Journal of Organometallic Chemistry, 405 (1991) C29–C31
Elsevier Sequoia S.A., Lausanne
JOM 21647PC

Preliminary communication

Palladium-mediated *ortho*-alkylation of 2-aryloxazolines

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(Received October 18th, 1990)

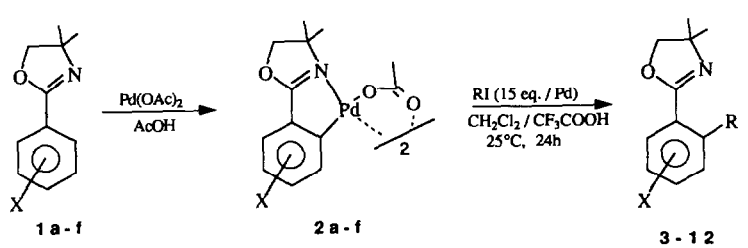
Abstract

The regioselective *ortho*-alkylation of 2-aryloxazolines through the reaction of their cyclopalladated complexes with 1-iodoalkanes is described. Depending upon the experimental conditions, either 2- or 2,6-substituted derivatives can be selectively prepared.

The chemistry of cyclometallated compounds has been extensively studied during the past two decades [1]. Among them, cyclopalladated complexes have proved to be valuable intermediates for the regio- and stereoselective formation of carbon–carbon bonds [2]. Their carbonylation and vinylation reactions have been thoroughly investigated [3], as well as the insertions of alkynes into the metal–carbon bond [4]. However, the reaction of cyclopalladated complexes with alkyl halides has only been little studied [5].

We recently described the reaction of palladium acetate with various 2-aryloxazolines **1** that give rise to the metallacycles **2** (Scheme 1) [6]. Exploitation of the synthetic potential of oxazolines continues to provide novel routes to various organic molecules owing to the easy synthesis of these heterocycles from carboxylic acid derivatives and their subsequent conversion into esters, aldehydes, ketones, etc. [7].

We present here our results of a study of the regioselective synthesis of a series of 2-(2-alkyl)aryloxazolines, **3**–**12**, via the reaction of preformed palladium complexes



Scheme 1.

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Table 1

ortho-Alkylated aryloxazolines **3–12** from cyclopalladated complexes **2a–f**

Complex	X	R	Product [a]	Yield (%) [b]
2a	H	CH_3	**3**	96 (86)
2a	H	CH_2=$CHCH_2$	**4**	88 (81)
2a	H	n-C_4H_9	**5**	52 (46)
2b	6-CH_3	CH_3	**6**	89 (83)
2b	6-CH_3	C_2H_5	**7**	84 (78)
2c	6-n-C_4H_9	CH_3	**8**	90 (84)
2d	6-OCH_3	CH_3	**9**	83 (76)
2e	4-OCH_3	CH_3	**10**	92 (82)
2f	4,5-OCH_3	CH_3	**11**	90 (84)
2f	4,5-OCH_3	CH_2=$CHCH_2$	**12**	92 (80)

[a] All new compounds have spectral and analytical data in agreement with the proposed structure. [b] GLC yields. Between parentheses are the isolated yields, based on the cyclopalladated complex, after purification by flash chromatography on silica gel.

2 with iodoalkanes (Scheme 1). Thus, treatment of the di-μ-acetato-bis[2-(4′,4′-dimethyl-2-oxazolinyl)phenyl-1-*C*,3′-*N*] dipalladium **2a** (X = H) with an excess of iodomethane (15 equiv.) in a CH_2Cl_2/CF_3COOH mixture affords the *ortho*-methylated oxazoline **3** in 86% isolated yield. The scope of this reaction has been investigated using various ring substituted complexes **2a–f** in conjunction with several alkyl iodides. The results are listed in Table 1.

Several points are noteworthy:

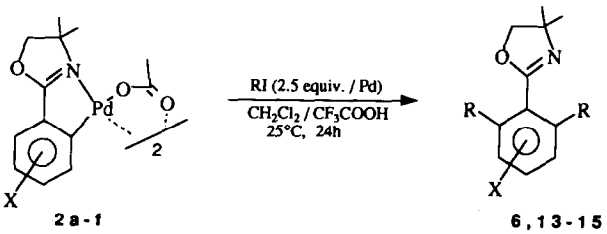
(a) Good yields of *ortho*-alkylated aryloxazolines are generally achieved from methyl, ethyl or allyl iodides. However, protodepalladation [8] becomes a significant side reaction when the less reactive 1-iodobutane is used.

(b) The competitive formation of the 2,6-alkylated aryloxazoline (*vide infra*) is eliminated only when a large excess of alkyl halides is used. In the case of less volatile iodoalkanes (i.e. n-BuI) the remaining starting material is easily recovered during the purification step.

(c) The cyclopalladation/alkylation of 2-aryloxazolines complements the known lithiation/alkylation approach described by Meyers [7], because of the different chemio- and regio-selectivities. While the alkylation of the *ortho*-tolyloxazoline **1b** occurs exclusively at the benzylic position in the lithiation pathway, the 6-substituted derivative is obtained via palladation (**2b** → **6–8**). The methoxy moiety of *ortho*-anisyloxazoline is substituted by lithio reagents, whereas alkylation takes place through palladium (**2d** → **9**). Finally, a different regioselectivity is observed for the 3,4-dimethoxyphenyloxazoline **1f**, for which alkylation is achieved at the more acidic 2 position via lithiation but at the less sterically hindered 6 position via palladation (**2f** → **11,12**).

(d) The introduction of different substituents at the 2- and 6-positions of the aromatic ring is feasible by carrying out two successive palladation/alkylation sequences. Thus, after the preparation of the *ortho*-substituted oxazolines **3** or **5** from **1a** (via the cyclopalladated complex **2a**), further reaction with palladium acetate leads to the complexes **2b** or **2c**, which can, in turn, be alkylated to **6**, **7** or **8**.

By modification of the experimental conditions, symmetrical 2,6-dialkylated aryloxazolines **6**, **13–15** (Scheme 2) have been selectively prepared in a one-pot



Scheme 2.

Table 2

Symmetrical 2,6-dialkylated aryloxazolines from complexes **2**

Complex	R	Product	Yield (% isolated)	Di-/monoalkylated
2a	CH_3	**6**	58	8.3:1
2a	n-C_4H_9	**13**	54	5.4:1
2e	CH_3	**14**	62	7.8:1
2f	CH_3	**15**	9	0.2:1

synthesis. Thus, a slow (2 h) addition of a slight excess of the electrophile (2.5 equiv./Pd) to a solution of the complexes **2** in a CH_2Cl_2/CF_3COOH mixture produces the disubstituted oxazolines in fair yields, suggesting an alkylation/palladation/alkylation sequence. The presence of a substituent at the 5 position of the aromatic nucleus (Table 2, complex **2f**) seems unfavourable for the palladation step, and the monoalkylated derivative remains the major product.

Two plausible mechanisms can account for this alkylation reaction, namely (i) an oxidative addition/reductive elimination pathway and (ii) an S_N2-type reaction taking place at the *ipso*-carbon of the aryloxazoline palladium trifluoroacetate intermediate. The complete abscence of arylated derivative when the condensation is carried out with iodobenzene seems to favour the last hypothesis.

In summary, a simple and efficient preparation of 2- and 2,6-substituted aryloxazolines is described. This procedure nicely complements the work of Tremont et al. concerning the alkylation of anilines and benzaldehyde via cyclopalladation [5], and provides a useful tool in the synthesis of highly substituted aromatic compounds.

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