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Application of the Tisler Triazolopyrimidine Cyclization to the Synthesis of a Crop Protection Agent and an Intermediate

Bruce M. Bell,[†] Phillip E. Fanwick,[§] Paul R. Graupner,[‡] and Gary A. Roth*[,⊥]

Dow Chemical Company, Analytical Sciences, 1897 Building, Midland, Michigan 48674, U.S.A., Purdue University, Department of Chemistry, West Lafayette, Indiana 47907, U.S.A., Dow AgroSciences LLC, Discovery Research, 306 Building, Indianapolis, Indiana 46268, U.S.A., and Dow Chemical Company, Process Sciences, 1710 Building, Midland, Michigan 48674, U.S.A.

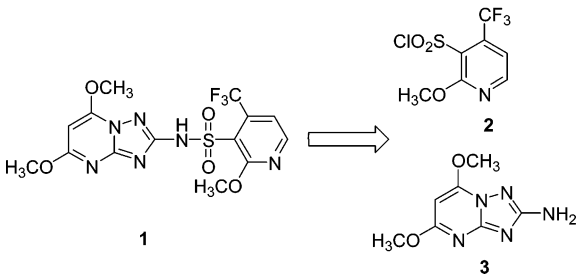
Abstract:

A new synthetic route to the Dow AgroSciences early stage sulfonamide herbicide 3-(2-methoxy-4-trifluoromethyl)-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)pyridinesulfonamide (pyroxsulam) has been developed. The synthesis is based on formation of the triazole ring as the final step, utilizing the Tisler triazolopyrimidine cyclization. A Tisler cyclization route to 2-amino-5,7-dimethoxy-1,2,4-trazolo[1,5-*a*]pyrimidine starting with 2-chloro-4,6-dimethoxypyrimidine has also been demonstrated.

Certain sulfonamides make up a class of compounds that are highly efficacious against a variety of weed species in a number of important agricultural crops.[1] A general synthetic entry into these materials has been the coupling of an appropriate sulfonyl chloride with a substituted amine. In the event of a stubborn coupling, sulfilimine catalysis can be very useful.[2] During the course of process research on the sulfonamide herbicide 3-(2-methoxy-4-trifluoromethyl)-*N*-(5,7-dimethoxy[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)pyridinesulfonamide (**1**), we encountered what originally appeared to be one of these difficult coupling reactions (Scheme 1).

Even with sulfilimine catalysis, yields of 55−75% were common, depending on the quality of the starting materials. Earlier work from these laboratories showed that sulfonyl chloride **2** could be induced to undergo coupling with other amino-heterocycles in yields approaching 90%. These results suggested that the lack of nucleophilicity of amine **3** may be a contributing problem in the present coupling. On the basis of this rationalization, we set out to devise an alternate synthetic route in which the sulfonyl chloride (**2**) coupling reaction would be conducted, using what we anticipated would be a more nucleophilic system. The final steps of the synthesis would then form the triazolopyrimidine ring system.

Scheme 1



A preface on the Tisler triazolopyrimidine cyclization is appropriate at this point.

Tisler and co-workers have found that the thermal cyclization of substituted 1,2,4-oxadiazol-5-ones can provide 2-amino-*s*-triazolo[1,5-*a*]pyrimidines in moderate yields.[3] The original preparation of triazolopyrimidine **3**[4] within Dow AgroSciences laboratories was based on Tisler's cyclization reaction.[5] Thus, commercially available amino pyrimidine **4** was treated with *N*-carboethoxyisothiocyanate (**5**) providing *N*-ethoxycarbonyl thiourea **6**. Reaction of **6** with hydroxylamine in ethanol followed by heating the reaction mixture afforded the desired triazolopyrimidine **3** via the intermediates (**7** and **8**) depicted in Scheme 2.

