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Palladium- and copper-catalyzed selective arylation of 5-aryltetrazoles by diaryliodonium salts[†]

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Abstract—Palladium(0)-catalyzed arylation of 5-aryltetrazoles in *t*-BuOH at 80°C with diaryliodonium salts proceeds in the presence of copper(II) phenylcyclopropyl carboxylate regioselectively at the N2 position. © 2002 Elsevier Science Ltd. All rights reserved.

2,5-Diaryltetrazoles are used as convenient precursors to a variety of nitrogen containing heterocycles[2] and for the preparation of tetrazolium salts possessing well-known biological activity.[3] Common methods for the synthesis of 2,5-diaryltetrazoles involve multistep procedures based on various cyclization protocols.[4–7] Thus, the development of a direct regioselective arylation of easily available 5-aryltetrazoles[8] at the N2 position of the tetrazole ring would be a desirable alternative. Generally, arylation can proceed forming two isomers—a 1,5-diaryltetrazole (**N1**) and a 2,5-diaryltetrazole (**N2**) (Scheme 1).

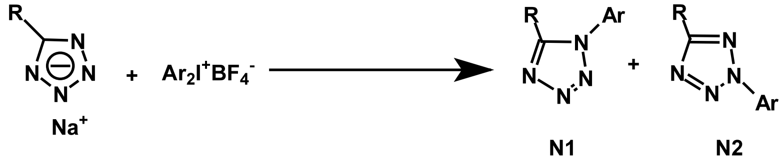
Recently, two methods for regioselective N2-arylation of 5-aryltetrazoles by $ArB(OH)_2$[9] or by $Ar_3Bi(OAc)_2$[10] in the presence of $Cu(OAc)_2$ were published. However the first method gives modest yields of 2,5-diaryltetrazoles, while in the second two aryl groups of the arylation agent are wasted.

Continuing our research on the Pd-catalyzed regioselective arylation of azoles,[11,12] we have discovered that sodium salts of 5-aryltetrazoles undergo regioselective arylation at the N2 position by diaryliodonium salts in the presence of the palladium catalyst, $Pd(dba)_2$/*rac*-BINAP, and a Cu(II) carboxylate salt in *t*-BuOH as shown below (Scheme 2).

The optimization of reaction conditions has been performed using 5-phenyltetrazole and $Ph_2I^+BF_4^-$. The data obtained are presented in Table 1.

Though the arylation of the Na-salt of 5-phenyltetrazole by $Ar_2I^+BF_4^-$ takes place in the absence of a catalyst,[13] the reaction is slow and non-selective (Table 1, entry 1). The use of stoichiometric amounts of the Cu(II)-salt (copper(II) phenylcyclopropyl carboxylate) leads to a dramatic increase of selectivity but the yields remain low (Table 1, entry 2). The use of $Cu(OAc)_2$ was unsuccessful.

On the other hand the addition of a Pd-catalyst ($Pd(dba)_2$/bidentate ligand) gave acceleration of reaction and an increase in yields to nearly quantitative, with *rac*-BINAP being particularly affective, although the product contains the minor **N1**-arylation isomer (Table 1, entries 3–6) Thus, it seemed sensible to explore the synergistic effect of Cu(II) on selectivity and



Scheme 1.

Keywords: 5-aryltetrazoles; arylation; Pd-catalysis; regioselectivity; iodonium salts; Cu(II).

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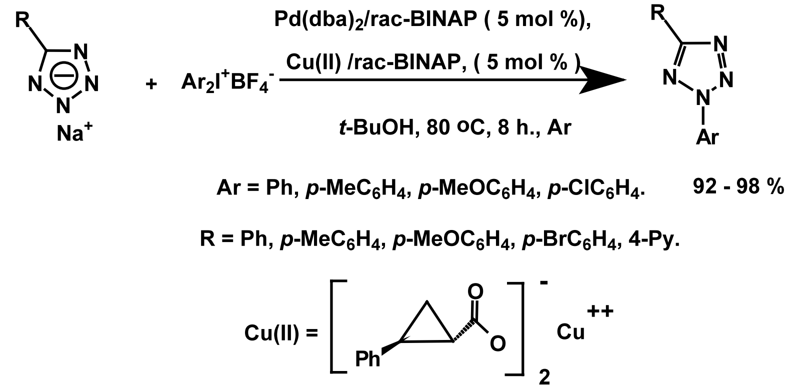

Scheme 2.

