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Novel One-pot Synthesis of Polysubstituted Isocoumarins from Arynes and Trifluoroacetylated β-Diketones

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Polysubstituted isocoumarins such as thunberginol A were synthesized by the reaction of substituted 2-(trimethylsilyl)-phenyl triflate with trifluoromethylated β-diketones in the presence of CsF. The reaction proceeded via carbon–carbon bond insertion of aryne followed by intramolecular cyclization and CF_3 anion extrusion. The –C(···O)CF_3 unit has high potential for not only the nucleophilic moiety but also a useful leaving group of CF_3.

Isocoumarins are valuable intermediates for the synthesis of several natural products and important hetero- and carbocyclic molecules, including isocarbostyrils, isoquinolines, and isochromenes.[1] Substituted isocoumarins are attractive synthetic targets because of their biological and pharmacological activities.[2] Recent syntheses of these heterocycles include the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes, vinylic stannanes, or terminal alkynes and the subsequent cyclization of π-allylnickel cross-coupling either unsaturated phthalides or 3-substituted isocoumarins as the major products.[3] However, to our knowledge, there is no report on the synthesis of isocoumarins from aryne precursors. The carbon–carbon insertion reaction of arynes with β-dicarbonyl compounds is one of the best methods for the synthesis of *ortho*-substituted benzenes.[4] Recently, we reported the reaction of β-diketones with benzyne, which afforded the corresponding 4-substituted 2-naphthols in good yields.[5] If trifluoromethyl-substituted β-diketones were used as substrates, corresponding *ortho*-substituted acetophenone intermediate **a** would be formed. Moreover, if the trifluoroacetyl group of intermediate **a** was attacked by an enolate, isocoumarin derivatives would be synthesized in a one-pot operation (Figure 1). We applied this method to the general synthesis of polysubstituted isocoumarins by using trifluoromethylated β-diketones and arynes. Herein, we describe a novel one-pot synthesis of isocoumarins from benzyne precursors and trifluoroacetylated β-diketones.

Starting 4,4,4-trifluoro-1-*p*-tolylbutane-1,3-dione (**2a**) was synthesized by the reaction of ethyl trifluoroacetate with acetophenones in the presence of *tert*-BuOK.[6] Treatment of 2-(trimethylsilyl)phenyl triflate (**1a**) with **2a** in the presence of CsF at rt resulted in the formation of 3-(*p*-tolyl)isocoumarin (**3a**), 1-trifluoromethyl-3-(*p*-tolyl)-1*H*-isochromen-1-ol (**4a**), and 2-(trifluoroacetyl)-2′-(*p*-toluoyl)diphenylmethane (**5**) in 36%, 8%, and 6% yields, respectively (Table 1, Entry 1). The structures of compounds **3a**, **4a**, and **5** were determined by spectroscopic analysis. The ^{19}F NMR spectra of **4a** and **5** showed characteristic peaks at −75 and −77 ppm, respectively. When 1.7 equiv of **1a** was used, compounds **3a**, **4a**, and **5** were isolated in 48, 22, and 20% yields, respectively (Entry 2). As the formation of isocoumarin clearly showed that CF_3 acted as a leaving group,

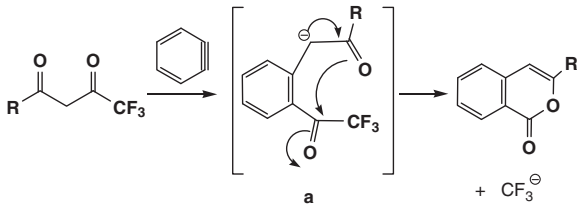
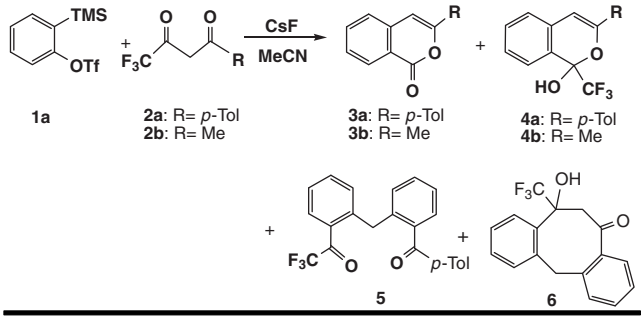


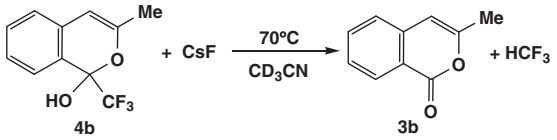
Figure 1.

