JOC*Note*

Lewis Acid Catalyzed Propargylation of Arenes with *O*-Propargyl Trichloroacetimidates: Synthesis of 1,3-Diarylpropynes

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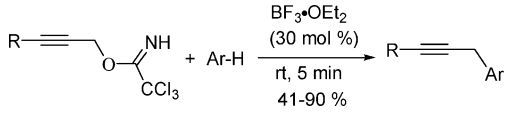

The BF_3·OEt_2-catalyzed Friedel−Crafts propargylation of aromatic compounds with *O*-propargyl trichloroacetimidates is highly efficient and affords 1,3-diarylpropyne derivatives in good yields.

1,3-Diarylpropynes are versatile building blocks in organic synthesis. The methods for access to this type of compounds include reaction of aryl Grignard reagent with propargyl halide and transition metal catalyzed cross-coupling reaction with organometallic reagents.[1,2] The reaction of arenes with dicobalthexacarbonyl-complexd propargyl cation, known as the Nicholas reaction, has been widely applied.[3] However, its drawback of the use of stoichiometric amounts of cobalt complex cannot be neglected. Recently, transition metal catalyzed propargylations of electron-rich arenes with propargyl alcohols have been reported.[2a−c,4] Although these reactions are mechanistically interesting, they have limitations in one way or another as synthetic methodologies. For example, these methods are usually limited to secondary propargyl alcohols and electron-rich aromatic substrates, and the catalysts are expensive and/or not easily available in some cases. Consequently, the development of new methods for synthesizing 1,3-diarylpropynes is still highly desirable.

Friedel−Crafts propargylation of aromatics can afford aromatic compounds bearing propargyl substituents. This type of reaction has been investigated previously with propargyl halides, but the products are either propargylated or allenylated aromatic products or a mixture of them.[5,6] This is attributed to the electronic and structure feature of the propargyl cation intermediate, which has ambident reactivity that is largely dictated by the substitution pattern (Scheme 1).[7] Recently, Ishikawa and Saito reported silyl ether as a leaving group in TMSOTf-catalyzed reactions. It generated propargyl cation, which was further reacted with electron-rich arenes.[6a] Rodríguez and coworkers have utilized *p*-TsOH as a catalyst in the substitution of propargyl alcohol with aromatics.[8] However, these reactions need secondary alcohols and electron-rich arenes as substrates. Here, we report a highly efficient BF_3·OEt_2-catalyzed Friedel−Crafts propargylation of unactivated arenes. This reaction provides a powerful method for the synthesis of 1,3-diarylpropyne derivatives.

The key feature of this approach is the utilization of *O*-propargyl trichloroacetimidates as the propargylation agents. Trichloroacetimidates have been widely used in organic synthesis.[9] In particular, they have been frequently utilized in the acid-catalyzed C−O bond forming reactions because the trichloroacetimidoxy group can be a good leaving group under mild acidic conditions.[10] For example, converting the *O*,*O*-hemiac-

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SCHEME 1. Friedel−Crafts Propargylation of Aromatics

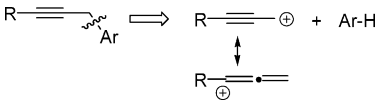
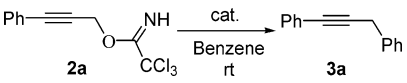


TABLE 1. Reaction of 2a and Benzene with Various Acid Catalysts[a]

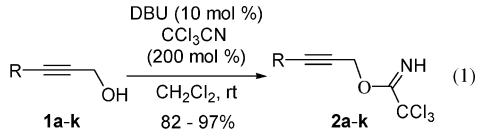


entry	cat. (mol %)	T (°C)	reaction time	yield[b] (%)
1	TMSOTf (10)	25	2 h	74
2	AuCl (5) + AgOTf (5)	80	20 min	35
3	$AuPPh_3Cl$ (5) + $AgSbF_6$ (5)	80	20 min	65
4	BF_3·OEt (30)	25	5 min	85
5	TfOH (10)	25	12 h	NR[c]
6	$TsOH·H_2O$ (10)	25	18 h	NR
7	$Zn(OTf)_2$ (5)	25	12 h	NR
8	$Cu(CH_3CN)_4PF_6$ (5)	25	12 h	NR

[a] Bezene used as solvent. [b] Isolated yield. [c] Starting material remains unchanged.

