Zinc-mediated Allylation of Aryl 2-Propynyl Acetates: A Facile Synthesis of 1,5-Enynes

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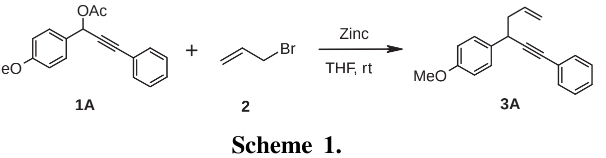
Aryl 2-propynyl acetates undergo smooth allylation with allylzinc bromide (generated in situ from allyl bromide and zinc metal) in THF at room temperature under mild conditions to furnish the corresponding 1,5-enynes in good to excellent yields and with high selectivity. Indium metal is also found to accomplish the nucleophilic substitution of aryl 2-propynylic acetates with allyl bromide.

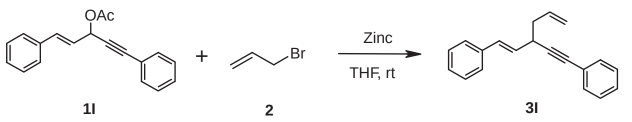
The stereoselective addition of allylmetal reagents to aldehydes referred to as the Barbier reaction has been recognized as one of the most efficient methods for carbon–carbon bond formation and has been extensively used in organic synthesis, especially in natural products synthesis.[1] Aryl 2-propynyl alcohols or acetates are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo nucleophilic substitution reactions contributes largely to their synthetic value.[2,3] The Nicholas reaction has been widely used as a powerful tool for the substitution of 2-propynylic alcohols.[2] However, this method generally requires a stoichiometric amount of $Co_2(CO)_8$ and several steps are necessary to obtain the 2-propynylic product from 2-propynylic alcohols through cationic 2-propynylic complexes.[4–6] Subsequently, several transition-metal-catalyzed 2-propynylic substitutions have been reported using ruthenium, rhenium(V), and gold(III) catalysts.[7–12] Recently, boron(III) and bismuth(III) reagents have also been used to accomplish this transformation.[13–15] However, there have been no reports on the allylation of aryl 2-propynylic acetates with allyl bromide using zinc metal.

Herein, we report a simple and convenient method for the allylation of aryl 2-propynyl acetates using allylzinc bromide to produce 1,5-enynes. Initially, we attempted the allylation of 1-(4-methoxyphenyl)-3-phenylprop-2-ynyl acetate (**1A**) with allyl bromide (**2**) in the presence of metallic zinc in THF. The reaction went to completion in 25 min at room temperature and the desired product **3A** was obtained in 85% yield (Scheme 1).

Similarly, various aryl 2-propynyl acetates underwent smooth allylation with allylzinc bromide to afford the corresponding pent-4-en-2-yl benzene derivatives in high yields (Entries B–H, Table 1). In all cases, the reactions proceeded rapidly at room temperature. Interestingly, doubly activated aryl 2-propynyl acetates reacted effectively with allylzinc bromide to furnish 1,5-enynes in high yields (Entries I and J, Table 1, Scheme 2).



Scheme 1.



Scheme 2.

Furthermore, the acetate derived from 3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-ol also participated in this reaction (Entries K and L, Table 1). Simple alkyl acetates failed to undergo allylation under the reaction conditions. This method was successful only with aryl 2-propynyl acetates. It is noteworthy to mention that 2-propynyl acetates bearing methoxy groups on aromatic ring gave comparatively high yields than non-methoxy 2-propynyl acetates. No additives or acidic promoters are required for the reaction to proceed. As solvent, dichloromethane gave the best results. All products were characterized by ^{1}H, ^{13}C NMR, IR, and mass spectrometry, and also by comparison with authentic samples.[4–15] However, in the absence of zinc metal, the reaction did not proceed even after an extended reaction time (12 h). Although, the reaction was successful with indium metal, the isolated yields (20–40%) were very low even after longer reaction times (12–18 h). In contrast to indium, zinc metal is readily available at low cost and is highly efficient in promoting allylation. It should be noted that the allylation of all substrates led exclusively to the formation of 2-propynylic products and no traces of allenic side products were detected. The scope of this process is illustrated with respect to various aryl 2-propynyl acetates and the results are presented in Table 1.[16]

In summary, we have demonstrated a simple, convenient, and efficient protocol for the allylation of aryl 2-propynyl acetates using allylzinc bromide. In addition to its efficiency, and mild reaction conditions, this method provides high yields of products with high selectivity, which makes it a useful and attractive process for the synthesis of 1,5-enynes from aryl propargyl acetates.

