Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 9085–9089

Tetrahedron
Letters

Reactivity of trihexyl(tetradecyl)phosphonium chloride, a room-temperature phosphonium ionic liquid

Ming-Chung Tseng,[†] Huang-Chuan Kan[†] and Yen-Ho Chu*

Department of Chemistry and Biochemistry, National Chung Cheng University, 168 University Road, Min-Hsiung, Chia-Yi, Taiwan, ROC

Received 21 September 2007; revised 24 October 2007; accepted 26 October 2007
Available online 30 October 2007

Abstract—Trihexyl(tetradecyl)phosphonium chloride **1**, a room-temperature ionic liquid, readily undergoes deuterium isotope exchange reaction in deuterated solvents. Under basic conditions, ionic liquid **1** was reactive and 50% deuterium exchanged on all four P–CH_2 methylene groups in 9 h at ambient temperature, 30 min at 50 °C, or 12 min at 65 °C. In addition, ionic liquid **1** reacted with sodium salts of substituted benzoates apparently through the direct S_N2 carboxylate alkylation to form esters **2** and the resulting esters further converted, via Wittig reaction, to finally afford aryl ketones **4**.

Ionic liquids are organic salts that are liquid at low temperatures (<100 °C).[1] The wide liquid range, superior thermal and chemical stability, strong solvent power, and very low vapor pressure have made ionic liquids, in particular room-temperature ionic liquids, attractive in many areas of applications such as organic synthesis, chemical catalysis, separation technology, and novel electrolytes for solar and fuel cells.[1]

Today the ionic liquid research continues to be dominated by dialkylimidazolium salts with fluorine-containing anions.[1] Studies of quaternary phosphonium systems, however, are much rare, although these tetraalkylphosphonium salts have long been used as phase transfer catalysts.[1,2] In our laboratory, we have been interested in developing new ionic liquids and have a program to evaluate ionic liquids as novel and stable media for chemical and biochemical applications.[3] While new and stable bicyclic imidazolium-based ionic liquids are being developed in our laboratory,[3a–c] the commercially available trihexyl(tetradecyl)phosphonium chloride **1** as a room-temperature phosphonium-based ionic liquid was recently reported to be chemically stable and remain inert with Grignard reagents such as phenylmagnesium bromide under strongly basic conditions (i.e., the phosphonium cation was not deprotonated to produce the corresponding phosphorane).[4,5] This result prompted us to further investigate phosphonium ionic liquids as we believed that these ionic liquids would potentially provide the needed chemical stability as useful media for organic synthesis and relevant biochemical applications.

We envisaged that, besides being reported to be sterically hindered at its central core,[4] phosphonium ionic liquids can be chemically stable for the reason that they lack the acidic ring protons of the common imidazolium cations, which limit their general use in synthetic reactions particularly when basic anions are employed.[6] Several ionic liquids, especially those based on imidazolium ions such as 1-butyl-3-methylimidazolium ([bmim]), have been known to be chemically reactive.[3f,6,7] Furthermore, these quaternary phosphonium salts were known to be more stable to high temperatures for longer periods of time than those nitrogen-based cations.[8] To test its chemical stability, we first investigated this commercially available ionic liquid **1** to see if it resists to solvent deuterium isotope exchange.[5,9]

Using NMR to monitor the reaction, we quickly found, however, that the ionic liquid **1** was chemically reactive and readily underwent H–D exchange in basic CD_3OD/D_2O (1:1, v/v) solution at ambient temperature (Fig. 1). Figure 1 shows the time-dependant exchange rate profile. The solvent exchange rate was measured by

---

* Corresponding author. Tel.: +886 5 2428148; fax: +886 5 2721965; e-mail: cheyhc@ccu.edu.tw

[†] Both authors contributed equally to this work.