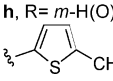
etals into *O*-trichloroacetimidoyl derivatives and their acid-catalyzed activation have been frequently applied in the formation of glycoside bonds. Schmidt and Michel have reported that the arylation reaction of *O*-glycosyl trichloroacetimidates with activated aromatic compounds under mild Lewis acid catalysis gives *C*-aryl glycosides.[10c] The study by Cramer and Hennrich has revealed that the BF_3·OEt_2-catalyzed reaction of *O*-allyl trichloroacetimidates with benzene gives the Friedel−Crafts products in low yields, accompanied by the formation of trichloroacetyl amides.[11] Very recently, Zhang and Schmidt have disclosed their study on the TMSOTf-catalyzed Friedel−Crafts benzylation with *O*-benzyl trichloroacetimidate.[10l] However, to the best of our knowledge, the utilization of *O*-propargyl trichloroacetimidates in Friedel−Crafts propargylation has not been documented in the literature.

O-Propargyl trichloroacetimidates **2a**−**k** can be easily prepared from the corresponding propargyl alcohols in good yields by standard procedure.[9] Compounds **2a**−**k** are stable compounds, which can be kept at room temperature (eq 1).



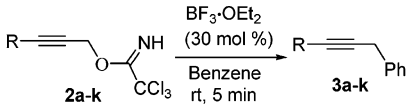
(1)

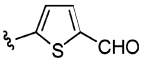
a, R = Ph; **b**, R = *p*-$CH_3C_6H_4$; **c**, R = *o*-$CH_3C_6H_4$;
d, R = *p*-$CH_3OC_6H_4$; **e**, R = *p*-$O_2NC_6H_4$; **f**, R= *p*-BrC_6H_4
g, R = *o*-$CH_3O_2CC_6H_4$; **h**, R= *m*-H(O)CC_6H_4

i, R = 1-naphthyl; **j**, R =  **k**, R = *n*-C_4H_9

With **2a**−**k** in hand, we first used **2a** as the model substrate in acid-catalyzed reaction with benzene. Thus, **2a** was dissolved in benzene, followed by the addition of a catalytic amount of acid. As shown in Table 1, the Friedel−Crafts propargylation product **3a** could be obtained with a variety of Lewis acid catalysts, including TMSOTf, AuOTf, $AuPPh_3Cl/AgSbF_6$, and BF_3·OEt_2 (Table 1, entries 1−4). Among them, BF_3·OEt_2 was found to be particularly effective. With 30 mol % of BF_3·OEt_2, the reaction could be completed in 5 min at room temperature, affording **3a** in 85% isolated yield (entry 4). When less BF_3·OEt_2 was used, the reaction took a longer time and the yield was diminished. Since BF_3·OEt_2 is cheap and easily available, the propargylation under the BF_3·OEt_2-catalyzed conditions is therefore practically useful. It was also noted that acids such as TfOH, TsOH, $Cu(MeCN)_4PF_6$, and $Zn(OTf)_2$ did not catalyze this reaction (entries 5−8).

TABLE 2. Reaction of 2a−k and Benzene with BF_3·OEt_2 as Catalyst[a]



entry	**3a-k** (R =)	yield (%)[b]
1	**3a**, R = Ph	85
2	**3b**, R = *p*-$CH_3C_6H_4$	90
3	**3c**, R = *o*-$CH_3C_6H_4$	80
4	**3d**, R = *p*-$CH_3OC_6H_4$	*trace*
5	**3e**, R = *p*-$O_2NC_6H_4$	86
6	**3f**, R= *p*-BrC_6H_4	87
7	**3g**, R = *o*-$CH_3O_2CC_6H_4$	88
8	**3h**, R= *m*-H(O)CC_6H_4	83
9	**3i**, R = 1-naphthyl	73
10	**3j**, R= 	89
11	**3k**, R = *n*-C_4H_9	82

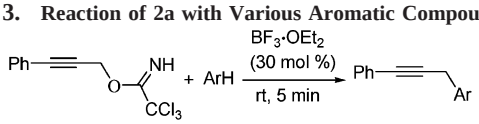
[a] The reaction was carried out in benzene solution. [b] Isolated yield. [c] The reaction gave a complex mixture.

