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Regioselective arylation of *N*-tributylstannylated 5-substituted tetrazoles by diaryliodonium salts in the presence of $Cu(OAc)_2$

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Abstract—The arylation of *N*-tributylstannylated 5-substituted tetrazoles with diaryliodonium salts at room temperature without base in CH_2Cl_2 in the presence of stoichiometric amounts of $Cu(OAc)_2$ proceeds regioselectively at the *N*-2 position of the tetrazole ring.

New catalytic methods of C–N bond formation have attracted attention over recent years due to the huge synthetic potential of these approaches[1–3] and the mild conditions required in comparison with the classical Ullmann reaction[4] particularly for labile substances such as 2,5-disubstituted tetrazoles, which demonstrate a broad spectrum of biological activity[5] and which are used as a convenient source of nitrylimines.[6] The most successful method of 2,5-disubstituted tetrazoles synthesis is the direct regioselective introduction of the required substituent at C(2) of readily available 5-substituted tetrazoles. Herein, we propose a mild and convenient method of regioselective arylation of readily available *N*-tributylstannylated 5-substituted tetrazoles[7,8] with diaryliodonium salts in the presence of $Cu(OAc)_2$ under neutral conditions.

Within the framework of reactions between stannylated tetrazoles and arylation agents, it is possible to identify different variations of 2,5-disubstituted tetrazole synthesis. These include the thermal arylation of substrates,[9] the Pd-catalyzed arylation of *N*-stannylated compounds,[10,11] and the arylation of *N*-tributylstannylated 5-substituted tetrazoles by boron[12] and bismuth[13] organoelement compounds in the presence of $Cu(OAc)_2$. Optimization of the reaction conditions was performed using *N*-tributylstannylated 5-phenyltetrazole as substrate.[7] The optimization data are summarized in Table 1.

First of all we considered the possibility of thermal reactions of the chosen substrate with the diphenyliodonium salt used earlier for arylation of the Na-salt of 5-tolyltetrazole.[9] It was shown that this process can be realized only on heating in high boiling solvents, such as *o*-xylene where fast decomposition of the product is observed (Table 1, entry 1) resulting in low yields.

The first example of Pd-catalyzed C–N bond formation by arylation of dialkylaminotrialkylstannanes with PhBr was published by Migita in 1983.[10] However, we failed to realize arylation by this way using *N*-stannylated 5-phenyltetrazole under a broad variety of reaction conditions (Table 1, entry 2) in good accordance with later data of the Migita group during attempts to arylate *N*-stanylated imines.[11]

Using *p*-tolylboronic acid,[12,13] as the arylation agent, arylation was also unsuccessful (Table 1, entry 3). It was shown that $Ph_3Bi(OAc)_2$[14] has a low activity as an arylation agent (Table 1, entry 4), moreover its large molecular weight and the fact that only one Ph-group can take part in the arylation process makes it an

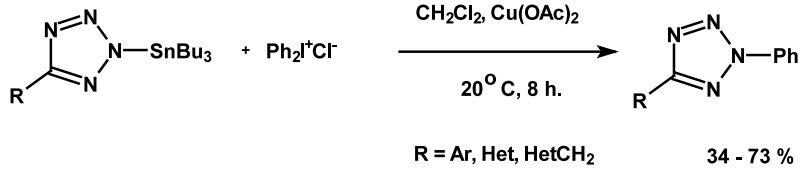

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Table 1. Arylation of *N*-tributylstannylated 5-phenyltetrazole under various conditions

N	Arylation agent	Catalyst, equiv.	Solvent, *T* (°C)	Reaction time (h)	2,5-Diphenyltetrazole yield (%)[a]
1	$Ph_2I^+BF_4^-$	–	*o*-Xylene, 144	1	Tars (traces of product)
2	PhI (PhBr)	'Pd'[b], 0.05	Solvent,[c] 20	8	No product
3	*p*-TolB(OH)$_2$	$Cu(OAc)_2$, 1.1	CH_2Cl_2, 20	16	No product
4	$Ph_3Bi(OAc)_2$	$Cu(OAc)_2$, 1.1	CH_2Cl_2, 20	8	Low yield
5	$Ph_2I^+BF_4^-$	Cu_2Hal_2,[d] 1.1	CH_2Cl_2 20	8	No product
6	$Ph_2I^+BF_4^-$	$Cu(OAc)_2$, 1.1	CH_2Cl_2, 20	8	75
7	$Ph_2I^+Cl^-$	$Cu(OAc)_2$, 1.1	CH_2Cl_2, 20	8	72

[a] Yields of the products were measured spectroscopically (UV–vis) after the separation of aliquots of the reaction mixture by TLC.
[b] Various complexes of Pd(O) and Pd(II) were used.
[c] EtOH, $C_6H_5CH_3$, CH_3CN, DMFA were applied as solvents.
[d] Cu(I) halides initiate slow decomposition of $Ph_2I^+BF_4^-$.

inefficient reagent for arylation. Cu(I) salts are not active as promoters of the arylation reaction (Table 1, entry 5).

During the course of these studies we found that arylation of *N*-tributylstannylated 5-phenyltetrazole does occur with $Ph_2I^+BF_4^-$ in the presence of $Cu(OAc)_2$ in CH_2Cl_2 at room temperature producing 2,5-diphenyltetrazole in high yield (Table 1, entry 6). We also found that $Ph_2I^+BF_4^-$ can be replaced by the less expensive $Ph_2I^+Cl^-$ without a decrease in the product yields (Table 1, entry 7). The results of arylation of some *N*-stannylated tetrazoles under these conditions are presented in Table 2.

