Sonogashira coupling reactions in biodegradable ionic liquids derived from nicotinic acid†

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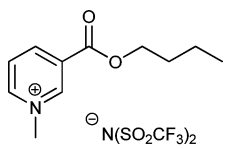
Received 17th September 2009, Accepted 11th January 2010
First published as an Advance Article on the web 10th February 2010
DOI: 10.1039/b919394d

The biodegradable ionic liquids, 3-butoxycarbonyl-1-methylpyridinium bis(trifluoromethanesulfonyl)imides (**1a–d**), have been evaluated as solvents for copper- and phosphine-free Sonogashira coupling reactions. The stability of these ionic liquids toward basic conditions was analysed in order to further probe their utility for transition metal catalyzed reactions which require the presence of a base.

Introduction

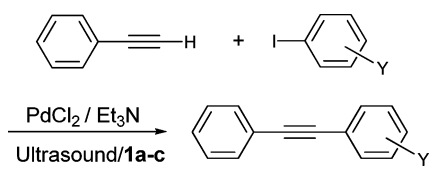
We have been engaged in the synthesis and application of biodegradable ionic liquids as alternative solvents for the last several years. We have found that a number of 1,3-dialkylimidazolium-[1] and *N*-alkylpyridinium[2]-based ionic liquids (ILs) have proven to be somewhat resilient to biodegradation as determined using the CO_2 headspace test (ISO 14593). However, when functionality known to enhance biodegradability is incorporated into ionic liquids, readily biodegradable salts result. Hence, when an ester functionality was built into the side chain of 1,3-disubstituted imidazolium salts they biodegraded well within the 28 days over which the experiments were conducted.[3] The rate of biodegradation increased if an octylsulfate or dodecylsulfate ion was used as the anionic component of these salts.[3] Pyridinium-based ionic liquids could also be designed to be readily biodegradable using a similar strategy.[2] Hence, *N*-alkylated butylnicotinates such as 3-(*n*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide (**1a**, Fig. 1) proved to be very biodegradable and were essentially degraded within 7 days of being treated with waste water organisms.

In another related area of interest, we have exploited the unique properties of ILs through the immobilization of transition metal catalysts.[4] Like many others, we have shown that expensive palladium catalysts can be easily immobilized and recycled in ILs, usually without loss of catalytic activity.[5] Of particular interest here is the Sonogashira reaction, which is used for the preparation of substituted and non-substituted alkynes.[6] This reaction typically requires the presence of a co-catalyst and a base.[7] Copper salts are most frequently used as co-catalyst while an amine is usually present as a base to absorb HX generated in the catalytic cycle. The presence of sterically hindered, electron-rich phosphines, such as P^tBu_3, are known to enhance the reactivity of the palladium catalysts used in the Sonogashira reaction.[8] In this manuscript we report the use of a series of readily biodegradable ILs, **1a–c**, for the immobilization of $PdCl_2$ as a catalyst for the Sonogashira reaction, without the need for the addition of a copper co-catalysts or a phosphine (Scheme 1).



1a

Fig. 1 3-(*n*-Butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide (**1a**).



Scheme 1 The Sonogashira reaction in biodegradable IL, **1a–c**.

Results and discussion

The absence of any copper salts in our reactions prevented the formation of detectable amounts of any Glaser-type coupling of the alkynes used. Ultrasonic irradiation was utilized in our systems to mitigate against any lack of catalytic activity of the palladium catalyst due to the absence of phosphines.[9] Use of ultrasonic irradiation also allowed us to conduct reactions at room temperature for comparatively shorter reaction times than

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† Electronic supplementary information (ESI) available: Additional experimental information; NMR spectra and HPLC data. See DOI: 10.1039/b919394d