References and Notes

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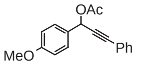
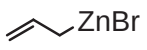
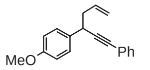
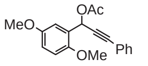
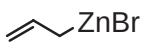
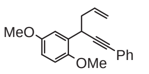
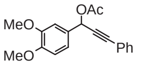
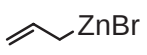
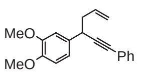
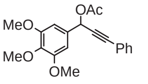
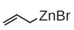
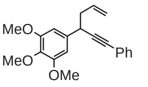
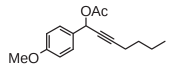
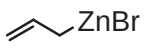
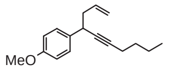
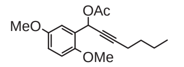
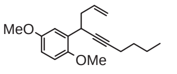
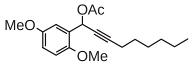
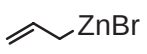
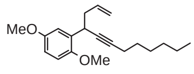
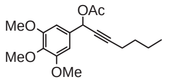
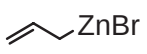
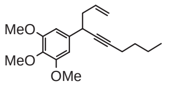
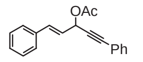
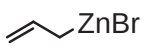
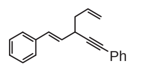
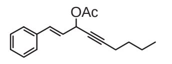
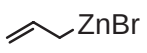
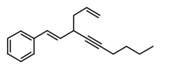
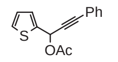
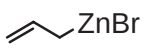
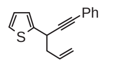
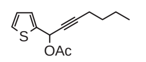
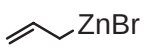
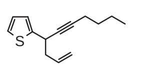
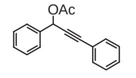
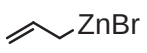
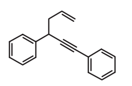
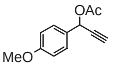
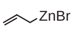
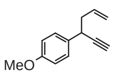
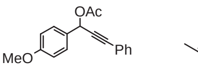
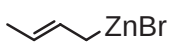
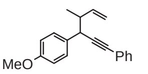
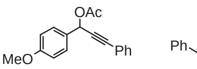
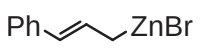
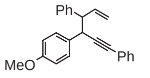
Table 1. Zinc-mediated allylation of aryl 2-propynyl acetates

Entry	2-propynyl alcohol	Allyl bromide	Product[a]	Time/min	Yield/%[b]
A				25	85
B				20	82
C				35	80
D				20	86
E				35	80
F				35	83
G				40	79
H				35	82
I				30	80
J				30	78
K				25	83
L				30	80
M				720[c]	58
N				60	65
O				30	70
P				45	75

[a]All products were characterized by NMR, IR, and mass spectrometry. [b]Yield refers to pure products after chromatography. [c]Reaction was performed in refluxing THF.

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16 General procedure. A mixture of aryl 2-propynyl acetate (5 mmol), allyl bromide (10 mmol), and zinc powder (10 mmol) in THF (10 mL) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated ammonium chloride (15 mL) and extracted with ethyl acetate (2 × 15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) afforded pure 1,5-enyne. Spectral data for selected products: **3A**: liquid, IR (Neat): ν 3070, 2928, 2839, 2198, 1603, 1510, 1446, 1250, 1175, 1032, 916, 830, 756, 691 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H), 7.23–7.14 (m, 5H), 6.73 (d, $J = 8.3$ Hz, 2H), 5.86–5.71 (m, 1H), 5.04–4.94 (m, 2H), 3.74 (t, $J = 7.1$ Hz, 1H), 3.69 (s, 3H), 2.50–2.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 135.4, 133.4, 131.5, 128.4, 128.1, 127.6, 123.6, 116.9, 113.7, 91.2, 83.5, 55.1, 42.7, 37.6; LCMS: m/z: $[M + H]^+$: 263; HRMS calcd for $C_{19}H_{19}O$: 263.1435. Found: 263.1447. **3F**: Liquid, IR (Neat): ν 2935, 2865, 1497, 1458, 1217, 1046, 914, 801, 709 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, $J = 3.0$ Hz, 1H), 6.71–6.60 (m, 2H), 5.90–5.75 (m, 1H), 5.03–4.95 (m, 2H), 4.08–4.00 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.47–2.27 (m, 2H), 2.26–2.18 (m, 2H), 1.58–1.39 (m, 4H), 0.93 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 150.4, 136.2, 131.7, 116.1, 114.9, 111.8, 111.3, 83.1, 81.1, 55.9, 55.5, 41.1, 31.4, 31.2, 21.8, 18.4, 13.5; LCMS: m/z: $[M + H]^+$: 273; HRMS calcd for $C_{18}H_{24}O_2Na$: 295.1673. Found: 295.1662. **3K**: liquid, IR (Neat): ν 3075, 2926, 2856, 1641, 1597, 1489, 1439, 1310, 1227, 993, 917, 755, 693 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.53–7.44 (m, 2H), 7.38–7.29 (m, 3H), 7.22 (dd, $J = 1.4$, 5.1 Hz, 1H), 7.08 (dd, $J = 1.4$, 3.6 Hz, 1H), 7.01–6.90 (m, 1H), 6.12–5.89 (m, 1H), 5.29–5.14 (m, 2H), 4.24 (t, $J = 6.9$ Hz, 1H), 2.80–2.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 134.8, 131.6, 128.2, 127.9, 126.5, 124.4, 123.9, 123.3, 117.5, 90.1, 83.4, 42.7, 33.; LCMS: m/z: $[M + H]^+$: 239.