts of AgOTf, Mg(OTf)$_2$, Cu(OTf)$_2$, Ni(OTf)$_2$, Sn(OTf)$_2$, Zn(OTf)$_2$, Hg(OTf)$_2$, Yb(OTf)$_3$, Sm(OTf)$_3$, Ga(OTf)$_3$, In(OTf)$_3$, La(OTf)$_3$, Sc(OTf)$_3$, Fe(OTf)$_3$, and Bi(OTf)$_3$ provided different results in $MeNO_2$ at 25 °C for 3 h. Among the catalysts screened, AgOTf, Hg(OTf)$_2$, or In(OTf)$_3$ provided **5a** as the sole product in 81%, 86%, or 88% yields, respectively (see Table 1, entries 1−3).[4a−d] Bi(OTf)$_3$ produced the desired product **3a** in an 80% yield along with a 10% yield of **5a** (entry 4). Under these conditions, the recovery of the starting material **4a** was only observed for the other 11 metal triflates. Furthermore, the use of other Bi(III) salts was examined for synthesizing **3a** and treatment of **4a** with $BiCl_3$, $BiBr_3$, Bi(OAc)$_3$, or $Bi_2(SO_4)_3$ produced **5a** in good yields (70%, 75%, 68%, and 66%) at 25 °C for 3 h with no isolation of **3a** (entries 5−8). In

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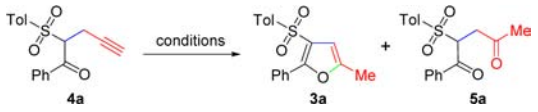
Table 1. Conditions for the Construction of 3a[a]



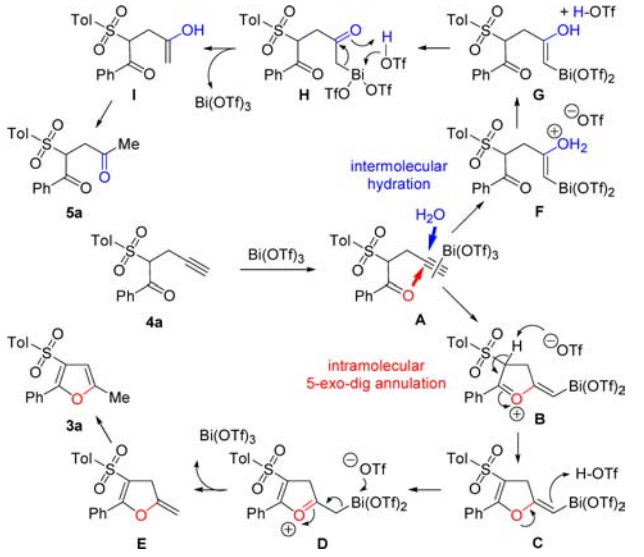
entry	catalyst (mol %), solvent (mL), temp (°C)	yield (%)[b] 3a	5a
1	AgOTf (2), $MeNO_2$ (5), 25		81
2	$Hg(OTf)_2$ (2), $MeNO_2$ (5), 25		86
3	$In(OTf)_3$ (2), $MeNO_2$ (5), 25		88
4	$Bi(OTf)_3$ (2), $MeNO_2$ (5), 25	80	10
5	$BiCl_3$ (2), $MeNO_2$ (5), 25		70
6	$BiBr_3$ (2), $MeNO_2$ (5), 25		75
7	$Bi(OAc)_3$ (2), $MeNO_2$ (5), 25		68
8	$Bi_2(SO_4)_3$ (2), $MeNO_2$ (5), 25		66
9	$Bi(OTf)_3$ (5), $MeNO_2$ (5), 25	76	8
10	$Bi(OTf)_3$ (2), $MeNO_2$ (10), 25	72	10
11	$Bi(OTf)_3$ (2), $MeNO_2$ (5), 100	70	12
12	$Bi(OTf)_3$ (2), MeCN (5), 25	8	80
13	$Bi(OTf)_3$ (2), $(CH_2Cl)_2$ (5), 25		15[c] (86)[d]
14	$Bi(OTf)_3$ (2), benzene (5), 25	60	27
15	$Bi(OTf)_3$ (2), 1,4-dioxane (5), 25		26[c] (85)[d]
16	$Bi(OTf)_3$ (2), $MeNO_2$ (5, dry),[e] 25	86	
17	$Bi(OTf)_3$ (2), $MeNO_2$ (5, wet);[f] 25	42	39

[a]Reaction was run on a 1.0 mmol scale with **4a**, 3 h. [b]Isolated yield. [c]72% (for entry 13) or 60% (for entry 15) of **4a** was recovered. [d]60 h (for entry 13); 45 h (for entry 15). [e]4 Å MS (100 mg) was added. [f]H_2O (0.1 mL) was added.

