Reactivity of 2-Aminothiazole and 2- or 6-Aminobenzothiazole Derivatives Towards the Triphenylbismuth Diacetate/Catalytic Copper Diacetate Phenylation System

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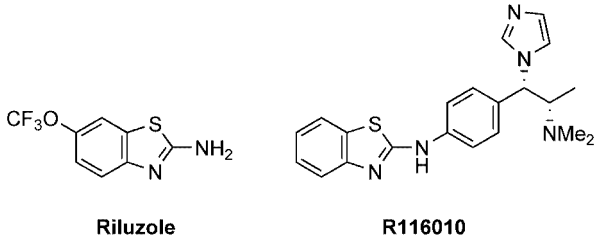
The copper diacetate catalysed reaction of triphenylbismuth diacetate with 6-aminobenzothiazole compounds afforded selectively the 6-phenylamino derivatives in good to high yields. A similar reaction with 2-aminothiazole or 2-aminobenzothiazole compounds gave mixtures of the monophenylated and diphenylated products 2-phenylaminothiazole and 2-(*N*-phenylamino)-3-*N*′-phenylthiazole derivatives, respectively, with the diphenyl product being predominant. Semi-empirical calculations with the SAM1/D and CHAIN methods performed on the evolution of a 2-aminobenzothiazole – copper(III) intermediate were in good qualitative agreement with the experimental results.

Introduction

Thiazole and benzothiazole derivatives have attracted continuing interest over the years because of their varied biological activities.[1,2] Among them, the 2-amino series was studied in the 1950s as a muscle relaxant acting under the central nervous system (CNS).[3] Interest in that series was revived by the recent discoveries of Riluzole (2-amino-6-trifluoromethoxybenzothiazole), a blocker of excitatory amino acid-mediated neurotransmission[4,5] and of R116010, a 2-(*para*-substituted phenylamino)benzothiazole which acts as a potent selective inhibitor of all-*trans*-retinoic acid metabolism.[6] (Scheme 1).

Among the various possible routes for the synthesis of R116010, an attractive approach is the convergent coupling of 2-aminobenzothiazole with an aryl derivative bearing a leaving group. However, aromatic nucleophilic substitution under either Goldberg, basic or palladium-catalysed conditions failed to give satisfactory results.[6]



Scheme 1. Structures of Riluzole and R116010

As an extension of our recent studies on the organobismuth-mediated copper-catalysed *N*-arylation of heterocyclic amines,[7] we decided to investigate the reaction of various aminothiazole derivatives with the triarylbismuth diacetate/copper diacetate system which is one of the mildest for *N*-arylation reactions.[8,9] It can be realized by using either the trivalent triarylbismuth/stoichiometric copper diacetate system[10,11] or the pentavalent triarylbismuth/catalytic copper diacetate system.[12] In view of the oxidizing properties of copper diacetate, which could lead to a competitive oxidative degradation of the thiazolic substrate, we selected the pentavalent triarylbismuth/catalytic copper diacetate system. Nucleophilic reactions of 2-aminothiazole derivatives take place on either the exocyclic or the endocyclic nitrogen centre, depending on the nature of the electrophile and the reaction conditions.[13] In nucleophilic aromatic substitution reactions of 2-aminothiazole derivatives with strongly activated aryl halides, the regiochemistry is governed essentially by the steric hindrance: the endocyclic nitrogen of the non-substituted 2-aminothiazole is the most

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reactive.[14] However, in the case of 4-substituted 2-aminothiazole and in the 2-aminobenzothiazole series, the exocyclic nitrogen is the most reactive for monoarylation,[15] the *N*,*N*′-diaryl derivative being obtained with an excess of the electrophilic reagent.[16]

Results and Discussion

Phenylation of 6-Aminobenzothiazole Derivatives

In a first series of reactions, the 6-aminobenzothiazole derivatives **1**, **3** and **5** were treated with 1.1 molar equivalents of triphenylbismuth diacetate and 0.1 equivalent of copper diacetate in dichloromethane at room temperature (Scheme 2). The three substrates afforded selectively the corresponding mono *N*-phenyl derivatives **2**, **4** and **6** in moderate to good yields (39−70%). In the case of the 2-methyl derivative **3**, the highest yield of the 6-monophenylaminobenzothiazole derivative **4** was obtained, even though the presence of the 2-methyl substituent could induce the formation of a tautomeric 2-methylenebenzothiazoline isomer leading to the 3-*N*-phenyl derivative by reaction with the triphenylbismuth diacetate/catalytic copper diacetate system.

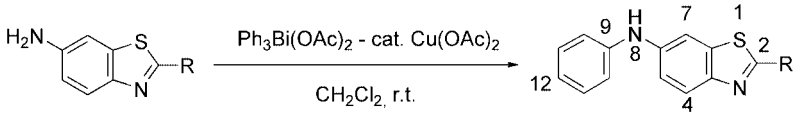
Phenylation of 2-Aminobenzothiazole Derivatives

The copper-catalysed *N*-phenylation reaction of the 2-aminobenzothiazole derivatives **7**, **10** and **13** led to more complex results (Scheme 3). Under classical reaction conditions [triphenylbismuth diacetate (1.1 equiv.)/copper diacetate (0.1 equiv.) in dichloromethane at room temperature], a mixture of two *N*-phenylation products was always obtained in relatively modest yields. One of the compounds was the expected product of monophenylation of the 2-amino group (respectively **8**, **11** and **14**).