Although this preparation of heterocycle **3** worked well, thiourea **9** was inevitably formed as a side-product (2−4% by HPLC analysis). Under reaction conditions in which the liberated hydrogen sulfide is not efficiently removed from the system, another impurity was formed in substantial quantities (up to 4 area % via HPLC) and was tentatively identified as guanidine **10**. An alternate synthesis of **3**, again based on the work of Tisler, is presented in Scheme 3. Reaction of chloropyrimidine **11** with sodium cyanamide gave cyanoaminopyrimidine **12**.[6] Treatment of **12** with hydroxylamine afforded *N*-hydroxyguanidine **13**,[6] which then was *O*-acylated by reaction with ethylchloroformate to give **14**.[7] Spectral and chromatographic data for **14** were much different than the same data obtained for **7**. Heating **14** in

* To whom correspondence should be addressed. E-mail: garoth@dow.com. Telephone: 989-638-6132.

[†] Dow Chemical Company, Analytical Sciences.

[§] Purdue University.

[‡] Dow AgroSciences LLC.

[⊥] Dow Chemical Company, Process Sciences.

(1) Kleschick, W. A. *Chem. Plant Prot.* **1994**, *10*, 119−143; CAN 122:153980.

(2) Ringer, J. W.; Scott, C. A.; Pearson, D. L.; Wallin, A. P. *N*-Arylsulfilimine Compounds and Their Use as Catalysts in the Preparation of *N*-Arylarylsufonamide Compounds. U.S. Patent 5,973,148, October 26, 1999. Ringer, J. W.; Pearson, D. L.; Scott, C. A.; Wallin, A. P. *N*-Arylsufilimine Compounds and Their Use as Catalysts in the Preparation of *N*-Arylarylsulfonamide Compounds. U.S. Patent 6,114,580, September 5, 2000.

(3) Vercek, B.; Ogoreve, B.; Stanovnik, B.; Tisler, M. *Monatsh. Chem.* **1983**, *114*, 789−798.

(4) For an earlier preparation of **3**, see: Bee, M. A.; Rose, F. *J. Chem. Soc. C* **1966**, 2031.

(5) Johnson, T. C.; Van Heertum, J. C.; Ouse, D. G.; Arndt, K. E.; Pobanz, M. A.; Walker, D. K. *N*-(5,7-Dimethoxy[1,2,]triazolo[1,5-*a*]pyrimidin-2-yl)-aryl Sulfonamide Coupounds and Their Uses as Herbicides. U.S. Patent 6,559,101 B2, May 6, 2003.

(6) Diehr, H. J.; Pest, C.; Kirsten, R.; Kluth, J.; Mueller, K. H.; Pfister, T.; Priesnitz, U.; Rieble, H. J.; Roy, W. EP 173321, 1986.

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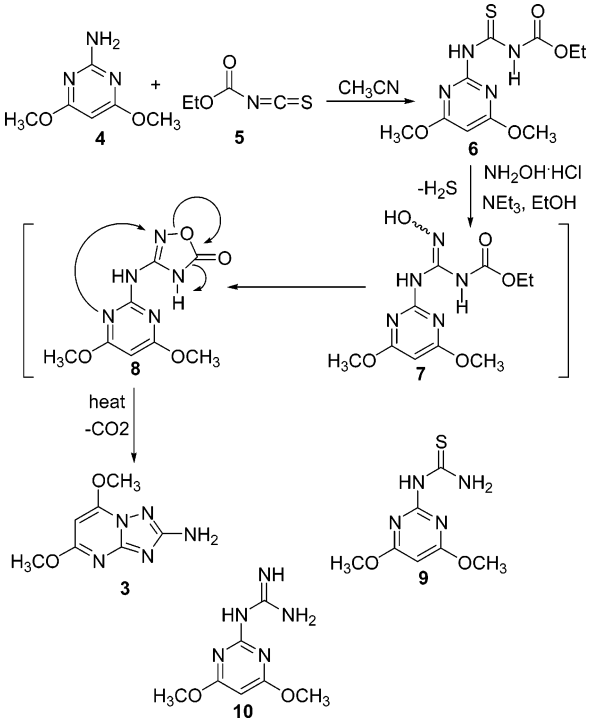
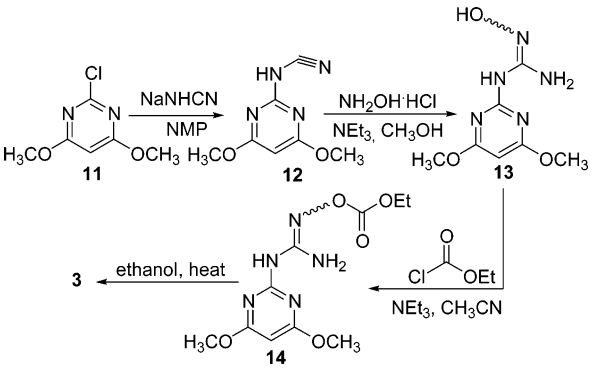
Scheme 2



