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Glaser oxidative coupling in ionic liquids: an improved synthesis of conjugated 1,3-diynes

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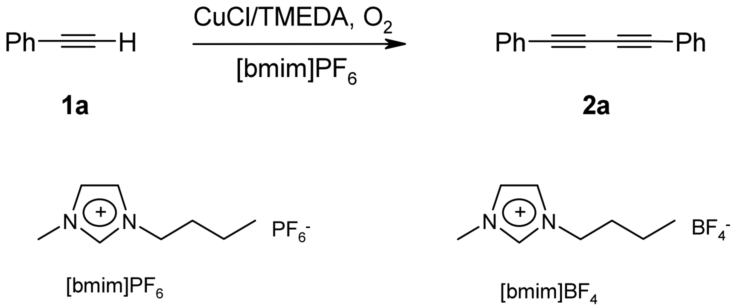
Abstract—Terminal alkynes undergo oxidative-coupling smoothly in the presence of the CuCl-TMEDA catalytic system in hydrophobic [bmim]PF_6 ionic liquid under aerobic conditions to produce 1,3-diynes in excellent yields under mild conditions. The substrates, alkynes, show enhanced reactivity and selectivity in ionic liquids (ILs). The recovery of the catalyst is facilitated by the hydrophobic nature of the [bmim]PF_6 ionic liquid.

Conjugated polyyne structures have attracted much attention,[1] since they are found in many natural products,[2] particularly anti-fungal agents.[3] They are useful precursors for the synthesis of monomers, polymers and functional host molecules.[4] The preparation of 1,3-diynes via coupling between *sp*-hybridized atoms represents one of the most important carbon–carbon bond formations in organic synthesis.[5] The Glaser coupling[6] and Eglinton procedures[7] for direct coupling of terminal alkynes and modifications thereof represent the most widely used alkyne coupling reactions for the synthesis of 1,3-diynes.[8,9] The classical oxidative alkyne-dimerization reactions are generally carried out in organic solvents such as methanol, acetone, pyridine, methyl cellosolve and toluene. However, many of these methods often require large volumes of organic solvents which always demand an aqueous work-up for their separation or recycling or disposal. Consequently, methods that successfully minimize their use are the focus of much attention. Thus, the use of solvents like water, supercritical fluids and ionic liquids has received a great deal of attention in recent times in the area of green synthesis.

Ionic liquids have recently gained recognition as possible environmentally benign alternative solvents in various chemical processes. Accordingly, they are emerging as a set of green solvents with unique properties such as good solvating ability, wide liquid range, tunable polarity, negligible vapor pressure, high thermal stability and ease of recyclability. Ionic liquids are attractive especially for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[10] Their unprecedented ability to solvate a broad spectrum of substrates has widened the horizon of their applicability. The properties of ionic liquids can be tailored by the fine-



Scheme 1.

Keywords: ionic liquids (ILs); alkynes; oxidative-coupling; 1,3-diynes.

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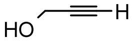
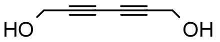
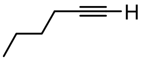
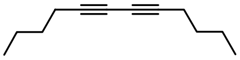
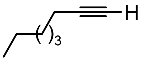
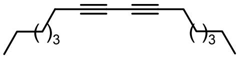
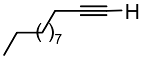
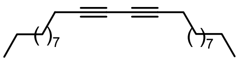
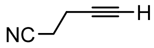
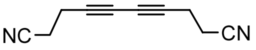
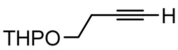
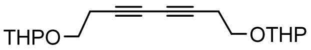
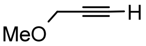
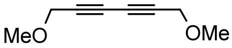
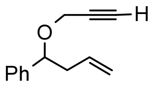
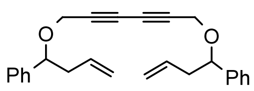
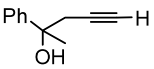
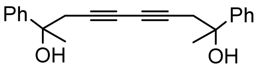
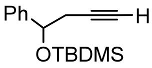
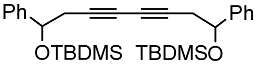
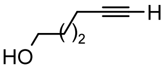
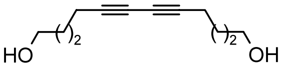
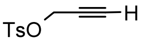
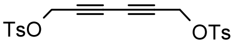
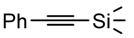
tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to an organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering for the needs of any particular process.