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.131

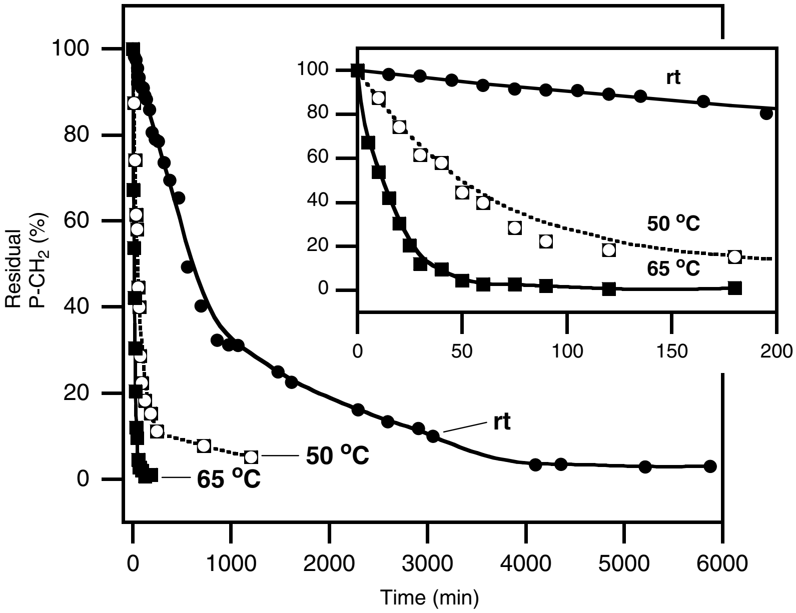


Figure 1. Solvent deuterium isotope exchanges at P–CH_2 of ionic liquid **1** (20 mM) in CD_3OD/D_2O (1:1, v/v; 0.5 mL) containing 0.1 M KOD at ambient temperature, 50 °C, and 65 °C, respectively. The progress of deuterium exchange reactions could be readily monitored by ^1H NMR. The inset detailed the progress of exchange reactions of the ionic liquid **1** within the first 200 min. Under the experimental condition, times required at 50% exchange for **1** were approximately 9, 0.5, and 0.2 h at ambient temperature, 50 °C and 65 °C, respectively.

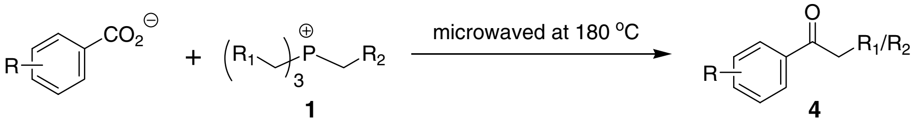
observing the changes in the ^1H NMR integrals of all four P–CH_2 protons to that of terminal methyl hydrogens (non-exchangeable position) on all alkyl groups. Results from Figure 1 showed that ionic liquid **1** was 50% deuterium exchanged at P–CH_2 protons in approximately 9 h ($t_{1/2}$) at ambient temperature. For comparison, under similar experimental conditions, a bicyclic imidazolium [b-3C-im][NTf_2] ionic liquid recently developed in our laboratory apparently was much more resistant than ionic liquid **1** to solvent isotope exchange ($t_{1/2} \sim 140$ h).[3b] This result clearly demonstrated that the commercial ionic liquid **1** possesses acidic and exchangeable P–CH_2 protons[10] and is not as chemically stable as expected.

Since many organic reactions take place under heated conditions, we accordingly performed the solvent deuterium isotope exchanges of **1** at elevated temperatures (50 and 65 °C) to further explore their suitability for use as solvents in organic synthesis.[9] Results shown in Figure 1 unambiguously demonstrated that, under basic conditions, ionic liquid **1** was highly reactive at elevated temperatures. To be specific, ionic liquid **1** was 50% deuterium exchanged within 30 min at 50 °C and 12 min at 65 °C, respectively.

Since in our laboratory we have been interested in developing microwave-accelerated reactions for organic synthesis in ionic liquids[3a,d,e] and also noted a recent report that nucleophiles such as sodium benzoate readily decomposed the [bmim][BF_4] ionic liquid under microwave heating at high temperatures (175–225 °C),[11] we decided to conduct experiments to further investigate the stability of the phosphonium ionic liquid **1** by microwaves under heated conditions. Previously, a mild and high yielding protocol was described and reported for direct carboxylate alkylation of organobromides with the presence of Hunig's base in trihexyl(tetradecyl)phosphonium bistriflamide ionic liquid.[12] In our hand, after several initial trials, it was quickly revealed that the phosphonium cation of ionic liquid **1** was electrophilic and evidently reacted with substituted benzoate salts by microwaves at elevated temperature.[13] Table 1 showed that, using microwaves (30 W) with temperature controlled at 180 °C, substituted benzoate salts readily reacted with ionic liquid **1** to afford aryl ketones **4**. All ketone products (**4a–f**) were isolated by chromatography and spectroscopically characterized.[13] For all compounds isolated, satisfactory ^1H and ^{13}C NMR, IR, and MS results were obtained. For example, in IR spectra, the strong carbonyl absorptions of ketone products **4** obtained by this reaction fall in the region of 1660–1685 cm^{-1}. This is consistent with the figures found generally for aryl ketones.[14]