Scheme 3

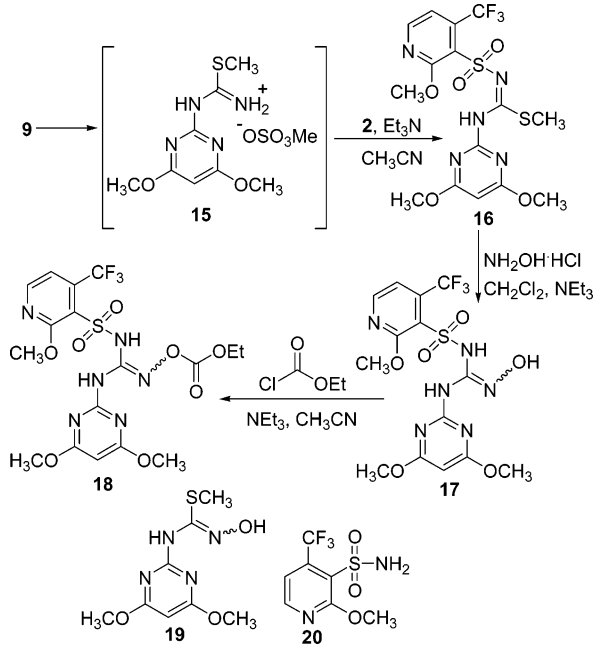


ethanol at reflux provided the desired heterocycle **3** via the intermediate **8** (Scheme 2), as determined by following the reaction using HPLC. This route provided material of higher quality than did the previous synthesis, and the byproducts **9** or **10** were avoided.

As stated previously, aminotriazolopyrimidine **3** seemed to be unreactive toward coupling with the desired sulfonyl chloride **2**, providing only moderate yields of sulfonamide **1**. Therefore, we devised an alternative route to **1** in which the coupling reaction would be conducted using the better nucleophile **15** as the free base, (Scheme 4). The final steps of the synthesis would then be directed at triazole ring formation.

Methylation of thiourea **9** using a literature method provided thioimidate **15**[8,9] which when reacted with **2** (Scheme 4) provided good yield of a compound whose ^{1}H

Scheme 4



NMR and mass spectrum were consistent with the desired product **16** (or imine isomer). We speculated, in conjunction with a literature reference,[10] that we had the desired material **16** (or a tautomer or imine isomer). However, on the basis of our spectroscopic data, we could not completely rule out that we had formed a regioisomer of **16** as a result of sulfonylation at the amine group connected to the pyrimidine ring. This issue is not readily resolved by NMR studies due to the absence of protons in the molecule. However, advances in the use of ^{15}N NMR at natural abundance has given rise to the use of two-dimensional heteronuclear multiple bond correlation spectroscopy (HMBC) experiments in solving similar problems.[11] In this case, the ^{15}N chemical shift of the protonated nitrogen should indicate the site of sulfonylation. For example imine nitrogen atoms resonate at about 300 ppm (wrt NH_3 at 0 ppm) and secondary amines at about 100 ppm. A single ^{15}N HMBC optimized for 4 Hz indicated a protonated nitrogen at 139 ppm. Additionally, a correlation was found from this proton to a nitrogen at 213 ppm, which also indicated a correlation to the pyrimidine proton. Thus, it was possible to assign the structure as tautomer **16** and neither of the other two possibilities. Final structural proof was established by X-ray diffraction analysis of compound **16** (Figure 1). It is interesting to note that the sulfone group of the sulfonamide and the NH of the thioimidate are in a syn relationship across the imine double bond (N9═C8). This stereochemistry is likely a result of the six centered hydrogen-bonding arrangement that these two functional groups can attain.

