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Silver(I)-Catalyzed Novel Cascade Cyclization Reactions: Incorporation of Allenes into the Isochromenes

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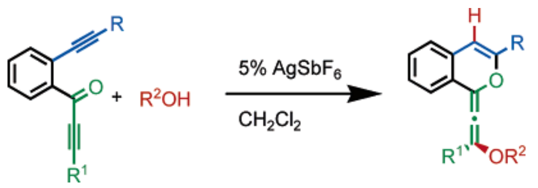
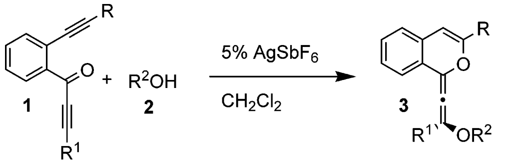


The silver(I)-catalyzed reaction of alkynones with alcohols represents a general tool for the synthesis of 1-allenyl isochromenes. The reaction most probably proceeds via the formation of benzopyrylium cation, which subsequently undergoes nucleophilic attack of an alcohol to give the annulation products.

Allenes are a common structural unit found in many biologically and medicinally important natural and non-natural products, and therefore they have received considerable attention in organic synthesis.[1] Apart from their occurrence in some natural compounds, allenes nowadays are considered as a versatile functional group that acts as an electrophile[2] as well as nucleophile[3] depending on the catalyst and reaction conditions leading to the formation of highly substituted carbon centers. It is thus not surprising that many new synthetic methods have been developed for their syntheses.[4] We envisaged that syntheses of highly substituted heterocycles can be achieved if the method permitting the introduction of allene moiety into heterocycles could be found.[5]

Recently, we reported a new method for the one-pot synthesis of cyclic alkenyl ethers from acetylenic aldehydes by using Pd(OAc)$_2$[6] and CuI[7a] catalysts. With this in mind, we envisioned that a substrate of type **1** would undergo cyclization with alcohols, and if successful this methodology might allow us novel and stereoselective access to a wide range of 1-allenyl chromenes **3**. Thus, we chose **1a** as a model substrate, which was treated under our previously developed reaction conditions.[6,7a] However, none of the reaction conditions gave the desired products; instead, a mixture of unidentified products was obtained. The use of AuCl$_3$ catalyst in CH$_2$Cl$_2$ also did not afford any products.[8] We then opted for other catalyst systems. After detailed investigation on the catalysts and solvents, we found that silver(I) salts[9] in CH$_2$Cl$_2$ gave very good results (eq 1). We report herein a detailed account of our results.



(1)

The results of catalytic activity of various Ag(I) salts are summarized in Table 1. In the absence of any catalysts the reaction does not proceed, and the starting material was recovered (Table 1, entry 1). The reaction of **1a** with 2 equiv of methanol in CH$_2$Cl$_2$ in the presence

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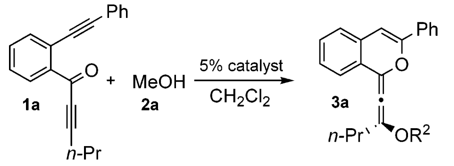
(8) (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164−11165. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679−7685. For homogeneous gold-catalyzed reactions, see also: (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65.

(9) Silver(I) salts acts as a Lewis acid as well as a transition metal catalyst. See: Yao, X.; Li C.-J. *J. Org. Chem.* **2005**, *70*, 5752−5755 and references therein.

10.1021/jo051524q CCC: $30.25

TABLE 1. Effect of Various Ag(I) Salts on Cyclization[a]



entry	catalyst (5%)	yield (%)[b]
1	none	0[c]
2	AgOTf	94
3	$AgSbF_6$	100 (95)[d]
4	$AgClO_4$	48
5	$AgBF_4$	56
6	$AgPF_6$	79
7	Ag_2SO_4	0[c]

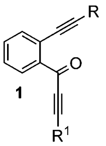
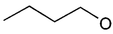
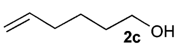
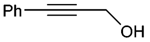
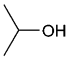
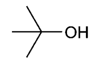
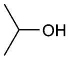
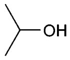
[a] Methanol (2 equiv) was added to a solution of **1** and catalyst (5 mol%) in CH_2Cl_2, and the mixture was heated at 35 °C for 16 h. [b] Yields were determined by ^1H NMR spectroscopy with dibromomethane as an internal standard. [c] Starting material recovered. [d] Isolated yields are shown in parentheses.

of AgOTf (5 mol %) at 35 °C gave the desired product **3a** in 94% yield (entry 2). In the case of $AgSbF_6$, the reaction proceeded well, leading to the formation of **3a** in quantitative yield (entry 3). However, silver(I) salts such as $AgClO_4$, $AgBF_4$, and $AgPF_6$ were not very effective (entries 4−6). The catalyst Ag_2SO_4 does not promote the reaction at all (entry 7).

