Investigation of the Effect of the Ligand/Palladium Ratio on the Catalytic Activity of Reusable Palladium/Phosphine/Ionic Liquid Systems in Aminocarbonylation of 17-iodo-androst-16-ene with Amino Acid Ester Nucleophiles

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Abstract: Ionic liquids as solvents were used effectively in palladium catalysed aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**) with L-amino acid esters. Interestingly, optimal conditions that are essential for the successful reuse of the ionic liquid/catalyst mixture differ greatly from those observed in the similar reaction with simple secondary amines as nucleophiles.

Keywords: Aminocarbonylation, palladium, amino acid esters, ionic liquids, alkenyl iodide.

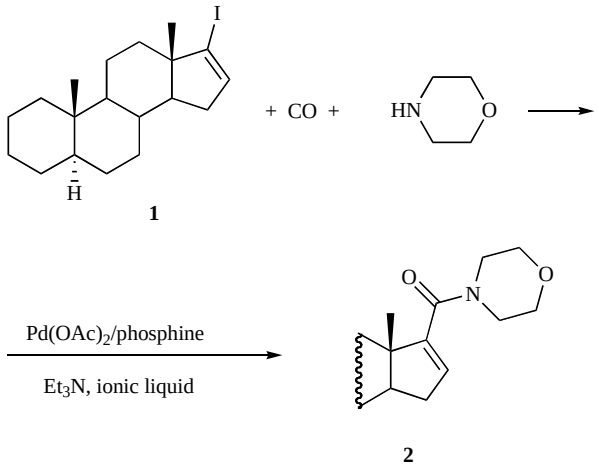
INTRODUCTION

Palladium-catalysed carbonylation of aryl or alkenyl halides is a highly effective method for the synthesis of various carbonyl compounds and carboxylic acids, esters and amides [1]. However, effective separation of the products as well as catalyst recycling are still questions to be solved.

Ionic liquids offer an attractive alternative to conventional organic solvents for transition metal catalysed reactions as they can stabilise organometallic compounds of metals in low oxidation state. The special solubility characteristics of the ionic liquids enable a biphasic reaction procedure in many cases. With the proper choice of ligands the complex remains in the ionic medium. This allows the catalyst to be isolated effectively from the product and to be reused several times [2].

In spite of the recent great interest in the exploitation of ionic liquids in homogeneous catalysis, there are only few reports on carbonylation of organic halides under these conditions [3]. Although in most examples carbonylation was carried out under moderate CO pressure (5-30 bar), we have shown that carboxamides can easily be prepared in ionic liquids even at atmospheric pressure starting from alkenyl iodides and secondary amines [4].

A detailed investigation of the effects of various reaction conditions in aminocarbonylation of steroidal 17-iodo-16-enes (e.g. **1**) with morpholine (Scheme **1**), leading to analogues of well-known 5α-reductase inhibitors, showed that the use of a 6-10-fold excess of phosphine ligand relative to palladium was necessary for effective catalyst recycling [4]. The optimal phosphine/palladium ratio depended greatly on the nature of the phosphine ligand. Best results were obtained either with the $Pd(OAc)_2$ + 6 PPh_3 (Table **1** entries 1,2) or with the $Pd(OAc)_2$ + 10 DPPBA (DPPBA: 4-(diphenylphosphino)benzoic acid) (Table **1** entries 3,4) catalytic systems. Catalysts with either smaller or higher phosphine/palladium ratio led to a considerable loss of activity upon reuse of the catalyst/ionic liquid mixture. As an example, the conversion dropped to 57% in the third run using the $Pd(OAc)_2$ + 4 PPh_3 system in $[bmim]^+[PF_6]^-$. Besides, $[bmim]^+[BF_4]^-$ was proved to be a superior solvent to $[bmim]^+[PF_6]^-$ in each parallel experiment using catalytic systems with the same phosphine ligand and phosphine/palladium ratio.



Scheme 1. Aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**) with morpholine as the nucleophile.

