Synthesis of functionalised acetophenone

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Nickel catalysed Heck arylation of the electron-rich olefin *n*-butyl vinyl ether with a wide variety of aryl bromides has been accomplished in the ionic liquid [bmim][BF_4], affording an efficient green chemistry synthetic procedure for preparing functionalised acetophenone. The reaction gave a high regioselectivity and high yield without the need for the costely or toxic halide scavengers, leading predominantly to a branch-arylated α–product.

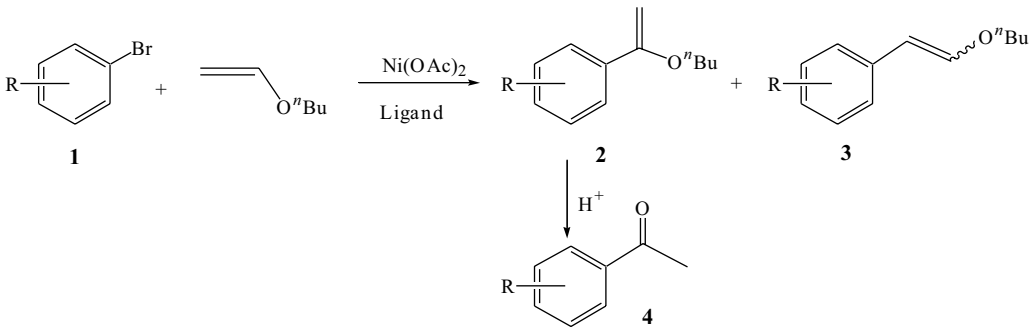
Keywords: functionalised acetophenone, Heck arylation, ionic liquid, *n*-butyl vinyl ether

Palladium catalysed arylation or vinylation of olefins by aryl halides are well known as the Mizoroki-Heck reaction and have proved to be of genuine synthetic utility for C–C bond formation.[1] Although a lot of progress has been made in Heck coupling reactions in both organic and medicinal chemistry, the olefinic substrates have so far mostly been limited to electronic deficient olefins.[2] With electron-rich olefins, such as vinyl ethers, the reaction is rarely regioselective under normal Heck conditions, giving rise to a mixture of α and β substituted olefins and thus hampering its wider application in synthetic chemistry.[3] For these olefins, the arylation is most frequently carried out by employing commercially inaccessible aryl triflates and, when aryl halides are chosen, stoichiometrical silver or thallium salts are generally needed.[4] However, a significant drawback of the chemistry is that triflates are in general not commercially available, thermally labile though, and the inorganic additives create new problems, for instances, toxicity and high cost.

Functionalised acetophenone are important intermediates for synthesis of pharmaceuticals. Most of the previous available methods for preparing these compounds were Grignard reaction, cadmium chloride reagent, diazotisation reaction and diazomethane reaction,[5,8] proved to have the disadvantages of handling dangerous, explosive intermediate, toxic and costly materials, and much waste water in processing. Therefore, to develop the green chemistry methodologies for synthesis of functionalised acetophenone has played a significant role in industrial activity.

Room temperature ionic liquids such as those based on imidazolium salts have widely been used as one of the most promising alternatives to hazardous organic solvents for clean chemical reactions, due to their novel physicochemical properties, such low vapor pressure and tunable solubility to organic or inorganic chemicals, and so on.[9] In a program aimed at developing metal-catalysed reactions in ionic liquids, we supposed that the ionic pathway, which prefers to producing branched olefins, could probably be promoted by using ionic liquids as solvent.[10] It is evident that the application of this catalytic process should provide an attractive and convenient route to functionalised acetophenones. However, to the best of our knowledge, there has been no report to describe this Ni-catalysed process. Herein, in our study of the Ni-catalysed reactions in ionic liquids, we have demonstrated that, using the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) as solvent, the Heck arylation of vinyl ethers, electron-rich olefins can be accomplished in excellent regioselectivity with a wide variety of aryl bromides with no need for aryl triflates or halide scavengers, providing a facile and effective green chemistry method for preparing functionalised acetophenone (Scheme 1).

Firstly we examined the feasibility of arylation of 1-bromo-3-trifluoromethylbenzene as model substrate. A variety of molecular solvents (toluene, dioxane, actinitrile, DMAc, DMF and DMSO) and [bmim][BF_4] were screened, and the results are presented in Table 1. In a typical reaction, a mixture of 1-bromo-3-trifluoromethylbenzene, *n*-butyl vinyl ether, nickel acetate tetrahydrate, 1,3-bis(diphenylphosphino) propane(DPPP), and triethylamine were heated in a chosen solvent for a certain period of time under an inert atmosphere after acidic hydrolysis to give the α-arylated product. As can be seen, all the reactions went to completion in 30 h, but the results differ considerably. Clearly, the regioselectivity is solvent-dependent. Among all these molecular solvents, some of which are commonly used in Heck reactions, none of the reactions could preferentially produce the α substituted olefins, and (Z)-and (E)-β substituted olefins are the major products. In sharp contrast, the use of [bmim][BF_4] as reaction medium predominately led to α substituted olefins. It is well-accepted that Heck reaction may proceed via two pathways, an ionic pathway to form predominately a branched product, and a neutral pathway to give a linear product, consistent with the reports on the Heck arylation of electron-rich olefins in ionic liquids[4,10]. Besides DPPP the other bidentate phosphine ligands such as DPPE, DPPB, DPPF in [bmim][BF_4] also resulted in the improvement in the ratio of α/β.



