

IMIDAZOLIUM-BASED IONIC LIQUID AS A GREEN SOLVENT FOR THE HECK REACTION BETWEEN IODOBENZENE AND STYRENE

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ABSTRACT

An easily accessible ionic liquid, 1-hexyl-3-methylimidazolium bromide, was synthesized from *n*-hexyl bromide and *N*-methylimidazole under microwave irradiation condition, and characterized by ^1H and ^{13}C NMR, and MS. The ionic liquid was demonstrated to be an efficient and recyclable solvent for the Heck cross-coupling reaction between iodobenzene and styrene to form *trans*-stilbene as the principal product. The reaction was performed in the ionic liquid, using 5 mol% of PdCl_2 at 140°C in the presence of triethylamine as the base. Reaction conversions of 60% and 97% were achieved after 7 hours, without and with using triphenylphosphine as an additive, respectively. The ionic liquid \square PdCl_2 system could be reused in subsequent reaction without significant degradation in activity. Furthermore, using the ionic liquid as the reaction solvent in conjunction with microwave irradiation, the reaction rate was dramatically enhanced, with 98% conversion being achieved within 2 minutes.

I - INTRODUCTION

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 [1, 2]. During the past few years, a variety of ionic liquids have been investigated, in which dialkylimidazolium-based ionic liquids exhibit several advantages such as keeping the liquid condition under a wide range of temperature and having excellent solubility for many substrates and molecular catalysts [3, 4]. Palladium-catalyzed Heck 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 [5 - 8]. Ionic liquids were previously shown to be excellent solvents for Heck reactions owing to

the facile separation of the products and recycling of the ionic liquids containing the palladium catalysts [9, 10].

In Vietnam, the synthesis of ionic liquids was reported for the first time by Le Ngoc Thach and co-workers during the 2006 — 2007 periods [11]. However, applications of the as-synthesized ionic liquids in organic synthesis as well as in other fields have not been reported yet. In this paper, we wish to report for the first time in Vietnam, to our best knowledge, the use of 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. It was observed that the ionic liquid containing the palladium catalyst could be reused in further Heck reaction without adding more PdCl_2 while the catalytic activity of the system did not degrade significantly. Moreover, almost quantitative conversion of the

reactant was achieved in a matter of minutes by using microwave irradiation, compared to conversions obtained after 7 hours under conventional conditions.

II - EXPERIMENTAL

1. Materials and instrumentation

Chemicals were purchased from Sigma-Aldrich and Merck, and used as received without further purification. ^1H 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, Vietnam Academy of Science and Technology. GC analyses were performed using a Shimadzu GC-17A equipped with a FID detector and a 30 m x 0.25 mm x 0.25 μm DB-5 column. The temperature program for GC analyses heated samples from 60°C to 140°C at 10°C/minute, held at 140°C for 1 minute, from 140°C to 300°C at 50°C/minute, and held at 300°C for 3 minutes.

2. Synthesis of the ionic liquid

In a typical reaction, *N*-methylimidazole (21.5 g, 0.26 mol) and *n*-hexyl bromide (43.2 g, 0.26 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 30 seconds, the irradiation was paused for 30 seconds, and the reaction mixture was then heated at the same power level for an additional 30 seconds. The procedure was repeated for a total of 3 minutes. The resulting ionic liquid was then cooled, triturated and washed with ethyl acetate (3 x 15 ml) and diethyl ether (2 x 15 ml) to remove unreacted starting materials. The solvent residue was then removed by a rotovap at 50°C, affording 50.0 g of 1-hexyl-3-methylimidazolium bromide (77% yield).

^1H -NMR (500 MHz, DMSO): δ = 0.807 (t, 3H; CH_3), 1.220 (m, 6H; $\text{CH}_2\text{CH}_2\text{CH}_2$), 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-CH=C), 7.883 (t, 1H; N-CH=C), 9.406 (s, 1H, N-CH=N). ^{13}C NMR (500 MHz, DMSO): δ = 13.704 (C-CH_3), 21.767 (CH_2), 25.029 (CH_2), 29.309 (CH_2), 30.446 (CH_2), 35.719 (N-CH_2), 48.614(N-CH_3), 122.161 (C=C-N), 123.421 (C=C-N), 136.435 (N-C=N). MS (ESI): m/z (%) 167.1 (100) [M-Br] $^+$.

