EFFICIENT SYNTHESIS OF PTEROCARPANS BY HECK-OXYARYLATION IN IONIC LIQUIDS

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Abstract: An efficient synthesis of pterocarpan (±)-**3** has been achieved in 69% yield by Heck coupling of 2*H*-chromene (**1**) with 2-iodophenol (**2b**) in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] and in the presence of the [$PdCl_2(PhCN)_2$]/Ph_3P/Ag_2CO_3 catalyst system.

Introduction

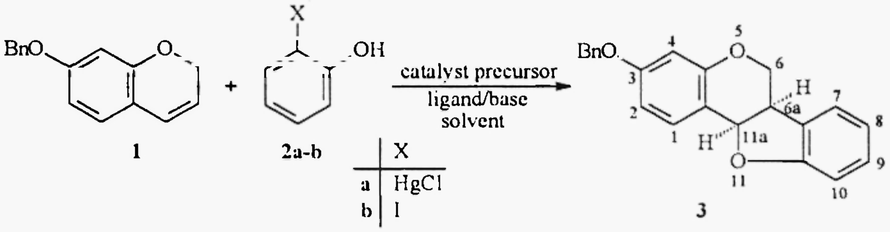
Pterocarpans are naturally occurring plant products carrying a *cis*-fused benzofuranyl-benzopyran ring system. This group of compounds is of great interest due to their well-known pathological activity as phythoalexins (1). Among the synthetic routes to pterocarpans, the Heck-oxyarylation of 2*H*-chromenes with 2-chloromercuriphenol (**2a**) using equimolar amount of $Li_2[PdCl_4]$ as a catalyst is a widely used method (2-6). Recently, we have published (7) an efficient modification of this method which starts from 2-iodophenol (**2b**) instead of the toxic 2-chloromercuriphenol (**2a**) and uses catalytic amount of $Pd(OAc)_2$ with a phosphine ligand (Ph_3P) and a base (Ag_2CO_3 and $CaCO_3$) in acetone.

Several recent publications describe (8,9) Heck coupling of aryl halides with alkenes with excellent yields (90-95%) in room temperature ionic liquids. These recyclable, "green" solvents not only allow relatively easy product isolation and catalyst recovery but often improve the yields of synthetic reactions through their interaction with the metal complex catalyst (10-12). It seemed reasonable to examine the above mentioned Heck-oxyarylation of 2*H*-chromene (**1**) with 2-iodophenol (**2b**) in this type of solvents as well.

Results and Discussion

The Heck-oxyarylation of 7-benzyloxy-2*H*-chromene (**1**) (4) with 2-iodophenol (**2b**), resulting in the *rac.*-3-benzyloxy-pterocarpan (**3**) (7) has been systematically studied with various catalyst systems such as $Pd(OAc)_2$ or $[PdCl_2(C_6H_5CN)_2]$ in ionic liquids (Scheme 1.).

Scheme 1.



The scope and limitation of this method were investigated and our results are summarized in the table. In comparasion with our further result (7) (entry 1), the ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate $[bmim][PF_6]$ proved (entries 2-4) to be a suitable alternative solvent for Heck-oxyarylation of **1** at 100°C. Not only the reaction time could be drastically shortened, but also the amount of palladium catalyst could be decreased resulting in a significant increase of the turnover number (TON) of the catalysts. If **1** was subjected to Heck-oxyarylation with **2b** using $[PdCl_2(C_6H_5CN)_2]$ as a precatalyst, *rac.*-**3** could be obtained with significantly higher yield (see entry 8 as well as entry 1 and 3). In this system the amount of palladium catalyst could be also decreased without remarkably decreasing of the yield of the transformation (entry 9). Addition of water or benzene to $[bmim][PF_6]$ blocked the reaction completely (entries 10, 11). Interestingly, while the halide-containing $[PdCl_2(C_6H_5CN)_2]$ provided the highest catalytic activities, addition of KI to $[bmim][PF_6]$ or the use of [bmim]Cl (entries 5,6) resulted in no formation of **3**. In accordance with recently published data (12,13), the Heck-oxyarylation could be performed without the addition of phosphine ligands (entries 12-15). On the bases of these results it seems reasonable to suppose that the imidazolium ion can also react with $[PdCl_2(C_6H_5CN)_2]$ to form an *N*-heterocyclic carbene complex *via* deprotonation at C-2 of the imidazolium skeleton and the generated carbene complex is also active for the C-C, as well as for the C-O bond coupling reaction.

In summary, an efficient synthesis of pterocarpan (±)-**3** has been achieved in 69% yield by Heck coupling of 2*H*-chromene (**1**) with 2-iodophenol (**2b**) in the ionic liquid 1-butyl-3-methylimidazolium hexaflourophosphate $[bmim][PF_6]$ and in the presence of the $[PdCl_2(C_6H_5CN)_2]$ $/Ph_3P/Ag_2CO_3$ catalyst system. This air and moisture-stable ionic liquid, served not only as an excellent solvating medium but it also participated in the formation of the active catalyst. This new method offers increased yield together with substantial savings in reaction time and in the amount of palladium required.