We have shown that ionic liquids are suitable solvents for carbonylation reactions leading to steroid - amino acid conjugates (Schemes **2** and **3**) [5] that can serve as starting material for steroid - peptide hybrids of biological importance, but no optimisation of the reaction conditions has been carried out. At the same time, the results indicated

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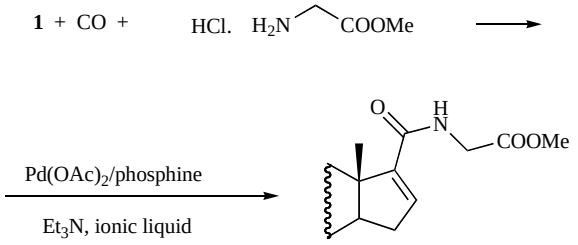
Table 1. Aminocarbonylation of 17-iodo-5α-androst-16-ene (1) with Morpholine in the Presence of $Pd(OAc)_2$ + 6 PPh_3 (A) and $Pd(OAc)_2$ + 10 DPPBA (B) Catalysts [4]

Entry	Catalyst	Solvent	Yield of 2 (%)				
			Run 1	Run 2	Run 3	Run 4	Run 5
1	A	$[bmim]^+[PF_6]^-$	100	100	95	93	82
2	A	$[bmim]^+[BF_4]^-$	100	100	99	98	94
3	B	$[bmim]^+[PF_6]^-$	100	97	96	95	73
4	B	$[bmim]^+[BF_4]^-$	100	100	100	99	87

that the replacement of the amine nucleophile of the aminocarbonylation by an amino acid ester could strongly affect the outcome of the reaction.



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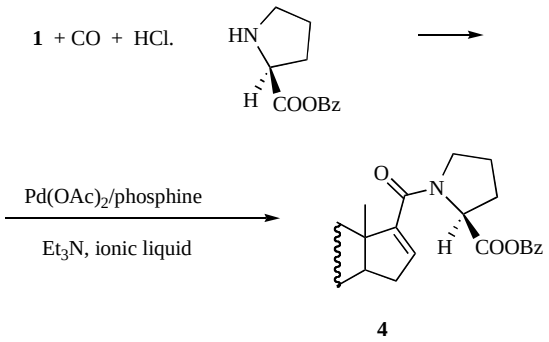
Scheme 2. Aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**) with glycine methyl ester.



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Scheme 3. Aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**) with L-proline benzyl ester.

So we decided to perform a more detailed investigation of the effects of changes in the ligand, the ionic liquid and ligand/palladium ratio on the aminocarbonylation reaction of 17-iodo-5α-androst-16-ene (**1**) with glycine methyl ester and L-proline benzyl ester as the nucleophiles. The results of these experiments are reported in the present paper.

RESULTS AND DISCUSSION

Aminocarbonylation of aryl/alkenyl halides is usually carried out in organic solvents (DMF, THF, 1,4-dioxane or toluene) in the presence of $Pd(OAc)_2$ as catalyst precursor together with a phosphine ligand (PPh_3) with the relatively low phosphine/palladium ratio of 2 [1]. The phosphine serves both as a ligand and as the reducing agent that converts Pd(II) to the catalytically active Pd(0) species [6].

However, in carbonylation reactions carried out in ionic liquids, the use of a higher phosphine/palladium ratio is essential in order to improve activity of the reused catalyst, as it was shown by us [4] and others [7]. Otherwise, a marked decrease in the conversion is observed. As an example, in the reaction of **1** with morpholine (Scheme **1**), the conversion dropped to 47% when the catalyst/$[bmim]^+[PF_6]^-$ mixture was recycled, though **2** was obtained in 100% yield in the first run using the $Pd(OAc)_2$ + 2 PPh_3 catalyst [4]. This is probably partly due to some leaching of the phosphine during extraction of the product that leads to the formation of catalytically inactive, or less active complexes. Some phosphine-free palladium-carbonyl complexes [8] are known to be inactive in carbonylation reactions. Also, palladium-carbene derivatives have reduced activity even in ionic liquids with non-coordinating anions such as $[PF_6]^-$ or $[BF_4]^-$ [9].

