Journal of Organometallic Chemistry, 364 (1989) 231–234
Elsevier Sequoia S.A., Lausanne – Printed in The Netherlands
JOM 09554

Palladium-catalyzed cross-coupling reactions of organomercurials with organic halides

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(Received September 9th, 1988)

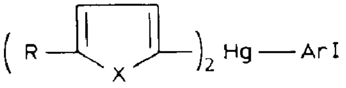
Abstract

Organomercurials, $(A)_2Hg$ (A = 5-methyl-2-furyl, thienyl) react with organic halides, ArI, in the presence of a palladium catalyst and iodide ion under argon to give cross-coupled products AAr, in high yields.

Introduction

Organomercurials are widely used in organic synthesis because of their commercial availability and stability towards water, air and alcohols. A number of research papers have been published, showing the potential and usefulness of organomercurials in organic synthesis [1]. The cross-coupling reactions of organomercurials with organic halides, catalyzed by transition metal complexes, provide an efficient method for selective carbon–carbon bond formation.

We recently showed that palladium-catalyzed cross-coupling reactions of organomercurials proceed with low selectivity owing to catalytic demercuration of organomercurials [2], but in the presence of a nucleophilic catalyst (iodide ion) and under mild conditions the selectivity towards the cross-coupling product increases [3]. Here we report on the synthesis of arylated heterocyclic and bi-heterocyclic compounds by the palladium-catalyzed cross-coupling reactions of the system (A)Hg–ArI (X = O, S; R = H, Me; Ar = 2-C_4H_3S, 2-C_5H_4N, p-$NO_2C_6H_4$, *p*-$C_5H_3NNO_2$).



$(A)_2Hg$—ArI

The cross-coupling reaction (reaction 1) proceeds under mild conditions (DMF, $ArPdI(PPh_3)_2$ (1 mol. %), NaI (2 eq.), argon atm., 20 °C), to give high yields of the cross-coupling products along with small quantities of the homo-coupling products (due to oxidative demercuration of the organomercurials).

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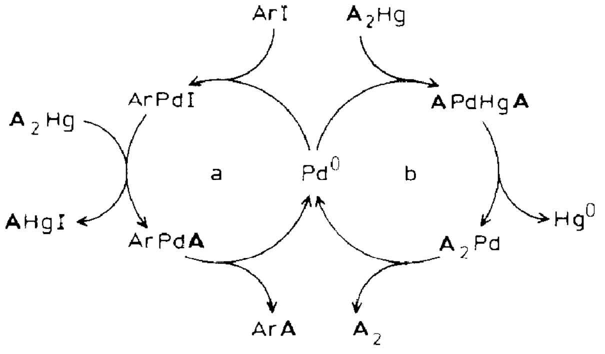


Scheme 1

$$(\mathbf{A})_2Hg + 2\ ArI \rightarrow 2\ (\mathbf{A})Ar + (\mathbf{A})_2 \qquad (1)$$

A catalytic cycle of the reaction is given in Scheme 1 (ligands are omitted).

Results and discussion

The palladium(0) complex, generated in situ from the initial palladium(II) complex under the reaction conditions, catalyzes both the aryldemetallation (a) and the oxidative demercuration processes (b) at the same time [4]. ArI adds oxidatively to Pd^0 complex to give arylpalladium(II) complex, ArPdI, which undergoes transmetallation with $\mathbf{A}_2Hg$ to give ArPd**A** complex. ArPd**A** complex reductively eliminates Ar**A** (cross-coupling product) with the recovery of Pd^0 complex. On the other hand, oxidative demercuration of $\mathbf{A}_2Hg$ takes place because of the insertion of Pd^0 into the C–Hg bond [4] to give the homo-coupling product.

A nucleophilic catalyst (iodide ion) plays an important role in the reaction. The iodide ion shifts the selectivity of the reaction towards the cross-coupling product. This may be connected to several functions of the iodide ion: (1) The iodide ion coordinates with Hg atom (in $\mathbf{A}_2Hg$) and helps in the polarization and heterolytic fission that take place at the transmetallation step. (2) The iodide ion may form an anionic complex with Pd^0 (as in the case of Rh^I complex [5]), which could enhance the oxidative addition of ArI to Pd^0 complex. (3) The coordination of the iodide ion to the Hg atom (in $\mathbf{A}_2Hg$) and to the Pd atom (in Pd^0 complex) to form the anionic complexes, $(\mathbf{A}_2HgI)^-$ and $(Pd(0)I)^-$, respectively, may lead to retardation of the oxidative demercuration process.

