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HECK REACTIONS OF ARYL HALIDES WITH STYRENE USING 1-BUTYL-3-METHYLIMIDAZOLIUM BROMIDE IONIC LIQUID AS A GREEN SOLVENT UNDER MICROWAVE IRRADIATION

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ABSTRACT

Easily accessible ionic liquids, 1-butyl-3-methylimidazolium bromide, 1-hexyl-3-methylimidazolium bromide, and 1-octyl-3-methylimidazolium bromide, respectively, were synthesized under microwave irradiation condition, and characterized by ^1H and ^{13}C NMR, and MS. The three ionic liquids were demonstrated to be an efficient and recyclable solvent for the Heck cross-coupling reaction between several aryl halides and styrene under microwave irradiation to form trans-stilbenes as the principal products. Interestingly, it was found that increasing the length of the alkyl chain in the ionic liquid caused a significant drop in the reaction rate. Higher reaction rate was observed for the Heck reaction using 1-butyl-3-methylimidazolium bromide, as compared to that of the reaction using 1-hexyl-3-methylimidazolium bromide, and 1-octyl-3-methylimidazolium bromide, respectively. Using the ionic liquid as the reaction solvent in conjunction with microwave irradiation, the reaction rate was dramatically enhanced, with 99% conversion being achieved within 1.5 minutes for the butyl-based ionic liquid, compared to conversions obtained after 2 hours under conventional conditions. Furthermore, the ionic liquid Pd^{2+} system could be reused in subsequent reaction without significant degradation in activity.

I - INTRODUCTION

Transition metal-catalyzed cross-coupling reactions have gained popularity over the past thirty years in organic synthetic chemistry, as they represent key steps in the building of more complex molecules from simple precursors [1]. Their applications range from the synthesis of complex natural products to supramolecular chemistry and materials science, from fine chemical to the pharmaceutical industries [2]. A wide variety of cross-coupling methodologies have been developed to achieve the most powerful and useful tool for the elaboration of molecular architecture, in which the Heck coupling reactions appear to have advantages over other processes [3]. Ionic liquids have recently been extensively evaluated as environmental-friendly or green alternatives to conventional organic solvents because their non-volatile nature can minimize the emission of toxic organic compounds and facilitate the separation of products and catalysts [4-6].

In Vietnam, the synthesis of ionic liquids was reported for the first time by Le Ngoc Thach and co-workers during the 2006 — 2007 period [7]. However, applications of the as-synthesized ionic liquids as green solvents for cross-coupling Heck reactions were *not previously reported in Viet Nam*. We recently employed an ionic liquid, 1-hexyl-3-methylimidazolium bromide, as the green solvent for the Heck reaction between iodobenzene and styrene in the presence of $PdCl_2$ as the catalyst and triethylamine as the base to form *trans*-stilbene as the principal product [8]. In this paper, we wish to report our further exploration on the ionic liquid-mediated Heck cross-coupling reactions of aryl halides with styrene under microwave irradiation. Interestingly, it was found that increasing the length of the alkyl chain in the ionic liquid caused a significant drop in the reaction rate. Higher reaction rate was observed for the Heck reaction using 1-butyl-3-methylimidazolium bromide, as compared to that of the reaction using 1-hexyl-3-methylimidazolium bromide. Using the butyl-based ionic liquid as the reaction solvent in conjunction with microwave irradiation, the reaction rate was dramatically enhanced, with 99% conversion being achieved *within 1.5 minutes*, compared to conversions obtained after 2 hours under conventional heating conditions.

II - EXPERIMENTAL

1. Materials and instrumentation

Chemicals were purchased from Sigma-Aldrich and Merck, and used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV 500 spectrometer, MS spectra were recorded using an Agilent LC-MSD-Trap-SL, Institute of Chemistry at Ha Noi, Vietnamese Academy of Science and Technology. GC-MS analyses were performed using an Agilent GC-MS 6890 at Analytical Laboratory, Institute of Chemical Technology at Ho Chi Minh City, Vietnamese Academy of Science and Technology. GC analyses were performed using a Shimadzu GC-17A equipped with a FID detector and a 30 m × 0.25 mm × 0.25 μm DB-5 column. The temperature program for GC analyses heated samples from 60ºC to 140ºC at 10ºC/minute, held at 140ºC for 1 minute, from 140ºC to 300ºC at 50ºC/minute, and held at 300ºC for 3 minutes.