The second products were always formed in slightly predominant yields. These compounds (respectively **9**, **12** and **15**), which could have been the 2-diphenylamino derivatives, were in fact found to be monophenylated on both nitrogen atoms, the 2-amino group and the endocyclic N-3 atom, as determined by a detailed NMR study of these compounds. The aromatic protons for both the mono- and the *N*,*N*′-diphenylated compounds were assigned after COSY experiments. The protonated carbon atoms were unambiguously assigned by HMQC correlation experiments, and the HMBC technique was used to show the long-range proton-carbon correlations of the quaternary aromatic carbon atoms. In the case of the 6-fluoro-3-phenyl-2-phenylimino-1,3-benzothiazoline **15**, NOESY experiments confirmed the substitution on the N-3 nitrogen atom by occurrence of cross correlation peaks between the 4-H and 20-H protons, revealing their direct proximity. The absence of correlation peaks between the 10-H and 16-H protons of the two phenyl groups is indicative of the *anti* configuration of the phenyl group present on the N-8 nitrogen atom.

The structures of **14** and **15** were confirmed by X-ray crystallography. The ORTEP drawings[17] of the two structures are shown in Figure 1 and 2 and selected geometrical parameters are collected in Table 1−3 with the respective atom-numbering schemes.

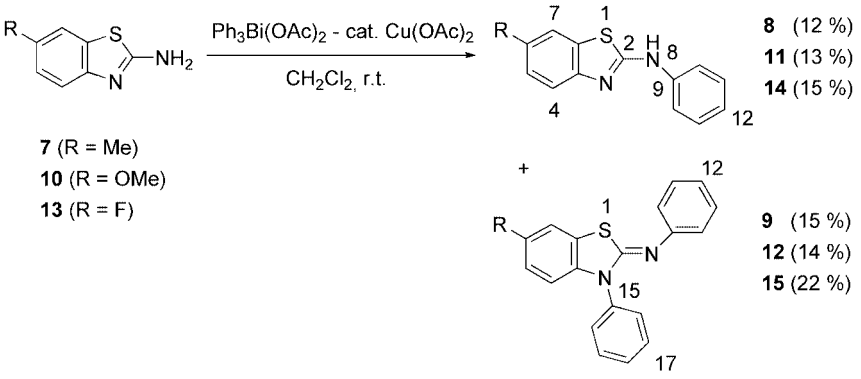
In the case of the *N*-phenyl bonds, similar values of 1.41−1.42 Å are observed for the bond between the exocyclic nitrogen atom and the *ipso* carbon atom, N(22)−C(8) in **14** and N(2)−C(14) in **15** (Table 2). The distances between the exocyclic nitrogen atom and the *ipso*



1 (R = H)
3 (R = Me)
5 (R = NEt_2)

2 (58 %)
4 (70 %)
6 (39 %)

Scheme 2. Phenylation of 6-aminobenzothiazole derivatives **1**, **3** and **5**



7 (R = Me)
10 (R = OMe)
13 (R = F)

8 (12 %)
11 (13 %)
14 (15 %)

9 (15 %)
12 (14 %)
15 (22 %)

Scheme 3. Phenylation of 2-aminobenzothiazole derivatives **7**, **10** and **13**

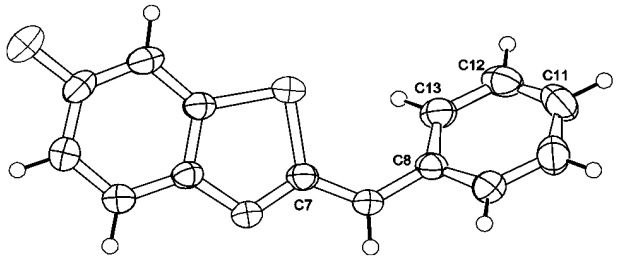


Figure 1. ORTEP view of compound **14**

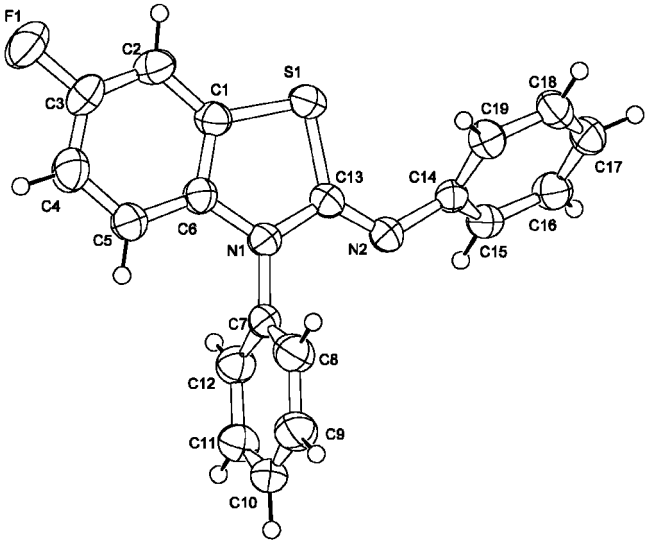


Figure 2. ORTEP view of compound **15**

Table 1. Selected bond lengths (Å) for **14** and **15**

14		**15**	
N(22)−C(7)	1.3515(6)	N(2)−C(14)	1.4095(4)
N(22)−C(8)	1.4194(6)	N(1)−C(7)	1.4419(4)
S(1)−C(7)	1.7662(5)	N(2)−C(13)	1.2729(4)
F(1)−C(3)	1.3632(6)	S(1)−C(13)	1.7868(3)
		F(1)−C(3)	1.3693(4)