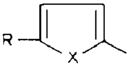
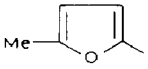
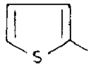
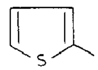
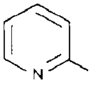
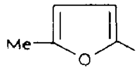
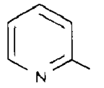
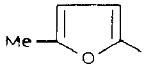
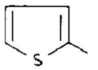
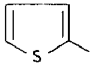
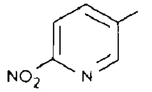
Arylated heterocyclic compounds are obtained in high yields by the palladium-catalyzed cross-coupling reactions of the $(\mathbf{A})_2Hg$-*p*-YC_6H_4I system under mild conditions. The stronger the electron withdrawing group (Y) is the greater is the selectivity of the reaction towards the cross-coupling product. For example, the reactions of bis(5-methyl-2-furyl)mercury and bis(2-thienyl)mercury with *p*-$NO_2C_6H_4I$ take place (within 10 min) under mild conditions to give the cross-coupling products in high yields and practically without by-products (reactions 2 and 3, Table 1, entries 1 and 2).

$$(\mathbf{A})_2Hg + 2\ p\text{-}NO_2C_6H_4I \rightarrow 2\ (\mathbf{A})C_6H_4NO_2\text{-}p \qquad (2)$$
$$(R = Me,\ X = O) \qquad (95\%)$$

$$(\mathbf{A})_2Hg + 2\ p\text{-}NO_2C_6H_4I \rightarrow 2\ (\mathbf{A})C_6H_4NO_2\text{-}p \qquad (3)$$
$$(R = H,\ X = S) \qquad (94\%)$$

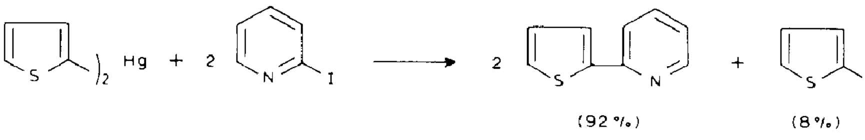
Table 1

Cross-coupling reactions of $(A)_2Hg$ with ArI, DMF, p-$NO_2C_6H_4PdI(PPh_3)_2$ (1 mol %), NaI (2 eq.), argon

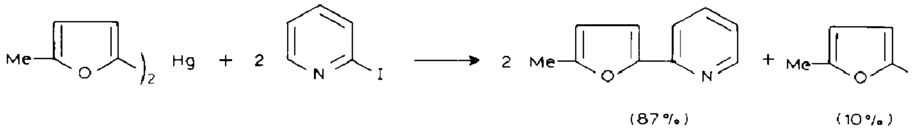
Entry		Ar	Reaction time (min)	Temp. °C	Yield [a] (%)	
					(A)Ar	$(A)_2$
1		p-$NO_2C_6H_4$	10	20	95 (80)	–
2		p-$NO_2C_6H_4$	10	20	94 (80)	–
3			10	20	92 (91)	8
4			10	20	87 (75)	10
5			120	80–90	60	20
6			120	80–90	75 (55)	15

[a] Yields were determined by TLC on Silufol UV-254 and UV-spectroscopy. Isolated yields are given in parentheses.

From a synthetic viewpoint it was of interest to study the cross-coupling reactions of organomercurials, $(A)_2$ Hg, with the ArI-containing heterocyclic moiety which yield bi-heterocyclic compounds. The reactions of bis(2-thienyl)mercury and bis(5-methyl-2-furyl)mercury with 2-iodopyridine proceed under mild conditions (within 10 min.) to give the cross-coupling products in high yields (92% and 87%, respectively) along with small quantities of the homo-coupling products (8% and 10%, respectively) (Reactions 4 and 5, Table 1, entries 3 and 4).

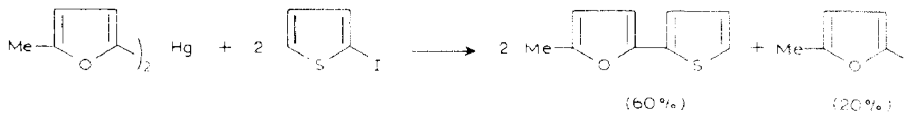


(4)

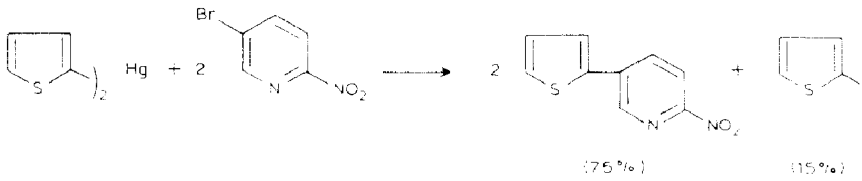


(5)

However in the case of 2-iodothiophene and (5-bromo-2-nitro)pyridine the cross-coupling reactions proceed slowly (2 h) at elevated temperature (80–90 °C) (reactions 6 and 7, Table 1, entries 5 and 6). A little more of the homo-coupling products was obtained as compared with that produced by the reaction of 2-iodopyridine (reactions 4 and 5).



(6)



(7)

Experimental

In a typical procedure 2.5 ml of DMF, 0.3 g (0.002 mol) of NaI, 0.250 g (0.001 mol) of p-$NO_2C_6H_4I$, 0.201 g (0.00055 mol) of bis(2-thienyl)mercury and 0.00879 g (0.00001 mol) of p-$NO_2C_6H_4PdI(PPh_3)_2$ were placed in a 5 ml round bottom flask and the slurry was stirred vigorously under argon. After 10 min, TLC on Silufol UV-254 and UV-spectroscopy showed that the mixture contained 94% of 2-(p-nitrophenyl)thiophene. The reaction mixture was diluted with 10 ml of water and extracted with 3 × 5ml of ether. The ether extracts were combined, and washed with an aqueous solution of NaI. The ether layer was dried over $MgSO_4$ and then evaporated to dryness to give 0.165 g (80%) of the product, m.p. 137–138°C [6].

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