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# The cation exchange resin-promoted coupling of alkynes with aldehydes: one-pot synthesis of α,β-unsaturated ketones

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ABSTRACT

Alkynes undergo smooth coupling with aldehydes in the presence of Amberlyst-15® at room temperature to produce the corresponding α,β-unsaturated ketones in high yields with *E*-geometry. The use of an inexpensive, readily available, and recyclable cation exchange resin makes this method quite simple and convenient.

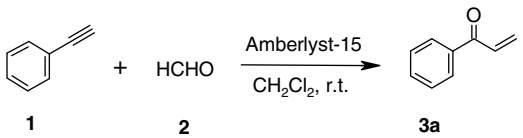


α,β-Unsaturated ketones have attracted increasing attention due to their numerous pharmacological properties such as anti-cancer activity, cytotoxicity, anti-inflammatory, analgesic, and antipyretic behavior.[1] Some of them are potential antibacterial, antifungal, and anti-ulcer agents.[2] They are also very useful intermediates in organic synthesis, especially for heterocycles.[3] These findings have attracted the attention of chemists, biochemists, and pharmacologists to this particular group of compounds. The stereoselective synthesis of α,β-unsaturated ketones is generally accomplished by various methods such as condensation, oxidation, elimination, acylation, and insertion of carbon monoxide among others.[4] However, in most cases, the stereoselective control of the carbon–carbon double bond remains unsolved. The coupling of alkynes to aldehydes is an important transformation in organic synthesis to generate carbon–carbon multiple bonds.[5] Though the addition of alkynylmetal reagents to aldehydes to produce propargyl alcohols has been studied extensively,[5] the reaction between alkynes and aldehydes to generate α,β-unsaturated ketones has received little attention. Only a few methods are known in the literature for the direct preparation of conjugated enones from alkynes and aldehydes. Lewis acids such as $SbF_5$, $Yb(OTf)_3$, and $In(OTf)_3$ are employed to accomplish this reaction.[6–8] Other reagents such as $VO(OSiPh_3)_3$ and $InCl_3$ have been used in the coupling of allenyl carbinols with aldehydes to generate β-hydroxy enones.[9,10]

In recent years, the use of heterogeneous catalysts such as ion-exchange resins, clay, and zeolites has received significant attention in different areas of organic synthesis because of their simplicity in operation, environmental compatibility, reusability, greater selectivity, non-corrosiveness, and ready availability of the reagents at low cost.[11] In particular, ion-exchange resins can make reaction processes simple, more convenient, economic, and environmentally benign which enable them to function as efficient catalysts for various transformations.[12]

In continuation of our interest in the use of solid acid catalysts,[13] herein, we report an efficient and metal-free method for the preparation of α,β-unsaturated ketones by means of coupling alkynes with aldehydes using a cheap and readily available cation exchange resin. Initially, we attempted the coupling of phenylacetylene (**1**) with paraformaldehyde (**2**) in the presence of Amberlyst-15®. The reaction was complete within 2.0 h and the product, 1-phenylprop-2-en-1-one **3a** was obtained in 86% yield (Scheme 1).

Other terminal alkynes such as *p*-methylphenylacetylene and 4-phenylbut-1-yne were also coupled effectively with paraformaldehyde under similar conditions (Table 1, entries b and c). These results provided the incentive for further study with various alkynes and aldehydes. Interestingly, several aldehydes such as cyclohexanecarboxaldehyde, *n*-hexanal, *n*-butyraldehyde, benzaldehyde,




