# Synthesis of 2-Sulfonylaminobenzimidazoles and 4,5-Dicyano-2-sulfonylaminoimidazoles from *N*-Dichloromethylenesulfonamides

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Because of the considerable therapeutic importance of the sulfonamido group, we became interested in the synthesis of several 2-sulfonylaminoimidazoles and 2-sulfonylaminobenzimidazoles. The latter compounds can be prepared by reaction of 2-aminobenzimidazoles with the corresponding sulfonyl chloride[1], but as previously stated[2], 1,2-diamino compounds are also useful precursors in the synthesis of imidazole derivatives.

Thus, 2-sulfonylaminobenzimidazoles have been obtained by reaction of *o*-phenylenediamine with sulfonylguanidines[3] and methyl *N*-sulfonyliminodithiocarbonates[4,5], but both methods suffer from some disadvantages. In the first one, high temperatures are required, and yields are only moderate. The second method, with less drastic conditions, works well with *o*-phenylenediamine itself, but when it bears several substituents (e.g. **1**; $R^1 = R^2 = CH_3$) we have found that yields are not good, and even in some cases (**1**; $R^1 = R^2 = Cl$), the expected 2-sulfonylaminobenzimidazole is not obtained at all.

Thus, we had to look for more reactive one-carbon atom synthons as condensing agents, and the use of *N*-dichloromethylenesulfonamides **2** became obvious. They can be easily prepared[6] by chlorination of the corresponding methyl *N*-sulfonyliminodithiocarbonates, and their condensation reactions have led to a variety of five- and six-membered heterocy-

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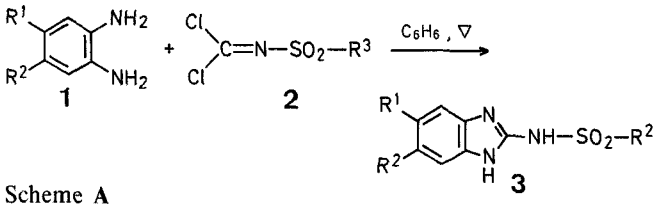
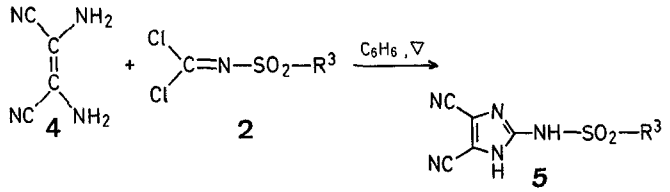
cles[7,8]. In order to extend these reactions, we report here a facile and general procedure for the synthesis of 2-sulfonylaminobenzimidazoles **3** (Table 1), which is carried out by addition of the corresponding compound **2** to a suspension of the *o*-phenylenediamine **1**, *and heating under reflux, using benzene* as solvent (Scheme **A**).



Scheme **A**

The wide applicability of this method was further confirmed by using another diamine of major interest, such as diaminomaleonitrile **(4)**. Apart from its role in the prebiotic synthesis of purines[9], it has given rise to seven-[10], six-[11], and five-membered rings, among them imidazoles, which have been obtained by condensation reactions with ortho esters[12], imino *ether hydrochlorides*[13], *formic acid*[14], and carbonimidoyl dihalides[10]. This prompted us to prepare several 4,5-dicyano-2-sulfonylaminoimidazoles **5** (Table 2) by reaction of **2** with diaminomaleonitrile **(4)** in benzene (Scheme **B**).