2. Synthesis of the ionic liquid

In a typical reaction, *N*-methylimidazole (51.75 g, 0.628 mol) and *n*-butyl bromide (95.25 g, 0.695 mol) were added to a 500 ml round-bottom flask equipped with a Dimroth condenser. The mixture was heated intermittently in a modified household microwave oven (Whirlpool M541-800W) at 200 W. After the first heating for 5 seconds, the irradiation was paused for 1 minute, and the reaction mixture was then heated at the same power level for an additional 5 seconds. The procedure was repeated for a total irradiation time of 1 minute. The resulting ionic liquid was then cooled, triturated and washed with diethyl ether (6 x 50 ml) to remove unreacted starting materials. The solvent residue was then removed by a rotovap at 30ºC, affording 133 g of 1-butyl-3-methylimidazolium bromide (97% yield).

^{1}H NMR (500 MHz, DMSO): δ = 0.887 (t, 3H; CH_3), 1.256 (m, 2H; CH_2CH$_3$), 1.770 (m, 2H; CH_2CH$_2$CH$_3$), 3.882 (s, 3H; N-CH_3), 4.204 (m, 2H; N-CH_2), 7.778 (t, 1H; N-C*H*=C), 7.856 (t, 1H; N-C*H*=C), 9.340 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO): δ = 13.173 (C-*C*H$_3$), 18.652 (*C*H$_2$), 31.279 (*C*H$_2$), 35.693 (N-*C*H$_3$), 48.357(N-*C*H$_2$), 122.172 (*C*=C-N), 123.461 (C=*C*-N), 136.435 (N-*C*=N). MS (ESI): *m*/*z* (%) 139.1 [*M*-Br]$^+$.

1-Hexyl-3-methylimidazolium bromide was synthesized from *n*-hexyl bromide and *N*-methylimidazole using a similar procedure, in which *n*-hexyl bromide was used in place of *n*-butyl bromide, affording 84% yield. ^{1}H NMR (500 MHz, DMSO): δ = 0.807 (t, 3H; CH_3), 1.220 (m, 6H; CH_2CH_2CH_2), 1.760 (m, 2H; CH_2), 3.879 (s, 3H; N-CH_3), 4.195 (m, 2H; N-CH_2), 7.798 (t, 1H; N-C*H*=C), 7.883 (t, 1H; N-C*H*=C), 9.406 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO): δ = 13.704 (C-*C*H$_3$), 21.767 (*C*H$_2$), 25.029 (*C*H$_2$), 29.309 (*C*H$_2$), 30.446 (*C*H$_2$), 35.719 (N-*C*H$_3$), 48.614(N-*C*H$_2$), 122.161 (*C*=C-N), 123.421 (C=*C*-N), 136.435 (N-*C*=N). MS (ESI): *m*/*z* (%) 167.1 [*M*-Br]$^+$.

1-Octyl-3-methylimidazolium bromide was synthesized from *n*-octyl bromide and *N*-methylimidazole using a similar procedure, in which *n*-octyl bromide was used in place of *n*-butyl bromide, affording 64% yield. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.871 (t, 3H; CH_3), 1.272 (m, 10H; CH_2CH_2CH_2CH_2CH_2), 1.916 (m, 2H; CH_2), 4.129 (s, 3H; N-CH_3), 4.327 (m, 2H; N-CH_2), 7.473 (t, 1H; N-C*H*=C), 7.641 (t, 1H;