Table 2. Selected typical angles (°) for **14** and **15**

14		**15**	
C(7)−N(22)−C(8)	126.85(4)	C(13)−N(2)−C(14)	122.95(2)
C(1)−S(1)−C(7)	88.47(2)	C(13)−N(1)−C(7)	121.66(2)
		C(1)−S(1)−C(13)	91.10(1)

carbon atom of the thiazole moiety are significantly shorter: 1.3515 Å for N(22)−C(7) in **14** and 1.2729 Å for N(2)−C(13) in **15**. The longest *N*-carbon bond is observed between the endocyclic nitrogen atom and the *ipso* carbon atom of the second phenyl group in **15** [1.4419 Å for N(1)−C(7)]. If we consider the dihedral angles between the planes of the phenyl groups and the thiazole moiety of both molecules, a value of 134.83° is found for the atoms C(7)−N(22)−C(8)−C(9) in the case of **14**, and a value of 133.55° for the corresponding dihedral angle involving the atoms C(13)−N(2)−C(14)−C(15) of **15**. In this latter case, the second phenyl ring linked to the endocyclic nitrogen is twisted with an angle of about 83.37° for the atoms C(13)−N(1)−C(7)−C(8) (Table 4). It must also be noted that, in the *N*,*N*′-diphenyl compound **15**, the two phenyl groups C(14)−C(19) and C(7)−C(12) represented in Figure 2, are in an *anti* position relative to the C(3)−N(1) double bond. Moreover, when the H atoms were treated as riding with a C−H distance of 0.96 Å and an N−H distance of 0.902 Å, adjacent molecules of **14** were found to be linked by a weak N−H···N hydrogen bond between N(1) and H(22) [mean distance of 2.111 Å between N(1) and H(22), distance of 3.0085(6) between N(1) and N(22), and angle of 172.9(5)° for N(22)−H(22)−N(1)]. A strong contact between H(12) and F(1) [mean distance of 3.2086(7) Å between C(12) and F(1), and mean distance of 2.644 Å between H(12) and F(1)] was also observed.

The modest yields obtained in the phenylation of compounds **7**, **10** and **13**, combined with the complete disappearance of the aminobenzothiazole substrate, led us to investigate the influence of the reaction conditions on the yields of the mono and diphenyl derivatives **14** and **15**, formed in the reaction of the 2-aminobenzothiazole derivative **13**. When the phenylation reaction was performed in dichloromethane, the amount of copper diacetate used had only a modest effect on the yields (Table 4, Entries 1 and 2), and a large excess of triphenylbismuth diacetate had to be used to reach a 40% yield of the diphenyl derivative **15** (Table 4, Entry 3). A slightly better selectivity was obtained when the reaction was performed in THF. Although formed in a relatively modest yield (26%), the monophenyl derivative **14** was obtained as the only product when the reaction was performed at room temperature with 1.1 equivalents of the bismuth reagent (Table 4, Entry 6). On the other hand, 39−40% yields of the diphenyl derivative **15** were obtained when 2.2 equivalents of the bismuth reagent was used (Table 4, Entries 7 and 9). However, optimisation of the reaction conditions failed to increase significantly either the selectivity or the overall yields due to the sensitivity of the

Table 3. Dihedral angles between selected atoms (°) of **14** and **15**

14		**15**	
C(7)−N(22)−C(8)−C(13)	−48.31(6)	C(13)−N(2)−C(14)−C(19)	51.93(3)
C(7)−N(22)−C(8)−C(9)	134.83(7)	C(13)−N(2)−C(14)−C(15)	−133.55(4)
		C(13)−N(1)−C(7)−C(8)	83.37(4)
		C(13)−N(1)−C(7)−C(12)	−96.15(4)

Table 4. Phenylation reactions of **13** with $Ph_3Bi(OAc)_2$/$Cu(OAc)_2$

Entry	Solvent	**13** (mmol/mL)	$Ph_3Bi(OAc)_2$ (equiv.)	$Cu(OAc)_2$ (equiv.)	Reaction conditions	**14** [%]	**15** [%]
1	CH_2Cl_2	0.12	1.1	0.1	room temp./5 h	15	22
2	CH_2Cl_2	0.1	1.1	1	room temp./5 h	16	31
3	CH_2Cl_2	0.1	1.1	0.1	reflux/5 h	10	30
4	CH_2Cl_2	0.1	2.2	0.1	room temp./5 h	15	33
5	CH_2Cl_2	0.1	3.3	0.1	room temp./5 h	10	40
6	THF	0.1	1.1	0.1	room temp./5 h	26	0
7	THF	0.3	2.2	0.1	room temp./5 h	12	39
8	THF	0.3	2.2	0.1	room temp./24 h	17	20
9	THF	0.3	2.2	0.1	reflux/5 h	7	40

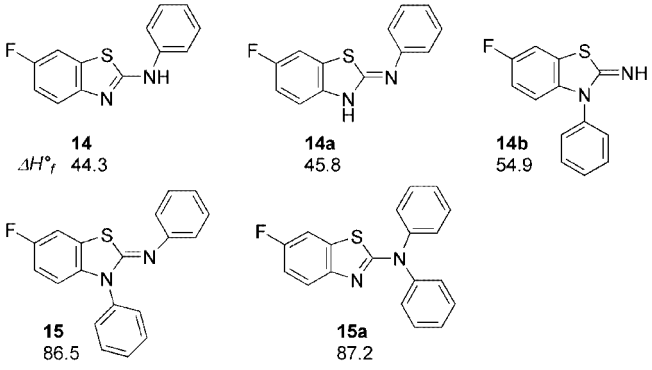
substrate and products towards competitive oxidation reactions.

Phenylation of 2-Aminothiazole

When 2-aminothiazole (**16**) was treated with triphenylbismuth diacetate/catalytic copper diacetate in dichloromethane at room temperature, a mixture of mono- and diphenylated compounds was also obtained. When 1.1 equivalents of the bismuth reagent was used, the monophenyl derivative **17** was isolated in 33% yield and the diphenyl derivative **18** in 29% yield. With an excess of the bismuth reagent (2.2 equivalents), the diphenyl derivative became predominant (55%) with only 9% of the monophenyl derivative being formed (Scheme 4).

