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Exploration of Ionic Liquids as Soluble Supports for Organic Synthesis. Demonstration with a Suzuki Coupling Reaction

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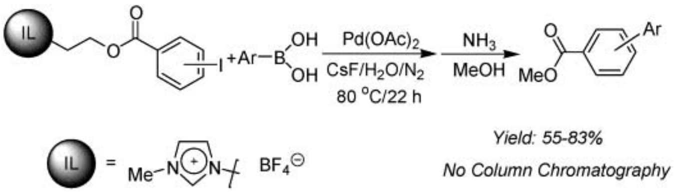
ABSTRACT



The efficiency of ionic liquid supported synthesis was demonstrated by the Suzuki reaction of ionic liquid supported iodobenzoate compounds with arylboronic acids in aqueous media to give, after cleavage with ammonia/methanol, biaryl products in good yields and high purities, without the need for chromatographic purification.

Since Merrifield introduced the use of polymer support for the synthesis of oligopeptides[1] the use of insoluble supports has become an important tool for phase separation and purification to remove excess reagents and side products. In recent years, the use of *soluble* polymer supports has received considerable attention because such "liquid phase" synthesis retains many of the advantages of conventional solution chemistry, and still permits the fairly facile purification of the product. Thus, soluble poly(ethylene glycol) (PEG) and other polymers have been used for the synthesis of oligopeptides,[2] nucleotides,[3] saccharides,[4] and small molecules.[5] Some limitations expressed for the use of soluble polymer supports include the following: loading capacity, limited solubility during the synthesis of longer peptides, aqueous solubility, and the insolubility in ether solvents. More recently, the use of the "fluorous phase" for organic synthesis has been advocated.[6] This is based on the concept that fluorinated reagents preferentially dissolved in perfluoroalkanes, the fluorous phase. Furthermore, a phase separation can be achieved between a fluorous phase and an organic phase by a temperature switch, thus facilitating separation. So far, the use of fluorous phase synthesis has been demonstrated for small molecules. However, the expense of perfluoroalkane solvents and the need for specialized reagents may limit its general application.

Recently, there has been considerable interest in the use of ionic liquids as an environmentally benign reaction media. Numerous chemical reactions, including some enzymic reactions, can be carried out in ionic liquids.[7,8] Room temperature

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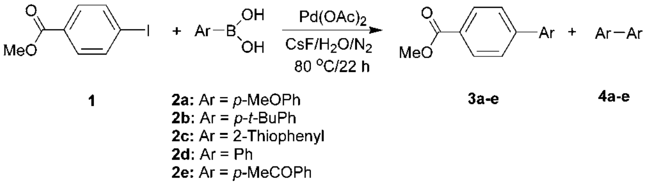
ionic liquids have also been widely explored as media for electrochemical technologies,[9] chemical extractions,[10] and other industrial processes.[11] This is due to several intriguing properties of ionic liquids: high thermal and chemical stability, no measurable vapor pressure, nonflammability, friction reduction, anti-wear performance, and high loading capacity. In many cases, the ionic liquids can be recycled easily. An attractive feature of ionic liquids is that their solubilities can be tuned readily so that they can phase separate from organic as well as aqueous media depending on the choice of cations and anions. Substrate solubility can also be tuned. For example, recently, "sugar-philic" ionic liquids have been prepared that are capable of dissolving carbohydrates such as glucose, cyclodextrin, and even glycosylated proteins.[12] This suggests the possibility of using these low molecular weight ionic liquids as soluble supports for organic synthesis. Phase separation between the "ionic liquid phase", the organic phase, and the aqueous phase can be achieved for product separation and purification.[13] We demonstrate the idea with a Suzuki reaction[14] by comparing the reaction under nearly identical conditions using conventional solution phase synthesis versus the ionic liquid supported synthesis (ILSS).