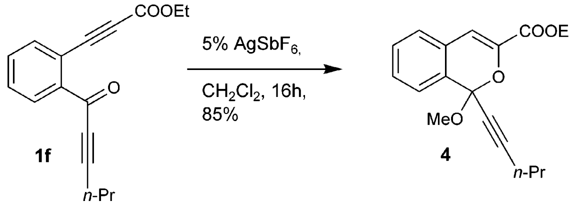
Since the optimal reaction conditions were in hand for the silver-catalyzed annulations, the reaction of **1** with various alcohols **2** was carried out, and the results are summarized in Table 2. The reaction of **1a** with **2b** was conducted with $AgSbF_6$ (5 mol %) in CH_2Cl_2 at 35 °C. The substrate **1a** was consumed in 16 h, and the annulation product **3b** was obtained in 93% isolated yield (Table 2, entry 1). Similarly, the homoallyl alcohol **2c** and 3-phenyl-2-propyn-1-ol **2d** reacted smoothly, with **1a** giving the corresponding annulation products in 95 and 78% yield, respectively (entries 2 and 3). It was possible to use a secondary alcohol, for instance 2-propanol **2e**, for the reaction. Thus, when **1a** was treated with **2e** under the standard conditions, **3e** was obtained in 92% yield (entry 4). However, the reaction of bulky *tert*-butyl alcohol **2f** with **1a** did not lead to the desired product; instead, a complex mixture of unidentified materials was obtained (entry 5). The reaction of α-phenylmethyl alcohol **2g** with **1a** gave the product **3g** with slightly lower yield (entry 6). The steric hindrance around the alcohol functionality seems to diminish the yield of annulation products. When **1b** and **1c** were treated with methanol and 2-propanol under the standard conditions, the corresponding products **3h**−**k** were obtained in high yields (entries 7−10). As shown in entries 11 and 12, the substrates **1d** and **1e** underwent smooth annulation reactions with MeOH to produce **3l** and **3m** in 65 and 93% yield, respectively. It should be noted that terminal alkynes or -TMS substituted alkynes (R = H, TMS) did not give the corresponding desired products under the present reaction conditions.[10] Similar to the previously reported case, no formation of a regioisomeric product due to 5-*exo-dig* cyclization was observed in any of the cases.[7a,11]

Quite astonishingly, the substrate **1f** (R = COOEt) gave **4** upon treatment with 5% $AgSbF_6$ under the standard conditions (eq 2). No formation of the corresponding 1-allenyl chromene was detected by ^1H NMR spectrum of the crude product.

TABLE 2. $AgSbF_6$-Catalyzed Cyclization of Alkynones[a]

entry	substrate(**1**)	R^2OH (**2**)	product (**3**)	yield (%)[b]
	 **1**	R^2OH **2**	 **3**	
1	**1a** R = Ph, R^1 = *n*-Pr	 **2b**	**3b**	93
2	**1a** R = Ph, R^1 = *n*-Pr	 **2c**	**3c**	95
3	**1a** R = Ph, R^1 = *n*-Pr	 **2d**	**3d**	78
4	**1a** R = Ph, R^1 = *n*-Pr	 **2e**	**3e**	92
5	**1a** R = Ph, R^1 = *n*-Pr	 **2f**	**3f**	*[c]
6	**1a** R = Ph, R^1 = *n*-Pr	BnOH **2g**	**3g**	73
7	**1b** R = C_6H_4-*p*-CH_3, R^1 = *n*-Pr	MeOH **2a**	**3h**	80
8	**1b** R = C_6H_4-*p*-CH_3, R^1 = *n*-Pr	 **2e**	**3i**	70
9	**1c** R = C_6H_4-*p*-CF_3, R^1 = *n*-Pr	MeOH **2a**	**3j**	99
10	**1c** R = C_6H_4-*p*-CF_3, R^1 = *n*-Pr	 **2e**	**3k**	94
11	**1d** R = R^1 = *n*-Pr	MeOH **2a**	**3l**	65
12	**1e** R = R^1 = Ph	MeOH **2a**	**3m**	93

[a] The reactions of **1** (0.2 mmol) with alcohol **2** (0.4 mmol) in the presence of $AgSbF_6$ (5 mol %) were carried out at 35 °C in CH_2Cl_2. [b] Isolated yields. [c] A mixture of unidentified products was obtained.



