Synthesis of β-Substituted Chalcones from Phenones via Conjugated Nucleophilic Substitution of Propargylic Alcohols

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Abstract: Phenones can be efficiently transformed into β-substituted chalcones in a two-step process. First, propargylic alcohols were obtained by addition of ethoxyacetylene anion to aromatic ketones. Activation of the propargylic alcohols using a catalytic amount of acid in the presence of an electron-rich aromatic ketone affords the title enones in moderate to good yields.

Key words: electrophilic aromatic substitution, ketones, olefination, propargylic alcohols, chalcones

The chalcones (generic structure **1**, R = H, Figure 1) constitute an interesting family of natural compounds. Not only are they synthetic intermediates for the important flavones[1] (generic structure **2**) but also many chalcones show useful biological properties, including anti-inflammatory, cytotoxic, antimalarial, antileishmanial, and antimicrobial activities.[2,3] In the context of medicinal chemistry programs, the synthesis of β-substituted chalcones (**1**, R ≠ H) has potential in the ongoing search for new compounds with interesting properties.

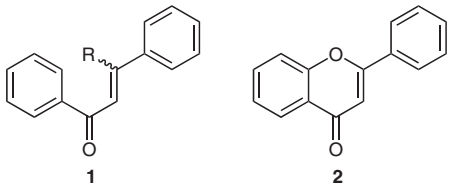

Figure 1 Generic structures of chalcones **1** and flavones **2**

The main approach to the synthesis of chalcones involves aldol condensation between phenones and aromatic aldehydes,[3,4] however, phenone cross-condensation that leads to β-substituted chalcones is limited by the low reactivity and by competition with autocondensation pathways. Aromatic enones can be prepared by using various carbonyl olefination reactions,[5] including the Horner–Wadsworth–Emmons[6] and the Julia–Kocienski[7] reactions. However, these methods have found limited applications for the synthesis of β-substituted chalcones, presumably due to the low reactivity of aromatic ketones towards most olefination reagents. Herein, we report a novel tandem process towards β-substituted chalcones from readily available propargylic alcohols as precursors.

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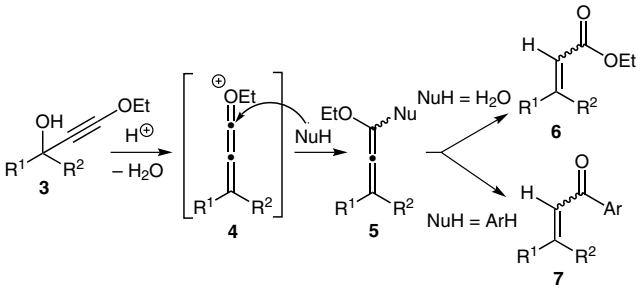
In 1922, Meyer and Schuster discovered a rearrangement in which propargylic alcohols are converted into α,β-unsaturated ketones.[8] This transformation seemingly involves cationic intermediates through the loss and gain of water.[9] Later, Tankard and Whitehurst realized that ethoxyacetylene-based propargylic alcohols such as **3** underwent this transformation, presumably via cationic intermediate **4**, and further ethoxyallene **5** (Nu=OH), to α,β-unsaturated esters **6** under mild conditions, as shown in Scheme 1.[10]



Scheme 1 Preparation of α,β-unsaturated esters **6** and ketones **7** from propargylic alcohols **3**

To the best of our knowledge, there have been no attempts to trap the cationic intermediates **4** with carbon-based nucleophiles. Such an extension would generate a new carbon–carbon bond, leading to the formation of conjugated enones **7**. In order to explore this transformation, we envisaged trapping intermediates such as **4** with electron-rich aromatic nucleophiles through electrophilic aromatic substitution. This overall transformation would provide a new tool for the synthesis of a range of β-substituted chalcones.

