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SUZUKI REACTIONS OF ARYL HALIDES WITH PHENYLBORONIC ACID USING IMIDAZOLIUM-BASED IONIC LIQUID AS A GREEN SOLVENT UNDER MICROWAVE IRRADIATION

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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 Suzuki cross-coupling reaction between several aryl halides and phenylboronic acid under microwave irradiation to form biphenyls as the principal products. The most commonly used base in several Suzuki reactions, Na_2CO_3, was found to be significantly less effective than triethylamine for the reaction carried out in the ionic liquid. 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 2 minutes, while less than 5% conversion was observed after 8 hours for the reaction under conventional heating condition. Furthermore, the ionic liquid could be reused without significant degradation in activity.

I - INTRODUCTION

Palladium-catalyzed Suzuki cross-coupling reactions have gained popularity in organic synthetic chemistry, as they have exhibited practical applications in the production of pharmaceuticals, herbicides, as well as engineering materials such as conducting polymers and liquid crystals [1 - 3]. Room temperature ionic liquids have been increasingly employed as green solvents since they are easy to recycle they possess a remarkably high thermal stability and show no effective vapour pressure, thus providing a way of avoiding the generation of contaminated waste and its subsequent treatment [4-6]. 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 [7, 8].

Ionic liquids were previously shown to be excellent solvents for Suzuki 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 period [11]. However, applications of the as-synthesized ionic liquids as solvents for cross-coupling reactions were *not previously reported in Vietnam*. 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 to form *trans*-stilbene as the principal product [12]. In this paper, we wish to report *for the first time in Viet Nam*, to our best knowledge, the Suzuki reactions of several aryl halides with phenylboronic acid in the ionic liquid as a green solvent under microwave irradiation. More than 99% reaction conversions were achieved *within 2 minutes,* while less than 5% conversion was observed after 8 hours for the reaction under conventional heating condition.

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, Vietnam 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 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 (20.7 g, 0.25 mol) and *n*-hexyl bromide (47.2 g, 0.28 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 ethyl acetate (3 x 50 ml) and diethyl ether (3 x 50 ml) to remove unreacted starting materials. The solvent residue was then removed by a rotovapor at 30 °C, affording 52.5 g of 1-hexyl-3-methylimidazolium bromide (84% yield).

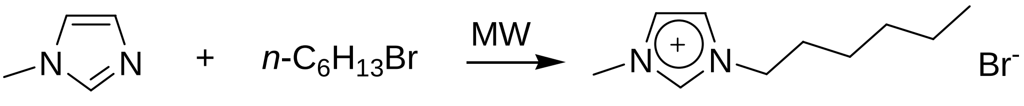
^{1}H NMR (500 MHz, DMSO-d$_6$): $\delta = 0.807$ (t, 3H; C*H*$_3$), 1.177-1.220 (m, 6H; C*H*$_2$C*H*$_2$C*H*$_2$), 1.732-1.760 (m, 2H; C*H*$_2$), 3.879 (s, 3H; N-C*H*$_3$), 4.180 - 4.209 (m, 2H; N-C*H*$_2$), 7.798 (t, 1H; N-C*H*=C), 7.883 (t, 1H; N-C*H*=C), 9.406 (s, 1H, N-*CH*=N). ^{13}C NMR (125 MHz, DMSO-d$_6$): 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]$^+$.

3. Catalysis studies

Unless otherwise stated, a mixture of 4-iodobenzene (0.24 ml, 2.15 mmol), phenylboronic acid (0.4 g, 3.30 mmol), triethylamine (0.9 ml, 6.45 mmol), and dodecane (0.24 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 (0.2 ml) from the reaction mixture at different time intervals, and quenching with saturated Na_2CO_3 solution. The organic components were extracted into diethylether (3 ml), dried over Na_2SO_4 and analyzed by GC with reference to dodecane. Product identity was also further confirmed by GC-MS.