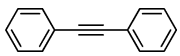
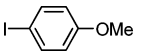
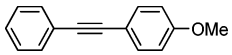
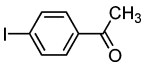
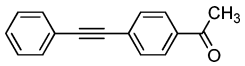
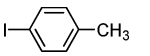
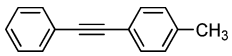
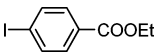
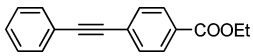
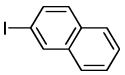
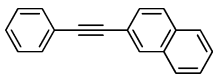
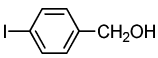
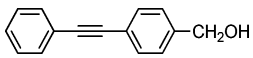
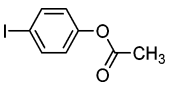
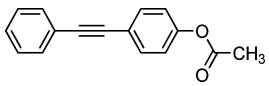
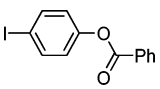
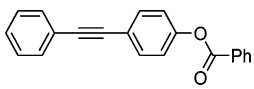
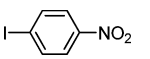
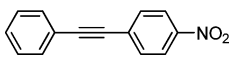
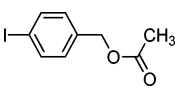
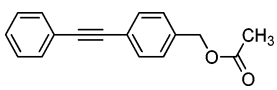
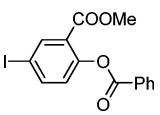
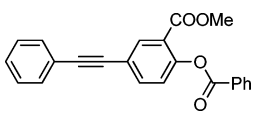
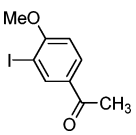
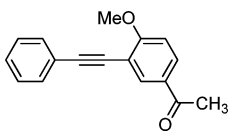
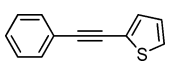
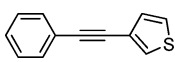
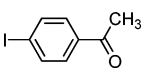
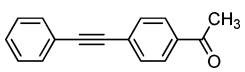
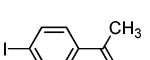
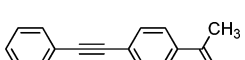
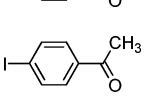
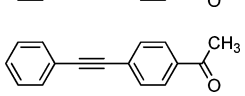
previously reported Sonogashira reactions conducted in ionic liquids at elevated temperatures.[10]

Hence, the prototypical Sonogashira coupling of iodobenzene with phenylacetylene afforded a very good yield (86%) of diphenylacetylene when it was conducted in the biodegradable IL **1a** at room temperature and under ultrasonic irradiation (Table 1, Entry 1). A variety of substituted iodoarenes also afforded very good to excellent yields of coupled products when conducted in **1a**. Electron-donating *para* substituents on the iodoarene appeared to have a deleterious effect on isolated yield (Table 1, Entries 2 and 4), while every other iodoarene trialed performed very well. In general, reactions were monitored until starting materials were consumed, and the lower yields obtained for 4-iodoanisole and 4-iodotoluene may be related to the efficiency of product extraction.

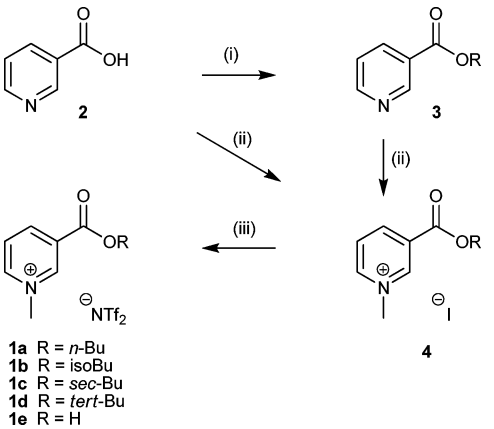
These yields are generally consistent with copper-free Sonogashira coupling reactions previously conducted in ionic liquids.[9–11] For example, Srinivasan and co-workers evaluated the $PdCl_2$-catalyzed coupling of iodobenzene with phenylacetylene in acetone and a panel of 10 dialkylimidazolium ionic liquids, and isolated yields of diphenylacetylene ranged from 85–93%.[9] Nokihara *et al.* also studied this reaction using the carbenoid catalyst [bmimPd(PPh_3)Cl_2] in four different ionic liquids.[11a] Yields of 94%, 89%, 82% and 66% were obtained in [bmim]PF_6, [bmim]BF_4, [bmim]NTf_2 and [bmpy]BF_4 (1-butyl-1-methylpyrrolidinium tetrafluoroborate), respectively. It is noteworthy that in our reactions and those performed by others in ionic liquids[9–11] that the relative mole ratios of solvent (*i.e.* ionic liquid) to solute (*i.e.* reactants) are lower than in conventional solvents. This results from the relatively higher molecular weight of ionic liquids compared to molecular solvents such as DMF. Whereas this can be viewed as a dilution of the ionic liquid, it is more relevant to note that the ionic liquid solvent is in excess relative to solutes in these cases, and that the use of ionic liquids as solvents results in the minimization of reaction volume – a "green" attribute of these systems.

