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PALLADIUM CATALYZED MONO- AND DIARYLATION OF 2-METHYLQUINOLINES

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ABSTRACT:
Reactions of 2-methylquinolines with aryl iodides in the system $Pd(OAc)_2$ (5 mol.%)/ dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / *t*-BuOK (1.3 eq.) in toluene afforded mono- and diarylated products in yields up to 44 %.

Keywords: Palladium catalyst, 2-methylquinolines, 2-benzyl-6-methoxy-quinoline, 6-Methoxy-2-(diphenylmethyl)quinoline, 6-methoxy-2-(4-methoxybenzyl)quinoline

INTRODUCTION

Benzylquinolines and diarylmethylquinolines are of interest as valuable intermediates in organic synthesis. Usually benzylquinolines were obtained by reaction of benzyl sodium with quinoline [1], benzyl magnesium bromide with quinoline [2], methylquinoline with chlorobenzene [3] or by homolytic benzylation of quinoline with toluene derivatives [4].

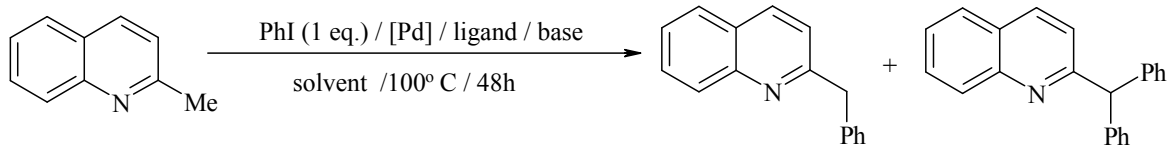
Diarylmethylquinolines were obtained from quinoline and benzene in the presence of dehydrating agent (for example, H_2SO_4) [5] or from quinoline aldehyde and benzene in the presence of triflic acid [6].

Palladium catalyzed arylation reactions of ketones, amides and related nucleophiles were recently described in some reviews [7-9]. The best catalytic systems for arylation of ketone enolates were found to be $Pd_2(dba)_3$ / BINAP / t-BuONa [10], $Pd_2(dba)_3$ / Tol-BINAP / t-BuONa / THF [11], $Pd(OAc)_2$ / Xantphos / t-BuONa or K_3PO_4 [12], $Pd(OAc)_2$ / PPh_3 / Cs_2CO_3 / DMF [13], $Pd(OAc)_2$ / RR_3 (R= alkyl, aryl) / Cs_2CO_3 [14] and (imidazol-2-ylidene)palladium acetate / t-BuONa / dioxane [15]. Palladium catalyzed arylation of nitriles [16] and sulfones [17] were described too. Recently was described simple arylation of 8-methylquinoline with 4-bromo-1-iodobenzene to corresponding benzylquinoline in the system $Pd(OAc)_2$ / AgOAc / AcOH [18]. However, only mono-arylated products were obtained in the above system. Recently we reported our first results in Pd-catalyzed mono- and diarylation of methylquinolines.[19] Now we are presenting a novel Pd-catalyzed method of synthesis of benzylquinolines and diarylmethylquinolines.

RESULTS AND DISCUSSION

We have developed a new and simple palladium catalyzed arylation method of methylquinolines. The influence of catalyst, base and solvent was studied in the arylation

reaction of 2-methylquinoline (**1**) with iodobenzene (2 eq.). Interestingly, the system $Pd(OAc)_2$ (5 mol.%)/ dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / t-BuOK (1.3 eq.) in toluene was found to be the most active for the diarylation of compound **1**. In this system compound **3** was obtained in the 41% yield, along with mono-arylated product **2** (17%). Increase in the amount of t-BuOK to 2.6 equiv. and using $P(o\text{-}Tol)_3$ as ligand diminishes the yields of products **2** and **3**. The systems $Pd(OAc)_2$ (5 mol.%) / CuI (10 mol.%) / t-BuOK / toluene, $Pd(OAc)_2$ (5 mol.%)/ dppb (10 mol.%) / t-BuOK (1.3 eq.) / CsOH (1.3 eq.) / 18-crown-6 (10 mol.%) / toluene and $Pd(PPh_3)_4$ (5mol.%) / t-BuOK (1.3 eq.) / toluene were essentially inactive in the arylation of compound **1** (Table 1.).

