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Sonogashira cross-coupling in a designer ionic liquid (IL) without copper, external base, or additive, and with recycling and reuse of the IL

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ABSTRACT

Application of a piperidine-appended dimethyl-imidazolium-NTf_2 ionic liquid as dual solvent and base in the Sonogashira cross-coupling reaction of aryl-iodides with terminal acetylenes under mild conditions has been demonstrated. The method employs $PdCl_2(PPh_3)_2$ without copper and external base. It is applicable to the synthesis of SF_5-substituted diaryl- and aryl-alkyl-acetylenes, and can also be utilized for efficient homo-coupling of terminal acetylenes under aerobic conditions. The potential for recycling and reuse of this designer-IL offers an added advantage.

The Sonogashira cross-coupling reaction is a powerful method for the synthesis of internal alkynes and enynes. This highly versatile C_{sp2}–C_{sp} bond forming protocol is widely exploited in the synthesis of natural products, pharmaceuticals, agrochemicals, and materials. The reactions are typically carried out by using catalytic amounts of palladium (most commonly $Pd(Ph_3P)_2Cl_2$) along with a copper halide (typically CuI) in the presence of an amine, used either as solvent or as cosolvent along with solvents such as DMF, THF, or toluene. Both homogeneous and heterogeneous Sonogashira coupling have been extensively studied, and progress in this ever expanding research area has been summarized in timely reviews.[1–5]

Research aimed at: (a) replacing Pd for the more readily available, cheaper metals, (b) copper-free conditions, (c) avoiding the use of large quantities of base, (d) replacing solvents such as DMF and DMSO with environmentally more acceptable alternatives, and (e) minimizing competing formation of homocoupling products, constitute active areas that are under continuous development. Along these lines, ligand-free Fe/Cu co-catalyzed Sonogashira coupling reactions have been reported by using $Fe(acac)_3$/CuI and Fe_2O_3/$Cu(acac)_2$.[6,7] These methods still require base and are typically performed at high temperatures in DMF or DMSO. By using $PdCl_2$ along with a water soluble phosphine ligand,[8] or by employing Pd-nanoparticles[9], the coupling reaction could be carried out in water/amine mixtures. Competing homocoupling was greatly lowered by performing the reaction in $Pd(Ph_3P)_2Cl_2$/CuI/TEA/MeCN under reflux and by working under $H_2 + N_2$ atmosphere.[10] Efficient homocoupling of terminal alkynes was reported with $Pd(OAc)_2$/DABCO/CuI/air/MeCN,[11] or via a Cu(I)-catalyzed method employing $CuCl/O_2$ together with an amine ligand (TMEDA, DBEDA, DABCO) in MeCN as solvent.[12]

Ionic liquids (ILs) have shown promise as versatile media for various Pd-catalyzed reactions including Sonogashira.[13] Apart from [BMIM][PF_6],[14–16] phosphonium type amino acid-ILs,[17] and biodegradable ILs[18] have been employed along with the Pd catalyst [$Pd(OAc)_2$, $PdCl_2$, or $Pd(Ph_3P)_2Cl_2$, or a phosphine-ligated Pd-complex] together with a base (TEA, iPr_2NH, or piperidine). The copper-free Sonogashira reaction employed ultrasound,[15] or a phosphine-ligated Pd-complex.[18]

A basic-IL with appended iPr_2N-groups was previously used in representative C–C bond forming reactions including Sonogashira.[19] The method utilized $Pd(Ph_3P)_2Cl_2$ along with piperidine or methanol and was accompanied by noticeable homocoupling (10–40%).

In continuation of our previous studies on metal-mediated transformations in ILs,[20] and in connection to our continuing interest in the synthesis of SF_5-aromatics,[21] we report here on the application of a piperidine-appended dimethyl-imidazolium-NTf_2 **IL-1** acting as dual solvent and base in the Sonogashira cross-coupling

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reaction of aryl-iodides with terminal acetylenes under mild conditions with minimal competing homocoupling.[22] The method employs $PdCl_2(PPh_3)_2$ and is copper and external-base free. The efficacy of the method was tested in the synthesis of SF_5-substituted diaryl- and aryl-alkyl-acetylenes. The **IL-1** was also utilized for efficient homo-coupling of terminal acetylenes under aerobic conditions.[23] The potential for recycling and reuse of this designer-IL was also studied.[24]

The **IL-1** (Fig. 1) is a dark-brown oily liquid at room temperature and is conveniently prepared from the chloride salt by standard metathesis with $LiNTf_2$ (see Supplementary file).