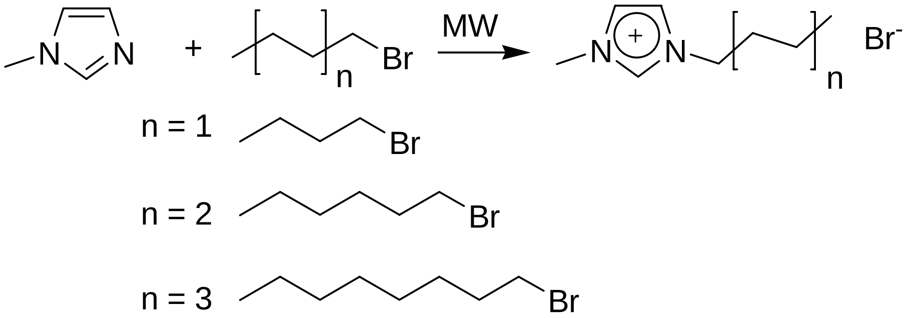
N-CH=C), 10.156 (s, 1H, N-CH=N). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 13.870 (C-CH$_3$), 22.390 (CH$_2$), 26.085 (CH$_2$), 28.772 (CH$_2$), 28.841 (CH$_2$), 30.137 (CH$_2$), 31.495 (CH$_2$), 36.642 (N-CH$_3$), 50.003 (N-CH$_2$), 121.860 (C=C-N), 123.641 (C=C-N), 137.076 (N-C=N). MS (ESI): *m*/*z* (%) 195.2 [*M*-Br]$^+$.

3. Catalysis studies

Unless otherwise stated, a mixture of 4-iodobenzene (0.24 ml, 2.15 mmol), styrene (0.40 ml, 3.22 mmol), triethylamine (0.9 ml, 6.45 mmol), and hexadecane (0.48 ml) as the internal standard in the ionic liquid (10 ml) were added to a round-bottom flask containing the required amount of the PdCl$_2$ or Pd(OAc)$_2$ catalyst. The flask was heated in a modified household microwave oven (Whirlpool M541-800W) at 800 W. Reaction conversions were monitored by withdrawing aliquots (0.1 ml) from the reaction mixture at different time intervals, and quenching with water. The organic components were extracted into diethylether (3 ml), dried over Na$_2$SO$_4$ and analyzed by GC with reference to hexadecane. Product identity was also further confirmed by GC-MS, and also referenced to standard *trans*-stilbene and *cis*-stilbene (Sigma-Aldrich). The Heck reaction of 4-iodobenzene and styrene was also carried out under conventional heating condition.

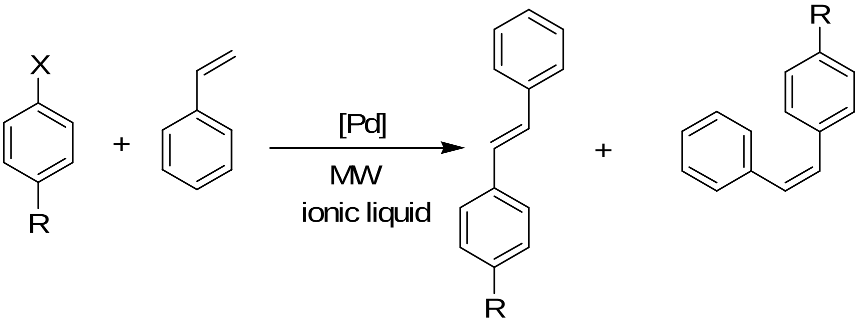
III - RESULTS AND DISCUSSION

The ionic liquid was synthesized according to a previously reported procedure [9]. In view of the green chemistry, it was decided to explore the synthesis of 1-butyl-3-methylimidazolium bromide, 1-hexyl-3-methylimidazolium bromide, and 1-octyl-3-methylimidazolium bromide from *N*-methylimidazole with *n*-butyl bromide, *n*-hexyl bromide, and *n*-octyl bromide, respectively, using microwave irradiation under solvent-free condition (Scheme 1). The formation of the ionic liquid could be monitored visibly in the reaction as it turned from clear solution to opaque, and finally clear. It was observed that partial decomposition of the ionic liquid could occur possibly due to the localized heating, eventually resulting in lower yields. To overcome this problem, the reaction was conducted with intermittent microwave irradiation as described in the experimental section. Isolated yields of 97%, 84%, 64% were achieved within a total irradiation time of 1 minute under solvent-free condition for 1-butyl-, 1-hexyl-, and 1-octyl-3-methylimidazolium bromide, respectively. The ionic liquid was characterized using ^{1}H and ^{13}C NMR, and MS, which were in good agreement with the literature [10].