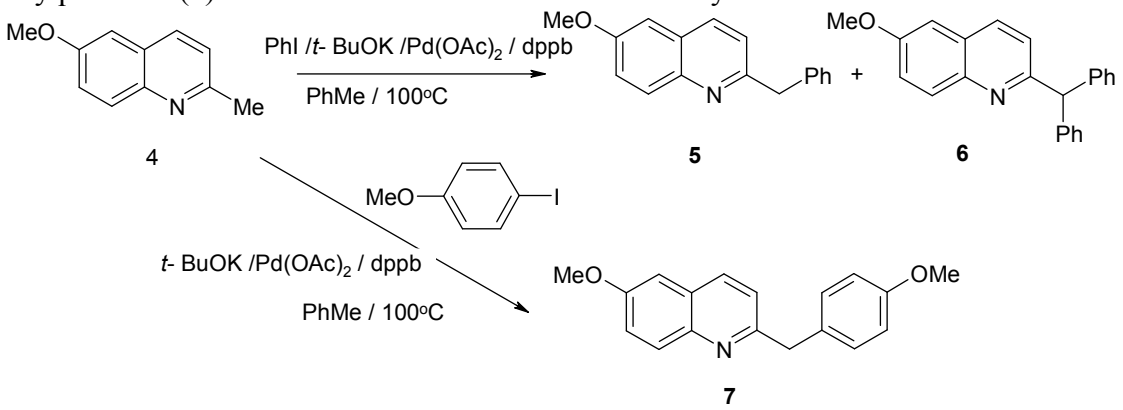


1 **2** **3**

Table 1. Palladium catalyzed arylation of 2-methylquinoline (1) with 2 equivalent of PhI at 100°C for 48 h.

Catalyst	Ligand	Base	Solvent	Yield of **2**, % (GC-MS data)	Yield of **3**, % (GC-MS data)
$Pd(OAc)_2$ (5 mol.%)	Dppb (10 mol.%)	*t*-BuOK (1.3 eq.)	Toluene	17	41
$Pd(OAc)_2$ (2.5 mol.%)	Dppb (5 mol.%)	*t*-BuOK (1.3 eq.)	Toluene	26	0
$Pd(OAc)_2$ (5 mol.%)	Dppb (10mol.%)	*t*-BuOK (2.6 eq.)	Toluene	13	5
$Pd(OAc)_2$ (5 mol.%)	Dppb (10 mol.%)	*t*-BuOK (1.3 eq.)	DMF	23	0
$Pd(OAc)_2$ (5 mol.%)	Dppb (10 mol.%)	CsOH (1.3 eq.) + 18-crown-6 (10 mol.%)	Toluene	0	0
$Pd(OAc)_2$ (5 mol.%)	$P(o\text{-}Tol)_3$ (10mol.%)	*t*-BuOK (1.3 eq.)	Toluene	17	7
$Pd(OAc)_2$ (5 mol.%)+ CuI (10 mol. %)	Dppb (10mol.%)	*t*-BuOK (1.3 eq.)	Toluene	2	0
$Pd(PPh_3)_4$ (5 mol.%)	-	*t*-BuOK (1.3 eq.)	Toluene	Traces	0

The catalytic system system $Pd(OAc)_2$ (5 mol.%)/ dppb (1,4-bis(diphenylphosphino)butane) (10 mol.%) / *t*-BuOK (1.3 eq.) in toluene, as the most active, was used in the arylation of 2-methyl-6-methoxyquinoline (**4**) with iodobenzene or 1-iodo-4-methoxybenzene.