With the optimized conditions in hand, we next examined the scope and limitation of this reaction. First, the scope of *O*-propargyl trichloroacetimidates was examined. As shown in Table 2, the reaction has good substituent tolerance in the alkyne moiety. The substrate with strong electron-withdrawing substituent such as *p*-NO_2 worked well to give the expected propargylation product **3e** in high yield (entry 5). This might be attributed to the destabilization effects of *p*-NO_2, which makes the allenyl cation structure unfavorable as compared with the propargyl cation in the resonance structures (Scheme 1). On the contrary, strong electron-donating substituent such as *p*-MeO worked in the opposite way. The reaction of **2d** under the identical condition gave a complex mixture with only trace amount of **3d** (entry 4). We speculate that in this case strong stabilization effect of *p*-MeO makes allenyl cation more favorable as compared with the corresponding propargylic cation (Scheme 1). This will lead to side reactions. Finally, it is worthwhile to note that substrate with alkyl substituent on alkyne moiety also worked well (entry 11).

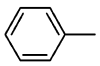
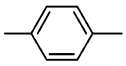
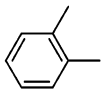
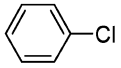
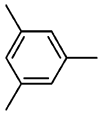
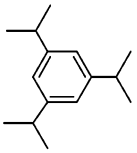
The scope of the aromatic substrates was then examined under the same reaction conditions (Table 3). With monosubstituted or ortho-disusbstituted benzene, the reaction with **2a** gave the expected propargylation products, but as mixture of regioisomers, because of high reactivity of these arenes (entries 1, 3, and 4). The reaction with furan or thiophene also worked well to give the corresponding 2-propagylated furan or thiophene as major products (entries 7 and 8). It should be noted that for the reaction with electron-rich arenes, the aromatic substrates were

(11) Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976−989.

TABLE 3. Reaction of 2a with Various Aromatic Compounds



2a **4a-h** **5a-h**

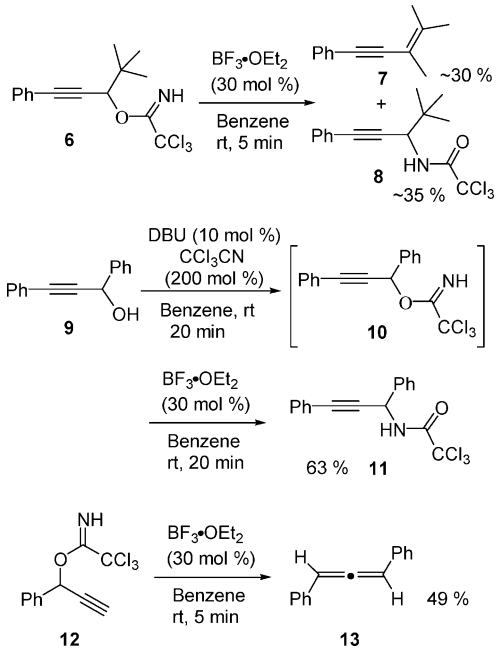
entry	4a-h	equiv	yield (%)[a]	ratio[b]
1	**4a**, 	solvent	85	3 : 3 : 1
2	**4b**, 	solvent	92	--[c]
3	**4c**, 	solvent	84	3 : 2
4	**4d**, 	solvent	79	5 : 1
5	**4e**, 	3[d]	60	--[c]
6	**4f**, 	3	41	--[c]
7	**4g**, 	5	76	--[e]
8	**4h**, 	5	65	--[f]

[a] Isolated yield. [b] The ratio of the regioisomers was determined by ^{1}H NMR and ^{13}C NMR. The regioisomers could not be separated by silica gel column. [c] The reaction gave only one compound. [d] For entries 5−8, CH_2Cl_2 is used as solvent. [e] The product was a 2:1 mixture of 2- and 3-propargylated regioisomers. [f] The product was a 10:1 mixture of 2- and 3-propargylated regioisomers.

used in 3 or 5 equiv amounts (entries 5−8), while in other cases the substrate arenes were the reaction solvent.

