An Expedient Synthesis of 3-Amino-1,2-benzisothiazoles

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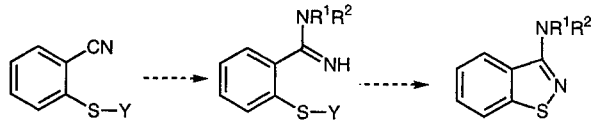
3-Amino-1,2-benzisothiazoles **3a–h** were synthesized in satisfactory yields under mild conditions by reaction of 2,2′-dithiobis(benzonitrile) **(2)** with several secondary amines and subsequent oxidation.

Several 3-amino-1,2-benzisothiazoles are known to have pharmacological activities such as antipsychotic activity[1] and antimycotic activity.[2] They have previously been prepared by reaction of secondary amines with 3-chloro-1,2-benzisothiazole[1] or 3-chloro-2-ethyl-1,2-benzisothiazolium chloride.[3] Their yields, however, are not good, because of some side reactions, which give a nitrile by attack at the sulfur atom[4] or due to the harshness of the reaction conditions.[1,3]

We thought that the isothiazole ring's lability was responsible for these moderate yields. Therefore, we conceived a synthetic plan as indicated in Figure 1, forming the isothiazole ring at the final step, after introducing the secondary amino groups.



(Y = leaving group)

Figure 1

We selected the 2-cyanophenylsulfanyl group as leaving group Y in Figure 1, and intended to introduce the secondary amino groups by reacting the Mg amides of secondary amines with the nitrile.[5]

The Mg amide of pyrrolidine **1a**, which was prepared by reaction of PrMgBr and pyrrolidine, was reacted with 2,2′-dithiobis(benzonitrile)[6] **(2)**. Unexpectedly, the reaction gave not 2,2′-dithiobis(benzamidine), but cyclized 3-(*N*-pyrrolidinyl)-1,2-benzisothiazole **(3a)** together with a more polar compound. The more polar compound was presumed to be the Mg salt of 2-sulfanylbenzamidine. Repeating the reaction using EtMgI instead of PrMgBr proceeded similarly.

Next, we attempted oxidation of the Mg salt of 2-sulfanylbenzamidine with several oxidizing reagents to give **3a**, without any byproducts. Initially, we tried Fe_2O_3, $FeCl_3$ and MnO_2 on oxidation, but either the Mg salt was not oxidized or the oxidation reaction was very slow. Oxidation by $KBrO_3$, I_2 or $NaIO_4$ gave several byproducts. Finaly, $CuCl_2$ was found to be the most suitable reagent. Oxidation by $CuCl_2$ proceeded smoothly and gave **3a** in excellent yield without any byproducts. Even using excessive amounts of $CuCl_2$ or at high temperatures, no byproducts were formed.

Several secondary amines were next examined to confirm the applicability of this reaction.

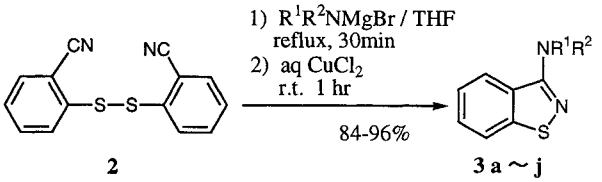


Figure 2

As indicated in Table 1, the reaction with several aliphatic secondary amines gave 3-amino-1,2-benzisothiazoles **3a–h, j** in 84–96% yields. However, the yield of **3i** in the reaction with *N*-methylaniline was 49%. We expected that the reason for the low yield is due to the low reactivity of the resulting Mg amide; even though the Mg amide can react with **2**, it cannot react with the Mg salt of 2-sulfanylbenzonitrile. The reaction of diisopropylamine gave a complex mixture probably because of the steric hindrance of the amine. The reaction of *N*-methylbenzamide did not proceed at all.

