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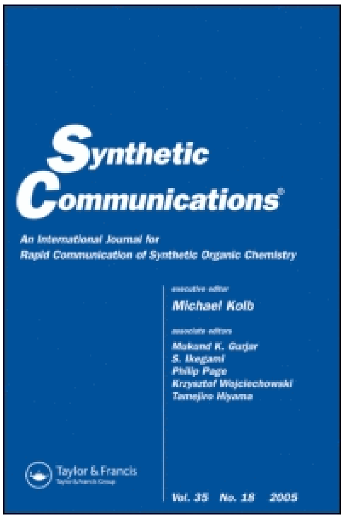

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Mild and Solvent-Free Alkynylation of Ketones on the KF/Alumina

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Abstract: The solvent-free alkynylation of various ketones on the surface of KF/alumina under mild conditions is described.

Keywords: Alkynes, alkynylation, ketones, KF/alumina, solvent-free

INTRODUCTION

Carbon–carbon bond formations are among the most important reactions in organic synthesis.[1] One significant example is alkynylation of carbonyl compounds for the preparation of propargylic alcohols. The traditional approach to these reactions involves the addition of alkynylide anions to carbonyl compounds. This process requires the conversion of alkynes to corresponding alkynylide anions using 1 equiv. of a strong air-sensitive base such as Grignard reagent,[2] alkyl lithium,[3] or sodium amide[4] in an anhydrous solvent. Adding the carbonyl compound gradually to this mixture prevents the competitive aldol reaction. More recent methods, making use of catalytic amounts of bases such as *t*-BuOK,[5] cesium hydroxide,[6] zinc alkynylides,[7] and quaternary ammonium hydroxide[8] are more favorable. However, these reactions suffer from the lack of generality and require the use of a solvent. Replacement of the organic solvents with ionic liquids,[9]

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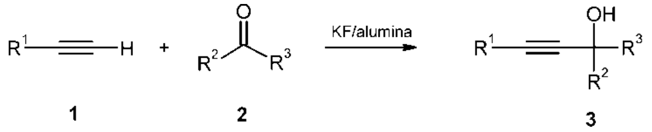
supercritical CO_2,[10] water,[11] or an adsorbent[12] seems to be more economical and ecological, and is garnering special interest. Recently, Miyamoto et al. have reported that the addition of ethynylbenzene to ketones using potassium *t*-butoxide or potassium hydroxide proceeds efficiently in the absence of a solvent.[13] However, the generality of this method has yet to be investigated for aliphatic acetylenes.

Earlier studies have revealed that potassium fluoride (KF), either alone or in the form of an adsorbed reagent, can be employed as a mild, effective, and nonnucleophilic base in organic reactions. In 1979, Yamawaki and Ando introduced KF/alumina as a useful, versatile reagent in alkylation reactions.[14] So far, the usefulness of this reagent has been widely investigated in many C–O, C–N, and C–C bond formation reactions.[15] With our continuing interest in developing practical, solvent-free reactions in mind,[16] we decided to investigate this reagent. We now report the reaction of terminal alkynes with ketones at room temperature using KF/alumina.

RESULTS AND DISCUSSION

This reaction of terminal alkynes with ketones proceeds on the surface of KF/alumina without solvent in up to 95% yield (Scheme 1). The results are summarized in Table 1. The solvent-free reaction appears to be more efficient than the solution phase reaction. For example, phenyl acetylene **1a** reacts with cyclohexanone **2h** on the surface of KF/alumina at room temperature to give 95% yield of the corresponding alcohol (Table 1, entry 8), whereas for the same substrates in DMSO using KO*t*Bu as a base, 83% yield has been reported.[13] The reaction of less acidic acetylenes fails when employing these conditions. For example, addition of 1-hexyne and



3a: R^1=Ph, R^2=Me, R^3=Me; **3b**: R^1=Ph, R^2=Me, R^3=Et; **3c**: R^1=Ph, R^2=Et, R^3=Et
3d: R^1=Ph, R^2=Me, R^3=*i*-Pr; **3e**: R^1=Ph, R^2=*i*-Pr, R^3=*i*-Pr; **3f** : R^1=Ph, R^2=Me, R^3=*n*-penthyl
3g: R^1=Ph, R^2=*n*-Bu, R^3=*n*-Bu; **3h**: R^1=Ph, R^2, R^3= $-CH_2-(CH_2)_3-CH_2-$
3i: R^1=Ph, R^2, R^3= $-CH_2-(CH_2)_4-CH_2-$; **3j**: R^1=$PhOCH_2$, R^2=Et, R^3=Et
3k: R^1=$PhOCH_2$, R^2=Me, R^3=*i*-Pr; **3l**: R^1=$PhOCH_2$, R^2=*i*-Pr, R^3=*i*-Pr
3m: R^1=*n*-Pentyl, R^2=Me, R^3=*n*-penthyl; **3n**: R^1=*n*-Hexyl, R^2=*n*-Bu, R^3=*n*-Bu
3o: R^1=2,4-DimethylphenylOCH_2, R^2, R^3= $-CH_2-(CH_2)_3-CH_2-$;
3p: R^1=1-NaphthylOCH_2, R^2, R^3= $-CH_2-(CH_2)_3-CH_2-$

Scheme 1.

