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Superbase-catalyzed addition of ketones to propargyl and allenyl ethers in the KOH (KOBu^t)/DMSO system

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Alkyl (het)aryl ketones undergo nucleophilic addition to propargyl or allenyl ethers in the KOH (KOBu^t)/DMSO system at 100 °C either at terminal (giving 1:2 adducts) or internal (giving 1:1 adducts) positions of the propargyl or allenyl fragment.

Unsaturated ketones are versatile building blocks in organic synthesis,¹ among them most common being α , β -enones. Much less accessible are β , γ -unsaturated ketones which are usually prepared by multi-step and laborious procedures.² Recently, we have discovered the direct stereoselective nucleophilic addition (KOH/DMSO,³ KOH/Bu^tOH/DMSO⁴ or KOBu^t/DMSO⁵ systems) of ketones to acetylenes to afford (*E*)- β , γ -enones in yields up to 92%.

This is a concise report on the extension of this finding over propargyl ethers, the reaction being carried out in the presence of KOH/DMSO or KOBu^t/DMSO systems at 100 °C.

Since propargyl ethers are known to readily isomerize to the corresponding allenyl ethers in the same superbase systems even at room temperature within 15 min (Scheme 1),⁶ actually, at 100 °C, we should consider the reaction as proceeding with allenyl ethers.



Indeed, under equal conditions we have obtained very close results with both types of ethers. Acetophenones **1a,b** add to propargyl and allenyl ethers **2a,b** both to their internal (most expected for nucleophilic attack at allenes)⁷ and terminal positions to give the 1:1 adducts **3a–c** in the former case and the 1:2 adducts **4a–c** in the latter case (Scheme 2) approximately in the same ratio.[†]

If the 1:1 adducts 3a-c seem to be not uncommon, the formation of the 1:2 adducts 4a-c needs special rationalization. One



Scheme 2

should wonder why nothing of the 1:1 adduct to terminal carbon is present in the reaction mixture. The plausible explanation is outlined in Scheme 3.



(E)-5-Methoxy-2-[(E)-(3-methoxyprop-2-en-1-yl)]-1-phenylpent-4-en-1-one **4a**: yield 0.11 g (24%), yellow oil. ¹H NMR, δ : 7.90–7.88 (m, 2 H, o-H), 7.53–7.48 (m, 2 H, m-H), 7.45–7.41 (m, 1H, p-H), 6.25 (d, 2 H, CH=CH–OMe, ³J 12.7 Hz), 4.59 (dt, 2 H, CH=CH–OMe, ³J 12.7 Hz, ³J 7.7 Hz), 3.42 (m, 1H, O=C–CH), 3.39 (s, 6 H, OMe), 2.35–2.32, 2.15–2.13 (m, 4 H, CH₂–CH=CH–OMe). ¹³C NMR, δ : 203.6 (C=O), 148.7 (2CH=CH–OMe), 137.7 (*i*-C), 132.8 (p-C), 128.6 (m-C), 128.3 (o-C), 99.5 (2 CH=CH–OMe), 55.9 (2 OMe), 48.5 (O=C–CH), 30.0 (2 CH₂–CH=CH–OMe). IR (film, ν_{max} /cm⁻¹): 3060, 2998, 2931, 2830, 1681, 1652, 1594, 1580, 1448, 1275, 1130, 1076, 1049, 1004, 957, 936, 757, 694. Found (%): C, 73.99; H, 7.69. Calc. for C₁₆H₂₀O₃ (%): C, 73.82; H, 7.74.

For characteristics of compounds **3b,c**, **4b,c**, **5a,b** and **6a,b** see Online Supplementary Materials.

[†] General procedure for the reaction of ketones **1** with allenyl (or propargyl) ethers **2a,b** in the KOH/DMSO or KOBu[/]/DMSO system. A mixture of ketone **1** (2 mmol), allenyl (or propargyl) ether **2** (2 mmol), KOH·0.5H₂O (0.13 g, 2 mmol) or KOBu¹ (0.22 g, 2 mmol) in DMSO (7 ml) was heated (100 °C) and stirred for 1 h. After cooling (20–25 °C), the mixture was diluted with H₂O (10 ml), neutralized with NH₄Cl and extracted with Et₂O (4×5 ml). The organic extract was washed with H₂O (3×10 ml) and dried with K₂CO₃. Column chromatography (SiO₂, eluent hexane–Et₂O with gradient from 1:0 to 3:1) of a crude residue after removal of the solvent gave the pure adducts **3–6**.

⁽Z)-4-Methoxy-3-methyl-1-phenylbut-3-en-1-one **3a**: yield 0.07 g (18%), yellow oil. ¹H NMR, δ : 7.89–7.87 (m, 2H, *o*-H), 7.53–7.49 (m, 2H, *m*-H), 7.42–7.39 (m, 1H, *p*-H), 5.88 (s, 1H, C=CH–OMe), 3.55 (s, 3H, OMe), 3.46 (s, 2H, O=C–CH₂), 1.63 (s, 3H, Me). ¹³C NMR, δ : 200.0 (C=O), 145.2 (C=CH–OMe), 136.8 (*i*-C), 132.6 (*p*-C), 128.5 (*m*-C), 128.3 (*o*-C), 101.5 (*C*=CH–OMe), 59.5 (OMe), 43.5 (O=C–CH₂), 13.2 (Me). IR (film, ν_{max}/cm^{-1}): 3059, 3000, 2933, 2832, 1680, 1654, 1597, 1580, 1448, 1376, 1275, 1211, 1132, 1076, 1049, 1002, 953, 936, 795, 757, 704. Found (%): C, 75.64; H, 7.39. Calc. for C₁₂H₁₄O₂ (%): C, 75.76; H, 7.42.

The primary adduct of deprotonated ketone **A** to the terminal allenic carbon, the initial vinyl carbanion **B**, does not trap a proton from the medium in the expected intermolecular manner. Instead, intramolecular proton transfer from the α -CH₂ group leads to α -carbanion **C** which then adds to the terminal carbon of the second molecule of the allenyl ether to deliver the final 1:2 adducts **4a–c**. Similar intramolecular proton transfer does not occur during the formation of the 1:1 adducts **3a–c** because *sp*³-centred carbanion **D** is much more basic than the *sp*²-centred one (**B**),⁸ moreover, its carbanionic centre is sterically more accessible for a medium proton (Scheme 4).



In support of this concept, the branching at the carbanionic centre of the ketone (carbanion A') prevents the above intramolecular proton transfer (Scheme 3) and thus only 1:1 adducts are formed as it is observed for propiophenone **1c** and 2-propionylthiophene **1d** (Scheme 5).



Scheme 5

In this case, along with 1:1 adducts **6a,b** to the terminal allenic carbon, the normal 1:1 adducts **5a,b** to the internal position of allene are formed (Scheme 5).

The Z configuration of enones **3a–c**, **5a,b** is probably due to the generation of the conjugated potassium dienolate stabilized as the seven-membered ring E by the specific interaction between potassium cation and the ether oxygen.

The *E* configuration of enones **4a–c**, **6a,b** is likely a result of steric repulsion of the encumbered substituents.



In conclusion, the previously unknown nucleophilic superbase-catalyzed addition of ketones to available propargyl/allenyl ethers paves a straightforward one-pot route to new families of promising synthetic intermediates which combine the ketone and E or Z enol ether structures in one molecule. This is just a preliminary pioneering communication and hence the product yields and selectivity are open for optimization.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.008.

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