At the same time, the degree of the loss of activity depends on the nature of the nucleophile, too. The use of the reaction conditions mentioned above resulted in markedly better results using glycine methyl ester and L-proline benzyl ester as the nucleophile, with 100%, 100%, 53% and 100%, 100%, 75% conversions in three consecutive runs, respectively. Amino acid esters are known to form complexes with palladium [10] through coordination either of the amino group or of both the alkoxycarbonyl and the amino groups of the amino acid ester to the metal. This coordination may hinder the formation of catalytically inert carbonyl complexes even at lower phosphine/palladium ratios.

Optimal conditions for carbonylation of 17-iodo-5α-androst-16-ene (**1**) were determined using two amino acid esters with considerably different structure, glycine methyl ester and L-proline benzyl ester, as the nucleophiles. The reactions were completely selective in all cases, leading to amide **3** and **4** (Schemes **2** and **3**), respectively.

In carbonylations with glycine methyl ester as the nucleophile (Scheme **2** and Table **2**), there are several differences in the effects of reaction conditions compared to those observed in the reaction depicted in Scheme **1**. First, optimal phosphine/palladium ratio decrease from 6 (in case of PPh_3) or 10 (in case of DPPBA) (Table **1**) to 4 in the $[bmim]^+[PF_6]^-$ solvent (Table **2** entries 1, 8) as it could be predicted on the basis of the preliminary experiments mentioned above. Secondly, there is no difference in the best phoshine /palladium ratio using either PPh_3 or DPPBA as ligand in $[bmim]^+[PF_6]^-$. It should be mentioned however,

Table 2. Carbonylation of 1 with Glycine Methyl Ester in Ionic Liquids Using $Pd(OAc)_2$ + *n* Phosphine *In Situ* Catalysts[a]

Entry	Solvent	Ligand	P/Pd	Yield of 3[b] (%)				
				Run 1	Run 2	Run 3	Run 4	Run 5
1	$[bmim]^+[PF_6]^-$	PPh_3	4	100	94	92	89	88
2	$[bmim]^+[PF_6]^-$		6	99	98	97	70	52
3	$[bmim]^+[PF_6]^-$		10	85	83	62	54	-
4	$[bmim]^+[BF_4]^-$		4	97	96	85	71	51
5	$[bmim]^+[BF_4]^-$		6	100	100	98	74	55
6	$[bmim]^+[BF_4]^-$		10	88	85	65	59	-
7	$[bmim]^+[PF_6]^-$	DPPBA[c]	2	100	100	92	53	35
8	$[bmim]^+[PF_6]^-$		4	100	100	100	94	87
9	$[bmim]^+[PF_6]^-$		6	100	100	100	91	86
10	$[bmim]^+[PF_6]^-$		10	100	100	86	55	-
11	$[bmim]^+[BF_4]^-$		4	97	93	66	60	55
12	$[bmim]^+[BF_4]^-$		6	100	88	87	83	64
13	$[bmim]^+[BF_4]^-$		10	100	100	98	88	70

[a]Reaction conditions: ionic liquid (600mg), **1** (0.2mmol), $Pd(OAc)_2$ (0.01mmol), the phosphine (as indicated), Et_3N (0.15ml), and glycine methyl ester hydrochloride (0.4 mmol) were heated in CO atmosphere for 8h at 100°C.
[b]Determined by GC as an average of three experiments.
[c]4-(diphenylphosphino)benzoic acid.

that the conversion of the reaction is less sensitive to a change of the P/Pd ratio when using DPPBA. In the presence of the $Pd(OAc)_2/PPh_3$ catalytic system, the increase of the P/Pd ratio from 4 to 6 results in a marked decrease of catalytic activity in the fourth run (entries 1, 2), while with DPPBA conversions obtained at P/Pd ratios of 4 and 6 are comparable (entries 8, 9). Thirdly, taking everything into account $[bmim]^+[BF_4]^-$ is less effective except for the use of the $Pd(OAc)_2$ + 10 DPPBA catalyst precursor (entry 13) where conversions are comparable (at least in the first four runs) to the results obtained in $[bmim]^+[PF_6]^-$ at optimal P/Pd ratios (entries 1,8).

