Synthesis of propargylic alcohols by base promoted alkynylation of ketones with ethynylbenzene using ionic liquid [(bmim) PF_6]

Sachin R. Jagtap and Bhalchandra M. Bhanage*

Department of Chemistry, Institute of Chemical Technology (Autonomous), University of Mumbai, N. Parekh Marg, Matunga, Mumbai – 400 019, India

A mild and efficient addition of ethynylbenzene with ketones using KOH in ionic liquid 1-butyl-3-methylimidazolium hexaflurophosphate [(bmim) PF_6] gives propargylic alcohols in high yields.

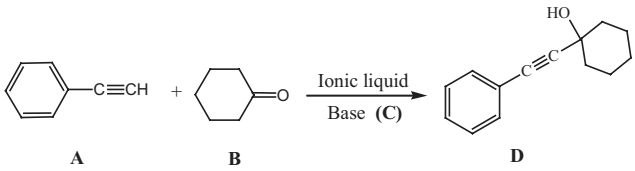
Keywords: alkynylation, ionic liquid, base, propargylic alcohols, reuse

Propargylic alcohols are well known as a versatile building block for the synthesis of many natural products such as prostaglandins, steroids, carotenoids, *etc*.[1] They are generally prepared by the addition of alkynylmetals to aldehydes and ketones using catalytic/stoichiometric amount of Lewis aãd or base. High aãdity and strong basiãty of many alkynylmetals including alkynyl-Li, Na, K and Mg, also causes undesired side reactions.[2] Recently, a considerable progress has been made in the alkynylation of carbonyl compounds using Lewis aãd *e.g.* $SnCl_4$,[3] GaI_3,[4] $Sn(OTf)_2$[5] and $Zn(OTf)_2$[6a] and $ZnCl_2$[6b] in combination with a base. Various bases such as quaternary ammonium hydroxide,[7] KF/Al_2O_3,[8] $CsOH.H_2O$[9] and *t*-BuOK[10] have also been reported for the alkynylation of carbonyl compounds. However, *t*-BuOK catalysed alkynylation of enolisable carbonyl compounds leads to a complex mixture of products,[10] Cs-catalysed alkynylation gave solution to this problem but have a limitation that they cannot be used for the alkynylation of aromatic carbonyl compounds.[9] Therefore, a versatile method for the synthesis of propargylic alcohols with a wider range of substrates, including both aldehyde or ketones and aromatic carbonyl compounds, is highly desirable. Despite a number of Lewis aãd and Lewis base systems have been developed for the alkynylation of carbonyl compounds, no attention was paid to carry out the reaction in ionic liquid as a solvent media and using inexpensive base.

Within a past few years the area of ionic liquids have emerged as a new class of 'green' solvents for the variety of chemical transformations and have attracted considerable attention. The nonvolatile nature of ionic liquids gives them significant advantage in minimising VOC's and solvent consumption. Their polarity renders them good solvents for homogeneous catalysis[11]. In many applications ionic liquids with weakly coordinating anions, such as BF_4^- and PF_6^-, together with suitably substituted cations often results in an altered chemical reactivity and selectivity. Among the commonly used ionic liquids, 1-butyl-3-methylimidiazolium hexafluorophosphate [(bmim) PF_6] is a common reaction medium for the various organic transformations such as hydrogenation,[12] hydroformylation,[13] oxidation,[14] *etc*. We now report the alkynylation of ketones promoted by potassium hydroxide in ionic liquid [(bmim) PF_6] as a solvent furnishing propargylic alcohol in moderate to high yields.

Using cyclohexanone as a typical representative of ketones, we investigated the addition reaction under various conditions using [(bmim) PF_6] in the presence of different bases and reaction conditions were optimised (Scheme 1). The typical results are summarised in Table 1.