Finally, *O*-propargyl trichloroacetimidates derived from secondary propargyl alcohols were examined (Scheme 2). With trichloroacetimidate **6**, the BF_3·OEt_2-catalyzed reaction in benzene gave enyne **7** and amide **8**, together with trace amounts of Friedel−Crafts propargylation product which could not be purified. Enyne **7** was formed through 1,2-methyl shift of the propargyl cation. The reaction of in situ generated **10**, on the other hand, afforded amide **11** in 63% yield. The rearrangement of trichloroacetimidate to the corresponding amide has been previously reported.[11] Finally, BF_3·OEt_2-catalyzed reaction of **12** gave allene **13** in 49% yield with trace amount of unidentified isomer. All of these results, together with the selective propargylations summarized in Tables 1 and 2, can be explained on the grounds of the steric effects of the substituents on the alkyne moiety. Bulky substituents will obviously prevent the approach of aromatic nucleophiles, thus enabling the intermediate carbon

SCHEME 2. Reaction with *O*-Propargyl Trichloroacetimidates Derived from Secondary Propargyl Alcohols



cation to follow other reaction pathways. These results are consistent with the previous investigation which has revealed that the ambident reactivity of propargyl cation is largely dependent on the substitution pattern at the α- and γ-positions.[5,7]

In summary, we have reported a highly efficient Friedel−Crafts method to synthesize 1,3-diarylpropynes in good to excellent yields in the presence of a catalytic amount of BF_3·OEt_2 at room temperature. The reaction conditions are mild, and the catalyst is cheap and easily available. The use of *O*-propargyl trichloroacetimidates derived from primary propargyl alcohols in this reaction is complementary to the transition metal catalyzed propargylations of arenes, which usually work with secondary propargyl alcohols only.[2a−c] This reaction is expected to find application in the preparation of 1,3-diarylpropynes.

Experimental Section

Typical Procedure for the Preparation of Substituted Prop-2-yn-1-yl Trichloroacetimidate. To a solution of 3-phenylprop-2-yn-1-ol **1a** (894 mg, 6.77 mmol) in CH_2Cl_2 was added DBU (103 mg, 0.68 mmol), and the mixture was stirred for 5 min at room temperature. Trichloroacetonitrile (1.96 g, 13.4 mmol) was added with ice cooling, and the resulting mixture was stirred for 10 min at room temperature. Then the solvent was removed under reduced pressure and the resulting crude product was purified by column chromatography (petroleum ether/ethyl acetate 100:1) to give the desired 3-phenylprop-2-yn-1-yl trichloroacetimidate **2a** (1.6 g, 93% yield) as a yellow oil.

3-Phenylprop-2-ynyl trichloroacetimidate (2a): 93%; light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.50−7.46 (m, 2H), 7.35−7.31(m, 3H), 5.15(s, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ 161.9, 131.9, 128.8, 128.2, 122.0, 90.9, 87.1, 82.3, 57.5; IR (neat, cm^{-1}) 3341 (w), 2238 (w), 1667 (s), 1289 (s); HRMS calcd for $C_{11}H_8NOCl_3$ 274.9672, found 274.9676.

Typical Procedure for the BF_3·OEt_2-Catalyzed Friedel−Crafts Reaction. To benzene (3 mL) were added 3-phenylprop-2-yn-1-yl trichloroacetimidates **2a** (107 mg, 0.387 mmol) and BF_3·

OEt_2(15 μL,0.116 mmol). The solution was stirred for 5 min at room temperature, the solvent was removed in vacuo, and the crude product was purified by column chromatography on silica gel with petroleum ether to give 1,3-diphenylprop-1-yne **3a** (63 mg, 85%) as a light yellow oil.

1,3-Diphenylprop-1-yne (3a):[1d] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.24 (m, 10H), 3.83 (s, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ 136.9, 131.7, 128.6, 128.3, 128.1, 127.8, 126.7, 123.9, 87.6, 82.8, 25.7.

1-(3-*p*-Tolylprop-2-ynyl)benzene (3b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.07 (m, 9H), 3.80 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (75 MHz $CDCl_3$) δ 137.7, 136.8, 131.5, 128.9, 128.5, 127.9, 126.5, 120.5, 86.7, 82.7, 25.7, 21.4; IR (neat, cm^{-1}) 3029 (w), 1605 (w), 1509 (m); HRMS calcd for $C_{16}H_{14}$ 206.1096, found 206.1091.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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