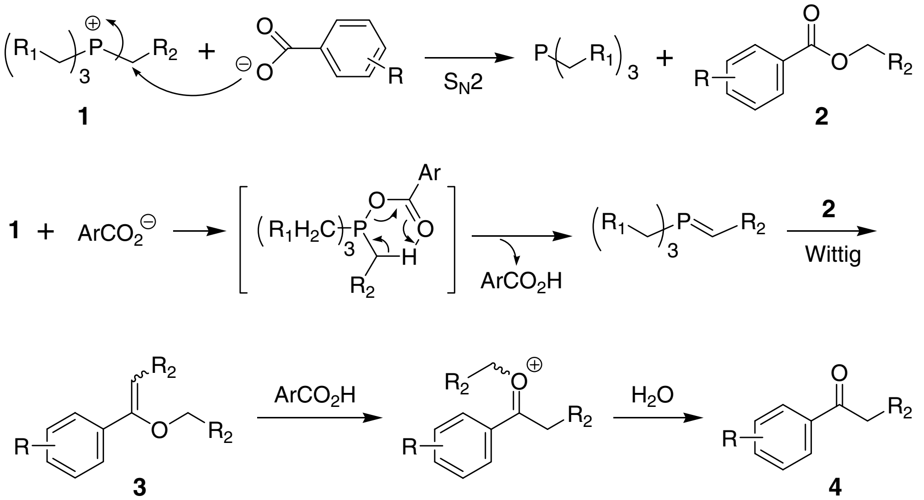
On the basis of infrared carbonyl absorption frequencies and characteristic NMR chemical shifts, we proposed a mechanism to account for the fact that aryl ketones **4** are reaction products and benzoate esters **2** are the most probable intermediates. Scheme 1 outlines the proposed reaction mechanism. As a first reaction intermediate in the sequence of reactions, the benzoate esters **2** were formed from the direct S_N2 attack of the carboxylate nucleophile on the electrophilic hexyl or tetradecyl groups attached to the phosphonium ionic liquid **1**. As soon as esters **2** were produced, each ester then served as a Wittig substrate and accordingly coupled with the deprotonated phosphonium **1** (ylide) to carry out the 'non-classical' Wittig reaction to ultimately lead to the formation of aryl ketone **4**.[15] Though aldehydes and ketones are convenient substrates of the Wittig olefination reaction, in the literature phosphonium ylides

Table 1. Reactions of benzoate salts with trihexyl(tetradecyl)phosphonium chloride **1**, a room-temperature phosphonium ionic liquid, by microwaves at 180 °C



Entry	Starting benzoate	Reaction time (min)	Ketone product **4**	Isolated yield (%)
1	R = H	20	$R_1 = C_5H_{11}$ (**4a**) $R_2 = C_{13}H_{27}$ (**4b**)	3.8 (14.8[a]) 3.5
2	R = 2-NH$_2$	20	$R_1 = C_5H_{11}$ (**4c**) $R_2 = C_{13}H_{27}$ (**4d**)	7.6 2.2
3	R = 4-CH$_3$	20 + 20	$R_1 = C_5H_{11}$ (**4e**) $R_2 = C_{13}H_{27}$ (**4f**)	4.5 2.1

[a] Yield analyzed and determined by HPLC. Due to product volatility, actual isolated yield was much lower than the analysis yield.