It can be seen from entries 1–4 (Table 1) that with increase in the amount of potassium hydroxide from 0.2 equivalents to 1 equivalent the yield of **D** increases from 34 to 92% (Table 1, entries 1–3). Further increase in the molar ratio of base leads to decrease in the yield of **D** (Table 1, entry 4). The higher yield of **D** was obtained when the **A: B: C** are in the ratio 1 : 1 : 1 at 70°C and the reaction was completed within shorter reaction time of 10 min giving 92% yield of **D**. In order to study the effect of temperature the reaction was carried out at various temperature (Table 1, entries 3 and 5, 6). At room temperature the yield of **D** was found to be very low 48% and it requires 90 min. However, with increase in the temperature, enhancement in the rate of reaction and yield was observed. Thus, at 45°C the yield of **D** was found to be 70% in 30 min and the higher yield of **D** (92%) was obtained at 70°C in 10 min. The effect of various bases on the reaction was also studied as shown in the entry 3 and 7–11 (Table 1) and among them potassium hydroxide was found to give best result *i.e.* 92% yield of **D** in 10 min at 70°C. The enhancement in the rate and the yield of reaction obtained is because of the solvent effect of the ionic liquid. When the same reaction is carried out using conventional organic solvents like DMSO, NMP and DMF, which gives only 15%, 13%, 13% yield of the **D** respectively. It indicates the role of ionic liquid in enhancement of rate and yield of reaction. After the completion of the reaction the product was extracted using diethyl ether. The ionic liquid recovered after the extraction was reused under identical reaction conditions with addition of fresh base. The recycling studies were performed for four times which gives identical results indicating reusability of ionic liquid. Thus our approach using ionic liquid has



Scheme 1 Alkynylation of cyclohexanone.

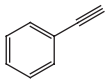
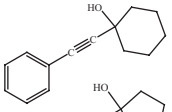
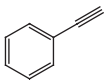
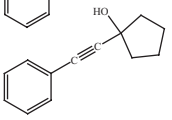
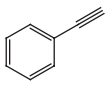
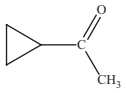
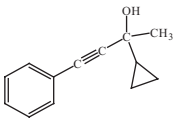
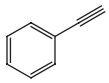
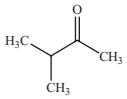
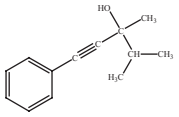
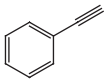
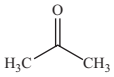
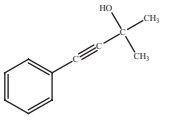
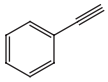
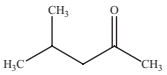
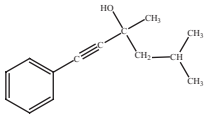
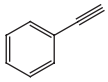
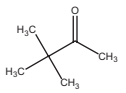
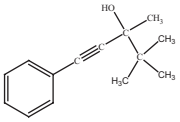
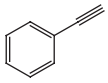
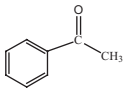
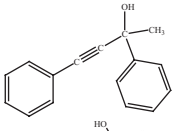
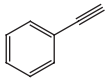
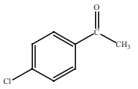
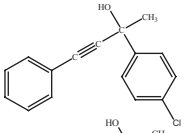
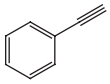
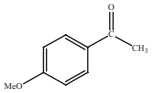
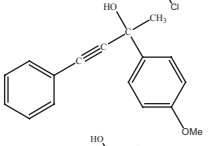
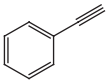
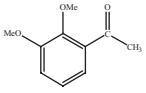
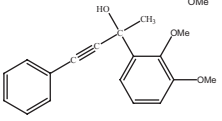
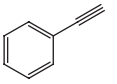
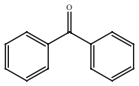
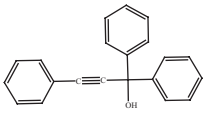
Table 1 Reaction of cyclohexanone with ethynylbenzene catalysed by various bases under different conditions using ionic liquid [(bmim) PF_6]

Entry	Base	Mol.ratio of A : B : C	Time/min	Temp/^{0}C	[a]Yield/%
1	KOH	1 : 1 : 0.2	10	70	34
2	KOH	1 : 1 : 0.5	10	70	67
3	KOH	1 : 1 : 1	10	70	92
4	KOH	1 : 1 : 1.5	10	70	78
5	KOH	1 : 1 : 1	90	R.T.	48
6	KOH	1 : 1 : 1	30	45	70
7	NaOH	1 : 1 : 1	10	70	74
8	NaOMe	1 : 1 : 1	10	70	27
9	NaOEt	1 : 1 : 1	10	70	25
10	K_2CO_3	1 : 1 : 1	10	70	0
11	Na_2CO_3	1 : 1 : 1	10	70	0

[a]Isolated yield.

