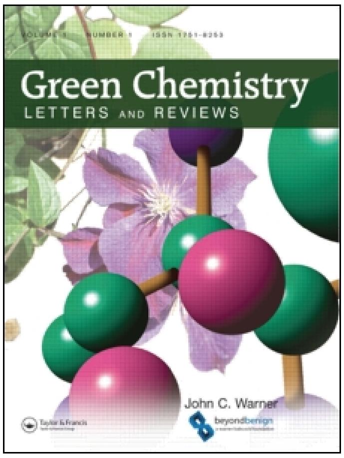

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The Heck reaction of aryl bromides: a green protocol for synthesis of 2-ethylhexyl-4-methoxy cinnamate

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RESEARCH LETTER

The Heck reaction of aryl bromides: a green protocol for synthesis of 2-ethylhexyl-4-methoxy cinnamate

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Deactivated aryl halide 4-bromoanisole and electron poor olefin 2-ethylhexyl acrylate were shown to undergo palladium catalyzed Heck reaction with the utilization of a cost-effective, thermally robust and unexplored morpholine-based ionic liquid. The developed protocol gives an environmentally friendly process for the synthesis of 2-ethylhexyl-4-methoxy cinnamate, an important UV-B sunscreen agent.

Keywords: Heck reaction; aryl bromides; UV-B sunscreen; ionic liquid

Introduction

Palladium-catalyzed Heck reaction is one of the most important C–C bond forming reactions for synthesis of drugs, fine chemicals, and natural products in laboratory as well as industrial scales (*1*). However, in spite of its applications and usefulness, there are certain drawbacks associated with this reaction. The Heck reaction, although simple when carried out with iodobenzene and short-chain acrylates, does not proceed smoothly when the deactivated bromoarenes or chloroarenes are used for coupling with the less reactive long-chain acrylates (*2–4*). Therefore, development of the catalytic system for coupling of such deactivated substrates is one of the challenges in Heck reaction. In order to activate the less reactive aryl bromides or aryl chlorides, bulky phosphine ligands are generally required to assist the initial oxidative-addition of C–X bond. However, under high-temperature Heck reaction conditions, phosphines and their palladium complexes are subject to decomposition (*2*). Hence it is desirable to explore a suitable substitute for these expensive ligands and develop a simple and cost-effective alternative Heck reaction of haloarenes with long-chain acrylates. One such option is use of ionic liquid.

Ionic liquids have gained much popularity in recent years and are extensively being used as the solvent of choice for Heck reaction because of their high thermal stability, low vapor pressure, and easy catalyst recycling. However, while utilizing ionic liquids on large scale, cost is the major issue for industries. Many commonly used ionic liquids are expensive due to the higher costs of cations and anions. The Heck reaction carried out in ionic liquids based on imidazole, guanidine, pyridine, phosphine, and piperdine cations suffer disadvantages such as high costs, requirement of specially designed palladium catalysts, and environmentally unfriendly reagents. Recently, Lei Wang and coworkers described the Heck reaction in hydroxyl-functionalized ionic liquid (*5*). The detailed description of Heck reaction in various ionic liquids can be obtained in a recent review (*6*). We have recently reported the applications of such cost-effective ionic liquids in various organic processes (*7,8*).

Many patents and papers are reported for the synthesis of 2-ethylhexyl-4-methoxy cinnamate which is an important UV-B sunscreen active pharmaceutical ingredient (API) in the cosmetic industry (*9–12*). However, these procedures suffer from various disadvantages, such as low yields, use of expensive iodobenzene as raw material, and tedious recycling of high boiling solvents like N-methyl pyrrolidone (NMP) using vacuum distillation.

Herein we report for the first time, application of a thermally robust morpholine-based ionic liquid for the Heck reaction. Synthesis of 2-ethylhexyl-4-methoxy cinnamate was carried out effectively using the Heck reaction.

Results and discussion

For the standardization of reaction conditions, the deactivated aryl halide, bromoanisole, and the

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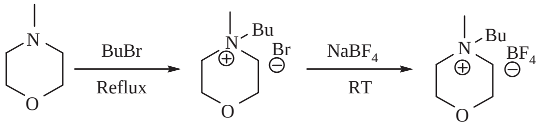


Scheme 1. Synthesis of N-methyl N-butyl morpholinium tetrafluroborate [Mor$_{1,4}$][BF$_4$].

electron-poor olefin 2-ethylhexyl acrylate were selected as appropriate substrates. The Heck reaction was standardized with respect to various parameters, such as type of ionic liquid and palladium catalyst, quantity of the palladium catalyst used, and the reaction temperature. As the Heck reaction of bromoarenes generally requires high temperature, a solvent with high boiling point and sufficient thermal stability is desirable. Considering these facts, morpholine-based cost-effective ionic liquid, N-methyl N-butyl morpholinium tetrafluroborate, proved to be a suitable candidate for this reaction. In addition, lack of solubility in solvents like hexane, petroleum ether, and toluene would make recycling of ionic liquid easier (Scheme 1).