Table 1. Reaction of 4,4,4-trifluorobutane-1,3-dione **2** with triflate **1a**

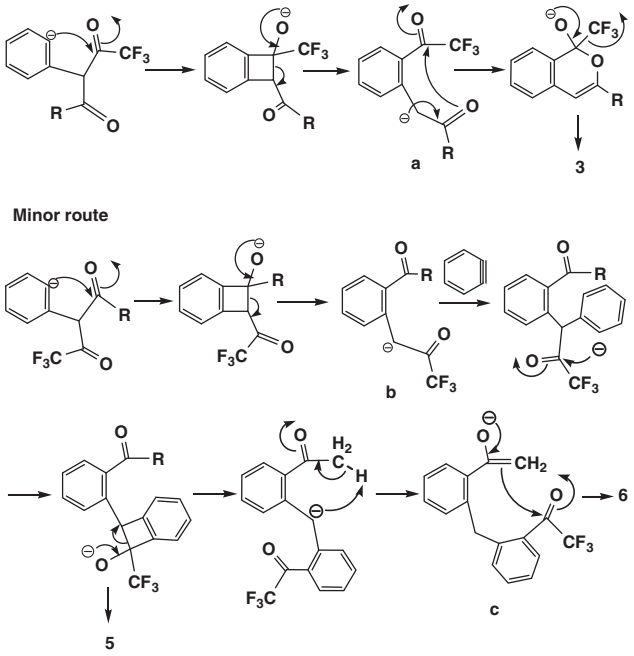


Entry	**1a** /equiv	**2**	Temp.	Products yields/%		
				3a or **3b**	**4a** or **4b**	**5** or **6**
1	1.2	**2a**	rt	36	8	6
2	1.7	**2a**	rt	48	22	20
3	1.1	**2a**	reflux	55	0	9
4	1.7	**2a**	reflux	71	0	12
5	1.7	**2b**	rt	46	22	12
6	1.7	**2b**	reflux	68	0	6

we tried to conduct the reaction under refluxing conditions. Treatment of triflate **1a** (1.7 equiv) with β-diketone **2a** and CsF in refluxing acetonitrile for 6 h resulted in the formation of 3-(*p*-tolyl)isocoumarine (**3a**), and diarylmethane **5** in 71% and 12% yields, respectively (Entry 4). When 1,1,1-trifluoropentane-2,4-dione (**2b**) was used as a starting β-diketone, 7,12-dihydro-7-hydroxy-7-trifluoromethyldibenzo[*a*,*d*]cycloocten-5(6*H*)-one (**6**) was isolated as a by-product in 12% yield (Entry 5).[7] We have already reported the reaction of butane-1,3-dione with triflate **1a** in the presence of CsF, which resulted in the formation of 4-methyl-2-naphthol via intramolecular aldol condensation in 80% yield.[5] Yoshida et al. have reported that the reaction of trifluoromethyl ketones with aryne gave C–C bond insertion products along with [2 + 2] cycloaddition and *O*-arylation products.[8] The result was quite different from ours except for the formation of **5**.



Scheme 1.



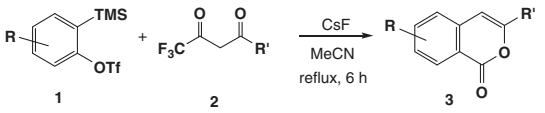
Scheme 2. Reaction mechanism.

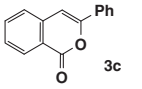
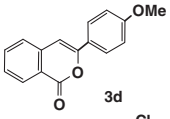
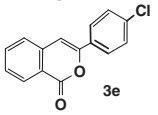
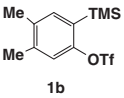
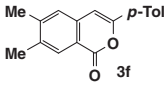
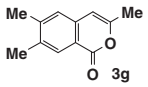
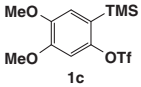
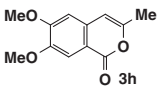
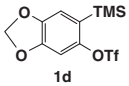
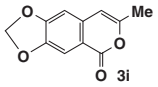
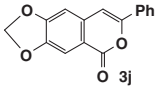
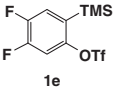
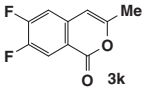
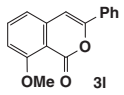
To confirm the leaving ability of trifluoroacetyl group under the reaction conditions, we performed the reaction of hemiacetal **4b** with CsF. Treatment of **4b** with CsF in CD_3CN at 70 °C for 6 h resulted in the complete formation of isocoumarin **3b** and fluoroform (Scheme 1). Without CsF, compound **4b** was recovered unchanged even after 2 days at 70 °C.

Thus, the reaction might proceed as follows: the reaction initially produced C–C insertion product anion **a**, which intramolecularly cyclized to give anion of hemiacetal **4**, and **4** extruded CF_3 anion to afford isocoumarin **3** (Scheme 2). At room temperature, intermediate **4** was also isolated (major route). Another initially formed C–C insertion product anion **b** was further reacted with another benzyne to give **5**. By using **2b** as a substrate, α-hydrogen of methyl ketone was further abstracted to give enolate **c**, which further attacked trifluoroacetyl carbonyl carbon to give **6** (minor route).