Scheme 1

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Table 1 The Heck arylation of *n*-butyl vinyl ether with 1-bromo-3-trifluoromethylbenzene **1a**[a]

Solvent	Ligand	Conv. (%)[b]	α/β[c]	*E*/*Z*[d]
Toluene	DPPP	100	20/80	80/20
Dioxane	DPPP	100	30/70	93/7
Acetonitrile	DPPP	100	25/75	97/3
DMAc	DPPP	100	13/87	95/5
DMF	DPPP	100	18/82	93/7
DMSO	DPPP	100	36/65	92/8
[Bmim][BF_4]	DPPP	100	99/1	>99/1
[Bmim][BF_4]	DPPE	85	98/2	97/3
[Bmim][BF_4]	DPPF	96	98/2	>99/1
[Bmim][BF_4]	DPPB	98	99/1	98/2

[a]The product was determined by ^{1}H NMR. [b]Conversion of **1a** to **2a** and **3a**. [c]Molar ratio of **2a**/**3a**. [d]Ratio of *trans*/*cis* isomers of **3a**.

Table 2 Heck arylation of *n*-butyl vinyl ether with aryl bromides **1** in [Bmim][BF_4] [a]

Entry	R	Product	Yield/%[b]
1	*m*-CF_3 (1a)	**4a**	94
2	*p*-CN (1b)	**4b**	87
3	*m*-OH (1c)	**4c**	79
4	2,4-F_2 (1d)	**4d**	73
5	*p*-CH_3CO (1e)	**4e**	90
6	*p*-OCH_3 (1f)	**4f**	92
7	2,4-Cl_2-5-F (1g)	**4g**	76
8	2,4-$(OH)_2$ (1h)	**4h**	91
9	*p*-NO_2 (1i)	**4i**	92
10	3,5-$(CH_3O)_2$ (1j)	**4j**	93
11	*p*-$COOCH_3$ (1k)	**4k**	84
12	*m*-CHO (1l)	**4l**	75

[a]DPPP was used as ligand. [b]Isolated yield.

Based on our initial results, the arylation of 1-bromo-3-trifluoromethylbenzene in [bmim][BF_4] was extended to a variety of aryl bromides. As shown in Table 2, good to excellent regioselectivities together with high isolated yields were achieved regardless of the nature of the substituents on the aryl ring.

In summary, we have developed a new and efficient green chemistry synthetic procedure for the synthesis of functionalised acetophenone by using Ni-catalysed regioselective Heck arylation reaction in ionic liquid. A variety of functionalised acetophenone can be obtained in high yields by this simple and direct approach. The protocol provides a practical supplement to the known methodologies.

Experimental

All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were performed on silica gel (mesh 300) by the flash technique. 1-Butyl-3-methylimidizolium tetrafluoroborate ([bmim][BF_4]) was prepared according to the literature method.[11] $Ni(OAc)_2{\cdot}4H_2O$, 1,2-bis(diphenylphosphino) ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis-(dipenylphosphino)butane (DPPB), 1,1-bis(diphenylphosphino) ferrocene (DPPF), *n*-butyl vinyl ether, and triethylamine were purchased from Acros and Aldrich. ^{1}H NMR spectra were recorded on a Bruker 400 spectrometre in ppm with reference to TMS internal standard in $CDCl_3$. Mass spectra were recorded on a HP5998B mass spectrometer by electron impact (EI). All the products were satisfactorily characterised by ^{1}H NMR, MS, and comparison of their NMR spectra with available literature.

General procedure for the synthesis of functionalised acetophenone in ionic liquid.

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl bromide (1.0 mmol), $Ni(OAc)_2$ (0.025 mmol), DPPP (0.05 mmol), and [bmim][BF_4] (2 ml) under nitrogen at room temperature. Following degassing three times, *n*-butyl vinyl ether (1.1 mmol) and triethylamine (1.2 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 130 °C. After a reaction time of 30 h, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for NMR analysis. In all of the reactions, the β-arylated product was not detected. To the rest of the mixture was added aqueous HCl (5 %, 5 ml), and after the mixture was stired for 30 min, extracted with CH_2Cl_2 (3 ↔ 20 ml), and the combined organic layer was washed with water until neutrality, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The α arylated product was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (5/95 to 30/70) as eluant. The identity and purity of the product was confirmed by ^{1}H NMR and MS by comparison of their NMR spectra with available literature data. The following compounds obtained in this paper have all been reported previously: **4a** [349–76–8],[12] **4b** [1443–80–7],[12] **4c** [99–93–4],[12] **4d** [364–83–0], **4e** [1009–61–6],[10] **4f** [100–06–1],[12] **4g** [704–10–9],[12] **4h** [89–84–9],[12] **4i** [100–19–6],[12] **4j** [39151–19–4],[12] **4k** [3609–53–8],[10] **4l** [41908–11–6].[10]

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