Whilst the ester moiety of **1a** confers high levels of biodegradability, its presence may also limit the utility of this IL for some Sonogashira couplings and related palladium-catalyzed carbon–carbon bond-forming reactions. Many such reactions require the presence of base and are conducted under forcing reaction conditions, which may result in cleavage of the IL ester. Previous attempts to replace this ester with more benign functionality such as alkyl and ether groups have afforded ILs which were poorly biodegradable. As a result, we decided to prepare a series of ester analogs of **1a** in which the *n*-butyl ester was replaced by more hindered esters (isobutyl, **1b**, *sec*-butyl, **1c**, and *tert*-butyl, **1d**) in order to improve stability under basic and nucleophilic conditions. This series of esters, along with the corresponding acid IL, were prepared using the straightforward approach outlined in Scheme 2. The *n*-butyl, isobutyl and *tert*-butyl esters were all prepared *via* the corresponding acid chloride. In the subsequent substitution reaction with the appropriate alcohol, a base catalyst (DMAP) was required for the synthesis of the *sec*-butyl ester, while potassium *tert*-butoxide was used directly in the synthesis of the *tert*-butyl ester. The isobutyl ester was prepared more directly *via* Fischer esterification. Once these esters were in hand they were quaternized with methyl iodide and then reacted with lithium bis(trifluoromethanesulfonyl)imide under

Table 1 Sonogashira reactions in the biodegradable ILs, **1a–d**

Entry	IL	Arene	Product	Yield (%)[a]
1	**1a**			86
2	**1a**			47
3	**1a**			88
4	**1a**			60
5	**1a**			93
6	**1a**			78
7	**1a**			72
8	**1a**			81
9	**1a**			76
10	**1a**			86
11	**1a**			93
12	**1a**			79
13	**1a**			78
14	**1a**			98
15	**1a**			84
16	**1b**			85
17	**1c**			77
18	**1d**			n/a

[a] Isolated yields of pure product after column chromatography.



Scheme 2 (i) Method A (**1a**, R = *n*-Bu); $SOCl_2$, then ROH, Method B (**1b**, R = isoBu); H_2SO_4, IsoBuOH, Method C (**1c**, R = *sec*-Bu); $SOCl_2$, DMAP (cat.); Method D (**1d**, R = *tert*-Bu); $SOCl_2$ then *tert*-BuOK. (ii) MeI, toluene. (iii) $LiNTf_2$, H_2O.

aqueous conditions to afford the target 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs, **1a–e**.

The effect of increasing steric demand around the ester moiety of the 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs **1a–d** on the Sonogashira reaction was next examined (Table 1, Entries 3 and 16–18). An increase in steric demand from *n*-butyl, **1a**, to isobutyl, **1b**, resulted in only a mild effect, if any, on the isolated yield of the diarylacetylene, 1-[4-(2-phenyl-1-ethynyl)phenyl]-1-ethanone (Table 1, Entries 3 and 16), whereas increasing the steric bulk at the carbon atom immediately adjacent to the ester moiety by incorporating a *sec*-butyl group, **1c**, resulted in a noticeable decrease in isolated yield of diarylacetylene (Table 1, Entry 17). The Sonogashira reaction was not conducted in 3-(*tert*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, **1d**, which is a solid at room temperature; a property that limits its utility as an alternative solvent. These results indicate that the ester moiety of the 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs, **1a–c**, must play a role in the solvation of reaction components in these Sonogashira reactions, since variation of the ester moiety in the salt affects the isolated yield of products.

