

Pd- and Cu-catalyzed selective Arylation of Benzotriazole

Irina P. Beletskaya^{a*}, Dmitri V. Davydov^a, Marcial Moreno-Mañas^b

^a Chemical Department of Moscow State University, Leninsky Gory, Moscow, 119899, GSP-3, Russia.

^b Department of Chemistry, Universitat Autònoma de Barcelona, Bellaterra, 08193-Barcelona, Spain.

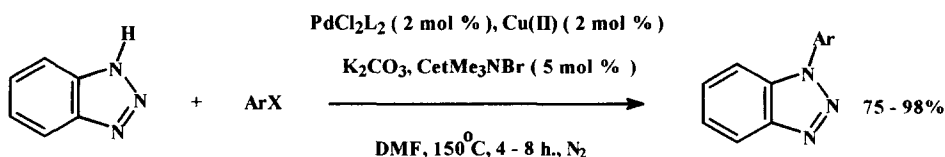
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Abstract: Palladium(0)-catalyzed arylation of 1*H*-1,2,3-benzotriazole (BTA) in DMF at 150°C in the presence of copper salt with arylhalides proceeds regioselectively at N-1 position. Best result has been obtained with the PdCl₂(dppe) as catalyst and the Cu(II) phenylcyclopropylcarboxylate as co-catalyst.

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1-Aryl-1*H*-1,2,3-benzotriazoles are useful synthons in some versions of the Graebe-Ullmann reaction,¹ especially in pyridoacridine^{1g} and carbolin synthesis,² for the preparation of tetraazapentalenes.³ However direct arylation of BTA is known only for the activated aryl halides.^{3,4} For the arylation of azoles by less reactive aryl halides classical Ullmann condensation is used.⁵ However BTA arylation requires much more drastic conditions^{5f} and thus it is often complicated by decomposition of products.¹ In this case for the synthesis 1-aryl-BTA the three step method is usually used, which involves the arylation of ortho-nitroanilines, reduction of nitro-group and diazotization followed by cyclization.^{2b, 2d} The alternative method involve the reaction of aryl azides with benzyne.^{1f} Additional possibility is to use Cu-catalyzed reaction of BTA with ArPb(OAc)₃, but it proceeds with very low yield and selectivity.⁶

Herein we propose direct regioselective Pd-catalyzed BTA arylation in the presence of copper salts under phase transfer (PT) conditions :



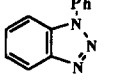
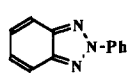
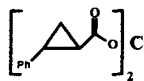
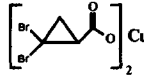
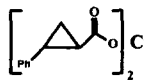
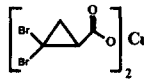
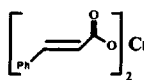
ArX = PhI, *p*-FC₆H₄I, *p*-ClC₆H₄I, *p*-BrC₆H₄I, *p*-IC₆H₄I, *p*-MeC₆H₄I, *p*-MeOC₆H₄I,

2-BrC₃H₄N, 3-BrC₃H₄N, 3-BrC₃H₆N, 2-IC₄H₃S, *p*-NCC₆H₄I, *p*-MeCOC₆H₄I, *p*-EtOOC₆H₄I

L = DPPM, DPPE, DPPP, DPPB, DPPF

The optimisation data obtained are compiled in Table 1.

Table 1. The Arylation of BTA catalyzed by PdCl₂L₂^a (2 mol %) and Copper salt^b (2 mol %) in DMF^c in the presence of Base and PT catalyst^d (5 mol %) at 150 °C.

NN	PdCl ₂ L ₂	Base and PT catalyst	Copper salt	Time h.	Product yields % and N-1/N-2 ratio ^f	
						
1	PdCl ₂ (dppe)	K ₂ CO ₃ or KOH CetMe ₃ NBr or 18-Crown-6	-	8	61 - 59.5	30.5 - 31.5
					1.94 - 1.95	
2	PdCl ₂ (dppb)	K ₂ CO ₃ , CetMe ₃ NBr	-	8	57	29.5
					1.98	
3	PdCl ₂ (dppm)	K ₂ CO ₃ , CetMe ₃ NBr	-	8	50	25
					2.00	
4	PdCl ₂ (dppf)	K ₂ CO ₃ , CetMe ₃ NBr	-	8	55	29
					1.90	
5	PdCl ₂ (dppe)	K ₂ CO ₃ , CetMe ₃ NBr	CuI	8	90	4
					22.5	
6	PdCl ₂ (dppe)	K ₂ CO ₃ , CetMe ₃ NBr		6	98	-
7	PdCl ₂ (dppe)	K ₂ CO ₃ , CetMe ₃ NBr		6	97	-
8	-	K ₂ CO ₃ , CetMe ₃ NBr		6	No reaction	
9	-	K ₂ CO ₃ , CetMe ₃ NBr		6	No reaction	
10	PdCl ₂ (dppe)	K ₂ CO ₃ , CetMe ₃ NBr		6	No reaction	