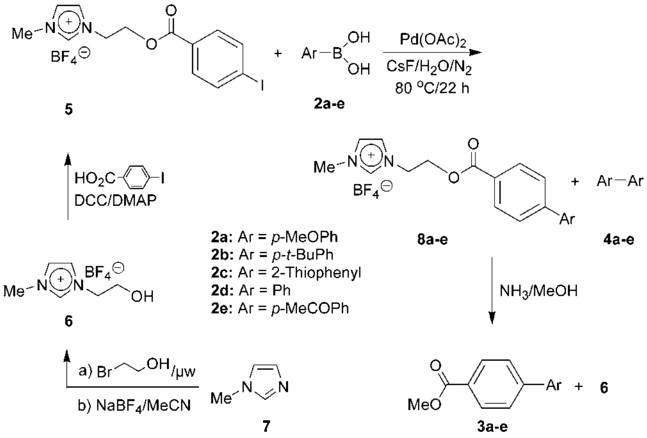
Methyl *p*-iodobenzoate (**1**) was coupled with *p*-methoxyphenylboronic acid (**2a**) with a catalytic amount of $Pd(OAc)_2$ in an aqueous solution of cesium fluoride under nitrogen at 80 °C for 22 h.[15] At the end of reaction, the mixture was extracted with ether to give the crude product, which contained the desired coupled product **3a**, together with the unreacted starting materials **1** and **2a** and a side product **4a** that was due to self-coupling of **2a** (Scheme 1). The relative amounts of each were determined by ^1H NMR of the crude. Typically, purification by chromatography of the crude mixture was performed to give the desired product **3a** in 60% yield.

Scheme 1. Suzuki Reactions of Methyl *p*-Iodobenzoate **1** with Aryl Boronic Acids **2** in Aqueous Media



By comparison, 3-*p*-iodobenzoyloxyethyl(l-methylimidazolium) tetrafluoroborate (**5**), prepared readily from 3-hydroxyethyl(l-methylimidazolium) tetrafluoroborate (**6**),[13a,16] was coupled with **2a** under identical reaction conditions. Evaporation of the reaction mixture under reduced pressure gave the crude product that contained, according to the ^1H NMR (acetone-d_6), the coupled product **8a**, unreacted **2a**, and the side product **4a**. However, extraction of the crude product with ether removed the ether soluble **2a** and **4a**, and left behind the ether insoluble product **8a**, relatively pure according to NMR. Cleavage of **8a** with ammonia/methanol gave **3a**, pure according to ^1H NMR, easily separated from the ionic liquid residue **6** by ether extraction (Scheme 2).[17]

Scheme 2. Suzuki Reactions of Ionic Liquid Supported *p*-Iodobenzoate **5** with Aryl Boronic Acids **2** in Aqueous Media



The overall yield of **3a** from **5** was 73% *without the need for chromatographic purification.*

We have examined the general scope of the reaction by coupling **5** with a number of arylboronic acids (Table 1). The corresponding reactions of **1** were also performed with the same set of arylboronic acids and the purities of the crude products were determined by ^1H NMR (Table 2). In all cases, the ionic liquid supported synthesis gave **3** in equal or superior yields, pure according to NMR, without the need

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(17) Methyl *p*-iodobenzoate was not observed in the final product under the reaction conditions. Separate experiments showed that any unreacted **5** would have been recovered as methyl *p*-iodobenzoate. The less than 100% yield of **3a** was attributed to mechanical loss in the work up process.

Table 1. Results of the Suzuki Coupling Reaction of Ionic Liquid Supported **5** and **9** with Boronic Acid **2**

entry	ionic liquid **5** or **9**	boronic acid **2**	molar ratio of **5** or **9**:**2**	yield of **3** or **11** (%, 2 steps)
1	**5**	**2a**	1:1.5	73
2	**5**	**2b**	1:1.5	82
3	**5**	**2c**	1:1.5	62
4	**5**	**2d**	1:1.5	83
5	**5**	**2e**	1:1.5	68
6	**5**	**2a**	1:2	72
7	**5**	**2b**	1:2	81
8	**5**	**2c**	1:2	60
9	**5**	**2d**	1:2	83
10	**5**	**2e**	1:2	71
11	**9**	**2a**	1:2	76
12	**9**	**2b**	1:2	73
13	**9**	**2c**	1:2	55
14	**9**	**2d**	1:2	77
15	**9**	**2e**	1:2	70