Scheme 1: The synthesis of ionic liquids:
1-butyl-, 1-hexyl-, and 1-octyl-3-methylimidazolium bromide

The three ionic liquids were evaluated for their suitability as reaction solvents initially for the Heck reaction between iodobenzene and styrene to form *trans*-stilbene as the principal product and *cis*-stilbene and the minor product (Scheme 2). The efficiency of microwave irradiation in accelerating organic transformations has recently been proven in several different fields of organic chemistry, in which reaction times can be dramatically reduced from days and hours to minutes and seconds [11]. Microwave-assisted chemistry is usually performed in high boiling polar solvents such as DMSO, NMP and DMF due to their high dipole moments [12]. Owing to the high polarity and thermal stability of ionic liquids, it was decided to carry out the Heck reaction of iodobenzene and styrene in the ionic liquid using a modified household microwave oven (Whirlpool M541-800W) at 800 W. It is generally accepted that a base is obviously necessary to neutralize the HI produced, and regenerate the active species to complete the catalytic cycle of the Heck reaction [13]. From our previous results [8], triethylamine in combination with 5 mol% palladium catalyst exhibited higher activity than other bases such as Na_2CO_3, CH_3COONa *etc* for the reaction in the ionic liquid. Triethylamine was therefore employed as the base for the Heck reaction between iodobenzene and styrene carried out in the three ionic liquids in the presence of 5 mol% $PdCl_2$ as the catalyst. Experimental results are shown in figure 1.



X: I, Br, Cl
R: H, CH_3, $COCH_3$ *trans*-stilbenes *cis*-stilbenes

Scheme 2: The Heck reaction of aryl halides and styrene in ionic liquid under microwave irradiation

It was observed that the Heck reaction carried out in the butyl-based ionic liquid afforded a conversion of 95% within just 1 minute, and more than 99% conversion was achieved within *1.5 minutes*. It should be noted that the reaction under conventional heating afforded 99% conversion within *2 hours* at 140 °C. Interestingly, it was found that increasing the length of the alkyl chain in the ionic liquid caused a significant drop in the reaction rate (Figure 1). The Heck reaction carried out in the hexyl-based solvent afforded 78% conversion within 1 minute, though more than 99% conversion was still obtained within 2.5 minutes. Replacing the butyl group with the octyl group in the ionic liquid structure slowed down the reaction dramatically, with only 69% conversion being achieved within 3 minutes. This could be rationalized based on the fact that increasing the length of the alkyl group would decrease the polarity of the solvent. Indeed, polar aprotic solvents such as DMF, DMA, MeCN *etc.* have been successfully employed for transition metal-catalyzed organic transformations such as the Heck and the Suzuki reactions [14]. Nonpolar solvents have been shown to be not suitable for the Heck reaction. It was also previously reported that several imidazolium-based ionic liquids had polarities similar to those of short-chain alcohol and other polar aprotic solvents such as DMSO, DMF *etc* [15].

With this result in mind, it was decided to employ the 1-butyl-3-methylimidazolium bromide as the reaction solvent for further studies. An other common homogeneous catalyst for the Heck cross-coupling carried out in ionic liquid, $Pd(OAc)_2$, was also used for the reaction of iodobenzene and styrene under microwave irradiation. Experimental results showed that at the catalyst concentration of 5 mol%, $Pd(OAc)_2$ exhibited similar activity to $PdCl_2$, with a conversion of 98% being achieved

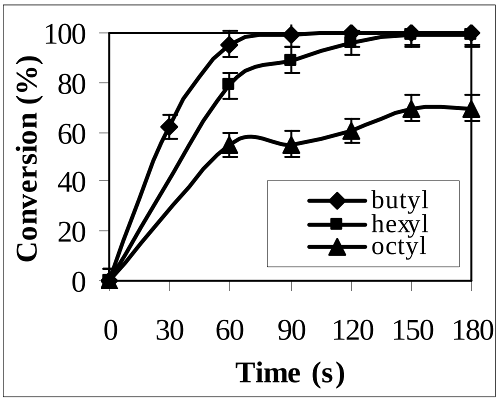


Figure 1: The Heck reactions of iodobenzene and styrene in 1-butyl-, 1-hexyl-, and 1-octyl-3-methylimidazolium bromide, respectively