Table. Effects of the promoter, base and solvent on the palladium-catalysed oxyarylation of **1**

Entry	Catalyst precursor (mol% Pd)	Ligand (mol%)	Base (mol%)	Solvent	Temp. (°C)	Reaction time (h)	Yield[a] %	TON[b]
1	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300) $CaCO_3$ (300)	acetone	reflux	48	51	5.07
2	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$	60	17	20	2
3	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	3	33	3.3
4	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$	120	0.5	14	1.4
5	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$ KI (1:1)	100	4	0	0
6	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][Cl]$	100	7	0	0
7	$Pd(OAc)_2$ (1)	PPh_3 (2)	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	2	32	32
8	$[PdCl_2(C_6H_5CN)_2]$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	3	69	6.9
9	$[PdCl_2(C_6H_5CN)_2]$ (1)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	4	45	45
10	$Pd(OAc)_2$ (10)	PPh_3 (20)	K_2CO_3 (300)	$[bmim][PF_6]$ H_2O	100	7	0	0
11	$Pd(OAc)_2$ (10)	PPh_3 (20)	Ag_2CO_3 (300)	$[bmim][PF_6]$ benzene	100	24	0	0
12	$Pd(OAc)_2$ (10)	–	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	4	31	3.1
13	$[PdCl_2(PPh_3)_2]$ (10)	–	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	2	33	3.3
14	$[Pd(PPh_3)_4]$ (10)	–	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	2	41	4.1
15	$[PdCl_2(C_6H_5CN)_2]$ (10)	–	Ag_2CO_3 (300)	$[bmim][PF_6]$	100	6	28	2.8

[a] isolated yield; [b] mmol product/mmol Pd

Experimental

All reagents and organic compounds used in this study were purchased from Sigma-Aldrich. 7-Benzyloxy-2*H*-chromene (**1**) and $[bmim][PF_6]$ were prepared according to the known procedures (3,14).

General procedures for the Heck-oxyarylation reaction:

a) 4.2×10^{-2} or $\times 10^{-3}$ mmol Pd(II) catalyst and 8.4×10^{-2} or $\times 10^{-3}$ mmol PPh_3 were stirred in [bmim][PF_6] (1 g) at 80°C for 5 min, respectively. Then 100 mg (0.42 mmol) **1**, 93 mg (0.42 mmol) **2b** and Ag_2CO_3 (348 mg, 1.26 mmol) were added. Stirring was continued at 100°C for the time indicated in the table and then the reaction mixture was cooled, extracted with toluene and concentrated in *vacuo*. The crude product was purified by preparative TLC on precoated silica gel plates (Kieselgel 60F250, 0.5 mm, Merck) (n-hexane/CH_2Cl_2, 2:1) to give *rac.*-**3** (10).

b) Pd(II) catalyst (4.2×10^{-2} or 4.2×10^{-3} mmol) was stirred in ionic liquid (1 g) at 80°C for 2h. Then the above mentioned amount of **1**, **2b** and Ag_2CO_3 were added. After stirring at 100°C for the time indicated in the table the reaction mixture was worked up as described above.

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References

1. P.M. Dewick, *in The Flavonoids: Advances in Research Since 1986*, J.B. Harborne (Ed.) Chapman and Hall, London, **1994**, pp. 166 and pp. 530
2. H. Horino and N. Inoue, *J. Chem. Soc. Chem. Commun.* **1976**, 500
3. J.C. Breytenbach and G.J.H. Rall, *J. Chem. Soc. Perkin Trans 1.* **1980**, 1804
4. D.D. Narkhede, P.R. Iyer and C.S.R. Iyer, *Tetrahedron*, *46*, 2031 (**1990**)
5. R.A. Lichtenfels, A.L. Coelho and P.R.R. Costa, *J. Chem. Soc. Perkin Trans 1.* **1995**, 949
6. A.L. Tőkés, Gy. Litkei, K. Gulácsi, S. Antus, E. Baitz-Gács, Cs. Szántay and L.L. Darkó, *Tetrahedron*, ***55***, 9283 (**1999**)
7. L. Kiss and S. Antus, *Het. Commun.* ***6***, 309 (2000)
8. V.P.W. Böhm and W.A. Herrmann, *Chem. Eur. J.* ***6***, 1017 (2000)
9. A.J. Carmichael, M.J. Earle, J.D. Holbrey, P.B. McCormac and K.R. Seddon, *Org. Lett.* ***1***, 997 (**1999**)
10. P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.* ***39***, 3772 (2000)
11. T. Welton, *Chem. Rev.* ***99***, 2071 (1999)
12. L. Xu, W. Chen and J. Xiao, *Organometallics* ***19***, 1123 (2000)
13. D.S. McGuinness, M.J. Green, K.J. Cavell, B.W. Skelton and A.H. White, ibid. ***565***, 165 (1998)
14. J.G. Huddleston, H.D. Willauer, R.P. Swatloshi, A.E. Visser and R.D. Rogers, *J.C.S. Chem. Commun.* **1998**, 1765

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