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Regioselective N^1- or N^2-modification of benzotriazoles with iodonium salts in the presence of copper compounds

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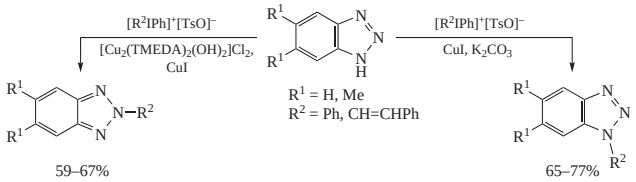
Modification of benzotriazoles with iodonium salts [diphenyl- and (*E*)-styrylphenyliodonium tosylates] occurs at the N^1-position in the presence of K_2CO_3 as a base and CuI as a catalyst in CH_2Cl_2, whereas in the presence of stoichiometric amount of $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ complex regioselective N^2-modification proceeds. Two new Cu^I complexes based on benzotriazoles were synthesized and their crystal structures were determined by X-ray powder diffraction analysis.



N^1-Modified benzotriazoles (BTAs) are of interest for their broad synthetic use[1] and high biological and pharmacological activity.[2] In contrary, 2-N-substituted benzotriazoles are known as UV-protectors and organic electronic materials.[3] Classical methods for the synthesis of N-modified BTAs are typically multistage. The key stage for N^1-arylated BTAs synthesis includes the cyclization of *o*-amino-*N*-arylanilines in the course of diazotation.[4] Alternatively, they are accessed by chemoselective addition of organoazides to benzynes.[5] Syntheses of N^2-arylated BTAs are based on decomposition of *C*,*N*-diaryl tetrazoles,[3(a),6] 2-(*o*-azidophenyl)diazenylarenes[7(a),(b)] or on reductive cyclization of 2-(*o*-nitrophenyl)-diazenylarenes with thiourea,[7(c)] SmI_2,[7(d)] Zn,[7(e),(f)] and *via* P^{III}/P^{V}=O catalyst recycling in the presence of $PhSiMe_3$.[7(g)]

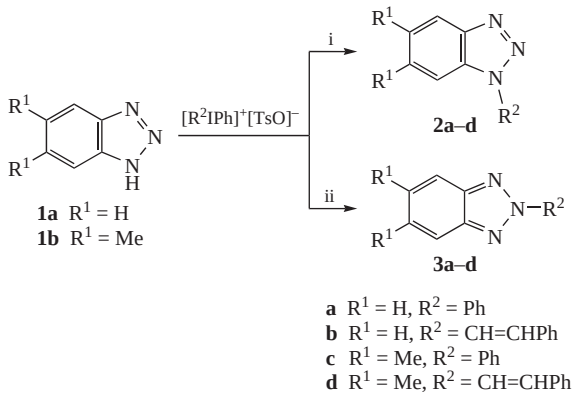
Traditional methods of cyclization leading to N-arylated BTAs can be implemented using transition metal catalysis. For example, N^1-arylated BTAs can be obtained by catalytic cyclization of various *ortho*-halogenated 1,3-diaryltriazenes or from resin-linked *o*-(arylamino)benzotriazenes in the presence of copper[8] or palladium catalysts,[9(c),(d)] or by Pd-catalyzed CH-activation of diaryltriazenes.[10] N^2-Arylated BTAs can be synthesized by copper(II)-catalyzed oxidative cyclization of *o*-aminodiphenyldiazenes[11(a)] or *o*-halodiphenyldiazenes with azide group in the presence of CuI.[11(b)] Modern approaches to N^2-arylated BTAs are based on CH-activation of diaryldiazenes and relative compounds catalyzed by palladium(II)[3(a)] and rhodium(III).[12] However, the complexity of multistage processes are the main disadvantage of the reported cyclization reactions.

