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A novel palladium intramolecular diaryl ether formation

Roberto Olivera, Raul SanMartin and Esther Domínguez*

Kimika Organikoa Saila, Zientzi Fakultatea, Euskal Herriko Unibertsitatea, PO Box 644, 48080 Bilbao, Spain

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Abstract

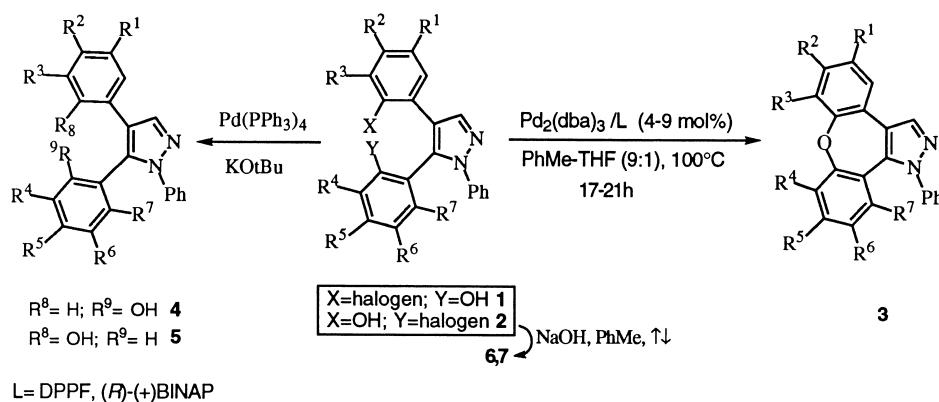
This paper presents an efficient methodology for the preparation of dibenzoxepino[4,5-*d*]pyrazoles using a novel intramolecular palladium catalyzed diaryl ether formation. The effect of different chelating ligand systems, along with the unusual coupling reaction of phenoxides with aryl iodides and non-activated aryl moieties are also reported. © 2000 Elsevier Science Ltd. All rights reserved.

Due to the wide range of biological properties exhibited by dibenzoxepine drugs their use is widespread. Some of these drugs have a heterocyclic moiety fused to the dibenz[*b,f*]oxepino framework.^{1,2} Encouraged by the potential pharmacological applications of such molecules,^{2,3} and following our ongoing research on the chemistry of diaryl substituted heterocycles,⁴ and their biaryl coupling reactions leading to new phenanthroheterocyclic systems,⁵ we planned a challenging approach to dibenzoxepino fused heterocycles from adequately *o,o'*-hydroxyhalosubstituted diaryl heterocycles via a final biaryl ether coupling step. In this context, the recent advances in practical palladium catalyzed carbon–heteroatom coupling methodologies⁶ have provided useful alternatives to copper mediated (Ullmann)⁷ and direct nucleophilic substitution,⁸ which usually require a large excess of reagent, strongly polar solvents, harsh reaction conditions or highly activated aryl halides.⁹ However, the scope of the palladium catalyzed diaryl ether synthesis is still limited and the influence of the catalytic system are difficult to be predicted, as the crucial step, the C–O bond forming reductive elimination of ethers from the palladium complex remains as a substrate dependant process.¹⁰ In fact, very few examples of this recent reaction have been reported up to date, all of them performed in an intermolecular fashion.¹¹

In this paper we wish to report the results obtained when Pd catalyzed C–O bond-forming coupling procedures (Buchwald–Hartwig reaction) were applied to the preparation of dibenzoxepino[4,5-*d*]pyrazoles.

Our initial assays were based on the procedure developed by Gingras et al. for the preparation of molecular wires.¹² Thus, phenolic diarylpyrazoles **1** and **2**¹³ were treated with KO^tBu and Pd(PPh₃)₄ as catalyst, but only the corresponding dehalogenated products **4** and **5** were obtained (66–77% yield) (Scheme 1).

* Corresponding author.



Scheme 1.

We then focussed our attention on the use of bulky, chelating phosphine ligands such as BINAP¹⁴ and DPPF¹⁵ which could significantly accelerate the reductive elimination step, as it has previously proposed.^{11a,16} Besides, in order to employ better oxygen nucleophiles, phenoxide derivatives **6** and **7** were prepared by treatment of phenols **1** and **2** under standard procedures and immediately submitted to the reaction conditions indicated below,¹⁷ affording the target dibenzoxepino[4,5-*d*]pyrazole tetracycles **3**¹⁸ with the results summarized in Table 1.

Table 1
Synthesis of dibenzoxepinopyrazoles **3**

Substrate	X	Y	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	Product	[Pd] ^a	t(h)	Yield (%) ^c
6a	I	ONa	H	H	H	H	H	H	H	3a	4 (6.5) ^b	17.5	69 (51) ^d
6b	I	ONa	H	H	H	H	NEt ₂	H	H	3b	5 (7.5) ^b	19	54 (44) ^c
6c	I	ONa	OMe	OMe	H	H	OMe	H	OMe	3c	9 (9) ^b	48	-- ^e
6d	I	ONa	OMe	OMe	H	OMe	OMe	H	H	3d	7 (9) ^b	18.5	16 (21) ^d
6e	Br	ONa	OMe	OMe	H	OMe	OMe	H	H	3d	7.5 (9) ^b	21	41 (24) ^d
7a	ONa	I	Cl	H	H	H	H	H	H	3e	4 (7) ^b	17	56 (44) ^d
7b	ONa	I	Cl	H	Cl	H	H	H	H	3f	4 (8) ^b	17	49 (41) ^d
7c	ONa	I	H	H	H	H	OMe	OMe	H	3g	5 (8.5) ^b	18.5	62 (51) ^d

^a Stoichiometry of the catalyst (mol %) employed when DPPF was used as chelating ligand

^b Figures in parenthesis refer to the stoichiometry of the catalyst (mol %) when (R)-(+)-BINAP was used as chelating ligand.