The stability and reactivity of catalyst was then tested using 1 mol% of the three different palladium sources: palladium acetate, palladium chloride, and palladium on charcoal (10%). Bromoanisole and 2-ethylhexyl acrylate were used as substrates and N-methyl N-butyl morpholinium tetrafluroborate was used as solvent. NaHCO$_3$ was used as base and N-phenyl urea was used as the ligand for all the three reactions. All the reactions were carried out at the temperature of 160°C. Although product was formed in all three cases, in case of palladium on charcoal, impurities (biphenyl) formation was observed (Table 1). Palladium chloride led to slow reaction rate (24 hrs), compared to palladium acetate (12 hrs). Hence, palladium acetate was selected as the palladium source.

The amount of the palladium acetate was standardized by performing a set of reaction with similar parameters and varying the amount of palladium acetate (Table 2). Palladium acetate with 1 mol% concentration was found the most suitable, as further increase in the concentration did not increase the yield of the product (Table 2).

With these standardized parameters, coupling reactions with several substrates were carried out. The results obtained (Scheme 2) are presented in Table 3.

The reactions with iodobenzene were, as expected, faster, occurred at lower temperature and resulted in higher yields. Reactions with bromobenzene required more time, while those with bromoanisole took longer because of deactivation. Chlorobenzene did not react under these conditions. A 10-g batch for bromoanisole and 2-ethylhexyl acrylate was carried out using similar molar ratios of reactants giving 74% yield.

Recyclability of the catalyst was studied by performing the reactions on recovered ionic liquid with palladium catalyst after washing with petroleum ether or hot toluene. Reactions were performed using iodobenzene and ethyl acrylate as substrate and the results are depicted in Table 4.

Experimental

General

The ionic liquid was prepared by the previously reported method (*13*) without any modifications (Scheme 1) and characterized by FTIR and ^{1}H NMR spectroscopy and melting point (82°C). The reagents and solvents were commercially available. The products were purified using column chromatography if necessary. All synthesized compounds were previously reported, and identified by spectroscopic data, and by comparison with available standards. FTIR spectra were obtained on a Perkin–Elmer infrared spectrometer with KBr discs and ^{1}H NMR spectra were recorded in CDCl$_3$ or DMSO-D$_6$ on a JEOL 300 MHz spectrometer with tetramethyl silane (TMS) as internal standard.

Table 1. Effect of palladium source on reaction.

Sr. no.	Palladium source (1 mol%)	% Conversion of substrate (% isolated yield)^{a,b,c}	Remark
1	Palladium on charcoal (10%)	78(52)	Impurity formation
2	Palladium chloride	72(67)	Slow reaction
3	Palladium acetate	75(72)	No impurity formation, less reaction time

[a] A 1.5 equivalent olefin was used.

[b] Yields after column purification based on the quantity of halide used.

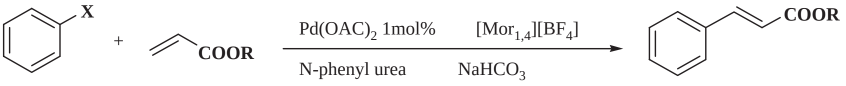
[c] All the compounds are known and identified by satisfactory spectroscopic data and also by matching with the available standards.

Table 2. Effect of palladium acetate concentration on reaction after 12 hours.

Sr. no.	Catalyst (mol%)	Yield (%)
1	0.01	Trace
2	0.1	Trace
3	0.5	35
4	1	74
5	1.5	75

Typical procedure for Heck reaction in ionic liquid (Table 1, entries 1–9)

To 2 g of ionic liquid in a 25 ml round bottom flask attached to a reflux condenser, was added (0.5 g, 0.0027 mol) bromoanisole and (0.73 g, 0.004 mol) 2-ethylhexylacrylate. Palladium acetate (0.006 g, 0.000027 mol), N-phenyl urea (0.007 g, 0.000054 mol), and sodium bicarbonate (0.336 g, 0.004 mol) were added to this and the reaction temperature was increased to 180°C. After completion (12 hrs), the reaction was cooled down to room temperature, extracted with hot toluene (3 × 10 ml), treated with sodium sulphate and evaporated under reduced pressure. The crude product was purified using column chromatography (EtOAc: Hex/5:95) and 0.55 g, (72%) of pure compound was obtained. The ionic liquid with palladium acetate and N-Phenyl urea can be reused after washing with hexane.