Treatment of thioimidate **16** with hydroxylamine hydrochloride and a tertiary amine base (e.g., Hunigs base, triethylamine) in methanol or acetonitrile resulted in forma-

(7) D'Alo, G.; Perghum, M.; Grunanger, P. *Ann. Chim.* (Rome) **1963**, *53*, 1405−1410; Gross, M.; Held, P.; Schubert, H. *J. Prakt. Chem.* **1974**, *316*, 434.

(8) The intermediate *S*-methylisothiourea **15** could be isolated; however, it was more convenient to use the acetonitrile solution of the intermediate in the following step.

(9) Riedel, H. J. EP 533012, 1993; CAN 119:72622.

(10) Gesing, E. R.; Fest, C.; Kirsten, R.; Kluth, J.; Mueller, K. H.; Helmut, K.; Riebel, H. J.; Santel, H. J.; Luerssen, K. S.; Rober, T. EP 413221, 1991; CAN:115:87494.

(11) For a review of 2D inverse NMR spectrosopy for ^{15}N see: Martin, G. E.; Hadden, C. E. *J. Nat. Prod.* **2000**, *63*, 543.

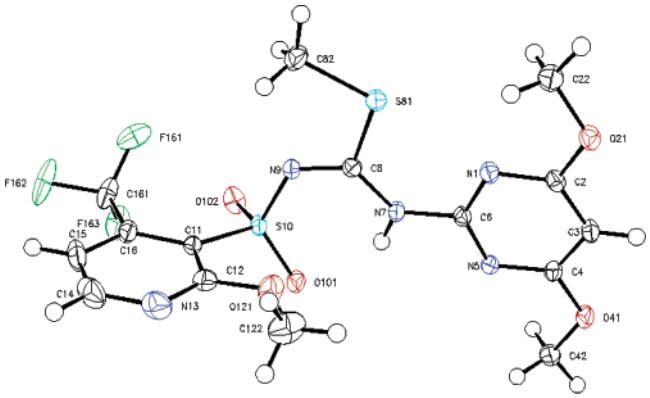
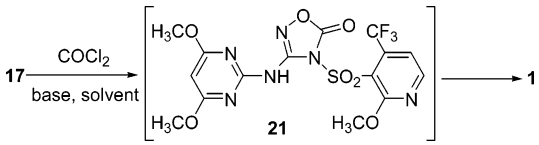


Figure 1. **ORTEP plot of 16.**

tion of **17**; however, this was accompanied by formation of significant quantities of **13** (Scheme 3). Use of sodium acetate as the base efficiently suppressed formation of **13**; however, under these conditions significant amounts of sulfonamide **20** and oxime **19** resulted. The reaction of **16** with hydroxylamine hydrochloride/triethylamine in methylene chloride gave the desired oxime **17** in good yield. Treatment of **17** with ethyl chloroformate in the presence of base provided the *O*-acylated oxime **18**. However, all attempts at cyclization of **18** to **1** resulted in very low yields and the formation of two major products as determined by LC/MS analysis. These products were identified (LC/MS) as an isomer of **1** and a reduction product of **17** in which a hydrogen atom had replaced the hydroxyl group of the oxime. It was at this point that we began to doubt our structural assignment of **16** and the previously described HMBC and X-ray studies were initiated. Eventually we found that treatment of a acetonitrile solution of **17** with phosgene in the presence of potassium carbonate rapidly produced oxadiazolone **21** (Scheme 5).

Scheme 5



Compound **21** (only characterized via LC/MS) could be isolated; however, even upon standing as a solid at room temperature the material slowly cyclized to the desired product (**1**). The best method of operation was to continue stirring the phosgenation reaction at room temperature or slightly above, thus producing **1** in the same reaction vessel.

Conclusions

A new synthetic route to the sulfonamide herbicide pyroxsulam (**1**) has been developed. This route relies on coupling of the appropriate pyridine sulfonyl chloride (**2**) with a nucleophilic thioimidate (**15**) followed by a Tisler triazolopyrimidine cyclization reaction. In addition, an alternative synthetic route to 2-amino-5,7-methoxy-1,2,4-trazolo[1,5-*a*]pyrimidine (**3**) starting with 2-chloro-4,6-dimethoxypyrimidine (**11**) has been demonstrated.

