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Solvent-Free Addition of Ethynylbenzene to Ketones

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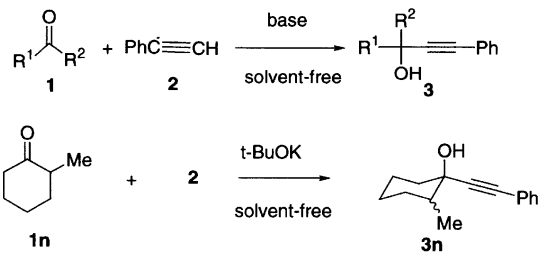
The addition of ethynylbenzene to ketones proceeded efficiently in the absence of a solvent to give tertiary alkynols in good yields.

The alkoxide-catalyzed addition of terminal alkynes to ketones, which proceeds in DMSO, has been known.[1] Recently, Tzalis et al. reported that $CsOH{\cdot}H_2O$ allowed a catalytic C–H activation of various alkynes in solution that leads, in the presence of aliphatic aldehydes or ketones, to propargylic alcohols.[2] We found that the solvent-free addition of ethynylbenzene to ketones using potassium *t*-butoxide or potassium hydroxide proceed efficiently at room temperature. We now report on an ecologically and economically valuable formation of new carbon–carbon bonds by the solvent-free addition of ethynylbenzene to ketones.

For example, after cyclohexanone **1k** (1.0 g, 10.2 mmol), ethynylbenzene **2** (1.1 g, 10.2 mmol), and potassium *t*-butoxide (1.1 g, 10.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. When **1k**, **2**, and potassium *t*-butoxide were well-mixed in the air, the reaction occurred immediately. After 20 min, the mixture was kept in the crystalline state. Also, the reaction product was mixed with 10% aqueous sodium chloride to give 1-(phenylethynyl)cyclohexanol (**3k**)[2] as colorless crystals (1.9 g, 93% yield). A similar treatment of dialkyl ketones (**1a–e**), alkyl phenyl ketones (**1f–i**), and cyclic ketones (**1j** and **1l**) in the absence of a solvent gave the corresponding tertiary alkynols **3a–j** and **3l** (Table 1). The addition of ethynylbenzene to 2-cyclohexenone (**1m**) using potassium *t*-butoxide did not occur either in the absence of a solvent or in solution (Scheme 1, Table 1). The addition of 1-hexyne as another terminal alkynes to cyclohexanone **1k** using potassium *t*-butoxide in the absence of a solvent gave the corresponding tertiary alkynol in low yield.

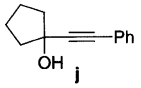
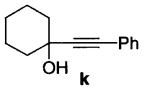
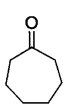
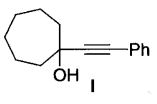
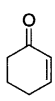
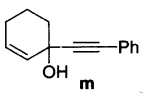


Scheme 1.

This solvent-free method is much simpler and the yield of the product is higher than that of a solution reaction. For example, a mixture of cyclohexanone **1k** (1.0 g, 10.2 mmol), ethynylbenzene **2** (1.0 g, 10.2 mmol), and potassium *t*-butoxide (0.22 g, 2.0 mmol) was stirred in DMSO (10 mL) at room temperature for 15 h. Also, the reaction product was mixed with 10% aqueous sodium chloride to give 1-(phenylethynyl)cyclohexanol (**3k**)[2] as colorless crystals (1.7 g, 83% yield). We found that these reactions proceed more efficiently in the absence of a solvent than in a DMSO solution (Table 1).

The addition of ethynylbenzene to ketones using potassium hydroxide in solution, which give tertiary alkynols, had been reported by Favorskii.[3] This reaction is known as the Favorskii reaction.[3] Tertiary alkynols **3** were also obtained using potassium hydroxide instead of potassium *t*-butoxide. For example, after cyclohexanone **1k** (1.0 g, 10.2 mmol), ethynylbenzene **2** (1.1 g, 10.2 mmol), and potassium hydroxide (1.1 g, 10.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. Also, the reaction product was mixed with 10% aqueous sodium chloride to give 1-(phenylethynyl)cyclohexanol (**3k**) as colorless crystals (1.34 g, 66% yield). The addition of ethynylbenzene to 2-butanone (**1b**) using potassium hydroxide in the absence of a solvent also gave the corresponding tertiary alkynols (**3b**) in 76%