3. Catalysis studies

Unless otherwise stated, a mixture of 4-iodobenzene (0.52 ml, 4.68 mmol), styrene (0.8 ml, 6.98 mmol), triethylamine (1.95 ml, 13.7mmol), and hexadecane (0.52 ml) as the internal standard in the ionic liquid (4 ml) were added to a round-bottom flask containing the required amount of the PdCl_2 catalyst. Triphenylphosphine was added if required. The flask was heated at the required temperature with magnetic stirring. 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 (2 ml), dried over Na_2SO_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.

III - RESULTS AND DISCUSSION

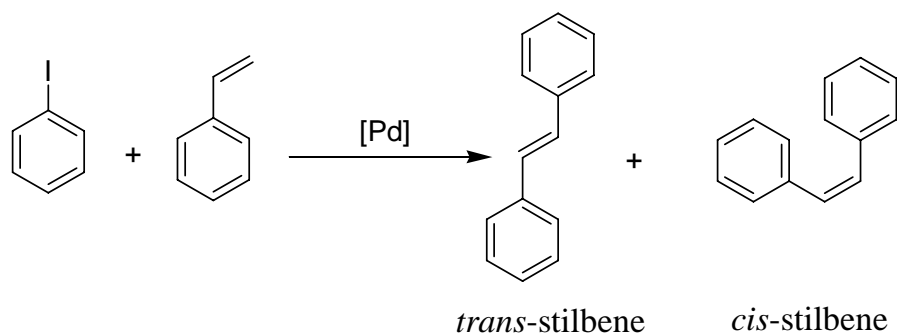
As mentioned earlier, ambient temperature ionic liquids encompassing 1,3-dialkylimidazolium cations have exhibited great promise as an attractive alternative to conventional solvents [3, 4]. The preparation of these ionic liquids *via* conventional heating method in refluxing solvents requires several hours to afford reasonable yields, and also uses a large excess of alkylhalides as well as a large amount of organic solvents [12]. In view of the green chemistry, it was decided to explore the synthesis of 1-hexyl-3-methylimidazolium bromide from *N*-methylimidazole and *n*-hexyl bromide 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. An isolated yield of 77% was achieved within only 3 minutes, without using an excess amount of *n*-hexyl bromide under solvent-free condition. The ionic liquid was characterized using ^1H and ^{13}C NMR, and MS, which were in good agreement with the literature [13].



Scheme 1: The synthesis of 1-hexyl-3-methylimidazolium bromide



Scheme 2: The Heck reaction of iodobenzene and styrene in ionic liquid

The ionic liquid was evaluated for its suitability as a solvent 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). 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 [6]. For a fast screening for a suitable base, the reaction was carried out in the presence of 5 mol% PdCl_2 as the catalyst at 140°C ; and triethylamine, Na_2CO_3 , and CH_3COONa were used as the base, respectively. It was observed that reasonable conversion (60%) was achieved after 7 hours for the reaction using triethylamine, while reactions using Na_2CO_3 or CH_3COONa proceeded slowly with products being detected only in traces. It should be noted that triethylamine could dissolve in the ionic liquid, while the inorganic bases remained almost insoluble during the

course of the reaction. Indeed, triethylamine was previously employed as the base for several ionic liquid-mediated Heck reactions [10].