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Table 1. Solvent-free alkynylation of ketones on the surface of KF/alumina

Entry	Alkyne	Ketone	Product[a]	Time/h (temp)	Yield (%)[b]
1	**1a**	**2a**	**3a**[8]	20 (rt)	90
2	**1a**	**2b**	**3b**[13]	20 (rt)	95
3	**1a**	**2c**	**3c**[8]	20 (rt)	90
4	**1a**	**2d**	**3d**[8]	15 (rt)	42
				15 (60°C)	90
5	**1a**	**2e**	**3e**[13]	17 (rt)	32
				15 (60°C)	95
6	**1a**	**2f**	**3f**[3a]	17 (rt)	46
7	**1a**	**2g**	**3g**[20]	17 (rt)	30
				15 (60°C)	93
8	**1a**	**2h**	**3h**[13]	17 (rt)	95
9	**1a**	**2i**	**3i**[13]	20 (rt)	40
				40 (rt)	70
10	**1b**	**2h**	**3j**[19]	20 (60°C)	90
11	**1b**	**2b**	**3k**[19]	20 (60°C)	95
12	**1b**	**2a**	**3l**[19]	5 (rt)	20
				17 (rt)	70
13	**1c**	**2h**	**3m**	20 (rt)	[c]
14	**1d**	**2h**	**3n**	20 (rt)	[c]
15	**1e**	**2h**	**3o**	20 (60°C)	92
16	**1f**	**2h**	**3p**	20 (60°C)	90

[a] Mp and/or spectral data (IR, ^{1}H-NMR and ^{13}C-NMR) of known compounds (**3a–l**) were compared with given references.

[b] Isolated yields.

[c] No reaction occurred.

1-heptyne to the cyclohexanone does not occur after 20 h at room temperature (Table 1, entries 13, 14).

The method is also suitable for functionalized acetylenes such as propargyl ethers **1b** and **1e–f**. They react with ketones to give the corresponding tertiary alcohols with moderate to high yields. These reactions are more efficient at higher temperatures (Table 1, entries 10, 15, 16). Raising the reaction temperature considerably affects the reaction rate and yield. For example, the addition of phenyl acetylene **1a** to the ketone **2g** results in 30% and 93% yields of the product **3g**, at room temperature and 60°C, respectively (Table 1, entry 7).

Using unsupported KF instead of KF/alumina dramatically decreases the reaction yields. The reason for this change might be explained by the lower basicity of unsupported KF compared with KF/alumina.[17] According to Ando,[17b] the basicity of KF/alumina not only results from the presence of active F^- (as in KF itself), but also from generated OH^- and Al–OH.

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In summary, we report here that KF/alumina is a very mild and efficient catalyst to promote the addition of primary alkynes to ketones, in an environmentally friendly reaction, without need of any reaction solvent and at room temperature.

EXPERIMENTAL

Mps were determined on a hot stage or oil-bath apparatus without correction. ^{1}H-NMR (80 MHz or 300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Bruker 80 MHz or Bruker WP 300 MHz in $CDCl_3$ using TMS as internal standard. HRMS were obtained on a Finnigan MAT system MAT 212.

Preparation of KF/Alumina[18]

Neutral alumina (60–80 mesh, 30 g) in water (150 ml) is added to a stirred solution of potassium fluoride (20 g) in water (150 ml). After 30 min the water is evaporated in a rotary evaporator at ~60°C. When most of the water has been removed, the remaining mixture is heated to 140–150°C and maintained at that temperature under vacuum (5 mmHg) for 6 h to give 50 g of KF/alumina reagent.

General Procedure for the Preparation of Tertiary Alcohols from Alkynes and Ketones

Alkyne (1 mmol), ketone (1.2 mmol), and KF/alumina (1 g) were mixed in a 25-mL flask at room or mentioned temperature. The progress of reaction was monitored by GC. After the given time, the reaction mixture was washed with petrol and filtered, and the solvent was evaporated on the rotavapour. The residue was purified with the bulb-to-bulb distillation technique or with a short silica-gel column (eluent: light petroleum ether/ethyl acetate, 20:1).

3o. Colorless oil, IR (KBr, ν, cm^{-1}): 3200–3500, 3020, 2932, 2856, 1256, 1215, 1130, 801. ^{1}H-NMR ($CDCl_3$): $\delta = 1.41-1.84$ (m, 10H), 2.15 (s, 3H), 2.19 (s, 3H), 2.30 (s, 1H), 4.83 (s, 2H), 6.60–6.80 (m, $3H_{arom}$). ^{13}C-NMR ($CDCl_3$): $\delta = 15.85$, 20.14, 22.88 (2C), 24.90, 39.47 (2C), 56.47, 58.50, 78.50, 91.34, 112.38, 126.63, 128.59, 130.63, 131.35, 154.93. MS (EI): $m/z = 55$ (46), 77 (38), 91 (40), 107 (42), 122 (100%), 136 (20), 160 (20), 258 (33) [M^+]. HRMS (EI): m/z calcd. for $C_{17}H_{22}O_2$: 258.1620; found: 258.1620.

3p. Colorless oil, IR (KBr, ν, cm^{-1}): 3200–3500, 3055, 2925, 2858, 1580, 1504, 1266, 1228, 1173, 1097, 1018, 791. ^{1}H-NMR ($CDCl_3$):

$\delta = 1.43{-}1.75$ (m, 10H), 2.10 (s, 1H), 4.86 (s, 2H), 6.80 (m, $1H_{arom}$), 7.30–7.50 (m, $4H_{arom}$), 7.70–7.80 (m, $1H_{arom}$), 8.20–8.40 (m, $1H_{arom}$). ^{13}C-NMR ($CDCl_3$): $\delta = 22.95$ (2C), 24.90, 39.52 (2C), 56.20, 68.32, 78.91, 91.36, 105.75, 120.85, 121.91, 124.80, 125.09, 125.39, 126.22, 127.25, 134.12, 153.48. MS (EI): $m/z = 41$ (38), 55 (35), 115 (28), 152 (88), 171 (62), 181 (100), 209 (53), 233 (42), 262 (22), 280 (93) [M^+]. HRMS (EI): m/z calcd. for $C_{19}H_{20}O_2$: 280.1463; found: 280.1464.

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