comparison with this Bi(III) complex, $Bi(OTf)_3$ is an optimal catalyst for the generation of **3a**. Controlling the $Bi(OTf)_3$ as the catalyst, the factors of equivalence, concentration, and temperature were studied next. When using 5 mol % of $Bi(OTf)_3$, the isolated yield was similar to 2 mol % (entry 9). No obvious changes occurred when decreasing the reaction concentration (5 → 10) or elevating the temperature (25 → 100) as shown in entries 10−11, respectively. After changing the solvents (from $MeNO_2$ to MeCN, dichloroethane, benzene, or 1,4-dioxane), different results were observed (entries 12−15). Entry 16 showed that removal of water decreased the yield of **3a** in the presence of molecular sieves (MS). On the contrary, the involvement of water increased the ratio of **4a** and **3a** (entry 17). The results show that the introduction of water caused competition between intermolecular hydration (for the methyl ketone skeleton) and intramolecular 5-*exo*-*dig* addition (for furan skeleton) during the $Bi(OTf)_3$-mediated process. Overall, we believed that the $Bi(OTf)_3/MeNO_2$/MS system should be an optimal combination for generating **3a**.

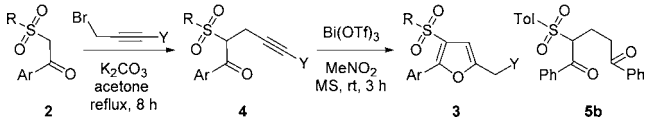
On the basis of the results, a possible reaction mechanism is shown in Scheme 3. How are **3a** and **5a** produced? The mechanism should be initiated to form **A** by complexation of an alkynyl motif of **4a** with $Bi(OTf)_3$, and participation of a carbonyl group could lead to the oxonium cation **B** via intramolecular 5-*exo*-*dig* annulation. Deprotonation of **B** should give vinyl bismuth intermediate **C**. Then, protonation by in situ generated HOTf achieves to alternative oxonium cation **D**, which following debismuthation is able to provide **E** and recover $Bi(OTf)_3$. Isomerization from **E** forms **3a**. However, **F** should be proposed via the involvement of **A** with water. After deprotonation of **F**, tautomerization of **G**, and then HOTf-promoted debismuthation of *β*-ketobismuth intermediate **H**, the removal of $Bi(OTf)_3$ affords **I**. Subsequently, the tautomerization of **H** generates **5a**.

Scheme 3. Possible Mechanism



With optimized conditions in hand (Table 1, entry 16), we further explored the substrate scope of the reaction, and the results are shown in Table 2. For the Ar and R substituents of **3** (Ar = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 4-PhC_6H_4, 2-naphthalene, and 2-furan; R = 4-MeC_6H_4, Ph, Me, 3-MeC_6H_4, 4-*t*BuC_6H_4, 4-$MeOC_6H_4$, and 4-FC_6H_4), the aromatic ring, with both electron-withdrawing and electron-donating

Table 2. Synthesis of 3[a−b]



entry	2, Ar, R; Y	yield (%)[c] 4	3
1	**2a**, Ph, 4-MeC_6H_4; H	**4a**, 90	**3a**, 86
2	**2b**, 4-FC_6H_4, 4-MeC_6H_4; H	**4b**, 92	**3b**, 76
3	**2c**, 4-$MeOC_6H_4$, 4-MeC_6H_4; H	**4c**, 88	**3c**, 75
4	**2d**, 4-MeC_6H_4, 4-MeC_6H_4; H	**4d**, 90	**3d**, 78
5	**2e**, 4-$CF_3C_6H_4$, 4-MeC_6H_4; H	**4e**, 85	**3e**, 80
6	**2f**, 4-PhC_6H_4, 4-MeC_6H_4; H	**4f**, 90	**3f**, 82
7	**2g**, 2-naphthalene, 4-MeC_6H_4; H	**4g**, 86	**3g**, 78
8	**2h**, 4-FC_6H_4, Ph; H	**4h**, 89	**3h**, 73
9	**2i**, 4-$MeOC_6H_4$, Ph; H	**4i**, 90	**3i**, 75
10	**2j**, 4-PhC_6H_4, Ph; H	**4j**, 90	**3j**, 78
11	**2k**, 4-MeC_6H_4, Me; H	**4k**, 86	**3k**, 76
12	**2l**, 4-PhC_6H_4, Me; H	**4l**, 89	**3l**, 80
13	**2m**, Ph, 3-MeC_6H_4; H	**4m**, 86	**3m**, 82
14	**2n**, Ph, 4-*t*BuC_6H_4; H	**4n**, 85	**3n**, 78
15	**2o**, Ph, 4-$MeOC_6H_4$; H	**4o**, 87	**3o**, 75
16	**2p**, Ph, 4-FC_6H_4; H	**4p**, 88	**3p**, 77
17	**2q**, 2-thiophene, 4-MeC_6H_4; H	**4q**, 85	**3q**, 78
18	**2r**, Ph, 4-MeC_6H_4; Me	**4r**, 84	**3r**, 62
19	**2s**, Ph, 4-MeC_6H_4; Et	**4s**, 83	**3s**, 60
20	**2t**, Ph, 4-MeC_6H_4; Ph	**4t**, 80	**3t**[d]

[a]*α*-Alkylation was run on a 1.0 mmol scale with **2**, K_2CO_3 (2.9 mmol), propargylic bromides (1.05 mmol), acetone (10 mL), reflux, 8 h. [b]Cycloisomerization was run on a 1.0 mmol scale with **4**, $Bi(OTf)_3$ (13 mg, 0.02 mmol), $MeNO_2$ (5 mL), rt, 3 h. [c]Isolated yield. [d]Compound **5b** was isolated in 78% yield.