The direct arylation of BTAs with iodonium salts occurring either as nucleophilic substitution[13(a),(b)] or *via* the aryne mechanism is practically unselective.[13(c)] N^1-Vinylated BTAs can be obtained by condensation of the corresponding N-derivatives of BTAs possessing active methylene groups with carbonyl compounds using Wittig,[14(a)] Peterson,[14(b)] or Horner–Wadsworth–Emmons[14(c)] reactions.

In view of N^1 and N^2 regioselectivitty and procedure convinience, transition metal-catalyzed amination reaction of aryl-(vinyl)halides with BTAs seems most challenging.[15] The absence of regioselectivity giving mixtures of N^1- and N^2-isomers[16] under harsh reaction conditions is reported. Other source[17] shows formation of practically single N^1-isomers,[17] but also under drastic conditions. The same trend is observed in the vinylation of BTAs. Two N-vinylation protocols are described: the one with formation of mixture of by-products and *N*-vinyl isomers[18(a)] and the other with regioselective N^1-vinylation.[18(b)]

Earlier we have investigated the regioselective arylation of ambident azoles of high NH-acidity with iodonium salts.[19] In the present work, we propose two protocols for both regioselective N^1- and N^2-modifications of benzotriazoles with iodonium salts (see ref. 20) under mild conditions in the presence of copper compounds. In the course of careful optimization with broad variation of arylation agents, bases, additives and solvents, we have found that regioselective N^1-arylation and vinylation of benzotriazoles with diphenyl- or (*E*)-styryl(phenyl)iodonium salts (Scheme 1) readily occurs in CH_2Cl_2 with K_2CO_3 as the base in the presence of CuI as catalyst at room temperature (Table 1, entries 1–4).† On the contrary, in the presence of 0.5 mol of $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ (for the structure, see ref. 21) serving as both the base and complexing additive, with the iodonium salts and CuI being introduced within 15 min after the additive, mostly the N^2-modification took place (see Table 1, entries 5–8).‡ However, if the iodonium salt and CuI were added after one hour following the additive, predominantly N^1-isomers were formed though in very low yields. The same results were obtained when pure complexes **4a** or **4b** isolated from reaction

† *General procedure for the synthesis of N^1-modified benzotriazoles* **2a**–**d**. Copper(I) iodide (0.05 mmol) in CH_2Cl_2 (30 ml) was added to a mixture of substrate **1a** or **1b** (0.5 mmol), anhydrous K_2CO_3 (0.55 mmol) and diphenyl- or (*E*)-styrylphenyliodonium tosylate (0.55 mmol) under argon after 5–6 min of stirring. The resulting mixture was stirred under argon for 12 h at room temperature and then filtered. The filtrate was dried ($MgSO_4$) and purified by flash chromatography through basic alumina (eluent CH_2Cl_2). The eluate was evaporated and the main product was isolated by preparative chromatography on Merck silica gel plates (UV-254) using ethyl acetate–*n*-hexane (1:6) as a solvent system. In the large scale (5 mmol) experiments, the main products were isolated and purified by crystallization from EtOH.



1a R^1 = H
1b R^1 = Me

a R^1 = H, R^2 = Ph
b R^1 = H, R^2 = CH=CHPh
c R^1 = Me, R^2 = Ph
d R^1 = Me, R^2 = CH=CHPh

Scheme 1 *Reagents and conditions*: i, K_2CO_3, 5% CuI, CH_2Cl_2, ~20 °C, 12 h; ii, 50% $[Cu_2(TMEDA)_2(OH)_2]Cl_2$, 5% CuI, CH_2Cl_2, ~20 °C, 12 h.