* Correspondent. Email: bhalchandra_bhanage@yahoo.com; bmb@udct.org

Table 2 Alkynylation of ketones in presence of potassium hydroxide in ionic liquid

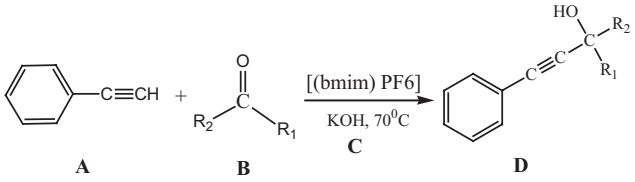
Entry	A	B	D	Time/min	[a]Isolated yield/%
1				10	92
2				10	90
3				10	85
4				10	90
5				10	90
6				10	92
7				10	95
8				20	75
9				25	72
10				20	70
11				30	68
12				30	65

Reaction conditions: Phenylacetylene 2 mmol, ketone 2 mmol, KOH 2 mmol, 1 gm [(bmim) PF_6] temperature 70°C.
[a]Isolated yield.

following advantages; shorter reaction time, high yield, low cost and environmentally friendly.

Therefore in the following investigations, we discussed the addition of ethynylbenzene to different ketones under all the above optimum conditions (Scheme 2). All the results obtained are listed in Table 2.

It is clearly observed from the Table 2, that the reaction of aliphatic acyclic or cyclic ketones proceeds very effiãently within short time of 10 min giving excellent yield of product (entries 1–7). While the addition of aromatic ketones with ethynylbenzene required longer reaction time and result in



Scheme 2 Alkynylation of various ketones using ethylylbenzene

lower yield of expected product (entries 8–11).

In conclusion, potassium hydroxide mediated synthesis of propargylic alcohols via addition of ethynylbenzene to ketones gives excellent yield in [(bmim) PF_6].

Experimental

A solution of KOH (2 mmol) in ethanol (3 ml) was added to 1 g of [(bmim) PF_6]. The clear solution was kept under vacuum at 50°C for 12 h. To this basic solution ethynylbenzene (2 mmol) was added and the reaction mixture was stirred for 5 min at room temperature then the ketone (2 mmol) was added to the reaction mixture and the reaction mixture was heated at 70°C with continuous stirring for the speãfic reaction time as mentioned in Table 1. The progress of the reaction is monitored by TLC. After completion of the reaction mixture the viscous solution was submitted to continuous liquid–liquid extraction with diethyl ether until no further product recovery was obtained. The organic extract were then concentrated in vacuum and the crude product obtained was subjected to column chromatography for further purification and all the products were analysed by GC–MS (SHIMADZU QB 2010), MS Thermo Finnigan LCQ Advantage Max, NMR (Varian 400 MHz) and IR (Perkin Elmer FTIR Spectrum 100) Spectroscopy. After the diethyl ether extraction the ionic liquid was kept at 40°C under reduced pressure for 12 h and a second run was performed under identical reaction conditions. Reuse of the ionic liquid was carried out four times successively.

Spectroscopic data of propargylic alcohols

D1[15]: IR (film) 3257, 2258 cm^{-1}; ^1H NMR δ 1.44–1.70 (m, 10H), 2.50 (s, 1H), 7.30 (t, 3H, J = 3.1 Hz), 7.43 (d, 2H, J = 2 Hz); Mass EI-MS *m/z* (rel. intensity) M^+199 (79), 185 (9), 171 (15), 157 (100), 144 (28), 129 (52), 115 (30), 102 (26), 91 (10), 81 (27).

D2[15]: IR (film) 3381, 2225 cm^{-1}; ^1H NMR δ 1.70–1.90 (m, 8H), 2.10 (s, 1H), 7.30 (t, 3H, J = 6 Hz), 7.43 (d, 2H, J = 3.9 Hz); Mass EI-MS *m/z* (rel. intensity) M^+ 186 (20), 185 (100), 171 (2), 157 (30), 143 (8), 129 (50), 115 (26), 102 (20), 91 (9), 77 (10), 67 (20), 55 (20).

