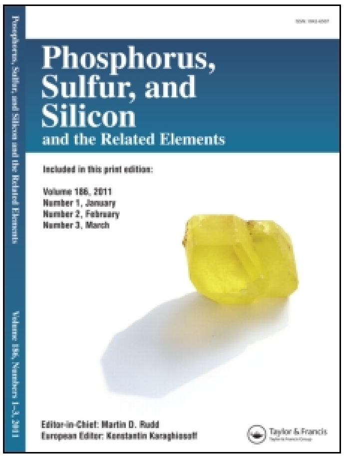

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THE MICHAELIS–BECKER REACTION IN PHOSPHONIUM AND IMIDAZOLIUM IONIC LIQUIDS

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The Michaelis–Becker reaction was performed in imidazolium ionic liquids using sodium hydroxide as base or sodium dialkylphosphites with good yield and selectivities. The analogous reaction performed in phosphonium ionic liquids resulted in decomposition to phosphine oxides.

Keywords Imidazolium; ionic liquid; Michaelis–Becker; phosphonium

INTRODUCTION

The Michaelis–Becker reaction is arguably one of the most important carbon–phosphorus bond forming reactions known. First reported in 1897,[1] it has become the reaction of choice for the synthesis of dialkyl esters of alkylphosphonic acids, along with the related Michaelis–Arbuzov reaction.[2] The Michaelis–Becker reaction involves the generation of a dialkylphosphite anion from an H-phosphonate using a strong anhydrous base, e.g., an alkali metal or alkali metal hydride, and then subsequent quenching with an electrophile to yield a phosphonate ester (Scheme 1). Due to the high concentrations of the powerful phosphite nucleophile, unwanted side reactions resulting from mono-dealkylation are often encountered. Replacing the highly reactive sodium metal or sodium hydride with aqueous sodium hydroxide results in base-promoted hydrolysis of the product phosphonate ester or H-phosphonate reactant, although these problematic side reactions can be mitigated by the use of a phase-transfer catalyst.[3]

In addition to the problems described above, the Michaelis–Becker reaction requires the use of anhydrous volatile organic compounds (VOCs) as solvents, with ether and THF being the most commonly employed. In addition to ether volatility, explosive peroxide

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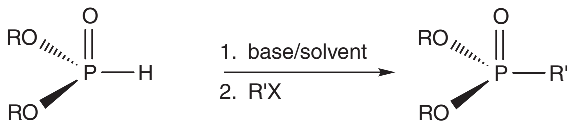


Scheme 1

formation and flammability are also of concern. The green chemistry community has embraced the use of ionic liquids (ILs) as solvents for a large number of organic reactions.[4] The advantages of replacing conventional organic solvents with ILs include (a) low volatility, (b) zero or low flammability/combustion, (c) high thermal capacity, and (d) ease of separation of solvent from reaction mixture. We recently initiated a program to study the formation of carbon–phosphorus bonds in ionic liquids, examples of which have not previously been reported. The discovery that sodium hydroxide can be employed as a base in imidazolium derived ionic liquids, e.g., [bmim][BF_4] (**1a**),[5] and that Grignard reactions can be performed in phosphonium ionic liquids such as CYPHOS IL101 (**2**)[6] prompted us to investigate the Michaelis–Becker reaction in this solvent medium. Herein we describe (a) the high-yielding and selective Michaelis–Becker reaction using NaOH as an anhydrous base in **1**; (b) the reaction of sodium dialkylphosphites with alkyl halides in **2**; and (c) exploratory ^{31}P NMR studies on the nature of the phosphite anion in **2**.

RESULTS AND DISCUSSION

Our initial exploratory experiments were focused on the alkylation of sodium dialkylphosphites generated from the corresponding secondary phosphites and sodium hydroxide in **1a**. The reaction conditions used are similar to the classical Michaelis–Becker reaction, although the yields are significantly improved due to the apparent suppression of unwanted side reactions.[3,7] For example, the reaction of dibutylphosphite with methyl iodide and sodium hydroxide in **1a** gave dibutyl methylphosphonate in 91% yield (Table I). Similarly, reaction of dimethylphosphite with methyl iodide in the presence of sodium hydroxide gave dimethyl methylphosphonate in 80% yield (Scheme 1: $R = R' = Me$). In situ monitoring of these reactions in the ionic liquid solvent using ^{31}P NMR showed major peaks at 31.5 and 34.3 ppm, respectively, corresponding to the phosphonate products, with very minor (<5%) peaks due to unwanted side-reactions. In a noteworthy comparison