^a) Such catalysts as PdCl₂(PPh₃)₂ or Pd(PPh₃)₄ gave low yields of the products. ^b) Cu(II)-salts were synthesised by reaction of corresponding Na-salts of carboxylic acids with CuSO₄·5H₂O in water. ^c) No reaction was observed in toluene, THF or H₂O. ^d) In absence of the PT catalyst reaction proceeds but requires much longer time. ^e) N-1/N-2 ratio and yields of the products were obtained after the separation of the reaction mixture aliquots by TLC spectroscopically (UV-Vis).⁷

We have found that arylation of BTA by PhI catalyzed by PdCl₂(dppe) in the presence of K₂CO₃ or KOH and phase transfer agent CetMe₃NBr or 18-crown-6 in refluxing DMF⁸ gives the mixture of two isomers (N-1 and N-2) in good yields in a near to statistical ratio 2:1 (Tab.1, entry 1). Earlier the mixture of allylation products has been observed in Pd-catalyzed reaction of BTA by allyl carbonate or acetate.⁸

The problems of selectivity has been solved by the addition of catalytic amount copper salts to reaction mixture. In the presence of CuI major product was N-1 (90 %) and only 4 % of N-2 was found (Tab.1,entry 5).

Interesting results have been obtained in the presence of Cu(II)-salts of cyclopropanecarboxylic acids. Only N-1 arylation product was found in reaction mixture (Tab.1, entries 6,7). These salts are stable at room temperature, but easily decompose on heating to 100° C and higher, producing very active low-valent Cu-species. However these copper salts gave no coupling product without Pd-catalyst (Tab.1, entries 8,9). No reaction has been observed in the presence of other copper salts of organic acids, for example Cu(II) cinnamate (Tab.1, entry 10). The absence of reaction can be explained by the fact that this salt does not decompose and can oxidize Pd(0).

Table 2. The Arylation of BTA catalyzed by PdCl₂(dppe) (2 mol %) and Cu(II) cyclopropylcarboxylate (2 mol %) with ArX and HetX in DMF in the presence of K₂CO₃ and CetMe₃NBr (5 mol %) at 150 °C.

NN	ArX	Time h. ^a	Product Yields % ^b
1	PhI	6	98
2	<i>p</i> -FC ₆ H ₄ I	6	93
3	<i>p</i> -ClC ₆ H ₄ I	6	95
4	<i>p</i> -BrC ₆ H ₄ I	6	90
5	<i>p</i> -IC ₆ H ₄ I	6	94
6	<i>p</i> -MeC ₆ H ₄ I	8	95
7	<i>p</i> -MeOC ₆ H ₄ I	8	92
8	<i>p</i> -CNC ₆ H ₄ I	4	97
9	<i>p</i> -MeCOC ₆ H ₄ I	4	96
10	<i>p</i> -EtO ₂ CC ₆ H ₄ I	4	94
11	<i>m</i> -CF ₃ C ₆ H ₄ I	4	98
12	2-BrC ₃ H ₄ N	4	89
13	3-BrC ₃ H ₄ N	4	87
14	3-BrC ₉ H ₆ N	4	90
15	2-IC ₄ H ₃ S	8	94

^a) Time of reaction can be decreased by preliminary reduction of PdCl₂(dppe) with NaBH₄ in EtOH especially for reaction with aryl halides bearing electron-donating substituents. ^b) All products were characterized by NMR, MS and elemental analysis.

We have carried out the reaction of BTA with different aryl and hetaryl halides at optimal conditions. High yields and selectivity have been obtained for aryl halides with both electron-donating and electron-withdrawing groups and some heterocyclic halides (Tab. 2).⁹ Double substituted product has been obtained in the reaction of BTA with diiodobenzene in the reagents ratio 2 : 1 (Tab.2, entry 5).

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- Synthetic procedure:** The mixture of 0.001 mol of BTA, 0.001 mol of K₂CO₃, 5 mol % of CetMe₃NBr, 2 mol % of PdCl₂(dppe), 2 mol % of CuX₂ and 0.001 mol of ArX was heated at reflux in 20 ml of anhydrous and degassed DMF under N₂ for 4-8 h. (TLC control). Reaction mixture was treated by slightly acidified water, extracted by CH₂Cl₂. Extract was washed by water, dried over MgSO₄, passed through the layer of silica and evaporated. The residue was recrystallized from appropriate solvent .

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