**1** **2** **3a**

**Scheme 1.**

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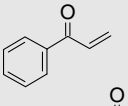
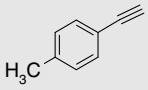
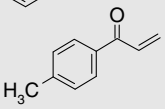
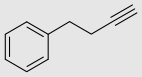
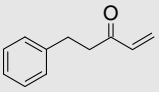
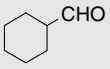
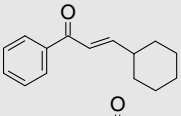
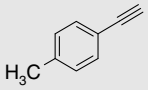
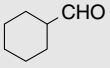
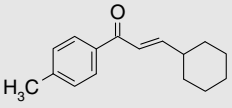
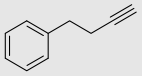
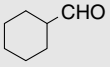
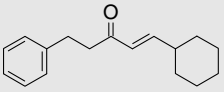
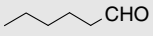
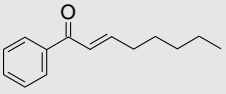
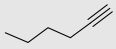
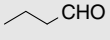
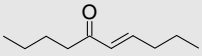
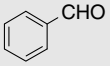
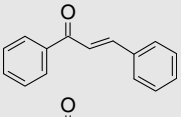
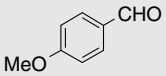
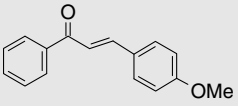
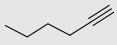
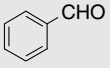
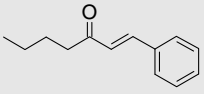
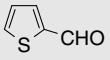
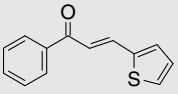
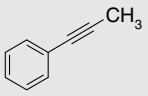
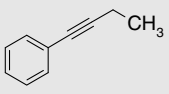
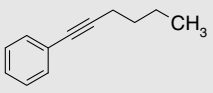
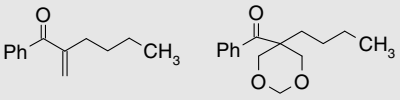
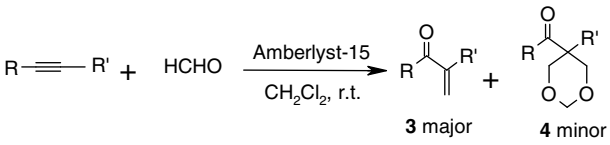
**Table 1**
Amberlyst-15-promoted coupling of alkynes with aldehydes

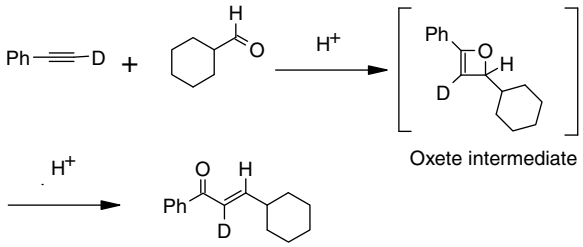
| Entry | Alkyne | Aldehyde | Product[a] | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| **a** |  | HCHO |  | 2.0 | 86 |
| **b** |  | HCHO |  | 2.0 | 90 |
| **c** |  | HCHO |  | 3.0 | 81 |
| **d** |  |  |  | 2.5 | 85 |
| **e** |  |  |  | 2.5 | 87 |
| **f** |  |  |  | 3.0 | 80 |
| **g** |  |  |  | 3.5 | 78 |
| **h** |  |  |  | 4.0 | 70 |
| **i** |  |  |  | 2.0 | 90 |
| **j** |  |  |  | 2.5 | 85 |
| **k** |  |  |  | 3.5 | 80 |
| **l** |  |  |  | 4.5 | 70 |
| **m** |  | HCHO |  | 2.0 | 85[c] |
| **n** |  | HCHO |  | 2.5 | 80[c] |
| **o** |  | HCHO |  | 3.0 | 78[c] |

[a] The products were characterized by $^1$H NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.
[c] Enone and dioxane (**3** and **4**) were obtained in a ratio of 2:1.

*p*-methoxy-benzaldehyde and thiophene-2-carboxaldehyde reacted well with alkynes under similar conditions to afford a wide range of conjugated enones (Table 1, entries d–l). This method worked equally well with aliphatic, heterocyclic and aromatic aldehydes (Table 1). Though the reaction proceeded with phenylacetylene and electron-deficient substrate, that is *p*-nitrobenzalde-




**Scheme 2.**




**Scheme 3.**

hyde, the yield is very low (35%) over a long reaction time (24 h). However, both aliphatic and aromatic alkynes underwent facile coupling with aldehydes to furnish disubstituted (*E*)-α,β-unsaturated ketones (Table 1). The cross-coupling between terminal alkynes and paraformaldehyde gave the corresponding vinyl ketones in good yields (Table 1, entries a–c). Surprisingly, the cross-coupling of internal alkynes such as 1-phenylprop-1-yne, 1-phenylbut-1-yne and 1-phenylhex-1-yne with paraformaldehyde gave a mixture of vinyl ketone and 1,3-dioxane in a 2:1 ratio (Scheme 2, Table 1 entries m–o).[14]

Both the enone and 1,3-dioxane could be separated easily by column chromatography. In all cases, the reactions proceeded efficiently in high yields at room temperature under mild conditions. As solvent, dichloromethane gave the best results. All the products were characterized by NMR, IR, and mass spectrometry. In the absence of acid resin, no reaction was observed between the aldehyde and alkyne. Furthermore, the reaction did not proceed with other solid acids including Montmorillonite KSF and the heteropolyacid $H_3PW_{12}O_{40}$. The catalyst could be separated easily by simple filtration, and the recovered acid resin was reused in subsequent reactions with only a gradual decrease in activity. For example, benzaldehyde and paraformaldehyde gave **3a** in 86%, 82%, 75%, and 72% yields over four cycles. The scope and generality of this process was illustrated with respect to various alkynes and aldehydes, and the results are presented in Table 1.[15] The probable reaction mechanism is depicted in Scheme 3.

