Synthesis of 1,2,4-Triazolo[1,5-*a*]pyrimidine-2-sulfonamides

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The 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamides are a new class of highly active herbicides. A novel cyclization method for the synthesis of these compounds is discussed.

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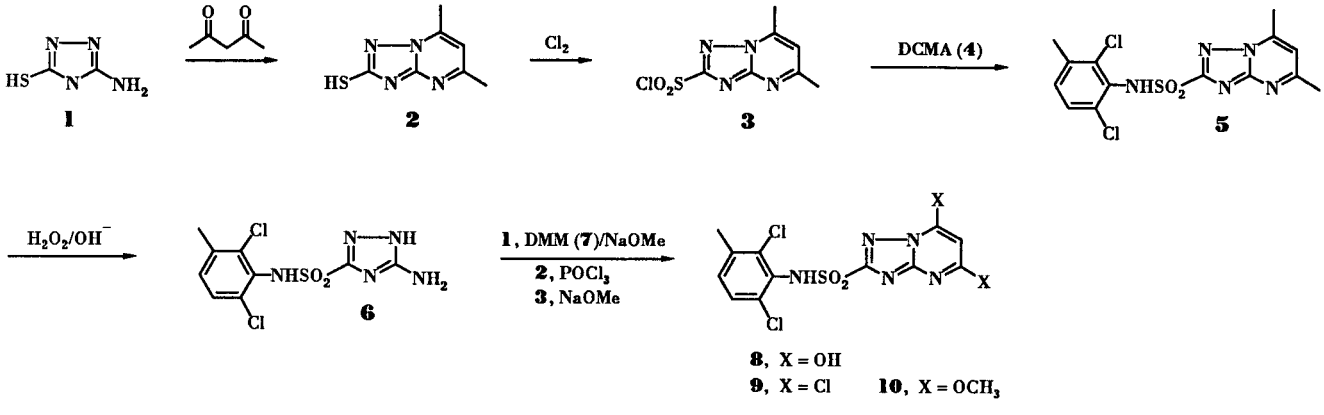
The chemistry of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives has been of considerable interest for many years. In 1935, 5-methyl-7-hydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine was found to be an excellent stabilizer for photographic emulsions. Since then, various derivatives of 1,2,4-triazolo[1,5-*a*]pyrimidine have found applications in pharmaceutical, agricultural and other areas. A recent review [1] covers the synthesis and properties of 1,2,4-triazolo[1,5-*a*]-pyrimidine derivatives. In the agricultural area, the 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide derivatives have shown excellent herbicidal and plant growth regulation activity [2]. We now report a novel cyclization method [3] in the synthesis of *N*-[aryl]1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide derivatives, specifically, its utility in the synthesis of *N*-[2,6-dichloro-3-methylphenyl]-5,7-dimethoxy-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide [10], an active herbicide for the control of broad leaf weeds in cereal crops.

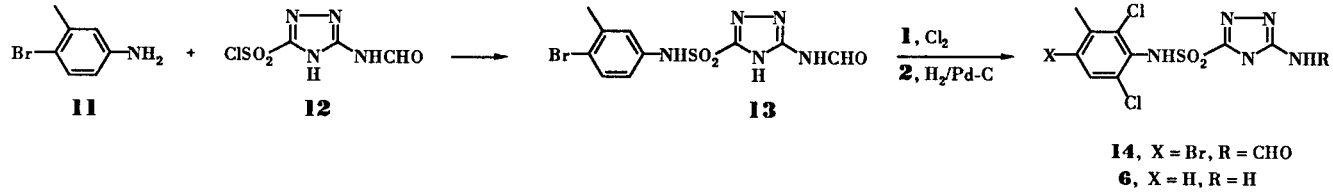
The original synthesis [4] of **10** is shown in Scheme 1. Condensation of 5-amino-3-mercapto-1,2,4-triazole with 2,4-pentanedione gave 5,7-dimethyl-3-mercapto-1,2,4-triazolo[1,5-*a*]pyrimidine **2**. Oxidation of **2** with chlorine gave the sulfonyl chloride **3**. The sulfonyl chloride is very labile to hydrolysis and to loss of sulfur dioxide on heating to give the chloro derivative. The low nucleophilicity of 2,6-dichloro-3-methylaniline **4** resulted in slow formation of the sulfonamide. The best results were obtained by allowing the aniline to react with **3** in pyridine. Deprotection to the coupled sulfonamide **5** was achieved through basic hydrogen peroxide oxidation. Condensation of **6** with dimethyl malonate **7** in the presence of base yields the trisodium salt of **8**. After neutralization of the salt, the dihydroxy compound **8** was converted with phosphorus oxychloride to the 5,7-dichloro derivative **9**. The overall yield of **6** to **9** was low due to the cleavage of the pyrimidine ring during condensation. Displacement of the 5,7-dichloro groups on **9** with sodium methoxide gave **10** in high yield.