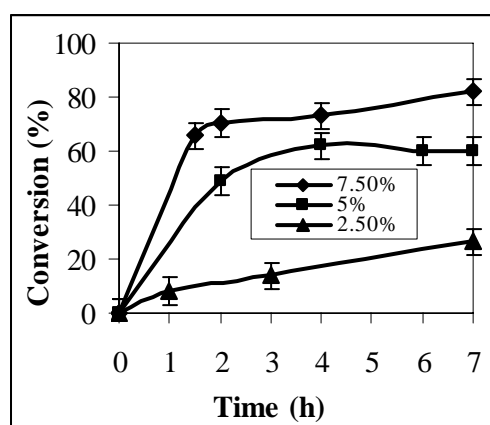


Figure 1: Effect of catalyst concentration on reaction conversions

With this result in mind, we then studied the effect of catalyst concentration on reaction conversions, using triethylamine as the base at 140°C in the ionic liquid. As with previous reports, the higher the catalyst concentration was used, the higher the reaction rate was observed (figure 1). Increasing the catalyst concentration from 5 mol% to 7.5 mol% resulted in enhance in reaction rate, with reaction conversions of 60% and 82% being observed after 7 hours, respectively. The reaction using 2.5 mol% catalysts proceeded with slower rate, with a conversion of 26% being achieved after 7 hours. The catalyst concentrations used in this study were comparable to those of several previous reports covering different aspects of the Heck reaction in ionic liquids, where the palladium concentrations varied from approximately 1 mol% to more than 10 mol%, depending on the nature of the catalysts as well as the substrates [5-8]. As the palladium was expensive, it was decided to use a cheaper additive to increase the reaction conversion, instead of employing a large amount of palladium catalyst. We therefore carried out the reaction using 5 mol% of palladium, in the presence of triphenylphosphine (molar ratio of triphenylphosphine : palladium = 3 : 1). The reaction conversion was subsequently increased to 81% after 7 hours, compared to 60% conversion without using the additive or 82% conversion using 7.5 mol% catalysts.

It is obviously accepted that the entry into the catalytic cycle of the Heck reaction includes the reduction of Pd (II) to Pd (0), which is most likely accomplished by the phosphine in phosphine-assisted systems. In phosphine-free reactions, the reduction of Pd (II) is believed to be achieved by bases, olefins and solvents, though the effect is less significant compared to that of the phosphine. However, in the presence of a large excess of phosphine, the concentration of active species is strongly decreased, which leads to the inhibition of the catalytic process [14]. It was therefore decided to investigate the effect of triphenylphosphine : palladium ratio on the reaction conversions in the ionic liquid-mediated Heck reaction, ranging from 0.5 : 1 to

4 : 1. Experimental results showed that the best reaction rate was observed at the triphenylphosphine : palladium ratio of 1 : 1, with 97% of iodobenzene being converted to the corresponding products after 7 hours at the catalyst concentration of 5 mol% (figure 2). Increasing this ratio to more than 1 : 1 or decreasing the ratio to less than 1 : 1 resulted in a significant drop in reaction conversions. For example, Heck reactions using ratio of 4 : 1, 3 : 1, 2 : 1 and 0.5 : 1 afforded conversions of 77%, 81%, 87%, and 45% after 7 hours, respectively. The useful phosphine to palladium ratio observed in this study was comparable to previous reports, where this ratio could range from 1 : 1 up to 20 : 1, depending on specific reaction conditions [5 - 8, 14].

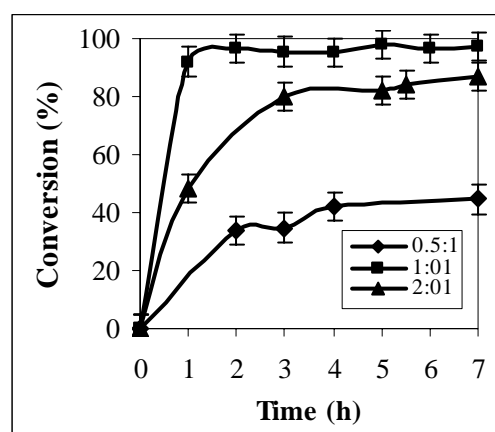


Figure 2: Effect of phosphine : palladium ratio on reaction conversions

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 [1, 2]. Furthermore, a crucial issue concerning the use of a precious metal catalyst is also its reuse and recyclables. We therefore investigated the possibility of recycling the solvent as well as the PdCl₂ catalyst in the ionic liquid-mediated Heck reaction. The reaction was carried out using 5 mol% catalyst at 140°C for 7 hours in the presence of triphenylphosphine (molar ratio 1 : 1). After the first run, reaction products as well as starting materials were

separated from the ionic liquid by extraction with ethyl acetate and diethyl ether. The recovered ionic liquid containing the PdCl₂ was then reused in a further reaction under identical conditions to the first run, *without adding more PdCl₂*. It was found that the catalytic activity of the recycled ionic liquid containing the PdCl₂ decreased slightly for the first few hours during the course of the reaction. However, after 4 hours, reaction conversions remained almost the same for the first and the second run, within experimental errors (figure 3). The fact that the solvent — catalyst system could be recycled and reused in further reaction without significant degradation in activity therefore exhibited advantages over conventional organic solvents.