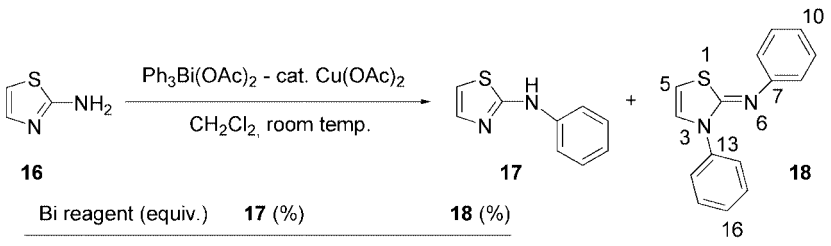
Semi-Empirical Calculations

In an attempt to rationalize the regioselectivity of these diphenylation reactions of either 2-aminothiazole or 2-aminobenzothiazole derivatives, semi-empirical calculations were performed on various isomers of **14** and **15**. The semi-empirical calculations were carried out with the Ampac 6.55 package[18] with the AM1[19] Hamiltonian at the restricted Hartree−Fock (RHF) level on a Silicon Graphics Origin 200 R10000 workstation. After geometry optimisation by application of the Newton−Raphson method (convergence limit of gradient norm of 4.18×10^{-3}, force calculations performed to ensure that the conformations are potential-energy minima), the enthalpies of formation of various isomers of **14** and **15** were calculated (Scheme 5). The 2-(phenylamino)benzothiazole **14** has the lowest enthalpy of formation, but the difference between **14** and **14a** is relatively small ($\Delta\Delta H^0_{f\,\mathbf{14a\text{-}14}} = 1.5$ kcal·mol^{-1}), compared to the 2-imino-3-phenyl-benzothiazoline **14b** ($\Delta\Delta H^0_{f\,\mathbf{14b\text{-}14}} = 10.6$ kcal·mol^{-1}). Thus, formation of the 2-(phenylamino)benzothiazole derivatives appears largely favoured. On the other hand, the difference between the enthalpies of formation of the two diphenyl regioisomers **15** and **15a** is small ($\Delta\Delta H^0_{f\,\mathbf{15a\text{-}15}} = 0.7$ kcal·mol^{-1}), but in favour of the observed product **15**.



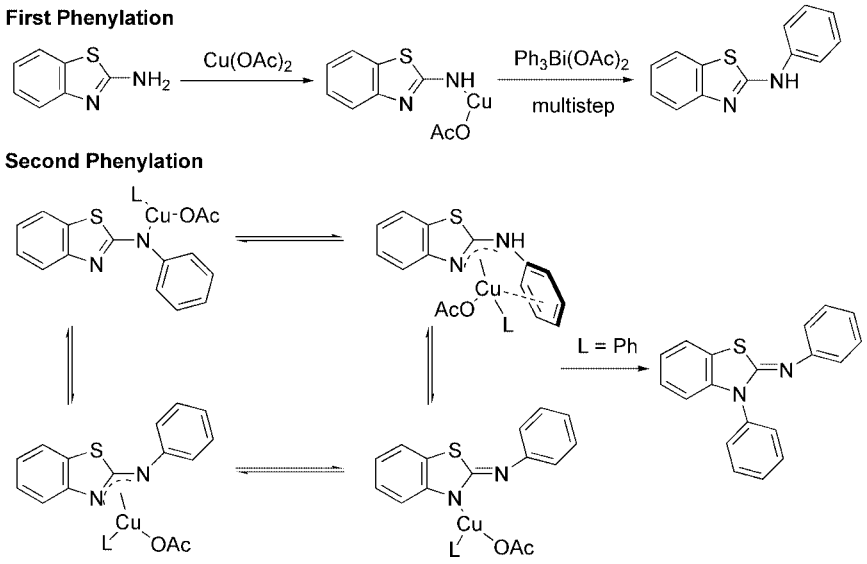
Scheme 5. Enthalpies of formation ΔH^0_f (kcal·mol^{-1}) of different isomers of **14** and **15** after geometry optimisation by AM1 (RHF) semi-empirical calculations

The selective formation of the diphenyl products **9**, **12** and **15** could benefit from two effects. The N=C−N system



Bi reagent (equiv.)	**17** (%)	**18** (%)
1.1	33	29
2.2	9	55

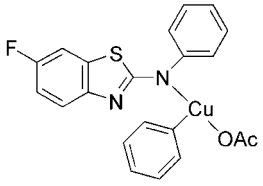
Scheme 4. Phenylation of 2-aminothiazole (**16**)



Scheme 6. Plausible copper intermediates involved in the ligand-transfer step

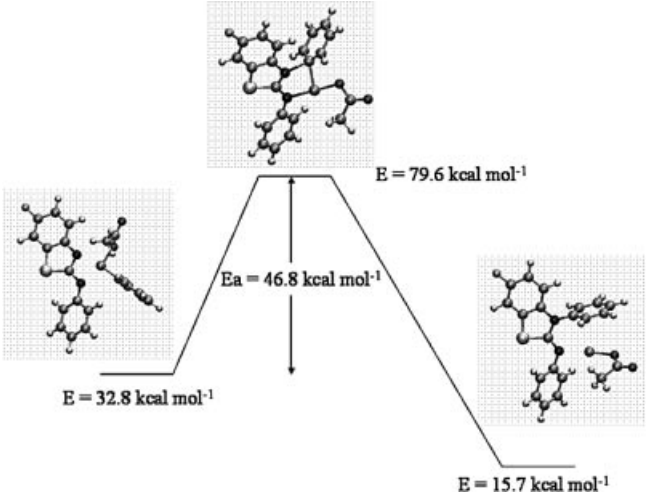
present in the intermediate hypervalent copper species[9,12] can be tridentate with a 1,3-diaza-π-allyl type structure. The copper atom can also enter into a π-interaction with the phenyl group bound to the 2-amino group (Scheme 6). These two interactions could lead to a facilitation of the formation of the diphenyl derivatives, which are predominant over the monophenyl derivatives. Moreover, combination of the difference between the enthalpies of formation of **15** and **15a** with the smaller steric hindrance around the N-3 nitrogen than around the 2-phenylamino group, which can freely rotate around the N−C_{ipso} bond, could be in favour of the formation of the observed product **15**.