Experimental Section

High performance liquid chromatography (HPLC) was performed on a Zorbax RX-C8 (4.6 mm × 250 mm) column using varying concentrations of CH_3CN and water as the eluent (0.1% formic acid) at 1.0 mL/min flow rate. Detection was accomplished at 250 nm. NMR spectra were obtained with a Bruker 300 FT-NMR. Additional NMR experiments were performed on a Bruker DRX600 spectrometer operating at 600.13 MHz (^{1}H) and 60.8 MHz (^{15}N). HPLC/MS analyses were conducted on a Waters Alliance 2690 (chromatography conditions as above)/Micromass QTOF2 quadrupole/time-of-flight MS/MS system via a Micromass Z-spray electrospray (ESI) interface, operating in the positive ion mode. Combustion analyses were performed at Galbraith Laboratories, Knoxville, TN. The X-ray cystallographic analysis was performed by Phil Fanwick, Department of Chemistry, Purdue University, West Lafayette, IN. All reported yields were determined by weight, assuming a product purity of 100%, unless stated otherwise.

2-Cyanamino-4,6-dimethoxypyrimidine (12). A 125-mL three-neck vessel was purged with N_2 and then fitted with a thermometer, condenser/N_2 inlet, a stopper, and a stir bar. To the pot was added the chloropyrimindine **11** (10.0 g, 57.3 mmol) and NMP (50 mL). The resulting solution was treated with sodium cyanamide (8.3 g, 0.13 mol) and the mixture stirred at room temperature until the reaction was complete as determined by HPLC (several days). To the thin slurry was added water (100 mL), causing complete dissolution of all solids. Concentrated HCl was added dropwise with stirring to a pH of 6. The resulting thick slurry was treated with ice (97 g) and the mixture stirred until all the ice had melted. The precipitate was collected by filtration, and the solid was washed with 1 cake volume of water. The material was air-dried overnight and then dried to a constant weight (55 °C/5 mmHg), providing the product as a fluffy, white solid (9.4 g, 91%): mp 195 °C; ^{1}H NMR (DMSO-d_6) 3.86 (s, 6H), 5.86 (s, 1H),11.46 (bs, 1H); MS (LC, ESI) 181 (M^+, 100).

***N*-4,6-Dimethoxy-2-pyrimidinyl-*N′*-hydroxyguanidine (13).** A 100-mL three-neck vessel was flushed with N_2 and then fitted with a thermometer, reflux condenser/N_2 inlet, a stopper, and a stir bar. The cyanamino-pyrimidine **12** (4.9 g, 27.2 mmol), CH_3OH (30 mL), and hydroxylamine hydrochloride (2.0 g, 29 mmol) were charged into the vessel. Triethylamine (4.2 mL, 30 mmol) was added, and the mixture was stirred at room temperature for 5 h. The reaction was warmed to 45 °C and stirred overnight. After stirring an additional 3 h at 45 °C, HPLC analysis indicated no change. Hydroxylamine hydrochloride (0.5 g) and triethylamine (1 mL) were added, and the mixture was stirred at 45 °C overnight. The off-white slurry was treated with water (30 mL) and stirred for 20 min. The resulting solid was collected by filtration and washed with 1 cake volume of water. The material was dried to a constant weight (60 °C/5 mmHg), providing the product as a white solid (4.7 g, 81%): mp 180−185 °C (dec, gassing); ^{1}H NMR (DMSO-d_6) 3.81 (s, 6H), 5.62 (s,1H), 6.27 (bs, 2H), 8.65 (bd, 2H); HRMS (LC/ESI) calcd for $C_7H_{11}N_5O_3$, 213.0862; found, 213.0847.