Table 2. Reaction of *p*-$IPhCO_2Me$ (**1**) with $ArB(OH)_2$ (**2**):[a] Composition of Crude Products and Yields of Biaryl Compounds **3**

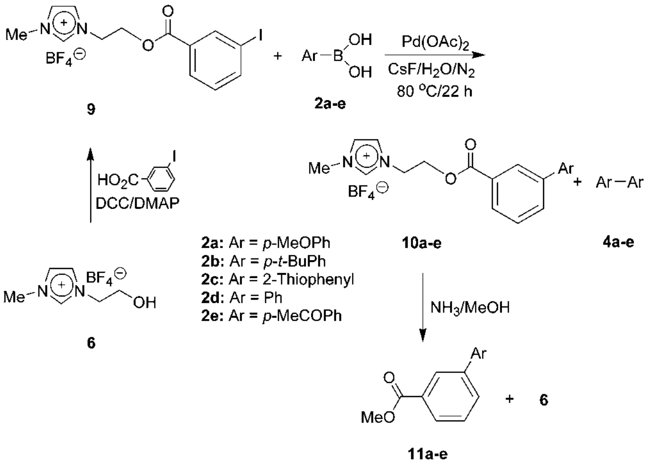
	composition of crude product[b,c]				yield of **3**[c] (%)
	1	**4a–e**	**2a–e**	**3a–e**	
1 + **2a**	2.9	19.8	12.3	54.0	70 (60)[d]
1 + **2b**	14.0	16.3	23.2	46.5	59
1 + **2c**	43.5	0	0	56.5	48
1 + **2d**	2.2	0	23.7	74.1	77
1 + **2e**	15.7	13.4	7.9	63.0	68

[a] Reactions were performed in a 1:1.5 molar ratio of **1** to **2**. [b] Percent by molar ratio. [c] Determined by ^1H NMR. [d] Isolated yields in parentheses.

for chromatography. To demonstrate the ease of purification further, the coupling of **5** with an even greater excess of the reagent **2** (2 equiv) was also carried out. In all cases, products **3** were obtained in similar yields and purity (Table 1).

We have also examined the Suzuki reaction of the *m*-iodobenzoate **9** with different arylboronic acids using the same ILSS protocol (Scheme 3). The results are summarized in Table 1. While we have not made the direct comparison with the reactions of methyl *m*-iodobenzoate itself, the products **11** obtained from the ILSS procedures, via the intermediate **10** after ether washing, were all pure according to ^1H NMR and required no chromatographic purification.

Scheme 3. Suzuki Reactions of Ionic Liquid Supported *m*-Iodobenzoate **9** with Aryl Boronic Acids **2** in Aqueous Media



These examples demonstrate that ILSS may offer a convenient approach for phase separation and product purification and find applications in other areas of organic synthesis. One must however offer a caveat. The mere presence of the ionic liquid moiety must have altered the nature of the reaction, either physically or chemically. The Suzuki coupling reaction appeared to proceed better with **5** than with **1**, as evidenced by the absence of starting iodobenzoate in the ILSS reactions. This may be due to the better solubility of **5** in the aqueous reaction media, the sublimation of **1** during the reaction, or the possible rate enhancing effect of the positive charge to the Suzuki reaction. Such adventitious benefits of the ionic liquid moiety may not always be there for other reactions. Nevertheless, for those reactions that are compatible with or enhanced by the presence of the ionic liquid moiety, easy phase separation and product purification can be realized.

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Supporting Information Available: Experimental procedures and characterization data for ionic liquids and Suzuki products. This material is available free of charge via the Internet at http://pubs.acs.org.

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