Scheme 1. Proposed mechanism for aryl ketone (**4**) formation from the reactions of ionic liquid **1** with sodium benzoates by microwaves with temperature controlled at 180 °C. Though both hexyl (–CH$_2$R$_1$) and tetradecyl (–CH$_2$R$_2$) groups were accessible to reactions, tetradecyl group was used here to demonstrate its involvement in the reaction mechanism.

were also known to readily react with reagents with functional groups such as esters, amides, and anhydrides to form olefins in a manner analogous to that commonly observed with aldehydes and ketones.[15] In addition, using benzoate salt as base, complete deprotonation of **1** might not occur. However, as long as the ylide was in equilibrium with the phosphonium salt, the Wittig reaction proceeded. In cases of sodium benzoate and anthranilate (entries 1 and 2 in Table 1), a reaction time of 20 min was sufficient to produce enough products for analysis while two consecutive 20 min microwave irradiations for the slow reacting sodium 4-methylbenzoate (entry 3 in Table 1) were however required. We noted further that, under the experimental condition, no Wittig adducts (vinyl ethers) **3** were observed or isolated, and only the hydrolyzed products (aryl ketones) **4** were obtained (Scheme 1). Under our microwave condition (30 W, 180 °C), we could not rule out the possibility of any Hoffmann elimination reaction being taking place in the presence of benzoate base, simply because of high volatility of any terminal alkenes if formed. Results in Table 1 clearly showed that isolated yields of all aryl hexyl ketones (**4a**, **4c**, and **4e**) obtained were higher than that of aryl tetradecyl ketones (**4b**, **4d**, and **4f**). This most likely was due to the higher molarity of hexyl groups present in **1**.

In summary, we report here for the first time that tetraalkylphosphonium cation in ionic liquid **1** is acidic, electrophilic, and can be chemically reactive.[16] We have demonstrated in this study that the commercial ionic liquid **1** reacted with nucleophiles and, under basic condition, readily underwent deuterium isotope exchange reaction in deuterated solvents.

Acknowledgments

We thank Ms. Ping-Yu Lin of Academia Sinica (Taiwan, ROC) for her excellence in mass analyses. This work was supported by a multi-year Grant-in-Aid from

ANT Technology (Taipei, Taiwan) and in part by the National Science Council (Taiwan, ROC). We also thank the reviewers for their constructive comments.