To realize the reaction mechanism, we have carried out the reaction between deuterated phenylacetylene and cyclohexanecarboxaldehyde. As shown in Scheme 3, no loss of deuterium label was observed in the product. This clearly indicates that the reaction proceeds via cyclic oxete intermediate as has been reported by Yamaguchi and co-workers.[6]

In summary, we have described a simple, convenient and metal-free protocol for the preparation of α,β-unsaturated ketones from alkynes and aldehydes using Amberlyst-15® as a novel promoter. In addition to its simplicity and mild reaction conditions, this method provides high yields of products in short reaction times with high selectivity. The use of an inexpensive and recyclable acid resin makes this method simple, convenient, and economically viable.

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15. *Experimental procedure*: A mixture of aldehyde (1 mmol), alkyne (1.2 mmol), and Amberlyst-15® (0.75 g) in dichloromethane (10 L) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with dichloromethane (2 × 10 mL). The combined organic extracts were concentrated in vacuo and the resulting product was charged on small silica gel column and eluted with a mixture of ethyl acetate–*n*-hexane (1:9) to afford pure enone. Spectral data for selected products: compound **3c**: Liquid, IR (KBr): $\nu$ 3443, 3019, 2923, 1715, 1455, 1216, 1029, 757 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.34–7.12 (m, 5H), 6.49–6.25 (m, 2H), 5.80 (d, 1H, $J$ = 16.2 Hz), 2.95–2.85 (m, 4H). EIMS: *m/z*: 160 ($M^+$) 105, 91, 56, 78; HRMS calcd for $C_{11}H_{12}O$: 160.2156, found: 160.2142. Compound **3g**: Liquid, IR (KBr): $\nu$ 3441, 3061, 2930, 2855, 1750, 1621, 1037, 761, 753 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.85 (d, 2H, $J$ = 7.5 Hz), 7.55–7.41 (m, 3H), 6.98 (d, 1H, $J$ = 6.9 Hz), 2.30–2.20 (m, 2H), 1.75–1.32 (m, 10H); EIMS:*m/z*: 202 ($M^+$) 131, 105, 77; HRMS calcd for $C_{14}H_{18}O$: 202.2963, found: 202.2951. Compound **3j**: Liquid, IR (KBr): $\nu$ 3423, 3058, 2924, 2850, 1891, 1657, 1597, 1255, 719 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.20 (d, 2H, $J$ = 8.7 Hz), 7.80 (d, 1H, $J$ = 16.3 Hz), 7.60–7.25 (m, 5H), 7.20 (d, 1H, $J$ = 16.3 Hz), 6.95 (d, 2H, $J$ = 8.7 Hz), 3.94 (s, 3H); EIMS: *m/z*: 238 ($M^+$) 161, 131, 105, 118. 77; HRMS calcd for $C_{16}H_{14}O_2$: 238.2859, found: 238.2839. Compound **3o**: Liquid, IR (KBr): $\nu$ 3453, 2957, 2868, 1740, 1659, 1076, 753 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.55 (d, 2H, $J$ = 7.9 Hz), 7.55–7.32 (m, 3H), 5.72 (s, 1H), 5.25 (s, 1H), 2.45 (t, 2H, $J$ = 7.1 Hz), 1.31–1.55 (m, 4H), 0.95 (t, 3H, $J$ = 6.7 Hz); EIMS: *m/z*: 188 ($M^+$) 145, 105, 77, 41; HRMS calcd for $C_{13}H_{16}O$: 188.2694, found: 188.2682. Compound **4o**: Liquid, IR (KBr): $\nu$ 3496, 2934, 2870, 1780, 1696, 1030, 770 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.65 (d, 2H, $J$ = 7.9 Hz), 7.55–7.35 (m, 3H), 4.75 (s, 2H), 4.21 (d, 2 H, $J$ = 9.5 Hz), 3.85 (d, 2H, $J$ = 10.1 Hz), 1.85 (t, 2H, $J$ = 7.5 Hz), 1.35–1.20 (m, 4H), 0.85 (t, 3H, $J$ = 7.2 Hz); EIMS: *m/z*:248 ($M^+$) 192, 105, 79, 77. HRMS calcd for $C_{15}H_{20}O_3$: 248.3221, found: 248.3214.