Next, we examined the quantity of PrMgBr needed by reacting 2.4 equivalents of the amine with various equivalents of PrMgBr.

As indicated in Table 2, the reactions using 2.4, 2.0 and 1.5 equivalents of PrMgBr proceeded satisfactorily and gave **3a** in good yields. However, the yield in the reaction using 1.0 equivalent was only 57%. Theoretically, 2.0 equivalents of PrMgBr are necessary. We propose that the reaction using 1.5 equivalents would proceed as indicated in Figure 3.

At first, the reaction of **2** with the first equivalent of Mg amide **1a**, followed by cyclization, gives 1 equivalent of **3a** and 1 equivalent of Mg salt of 2-sulfanylbenzonitrile. Next, the Mg salt of 2-sulfanylbenzonitrile is attacked by the second equivalent of Mg amide **1a** to give the dianion of 2-sulfanylbenzamidine. This dianion then abstracts a hydrogen from the amine pyrrolidine to regenerate **1a**. Hence 1.5 equivalents of PrMgBr are adequate for complete reaction.

In conclusion, the given reaction procedure provides a facile and convenient route to 3-amino-1,2-benzisothiazoles under mild conditions and in satisfactory yield.

^{1}H NMR spectra and ^{13}C NMR spectra were measured on a JEOL JNM-GX270 FT NMR spectrometer in $CDCl_3$ with TMS as an internal standard. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Refractive indexes were measured on an Atago Abbe refractometer 16525. IR spectra were measured on a Model 260–10 Hitachi infrared spectrophotometer.