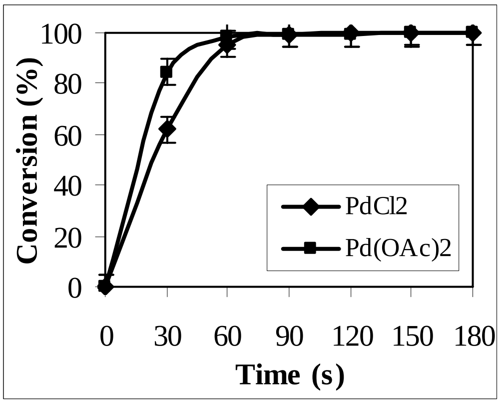


Figure 2: The Heck reaction in the 1-butyl-3-methylimidazolium bromide under microwave irradiation using 5 mol% $PdCl_2$ and $Pd(OAc)_2$, respectively

within 1 minute. As with the Heck reaction using $PdCl_2$ catalyst, more than 99% conversion was also obtained within 1.5 minutes (figure 2). From a mechanistic point of view, it was previously proposed that for the Suzuki and the Heck coupling reactions, the true active catalytic species are palladium nanoparticles generated from palladium precursor such as palladium salts or complexes [13]. It was previously reported that palladium nanoparticles could be produced in imidazolium-based ionic liquids [16]. However, further studies are needed to elucidate the real catalytic cycles and the effect of the palladium precursor on the ionic liquid-mediated reaction.

It should be emphasized that among basic types of palladium-catalyzed transformations, the Heck reaction and related chemistry occupy a special place. Indeed, most organic reactions, particularly catalytic ones, are well defined and specific and require some particular reagents and catalysts, to operate within a confined domain. The definition of this includes a more or less limited scope and optimal conditions. Yields for similar substrates can be extrapolated. Nothing like that, however, is true for Heck chemistry. A small variation of substrate, structure, nature of base, ligands, temperature, pressure, *etc.* often leads to unpredictable results. Trends in reactivity and selectivity are uneven and often break when would not be expected. Brand name precious ligands which worked miraculously for some sophisticated transformations often fail in the simplest cases. An obvious question of what is the best catalyst and procedure for the Heck reaction still remains unanswered even for the simplest cases, though studied in hundreds of works [17].

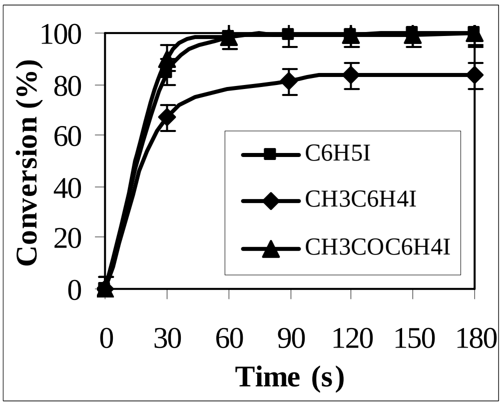
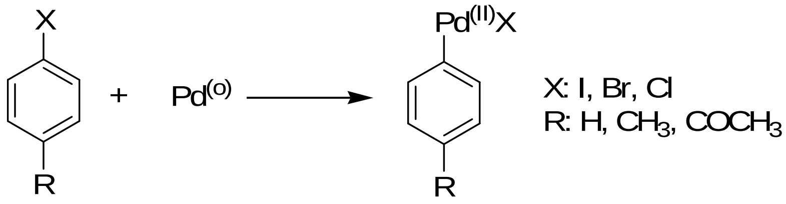


Figure 3: The Heck reactions of iodobenzene, 4-iodotoluene, and 4-iodoacetophenone with styrene in the 1-butyl-3-methylimidazolium bromide, respectively

In order to investigate the effect of different substituents on reaction conversions, the study was then extended to the reaction of substituted iodobenzenes containing electron-donating (*i.e.*

