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The Sonogashira Reaction in Ionic Liquids

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Summary. The *Sonogashira* reaction of iodobenzene with phenylacetylene in several room temperature ionic liquids was studied. A regeneration of the catalytical system immobilized in 1-butyl-3methylimidazolium hexafluorophosphate ([*bmim*]PF₆) has been also investigated. The reactivity of different iodoarenes with terminal alkynes in [*bmim*]PF₆ was studied as well.

Keywords. Sonogashira reaction; Ionic liquids.

Introduction

Room temperature ionic liquids have been used frequently in the last years as an alternative reaction medium for a broad range of different chemical transformations [1–6]. Ionic liquids have been utilized as solvents in many transition-metal catalysed C–C bond formation reactions: *Heck* reactions [7–14], *Stille*-coupling [15], *Negishi*-coupling [16], *Suzuki*-coupling [17], *Kumada*-coupling [18], *Ullmann* reaction [19] and *Tsuji-Trost* allylation [20, 21]. Another important reaction for C–C coupling is the *Sonogashira* reaction [22–29], which has been not yet studied for its performance in ionic liquids [30].

Therefore, we decided to study the performance of the *Sonogashira* reaction in several room temperature ionic liquids (Scheme 1).



Scheme 1

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Results and Discussion

At first, the reaction of iodobenzene (**1a**) with phenylacetylene (**2a**) catalyzed by $4 \mod \% \operatorname{Pd}(\operatorname{OAc})_2$, $8 \mod \% \operatorname{PPh}_3$, and $4 \mod \% \operatorname{CuI}$ in the presence of NEt₃ as base in five different ionic liquids, namely, 1-butyl-3-methylimidazolium hexafluorophosphate ([*bmim*]PF₆), 1-hexyl-3-methylimidazolium hexafluorophosphate ([*bmim*]BF₄), 1-hexyl-3-methylimidazolium tetrafluoroborate ([*bmim*]BF₄), 1-hexyl-3-methylimidazolium tetrafluoroborate ([*dbim*]BF₄), and 1,3-dibutylimidazolium tetrafluoroborate ([*abim*]BF₄) was investigated. The expected product **3a** was formed in all cases in virtually quantitative yields after 2 hours at 80°C (Table 1).

To examine the possibility for a catalyst/ionic liquid recovery system, we tested the same reaction in [*bmim*]PF₆ in several subsequent reactions. And indeed, **3a** was obtained in high yield (93%) after the second run. However, during the next three runs a more significant drop of activity was observed (67%, 58%, and 52%). Nevertheless, when a small amount of catalyst (1 mol% Pd(OAc)₂, 2 mol% PPh₃, and 1 mol% CuI) was added, **3a** was again obtained in 94% yield. From the outcome of the last experiment one can conclude that the decrease of reaction yields probably is caused by catalyst leaching during the extractive work-up.

It was also found that the high yields of product were preserved in the first and second runs (97% and 82%) when addition of CuI as a co-catalyst was omitted (entries 11 and 12). However, in the third run a significant drop of the reaction yield was observed (48%, entry 13).

Taking the developed reaction conditions as a standard, we next examined the reactivity of several iodoarenes (1b-1g) with 2a in [bmim]PF₆. The results (Table 2) demonstrate that the reaction proceeds well for the various substrates under standard conditions, the yields (65–87%) should even be further increasable by individual optimization. In several cases the recovered ionic solvent, still containing the

Entry	Ionic liquid	Comment	Yield/% ^a	
1	[bmim]PF ₆		97	
2		2. run	93	
3		3. run	67	
4		4. run	58	
5		5. run	52	
6		6. run	94 ^b	
7	[hmim]PF ₆		95	
8	[bmim]BF ₄		99	
9	[hmim]BF ₄		96	
10	[dbim]BF ₄		97	
11	[bmim]PF ₆		97°	
12		2. run	82 ^c	
13		3. run	$48^{\rm c}$	

Table 1. Yields of *Sonogashira* reaction of iodobenzene (1a) with phenylacetylene (2a) in different ionic liquids

^a isolated yields after column chromatography; ^b after addition of catalyst, see text; ^c reaction performed without CuI

Entry	Substrate	Ar	Comment	Yield/% ^a
1	1b	$4-Cl-C_6H_4$		87
2			2. run	65
3			3. run	57
4	1c	$4-CH_3O-C_6H_4$		65
5			2. run	38
6	1d	$4-CH_3-C_6H_4$		71
7	1e	4-CH ₃ CO-C ₆ H ₄		84
8			2. run	71
9			3. run	69
10	1f	1-Napthyl		87
11			2. run	79
12	1g	$4 - O_2 N - C_6 H_4$		80

Table 2. Yields of *Sonogashira* reaction of **2a** with different iodoarenes in [*bmim*]PF₆

^a isolated yields after column chromatography

Table 3. Yields of Sonogashira reaction of 1a with different 1-alkynes in [bmim]PF₆

Entry	Alkyne	R	Comment	Yield/% ^a
1	2b	TMS		97
2			2. run	68
3	2b	TMS		31 ^b
4			2. run	23 ^b
5	2c	Ви		46
6	2c	Ви		41 ^c

^a isolated yields after column chromatography; ^b isolated yield after distillation; ^c ZnBr₂ was used as a co-catalyst

catalytic system, was reused in a subsequent reaction. Furtheron an attempt was made to employ the cheaper bromobenzene instead of iodobenzene, but the product was obtained in 20% yield only after the first run and the reused catalyst gave an 11% yield only. The formation of palladium black was also observed in this case.

The reactivity of **1a** with trimethylsilylacetylene (**2b**) and hex-1-yne (**2c**) was studied as well (Table 3). Trimethylsilylacetylene gave good yields after extractive isolation (97% after the first run and 68% after the second run, entries 1 and 2). However, polymerisation was observed during the isolation of the product by vacuum distillation and it was obtained only in 31% and 23% yields in the two subsequent experiments (entries 3 and 4). A reaction with **2c** led to the product in 46% yield and 42% yield when CuI was replaced by $ZnBr_2$ [31] (entries 5 and 6).

In conclusion, we have demonstrated that the *Sonogashira* reaction proceeds with high yield in several different ionic liquids. In addition, the possibility of catalyst recovery in $[bmim]PF_6$ was examined and found to be working properly.

Experimental

Typical procedure: $Pd(OAc)_2$ (4 mol%) and PPh₃ (8 mol%) were added to 5 cm³ of pre-dried ionic liquid and the mixture was stirred at 80°C under Ar for 1 h. The resulting ionic liquid/catalyst system was cooled to ambient temperature. CuI (4 mol%), 2 mmol aryl halide, 1.2 eq. terminal alkyne, and 0.4 cm³ of NEt₃ were added and the reaction mixture was stirred at 80°C in a flask equipped with a reflux condenser for 2 h under Ar. *n*-Hexane (10 cm³) was added to the cooled mixture, after vigorous stirring for 5 min the hexane layer was collected and the procedure was repeated until no product was detected in the hexane layer (about 10 times). The solvent was evaporated and the residue was purified by chromatography on a SiO₂-column with *n*-hexane as eluent. All reaction products had physical constants and NMR spectra in accordance with published data. The ionic liquid/catalyst system was dried *in vacuo* at 40°C for 4 h and stored under Ar in the freezer before reuse in next reaction.

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