Scheme **B**

**Table 1.** 2-Sulfonylamino-benzimidazoles **3**

| $R^1$ | $R^2$ | $R^3$ | Yield [%] | m.p. [°C] (solvent) | Molecular Formula[a] or Lit. m.p. [°C] | I.R. (Nujol) $\nu$ [cm$^{-1}$] NH | C=N | $SO_2$ | $^1$H.N.M.R. (DMSO-$d_6$) $\delta$ [ppm] |
|---|---|---|---|---|---|---|---|---|---|
| H | H | $CH_3$ | 68 | 329–330° (DMF) | $C_8H_9N_3O_2S$ (211.2) | 3320, 3175 | 1640 | 1285, 1125, 1080 | 2.95 (s, 3H, $CH_3$); 3.5 (s, 1H, $NHSO_2$); 7.1–7.5 (m, 4H); 12.2 (s, 1H, NH) |
| H | H | $C_6H_5$ | 72 (69)[4] | 352–353° (DMF) | 355°[4] | 3380, 3160 | 1635 | 1295, 1145, 1100 | 3.6 (s, 1H, $NHSO_2$); 7.0–7.6 (m, 9H); 12.3 (s, 1H, NH) |
| H | H | 4-$H_3C$—$C_6H_4$ | 82 (72)[4] | 358–359° (DMF) | 360°[4] | 3375, 3165 | 1640 | 1300, 1140, 1110 | 2.4 (s, 3H, $CH_3$); 3.4 (s, 1H, $NHSO_2$); 7.1–7.5 (m, 4H); 7.8–8.0 (dd, 4H); 12.7 (s, 1H, NH) |
| H | H | 4-Cl—$C_6H_4$ | 64 | 344–346° (DMF) | $C_{13}H_{10}ClN_3O_2S$ (307.7) | 3380, 3160 | 1635 | 1305, 1150, 1100 | 3.45 (s, 1H, $NHSO_2$); 7.1–7.6 (m, 4H); 7.8–8.0 (dd, 4H); 12.0 (s, 1H, NH) |
| H | H | 4-$H_3CO$—$C_6H_4$ | 78 | 304–306° ($CH_3CN$) | $C_{14}H_{13}N_3O_3S$ (303.3) | 3375, 3165 | 1635 | 1290, 1145, 1110 | 3.4 (s, 1H, $NHSO_2$); 3.9 (s, 3H, $OCH_3$); 7.1–7.5 (m, 4H); 7.7–7.9 (dd, 4H); 12.2 (s, 1H, NH) |
| Cl | Cl | $CH_3$ | 75 | 356–358° (DMF) | $C_8H_7Cl_2N_3O_2S$ (280.1) | 3300, 3175 | 1640 | 1290, 1125, 1070 | 2.9 (s, 3H, $CH_3$); 3.5 (s, 1H, $NHSO_2$); 7.4–7.6 (m, 2H); 12.0 (s, 1H, NH) |
| Cl | Cl | $C_6H_5$ | 86 | 332–334° (dioxan) | $C_{13}H_9Cl_2N_3O_2S$ (342.2) | 3320, 3100 | 1635 | 1295, 1140, 1095 | 3.5 (s, 1H, $NHSO_2$); 7.0–7.6 (m, 7H); 12.2 (s, 1H, NH) |
| Cl | Cl | 4-$H_3C$—$C_6H_4$ | 84 | 350–352° (DMF) | $C_{14}H_{11}Cl_2N_3O_2S$ (356.2) | 3300, 3150 | 1625 | 1290, 1145, 1110 | 2.45 (s, 3H, $CH_3$); 3.5 (s, 1H, $NHSO_2$); 7.4–7.6 (m, 2H); 7.8–8.0 (dd, 4H); 12.6 (s, 1H, NH) |
| Cl | Cl | 4-Cl—$C_6H_4$ | 78 | 343–344° (DMF/$C_2H_5OH$) | $C_{13}H_8Cl_3N_3O_2S$ (376.6) | 3335, 3100 | 1630 | 1300, 1140, 1100 | 3.45 (s, 1H, $NHSO_2$); 7.4–7.6 (m, 2H); 7.8–8.0 (dd, 4H); 12.0 (s, 1H, NH) |
| Cl | Cl | 4-$H_3CO$—$C_6H_4$ | 69 | 287–289° ($CH_3CN$) | $C_{14}H_{11}Cl_2N_3O_3S$ (372.2) | 3410, 3120 | 1630 | 1280, 1145, 1100 | 3.4 (s, 1H, $NHSO_2$); 3.9 (s, 3H, $OCH_3$); 7.3–7.5 (m, 2H); 7.7–7.9 (dd, 4H); 12.2 (s, 1H, NH) |
| $CH_3$ | $CH_3$ | $CH_3$ | 90 | 324–326° (DMF) | $C_{10}H_{13}N_3O_2S$ (239.3) | 3330, 3150 | 1630 | 1295, 1125, 1075 | 2.5 (s, 6H, $2CH_3$); 2.9 (s, 3H, $CH_3$—$SO_2$); 3.5 (s, 1H, $NHSO_2$); 7.4–7.7 (m, 2H); 12.1 (s, 1H, NH) |
| $CH_3$ | $CH_3$ | $C_6H_5$ | 94 | 297–299° (dioxan) | $C_{15}H_{15}N_3O_2S$ (301.3) | 3340, 3165 | 1630 | 1290, 1145, 1095 | 2.5 (s, 6H, $2CH_3$); 3.45 (s, 1H, $NHSO_2$); 7.0–7.3 (m, 5H); 7.4–7.7 (m, 2H); 12.2 (s, 1H, NH) |
| $CH_3$ | $CH_3$ | 4-$H_3C$—$C_6H_4$ | 76 | 292–294° (DMF/$H_2O$) | $C_{16}H_{17}N_3O_2S$ (315.4) | 3340, 3150 | 1635 | 1305, 1140, 1095 | 2.4 (s, 9H, $3CH_3$); 3.5 (s, 1H, $NHSO_2$); 7.4–7.6 (m, 2H); 7.8–8.0 (dd, 4H); 12.5 (s, 1H, NH) |
| $CH_3$ | $CH_3$ | 4-Cl—$C_6H_4$ | 74 | 285–286° (DMF/$H_2O$) | $C_{15}H_{14}ClN_3O_2S$ (335.8) | 3380, 3250 | 1650 | 1295, 1125, 1090 | 2.5 (s, 6H, $2CH_3$); 3.4 (s, 1H, $NHSO_2$); 7.4–7.6 (m, 2H); 7.9–8.1 (dd, 4H); 12.2 (s, 1H, NH) |
| $CH_3$ | $CH_3$ | 4-$H_3CO$—$C_6H_4$ | 65 | 275–277° ($CH_3CN$) | $C_{16}H_{17}N_3O_3S$ (331.4) | 3380, 3300 | 1645 | 1280, 1130, 1095 | 2.6 (s, 6H, $2CH_3$); 3.4 (s, 1H, $NHSO_2$); 3.9 (s, 3H, $OCH_3$); 7.3–7.5 (m, 2H); 7.8–8.0 (dd, 4H); 12.0 (s, 1H, NH) |

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.24, N ±0.24.