However, the mechanism depicted in Scheme 6 implies a kinetic control of the formation of products, whereas the enthalpies of formation of the final products are related to a thermodynamic control. Thus we considered that the enthalpies of formation of the copper intermediates should give a more accurate view, as the evolution of these intermediates should govern the outcome of the overall reaction. Semi-empirical calculations were performed on a postulated hypervalent copper(III) intermediate, with the substrate and the incoming phenyl group being two of the copper substituents.[9,12] (Scheme 7).



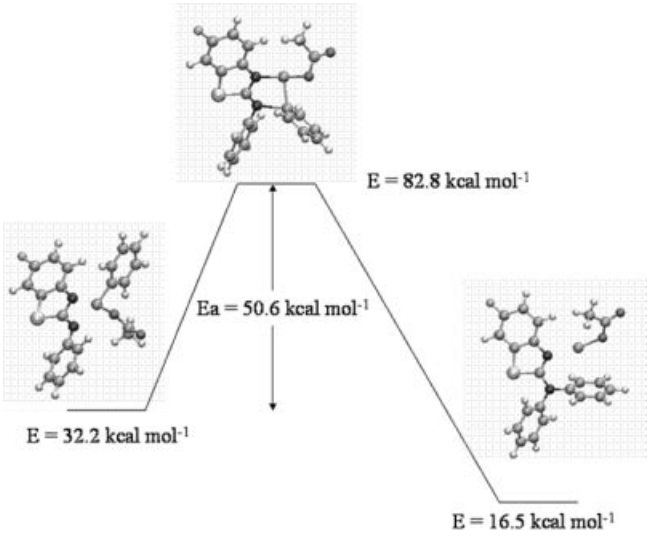
Scheme 7. Model copper(III) intermediate used for the semi-empirical calculations

Semi-empirical SAM1/D calculations[20] were performed with the Ampac 6.55 package. The SAM1/D method was preferred because it is the only method parametrized for the copper atom. First, the structure of the model tricoordinate intermediate was optimised by Newton−Raphson calculations (convergence limit of gradient norm of 4.18×10^{-3}, force calculations performed to ensure that the conformations are potential-energy minima). Then, the two reaction pathways were calculated using the CHAIN method.[21] All transition structures were confirmed by frequency calculations and the corresponding two minima were established by tracing the intrinsic reaction coordinates (IRC).[22] The reaction pathways for the second phenylation on the endocyclic and the exocyclic nitrogen atoms are depicted in Schemes 8 and 9.



Scheme 8. Reaction pathway for the formation of **15**: second phenylation on the endocyclic nitrogen atom

The barrier-height values of the transition states are 79.6 kcal·mol^{-1} for the pathway leading to **15** and 82.8 kcal·mol^{-1} for the pathway leading to **15a**. Five-membered metallacyclic transition states are found on both routes. In the path leading to **15**, the lengths between the copper cen-



Scheme 9. Reaction pathway for the formation of **15a**: second phenylation on the exocyclic nitrogen atom

tre and the nitrogen atoms are: Cu−N(3) 2.59 Å and Cu−N(8) 2.03 Å. In the path leading to **15a**, the corresponding lengths are: Cu−N(3) 2.06 Å and Cu−N(8) 2.60 Å. Moreover, the C_{ipso}−N distances are 2.0 Å [C_{ipso}−N(3)] in the transition state to **15** and 2.06 Å [C_{ipso}−N(8)] in the transition state to **15a**. These calculations show that the second phenylation on the endocyclic nitrogen atom is favoured by a difference of activation energies of 3.8 kcal·mol^{-1}. The values of the enthalpies of formation of the products give the same trends ($\Delta\Delta H_f^0$ = 0.8 kcal·mol^{-1}). These values of the barrier heights are in good agreement with the experimental observations, even if they are of only qualitative value as the actual nature of the key intermediate still remains a matter of speculation.

Conclusion

The reaction of triphenylbismuth diacetate/catalytic copper diacetate with the tautomeric 2-aminothiazole system shows a unique behaviour: *N*,*N*′-diphenylation is favoured over monophenylation of the exocyclic nitrogen atom. This reactivity is in sharp contrast with all the previously reported reactions using this combination of reagents, in which either mono- or diphenylation was possible but completely selective. Moreover, after the first phenylation of the exocyclic nitrogen atom, the second phenylation takes place on the endocyclic nitrogen atom. Semi-empirical AM1 calculations were in qualitative agreement with the experimental regioselectivity. Unfortunately, the overall yields of the products do not reach the range required for industrial preparation of derivatives of this type due to competitive oxidative processes affecting the thiazolic reactants. Moreover, in a recent paper, Knochel et al. reported an interesting alternative approach for the synthesis of 6-(phenylamino)benzothiazoles involving the reaction of an arylmagnesium reagent with 6-nitrobenzothiazole.[23] If applicable to 2-nitrobenzothiazole, this method could also be a valuable alternative to our method, but is unlikely to be useful for the synthesis of the diphenylated derivatives.

Experimental Section

General Remarks: Melting points were recorded with a Büchi Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance 300 spectrometer operating at 300 MHz, using [D$_6$]DMSO (δ_H = 2.48 ppm and δ_C = 39.70 ppm) as solvent unless otherwise stated, and *J* values in Hertz. Combustion analyses were performed in the "Laboratoire de Microanalyse du Centre National de la Recherche Scientifique", Vernaison (France). Column chromatography separations were performed with Merck "Silicagel 60" 60−230 mesh. Ether refers to diethyl ether. All solvents were purified by standard techniques.