Table 1. Yield of Tertiary Alkynols (**3**) at Room Temperature in the Absence of a Solvent and Solution[a)]

Ketone			Product and yield/%		
			product		
1	R^1	R^2	**3**	solvent-free	solution[a)]
a	Me	Me	**a**	94	91
b	Me	Et	**b**	93	78
c	Me	nPr	**c**	87	73
d	Et	Et	**d**	83	69
e	iPr	iPr	**e**	70	58
f	Ph	Me	**f**	65	43
g	Ph	Et	**g**	68	51
h	Ph	nPr	**h**	96	39
i	Ph	iPr	**i**	72	43
j				40	35
k				93	83
l				84	46
m				b)	b)

a) All reaction in solution were carried out in DMSO.
b) No reaction occurred.

yield.

The solvent-free addition of alkyne to carbonyl compounds with diastereotopic faces, such as 2-methylcyclohexanone (**1n**), gave a 1:1 mixture of diastereomeric propargyl alcohols (**3n**)[2] in 70% yield.

Various organic reactions have also been found to proceed efficiently in the solid state.[4]

In summary, we have found that the addition of ethynylbenzene to ketones is very useful and proceeds more efficiently in the absence of a solvent than in a DMSO solution at room temperature.

Experimental

General Methods. IR spectra were measured with a JASCO FT/IR-350 IR spectrometer, using Nujol mulls. ^{1}H NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-LA300 (300 MHz) spectrometer.

Typical Procedure in the Absence of a Solvent: Preparation of 2-Methyl-4-phenyl-3-butyn-2-ol (3a)[5] in the Absence of a Solvent. After acetone **1a** (1.0 g, 17.2 mmol), ethynylbenzene **2** (1.8 g, 17.2 mmol), and potassium *t*-butoxide (1.9 g, 17.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. The reaction product was mixed with 10% aqueous sodium chloride, filtered, washed with water, and dried to give **3a** as colorless crystals (2.6 g, 94% yield). **3a**: mp 41–43 °C; IR (Nujol) 3270 cm^{-1}; ^{1}H NMR δ 1.64 (s, 6H), 2.03 (s, 1H), 7.31–7.42 (m, 5H). Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55%. Found: C, 82.59; H, 7.73%. By the same procedure, the following compounds **3e**,[2] **3f**, **3h**, **3i**,[2] **3k**,[2] **3l**, and **3n**[2] as colorless crystals were prepared, in the yields shown in Table 1. **3e**: mp 39–41 °C; IR (Nujol) 3350 cm^{-1}; ^{1}H NMR δ 1.05 (d, 6H), 1.09 (d, 6H), 1.81 (s, 1H), 2.04 (m, 2H), 7.32–7.43 (m, 5H). Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.37%. Found: C, 83.12; H, 9.37%. **3f**: mp 57–58 °C; IR (Nujol) 3300 cm^{-1}; ^{1}H NMR δ 1.92 (s, 3H), 2.42 (s, 1H), 7.36–7.74 (m, 10H). Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35%. Found: C, 86.61; H, 6.40%. **3h**: mp 59–61 °C; IR (Nujol) 3300 cm^{-1}; ^{1}H NMR δ 0.92 (m, 3H), 1.48 (m, 2H), 1.98 (m, 2H), 2.41 (s, 1H), 7.34–7.70 (m, 10H). Calcd for $C_{18}H_{18}O$: C, 83.36; H, 7.25%. Found: C, 86.21; H, 7.27%. **3i**[2]: mp 54–56 °C; IR (Nujol) 3310 cm^{-1}; ^{1}H NMR δ 0.88 (d, 3H), 1.21 (d, 3H), 2.17 (m, 1H), 2.41 (s, 1H), 7.30–7.70 (m, 10H). Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25%. Found: C, 86.42; H, 7.32%. **3k**[2]: mp 49–50 °C; IR (Nujol) 3220 cm^{-1}; ^{1}H NMR δ 1.27–2.02 (m, 10H), 2.03 (s, 1H), 7.30 (t, 3H), 7.44 (d, 2H). Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05%. Found: C, 84.06; H, 8.20%. **3l**: mp 38–40 °C; IR (Nujol) 3270 cm^{-1}; ^{1}H NMR δ 1.56–2.15 (m, 12H), 1.96 (s, 1H), 7.31–7.43 (m, 5H). Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%. Found: C, 84.08; H, 8.62%. **3n**: mp 80–82 °C; IR (Nujol) 3370 cm^{-1}; ^{1}H NMR δ 1.12 (d, 3H), 1.22–1.78 (m, 9H), 2.17 (s, 1H), 7.26–7.47 (m, 5H). Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47%. Found: C, 84.07; H, 8.47%.