We have now developed a synthesis [5] of **10** which overcomes the coupling and cyclization problems described in Scheme 1. The novel six-step synthesis of **10** is outlined in Scheme 2. Condensation of 4-bromo-3-methylaniline **11** with the sulfonyl chloride **12** is very facile to yield the sulfonamide **13**. Chlorination proceeds smoothly to introduce the chlorine in the *ortho* position of the aniline portion of the sulfonamide. Hydrogenation of the sulfonamide **14** over palladium on carbon deprotects the formyl group and reduces the 4-bromo substituent on the aromatic ring to yield the same intermediate **6** as in Scheme 1. The protecting formyl group on the triazole is essential; otherwise, the chlorination reaction gives a mixture of products. In addition, the chlorination reaction must be carried out in dilute solution to avoid precipitation of un-

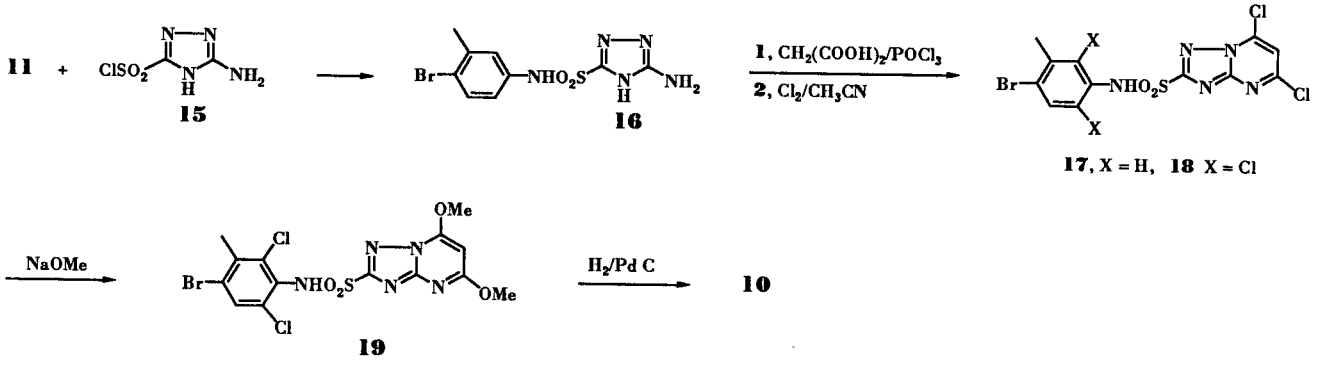
Scheme 1



Scheme 2



Scheme 3



derchlorinated intermediates. The formation of the pyrimidine ring was achieved under acidic conditions *via* condensation of **6** with malonyl chloride in acetonitrile to yield the dihydroxy derivative **8** in high yield. Triazolopyrimidine **8** was characterized by its elemental, mass spectral, and nmr analyses. Compound **8** did not undergo ring opening under hplc conditions (*p*H-2) employed to monitor the reaction. When compared to the synthesis of **8** in Scheme 1 with dimethyl malonate, the neutralization step is eliminated. Dihydroxy compound **8** is readily converted to the dimethoxy derivative **9** *via* the dichloride **10**.