The biodegradability of 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs was examined using the CO_2 headspace test (ISO 14593, OECD 310). Ready biodegradability tests of this type measure non-specific parameters such as dissolved organic carbon, biochemical oxygen demand and CO_2 production, and are performed under stringent conditions of low microbial density and high concentrations of the test substance. A substance achieving a pass level in these tests at a certain rate after termination of the lag phase may be classified as "readily biodegradable". In the CO_2 headspace test (OECD 310) the pass level is achieved when at least 60% of the theoretical carbon dioxide is liberated within the first 28 days. A positive result in a test for ready biodegradability can be considered as indicative of rapid and ultimate degradation in most environments.

Table 2 Percentages of biodegradation of 3-(alkoxycarbonyl)-1-methylpyridinium triflimide ILs, **1a–d**, after 28 days. The 95% confidence interval is in parentheses

Compound	Biodegradation (%)
1a	68 (65–71)
1b	70 (67–73)
1c	69 (65–73)
1d	72 (68–76)

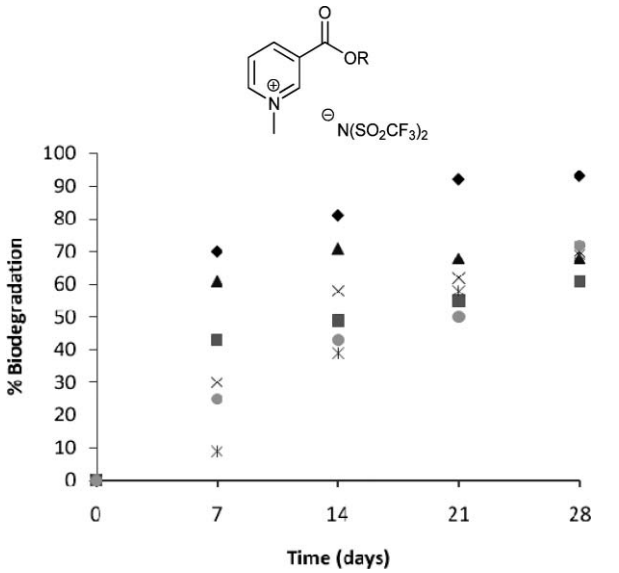


Fig. 2 Biodegradation of 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs, **1a–e**, as measured using the CO_2 headspace test; **1a** (▲), **1b** (×), **1c** (✳), **1d** (●),**1e** (■), SDS (◆).

After 7 days, the *n*-butyl ester IL, **1a**, had already achieved the level of biodegradation (61%) which is ultimately required for classification as "readily biodegradable" after 28 days (Fig. 2). The initial rate of biodegradation was slower for the more hindered esters (with percentage biodegradation ranging from 9–30% after 7 days) and the corresponding acid (43%). However, after the full 28 day period all of these ILs degrade to a similar extent (70 ± 2%) and all exceeded the mark required for classification as "readily biodegradable".

Table 2 shows the percentages of biodegradation after the full 28 day period with the 95% confidence interval being given in parentheses.

We next tested the hydrolytic stability of the 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)-imide ILs, **1a–d**. When exposed to a 50 : 50 solution of CD_3OD–D_2O, no hydrolysis products were observed for any of these ILs over a 30 day period, as monitored by ^{1}H-NMR. However, when compounds **1a–d** were reacted with an equimolar amount of hydroxide they all underwent base hydrolysis, forming the sodium carboxylate salt, **1e** (Fig. 3).

As the steric demand of the ester alkyl moiety increased from *n*-butyl to isobutyl to *sec*-butyl to *tert*-butyl, the degree to which hydrolysis occurred decreased. The *n*-butyl analog, **1a**, underwent base hydrolysis essentially to completion over the time frame of the experiment (Fig. 3). The isobutyl analog, **1b**, underwent base hydrolysis to a slightly lower degree. Increasing