4-iodotoluene) and electron-withdrawing (*i.e.* 4-iodoacetophenone) groups. All reactions were carried out in the 1-butyl-3-methylimidazolium bromide under microwave irradiation, in the presence of 5 mol% Pd(OAc)$_2$ catalyst. It was observed that the reaction of 4-iodotoluene with styrene proceeded with slightly slower rate than the Heck reaction of iodobenzene, with a total conversion of only 81% being achieved after 1.5 minutes under microwave irradiation (Figure 3). As expected, the reaction rate of the Heck cross-coupling between 4-iodoacetophenone and styrene was slightly higher than the case of iodobenzene. This result indicated that the Heck reaction under microwave irradiation was favoured by electron-withdrawing groups on benzene ring, while electron-donating groups slowed down the cross-coupling processes.



Scheme 3: The rate-determining oxidative step in the catalytic cycle of the Heck reaction

It was also previously reported that the use of electron-withdrawing ring substituents normally lead to enhanced reactivity in palladium-catalyzed cross-coupling reactions [17]. The effect of substituents on reaction conversions of iodobenzene derivatives observed in this research was therefore in good agreement with the literature. This could be rationalized based on the fact that oxidative addition is normally a rate-limiting step (*i.e.* rate-determining step) in the catalytic cycle of transition metal-catalyzed cross-coupling reactions [18]. The very first step in the catalytic cycle of the Heck reaction is the reduction of palladium (II) to palladium (0) as the active catalytic species by the the phosphine for phosphine-based catalyst systems, or by the solvent, the base, and the olefin for phosphine-free systems [17]. The next step of the catalytic cycle is the oxidative addition of the palladium (0) to the aryl halide to form the palladium (II) complex [13] (scheme 3), where electron-withdrawing groups on the benzene ring facilitate the process. The similar trend in electronic effect of substituents observed in this research could be rationalized based on the same reasons. However, a complete catalytic pathway for the ionic liquid-mediated Heck reaction still remains to be elucidated in further investigation.

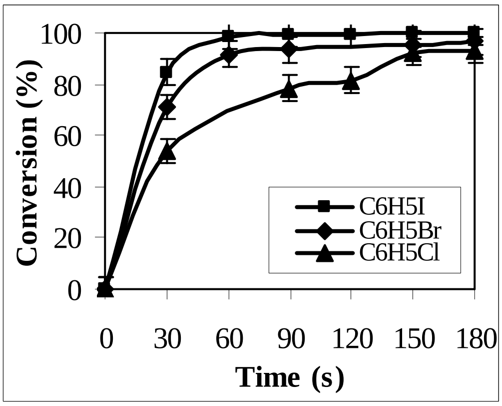


Figure 4: The Heck reactions of iodo-, bromo-, and chlorobenzene with styrene, respectively, in the ionic liquid under microwave irradiation

Although the Heck reaction of iodoarene with terminal olefin is successful in most cases, several efforts have been devoted to the investigation on the cross-coupling of bromoarene and chloroarene with terminal olefin [17, 18]. The reason for this trend is that iodoarene derivatives are normally significantly more expensive than bromoarenes, while chloroarenes require lowest cost and therefore they are the most desirable starting materials. However, chloroarenes are unreactive in most cases, though the Heck reactions of activated chloroarene (*i.e.* containing strong electron-withdrawing groups) are usually successful by using special catalyst systems. We therefore decided to investigate the Heck reaction of bromo- and chlorobenzene with styrene, respectively, under microwave irradiation. The coupling reaction was carried out using 5 mol% $Pd(OAc)_2$ as the catalyst, in the 1-butyl-3-methylimidazolium bromide as the solvent and in the presence of triethylamine as the base. As expected, it was observed that the Heck reaction of bromobenzene proceeded slower compared with the case of iodobenzene, with a conversion of over 93% being observed within 1.5 minutes. The Heck reaction of chlorobenzene proceeded with difficulty, though the reaction still afforded a conversion of over 78% within 1.5 minutes (figure 4).