D3: IR (film) 3404, 2232 cm^{-1}; ^1H NMR δ 0.45 (m, 4H), 0.65 (s, 1H), 1.01 (s,3H), 2.0 (s, 1H), 7.31 (t, 3H, J = 4.3 Hz), 7.43 (d, 2H, J = 2.8 Hz); Mass EI-MS *m/z* (rel. intensity) M^+186 (7), 171 (35), 158 (80), 145 (20), 129 (45), 115 (25), 102 (18), 91 940, 77 (12), 69 (10), 43 (100).

D4[16]: IR (film) 3406, 2230 cm^{-1}; ^1H NMR δ 1.16–1.19 (m, 6H), 1.70 (s, 3H), 2.21 (s, 3H), 7.30 (t, 3H, J = 6 Hz), 7.42 (d, 2H, J = 2.1 Hz); Mass EI-MS *m/z* (rel. intensity) M^+188 (2), 173 (5), 155 (2), 145 (100), 129 (9), 115 (4), 102 (7), 91 (2), 77 (4), 63 (2), 43 (55).

D5[15]: IR (film) 3361, 2229 cm^{-1}; ^1H NMR δ 1.60 (s, 6H), 2.90 (s, 1H), 7.30 (t, 3H, J = 6.4 Hz), 7.42 (d, 2H, J = 3.2 Hz); Mass EI-MS *m/z* (rel. intensity) M^+160 (27), 145 (100), 129 (9), 115 (15), 102 (10), 91 (7), 72 (10), 63 (5), 43 (85).

D6: IR (film) 3396, 2229 cm^{-1}; ^1H NMR δ 1.05(m, 6H), 1.60 (s, 3H), 1.70 (d, 2H, J = 1.8 Hz), 2.10 (s, 1H), 7.30 (t, 3H, J = 4.6 Hz), 7.42 (d, 2H, J = 5.9 Hz); Mass EI-MS *m/z* (rel. intensity) M^+ 202 (2), 201 (2), 187 (10), 169 (2), 159 (3), 145 (100), 129 (10), 115 (8), 102 (9), 91 (2), 77 (4), 57 (2), 43 (50).

D7: IR (film) 3458, 2228 cm^{-1}; ^1H NMR δ 1.10 (s, 9 H), 1.58 (s, 3H), 2.0 (s, 1H), 7.30 (t, 3H, J = 4.7 Hz), 7.40 (d, 2H, J = 1.6 Hz); Mass EI-MS *m/z* (rel. intensity) M^+ 202 (2), 187 (7), 172 (2), 159 (3), 145 (100), 129 (10), 115 (8), 102 (5), 91 (2), 77 (3), 57 (9), 43 (41).

D8[15]: IR (film) 3302, 2250 cm^{-1}; ^1H NMR δ 2.20 (s, 3H), 2.45 (s, 1H), 7.30–7.78 (m, 10H); Mass EI-MS *m/z* (rel. intensity) M^+ 222 (35), 221 (100), 207 (95), 189 (9), 179 (75), 165 (5), 145 (8), 129 (78), 115 (10), 105 (35), 89 (7), 77 (40), 63 (8), 43 (28).

D9: IR (film) 3379, 2234 cm^{-1}, ^1H NMR δ 2.80 (s, 3H), 2.90 (s, 1H), 7.30–7.62 (m, 9H); Mass CI-MS $(M + 1)^+$ 257.5 (50), 239 (100), 204 (22), 179 (15), 170 (33), 144 (5), 126 (20), 113 (6), 103 (22).

D11: IR (film) 3491, 2290 cm^{-1}, ^1H NMR δ 1.84 (s,3H), 2.01 (s, 3H), 3.90 (m, 6H), 6.85 (t, 3H, J = 5.6 Hz), 7.25–7.60 (m, 5H); Mass CI-MS $(M + 1)^+$ 283 (15), 265 (20), 234 (93), 219 (100), 204 (45), 181 (32), 153 (18), 137 (30), 126 (58).

D12: IR (film) 3368, 2230 cm^{-1}, ^1H NMR δ 3.0 (s, 1H), 7.20–7.80 (m, 15H); Mass CI-MS $(M + 1)^+$ 285 (12), 267 (100), 183 (7), 165 (10).

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