Table I Yields and NMR data for Michaelis–Becker reactions in ionic liquids

Entry	R	R′	base	IL	**3**[a] (%)	^{31}P NMR[c]
1	Bu	Me	NaOH	**la**	91	31.5
2	Me	Me	NaOH	**la**	80	34.3
3	Bu	Me	Na[b]	**la**	60	31.5
4	Bu	Me	Na[b]	**lb**	82	31.5
5	Bu	Bz	Na[b]	**la**	60	32.8
6	Et	Me	Na[c]	**2**	16	30.1
7	Bu	Me	Na[b]	**2**	75	31.5

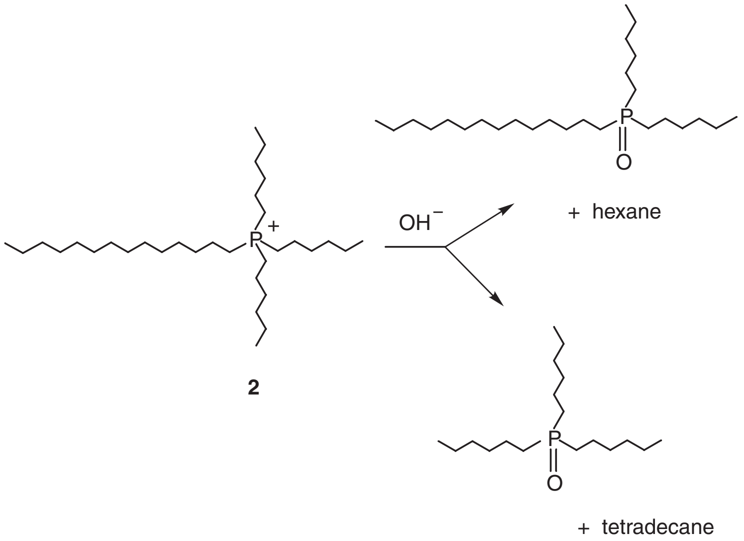
[a] Isolated yields.

[b] Sodium organophosphonates were pre-prepared from Na metal prior to use.

[c] ^{31}P NMR spectra were recorded at 161.9 MHz in $CDCl_3$ and referenced to external H_3PO_4.

of selectivity, the reaction of dimethylphosphite with methyl iodide in the presence of a phase transfer catalysts and using aqueous sodium hydroxide as a base, gave dimethyl methylphosphonate in only 22% yield with a significant amount of H_3PO_3 as a byproduct.[3] Isolation of the phosphonate products from the ionic liquid reaction was achieved via a three-phase extraction process (organic solvent/water/IL) and recovery/recycle of the ionic liquid after washing with water to remove sodium salts followed by purification of the phosphonate using column chromatography. The purity of isolated phosphonates was confirmed with ^{1}H and ^{31}P NMR spectroscopy (see Table I) and compared to literature values.[9]

We also wanted to investigate the use of phosphonium ionic liquids such as **2** for the Michaelis–Becker reaction, but under the conditions of our reactions, **2** could not be utilized for the hydroxide promoted Michaelis–Becker reaction. Although Ramnial et al. recently reported the use of phosphonium ionic liquids for reactions involving strong bases such as Grignard reagents and *N*-heterocyclic carbenes,[6] we discovered that **2** undergoes base promoted decomposition in the presence of sodium hydroxide under the conditions of the Michaelis–Becker reaction to give the corresponding trialkylphosphine oxides and alkanes (Scheme 2). This is not too surprising as it has been known for some time that tetralkylphosphonium hydroxides undergo base-promoted decomposition to give the corresponding phosphine oxides.[10] The identity of the phosphine oxides were confirmed by IR, mass spectrometry, ^{1}H, ^{13}C, and ^{31}P NMR. Further studies are underway to determine whether use of an ionic liquid solvent results in any kinetic acceleration or deceleration of the hydrolysis reaction compared to other polar solvent systems.



Scheme 2

Although phosphonium ionic liquids cannot be used with sodium hydroxide for the Michaelis–Becker reaction, preformed sodium dialkylphosphites can be employed without any noticeable decomposition of the ionic liquid. For example, the reaction of methyl iodide and sodium dibutylphosphite, isolated as a crystalline solid from the reaction of sodium metal with dibutylphosphite in *n*-butanol, gave dibutyl methylphosphonate in 75% yield with no detectable phosphonium salt decomposition. Workup of the reaction was readily achieved with an exhaustive three-phase extraction process. The addition of water and hexane to the ionic liquid results in a three-phase mixture with the lower layer consisting of water, the upper layer containing the organic product in hexane, and the middle layer composed of the ionic liquid. Our attempts to prepare sodium dibutylphosphite directly in the ionic liquids using Na metal or NaH were all unsuccessful. Similarly, the reaction of sodium dibutylphosphite with methyl iodide in [bmim]BF_4 and [bmim]PF_6 gave dibutyl methylphosphonate in 60% and 82% yields, respectively, and the extension to benzyl chloride as an alkylating agent is summarized in Table I.