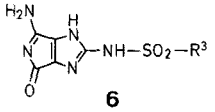
**Table 2.** 4,5-Dicyano-2-sulfonylaminoimidazoles **5**

| $R^3$ | Yield [%] | m.p. [°C] (solvent) | Molecular Formula[a] | I.R. (Nujol) $\nu$ [cm$^{-1}$] | | | |
|---|---|---|---|---|---|---|---|
| | | | | NH | C≡N | C=N | $SO_2$ |
| $CH_3$ | 90 | 295–297° ($CH_3CN$) | $C_6H_5N_5O_2S$ (211.2) | 3270, 3160 | 2240 | 1600 | 1310, 1140, 1075 |
| $C_6H_5$ | 79 | 232–233° ($CH_3CN$) | $C_{11}H_7N_5O_2S$ (273.3) | 3270, 3160 | 2250 | 1600 | 1320, 1160, 1080 |
| 4-$H_3C$—$C_6H_4$ | 82 | 270–271° ($CH_3CN$) | $C_{12}H_9N_5O_2S$ (287.3) | 3300, 3160 | 2260 | 1595 | 1315, 1165, 1080 |
| 4-Cl—$C_6H_4$ | 85 | 280–281° ($CH_3CN$) | $C_{11}H_6ClN_5O_2S$ (307.7) | 3320, 3100 | 2240 | 1590 | 1310, 1150, 1075 |
| 4-$H_3CO$—$C_6H_4$ | 75 | 215–217° ($CH_3CN/H_2O$) | $C_{12}H_9N_5O_3S$ (303.3) | 3280, 3170 | 2240 | 1600 | 1315, 1160, 1060 |
| 4-$O_2N$—$C_6H_4$ | 55 | 250–252° ($CH_3NO_2$) | $C_{11}H_6N_6O_4S$ (318.3) | 3295, 3185 | 2245 | 1620 | 1325, 1165, 1085 |

[a] Satisfactory microanalyses obtained: C ±0.38, H ±0.29, N ±0.35.

Yields of products **5** (Table 2) are much higher than those reported[10] using *t*-butyl and phenyl isocyanide dichlorides (11% and 39%, respectively) and work-up is simpler.

Several attempts at selective hydration of the nitrile groups of compounds **5** were performed, but no pure product could be isolated. Hydrolysis with 1 normal aqueous sodium hydroxide[15] yielded a mixture, in which the corresponding 5-cyano-4-carboxamido- and 4,5-dicarboxamidoimidazole derivatives were identified, while in the hydrolysis of **5** using 1 normal aqueous sodium hydroxide and 30% hydrogen peroxide[16], the 4,5-dicarboxamide compound and 6-amino-2-sulfonylamino-1*H*,4*H*-pyrrolo[3,4-*d*]imidazole-4-one (**6**; as a result of *in situ* cyclization[16]) could be detected by I.R. and N.M.R. spectroscopy.



**6**

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. I.R. spectra were recorded with a Perkin-Elmer 257 spectrophotometer and $^1$H-N.M.R. spectra were recorded with a Perkin-Elmer R-12 spectrometer, using TMS as internal reference. Microanalyses were performed at the Centro Nacional de Química Orgánica, C.S.I.C., Madrid. *N*-Dichloromethylenesulfonamides were obtained according to the method of Ref.[6], although minor changes in the use of solvents were introduced[17].

**2-Sulfonylaminobenzimidazoles 3; General Procedure:**
To a suspension of the *o*-phenylenediamine **1** (0.05 mol) in benzene (100 ml) is added dropwise, with stirring, at room temperature, a solution of the *N*-dichloromethylenesulfonamide **2** (0.05 mol) in benzene (100 ml). When the addition is complete, the mixture is refluxed for 5 h, cooled, the precipitate obtained is filtered off, dried, and purified by recrystallization (Table 1).

**4,5-Dicyano-2-sulfonylaminoimidazoles 5; General Procedure:**
To a suspension of diaminomaleonitrile (**4**; 2.7 g, 0.025 mol) in anhydrous benzene (100 ml) is added with vigorous stirring, dropwise at room temperature a solution of the *N*-dichloromethylenesulfonamide **2** (0.025 mol) in benzene (100 ml). After refluxing for 8–10 h, the reaction mixture is cooled, the precipitate so obtained is isolated by suction, dried, and purified by recrystallization (Table 2).

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