An alternative to Scheme 2 that eliminates the need to protect the aminotriazole **1** for chlorination is to carry out the coupling and cyclization prior to chlorination and reduction as outlined in Scheme 3. Condensation of **11** with the aminotriazolosulfonyl chloride **15** gave sulfonamide **16**. Due to the poor thermal stability of malonyl chloride, *in situ* generation of the latter with malonic acid and phosphorus oxychloride in the presence of **16** gave **17** in high yields. Chlorination of **17** in acetonitrile/water mixture gave the bromodichloro derivative **18**. The presence of water, which acts as a buffer for hydrogen chloride generated during the electrophilic substitution, is essential for completion of chlorination. Conversion of **18** to **19** with sodium methoxide and subsequent selective reduction with hydrogen on palladium on carbon gave the desired dimethoxytriazolopyrimidine derivative **10**.

In summary, a novel cyclization method for the synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide derivatives has been demonstrated. The conversion of **16** to **17** is quite general and has been utilized for the synthesis of other 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide derivatives [6].

EXPERIMENTAL

General Methods.

All melting points are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer. The ^1H and ^{13}C nmr chemical shifts are expressed as δ values (ppm) relative to a TMS internal standard. The hplc samples were prepared in the eluant and analyzed on a HP1090 system equipped with a HP ODS 200 x 2.1 mm column eluted with 35:65 acetonitrile:water buffered with 0.1 wt% sulfuric acid at a flow rate of 0.6 ml per minute and diode array detector with uv wavelength set at 240 nm and a bandwidth of 80 nm. The mass spectra were recorded on Finnigan MAT model 4600 spectrometer employing electron impact ionization and on an HP 5995 GC-MS *via* direct insertion probe method. In general, the reactions were conducted under a positive pressure of nitrogen, and the acetonitrile employed was dried by distillation over calcium hydride.

5-*N*-(formyl)-1,2,4-triazole-3-sulfonyl Chloride (**12**).

A mixture of 24.4 g (0.2 mole of 95%) of 5-amino-3-mercapto-1,2,4-triazole and 100 ml of formic acid (89%) was stirred rapidly and heated to reflux for 4 hours and allowed to cool to room temperature. The mixture was diluted with 200 ml of water and cooled to 5°. Chlorine gas (3 equivalents) was bubbled through the mixture while maintaining the temperature below 15°. The mixture was filtered and dried to yield 33.7 g (80%) of **12**, mp 194-196°; ir (potassium bromide): ν 1700 (CO), 1600, 1400, 1175 (SO_2) cm^{-1}; ms: m/z 212 (M^+).

Anal. Calcd. for $C_3H_3ClN_4O_3S$: C, 17.11; H, 1.44; N, 26.6. Found: C, 17.14; H, 1.45; N, 27.00.

N-(4-Bromo-3-methylphenyl)-5-*N*-(formyl)-1,2,4-triazole-3-sulfonamide (**13**).

A mixture of 3.72 g (0.02 mole) of **11** and 2.10 g (0.01 mole) of **12** in 50 ml of acetonitrile was refluxed under nitrogen until all

the sulfonyl chloride was consumed (1 hour). The mixture was cooled and filtered. The precipitate was dispersed in 200 ml of 1% aqueous hydrochloric acid solution and filtered to yield 3.0 g (84%) of **13**, mp 282-284°; ^{1}H nmr (DMSO-d_6): δ 12.0 (1H, s), 10.83 (1H, s), 8.40 (1H, s), 7.47 (d, 1H, J = 8.7 Hz), 7.16 (d, 1H, J = 2.1 Hz), 6.98 (dd, 1H, J = 2.7, 8.5 Hz), 2.27 (s, 3H); ^{13}C nmr (DMSO-d_6): 162, 160.27, 158.23, 148.48, 137.85, 136.89, 132.49, 122.14, 119.14, 118.69, 22.34; ms: m/z 280 (M^+–Br).

Anal. Calcd. for $C_{10}H_{10}BrN_5O_3S$: C, 33.35; H, 2.8; N, 19.44. Found: C, 33.45; H, 2.81; N, 19.12.

N-(4-Bromo-2,6-dichloro-3-methylphenyl)-5-*N*-(formyl)-1,2,4-triazole-3-sulfonamide (**14**).