Arylation of quinoline **4**, having electrondonating group in the position 6, with iodobenzene in above system leads to mixture of mono- (**5**) (yield 12%) and diarylated product (**6)** (yield 13%). However, reaction of compound **4** with 1-iodo-4-methoxybenzene was selective so that 6-methoxy-2-(4-methoxybenzyl)quinoline (**7**) was isolated in 44 % yield as single product. Diarylation of compound **4** in this case did not occurred due to deactivation of methylene group in the compound **7** by methoxy group in *para*-position.

Thus, palladium catalyzed arylation of methylquinolines is a simple method for the synthesis of benzylquinolines and diarylmethylquinolines which otherwise are difficult to obtain.

EXPERIMENTAL SECTION

^1H spectra were recorded on a Varian Mercury BB 400 MHz in $CDCl_3$ using HMDS as internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV).

General procedure for the arylation of 2-methylquinoline with iodobenzene in the presence of palladium catalyst

2-Methylquinoline (0.14 ml, 1 mmol), iodobenzene (0.22 ml, 2 mmol) and base (see Table 1) were added to stirred solution of palladium catalyst and ligand (see Table 1) in dry toluene (1.25 ml) in a Pierce reacti-vial (5 ml) under argon atmosphere. The mixture was stirred at 100°C (GC-MS control) for 48 h, filtered and the solvent was evaporated under reduced pressure. The residue was purificated by column chromatography on silica gel (eluent: toluene: ethyl acetate 10:1) to obtain desired products **2** and **3** [5, 6] as colorless oils (see Table 1)**.**

General procedure for the arylation of 2-methyl-6-methoxyquinoline (4) with iodobenzene or 1-iodo-4-methoxybenzene in the presence of palladium catalyst.

2-Methyl-6-methoxyquinoline (**4**)(0.224 g, 1 mmol), aryl iodide (2 mmol) and *t*-BuOK (0.146 g, 1.3 mmol) were added to stirred solution of $Pd(OAc)_2$ (0.011 g, 0.05 mmol) and 1,4-bis(diphenylphosphino)butane (dppb) (0.043 g, 0.1 mmol) in dry toluene (1.25 ml) in a Pierce reacti-vial (5 ml) under argon atmosphere. The mixture was stirred at 100°C (GC-MS control) for 48 h, filtered and the solvent was evaporated under reduced pressure. The residue was purificated by column chromatography on silica gel (eluent: toluene: ethyl acetate 10:1) to obtain desired products **5-7** as colourless oils**.**

The properties of obtained products were as follows:

2-Benzyl-6-methoxy-quinoline (5). Yield 12 %. ^{1}H NMR δ (ppm): 3.91 (s, 3H, Me), 4.30 (s, 2H, CH_2), 7.02-7.38 and 7.90-8.00 (both m, 10H, Ph and quinoline ring protons). MS: *m/z* (%): 249 (M^+, 58), 248 (100), 234 (10), 205 (21).

6-Methoxy-2-(diphenylmethyl)quinoline (6). Yield 13 %. ^{1}H NMR δ (ppm): 3.91 (s, 3H, Me), 5.87 (s, 1H, CH), 7.03-7.31 and 7.93-7.97 (both m, 15H, Ph and quinoline ring protons). MS: *m/z* (%): 326 (M^+, 15), 324 (100), 281 (16), 204 (26), 165 (33), 152 (13).

6-Methoxy-2-(4-methoxybenzyl)quinoline (7). Yield 44 %.^{1}H NMR δ (ppm): 3.76 (s, 3H, MeO in Ph ring) 3.91 (s, 3H, MeO in quinoline ring), 4.23 (s, 2H, CH_2), 6.81-7.37 and 7.89-7.99 (both m, 9H, Ph and quinoline ring protons). MS: *m/z* (%): 279 (M^+, 98), 278 (100), 264 (66), 221 (11), 192 (12), 121 (14).

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