***N*-4,6-Dimethoxy-2-pyrimidinyl-N′-ethoxycarbonyloxy guanidine (14).** A 50-mL three-neck vessel was purged with N_2 and then fitted with a thermometer, condenser/N_2 inlet, a stir bar, and a stopper. To the reactor was added **13** (1.0 g, 4.7 mmol) and CH_3CN (15 mL). The slurry was treated with ethyl chloroformate (0.66 mL, 6.9 mmol) followed by triethylamine (0.96 mol, 6.9 mmol). At first the slurry thinned and then became very thick while exotherming to 35 °C. The thick slurry was stirred at ambient temperature for 30 min, and then water (20 mL) was added. The aqueous slurry was stirred for 15 min, and the solid was collected by filtration. The cake was washed with a little water, and the material was air-dried to a constant weight, affording **14** as a fluffy, white solid (0.8 g, 60%): ^{1}H NMR (DMSO-d_6) 1.24 (t, J = 7.5 Hz, 3H), 3.82 (s, 6H), 4.16 (q, J = 7.5 Hz, 2H), 5.75 (s, 1H), 7.27 (bs, 2H), 9.65 (s, 1H); MS (LC/ESI) 286 (M + H); Anal. Calcd for $C_{10}H_{15}N_5O_5$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.92; H, 5.27; N, 24.32.

2-Amino-5,7-methoxy-1,2,4-triazolo[1,5-*a*]pyrimidine (3) by Cyclization of 14. The guanidine **14** was slurried in ethanol (7 mL) and the mixture heated to reflux under nitrogen. All solids went into solution, and then a precipitate soon began to form. The slurry was heated at reflux a total of 5.5 h at which time HPLC analysis indicated that the reaction was complete. The slurry was cooled to room temperature, and the precipitate was collected by filtration and washed with ethanol (5 mL). The material was dried to a constant weight at 60 °C/5 mmHg providing **3** as a white solid (240 mg, 88%). ^{1}H NMR (DMSO-d_6) 3.33 (s, H_2O), 3.90 (s, 3H), 4.07 (s, 3H), 5.94 (bs, 2H), 6.07 (s, 1H).

***N*-[*N*-(4,6-Dimethoxypyrimidin-2-yl)-*S*-methylthiocarbamoyl]-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide (16) via a One-Pot Process from 9.** A 250-mL three-neck vessel was flushed with N_2 and then fitted with a condenser/N_2 inlet, a thermometer, and a stopper. The thiourea (**9**, 11.6 g, 54.5 mmol), CH_3CN (60 mL), and dimethyl sulfate (5.8 mL, 61.3 mmol) were added, and the slurry was heated to reflux. After 2 h most of the solid had gone into solution. The mixture was allowed to reflux an additional 0.5 h, and then was cooled to room temperature and allowed to stir overnight. The reaction had set up into a white mass, and thus CH_3CN (40 mL) was added which allowed stirring. To the white slurry was added **2** (18 g, 65 mmol) and triethylamine (23 g, 0.23 mol). All solids went into solution over 5 min, and the temperature rose to 30 °C. The mixture was warmed to 45 °C and allowed to stir overnight. The amber slurry was transferred to a 500-mL flask and then chilled in an ice bath. To the slurry was added 2 M HCl (116 mL) in portions. After the addition was complete, the slurry was stirred in an ice bath for 45 min (6 °C). The solid was collected by filtration and washed with 2 cake volumes of water. The material was dried to a constant weight (60 °C/5 mmHg), providing **16** as light-beige crystals (17.1 g, 67%). A small sample was recrystallized from ethyl acetate, providing an analytical sample: mp 184−85 °C; ^{1}H NMR ($CDCl_3$) 2.18 (s, 3H), 3.97 (s, 6H), 4.04 (s, 3H), 5.83 (s, 1H), 7.35 (d, J = 5.2 Hz, 1H), 8.44 (d, J = 5.2 Hz, 1H), 11.02 (bs, 1H); HRMS (LC/ESI) calcd for $C_{15}H_{16}F_3N_5O_5S_2$, 467.0545; found, 467.0557. Anal. Calcd for: C, 38.54; H, 3.45; N, 14.98. Found: C, 38.62; H, 3.48; N, 14.99.