The data included in Table 2 show that stanylated 5-aryltetrazoles containing alkyl substituents in the aromatic ring, for example a methyl group (Table 2, entry 2), or a halogen atom, such as Br (Table 2, entry 3), react readily with $Ph_2I^+Cl^-$. However, the presence of an electron-withdrawing group in the aromatic ring, for example an NO_2 group, prevented the arylation process (Table 2, entry 6). Similarly a negative result was observed when a 4-pyridyl fragment was in the 5-position of the tetrazole ring (Table 2, entry 7). Thus, the success of the reaction probably depends on the Red–ox potential of the stannylated tetrazole according to classical mechanism of R_4Sn oxidation by $Cu(OAc)_2$.[15]

The reaction conditions found were used for obtaining some biologically active tetrazoles containing the indole fragment in the 5-position of the tetrazole ring. *N*-Stannylated 5-(3-indolyl)tetrazole reacted readily with $Ph_2I^+Cl^-$ giving 2,5-disubstituted tetrazole in high yield (Table 2, entry 4). The introduction of a methylene bridge between the indole and tetrazole parts of the substrate led to a decrease in the product yield (Table 2, entry 5). With a benzhydryl substituent at the 5-position of the tetrazole ring no arylation product was observed (Table 2, entry 9). Probably the result of this reaction also depends on the stability of the radical which is formed on the first oxidative stage of the process. This radical must be intercepted by $Ph_2I^+Cl^-$ in order for the reaction to proceed.[16] The ion-radical mechanism can be demonstrated with a benzhydryl substituent in the 5-position of the tetrazole ring (Table 2, entry 8), when addition of *p*-dinitrobenzene leads to disappearance of the arylation product in the reaction mixture. The details of reaction mechanism are under investigation.

Thus, this method allows the direct regioselective arylation of *N*-stannylated tetrazoles under mild and neutral conditions.

Synthetic procedure: To 0.001 mol of *N*-tributylstannylated 5-substituted tetrazole and 0.001 mol of $Ph_2I^+Cl^-$

Table 2. Arylation of *N*-tributylstannylated tetrazoles with $Ph_2I^+Cl^-$ in the presence of $Cu(OAc)_2$ in CH_2Cl_2 at 20°C

N	Substituent at the 5-position of the substrate[a]	Reaction time (h)	Isolated yield of 2,5-disubstituted tetrazole (%)
1	Ph	8	70
2	*p*-$CH_3C_6H_4$	8	65
3	*p*-BrC_6H_4	8	73
4	3-(1*H*-Indol-3-yl)	8	68
5	3-(1*H*-Indol-3-ylmethyl)	8	34
6	*p*-$NO_2C_6H_4$[b]	16	No product
7	4-Py[b]	16	No product
8	3-(1*H*-Indol-3-ylmethyl)[c]	16	No product
9	3-[1*H*-Indol-3-yl(phenyl)methyl]	16	No Product

[a] All substrates were obtained by known methods and their spectral characteristics were in good agreement with literature data.
[b] We did not observe products of arylation even under reflux with an excess of $Cu(OAc)_2$ over 16 h.
[c] In the presence of 1 equiv. of *p*-dinitrobenzene.

in 10 ml dry CH_2Cl_2, 0.0012 mol of $Cu(OAc)_2$ was added and the mixture was stirred under dry N_2 for 8 h (TLC control). The reaction mixture was then passed through a layer of silica and evaporated. The residue was recrystallized from CCl_4.

3-(2-Phenyl-2*H*-1,2,3,4-tetrazol-5-yl)-1*H*-indole

Yield 68%; mp 154–156°C from CCl_4; ^1H NMR (CD_3CN, 200 MHz, δ_H (ppm), J_{HH} (Hz)): 7.28 (m, 1H, $H(5)_{ind}$), 7.31 (m, 1H, $H(6)_{ind}$), 7.58 (m, 1H, $H(7)_{ind}$), 7.58 (m, 1H, *p*-Ph), 7.66 (m, 2H, *m*-Ph), 8.11 (m, 1H, $H(2)_{ind}$, 2.75), 8.23 (m, 2H, *o*-Ph), 8.36 (m, 1H, $H(4)_{ind}$), 9.83 (broad s, 1H, NH); MS (EI, 70 eV, m/z, I_r,%): 261 $[M]^+$ (11), 233 $[M-N_2]^+$ (100). Anal. found: C, 68.75; H, 4.12; N, 26.46. Calcd for $C_{15}H_{13}N_5$: C, 68.95; H, 4.24; N, 26.80%.

3-[(2-Phenyl-2*H*-1,2,3,4-tetrazol-5-yl)methyl]-1*H*-indole

Yield 34%; mp 123.5–125°C from CCl_4; ^1H NMR (CD_3CN, 200 MHz, δ_H (ppm), J_{HH} (Hz)): 4.45 (s, 2H, CH_2), 7.05 (m, 1H, $H(5)_{ind}$), 7.15 (m, 1H, $H(6)_{ind}$), 7.23 (m, 1H, $H(2)_{ind}$, 2.20), 7.41 (m, 1H, $H(7)_{ind}$), 7.60 (m, 3H, *p*-Ph, *m*-Ph), 7.60 (m, 1H, $H(4)_{ind}$), 8.05 (m, 2H, *o*-Ph), 9.19 (br s, 1H, NH); MS (EI, 70 eV, m/z, I_r,%): 261 $[M]^+$ (11), 233 $[M-N_2]^+$ (100). Anal. found: C, 68.75; H, 4.12; N, 26.46. Calcd for $C_{15}H_{13}N_5$: C, 68.95; H, 4.24; N, 26.80%.

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