The Synthesis of Several Novel Triazine Ring Hydrolysis Products of *N*-[[(4-Methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]-2-(3,3,3-trifluoropropyl)benzenesulfonamide [1]

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The syntheses of four hydrolysis products isolated from environmental studies on the title compound are reported. Spectral comparison of these synthetic standards with study isolates provided proof for sulfonyl urea intact triazine ring hydrolysis.

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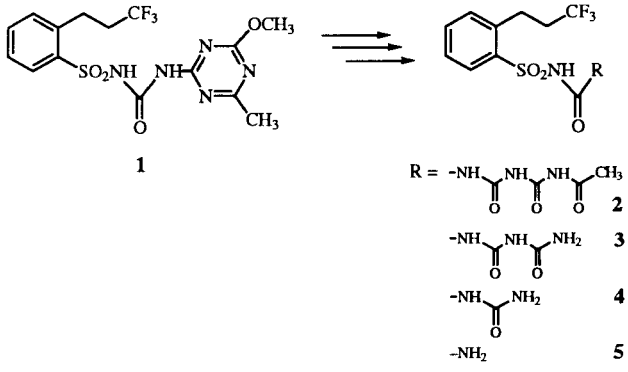
Because of their reputation as low use rate herbicides [2], sulfonylureas have enjoyed great popularity since their initial discovery by DuPont in the mid-1970's [3]. Typically these compounds are comprised of three distinct moieties: an aryl portion, a sulfonyl urea bridge and a heterocyclic substituent. Early in the development of sulfonylureas, researchers discovered that certain aromatic heterocycles greatly enhanced herbicidal activity when coupled to various aryl substituents. One such class of compounds, which not only demonstrate biological activity when coupled as a sulfonylurea but also independently, are the 1,3,5-triazines. The title sulfonylurea (CGA-152005) **1**, is but one example of the many herbicidal sulfonylureas containing such a triazinyl substituent. As with all potential agricultural products, one of our main concerns was the environmental fate of **1**. During the course of a *p*H 5 hydrolysis study and a subsequent aerobic aquatic study on sulfonylurea **1**, several novel products (**2-5**) were identified by mass spectral and ^{1}H nmr analyses. In this article, we would like to report the synthesis of compounds **2-5** which were used as synthetic standards for structural confirmation of these isolates [4].



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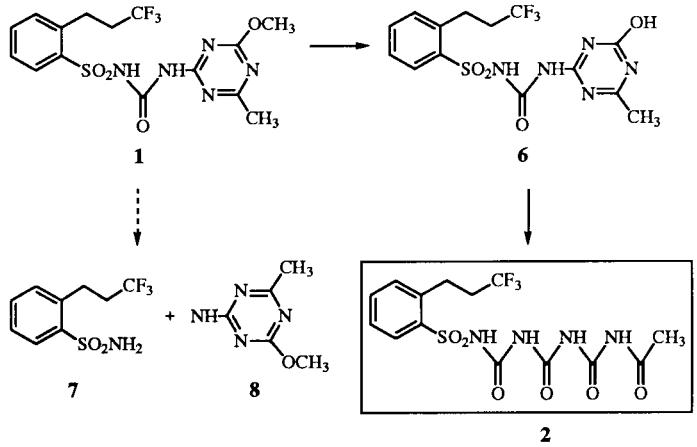
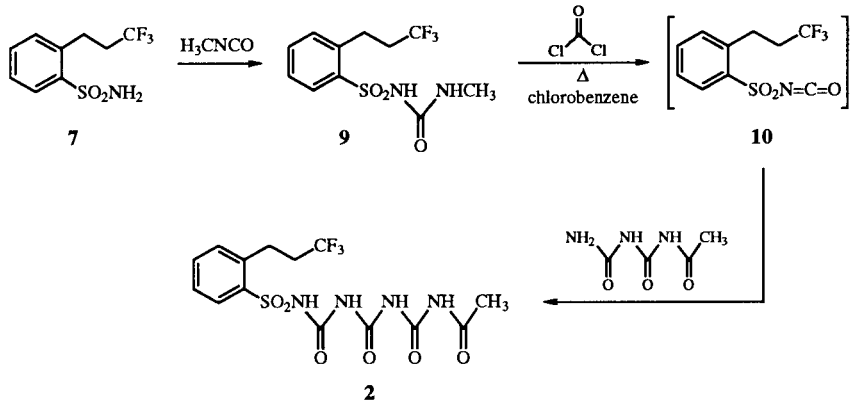
During the early stages of our research, Reiser *et al.* [5] of DuPont published an article which postulated the existence of a ring-opened 1,3,5-triazine intermediate from the sulfonylurea chlorsulfuron. Interestingly, this compound bears the same 2-amino-4-methoxy-6-methyltriazine substituent as **1**. The degradation pathway proposed by Reiser was identical to that proposed for the hydrolysis of compound **1** (Scheme 1), but in the absence of a synthetic standard for the hypothesized ring opened triazine analogous to **2**, it was not possible to obtain absolute confirmation of the suspected product. As in the DuPont study, identification of several other products from *p*H 5 hydrolysis such as bridge cleavage products **7** and **8** and demethylated triazine derivative **6** was accomplished here at Ciba by comparison of the isolates' spectral data to that of synthesized standards.