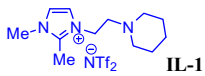


Figure 1. Task-specific IL as dual solvent/base for the Sonogashira reaction.

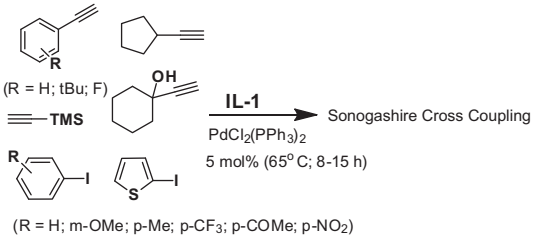


Figure 2. Scope of the Sonogashira cross-coupling reaction using **IL-1**.

Figure 2 gives a summary of the alkynes and the iodides used in this study and Table 1 gives a summary of the experimental results.

The efficacy of the **IL-1** catalyzed Sonogashira reaction was subsequently tested in the synthesis of SF_5-substituted analogs (Fig. 3) and results are summarized in Table 2.

The iodo-pentafluorosulfanylbenzene was prepared via the diazonium salt[21] by reaction with KI (see Supplementary file).

The method was also applied to the synthesis of diynes via homocoupling under aerobic condition and the results are summarized in Table 3.

The potential for recycling and reuse of **IL-1** was tested in the Sonogashira reaction of 4-iodoacetophenone and phenylacetylene (entry 4 in Table 1) by repeating the reaction four additional times using the same IL. The results (Chart 1) show a gradual decrease in the isolated yields from 85% to 68% after a total of 5 runs.

In summary we have discovered a facile one-pot approach for the preparation of a library of diaryl- and aryl-alkyl-acetylenes including the SF_5-substituted derivatives by using a designer IL functioning as dual solvent/base in the Sonogashira reaction without the need for any other additive. The method is also suitable for

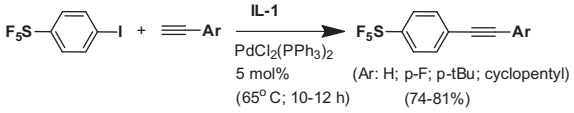
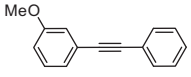
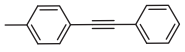
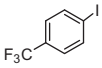
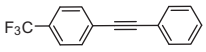
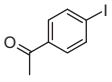
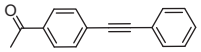
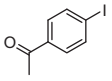
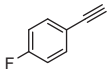
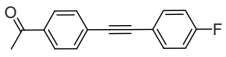
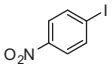
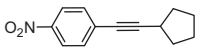
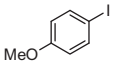
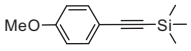
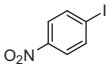
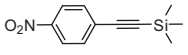
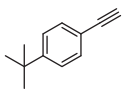
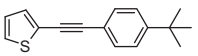
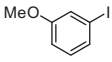
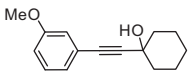


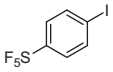
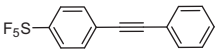
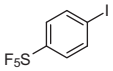
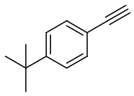
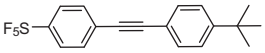
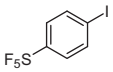
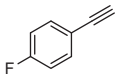
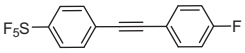
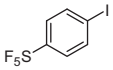
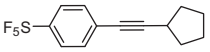
Figure 3. Synthesis of SF_5-substituted analogs.

Table 1
Scope of the Sonogashira coupling reaction in **IL-1**

Entry	ArX	Alkyne	Product	Time (h)	Temp (°C)	Yield[a,b] (%)	Homocoupling (%)
1				10	65	84	8
2				12	65	76	11
3				10	65	83	12
4				12	65	85	9
5				12	65	79	13
6				10	65	78	15
7				8	65	79	No
8				8	65	81	No
9				12	65	78	6
10				15	65	72	19

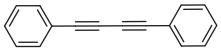
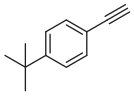
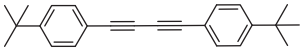
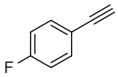
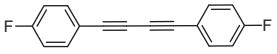
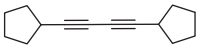
[a] Product characterized by NMR, IR, and MS.
[b] Yields refer to isolated products after purification; no = not observed.