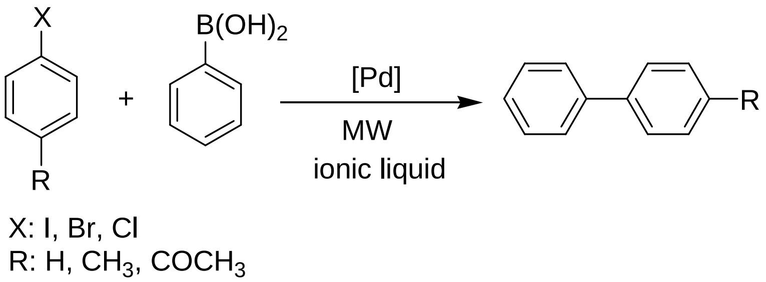
III - RESULTS AND DISCUSSION

The ionic liquid was synthesized according to a previously reported procedure [13]. 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 84% was achieved within a total irradiation time of 1 minute under solvent-free condition. The ionic liquid was characterized using ^{1}H and ^{13}C NMR, and MS, which were in good agreement with the literature [14].



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

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]. Microwave-assisted chemistry is usually performed in high boiling polar solvents such as DMSO, NMP and DMF due to their high dipole moments [16]. Owing to the high polarity and thermal stability of ionic liquids, it was decided to carry out the Suzuki reaction of iodobenzene and phenylboronic acid in the ionic liquid using a modified household microwave oven (Whirlpool M541-800W) at 800 W (scheme 2). It is generally accepted that a base is obviously necessary to accelerate the transmetallation step in the catalytic cycle of the Suzuki reaction [17]. We then decided to investigate the effect of bases on the reaction conversion of the ionic liquid-mediated Suzuki transformation between iodobenzene and phenylboronic acid.



Scheme 2: The Suzuki reaction of aryl halides and phenylboronic acid in ionic liquid under microwave irradiation

The ionic microwave-assisted Suzuki reaction was carried out using 5 mol% $PdCl_2$ as a catalyst, without added toxic phosphine ligands, in the presence of Na_2CO_3, K_3PO_4, and triethylamine as a base, respectively. The commonly used base in the Suzuki reaction is Na_2CO_3, but stronger bases such as NaOH, K_3PO_4 and $Ba(OH)_2$, and organic bases were previously reported to give better results in some cases. In this research, however, the ionic liquid-mediated Suzuki reaction using Na_2CO_3 afforded the coupling product in a significantly lower conversion than reactions using K_3PO_4, and triethylamine (figure 1). It was observed that up to 99% conversion was achieved within 2.5 minutes for the reaction using triethylamine, while the Suzuki reaction using Na_2CO_3 proceeded with only 23% conversion being obtained under the same conditions. Indeed, amines were previously employed as the bases for several Suzuki cross-coupling reactions [18]. It should be noted that less than 5% conversion was observed after 8 hours for the reaction using triethylamine as the base at 140°C under conventional heating condition.

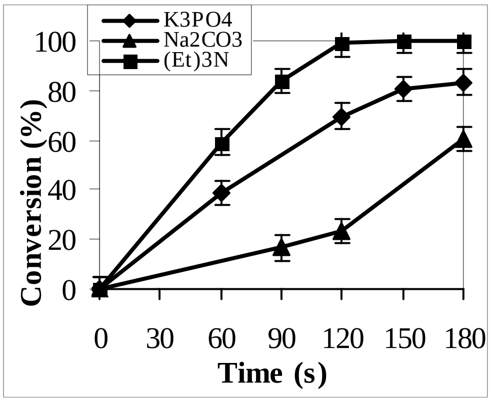


Figure 1: Effect on bases on reaction conversions

With this result in mind, we then studied the the effect of catalyst concentration on reaction conversions, using triethylamine as the base and $PdCl_2$ as the catalyst in the ionic liquid as the solvent under microwave irradiation. As mentioned before, triphenylphosphine was not used in the reaction for the reason of green and clean processes. As with previous reports, the higher the catalyst concentration was used, the higher the reaction rate was observed (figure 2). Increasing the catalyst concentration from 5 mol% to 7.5 mol% resulted in an enhancement in reaction rate. The reaction using 2.5 mol% catalyst proceeded with slower rate, though a conversion of 77% was still achieved after 3 minutes. The catalyst concentrations used in this study were comparable to those of several previous reports covering different aspects of the Suzuki 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 and the substrates [18].