A solution of 2.0 g (0.055 mole) of **13** in 60 ml of acetonitrile and 40 ml of water was stirred rapidly and cooled in an ice water bath to 15°. Chlorine gas (2.2 g) was bubbled through the mixture and allowed to stir at room temperature for 2 hours. The mixture was filtered and the precipitate was dried to yield 1.95 g (81%) of **14**, mp >290°; ^{1}H nmr (DMSO-d_6): 11.98 (s, 1H), 10.60 (s, 1H), 8.44 (s, 1H), 7.89 (s, 1H), 2.46 (s, 3H); ms: m/z 430 (M^+).

Anal. Calcd. for $C_{10}H_8BrCl_2N_5O_3S$: C, 27.99; H, 1.88; N, 16.32. Found: C, 28.05; H, 1.89; N, 16.45.

N-(2,6-Dichloro-3-methylphenyl)-5-amino-1,2,4-triazole (**6**).

A mixture of 2 g (0.046 mole) of **14** in 100 ml of ethanol was stirred rapidly and purged with nitrogen and 0.15 g of 10% palladium on carbon was added. Hydrogen gas was bubbled through the mixture while heating to reflux. After 3 hours of reflux the reaction was essentially complete. The mixture was purged with nitrogen and filtered. The filtrate was concentrated to yield 1.5 g (98%) of **6**, mp 198-200° [3]; ^{1}H nmr (DMSO-d_6): δ 7.32 (d, 1H, J = 8.4 Hz), 7.38 (d, 1H, J = 8.4 Hz); ^{13}C nmr (DMSO-d_6): δ 159.45, 157.52, 136.10, 135.94, 133.011, 131.20, 127.63, 20.10.

N-(2,6-Dichloro-3-methylphenyl)-5,7-dihydroxy-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide (**8**).

To a stirred solution of 2.52 g (0.0078 mole) of **6** in 100 ml of dry acetonitrile was added 1.5 g (0.01 mole) of freshly distilled malonyl chloride. The mixture was stirred at room temperature overnight and the yellow precipitate formed was collected and dried. Additional product was recovered by concentrating the filtrate to dryness. The combined yield of **8** was 2.58 g (85%), mp 280-282° dec; ir (potassium bromide): ν 3200-2800, 1712, 1696, 1186 cm^{-1}; ms: m/z 389 (M^+), 354, 174.

Anal. Calcd. for $C_{12}H_9Cl_2N_5O_4S$: C, 36.93; H, 2.32; N, 17.94. Found: C, 37.07; H, 2.42; N, 17.86.

N-(4-Bromo-3-methylphenyl)-5-amino-1,2,4-triazole-3-sulfonamide (**16**).

To a stirred solution of 6.11 g (0.032 mole) of **11** in 80 ml of dry acetonitrile was added in portions 3 g (0.016 mole) of 3-amino-1,2,4-triazolo-5-sulfonyl chloride, **15**, and the mixture was refluxed for 1 hour. The reaction mixture was concentrated and slurried in 100 ml of water containing sodium hydroxide (4 g) and extracted with methylene chloride (2 x 75 ml). The aqueous layer was separated and acidified to yield the sulfonamide as a white solid, 5.1 g (96%), mp 254-256°; ^{1}H nmr (DMSO-d_6): δ 12.8 (br s, 1H), 10.6 (br s, 1H), 7.45 (d, 1H, J = 8.73 Hz), 7.14 (s, 1H), 7.03 (d, 1H, J = 8.7 Hz), 6.49 (s, 2H), 2.26 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 158.61, 158.06, 138.05, 137.80, 132.78, 121.93, 119.01, 118.52, 23.04.

Anal. Calcd. for $C_9H_{10}BrN_5O_2S$: C, 32.54; H, 3.03; N, 21.08. Found: C, 32.40; H, 3.01; N, 20.50.

N-(4-Bromo-3-methylphenyl)-5,7-dichloro-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide (**17**).

A mixture of 6.62 g (0.02 mole) of **16**, 2.08 g (0.02 mole) of malonic acid, and 20 ml (0.21 mole) of phosphorus oxychloride was stirred and heated in an oil bath to 90° for 24 hours. The mixture was worked up by pouring to ice water and filtering the solid. The yield of the light brown solid was 8.40 g (96%, assay 85-88%). The light brown solid (7 g) was slurried in 50 ml of hot (120-140°) *o*-dichlorobenzene and filtered. The filtrate on cooling gave 5.2 g of **17**, mp 220-222° dec; ir (potassium bromide): ν 3100, 1587, 1501, 1172 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 11.32 (s, 1H), 8.18 (s, 1H), 7.48 (d, 1H, J = 8.67 Hz), 7.25 (d, 1H, J = 2.43 Hz), 7.06 (dd, 1H, J = 2.73, 8.6 Hz), 2.28 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 160.91, 155.58, 153.53, 149.81, 138.03, 132.66, 122.70, 119.69, 119.14, 98.30, 22.73.