(2)

A plausible mechanism for the silver(I)-catalyzed annulation is depicted in Scheme 1. The reaction most probably proceeds through the benzopyrylium cation **I**,

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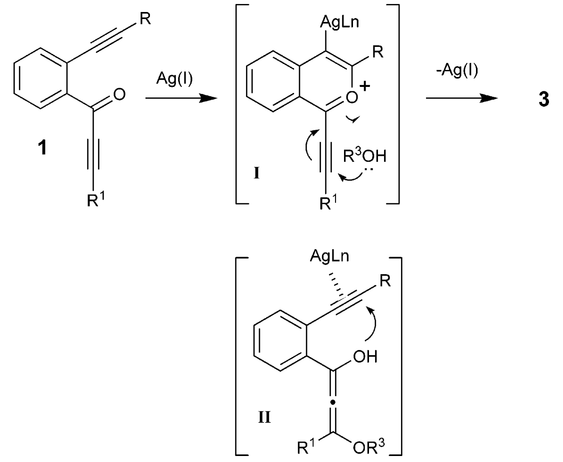
[10] The reason for the failure of reaction in the case of terminal alkynes (R = H) and TMS (R = TMS)-protected alkynes can be well accounted. The reaction of terminal alkynes with Ag(I) salts would lead to the formation of silver acetylide, thereby hampering the cyclization. See: Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395−4398. However, in the TMS-protected alkynes, steric hindrance created by three methyl groups might hamper the cyclization.

[11] The intramolecular 5-*exo-dig*/6-*endo-dig* cyclization of oxygen nucleophiles to alkynes has been reported. See, for instance: (a) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145−1148. (b) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533−2545. (c) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251−6259.

SCHEME 1. Plausible Mechanism for Cyclization Reaction



which would be formed by the nucleophilic attack of carbonyl oxygen to the silver coordinated alkyne.[12] The benzopyrylium ion formed in this way would undergo subsequent trapping with alcohols. The protonation and regeneration of the Ag(I) catalyst produce the annulation products. Another conceivable pathway is that silver salts act as a catalysts[13] for Michael reaction forming the intermediate **II**, which would then cyclize with the proximal alkyne activated by the Ag(I) coordination. However, the fact that 1-benzoyl pentyne[14] does not undergo the reaction under the present catalytic system might exclude the possibility. To support the formation of benzopyrylium cation in the present reaction, ^{13}C NMR studies of a 1:1 mixture of **1a** and AgSbF$_6$ in CD$_2$Cl$_2$ at room temperature (1 h) were carried out. Disappearance of two acetylenic carbons and the shift of the carbonyl carbon in the presence of AgSbF$_6$ clearly indicate the involvement of such a cationic intermediate.[15]

Silver-catalyzed cascade cyclization reaction of alkynones with alcohols described herein represents a general and versatile approach to the 1-allenyl chromenes. The mild reaction conditions, simple procedure, easily available starting materials, and reasonable yields make the method attractive. The allenyl moiety can be easily introduced in the heterocycle by using this procedure, which on further functionalization may give access to highly substituted heterocycles.

Experimental Section

The preparation of **3a** is representative. **1a** (0.050 g, 0.1838 mmol), MeOH (0.012 g, 0.3676 mmol), AgSbF$_6$ (5 mol %), and CH$_2$Cl$_2$ (2 mL) were stirred at 35 °C in a screw-capped vial for 16 h. Water (10 mL) was added, and the resulting reaction mixture was extracted with ethyl acetate. The extracts were concentrated to give a thick residue. The resulting residue was purified by column chromatography with use of silica gel as a solid phase and 9:1 hexanes−ethyl acetate as an eluent to afford pure **3a** (0.053 g, 95%).

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Supporting Information Available: Experimental details, synthetic method for starting material preparation, characterization data, and ^{1}H NMR spectra of newly synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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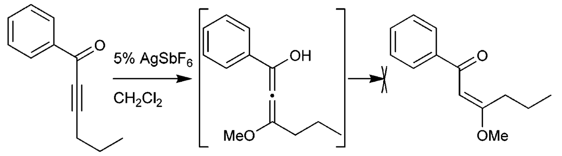
[12] Such type of transition metal-catalyzed benzopyrylium cation formation is known in the case of the compounds containing alkynes tethered with carbonyl groups. See: (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc*. **2002**, *124*, 12650−12651. (b) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **2004**, *126*, 7458−7459. (c) Sato, K.; Yudha, S. S.; Asao, N.; Yamamoto, Y. *Synthesis* **2004**, *9*, 1409−1412. (d) Asao, N.; Nogami, T.; Lee, S.; Yamamoto Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921−10925. (e) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc*. **2005**, *127*, 2709−2716. (f) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531−4534. (g) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239−1239.

[13] Aza-Michael reaction of enones catalyzed by transition metal salts are known. See: Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett*. **2002**, *4*, 1319−1322.

[14] The reaction of 1-benzoyl pentyne (0.2 mmol), MeOH (2 equiv), AgSbF$_6$ (5 mol %) in CH$_2$Cl$_2$ was carried out at 35 °C in a screw-capped vial for 16 h. However, no Michael addition product was noticed; slight decomposition of starting material was observed by the TLC and ^{1}H NMR analysis.



[15] See Supporting Information for the ^{13}C NMR spectra (**1a** and **1a** + AgSbF$_6$).