Table 2
Application of the method in the synthesis of SF_5-analogs

Entry	ArX	Alkyne	Product	Time (h)	Temp (°C)	Yield[a,b] (%)	Homocoupling (%)
11				10	65	81	13
12				12	65	77	14
13				12	65	76	14
14				10	65	74	17

[a] Products characterized by NMR, IR, and MS.
[b] Yields refer to isolated products after purification.

Table 3
Efficacy in the synthesis of diynes by homocoupling

Entry	Alkyne	Product	Time (h)	Temp (°C)	Yield[a,b] (%)
15			10	Rt	93
16			10	70	92
17			10	Rt	89
18			10	70	87

[a] Products characterized by NMR, IR, and MS.
[b] Yields refer to isolated products after purification.

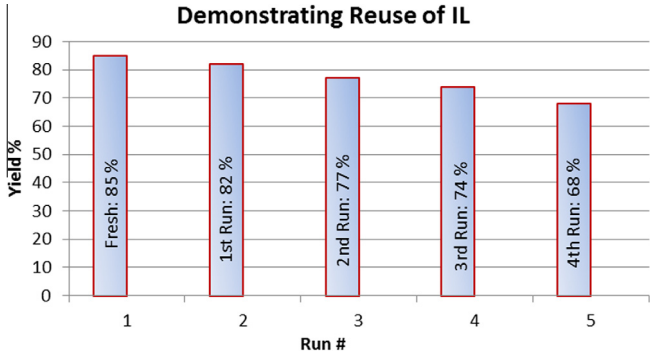


Chart 1. Recycling and reuse of **IL-1** in the Sonogashira reaction of 4-iodoacetophenone and phenylacetylene.

homocoupling reactions. Simple product isolation and recycling and reuse of the IL are added advantages of this method.

Acknowledgement

K.L. thanks UNF for the award of Presidential Professorship and for research support.

Supplementary data

Supplementary data (complete experimental procedures and characterization data for the reported products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.067.

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22. *General procedure for the coupling of aryl iodides with terminal alkynes*: Reactions were typically carried out on 50–60 mg scale. The basic ionic liquid (15 equiv) was charged into a 10 mL Schlenk tube and degassed under reduced pressure at room temperature for 15 min. Following which, $PdCl_2(PPh_3)_2$ (0.012 mmol), aryl iodide (0.25 mmol), and the terminal alkyne (0.25 mmol) were introduced under a blanket of nitrogen, and the resulting mixture was stirred at 65 °C for 8–15 h. After completion of the reaction (TLC monitoring), the reaction mixture was extracted several times with 40% ethyl acetate in hexane (4 × 10 mL) and the combined organic extracts was evaporated under vacuum. The crude reaction mixture was purified by silica gel column chromatography using hexane as eluent with up to 5% ethyl acetate (as needed).
23. *General procedure for homocoupling reaction of terminal alkynes*: The terminal alkyne (0.5 mmol) and $PdCl_2(PPh_3)_2$ (0.025 mmol) were added to the basic IL (10 equiv) in a reaction tube open to air, and the mixture was stirred at 70 °C for 8–12 h and in some cases overnight at rt. After completion of the reaction (TLC monitoring), the reaction mixture was extracted several times with 20% ethyl acetate in hexane (4 × 10 mL) and the combined organic extract was evaporated under vacuum. The crude mixture was purified by silica gel column chromatography using hexane as eluent.
24. *Recycling and re-use of the IL*: Following extraction of the product(s) from the ionic liquid phase (as described above), the reaction tube containing the basic IL was placed under vacuum at 60 °C for about 8 h. After cooling to rt the reaction tube was re-charged with the aryl iodide and the alkyne and 1 mol % of fresh $PdCl_2(PPh_3)_2$ (refer to Chart 1 for an indication of the efficiency of the recycling and reuse).