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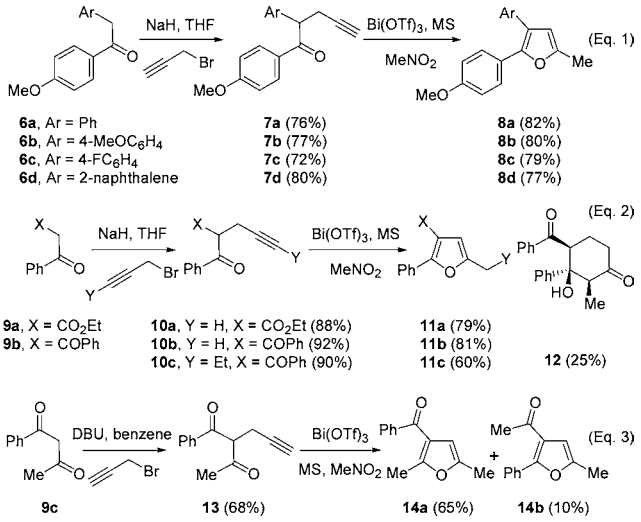
substituents, was well tolerated, providing the desired products **4** and **3** in moderate to good yields. First, by controlling the use of 1.05 equiv of propargylic bromides (Y = H, Me, Et, and Ph), **4a−t** with an α-propargyl group was yielded in good yields (entries 1−20). The cycloisomerization reaction of **4** with the combination of $Bi(OTf)_3/MeNO_2/MS$ was next examined. All entries showed that **3a−t** were isolated in a range of 60%−86% yields when Ar and R were the alkyl or aryl groups. For **3a−q**, the involvement of different substituents did not affect the reaction procedure and the isolated yield was maintained (entries 1−17). When Y was changed to Me and Et groups, the isolated yields of **3r−s** were decreased to 60% and 62%, respectively (entries 18−19). Furthermore, Y was adjusted to the Ph group, **5b** was isolated in a 78% yield, and no desired **3t** was formed (entry 20). The structures of sulfonyl 2-arylfurans **3e−f**, **3h**, and **3k** were determined by single-crystal X-ray crystallography.[12]

Moreover, when 1.56 g of **4a** (5.0 mmol) was treated with the combination, 1.17 g of **3a** was isolated in a 75% yield. This route can be enlarged to gram scale. To examine the limitation of this route (see Scheme 4), the sulfonyl group was first changed to the

Scheme 4. Synthetic Routes to 8, 11, and 14a−b



aryl, ethyl ester, and benzoyl substituents. The intramolecular cyclization of **7a−d** (prepared from α-alkylation of **6a−d** with NaH in THF) with the optimal combination of $Bi(OTf)_3/MeNO_2/MS$ afforded a skeleton of 2,3-diarylfurans **8a−d** (Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-naphthalene) with similar distribution of yields (77−82%) under the above reaction conditions (see eq 1, Scheme 4). The structure of **8b** was determined by single-crystal X-ray crystallography.[12] Furthermore, α-alkylation of **9a−b** provided **10a−c** in good yields (88%−92%) for generating the skeleton of 2-arylfuran with a 3-electronwithdrawing group (see eq 2, Scheme 4). With **10a−c** in hand, $Bi(OTf)_3$-mediated cycloisomerization of γ-alkynones **10a−c** with the α-ester and benzoyl groups in the presence of molecular sieve in $MeNO_2$ at rt for 3 h afforded furans **11a−c** in 60−81%.[13] In particular, **12** was isolated in a 25% yield via an intramolecular aldolization of the resulting benzoyl δ-diketone of **10c**. To investigate the unsymmetrical cycloisomerization of β-diketones (see eq 3, Scheme 4), the $Bi(OTf)_3$-mediated reaction of **13** (generated from α-alkylation of **9c** in 68% yield) was examined next. Under the above conditions, a major isomer **14a** was isolated (65%) along with 10% of **14b** because the stable β-phenyl chalcone intermediate of **13** bearing a full conjugation was generated easily.[14]

In summary, $Bi(OTf)_3$-mediated cycloisomerization of α-substituted γ-alkynyl arylketones is developed for synthesizing a series of 2-arylfurans in good yields. The structures of the key products were confirmed by X-ray crystallography. This atom-economic route can be enlarged to gram scale. Further investigation regarding synthetic applications of α-sulfonyl ketones will be conducted and published in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental data and scanned photocopies of ^1H and ^{13}C NMR spectral data. 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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(12) CCDC 1041267 (**3e**), 1041265 (**3f**), 1041266 (**3h**), 1041529 (**3k**), and 1044470 (**8b**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax, 44−1223−336033; e-mail, deposit@ccdc.cam.ac.uk).

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