General Procedure for the Synthesis of Arylamines. Copper Diacetate Catalysed Phenylation with Triphenylbismuth Diacetate: A mixture of the appropriate aminothiazole (4 mmol, 1 equiv.), $Ph_3Bi(OAc)_2$ (1.1 equiv.) and $Cu(OAc)_2$ (0.1 equiv.) in dichloromethane (10 mL/mmol) was stirred at room temperature during 4 h, unless otherwise stated. The mixture was filtered and the solvent was distilled under reduced pressure to afford an oil which was purified by chromatography on silica gel to give the *N*-phenylation products.

6-Phenylamino-1,3-benzothiazole (2): Elution with ether/pentane (1:1); 0.52 g; 58%; m.p. 142 °C: ^{1}H NMR ($CDCl_3$): δ = 5.89 (s, 1 H, NH), 6.92 (t, *J* = 7.6 Hz, 1 H, 12-H), 7.04 (d, *J* = 8 Hz, 2 H, 10-H and 14-H), 7.11 (m, 1 H, 5-H), 7.24 (t, *J* = 7.7 Hz, 2 H, 11-H and 13-H), 7.53 (m, 1 H, 7-H), 7.92 (d, *J* = 8.6 Hz, 1 H, 4-H) and 8.71 (s, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 108.53 (C-7), 118.90 (C-10), 118.90 (C-5), 122.17 (C-12), 124.38 (C-4), 129.89 (C-11), 135.74 (C-7a), 142.10 (C-6), 143.02 (C-9), 148.41 (C-3a) and 151.48 (C-2) ppm. $C_{13}H_{10}N_2S$ (226.30): calcd. C 69.00, H 4.45, N 12.38; found C 68.79, H 4.66, N 12.50.

2-Methyl-6-phenylamino-1,3-benzothiazole (4): Elution with ether/pentane (1:4); 0.67 g; 70%; m.p. 138−139 °C. ^{1}H NMR: δ = 2.71 (s, 3 H, Me), 6.84 (t, *J* = 7.1 Hz, 1 H, 12-H), 7.12 (d, *J* = 8.3 Hz, 2 H, 10-H and 14-H), 7.14 (m, 1 H, 5-H), 7.24 (t, *J* = 7.6 Hz, 2 H, 11-H and 13-H), 7.63 (m, 1 H, 7-H), 7.74 (d, *J* = 8.8 Hz, 1 H, 4-H) and 8.33 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 19.68 (Me), 107.72 (C-7), 117.06 (C-10), 117.36 (C-5), 120.14 (C-12), 122.47 (C-4), 129.42 (C-11), 136.99 (C-7a), 141.12 (C-6), 143.50 (C-9), 147.16 (C-3a) and 163.15 (C-2) ppm. $C_{14}H_{12}N_2S$ (240.32): calcd. C 69.97, H 5.03, N 11.66; found C 69.76, H 4.92, N 11.42.

2-Diethylamino-6-phenylamino-1,3-benzothiazole (6): Elution with ether/pentane (1:4); 0.46 g; 39%; m.p. 150−151 °C. ^{1}H NMR: δ = 1.18 (t, *J* = 7 Hz, 6 H, Me), 3.49 (q, *J* = 7.1 Hz, 4 H, N−CH_2), 6.72 (t, *J* = 7.2 Hz, 1 H, 12-H), 6.96 (d, *J* = 7.9 Hz, 2 H, 10-H and 14-H), 7.00 (m, 1 H, 5-H), 7.16 (t, *J* = 7.3 Hz, 2 H, 11-H and 13-H), 7.33 (d, *J* = 8.5 Hz, 1 H, 4-H), 7.45 (m, 1 H, 7-H) and 7.96 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 12.94 (Me), 45.07 (CH_2), 110.92 (C-7), 115.36 (C-10), 118.60 (C-12), 129.30 (C-11), 130.80 (C-5), 131.33 (C-4), 136.94 (C-7a), 137.48 (C-6), 145.05 (C-9), 147.78 (C-3a) and 165.12 (C-2) ppm. $C_{17}H_{19}N_3S$ (297.42): calcd. C 68.65, H 6.44, N 14.13; found C 68.81, H 6.67, N 14.27.

6-Methyl-2-phenylamino-1,3-benzothiazole (8) and 6-Methyl-3-phenyl-2-phenylimino-1,3-benzothiazoline (9): Elution with ether/pentane (1:4) afforded **9** and then **8**.

8: 0.11 g; 12%; m.p. 154−155 °C. ^{1}H NMR: δ = 2.37 (s, 3 H, Me), 7.02 (t, *J* = 7.3 Hz, 1 H, 12-H), 7.14 (m, 1 H, 5-H), 7.36 (t, *J* = 7.5 Hz, 2 H, 11-H and 13-H), 7.48 (d, *J* = 8.1 Hz, 1 H, 4-H), 7.55 (m, 1 H, 7-H), 7.76 (d, *J* = 7.8 Hz, 2 H, 10-H and 14-H) and 10.38 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 20.89 (Me), 117.66 (C-10), 118.90 (C-4), 120.93 (C-7), 121.89 (C-12), 126.97 (C-5), 128.99 (C-11), 130.07 (C-7a), 131.57 (C-6), 140.75 (C-9), 150.03 (C-3a) and 160.82 (C-2) ppm. $C_{14}H_{12}N_2S$ (240.32): calcd. C 69.97, H 5.03, N 11.66; found C 69.71, H 5.11, N 11.82.