Table 1. Oxidative coupling of acetylenes in ionic liquids at room temperature

Entry	Substrate **1**	Product[a] **2**	Time(h)	Yield(%)[b]
a	Ph—≡—H	Ph—≡—≡—Ph	4.5	95
b			7.5	89
c			6.0	95
d			6.5	89
e			7.0	90
f			5.0	87
g			6.5	90
h			5.5	89
i			8.0	87[c]
j			7.5	85[c]
k			7.0	88[c]
l			6.0	90
m			6.5	85
n		Ph—≡—≡—Ph	7.5	no reaction

a:All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
b:Isolated and unoptimized yields.
c:The products were obtained as diastereomeric mixtures.

Table 2. Recyclability of 2 mL of [bmim]PF_6 ionic liquid for oxidative dimerizaton of 2-propyn-1-ol

Runs	2-Propyn-1-ol (mmol)	% CuCl/ TMEDA	Time (h)	Yield (%)
1	1	0.2/0.2 mmol	7.5	89
2	1		8.5	87
3	1	0.2/0.2 mmol	6.0	92
4	1		7.5	90
5	1	0.2/0.2 mmol	5.5	95
6	1		6.5	92

Hence, there is significant interest in using them as replacements for conventional organic solvents. However, there are no examples of the use of ionic liquids as solvents for the oxidative coupling of alkynes.

In this paper, we wish to report the use of ionic liquids as solvents for the oxidative-dimerization of alkynes to produce 1,3-diynes under mild conditions. Ionic liquids allow the recycling and reuse of this catalytic system. Thus, the treatment of phenylacetylene with 0.2 mol% CuCl and TMEDA (0.2 mol%) in [bmim]PF_6 ionic liquid under an oxygen atmosphere afforded the corresponding 1,4-diphenyl-1,3-butadiyne in 95% yield (Scheme 1).

These results prompted us to investigate the scope of this process for various alkynes. Interestingly, a wide range of alkynes underwent oxidative-dimerization under these reaction conditions to produce the corresponding 1,3-diynes in excellent yields (see Table 1). The reactions proceed smoothly at room temperature with high functional group selectivity. The products were obtained in high to quantitative yields after simple extraction with toluene. In contrast to organic solvents, enhanced reaction rates, improved yields and high functional group compatibility are features obtained in ionic liquids. For example, the treatment of phenylacetylene with 0.2 mol% CuCl and TMEDA (0.2 mol%) in [bmim]PF_6 for 4.5 h afforded the corresponding 1,4-diphenyl-1,3-butadiyne **2a** in 95% yield whereas the same reaction in methanol after 12 h gave the product in 75% yield. The major advantage of the use of ionic liquids as reaction media is that these ionic liquids can be easily recovered and recycled in subsequent runs. Since the products were moderately soluble in the ionic phase, they can be easily separated by simple extraction either with toluene or with ether. The remaining ionic liquid was further washed with toluene and reused in four to six successive runs. The yields gradually decreased in runs carried out using recovered ionic liquid. However, on the addition of more catalyst to each alternate run, the yields and reaction rates were enhanced significantly as shown in Table 2.