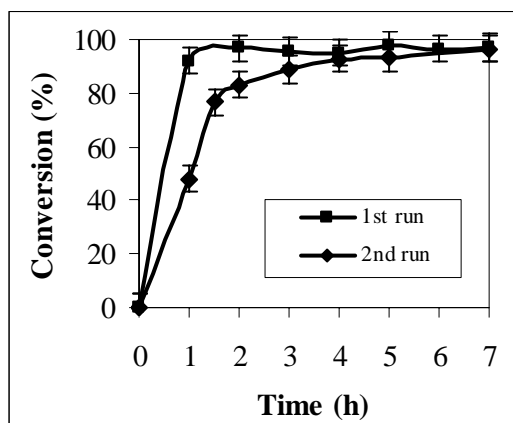


Figure 3: Solvent and catalyst recycling studies

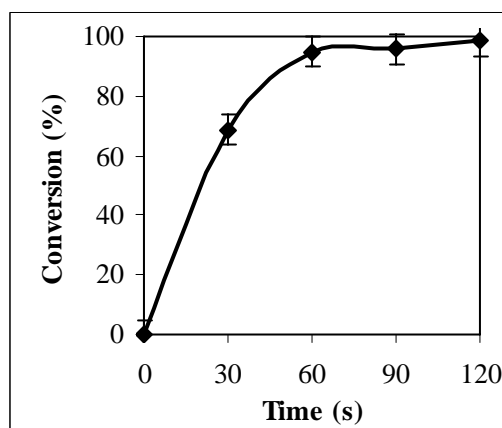


Figure 4: The Heck reaction in ionic liquid under microwave irradiation

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 [15-17]. Microwave-assisted chemistry is usually performed in high boiling polar solvents such as DMSO, NMP and DMF due to their high dipole moments [18]. 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 with 5 mol% PdCl₂ catalyst in the presence of triphenylphosphine (molar ratio 1 : 1), using a modified household microwave oven (Whirlpool M541-800W) at 800 W. It was observed that the reaction rate was dramatically enhanced as compared to conventional methods, with 98% conversion being achieved *within only 2 minutes* (Figure 4). Under microwave irradiation, the selectivity of *trans*-stilbene over *cis*-stilbene remained almost similar to that of reactions using conventional heating methods. For example, the selectivity of *trans*-stilbene ranged from 91% to 94% under conventional conditions, while microwave-assisted reactions offered *trans*-stilbene selectivity of 90 — 92 %.

IV - CONCLUSIONS

In summary, an imidazolium-based ionic liquid, 1-hexyl-3-methylimidazolium bromide, was synthesized from *n*-hexyl bromide and *N*-methylimidazole under microwave irradiation condition in a yield of 77% within 3 minutes. The ionic liquid was characterized by ¹H and ¹³C NMR, and MS, which were in good agreement with the literature. The Heck reaction of iodobenzene and styrene was performed in the ionic liquid, using 5 mol% of PdCl₂ at 140°C in the presence of triethylamine as the base. Reaction conversions of 60% and 97% were achieved after 7 hours, without and with using triphenylphosphine as an additive, respectively. The ionic liquid — PdCl₂ system could be recovered and reused in subsequent reaction without adding more PdCl₂. The fact that the solvent — catalyst system could be recycled

without significant degradation in activity therefore exhibited advantages over conventional organic solvents. Furthermore, using the ionic liquid as the reaction solvent in conjunction with microwave irradiation, the reaction rate was dramatically enhanced with 98% conversion being achieved within only 2 minutes, compared to conversions obtained after 7 hours under conventional conditions. 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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