Table 1. Characterization of 3-Amino-1,2-benzisothiazoles **3a–j**

Product	R^1	R^2	Yield (%)	mp/n_D^{20}	Molecular Formula[a]/ Lit. Data of n_D^{20}	^{1}H NMR	^{13}C NMR	IR (thin film)
3a	$-(CH_2)_4-$		96	49–50°C (CH_2Cl_2/hex)	$C_{11}H_{12}N_2S$	1.95–2.15 (4H, m), 3.75–4.00 (4H, m),7.28 (1H, t, J = 8.3 Hz), 7.42 (1H, t, J = 8.3 Hz), 7.75 (1H, d, J = 8.3 Hz), 8.12 (1H, d, J = 8.3 Hz)	160.35, 153.22, 127.22, 124.61, 123.33, 120.29, 49.58, 25.66	2975, 2870, 1566,1510, 1416, 1380, 1316, 770, 736
3b	$-(CH_2)_5-$		92	1.6216	$C_{12}H_{14}N_2S$ 1.6205[3]	1.60–1.90 (6H, m), 3.40–3.55 (4H, m), 7.34 (1H, t, J = 8.3 Hz), 7.45 (1H, t, J = 8.3 Hz), 7.79 (1H, d, J = 8.3 Hz), 7.91 (1H, d, J = 8.3 Hz)	164.99, 152.56, 128.35, 127.40, 124.10, 123.73, 120.48, 51.44, 25.94, 24.65	2935, 2855, 1493, 1426, 1380, 1280, 1256, 769, 736
3c	Bu–	Bu–	89	1.5662	$C_{15}H_{22}N_2S$ 1.5681[3]	0.94 (6H, m), 1.37 (4H, sextet, J = 7.4 Hz), 1.69 (4H, qui, J = 7.4 Hz), 3.48–3.62 (4H, m), 7.31 (1H, t, J = 8.3 Hz), 7.4 (1H, t, J = 8.3 Hz), 7.77 (1H, d, J = 8.3 Hz), 7.92 (1H, d, J = 8.3 Hz)	162.58, 153.00, 128.07, 127.08, 124.21, 123.56, 120.46, 51.48, 30.40, 20.36, 14.04	2965, 2880, 1513, 1469, 1431, 1372, 1320, 1300, 1103, 736
3d	Et–	Et–	84	1.6033	1.6071[3,7]	1.27 (6H, t, J = 7.0 Hz), 3.60 (4H, q J = 7.0 Hz), 7.29 (1H, t, J = 7.9 Hz), 7.40 (1H, t, J = 7.9 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.92 (1H, d, J = 8.3 Hz)	162.19, 152.91, 127.95, 127.12, 124.18, 123.60, 120.42, 45.20, 13.45	2975, 2880, 1562, 1515, 1430, 1377, 1319, 1292, 1100, 734
3e	Pr–	Pr–	90	1.5828	1.5852[3]	0.95 (6H, t, J = 7.4 Hz), 1.73 (4H, sextet, J = 7.6 Hz), 3.45–3.60 (4H, m), 7.30 (1H, d, J = 7.9 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.91 (1H, d, J = 8.3 Hz)	162.39, 153.03, 127.96, 127.06, 124.19, 123.57, 120.45, 53.46, 21.40, 11.45	2970, 2880, 1563, 1513, 1426, 1380, 1323, 1302, 1102, 737
3f	$PhCH_2-$	$PhCH_2-$	85	1.6611	$C_{21}H_{18}N_2S$	4.70 (4H, s), 7.30 (1H,t, J = 8.3 Hz), 7-10–7.35 (1H, m), 7.59 (1H, d, J = 8.3 Hz), 7.80 (1H, d, J = 8.3 Hz)	162.23, 153.19, 137.84, 128.37, 127.72, 127.25, 127.14, 127.04, 123.91, 123.69, 120.36, 77.56, 77.09, 76.63, 53.73	3080, 3040, 2930, 1566, 1520, 1460, 1446, 1370, 740, 700
3g	$-(CH_2)_2N(CH_2Ph)(CH_2)_2-$		94	1.6331	$C_{18}H_{19}N_2S$	2.63–2.75 (4H, m), 3.50–3.63 (4H, m), 3.60 (2H, s), 7.10–7.42 (6H, m), 7.43 (1H, t, J = 8.3 Hz), 7.78 (1H, d, J = 8.3 Hz), 7.88 (1H, d, J = 8.3 Hz)	163.96, 152.72, 137.93, 129.18, 128.26, 128.06, 127.45, 127.12, 123.90, 123.80, 120.52, 63.12, 52.90, 50.06	2810, 1494, 1451, 1421, 1378, 1255, 1135, 1001, 734, 694
3h	$-(CH_2)_2O(CH_2)_2-$		92	44–45°C (CH_2Cl_2/hex)	$C_{11}H_{12}N_2OS$	3.46–3.57 (4H, m), 3.85–3.98 (4H, m), 7.33 (1H, t, J = 8.3 Hz), 7.44 (1H, t, J = 8.3 Hz), 7.78 (1H, d, J = 8.3 Hz), 7.87 (1H, d, J = 8.3 Hz)	163.73, 152.83, 127.79, 127.57, 123.94, 123.68, 120.57, 66.70, 50.54	2965, 2860, 1491, 1448, 1422, 1380, 1259, 1117, 737
3i	Ph–	Me–	49	1.6686	$C_{14}H_{12}N_2S$	3.57 (3H, s), 6.89 (1H, d, J = 8.3 Hz), 6.98 (1H, t, J = 8.3 Hz), 7.12 (2H, d, J = 7.3 Hz), 7.16 (1H, t, J = 8.0 Hz), 7.25–7.38 (3H, m), 7.72 (1H, d, J = 7.9 Hz)	160.64, 152.70, 147.88, 129.40, 127.68, 127.17, 125.17, 124.91, 124.53, 123.42, 120.06, 42.23	3060, 1597, 1560, 1495, 1431, 1405, 1375, 1321, 1107, 1023, 767, 734, 695
3j	$PhCH_2-$	Me–	94	1.6493	$C_{15}H_{14}N_2S$	3.12 (3H, s), 4.74 (2H, s), 7.20–7.50 (7H, m), 7.77 (1H, d, J = 8.3 Hz), 7.88 (1H, d, J = 8.3 Hz)	163.58, 153.08, 138.25, 128.68, 127.60, 127.35, 127.31, 124.11, 123.79, 120.52, 57.52, 38.82	3070, 3035, 1563, 1514, 1457, 1411, 1385, 1360, 1260, 1057, 738