Scheme 1



The existence of ring opened triazine degradates and metabolites has been postulated by several other groups [6,7], but in the absence of isolation and definitive characterization, never confirmed. Thus, in order to conclusively prove the presence of compound **2** in the hydrolysis mixture, we devised the following synthesis:

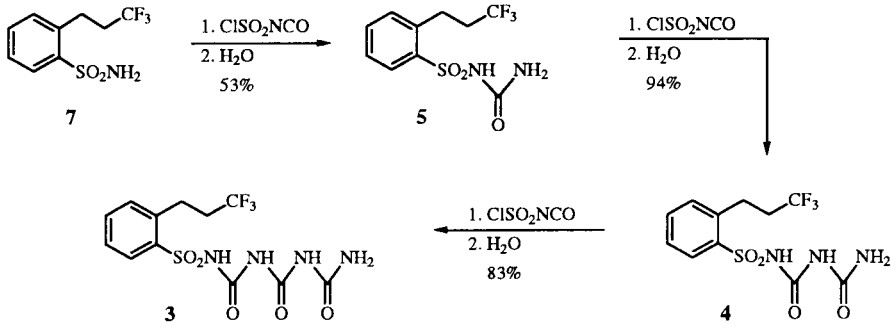
The sulfonamide **7** [8] was converted to the corresponding sulfonylurea **9** [8] in quantitative yield by treatment with *N*-methylisocyanate. *In situ* generation of the isocyanate **10** from **9** was accomplished with phosgene in refluxing chlorobenzene. Isocyanate **10** was not isolated



7 9 10 2

but coupled directly with acetyl biuret to provide the desired acetamide derivative **2** in an overall yield of 13% from **7**. Compound **2** was compared to the ø-^{14}C-labelled compound isolated from a pH 5.0 hydrolysis study by preparative tlc and was found to match the isolate by mass spectral analysis and ^{1}H nmr data. Further synthesis of ø-^{14}C-labelled **2** also permitted identification by co-chromatography (hplc and tlc).

In summary, we have successfully synthesized several novel triazine ring hydrolysis products **3-6** in fair to high yields. Comparisons between the spectral data of the isolated compounds and the synthetic standards by our environmental fate group conclusively proved ring hydrolysis of appropriately 2,4,6-substituted-1,3,5-triazines. Further studies involving these new and interesting compounds are currently under investigation.



7 5 3 4

In a subsequent anaerobic aquatic metabolism study on ø and Ø-^{14}C-labelled sulfonylurea **1**, three additional compounds postulated as **3, 4** and **5** were identified by mass spectral analysis. The synthesis of these compounds was accomplished using chlorosulfonylisocyanate [9] to sequentially add urea units to the starting sulfonamide. Sulfonamide **7** was treated with chlorosulfonylisocyanate as shown above to afford **5** in a 53% yield. Subsequent reaction of **5** in the same manner gave **4** in 94% yield. Compound **3** was synthesized in a similar manner from **4** in a yield of 83%.

Comparison of the mass spectral data of synthetic materials **3, 4** and **5** to that of the anaerobic aquatic metabolites confirmed the identity of these materials. We believe compounds **3-5** may have formed by sequential hydrolysis of acetamide **2**, eliminating acetic acid and urea units as by-products.

EXPERIMENTAL

Melting points are uncorrected. All reagents and solvents were used as received from commercial sources unless otherwise noted. The nmr spectra were recorded in dimethyl sulfoxide-d_6 or the solvent indicated on a Bruker AMX400 FTNMR instrument at 400.13 (^{1}H) and 100.61 (^{13}C) MHz. The chemical shifts (δ) are reported in ppm relative to residual dimethyl sulfoxide for proton (δ = 2.49) and for carbon (δ = 39.5). *J* values are given in Hertz and the following proton multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quint = quintet, br = broad. Mass spectral analysis (ms) was performed on a Finnegan TSQ700 instrument using Xenon bombardment at 6 kilo volts and 1 milliampere. Pseudomolecular ions and important fragments are reported in *m/z* (percent base peak). Infrared spectra (ir) were recorded on a Mattson 2020 FTIR and values are listed in

cm^{-1}. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. High performance liquid chromatography (hplc) was performed on a HP 1050 under the conditions indicated and at a flowrate of 1 ml per minute and detector wavelength of 220 nanometers. All moisture sensitive reactions were performed under inert atmosphere conditions using oven-dried glassware.

N-[[[[[[[[2-(3,3,3-trifluoropropyl)phenyl]sulfonyl]amino]carbonyl]amino]carbonyl]-amino]carbonyl]acetamide (**2**).