Table 1 N-modification of benzotriazoles **1a**,**b** with iodonium salts $[R^2IPh]^+[TsO]^-$.[a]

Entry	Sub-strate	R^2 in iodonium salt	Co-reagent	Products		Yield[b] (%)	**2**:**3** ratio[c]
				N^1	N^2		
1	**1a**	Ph	K_2CO_3	**2a**	**3a**	65	15:1
2	**1a**	PhCH=CH	K_2CO_3	**2b**	**3b**	77	18:1
3	**1b**	Ph	K_2CO_3	**2c**	**3c**	69	20:1
4	**1b**	PhCH=CH	K_2CO_3	**2d**	**3d**	58	19:1
5	**1a**	Ph	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	**2a**	**3a**	59	1:16
6	**1a**	PhCH=CH	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	**2b**	**3b**	62	1:18
7	**1b**	Ph	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	**2c**	**3c**	67	1:20
8	**1b**	PhCH=CH	$[Cu_2(TMEDA)_2(OH)_2]Cl_2$	**2d**	**3d**	61	1:19

[a] Conditions: 5% CuI, CH_2Cl_2, ~20 °C, 12 h, argon. [b] Isolated total yield after column chromatography. [c] NMR data.

mixture were used as substrates in the absence of reagent and catalyst.

We suppose that initially the $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ additive reacts with substrates **1** to form complexes with BTAs anions involved as μ-ligand bonded *via* N^1- and N^3-atoms. Such complexes were earlier suggested to be involved in corrosion protection of Cu-surface in the presence BTA[22] (Figure 1). Due to such a manner

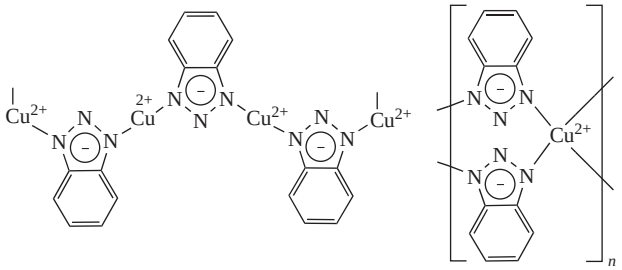


Figure 1 The expected structures of kinetically controlled benzotriazole complexes.

‡ *General procedure for the synthesis of N^2-modified benzotriazoles* **3a**–**d**. Copper(I) iodide (0.05 mmol) in CH_2Cl_2 (30 ml) was added to a mixture of substrate **1a** or **1b** (0.5 mmol), $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ (0.25 mmol) and diaryl- or (*E*)-styrylphenyliodoniun salt (0.55 mmol) in CH_2Cl_2 (30 ml)after 15 min of stirring. The mixture was stirred for 12 h under argon atmosphere at room temperature, then treated with 10% aqueous NH_3 and extracted several times with CH_2Cl_2. The extract was dried ($MgSO_4$) and purified by flash chromatography through basic alumina (eluent CH_2Cl_2). The eluate was evaporated and the main product isolated by preparative chromatography on Merck silica gel plates (UV-254) using ethyl acetate–*n*-hexane (1:6) as a solvent system. In the experiment of 1 mmol scale, the main product was isolated and purified by crystallization from EtOH.

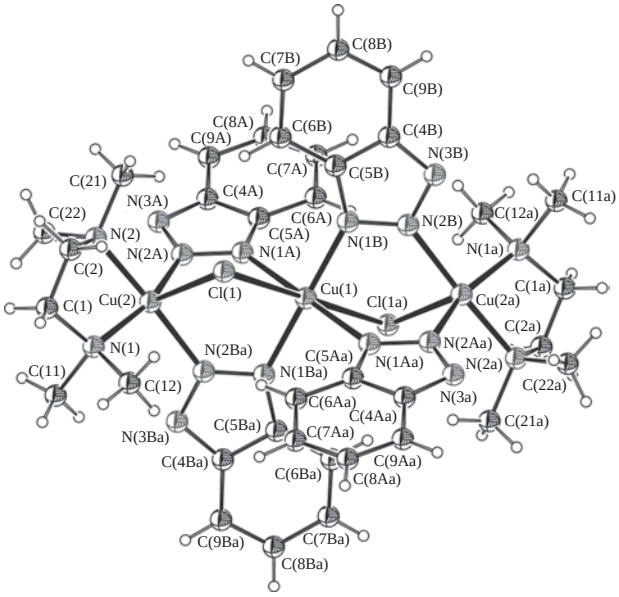


Figure 2 Molecular structure of complex $C_{36}H_{48}Cl_2N_{16}Cu_3$ **4a**.