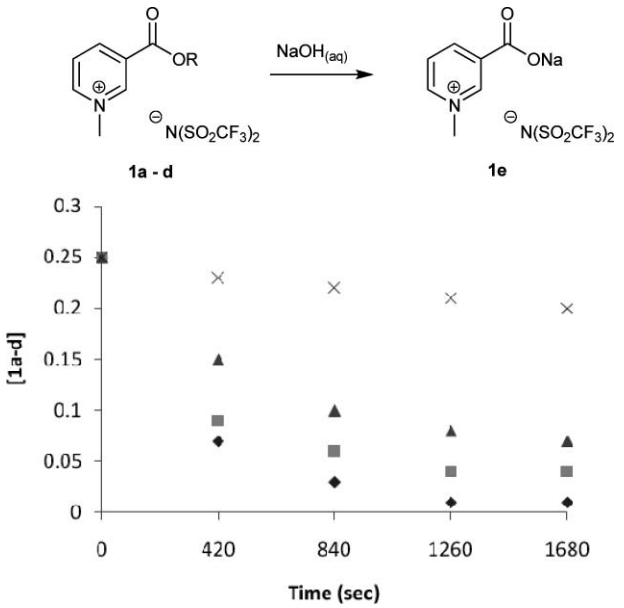


Fig. 3 Concentration of 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide ILs, **1a–d**, *versus* time for the base hydrolysis of ester analogs **1a–d**; **1a** (◆), **1b** (■), **1c** (▲), **1d** (×).

the steric demand in an iterative fashion to a *sec*-butyl moiety and then to a *tert*-butyl moiety resulted in the corresponding decreases in the extent of reaction (Fig. 3) over the time frame of the experiments. These results are consistent with those found in the biodegradation tests of these compounds, *vide supra*, and indicate an increase in stability under basic and nucleophilic conditions.

Conclusions

In conclusion, we have developed an efficient, palladium-catalyzed Sonagashira coupling reaction conducted in 3-(butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide salts, **1a–c**, biodegradable ionic liquids. The reactions were conducted in the absence of a copper salt or a bulky phosphine and made use of ultrasonic irradiation at room temperature. Aryl iodides with a range of appended functionality were investigated as coupling partners with phenylacetylene and typically form the desired disubstituted alkynes in good to excellent yield.

Variation of the steric demand of the alkyl moiety of the 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide salts had little to no effect on their biodegradability (*i.e.* all salts tested, **1a–d**, were readily biodegradable), but did result in an increase in their stability under basic and nucleophilic conditions. Those analogs that were liquids at room temperature, **1b** and **1c**, could also be used in Sonogashira reactions in a similar fashion as 3-(*n*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, **1a**.

Experimental

Starting materials were purchased from Sigma-Aldrich and had a purity of 96% or greater. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. All ^{1}H NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer at 300.13 MHz. All ^{13}C NMR spectra were recorded on a Varian Unity Inova 600 spectrometer at 150.8 MHz, or on a Bruker Avance DPX 300 spectrometer at 75.4 MHz. Unless stated otherwise, $CDCl_3$ was used as the solvent for NMR samples. Low resolution electrospray mass spectra (LRMS) using electrospray ionisation (ESI) were obtained on a Micromass Platform II spectrometer. Unless otherwise stated, the cone voltage was 20 eV. High resolution mass spectra (HRMS) were obtained on a Bruker Daltronics microtof instrument. Kinetics studies were performed using an Agilent 110 liquid chromatograph (LC) equipped with an Agilent–Zorbax reverse phase column (5 μm particle size; 4.6 mm × 150 mm).