References and notes

1. For recent reviews, see: (a) Xue, H.; Verma, R.; Shreeve, J. M. *J. Fluorine Chem.* **2006**, *127*, 159–176; (b) Singh, R. P.; Verma, R. D.; Meshri, D. T.; Shreeve, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3584–3601; (c) MacFarlane, D. R.; Pringle, J. M.; Johansson, K. M.; Forsyth, S. A.; Forsyth, M. *Chem. Commun.* **2006**, 1905–1917; (d) Canal, J. P.; Ramnial, T.; Dickie, D. A.; Clyburne, J. A. C. *Chem. Commun.* **2006**, 1809–1818; (e) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267–278; (f) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015–1060; (g) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275–297.
2. Bradaric, C. J.; Downard, A.; Kennedy, C.; Robertson, A. J.; Zhou, Y. *Green Chem.* **2003**, *5*, 143–152.
3. (a) Lin, Y.-L.; Kan, H.-C.; Chu, Y.-H. *Tetrahedron* **2007**, *63*, 10949–10957; (b) Kan, H.-C.; Tseng, M.-C.; Chu, Y.-H. *Tetrahedron* **2007**, *63*, 1644–1653; (c) Cheng, J.-Y.; Chu, Y.-H. *Tetrahedron Lett.* **2006**, *47*, 1575–1579; (d) Tseng, M.-C.; Liang, Y.-M.; Chu, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 6131–6136; (e) Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 8137–8140; (f) Hsu, J.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron Lett.* **2004**, *45*, 4673–4676.
4. (a) Ramnial, T.; Ino, D. D.; Clyburne, J. A. C. *Chem. Commun.* **2005**, 325–327; (b) Gorodetsky, B.; Ramnial, T.; Branda, N. R.; Clyburne, J. A. C. *Chem. Commun.* **2004**, 1972–1973.
5. This ionic liquid is available from Cytec (CYPHOS® IL 101) and Fluka/Riedel-de Haën. According to Cytec product description, the ionic liquid typically assays 96 to 97% trihexyl(tetradecyl)phosphonium chloride (**1**) with trace contaminants of tetradecene isomers (0.1–0.4%), hydrochloric acid (0.1–0.5%), and trihexylphosphonium hydrochloride (0.1–1.2%).
6. For a recent review on the reactivity of ionic liquids, see: Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363–D2389.
7. Acidity values for C-2 protons ($\mathrm{p}K_\mathrm{a} \sim 20$–30) of a series of 1,3-dialkylimidazolium cations have been measured and reported: (a) Wang, R.; Yuan, L.; Macartney, D. H. *Chem. Commun.* **2006**, 2908–2910; (b) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366–4374; (c) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717–8724.
8. Del Sesto, R. E.; Corley, C.; Robertson, A.; Wilkes, J. S. *J. Organomet. Chem.* **2005**, *690*, 2536–2543.
9. *General procedure for deuterium isotope exchange experiments*: The ^{1}H NMR of a mixture of CD_3OD/D_2O (1:1, v/v; 0.5 mL) containing 0.02 M ionic liquid **1** (5.2 mg) was recorded first. To it was then added 0.1 M KOD (3.0 mg). The ^{1}H NMR spectrum was therefore collected at regular intervals. The ratio of the integrals of the P–CH_2 position hydrogens to that of the terminal methyl hydrogens (a non-exchangeable position) on the alkyl group in **1** was obtained. These values were finally plotted to determine the rates of the exchange reactions.
10. The proton removed to form the corresponding ylide in alkyl(triphenyl)phosphonium salts in dimethyl sulfoxide has been reported to have a $\mathrm{p}K_\mathrm{a}$ value in the range of 21–23. For references, see: (a) Russell, M. G.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 505–513; (b) Zhang, X.-M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1994**, *116*, 968–972.
11. Glenn, A. G.; Jones, P. B. *Tetrahedron Lett.* **2004**, *45*, 6967–6969.
12. McNulty, J.; Cheekoori, S.; Nair, J. J.; Larichev, V.; Capretta, A.; Robertson, A. J. *Tetrahedron Lett.* **2005**, *46*, 3641–3644.
13. *General procedure for the reactions of ionic liquid* **1** *with substituted benzoate salts by microwaves*: To a microwave reaction vessel containing the ionic liquid **1** (0.8 g) was added the substituted benzoic acid (150 mg; 1.23 mmol for benzoic acid, 1.10 mmol for *p*-toluic acid, 1.09 mmol for anthranilic acid) and sodium carbonate powder (300 mg, 2.8 mmol). The vessel was placed inside a CEM Discover single-mode microwave synthesizer equipped with a magnetic stirrer where it was exposed to microwaves at 180 °C (30 W) for 20 min. The progress of the reaction could be monitored by thin layer chromatography and the experimental condition was, however, not optimized. After microwaves, the reaction solution was mixed with ethyl acetate (5 mL), filtered and then concentrated to dryness in vacuo. The desired products were purified by chromatography (ethyl acetate/hexane = 1:40, v/v) to finally afford the corresponding aryl ketones (2.1–7.6% yield). Satisfactory ^{1}H and ^{13}C NMR, IR, and MS results were obtained for all products. Heptanophenone **4a** is a commercially available compound.

   Pentadecanophenone **4b**: 13 mg (3.5% isolated yield); white solid; mp 43–44 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, $J = 7.0$ Hz, CH_3, 3H), 1.24 (br s, $11 \times CH_2$, 22H), 1.71 (qn, $J = 7.5$ Hz, CH_2, 2H), 2.94 (t, $J = 7.4$ Hz, $CH_2C(=O)$, 2H), 7.43 (t, $J = 7.5$ Hz, aryl H, 2H), 7.53 (t, $J = 7.2$ Hz, aryl H, 1H), 7.94 (d, $J = 7.3$ Hz, aryl H, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 24.4, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 38.6, 128.0, 128.5, 132.8, 137.2, 200.6; FTIR (KBr) ν 1685 (s) cm^{-1}; EI-HRMS m/z [M$^+$] calcd for $C_{21}H_{34}O$: 302.2610; found, 302.2608.

   1-(2-Aminophenyl)heptan-1-one **4c**: 17 mg (7.6% isolated yield); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, $J = 6.9$ Hz, CH_3, 3H), 1.23–1.32 (m, $3 \times CH_2$, 6H), 1.68 (qn, $J = 7.5$ Hz, CH_2, 2H), 2.31 (t, $J = 7.6$ Hz, $CH_2C(=O)$, 2H), 7.05 (t, $J = 7.3$ Hz, aryl H, 1H), 7.26 (t, $J = 7.8$ Hz, aryl H, 2H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.69 (br s, NH_2, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.4, 25.6, 28.9, 31.5, 27.7, 119.9, 119.9, 124.1, 128.8, 128.8, 138.1, 171.7; FTIR (KBr) ν 1661 (s) cm^{-1}; EI-HRMS m/z [M$^+$] calcd for $C_{13}H_{19}NO$: 205.1467; found, 205.1471.