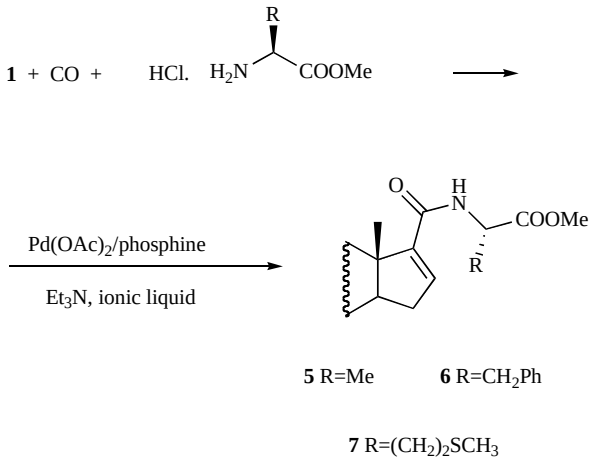
In the $[bmim]^+[BF_4]^-$ solvent, catalytic systems with P/Pd ratios of 6 (for PPh_3, entry 5) or 10 (for DPPBA, entry 13) turned out to be the most effective, similar to the reaction of **1** with morpholine (Table **1**). However, the loss of activity is much greater after the third run with both catalysts using the amino acid ester as the nucleophile.

The same conclusions can be drawn from the results of aminocarbonylation of **1** with L-proline benzyl ester (Scheme **3** and Table **3**). The $[bmim]^+[BF_4]^-$ ionic liquid is clearly the less suitable solvent here. Total conversion of **1** cannot be achieved even in the first runs (entries 3-5 and 10-12) under the conditions used before with the exception of

Table 3. Carbonylation of 1 with L-Proline Benzyl Ester in Ionic Liquids Using $Pd(OAc)_2$ + *n* Phosphine *In Situ* Catalysts[a]

Entry	Solvent	Ligand	P/Pd	Yield of 4[b] (%)				
				Run 1	Run 2	Run 3	Run 4	Run 5
1	$[bmim]^+[PF_6]^-$	PPh_3	4	100	100	100	88	80
2	$[bmim]^+[PF_6]^-$		6	100	64	51	33	20
3	$[bmim]^+[BF_4]^-$		4	91	62	47	41	31
4	$[bmim]^+[BF_4]^-$		6	93	74	73	68	64
5	$[bmim]^+[BF_4]^-$		10	98	95	78	60	32
6	$[bmim]^+[PF_6]^-$	DPPBA[c]	2	94	89	52	45	42
7	$[bmim]^+[PF_6]^-$		4	100	100	95	84	68
8	$[bmim]^+[PF_6]^-$		6	100	93	85	84	67
9	$[bmim]^+[PF_6]^-$		10	100	88	83	80	65
10	$[bmim]^+[BF_4]^-$		2	93	74	64	40	30
11	$[bmim]^+[BF_4]^-$		4	94	75	70	42	39
12	$[bmim]^+[BF_4]^-$		6	94	78	76	45	41
13	$[bmim]^+[BF_4]^-$		10	100	98	94	88	76

[a]Reaction conditions: ionic liquid (600mg), **1** (0.2mmol), $Pd(OAc)_2$ (0.01mmol), the phosphine (as indicated), Et_3N (0.15ml), and L-proline benzyl ester hydrochloride (0.4 mmol) were heated in CO atmosphere for 8h at 100°C.
[b]Determined by GC as an average of three experiments.
[c]4-(diphenylphosphino)benzoic acid.



5 R=Me **6** R=CH_2Ph

7 R=$(CH_2)_2SCH_3$

Scheme 4. Aminocarbonylation of 17-iodo-5α-androst-16-ene (**1**) with L-alanine-, L-phenylalanine- and L-methionine methyl esters.

the $Pd(OAc)_2$ + 10 DPPBA catalyst (entry 13) that gives the best results in this solvent again.