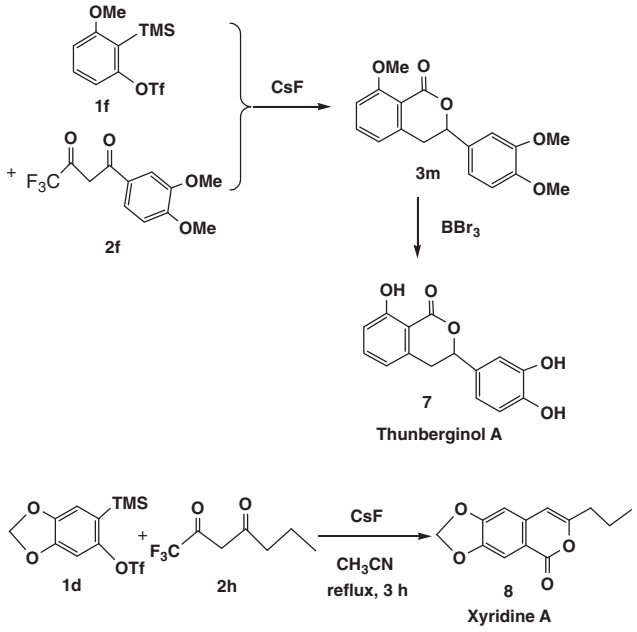
Jablonski et al. reported that the reaction of trifluoroacetophenone with potassium *tert*-butoxide gave trifluoromethyl anion, which further reacted with benzophenones to give trifluoromethylated diaryl alcohols.[9] Trifluoroacetophenones also reacted with alkoxide or hydroxide to give benzoates.[10] Recently, Prakash et al. reported the nucleophilic trifluoromethylation of carbon centers, in which trifluoromethane was used as trifluoromethyl anion source.[11] However, to our knowledge, there is no report on the intramolecular nucleophilic cyclization of trifluoroacetophenone derivatives.

Table 2. Reaction of triflate **1** with trifluoromethylated 1,3-diketones **2**



Entry	1	2	R′		Yield/%
1	 1a	2c	Ph	 3c	70
2	1a	2d	*p*-$MeOC_6H_4$	 3d	68
3	1a	2e	*p*-ClC_6H_4	 3e	50
4	 1b	2a	*p*-Tol	 3f	71
5	1b	2b	Me	 3g	73
6	 1c	2a	Me	 3h	70
7	 1d	2b	Me	 3i	67
8	1d	2c	Ph	 3j	51
9	 1e	2b	Me	 3k	61
10	 1f	2c	Ph	 3l	53

We then applied this method to the synthesis of other polysubstituted isocoumarins. Treatment of benzoylacetone **2c** with triflate **1a** in the presence of CsF in refluxing acetonitrile resulted in the formation of 3-phenylisocoumarin (**3c**) in 70% yield. Other isocoumarins were similarly obtained in moderate to good yields (Table 2). The yields were higher when electron-donating groups (Me and MeO) were substituted at *para*-position of aroylacetone **2** than when electron-withdrawing group (Cl) was substituted (Entries 1–3). Generally, when electron-donating groups, such as Me and MeO, were substituted at aryne precursors, higher yields of isocoumarins were obtained (Entries 4–7). When 4,5-difluoro-2-trimethylsilylphenyl triflate (**1e**) was used as the substrate, 6,7-difluorinated isocoumarin **3k**



Scheme 3. Synthesis of thunberginol A and xyridine A.

was obtained in 61% yield (Entry 9). When 3-methoxy-2-trimethylsilylphenyl triflate (**1f**) was used as the aryne precursor, only one regioisomer of isocoumarin **3l** was formed, while the yield was relatively low (Entry 10).

The present method provides a general synthesis of 3,6,7,8-substituted isocoumarins in a one-pot operation. To highlight the utility of the developed isocoumarin chemistry we embarked on the synthesis of naturally occurring isocoumarins, thunberginol A (**7**)[12] and xyridine A (**8**).[13] The reported biological activity of these compounds (antimicrobial, antiallergic, antidiabetic, and anticancer) has resulted in a number of successful syntheses.[2,14] Treatment of **1f** with **2f** in the presence of CsF at rt resulted in the formation of 3-(3,4-dimethoxyphenyl)-8-methoxyisocoumarin (**3m**) (53%), which was treated with BBr_3 to afford thunberginol A (**7**) (93%). Similarly, reaction of **1d** with 1,1,1-trifluoroheptane-2,4-dione (**2g**) in the presence of CsF gave xyridine A **8** in 69% yield (Scheme 3).

In summary, polysubstituted isocoumarins were synthesized by the reaction of triflate **1** with trifluoromethylated β-diketones **2** in moderate to good yields. The most interesting feature of this reaction include intramolecular cyclization of enolate to trifluoroacetyl moiety. This method provides a versatile synthesis of polysubstituted isocoumarins in a one-pot operation.[15]

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7 Structure of **6** was confirmed by spectroscopic and X-ray crystallographic analysis. Crystallographic data for **6**: triclinic, space group $P\bar{1}$, $a = 8.816(3)$, $b = 11.502(4)$, $c = 14.546(5)$ Å, $\alpha = 107.236(5)$, $\beta = 100.16(3)$, $\gamma = 93.981(4)°$, $Z = 4$, $R_1 = 0.0353$, wR_2 (all data) $= 0.0888$. CCDC 967214 contains the supplementary crystallographic data for compound **6**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.