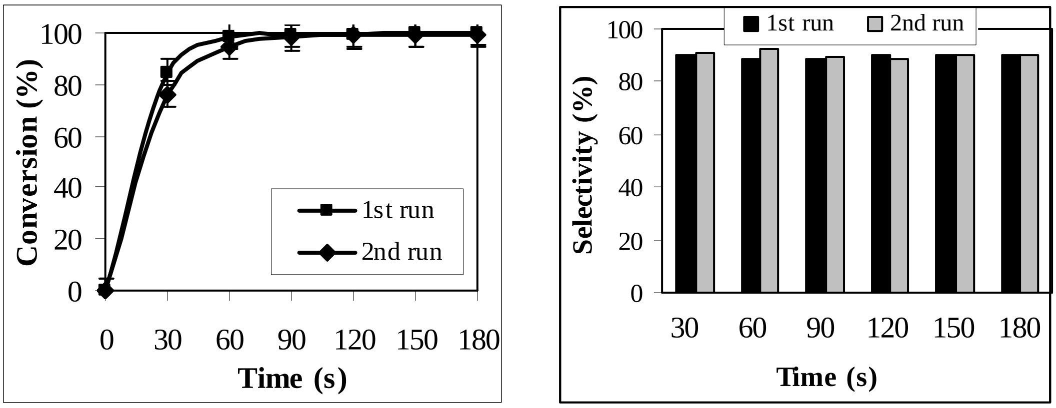


Figure 5: Solvent and catalyst recycling studies in microwave-assisted reactions using the 1-butyl-3-methylimidazolium bromide: reaction conversion (left) and selectivity of *trans*-isomer (right)

Ionic liquids have been considered as *green solvents* not only due to their non-volatile nature, minimizing emission of toxic organic compounds, but also because of their reuse and recyclability [4-6]. Furthermore, a crucial issue concerning the use of a precious metal catalyst is also its reuse and recyclability. We therefore investigated the possibility of recycling the solvent as well as the $Pd(OAc)_2$ catalyst in the ionic liquid-mediated Heck reaction. As described before, the reaction was carried out using 5 mol% palladium under microwave irradiation in 3 minutes. After the first run, reaction products as well as unreacted starting materials were separated from the ionic liquid by extraction with diethyl ether. The recovered ionic liquid containing the $Pd(OAc)_2$ was then reused in a further reaction under identical conditions to the first run, *without adding more* $Pd(OAc)_2$. It was found that the recycled ionic liquid containing the $Pd(OAc)_2$ could be recycled and reused in further reaction without significant degradation in activity, and therefore exhibiting advantages over conventional organic solvents (figure 5). As expected, the selectivity of the *trans*-isomer to the *cis*-isomer remained almost unchanged, being around 90% of *trans*-isomer, during the recycle of the solvent-catalyst system (figure 5).

IV - CONCLUSIONS

In summary, three ionic liquids including 1-butyl-3-methylimidazolium bromide, 1-hexyl-3-methylimidazolium bromide, and 1-octyl-3-methylimidazolium bromide, respectively, were synthesized under microwave irradiation condition, and characterized by ^1H and ^{13}C NMR, and MS. The three ionic liquids were used as green solvents the Heck cross-coupling reaction between several aryl halides and styrene under microwave irradiation to form *trans*-stilbenes as the principal products. It was found that higher reaction rate was observed for the Heck reaction using 1-butyl-3-methylimidazolium bromide, as compared to that of the reaction using 1-hexyl-3-methylimidazolium bromide, and 1-octyl-3-methylimidazolium bromide, respectively. Using the butyl-based ionic liquid as the reaction solvent in conjunction with microwave irradiation, the reaction rate was dramatically enhanced, with 99% conversion being achieved *within 1.5 minutes*, compared to conversions obtained after 2 hours under conventional heating conditions. Furthermore, the ionic liquid — Pd^{2+} system could be reused in subsequent reaction without significant degradation in activity. The fact that the solvent — catalyst system could be recycled without significant degradation in activity therefore exhibited advantages over conventional organic solvents. Current research in our laboratory has been directed to the design of several ionic liquids for a wide range of organic transformations, and results will be published in due course.

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