Synthesis of 3-(*n*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, 1a

Thionyl chloride (9.67 g, 81.30 mmol) was added to a mixture of nicotinic acid (5.00 g, 40.65 mmol) in 100 mL toluene and refluxed for 24 h at 110 °C. The resulting white solid was filtered, washed with diethyl ether (5 × 50 mL), and dried *in vacuo*. The resulting acyl chloride (5.75 g, 40.65 mmol) was dissolved in CH_2Cl_2 (200 mL) and treated with 1-butanol (6.03 g, 7.44 mL, 81.30 mmol) followed by triethylamine (8.22 g, 11.32 mL, 81.30 mmol) at −78 °C. After stirring at 45 °C for 24 h the organic layer was washed with water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were then washed with water and dried over $MgSO_4$. The combined extracts were then concentrated *in vacuo* to afford *n*-butylnicotinate (11.42 g, 78% yield). Iodomethane (4.26 g, 1.87 mL, 30 mmol) was then added to a toluene suspension of *n*-butyl nicotinate (4.00 g, 22.32 mmol) under an inert atmosphere at room temperature. The reaction was then refluxed at 45 °C for 24 h, with the resulting iodide salt separating out in the bottom of the flask. Recrystallization with acetonitrile and diethyl ether afforded a light yellow powder that was dried *in vacuo* (6.91 g, 97%). The resulting compound (3.94 g, 12.3 mmol) was dissolved in water (100 mL) and then treated with bis(trifluoromethanesulfonimide) lithium salt (5.17 g, 18.0 mmol) and stirred for 1 h. Extraction with CH_2Cl_2 (3 × 50 mL) followed by drying ($MgSO_4$) and concentration *in vacuo* afforded the desired product (5.14 g, 88%). ^{1}H NMR (DMSO-d_6): δ 0.94 (t, J = 7.5 Hz, 3H), 1.48 (m, 2H), 1.74 (m, 2H), 4.41 (t, J = 6.6 Hz, 2H), 4.43 (s, 3H), 8.25 (m, 1H), 8.96 (d, J = 8.1 Hz, 1H), 9.17 (d, J = 6.3 Hz, 1H) 9.53 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 13.5, 18.6, 30.1, 48.3, 66.2, 119.5 (q, J_{C-F} = 322 Hz), 127.9, 129.6, 144.8, 146.8, 148.9, 161.8. LRMS (ESI, +ve) calcd for $C_{11}H_{16}NO_2$ 194.1, found 194.2, LRMS (ESI, −ve) calcd for $N(SO_2CF_3)_2$ 279.9, found 280.1.

Synthesis of 3-(isobutoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, 1b

Concentrated sulfuric acid (30.67 g, 16.67 mL, 313 mmol) was slowly added to a neat mixture of nicotinic acid (12.76 g, 104.0 mmol) and isobutanol (49.48 g, 61.7 mL, 666 mmol) and refluxed at 100 °C for 18 h. After cooling to room temperature the reaction was poured over ~250 g of ice and neutralized with

$NH_4OH_{(aq)}$. After extraction with diethyl ether (5 × 25 mL) the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* (12.9 g, 69%). Iodomethane (4.55 mL, 73.0 mmol) was then slowly added to the resulting isobutyl nicotinate (12.87 g, 71.8 mmol) in toluene (200 mL) under inert atmosphere at room temperature. The reaction was then refluxed at 45 °C for 24 h, with the resulting iodide salt separating out in the bottom of the flask. Recrystallization with acetonitrile and diethyl ether afforded a light yellow powder that was dried *in vacuo* (21.2 g, 92%). The resulting IL (3.94 g, 12.3 mmol) was dissolved in water (100 mL) and then treated with bis(trifluoromethanesulfonimide) lithium salt (5.17 g, 18.0 mmol) and stirred for 1 h. Extraction with CH_2Cl_2 (3 × 50 mL) followed by drying ($MgSO_4$ anhyd.) and concentration *in vacuo* afforded the desired product (27.5 g, 91%). ^{1}H NMR (DMSO-d_6): δ 1.01 (d, J = 6.5 Hz, 6H), 2.077 (m, 1H), 4.20 (d, J = 6.5 Hz, 2H), 4.44 (s, 3H), 8.25 (m, 1H), 8.98 (d, J = 8.4 Hz, 1H), 9.18 (d, J = 6.0 Hz, 1H) 9.53 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 18.8, 27.4, 48.4, 72.1, 119.6 (q, J_{C-F} = 322 Hz), 128.0, 129.6, 144.9, 146.8, 149.0, 161.8. HRMS (ESI, +ve) calcd for $C_{11}H_{16}NO_2$ 194.1176, found 194.1177, HRMS (ESI, −ve) calcd for $N(SO_2CF_3)_2$ 279.9178, found 279.9167.