[a] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.30, N ± 0.28, S ± 0.21

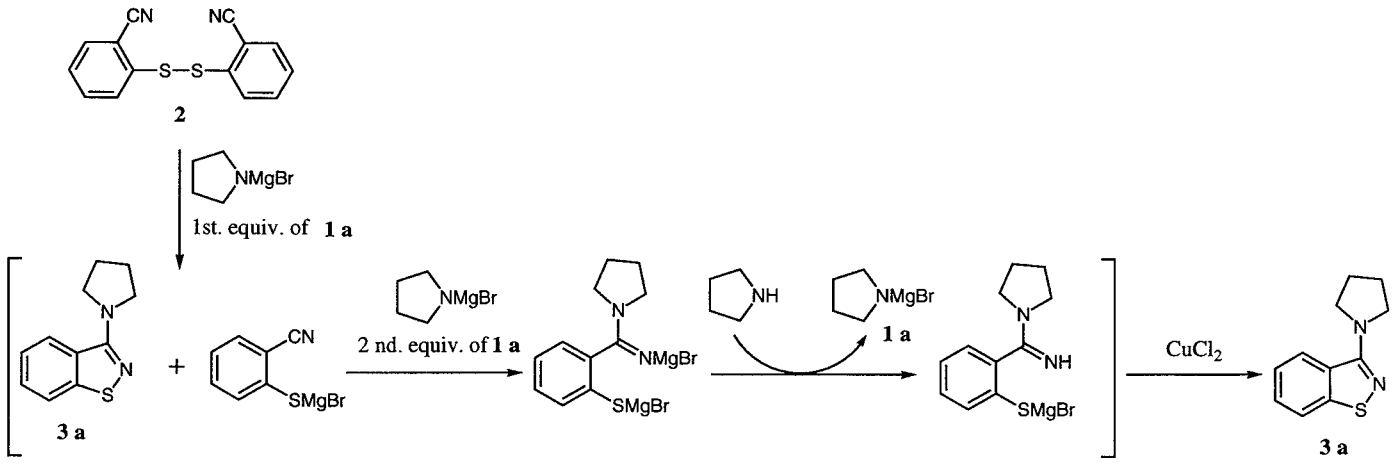


Figure 3

Table 2. Quantity of PrMgBr and Pyrrolidine

PrMgBr	Pyrrolidine	Yield of **3a**
2.4 equiv	2.4 equiv	96%
2.0	2.4	97%
1.5	2.4	96%
1.0	2.4	57%

3-Amino-1,2-benzisothiazoles 3a–j; General Procedure:
To a THF solution of PrMgBr (prepared with Mg (95 mg, 3.9 mmol) and PrBr (354 μL, 3.9 mmol) was added amine (3.6 mmol) under N_2, and the mixture was stirred under reflux for 30 min. A solution of 2,2′-dithiobis(benzonitrile)[6] (403 mg, 1.5 mmol) in THF (1.5 mL) was added, and the mixture was stirred at reflux for 30 min. To this cooled solution was added a solution of $CuCl_2 \cdot 2H_2O$ (511 mg, 3.0 mmol) in H_2O (6 mL), and the mixture was stirred for 1 h at r.t. Conc. HCl (10 mL) was added, and the mixture stirred for 5 min. After 29% aq NH_4OH (10 mL) was added to the mixture, the mixture was extracted with $CHCl_3$ (2 × 20 mL), dried ($MgSO_4$) and purified by silica gel chromatography (5% EtOAc/hexane) to give **3a–j**.

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