The optimal reaction conditions, the $Pd(OAc)_2$ + 4 PPh_3 catalyst precursor and $[bmim]^+[PF_6]^-$ solvent, were applied successfully in the aminocarbonylation of **1** with methyl esters of L-alanine, L-phenylalanine and L-methionine (Scheme **4**, Table **4**) leading to the steroid-amino acid conjugates **5**, **6** and **7**, respectively. The results turned out to be slightly better in most cases than those obtained before with either the $Pd(OAc)_2$ + 6 PPh_3 /$[bmim]^+[PF_6]^-$ (A) or the $Pd(OAc)_2$ + 10 DPPBA / $[bmim]^+[BF_4]^-$ (B) systems [11], where conversions dropped to 92%, 87%, 70% (system A) and 94%, 88%, 79% (system B) in the third runs of the reactions of L-Ala-OMe, L-Phe-OMe and L-Met-OMe, respectively. However, the differences are less marked here than in the reaction of the secondary amine L-proline benzyl ester (see Table **3**).

CONCLUSIONS

In aminocarbonylation reactions using amino acid esters as nucleophiles, $[bmim]^+[PF_6]^-$ was proved to be a superior solvent to $[bmim]^+[BF_4]^-$ in contrast to a similar reaction of the secondary amine morpholine. In the first ionic liquid, optimal phosphine/palladium ratio is 4 irrespective of the use of either PPh_3 or the more polar ligand DPPBA. In $[bmim]^+[BF_4]^-$ the best results can be obtained with the $Pd(OAc)_2$ + 10 DPPBA system, though the loss of activity is greater in this ionic liquid upon the reuse of the catalyst/ionic liquid mixture than at optimal P/Pd ratios in $[bmim]^+[PF_6]^-$.

The results show that the catalyst/ionic liquid systems should be fine-tuned for each particular aminocarbonylation reaction when using nucleophiles of diverse structures.

EXPERIMENTAL

The ionic liquid $[bmim]^+[PF_6]^-$ was prepared as described previously [12]. $Pd(OAc)_2$, phosphine ligands, amino acid esters and $[bmim]^+[BF_4]^-$ were good quality commercial products and were used as received without further purification.

Catalytic Experiments

In a typical procedure, 17-iodo-5α-androst-16-ene (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), the ligand (PPh_3 or DPPBA as indicated in Tables **2** and **3**), glycine methyl ester or L-proline benzyl ester (0.4 mmol) and the ionic liquid (600 mg) were placed in a Schlenk-tube equipped with a magnetic stirrer, a septum inlet and a reflux condenser with a balloon on the top. This was placed under carbon monoxide, and Et_3N (0.15 ml) was added. The reaction mixture was heated at 100°C for 8 h. The mixture was extracted twice with 0.4 ml toluene. The extracts were analysed by GC. Any volatiles were removed from the ionic liquid in vacuo and new load of starting materials (steroid, Et_3N and amino acid ester) for the next catalytic run were added to the ionic liquid/catalyst mixture and the atmosphere was changed to carbon monoxide. The consecutive runs were conducted for the same reaction time.

Toluene extracts were analysed by gas chromatography (Hewlett Packard 5890) and occasionally by GC-MS (Hewlett Packard 5971A GC-MSD, HP-1 column) and ^1H NMR spectroscopy (BRUKER AVANCE 400 spectrometer, $CDCl_3$ solutions).

The analytical data of the products corresponded well to authentic samples of the same compounds [5, 11].

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Table 4. Carbonylation of 1 with L-alanine-, L-phenylalanine- and L-methionine Methyl Esters Using the $Pd(OAc)_2$ + 4 PPh_3 /$[bmim]^+[PF_6]^-$ System[a]

Nucleophile	Product	Yield[b] (%)				
		Run 1	Run 2	Run 3	Run 4	Run 5
L-Ala-OMe	**5**	100	100	97	68	66
L-Phe-OMe	**6**	100	100	99	78	76
L-Met-OMe	**7**	100	98	76	65	61

[a]Reaction conditions: $[bmim]^+[PF_6]^-$ (600mg), **1** (0.2mmol), $Pd(OAc)_2$ (0.01mmol), PPh_3 (0.04mmol), Et_3N (0.15ml), and amino acid ester hydrochloride (0.4 mmol) were heated in CO atmosphere for 8h at 100°C.
[b]Determined by GC as an average of three experiments.

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