The maximum conversion was obtained in the fifth cycle. This is probably due to the high concentration of catalyst and increased solubility of oxygen in the ionic liquid. Compared to conventional solvents, the solubility of gases in ionic liquids is generally high.[11] This is another advantage of the use of ionic liquids for hydrogenation or aerobic oxidation reactions. In particular, the recovery of the catalyst is extremely simple in ionic liquids (ILs) when compared to organic solvents. As is evident from Table 1, acid sensitive protecting groups such as THP, TBDMS and allyl ethers are compatible with these reaction conditions.[12] Thus, the present method is mild enough to tolerate a wide range of functional groups present in the substrate. Finally, the reactivity of various alkynes was tested in the hydrophilic [bmim]BF_4 and the hydrophobic [bmim]PF_6 ionic liquids. The [bmim]BF_4 ionic liquid was found to be equally good for this conversion. Both the PF_6^- and BF_4^- ionic liquids were obtained from Fluka and used without any further purification. Ionic liquids have also been prepared in our laboratory from the readily available and inexpensive *N*-methyl imidazole, 1-chlorobutane and hexafluorophosphoric acid or sodium tetrafluroborate. The purity of the ionic liquids prepared in the lab was determined by comparison of their ^1H NMR spectra with commercial samples. The purity of [bmim]PF_6 ionic liquid was $\geq$97.0% (NMR).

In summary, this paper describes a novel and efficient protocol for the synthesis of conjugated diynes through oxidative dimerization of terminal alkynes in ionic liquids. The alkynes show a significant increase in reactivity in ionic liquids thereby reducing the reaction times and improving the yields. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of this green strategy for the synthesis of 1,3-conjugated diynes.

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12. General procedure: A mixture of terminal alkyne (1 mmol), TMEDA (0.2 mmol), CuCl (0.2 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate (2 mL) was stirred under an atmosphere of air or O_2 (balloon) at ambient temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on a small silica gel column and eluted with n-hexane to afford pure symmetrical diyne. The remaining oily ionic liquid was further washed with ether and recycled in subsequent runs. Finally, the ionic liquid was extracted with ethyl acetate to remove any copper salt. Then the organic layer was concentrated in vacuo to recover the ionic liquid. The products were characterized by comparison of their NMR, IR, mass, TLC, mixed TLC analysis and physical data with those of authentic samples. The spectroscopic data for all the products other than **2i** and **2k** were identical with data reported in literature.[13]

    2i: Liquid, IR (KBr): ν 3073, 2925, 2855, 2221, 1642, 1455, 1345, 1079, 916, 758, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (ddd, 2H, $J=4.5$, 6.9, 11.5 Hz), 2.65 (ddd, 2H, $J=5.0$, 7.9, 11.5 Hz), 3.98 (d, 2H, $J=13.5$ Hz), 4.25 (d, 2H, $J=13.5$ Hz), 4.60 (t, 2H, $J=6.9$ Hz), 5.09 (dd, 2H, $J=1.9$, 10.3 Hz), 5.13 (dd, 2H, $J=1.9$ 17.4 Hz), 5.80 (ddt, 2H, $J=6.9$, 10.3, 17.4 Hz), 7.30–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, proton decoupled, 75 MHz): δ 29.6, 42.0, 56.0, 75.3, 80.6, 117.1, 127.0, 128.0, 128.5, 134.3, 140.2. FAB Mass: m/z: 370 M$^+$, 221, 181, 165, 153, 131, 123, 115, 103, 91, 81, 69, 57. HRMS calcd for $C_{26}H_{26}O_2$: 370.1932. Found: 370.1969.

    2k: Liquid, IR (KBr): ν 3032, 2932, 2858, 2122, 1467, 1367, 1255, 1096, 935, 838, 778. ^{1}H NMR ($CDCl_3$): δ 0.0 (s, 6H), 0.15 (s, 6H), 0.90 (s, 18H), 2.45–2.60 (m, 4H), 4.80 (t, 2H, $J=6.5$ Hz), 7.30–7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, Proton decoupled, 75 MHz): δ −4.9, 18.2, 25.7, 30.9, 69.8, 73.7, 81.6, 125.8, 127.4, 128.0, 143.9. FAB Mass: m/z: 518 M$^+$, 469, 367, 327, 301, 216, 165, 135, 107, 89, 77, 63, 55. HRMS calcd for $C_{32}H_{46}Si_2O_2$: 518.3036. Found: 518.3081.

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