Synthesis of 3-(*sec*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, 1c

Thionyl chloride (9.67 g, 5.90 mL, 81.30 mmol) was added to a mixture of nicotinic acid (5.00 g, 40.65 mmol) in 100 mL toluene and refluxed for 24 h at 110 °C. The resulting white solid was filtered, washed with diethyl ether (5 × 50 mL), and dried *in vacuo*. The resulting acyl chloride (5.75 g, 40.7 mmol) was dissolved in CH_2Cl_2 (200 mL) and treated with 2-butanol (6.03 g, 7.46 mL, 81.3 mmol) followed by the addition of triethylamine (8.22 g, 11.32 mL, 81.3 mmol) and 4-dimethylaminopyridine (0.366 g, 3.0 mmol) at −78 °C. The reaction flask was allowed to stir at 50 °C for 24 h after which the organics were washed with saturated $NaHCO_3$ followed by H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to afford *sec*-butyl nicotinate (3.7 g, 51%). Iodomethane (0.62 mL, 10 mmol) was then slowly added to *sec*-butyl nicotinate (1.50 g, 8.37 mmol) suspended in toluene (50 mL) under inert atmosphere at room temperature. The reaction was then refluxed at 45 °C for 24 h, with the resulting iodide salt separating out in the bottom of the flask. Recrystallization with acetonitrile and diethyl ether afforded a light yellow powder that was dried *in vacuo* (3.2 g, 50%). The resulting IL (3.94 g, 12.3 mmol) was dissolved in water (100 mL) and then treated with bis(trifluoromethanesulfonimide) lithium salt (5.17 g, 18.0 mmol) and stirred for 1 h. Extraction with CH_2Cl_2 (3 × 50 mL) followed by drying ($MgSO_4$) and concentration *in vacuo* afforded the desired product (4.16 g, 97%). ^{1}H NMR (DMSO-d_6): δ 0.95 (t, J = 7.5 Hz, 3H), 1.35 (d, J = 6.3 Hz, 3H), 1.73 (m, 2H), 4.43 (s, 3H), 5.11 (sextet, J = 6.0 Hz, 1H), 8.24 (m, 1H), 8.96 (d, J = 8.1 Hz, 1H), 9.17 (d, J = 6.3 Hz, 1H) 9.52 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 9.4, 19.0, 28.2, 48.3, 75.2, 119.6 (q, J_{C-F} = 322 Hz), 128.0, 130.0, 144.8, 146.8, 148.9, 161.3. HRMS (ESI, +ve) calcd for $C_{11}H_{16}NO_2$ 194.1176, found 194.1171, HRMS (ESI, −ve) calcd for $N(SO_2CF_3)_2$ 279.9178, found 279.9163.

Synthesis of 3-(*tert*-butoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, 1d

Thionyl chloride (9.67 g, 5.90 mL, 81.3 mmol) was added to a mixture of nicotinic acid (5.00 g, 40.7 mmol) in 100 mL toluene and refluxed for 24 h at 110 °C. The resulting white solid was filtered, washed with diethyl ether (5 × 50 mL), and dried *in vacuo*. The resulting acyl chloride (10.0 g, 70.95 mmol) in THF (150 mL) was treated with potassium *tert*-butoxide (8.98 g, 80.0 mmol) at −5 °C and stirred for 2 h. Solvent was then removed *in vacuo* and the resulting white solid was dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ followed by water. The organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford *tert*-butyl nicotinate (6.5 g, 52%). Iodomethane (2.49 mL, 40.0 mmol) was slowly added to a toluene (100 mL) suspension of *tert*-butyl nicotinate (6.04 g, 33.7 mmol) under inert atmosphere at room temperature. The reaction was then refluxed at 45 °C for 24 h, with the resulting iodide salt separating out in the bottom of the flask. Recrystallization with acetonitrile and diethyl ether afforded a light yellow powder that was dried *in vacuo* (3.28 g, 30%). The resulting IL (3.94 g, 12.3 mmol) was dissolved in water (100 mL) and then treated with bis(trifluoromethanesulfonimide) lithium salt (5.17 g, 18.0 mmol) and stirred for 1 h. Extraction with CH_2Cl_2 (3 × 50 mL) followed by drying ($MgSO_4$) and concentration *in vacuo* afforded the desired product (2.9 g, 95%). ^{1}H NMR (DMSO-d_6): δ 1.60 (s, 9H), 4.41 (s, 3H), 8.23 (m, 1H), 8.91 (d, J = 8.4 Hz, 1H), 9.15 (d, J = 6.0 Hz, 1H) 9.45 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 27.6, 48.3, 84.1, 119.5 (q, J_{C-F} = 322 Hz), 127.8, 130.7, 144.7, 146.7, 148.7, 160.7. HRMS (ESI, +ve) calcd for $C_{11}H_{16}NO_2$ 194.1176, found 194.1179, HRMS (ESI, −ve) calcd for $N(SO_2CF_3)_2$ 279.9178, found 279.9178.