9: 0.19 g; 15%; m.p. 150−151 °C. ^{1}H NMR: δ = 2.28 (s, 3 H, Me), 6.51 (d, *J* = 8.2 Hz, 1 H, 4-H), 6.95 (d, *J* = 8.2 Hz, 2 H, 10-H and 14-H), 7.00 (m, 1 H, 5-H), 7.06 (t, *J* = 7.4 Hz, 1 H, 12-H), 7.33 (t, *J* = 7.8 Hz, 2 H, 11-H and 13-H), 7.37 (m, 1 H, 7-H), 7.52 (t, *J* = 7.4 Hz, 1 H, 18-H), 7.55 (d, *J* = 7.8 Hz, 2 H, 16-H and 20-H) and 7.63 (t, *J* = 7.8 Hz, 2 H, 17-H and 19-H) ppm ^{13}C NMR: δ = 20.47 (Me), 109.90 (C-4), 121.03 (C-10), 122.80 (C-7), 122.80 (C-7a), 123.45 (C-12), 127.17 (C-5), 128.60 (C-16), 128.60 (C-18), 129.54 (C-11), 129.96 (C-17), 131.67 (C-6), 136.69 (C-15), 151.00 (C-9), 138.42 (C-3a) and 156.07 (C-2) ppm. $C_{20}H_{16}N_2S$ (316.42): calcd. C 75.92, H 5.10, N 8.85; found C 75.59, H 4.88, N 8.77.

6-Ethoxy-2-phenylamino-1,3-benzothiazole (11) and 6-Ethoxy-3-phenyl-2-phenylimino-1,3-benzothiazoline (12): Elution with ether/pentane (1:4) afforded **12** and then **11**.

11: 0.13 g; 13%; m.p. 135 °C. ^{1}H NMR: δ = 1.36 (t, *J* = 7 Hz, 3 H, Me), 4.09 (q, *J* = 7 Hz, 2 H, O−CH_2), 6.93 (m, 1 H, 5-H), 7.02 (t, *J* = 7.3 Hz, 1 H, 12-H), 7.35 (t, *J* = 7.4 Hz, 2 H, 11-H and 13-H), 7.36 (m, 1 H, 7-H), 7.49 (d, *J* = 8.7 Hz, 1 H, 4-H), 7.73 (d, *J* = 7.7 Hz, 2 H, 10-H and 14-H) and 9.90 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 14.10 (Me), 63.66 (CH_2), 106.19 (C-7), 113.92 (C-5), 117.59 (C-10), 119.12 (C-4), 121.37 (C-12), 128.26 (C-11), 130.82 (C-7a), 140.58 (C-9), 145.89 (C-3a), 154.21 (C-6) and 159.78 (C-2) ppm. $C_{15}H_{14}N_2OS$ (270.35): calcd. C 66.64, H 5.22, N 10.36; found C 66.44, H 5.20, N 9.97.

12: 0.18 g; 14%; m.p. 121 °C. ^{1}H NMR: δ = 1.28 (t, *J* = 6.9 Hz, 3 H, Me), 3.95 (q, *J* = 7 Hz, 2 H, OCH_2), 6.51 (d, *J* = 8.9 Hz, 1 H, 4-H), 6.75 (m, 1 H, 5-H), 6.94 (d, *J* = 7.4 Hz, 2 H, 10-H and 14-H), 7.04 (t, *J* = 7 Hz, 1 H, 12-H), 7.22 (m, 1 H, 7-H), 7.31 (t, *J* = 8.1 Hz, 2 H, 11-H and 13-H), 7.45 (t, *J* = 7.3 Hz, 1 H, 18-H), 7.53 (d, *J* = 7.5 Hz, 2 H, 16-H and 20-H) and 7.60 (t, *J* = 7.8 Hz, 2 H, 17-H and 19-H) ppm. ^{13}C NMR: δ = 14.81 (Me), 63.91 (CH_2), 109.14 (C-7), 110.74 (C-4), 113.37 (C-5), 121.24 (C-10), 123.55 (C-12), 128.67 (C-18), 128.74 (C-16), 129.93 (C-11), 130.08 (C-17), 137.14 (C-3a), 151.37 (C-9), 155.31 (C-6), 155.84 (C-2) and 160.16 (C-6) ppm. $C_{21}H_{18}N_2OS$ (346.45): calcd. C 72.80, H 5.24, N 8.09; found C 72.53, H 5.01, N 8.05.

6-Fluoro-2-phenylamino-1,3-benzothiazole (14) and 6-Fluoro-3-phenyl-2-phenylimino-1,3-benzothiazoline (15): Elution with ether/pentane (1:9) afforded **15** and then elution with ether/pentane (1:4) gave **14**.

14: 0.15 g; 15%; m.p. 156 °C. ^{1}H NMR: δ = 7.04 (t, *J* = 7.4 Hz, 1 H, 12-H), 7.13 (m, 1 H, 5-H), 7.36 (t, *J* = 7.6 Hz, 2 H, 11-H and 13-H), 7.57 (dd, *J* = 4.8 Hz and 8.3, 1 H, 4-H), 7.63 (m, 1 H, 7-H), 7.74 (d, *J* = 7.3 Hz, 2 H, 10-H and 14-H) and 10.08 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 107.10 (C-7), 112.70 (C-5), 117.90 (C-10), 119.31 (C-4), 121.81 (C-12), 128.32 (C-11), 130.86 (C-7a), 140.44 (C-9), 148.37 (C-3a), 157.62 (C-6) and 161.44 (C-2) ppm. $C_{13}H_9FN_2S$ (244.29): calcd. C 63.92, H 3.71, N 11.47; found C 64.01, H 3.73, N 11.05.