We first prepared propargylic alcohols **3a–c** by treatment of phenones **8** in the presence of lithiated ethoxyacetylene (Table 1).[11]

Propargylic alcohol **3a** was further treated with a catalytic amount of acid in the presence of electron-rich aromatic nucleophiles, in anhydrous acetonitrile at room temperature (Table 2).[12] First, 1,3-dimethoxybenzene was used as the aromatic nucleophilic entity. We were pleased to observe, using PTSA (Table 2, entry 1), the formation of β-methylchalcone **9a**, albeit in a low yield (9%) together with large amounts of undesired α,β-unsaturated ester **6a** (R^1 = Ph, R^2 = Me) resulting from water addition to the putative cationic intermediate. It was clear that the use of an-

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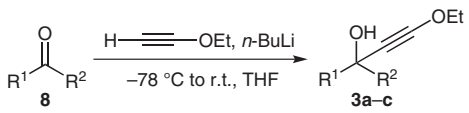
Table 1 Formation of Propargylic Alcohols from Ethoxyacetylene and Phenones



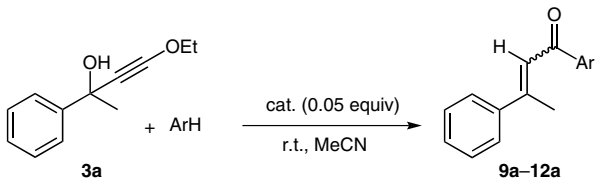
Entry	R^1	R^2	Product	Time (h)	Yield (%)
1	Ph	Me	**3a**	6	80
2	$R^1 = R^2 =$ Ph		**3b**	4	92
3	$R^1 = R^2 = p$-$MeOC_6H_4$		**3c**	4	96

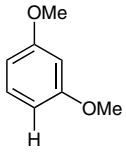
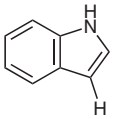
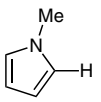
hydrous solvent and catalyst (conditions that were hard to achieve with highly hygroscopic PTSA) could minimize formation of the unsaturated ester. To further improve the formation of the desired compound **9a**, resulting from the arene-based attack, a range of protic and Lewis acids were tested. In order to efficiently trap moisture, resulting from external sources as well as from the propargylic alcohol, phosphoric anhydride was used as both an acid and a desiccant, resulting in a slight improvement of the yield of ketone **9a** (Table 2, entry 2). In fact, we found that the mild Lewis acid ferric chloride was the catalyst of choice, affording **9a** in an average yield of 38% (Table 2, entry 3). Being aware that benzene-based aromatics (even if electron-rich) could be the limiting cases as nucleophiles, we reasoned that heteroaromatics would afford better yields of the desired olefinic ketone products. This was effectively the case when indole was used, and 38% yield of ketone **10a** (using PTSA or P_2O_5 as catalyst, entries 4 and 5) and even 72% yield (using $FeCl_3$, entry 6) was obtained. Using *N*-methylpyrrole as nucleophile, similar yields of compound **11a** were achieved; indeed the yields were improved going from PTSA to P_2O_5 and to $FeCl_3$ (Table 2, entries 7–9). The same tendency was observed for **12a**, albeit in slightly lower yields, presumably due to the lower nucleophilicity of furan (Table 2, entries 10–12)

Chalcones **9**–**12a** produced in this reaction were obtained as separable mixtures of *E*/*Z* geometric isomers.[13] The extent to which the *E*/*Z* ratios are related to the reaction conditions (nature of the acid, reaction time, etc.) is unclear at this time. Work is ongoing to better understand factors affecting the ratios, as well as to gain stereoselectivity.

Similarly, propargylic alcohols **3b** and **3c**, derived from benzophenone and 4,4′-dimethoxybenzophenone, were treated with ferric chloride and heteroaromatic nucleophiles (Table 3). Indole, *N*-methylpyrrole and pyrrole afforded good yields of β-aryl-substituted chalcones **10b**/**c**, **11b**/**c**, and **13b**/**c** (Table 3, entries 1–4, 7, and 8). However, furan again proved to be a somewhat weaker nucleophile, with yields being modest for **12c** to useful for **12b** (Table 3, entries 5 and 6). It should be noted that use of pyrrole as a nucleophile (Table 3, entries 7 and 8) led to the formation of approximately 20% of the 3-substituted regioisomers, along with the major 2-substituted isomers

Table 2 Formation of β-Methyl-Substituted Chalcones from Propargylic Alcohol **3a** in the Presence of Electron-Rich Aromatics under Acidic Conditions