Anal. Calcd. for $C_{12}H_8BrCl_2N_5O_2S$: C, 32.97; H, 1.84; N, 16.02. Found: C, 33.05; H, 1.95; N, 15.90.

N-(4-Bromo-2,6-dichloro-3-methylphenyl)-5,7-dichloro-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide (**18**).

A solution of 5 g (0.011 mole) of **17** in 50 ml of acetonitrile/water (45/5) was cooled in ice water, and chlorine gas (3.25 g, 0.04 mole) was bubbled through the solution and left to stir overnight. The resulting precipitate was filtered and dried to yield the sulfonamide **18** as yellow solid, 4.71 g (85%), mp 226-227°; ^{1}H nmr (DMSO-d_6): δ 8.23 (s, 1H), 7.88 (s, 1H), 2.44 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 161.56, 155.64, 153.26, 149.91, 135.99, 133.68, 131.34, 130.76, 124.48, 98.26, 21.27; ms: m/z 505 (M^+), 470, 254.

Anal. Calcd. for $C_{12}H_6BrCl_4N_5O_2S$: C, 28.49; H, 1.2; N, 13.84. Found: C, 28.57; H, 1.19; N, 13.68.

N-(4-Bromo-2,6-dichloro-3-methylphenyl)-5,7-dimethoxy-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide (**19**).

A solution of 11.6 g (0.023 mole) of **18** in 120 ml of methanol was cooled in ice water and to it was added sodium methoxide (4.95 g, 0.0920 mole, 20 ml of 25 wt% in methanol) dropwise and stirred at ice bath temperature. After 30 minutes, the reaction was quenched with acetic acid (4 equivalents) and poured into 200 ml of water. The white precipitate was filtered and dried to yield 10.8 g (95%) of **19**, mp 198-200°; ir (potassium bromide): ν 3100, 1660, 1555, 1387, 1226, 1172 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.99 (s, 1H), 6.67 (s, 1H), 4.34 (s, 3H), 4.16 (s, 3H), 2.55 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 168.68, 163.98, 157.2, 155.17, 136.82, 135.77, 131.19, 130.60, 124.33, 81.82, 58.60, 54.84, 21.08; ms: m/z 498 (M^+).

Anal. Calcd. for $C_{14}H_{12}BrCl_2N_5O_4S$: C, 33.82; H, 2.43; N, 14.09. Found: C, 33.95; H, 2.42; N, 14.00.

N-(2,6-Dichloro-3-methylphenyl)-5,7-dimethoxy-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide (**10**).

A mixture of 5.0 g (0.01 mole) of **19**, 1.36 g (0.01 mole) of sodium acetate hydrate, 0.53 g of palladium on carbon (10%) in 130 ml of acetonitrile and 10 ml of water was pressurized with 50 psi of hydrogen in a Parr reactor. The mixture was stirred for 0.5 hour and the hydrogen vented. Filtration and concentration of the filtrate gave **10** as a white solid, 3.75 g (90%, assay of 91%). Digestion with dimethyl formamide/acetic acid and diluting with methanol gave pure **10**, mp 224-226° [3]; ir (potassium bromide): ν 3100, 1649, 1552, 1388, 1225, 1171 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ

10.80 (s, 1H), 7.40 (d, 1H, J = 8.3 Hz), 7.35 (d, 1H J = 8.3 Hz), 4.20 (s, 3H), 4.02 (s, 3H), 2.29 (s, 3H); ^{13}C nmr (DMSO-d_6): δ 168.55, 164.15, 157.18, 155.15, 136.19, 136.05, 132.87, 131.16, 130.59, 127.76, 81.74, 58.56, 54.82, 20.03; ms: m/z 498 (M^+).

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