Synthesis of 3-(carboxy)-1-methylpyridinium bis(trifluoromethanesulfonyl)imide, 1e

Iodomethane (5.70 g, 40 mmol) was added to nicotinic acid (4.29 g, 34.8 mmol) in dry THF (200 mL) and refluxed at 45 °C for 5 d. Removal of the solvent *in vacuo* afforded a white solid (5.12 g, 56%). The resulting IL (4.06 g, 15.4 mmol) was dissolved in water (100 mL) and treated with lithium bis(trifluoromethanesulfonimide) (8.61 g, 30.0 mmol) and stirred for 1 h. The reaction was then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were then washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford the product (0.29 g, 33%). ^{1}H NMR (DMSO-d_6): δ 4.41 (s, 3H), 8.23 (m, 1H), 8.93 (d, J = 8.1 Hz, 1H), 9.14 (d, J = 6.0 Hz, 1H) 9.51 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 48.3, 119.7 (q, J_{C-F} = 322 Hz), 128.0, 130.9, 145.1, 147.1, 148.6, 163.3. HRMS (ESI, +ve) calcd for $C_7H_8NO_2$ 138.0550, found 138.0549, HRMS (ESI, −ve) calcd for $N(SO_2CF_3)_2$ 279.9178, found 279.9181.

General procedure for Sonogashira reactions in 3-(alkoxycarbonyl)-1-methylpyridinium bis(trifluoromethanesulfonyl)imides (1a–d)

The arene (3.0 mmol) was sonicated in the biodegradable IL (**1a–d** where indicated) (4.0 g) for 10 min under a nitrogen atmosphere to facilitate dissolution of the arene in the ionic

liquid. (Note: ILs used as reaction solvents were typically dried under high vacuum while heating at 60 °C.) Phenylacetylene (0.34 g, 3.3 mmol), triethylamine (0.46 g, 4.5 mmol) and palladium(II) chloride (10.6 mg, 0.06 mmol) were added to the reaction mixture. Ultrasonic irradiation was continued for 2 h at room temperature with occasional stirring to ensure reaction homogeneity. Product isolation involved extraction of the reaction mixture with diethyl ether (3 × 50 mL), drying of the combined ether extracts followed by evaporation of solvent *in vacuo*. The product was purified by column chromatography (either neat petroleum spirits or 5–15% diethyl ether in petroleum spirits). ^{1}H and ^{13}C NMR spectra of all products agreed with those reported elsewhere in the literature and has been included in the ESI†.

ISO 14593-Carbon dioxide head space test

To evaluate the biodegradability of the test pyridinium ILs, the "CO_2 headspace" test (ISO 14593, OECD 310) was applied. This method allows the evaluation of the ultimate aerobic biodegradability of an organic compound in an aqueous medium at a given concentration of microorganisms by analysis of inorganic carbon (IC). The test chemical, as the sole source of carbon and energy, was added at a concentration of 10 to 20 mg C per L to a buffer–mineral salts medium. These solutions were inoculated with activated sludge collected from an activated sludge treatment plant, washed and aerated prior to use and incubated in sealed vessels with a headspace of air. Biodegradation (mineralisation to carbon dioxide) was determined by measuring the IC produced in the test bottles in excess of that produced in blank vessels containing inoculated medium only. Sodium *n*-dodecyl sulfate (SDS) was used as reference substance. The test ran for 28 days and the extent of biodegradation was expressed as a percentage of the theoretical amount of inorganic carbon (ThIC) based on the amount of test compound added initially. Comparable results were obtained for replicates (<20% difference) and mean degradation percentages are reported in Fig. 2 and Table 2.

Acknowledgements

The authors thank Pfizer Global R&D, the Spanish Ministerio de Educación y Ciencia (CTQ2007-60364/PPQ), the Australian Research Council (LX0561094), and the Natural Sciences and Engineering Research Council of Canada (NSERC Discovery to R.D.S. and NSERC-PGSA to A.T.G.) for financial support.

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