Preparation of 3-Methyl-1-phenyl-1-pentyn-3-ol (3b)[6] in the Absence of a Solvent. After 2-butanone **1b** (1.0 g, 13.9 mmol), ethynylbenzene **2** (1.4 g, 13.9 mmol), and potassium *t*-butoxide (1.6 g, 13.9 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. The reaction product was mixed with 10% aqueous sodium chloride and extracted twice with ether 10 mL. The ether solution was dried over $MgSO_4$, evaporated to give **3b** as colorless oil (2.2 g, 93% yield). **3b**: IR (Neat) 3370 cm^{-1}; ^{1}H NMR δ 1.13 (m, 3H), 1.58 (s, 3H), 1.78 (m, 2H), 2.06 (s, 1H), 7.26–7.48 (m, 5H). Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10%. Found: C, 82.72; H, 8.10%. By the same procedure, the following compounds **3c**, **3d**,[1,6] **3g**, and **3j** as colorless oil were prepared, in the yields shown in Table 1. **3c**: IR (Neat) 3360 cm^{-1}; ^{1}H NMR δ 1.02 (m, 3H), 1.56 (s, 3H), 1.63 (m, 2H), 1.75 (m, 1H), 2.06 (s, 1H), 7.30–7.43 (m, 5H). Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57%. Found: C, 82.65; H, 8.67%. **3d**: IR (Neat) 3380 cm^{-1}; ^{1}H NMR δ 1.11 (m, 6H), 1.76 (m, 4H), 1.99 (s, 1H), 7.31–7.42 (m, 5H). Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57%. Found: C, 82.54; H, 8.72%. **3g**: IR (Neat) 3380 cm^{-1}; ^{1}H NMR δ 1.01 (m, 3H), 2.08 (m, 2H), 2.59 (s, 1H), 7.28–7.69 (m, 10H). Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82%. Found: C, 86.08; H, 6.82%. **3j**: IR (Neat) 3350 cm^{-1}; ^{1}H NMR δ 1.75–2.08 (m, 8H), 1.87 (s, 1H), 7.30–7.12 (m, 5H). Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58%. Found: C, 83.39; H, 7.70%.

Preparation of 1-(Phenylethynyl)cyclohexanol (3k)[2] in the Absence of a Solvent. Using potassium hydroxide as a base, after cyclohexanone **1k** (1.0 g, 10.2 mmol), ethynylbenzene **2** (1.0 g, 10.2 mmol), and potassium hydroxide (1.1 g, 10.2 mmol) were well-mixed with agate mortar and pestle, the mixture was kept at room temperature for 20 min. The reaction product was mixed with 10% aqueous sodium chloride, filtered, washed with water, and dried to give 1-(phenylethynyl)cyclohexanol (**3k**) as colorless crystals (1.34 g, 66% yield).

Typical procedure in DMSO: Preparation of 1-(Phenylethynyl)cyclohexanol (3k) in DMSO. A mixture of cyclohexanone **1k** (1.0 g, 10.2 mmol), ethynylbenzene **2** (1.0 g, 10.2 mmol), and potassium *t*-butoxide (0.22 g, 2.0 mmol) was stirred in DMSO 10 mL at room temperature for 15 h. The reaction product was mixed with 10% aqueous sodium chloride, filtered, and washed with water, and dried to give 1-(phenylethynyl)cyclohexanol (**3k**) as colorless crystals (1.7 g, 83% yield).

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