***N*-[*N*-(4,6-Dimethoxypyrimidin-2-yl)-*N*′-hydroxycarbamimidoyl]-2-methoxy-4-(trifluoromethyl)pyridine-3-sulfonamide (17).** A 100-mL single-neck flask was purged with N_2 and then fitted with a stir bar and a condenser/N_2 inlet. To the vessel was added **16** (5.5 g, 11.8 mmol) and CH_2Cl_2 (40 mL). To the slurry was added NH_2OH hydrochloride (1.56 g, 22 mmol) followed by triethylamine (3.1 mL, 22 mmol). The mixture was stirred at room temperature for a total of 3 h at which time HPLC analysis indicated the reaction was complete. Water (15 mL) was added, and then the vessel was fitted with a N_2 sparge tube which was connected to a bleach scrubber. The two-phase mixture was sparged with N_2, causing most of the CH_2Cl_2 to evaporate and a solid to precipitate. Methanol (25 mL) was added, and sparging was continued for 30 min to ensure that all the CH_2Cl_2 had been removed. The white precipitate was collected and washed with water, leaving 5.8 g of wet solid. The material was allowed to air-dry overnight, providing 4.7 g of white crystals. The solid was dissolved in 150 mL of boiling methanol and then concentrated to a total volume of 50 mL. After cooling in an ice bath the product was collected by filtration and washed with a little methanol. The solid was dried to a constant weight (5 mmHg/room temperature) providing **17** as white crystals (4.1 g, 77%): mp 186−187 °C (dec, off-gassing); ^{1}H NMR (DMSO-d_6) 3.23 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 6.07 (s, 1H), 7.51 (d, J Hz, 1 H), 8.59 (d, J = 5.1 Hz, 1H), 10.08 (bs, 2H), 11.46 (bs, 1H); HRMS (LC/ESI) calcd for $C_{14}H_{15}F_3N_6O_6S$, 452.07259; found, 452.0729.

(3-(2-Methoxy-4-trifluoromethyl)-*N*-(5,7-dimethoxy-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)pyridinesulfonamide) (1). Hydroxyguanidine **17** (2.0 g, 4.4 mmol) was slurried in CH_3CN (20 mL) and cooled to −5 °C under N_2. Potassium carbonate (1.38 g, 10 mmol) was added, followed by dropwise addition of phosgene in toluene (ca. 20%, 2.6 mL, ca. 4.9 mmol). The reaction was stirred at this temperature for 40 min at which time HPLC analysis indicated 15% of **17** remained. After stirring an additional 30 min HPLC analysis indicated 15% of **17** still remained. Additional phosgene/toluene (0.25 mL) was added and the reaction stirred at −5 °C for 30 min at which time HPLC indicated that less than 2% of **17** remained. The white slurry was warmed to room temperature and allowed to stir overnight. HPLC analysis indicated that 9% of oxadiazolone **21** remained. The white slurry was warmed to 35 °C and was held there for 30 min at which time HPLC indicated the cyclization was complete. The slurry was cooled to room temperature and then treated with water (15 mL). The pH was adjusted to 2 by dropwise addition of concentrated HCl. The volatiles were removed on the rotary evaporator (35 °C/25 mmHg), leaving a white slurry. The solid was collected by filtration and washed with a little water to give 2.74 g of crude wet material. HPLC analysis of the wet material revealed three major peaks: (1) rt 3.07 min, 7.9%; HRMS indicated this impurity is an isomer of **1**; (2) rt 3.52 min, 79.5% **1**; (3) rt 5.84 min, 10.9%, toluene. The wet solid

was dried to a constant weight (80 °C/ 25 mmHg), providing the product as a white solid (1.84 g). A 1.0 g sample was dissolved in boiling CH_3OH/CH_3CN (60 mL/10 mL) and then concentrated to a total volume of 15 mL. The mixture was cooled in an ice bath, and the resulting crystals were collected and washed with a little CH_3OH. The material was dried to a constant weight (5 mmHg/room temperature) providing **1** as white needles (944 mg, 91.1% purity via external standard HPLC analysis, 83% yield based on recrystallization of all of the 1.84 g of crude material). This sample contained 2.3 area % of an isomer of **1** and 6.6 wt % CH_3CN.

Acknowledgment

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