Table 1. Arylation of the Na-salt of 5-phenyltetrazole by $Ar_2I^+BF_4^-$ at 80°C in *t*-BuOH

N	Catalyst (mol%)	Ligand	Time (h)	Ratio of **N2**:**N1** isomers[a]	Yield of **N2**+**N1** isomers (%)[a,b]
1	–	–	18	~50:50	42
2	Cu(II) (100)	–	18	100:0	35
3	$Pd(dba)_2$ (5)	DPPE	6	50:10	92
4	$Pd(dba)_2$ (5)	DPPB	6	60:10	94
5	$Pd(dba)_2$ (5)	DPPF	6	85:10	95
6	$Pd(dba)_2$ (5)	*rac*-BINAP	6	90:10	98
7	$Pd(DBA)_2$ (5), Cu(II) (5)	*rac*-BINAP	6	100:0	98
8	$Pd(DBA)_2$ (5)	L_2	18	–	No product

[a] **N2**:**N1** ratio and yields of the products were measured by spectrophotometry after separation of reaction mixture aliquots by TLC.

[b] All products were characterized by NMR and MS spectra in good accordance with literature data.[4–7]

Table 2. Regioselective arylation of Na-salts of some 5-aryltetrazoles by various diaryliodonium salts catalyzed by $Pd(dba)_2$/*rac*-BINAP (5 mol%) and Cu(II)-salt (5 mol%) in *t*-BuOH at 80°C

N	5-Aryltetrazole	$Ar_2I^+BF_4^-$	Yield of **N2** (%)[a,b]
1	5-(C_6H_5)-Tetrazole	$Ph_2I^+BF_4^-$	98
		$(p\text{-}CH_3C_6H_4)_2I^+BF_4^-$	97
		$(p\text{-}CH_3OC_6H_4)_2I^+BF_4^-$	94
		$(p\text{-}ClC_6H_4)_2I^+BF_4^-$	97
2	5-(*p*-$CH_3C_6H_4$)-Tetrazole	$Ph_2I^+BF_4^-$	93
		$(p\text{-}CH_3C_6H_4)_2I^+BF_4$	94
		$(p\text{-}CH_3OC_6H_4)_2I^+BF_4$	90
		$(p\text{-}ClC_6H_4)_2I^+BF_4^-$	92
3	5-(*p*-$CH_3OC_6H_4$)-Tetrazole	$Ph_2I^+BF_4^-$	94
		$(p\text{-}CH_3C_6H_4)_2I^+BF_4^-$	93
		$(p\text{-}CH_3OC_6H_4)_2I^+BF_4$	93
		$(p\text{-}ClC_6H_4)_2I^+BF_4^-$	97
4	5-(*p*-BrC_6H_4)-Tetrazole	$Ph_2I^+BF_4^-$	97
		$(p\text{-}CH_3C_6H_4)_2I^+BF_4$	96
		$(p\text{-}CH_3OC_6H_4)_2I^+BF_4^-$	94
		$(p\text{-}ClC_6H_4)_2I^+BF_4^-$	97
5	5-(4-Py)-Tetrazole	Ph_2IBF_4	95
		$(p\text{-}CH_3C_6H_4)_2I^+BF_4$	96
		$(p\text{-}CH_3OC_6H_4)_2I^+BF_4^-$	93
		$(p\text{-}ClC_6H_4)_2I^+BF_4^-$	97

[a] Yields of the products isolated by preparative TLC.

[b] All products were characterized by NMR, MS and elemental analysis and are in a good agreement with the published data.

Pd on the yield. Indeed the combination of Pd and Cu complexes in catalytic amounts has resulted in the development of a high-yielding regiospecific procedure (Table 1, entry 7). We used the same copper salt (the easy available Cu(II) phenylcyclopropyl carboxylate) which already had proven its effectiveness in the early developed procedures for regioselective arylation of benzotriazole.[11,12] However, while in the latter case both Ar-groups of iodonium salts were incorporated the product, in the arylation of 5-aryltetrazoles only one residue is transferred. We were not able to perform the arylation of 5-phenyltetrazole by ArI or ArBr as all catalyst systems tried proved ineffective (Table 1, entry 8).

This procedure has been applied successfully for arylation of a series of 5-aryltetrazoles bearing both electron-donating or electron-withdrawing substituents.[14] The data are gathered in Table 2.

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14. **Synthetic procedure**: A mixture of the Na-salt of 5-aryltetrazole obtained from 0.001 mol of 5-aryltetrazole and 0.001 mol of *t*-BuONa, 2 mol% of $Pd(dba)_2$, 4 mol% of *rac*-BINAP, 2 mol% of the Cu(II)-salt and 0.001 mol of $Ar_2I^+BF_4^-$ was heated under reflux in 20 ml. of *t*-BuOH under N_2 for 8 h (TLC control). The reaction mixture was evaporated and residue was extracted by CH_2Cl_2. The extract was passed through a layer of silica and evaporated. The residue was recrystallized from an appropriate solvent.