Entry	ArH	Products	Time (h)	Catalyst	Ratio (*E*/*Z*)[a]	Yield (%)[b]
1		(*E*)-**9a**/(*Z*)-**9a**	2	PTSA	(3.3:1)	9
2			1	P_2O_5	(3.3:1)	24
3			2	$FeCl_3$	(12:1)	**38**
4		(*E*)-**10a**/(*Z*)-**10a**	2	PTSA	(1.2:1)	38
5			3	P_2O_5	(0.6:1)	40
6			24	$FeCl_3$	(1.2:1)	**72**
7		(*E*)-**11a**/(*Z*)-**11a**	19	PTSA	(3.3:1)	23
8			19	P_2O_5	(0.9:1)	60
9			20	$FeCl_3$	(3:1)	**67**
10		(*E*)-**12a**/(*Z*)-**12a**	15 min	PTSA	(1.4:1)	15
11			45 min	P_2O_5	(5:1)	46
12			45 min	$FeCl_3$	(2:1)	**56**

[a] Ratios were determined by NMR analysis of the crude reaction mixture.
[b] Isolated yield after chromatography.

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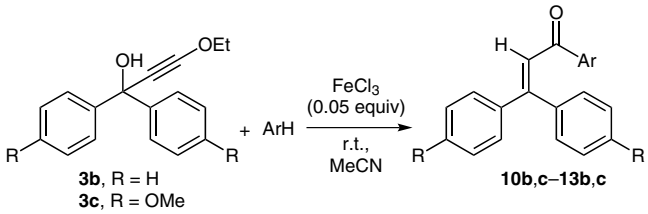
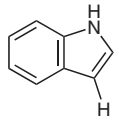
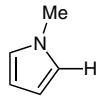
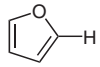
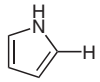
(**13b** and **13c**), which is consistent with the known preference of pyrrole to undergo electrophilic substitution at the 2-position rather than the 3-position.[14] It is noteworthy that the present method affords good yields of trisubstituted olefins from phenones, which are typically difficult substrates in the context of Wittig or aldol transformations.

Table 3 Formation of β-Aryl-Substituted Chalcones from Propargylic Alcohols **3b** and **3c** Using Ferric Chloride as Catalyst



3b, R = H
3c, R = OMe

10b,c–13b,c

Entry	ArH	Substrate	Time (h)	Product	Yield (%)
1		**3b**	22	**10b**	81
2		**3c**	24	**10c**	83
3		**3b**	23	**11b**	84
4		**3c**	24	**11c**	90
5		**3b**	1	**12b**	58
6		**3c**	0.5	**12c**	25
7		**3b**	23	**13b**	85
8		**3c**	20	**13c**	87

In conclusion, a practical and new method for the synthesis of β-substituted chalcones from propargylic alcohols and electron-rich aromatic systems has been developed. This transformation combines an electrophilic aromatic substitution together with the activation of propargylic alcohols under acidic conditions. The transformation, in addition to affording a new route to flavonoids, thus provides a new strategic opportunity that could be applied to the synthesis of chalcones in general.

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(11) **Preparation of Propargylic Alcohols; Typical Procedure**: At –78 °C, *n*-BuLi (2.5 M in hexanes, 400 μL, 1.00 mmol) was added dropwise to a solution of ethoxyacetylene (40% in hexanes, 240 μL, 1.00 mmol) in anhydrous THF (3 mL). The solution was stirred for 5 min, warmed slowly to 0 °C over 1 h and stirred for 30 min. After cooling to –78 °C, acetophenone (50 μL, 0.43 mmol) was added in one portion. The solution was warmed to r.t. over 1 h and stirred for 1.5 h. Saturated aqueous NH_4Cl was added, the aqueous phase was extracted with EtOAc, and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (hexanes–EtOAc, 95:5→75:25) to afford the desired compound **3a** (65 mg, 80%) as a yellow oil.
(12) **Preparation of β-Substituted Chalcones; Typical Procedure**: To a solution of propargylic alcohol (**3a**; 26.6 mg, 0.140 mmol) in anhydrous acetonitrile (0.7 mL), indole (49 mg, 0.42 mmol) and $FeCl_3$ (1 mg, 0.007 mmol) were added. The solution was stirred for 24 h, then the solvent was evaporated under vacuum. Analysis of the crude reaction mixture by NMR indicated an *E*/*Z* ratio of 1.2:1. The crude mixture was purified by flash chromatography on silica gel (hexanes–EtOAc, 90:10→60:40) to afford the corresponding β-substituted chalcones (*E*)-**10a** (14.3 mg, 39%) and (*Z*)-**10a** (11.9 mg, 33%), respectively, as white and yellowish solids.
(13) Stereochemistry was established by NOE experiments.
(14) The regioisomers were separable by chromatography; see the Supporting Information.

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