Another common homogeneous catalyst for the Suzuki cross-coupling carried out in ionic liquid, $Pd(OAc)_2$, was also used for the ionic liquid-mediated reaction of iodobenzene and phenylboronic acid under microwave irradiation. Experimental results showed that at the catalyst concentration of 5 mol%, $Pd(OAc)_2$ exhibited slightly higher activity compared with that of $PdCl_2$. A conversion of more than 99% being achieved within 1.5 minutes for the $Pd(OAc)_2$ — catalyzed Suzuki coupling, while the reaction using $PdCl_2$ catalyst proceeded with 84% conversion being obtained after the same reaction time (figure 3). From a mechanistic point of view, it was previously proposed that for the Suzuki and Heck coupling reactions, the true active catalytic species are palladium nanoparticles generated from palladium precursors such as palladium salts or complexes [19]. However, further studies are needed to elucidate the real catalytic cycles and the effect of the palladium precursor on the ionic liquid-mediated reaction.

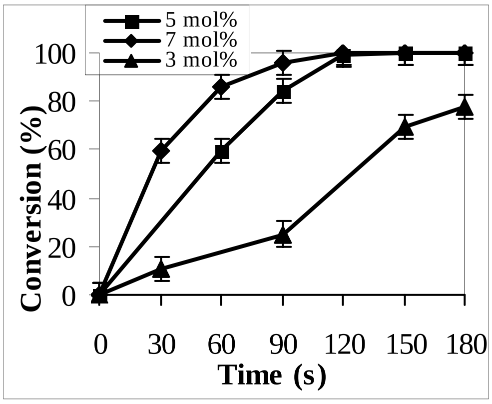


Figure 2: Effect of catalyst concentration on reaction conversions

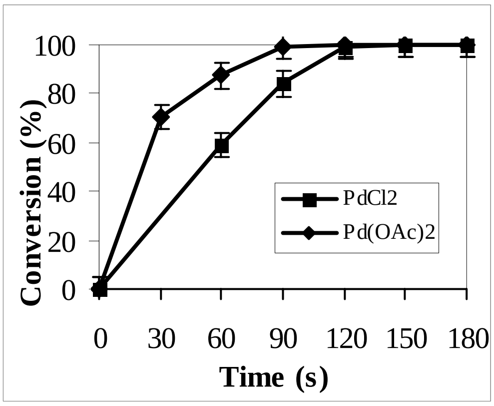


Figure 3: The Suzuki reaction using 5 mol% $PdCl_2$ and $Pd(OAc)_2$, respectively

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. It was observed that the reaction of 4-iodotoluene with phenylboronic acid proceeded with slightly slower rate than the Suzuki reaction of iodobenzene, with a total conversion of around 80% being achieved within 1.5 minutes under microwave irradiation (Figure 4). As expected, the reaction rate of the Suzuki cross-coupling between 4-iodoacetophenone and phenylboronic acid was higher than the case of iodobenzene. It should be noted that biphenyl was also formed as a by-product in these reactions. This result indicated that the Suzuki reaction under microwave irradiation was favoured by electron-withdrawing groups on benzene ring, while electron-donating groups slowed down the cross-coupling processes.

Indeed, It was previously reported that the use of electron-withdrawing ring substituents normally lead to enhanced reactivity in palladium-catalyzed cross-coupling reactions [18]. 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 [20]. The very first step in the catalytic cycle of the Suzuki reaction and the Heck reaction is the reduction of palladium (II) to palladium (0) as the active catalytic species by the phosphine for phosphine-based catalyst systems, or by the solvent and the base for phosphine-free systems. 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 [19] (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.