Scheme 2. Heck reaction in morpholine-based ionic liquid.

Table 4. Recyclability of ionic liquid.

Sr. no.	Cycle number	Isolated yield (%)
1	Fresh	86
2	1	85
3	2	83
4	3	83

Conclusion

Heck reaction of aryl bromides with electron-poor olefins requires high thermal energy to overcome the high bond dissociation energy associated with aryl bromides (96 Kcal/mol). The present morpholine-based ionic liquid is thermally robust and stable at such high temperature unlike usual organic solvents and some previously reported ionic liquids for the Heck reaction. The mechanistic role of ionic liquid is still not clear and is being studied. However, ease of recycling is an added advantage for the present method. Considering all these factors, morpholine-based ionic liquid is effective in the present system. A common API in the cosmetic industry, 2-ethylhexyl-4-methoxy cinnamate, and a UV-B sunscreen agent, were effectively synthesized from bromoanisole. Use of N-phenyl urea as a cost-effective ligand instead of expensive phosphine-based ligand was an added advantage. The ionic liquid was recycled three times effectively without significant loss in activity.

Table 3. Heck reaction in morpholine-based ionic liquid.

Sr. no.	Aryl halide	Olefin[a]	Time (h)	Temperature (°C)	Yield[b,c] (%)
1	4-MeO-Ph-Br	2-Ethylhexyl acrylate	12	180	72
2	4-MeO-Ph-Br	Ethyl acrylate	12	180	78
3	4-MeO-Ph-Br	Butyl acrylate	12	180	75
4	Ph-Br	2-Ethylhexyl acrylate	8	160	76
5	Ph-Br	Ethyl acrylate	8	160	80
6	Ph-Br	Butyl acrylate	8	160	78
7	Ph-I	2-Ethylhexyl acrylate	5	150	85
8	Ph-I	Ethyl acrylate	5	150	88
9	Ph-I	Butyl acrylate	5	150	86
10	Ph-Cl	Ethyl acrylate	15	180	NR

[a] A 1.5 equivalent olefin was used.

[b] Isolated yields after column purification based on the quantity of halide used.

[c] All the compounds are known and identified by satisfactory spectroscopic data and also by matching with the available standards.

Acknowledgement

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References

(1) De Vries, J.G. *Can. J. Chem.* **2001,** *79,* 1086–1092.

(2) Chuluo, Y.; Hon, M.L.; Steven, P.N. *Org. Lett.* **2001,** *3,* 1511–1514.

(3) Adam, F.L.; Gregory, C.F. *J. Am. Chem. Soc.* **2001,** *123,* 6989–7000.

(4) Shenghai, L.; Yingjie, L.; Haibo, X.; Suobo, Z.; Jianing, X. *Org. Lett.* **2006,** *8,* 391–394.

(5) Wang, L.; Li, H.; Li, P. *Tetrahedron* **2009,** *65,* 364–368.

(6) Shifang, L.; Jianliang, X. *J. Mol. Cat. A: Chemical* **2007,** *270,* 1–43.

(7) Sharma, Y.O.; Degani, M.S. *J. Mol. Cat. A: Chemical* **2007,** *277,* 215–220.

(8) Sharma, Y.O.; Degani, M.S. *Green Chem.* **2009**, *55*, 526–530.

(9) Anatoly, A.; Ratan, C. Process for Preparation of Cinnamate Sunscreen Agents. US Patent 5527947. 1996.

(10) Douglas, C. Process for Producing 2-ethylhexyl-p-methoxy-cinnamate. US Patent 4970332, 1990.

(11) Peter G., Process for the Manufacture of Cinnamic Acid Derivatives. US Patent 5457226, 1995.

(12) Alan, J.C.; Joseph, A.V.; Laszlo, W.; Theresa, B.W. Process for the Palladium Catalyzed Coupling of a Diazonium Salt with an Olefinic Bond. US Patent 5274171, 1993.

(13) Jong-Ho, C.; Ki-Sub, K.; Sukjeong, C.; Sun-Hwa, Y.; Huen, L.; Chul-Soo, L.; Jae-Jin, S. *Korean J. Chem. Eng.* **2007,** *24,* 1089–1094.