   1-(2-Aminophenyl)pentadecan-1-one **4d**: 7.7 mg (2.2% isolated yield); white solid; mp 79–80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, $J = 7.0$ Hz, CH_3, 3H), 1.24 (br s, $11 \times CH_2$, 22H), 1.70 (qn, $J = 7.3$ Hz, CH_2, 2H), 2.32 (t, $J = 7.6$ Hz, $CH_2(C=O)$, 2H), 7.07 (t, $J = 7.3$ Hz, aryl H, 1H), 7.23 (br s, NH_2, 2H), 7.29 (t, $J = 7.8$ Hz, 2H), 7.49 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 25.6, 29.3, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.7, 29.7, 31.9, 37.9, 119.8, 119.8, 124.1, 129.0, 129.0, 138.0, 171.4; FTIR (KBr) ν 1660 (s) cm^{-1}; EI-HRMS m/z [M$^+$] calcd for $C_{21}H_{35}NO$: 317.2719; found, 317.2642.

   1-*p*-Tolylheptan-1-one **4e**: 9.2 mg (4.5% isolated yield); white solid; mp 38–39 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, $J = 7.0$ Hz, CH_3, 3H), 1.29–1.35 (m, $3 \times CH_2$, 6H), 1.70 (qn, $J = 7.4$ Hz, CH_2, 2H), 2.38 (s, $ArCH_3$, 3H), 2.90 (t, $J = 7.3$ Hz, $CH_2C(=O)$, 2H), 7.23 (d, $J = 8.0$ Hz, aryl H, 2H), 7.84 (d, $J = 8.0$ Hz, aryl H, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 21.6, 22.5,29.1, 31.7, 38.5, 128.2, 129.2, 134.7, 143.5, 200.3; FTIR (KBr) ν 1675 (s)

cm^{-1}; EI-HRMS *m/z* [M^+] calcd for $C_{14}H_{20}O$: 204.1514; found, 204.1518.

1-*p*-Tolylpentadecan-1-one **4f**: 6.5 mg (2.1% isolated yield); white solid; mp 45–46 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.86 (t, $J = 7.0$ Hz, CH_3, 3H), 1.23 (br s, $11 \times CH_2$, 22H), 1.68 (qn, $J = 7.4$ Hz, CH_2, 2H), 2.38 (s, $ArCH_3$, 3H), 2.90 (t, $J = 7.4$ Hz, $CH_2C(=O)$, 2H), 7.23 (d, $J = 8.1$ Hz, Aryl H, 2H), 7.83 (d, $J = 8.1$ Hz, Aryl H, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 24.5, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9, 38.5, 128.2, 129.2, 134.7, 143.5, 200.3; FTIR (KBr) ν 1682 (s) cm^{-1}; EI-HRMS *m/z* [M^+] calcd for $C_{22}H_{36}O$: 316.2766; found, 316.2760.

14. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981, pp 117–123.
15. For a review on Wittig reaction of carbonyl compounds other than aldehydes and ketones, see: Murphy, P. J.; Brennan, J. *Chem. Soc. Rev.* **1988**, *17*, 1–30.
16. Recently, Clyburne and co-workers have reported excellent chemical stability of a Grignard reagent (PhMgBr) in phosphonium ionic liquids such as trihexyl(tetradecyl)phosphonium decanoate and proposed that this stability was the result of strong Mg–O interactions between the decanoate anion of the ionic liquid and the organomagnesium reagent: Ramnial, T.; Taylor, S. A.; Clyburne, J. A. C.; Walsby, C. J. *Chem. Commun.* **2007**, 2066–2068, This strong complexation of the relatively large, basic PhMgBr with trihexyl(tetradecyl)phosphonium decanoate ionic liquid may likely contribute its stability in the ionic liquid and consequently no reaction or decomposition with ionic liquid was observed.