^c Isolated yield obtained when DPPF was used as chelating ligand

^d Yields in parenthesis refer to the isolated yield when (R)-(+)-BINAP was used as chelating ligand

^e Only traces of the target compound were observed by GC/MS

Although the use of both BINAP and DPPF bidentate ligands, which have slightly different bite angle values,¹⁹ provided dibenzoxepines **3**, better results were obtained when DPPF was used as the catalyst chelating ligand. Otherwise, considering that the reported outcomes constitute the first example of an intramolecular palladium catalyzed diaryl ether synthesis so far, it should be also pointed out not only the moderate to good yields obtained from the reaction of iodide derivatives **6a**, **6b**, **6d** and **7a-c**,²⁰ but also the observed coupling of electron rich or neutral

haloarenes **6–7**. These significant, unusual features are the consequence of the intramolecular nature of the reported reaction, as the high constraint generated in the corresponding oxidative addition intermediate would be released by the otherwise difficult reductive elimination process. The latter theory would also explain the lack of reactivity of pyrazole **6c**, since the steric hindrance induced by the methoxy ($R^7 = \text{OMe}$) and *N*-phenyl substituents could even avoid the displacement of the halide ligand to form the corresponding octacyclic Ar-Pd-OAr' complex.²¹ On the other hand, the comparison of the obtained results from the coupling of substrates **6d** and **6e** suggests that the presence of an electron-donating substituent *ortho* to the hydroxy group might difficult the formation of the latter intermediate, probably due to the unstability of the initially formed aryl palladium(II) halide, which is more remarkable in the case of iodide derivative **6d**. This behaviour of aryl iodides for this type of transformation has been previously reported.^{11b}

To sum up, a series of new dibenzoxepino[4,5-*d*]pyrazoles has been obtained by a convenient palladium catalyzed C–O coupling reaction of *o,o'*-halohydroxysubstituted diarylpyrazoles. This novel palladium catalyzed intramolecular diaryl ether formation has been carried out with two different chelating ligands, affording moderate to good yields of the target tetracycles prepared by coupling of phenoxides with non-activated arene and aryl iodide moieties.

We are currently investigating the expansion of the scope of the coupling conditions set up to other diaryl heterocyclic systems, as well as trying to develop new palladium catalytic systems for related transformations.

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14. BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl.
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17. Typical procedure: 1-Phenyldibenzo[2,3:6,7]oxepino[4,5-*d*]pyrazole **3a**. Ground NaOH (0.023 g, 0.56 mmol) was added to a stirred solution of pyrazole **1a** (0.222 g, 0.51 mmol) in dry toluene (14 cm³) under argon at room temperature. After refluxing for 30 min, the mixture was allowed to cool without stirring. The resulting supernatant orange solution of phenoxide **6a** was separated from the precipitate by transferring via cannula to an empty flask and degassed by bubbling argon through it for 20 min. A mixture of Pd₂(dba)₃ (16.5 mg, 0.018 mmol) and DPPF (mg, 0.072 mmol) in dry, degassed THF (1.6 ml) was stirred for 20 min and added dropwise to the previously prepared solution of fenoxide **6a**. This reaction mixture was heated to 100°C for 17 h, and after cooling, it was filtered through Celite[®] and the solid washed with THF. Evaporation of the solvents in vacuo afforded a yellow oil which was purified by flash chromatography using 20% hexane/CH₂Cl₂ as eluent, providing dibenzoxepine **3a** (0.109 g, 69%) as a white powder.
18. Selected data of representative dibenzoxepino[4,5-*d*]pyrazole **3a**: 250 MHz ¹H NMR (CDCl₃) δ 6.81 (1H, dd, *J* = 7.9, 1.6 Hz, H_{arom}), 6.94 (1H, ddd, *J* = 8.1, 7.9, 1.6 Hz, H_{arom}), 7.20–7.52 (10H, m, H_{arom}), 7.57 (1H, dd, *J* = 6.9, 1.6 Hz, H_{arom}) and (1H, s, H-3); 63 MHz ¹³C NMR (CDCl₃) δ 120.3 (C_{arom}-C, C-4), 121.5, 122.3 (C_{arom}-H), 122.9 (C_{arom}-C, C-4), 124.7, 125.1, 125.5, 127.0, 127.9, 128.6, 128.7, 129.2, 130.2 (C_{arom}-H), 136.2 (C_{arom}-N), 137.9 (C-3), 140.2 (C-12b), 155.9, 156.5 (C_{arom}-O); EIMS (*m/z* %) 310 (M⁺, 100), 281 (12), 206 (12), 151 (8), 127 (7), 77 (12). Anal. calcd for C₂₁H₁₄N₂O: C, 81.27; H, 4.55; N, 9.03. Found: C, 81.39; H, 4.64; N, 9.17.
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20. The observed GC/MS yields for dibenzoxepinopyrazole **3b** were 64 and 51% when DPPF and BINAP were the chelating ligands, respectively. The difference between the observed and isolated yields is adduced to the resinous nature of the product and the substrate, which made the purification of the target compound considerably difficult.
21. Similar intermediates have been proposed in the arylation of alkoxides and phenoxides. See Ref. 11b–c