We were curious as to the nature of the phosphite anion in ionic liquid solution. Doak and Freedman proposed five possible structures for the alkali salts of H-phosphonates.[11] The phosphonate form of the anion **I** and the phosphite form **II** are ambidentate ions, with structure **I** being the most likely based on ^{31}P NMR chemical shift values in coordinating solvents such as THF and ether.[12] In addition, there has been speculation as to whether the sodium dialkylphosphites are truly ionic complexes, or whether they are covalent molecular species such as **III** or **IV** (Figure 1).[11] A dimeric structure was also suggested (not shown). The presence of either the phosphite or phosphonate forms may be probed easily using ^{31}P NMR in ionic liquids because of the expected large difference in chemical shift between the structural forms. Sodium dibutylphosphite was prepared in *n*-butanol, isolated as a solvent-free solid and dissolved in **2**. A ^{31}P NMR spectrum was recorded immediately and showed, in addition to the peak corresponding to **2**, a broad resonance at 142.3 ppm,

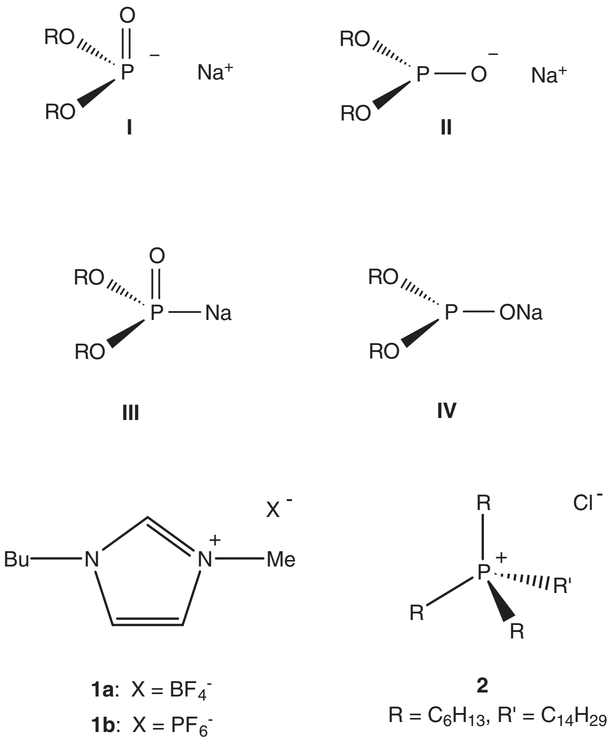


Figure 1 The structures of H-phoshonates (**I–IV**) and ionic liquids.

which is entirely consistent with the exclusive existence of either ionic or molecular phosphite forms **II** and **IV** within NMR detection limits. Sodium diethylphosphite recorded in THF shows a single peak at 150.7 ppm,[12] suggesting that alkali metal salts of secondary dialkylphosphites have similar structures in both conventional polar organic solvents and ionic liquids, and as such the higher selectivity for the Michaelis–Becker reaction in ionic liquids remains to be explained. In summary, ionic liquids have been explored as alternative solvents for the classical Michaelis–Becker reaction with the unexpected outcome that the sodium hydroxide–promoted reaction proceeds relatively cleanly without dealkylation of the phosphite or phosphonate product. We are currently investigating the mechanism of this reaction and exploring additional C–P bond forming reactions in ionic liquids.

EXPERIMENTAL

Typical Procedure for Synthesis of Phosphonates

A 25 mL flask was charged with 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]BF_4 (ca. 5 mL), pulverized NaOH (0.0512 g, 1.28 mmol), and a magnetic stir bar. The flask was stirred and heated in an oil bath until the sodium hydroxide dissolved and then removed from the oil bath. Then, dibutylphosphite (0.25 mL, 1.3 mmol) was added to via syringe. The resulting mixture was stirred for 15 min, and iodomethane (0.08 mL, 1 mmol) was added to the flask in a single portion and the mixture was stirred for 12 h. The ionic liquid layer was extracted with diethyl ether (ca. 3 mL) and the ether layer was removed under oil-pump vacuum. The resulting residue was chromatographed (silica gel, 90:10 hexane:EtOAc) to give methyl dibutylphosphonate (0.189 g, 0.908 mmol, 91% yield).

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