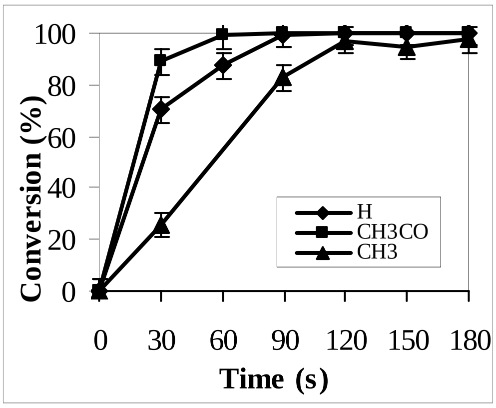
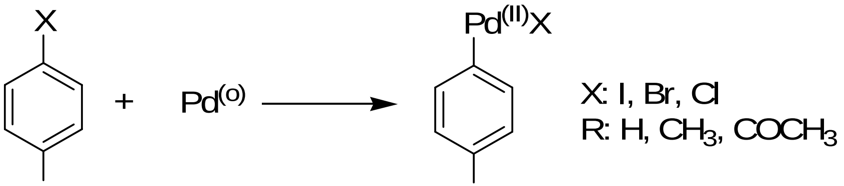


Figure 4: The Suzuki reactions of iodo-, bromo-, and chlorobenzene with phenylboronic acid, respectively



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

Although the Suzuki reaction of iodoarene with phenylboronic acid is successful in most cases, several efforts have been devoted to the investigation on the cross-coupling of bromoarene and chloroarene with phenylboronic acid [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 Suzuki reactions of activated chloroarene (*i.e.* containing strong electron-withdrawing groups) are usually successful by using special catalyst systems [21]. We therefore decided to investigate the Suzuki reaction of bromo- and chlorobenzene with phenylboronic acid, respectively, under microwave irradiation. The coupling reaction was carried out using 5 mol% $Pd(OAc)_2$ as the catalyst, in the ionic liquid as the solvent and in the presence of triethylamine as the base. As expected, it was observed that the Suzuki reaction of bromobenzene proceeded slower compared with the case of iodobenzene, with a conversion of around 60% being observed after 1.5 minutes. The Suzuki reaction of chlorobenzene proceeded with difficulty, though the reaction still afforded a conversion of over 61% after 3 minutes (figure 5).

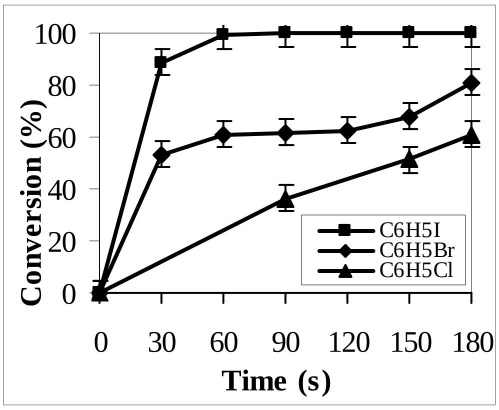


Figure 5: The Suzuki reactions of iodo-, bromo-, and chlorobenzene with phenylboronic acid, respectively

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 [22, 23]. Furthermore, a crucial issue concerning the use of a precious metal catalyst is also its recyclability. We therefore investigated the possibility of recycling the solvent as well as the $Pd(OAc)_2$ catalyst in the ionic liquid-mediated Suzuki reaction. The reaction was carried out using 5 mol% palladium catalyst under microwave irradiation as previously described. 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 palladium 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 catalytic activity of the recycled ionic liquid containing the palladium catalyst decreased slightly during the course of the reaction. However, 99% conversion was still achieved after 3 minutes for the reaction using the recycled ionic liquid. 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. However, the problem still needs further investigation.

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 84% within 1 minute. The ionic liquid was characterized by ^1H, ^{13}C NMR and MS spectra, which were in good agreement with the literature. The ionic liquid was demonstrated to be an efficient and recyclable solvent for the Suzuki cross-coupling reaction between several aryl halides and phenylboronic acid under microwave irradiation to form biphenyls as the principal products. The most commonly used base in several Suzuki reactions, Na_2CO_3, was found to be significantly less effective than triethylamine for the reaction carried out in the ionic liquid. 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 2 minutes,* while less than 5% conversion was observed after 8 hours for the reaction under conventional heating condition. Furthermore, the ionic liquid could be reused in subsequent reaction. 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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