15: 0.28 g; 22%; m.p. 138 °C. ^{1}H NMR: δ = 6.56 (dd, *J* = 4.3 Hz and 8.8 Hz, 1 H, 4-H), 6.80 (m, 1 H, 5-H), 6.98 (d, *J* = 7.6 Hz, 2 H, 10-H and 14-H), 7.03 (m, 1 H, 7-H), 7.06 (t, *J* = 7.4 Hz, 1 H, 12-H), 7.30 (t, *J* = 7.8 Hz, 2 H, 11-H and 13-H), 7.46 (t, *J* = 7.7 Hz, 1 H, 18-H), 7.49 (d, *J* = 7.6 Hz, 2 H, 16-H and 20-H) and 7.58 (t, *J* = 7.7 Hz, 2 H, 17-H and 19-H) ppm. ^{13}C NMR: δ = 109.59 (C-7), 110.80 (C-4), 113.00 (C-5), 121.56 (C-10), 123.95 (C-7a), 123.95 (C-12), 128.64 (C-16), 128.91 (C-18), 129.53 (C-11), 130.20 (C-17), 136.86 (C-15), 137.68 (C-3a), 151.53 (C-9), 156.71 (C-2) and 158.56 (C-6) ppm. $C_{19}H_{13}FN_2S$ (320.38): calcd. C 71.23, H 4.09, N 8.74; found C 70.85, H 3.91, N 8.74.

2-Phenylamino-1,3-thiazole (17) and 3-Phenyl-2-phenylimino-1,3-thiazoline (18): Elution with ether/pentane (1:4) afforded **18** and then **17**, with 1.1 equiv. of Bi reagent.

17: 0.23 g; 33%; m.p. 127−128 °C ref.[24] 128−129 °C. ^{1}H NMR: δ = 7.23 (d, *J* = 3.6 Hz, 1 H, 4-H), 6.88 (d, *J* = 3.6 Hz, 1 H, 5-H), 7.62 (d, *J* = 7.7 Hz, 2 H, 8-H and 12-H), 7.28 (t, *J* = 7.5 Hz, 2 H, 9-H and 11-H), 6.91 (t, *J* = 7.1 Hz, 1 H, 10-H) and 10.15 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 108.32 (C-5), 116.69 (C-8), 120.96 (C-10). 128.88 (C-9), 138.80 (C-4), 141.30 (C-7) and 163.84 (C-2) ppm. $C_9H_8N_2S$ (176.24): calcd. C 61.33, H 4.58, N 15.90; found C 61.01, H 4.28, N 16.

18: 0.29 g; 29%; m.p. 124−125 °C. ^{1}H NMR: δ = 7.24 (d, *J* = 5.1 Hz, 1 H, 4-H), 6.38 (d, *J* = 5 Hz, 1 H, 5-H), 6.94 (d, *J* = 7.4 Hz, 2 H, 8-H and 12-H), 7.31 (t, *J* = 8.1 Hz, 2 H, 9-H and 11-H), 7.01 (t, *J* = 7.3 Hz, 1 H, 10-H), 7.64 (d, *J* = 7.4 Hz, 2 H, 14-H and 18-H), 7.48 (t, *J* = 8.1 Hz, 2 H, 15-H and 17-H) and 7.33 (t, *J* = 7.2 Hz, 1 H, 16-H) ppm. ^{13}C NMR: δ = 99.41 (C-5), 121.10 (C-8), 123.08 (C-10), 125.19 (C-14), 126.92 (C-16), 128.32 (C-4), 129.15 (C-9), 129.68 (C-15), 138.62 (C-13), 151.82 (C-7) and 157.41 (C-2) ppm. $C_{15}H_{12}N_2S$ (252.33): calcd. C 71.40, H 4. 79, N 11.10; found C 71.29, H 4.68, N 10.90.

X-ray Crystallographic Study: The X-ray diffraction data were measured at room temperature on an Bruker−Nonius−Kappa CCD diffractometer with graphite-monochromated Mo-K_α (λ = 0.71073 Å) radiation.[25] A set of 90 frames was measured for 14 and 15 through a 180° scan in the following conditions: 2° steps, 120 seconds per frame repeated twice. Lorentz and polarisation corrections were applied to the raw data, which were not corrected for absorption.[26] The structures were solved by direct methods using SIR92.[27] All non-hydrogen atoms were refined anisotropically through cycles of full-matrix least-squares using Maxus.[28]

Crystal Data of 14: White prisms (0.2 × 0.2 × 0.1) of $C_{13}H_9FN_2S$, *M* = 244.29, triclinic, *a* = 3.9808(2) Å, *b* = 11.1672(9) Å, *c* = 12.545(1) Å, β = 94.600(5)°, *V* = 551.54(7) Å^3, *Z* = 2, space group: P_{-1}, $D_{calcd.}$ = 1.471 gcm^{-3}. $\theta_{max.}$ = 26.33°. Unique reflections used were 2020 with *R*(*F*) = 0.035 (1702 refl. > 3σ(*I*)], and *wR*(F^2) = 0.048 [$w = 1/(\sigma^2(F_o^2) + 0.03F_o^2)$].

Crystal Data of 15: White prism crystals (0.2 × 0.2 × 0.1) of $C_{19}H_{13}FN_2S$, *M* = 320.39, monoclinic, *a* = 22.231(1) Å, *b* = 5.5046(1) Å, *c* = 26.976(1) Å, β 109.684(1)°, *V* = 3108.2(2) Å^3, *Z* = 8, space group: calcd. $C_{2/c}$, $D_{calcd.}$ = 1.369 gcm^{-3}. $\theta_{max.}$ = 26.33°. Unique reflections used were 2677 with *R*(*F*) = 0.042 [2274 refl. > 3σ(*I*)], and *wR*(F^2) = 0.054 [$w = 1/(\sigma^2(F_o^2) + 6F_o^2)$].

CCDC-214417 and -214418 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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