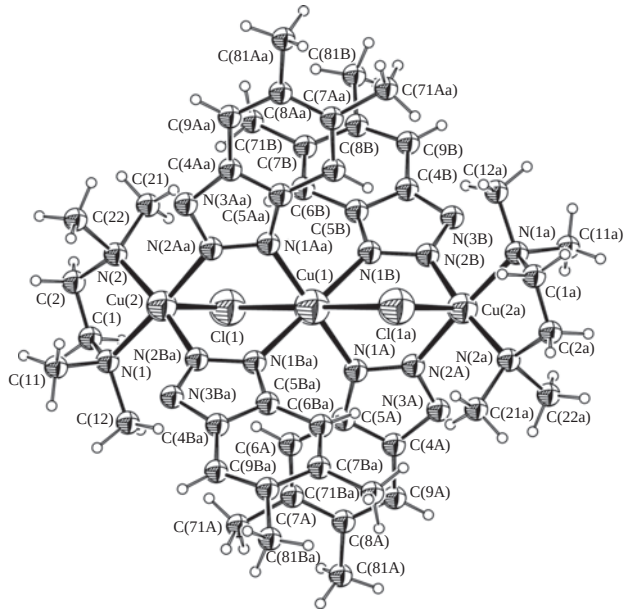


Figure 3 Molecular structure of complex $C_{44}H_{64}Cl_2N_{16}Cu_3$ **4b**.

of binding, N^2-atom of BTA becomes available for reaction with iodonium salts. Probably, these complexes are kinetically controlled species that are further transformed to thermodynamically controlled complexes such as **4a** (Figure 2) and **4b** (Figure 3)[§,¶]

§ *Complexes* **4a**,**b**. $[Cu_2(TMEDA)_2(OH)_2]Cl_2$ powder (0.01 mmol) was added to a solution of **1a** or **1b**·H_2O (2 μmol) in CH_2Cl_2 (30 ml). After 10 min of stirring, the mixture was filtered and the filtrate was kept in a refrigerator overnight. The blue microcrystals were collected, washed with THF and CH_2Cl_2 and dried *in vacuo*.

¶ *Crystal data for* **4a**: $C_{36}H_{48}Cl_2N_{16}Cu_3$ (M = 966.45), monoclinic, space group $P2_1/n$, at 295 K: a = 15.7709(14), b = 12.2614(12) and c = = 11.3651(11) Å, β = 108.627(17)°, V = 2082.6(4) Å^3, Z = 2, d_{calc} = = 1.541 g cm^{-3}, μ(CuKα) = 3.354 mm^{-1}, $R_p/R_{wp}/R_{exp}$ = 0.0343/0.0446/0.0149.

Crystal data for **4b**: $C_{44}H_{64}Cl_2N_{16}Cu_3$ (M = 1078.64), monoclinic, space group $P2_1/c$ at 295 K: a = 12.7381(12), b = 11.9853(11) and c = 17.3467(15) Å, β = 108.223(17)°, V = 2515.5(4) Å^3, Z = 2, d_{calc} = = 1.424 g cm^{-3}, μ(CuKα) = 2.835 mm^{-1}, $R_p/R_{wp}/R_{exp}$ = 0.0435/0.0602/0.0399.

CCDC 1563239 and 1563250 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

which are similar to the previously obtained,[23] but proved to be inert in reactions of this type.

In summary, a herein developed convenient method allows one to perform direct regioselective modification of BTAs with various iodonium salts at either N^1 or N^2 sites under mild conditions. The regioselectivity is believed to result from differences in coordination between copper complexes used.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.05.019.

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