N-Methylsulfonylurea (**9**) (380 mg, 1.2 mmoles) was suspended in chlorobenzene (7.5 ml) and the flask placed in an oil bath at 160°. A solution of phosgene in toluene (1.93M, 3.8 ml, 7.3 mmoles) was added in one portion and the resulting solution refluxed for 1.5 hour. The solution was cooled to room temperature and stirred for an additional 0.5 hour. Chlorobenzene was removed by rotary evaporation at 65° and at the vacuum pump. The tan solid residue was sonicated briefly in ether to remove sulfonamide **8** formed during the reaction as well as a dimer of this compound [10]. This afforded crude **2** as a white solid (312 mg, 56%). Analysis (hplc) of this sample by area % provided a purity value of 90%. An analytically pure sample of **2** was obtained by recrystallization from hot 2-propanol followed by cooling in ice to afford **2** as a white crystalline solid (67.1 mg, 13%), mp 180-182°; ms: (MW = 424.36), m/z 425, 405, 383, 280, 260, 237, 104; hplc: HP LiChropher 100 RP-18 (12.5 x 0.40 cm) acetonitrile:20 *mM* aqueous phosphoric acid = 2:3, Tr = 5.6 minutes; ir (potassium bromide): 3182, 1734, 1682, 1477, 1427, 1253, 1126, 763; ^{1}H nmr: δ 2.08 (s, 3H), 2.59 (m, 2H), 3.20 (m, 2H), 7.49 (t, J = 7.3, 1H), 7.55 (d, J = 7.1, 1H), 7.65 (dt, J = 7.5, 1.2, 1H), 8.00 (dd, J = 6.9, 1.2, 1H), 10.08 (bs, 1H), 10.95 (bs, 1H), 10.98 (s, 1H); ^{13}C nmr: 23.9, 24.8, 34.0 (t, J = 28.2), 127.2 (q, J = 267.0), 127.2, 130.7, 131.9, 134.0, 137.2, 138.2, 148.0, 148.9, 150.5, 172.9.

Anal. Calcd. for: $C_{14}H_{15}F_3N_4O_6S$: C, 39.62, H, 3.56, N, 13.21. Found: C, 39.55, H, 3.67, N, 12.88

N-(Aminocarbonyl)-2-(3,3,3-trifluoropropyl)benzenesulfonamide (**5**).

Sulfonamide **7** (10 g, 39.5 mmoles) was suspended in acetonitrile (40 ml). To this was added dropwise chlorosulfonylisocyanate (5.69 g, 40.2 mmoles) in acetonitrile (10 ml). After 45 minutes, water (20 ml) was added dropwise then heated to 40° for 15 minutes. The acetonitrile was removed under reduced pressure. The crude product (11.2 g) was filtered and washed with cold water. The solid was purified by chromatography on Merck Silica gel 60, 230 mesh (dichloromethane:acetonitrile = 8:2 followed by acetonitrile) to give **5** (6.3 g, 53%) as a white solid, mp 166-167° dec; ms: (MW = 296.27), m/z 297, 280, 260, 254, 190, 232; hplc: HP LiChrospher 100 RP-18 (12.5 x 0.4 cm) acetonitrile:20 *mM* aqueous phosphoric acid = 3:7, Tr = 5.9 minutes; ir (potassium bromide): 3483, 3296, 1720, 1467, 1163, 1026; ^{1}H nmr: δ 2.57 (m, 2 H), 3.2 (m, 2H), 6.1 (bs, 1H), 6.8 (bs,1H), 7.48 (m, 2H), 7.6 (t, J = 7.2, 1H), 7.91 (d, J= 7.7, 1H), 10.8 (bs, 1H); ^{13}C nmr 24.8, 33.9 (q, J = 27.6), 127.0 (q, J = 277.0), 127.1 130.0, 131.7, 133.4, 137.6, 138.0, 152.1.

Anal. Calcd. for $C_{10}H_{11}F_3N_2O_3S$: C, 40.54; H, 3.72; N, 9.46. Found: C, 40.75; H, 3.77; N, 9.23.

N-[[(Aminocarbonyl)amino]carbonyl]-2-(3,3,3-trifluoropropyl)benzenesulfonamide (**4**).

Compound **5** (2.7 g, 9.4 mmoles) was suspended in acetonitrile (20 ml). To this was added dropwise chlorosulfonylisocyanate (2.6 g, 18.9 mmoles) in acetonitrile (5 ml). After 1.5 hours, water (10 ml) was added dropwise. The mixture was heated to 40° for 15 minutes. The acetonitrile was removed under reduced pressure and the crude product was filtered and washed with ice cold water. The solid (644 mg) was purified by trituration with ether to yield **4** as a white solid (606.1 mg, 94%), mp 172-174°; ms: (MW = 339.29); m/z 339, 279, 172; hplc: HP LiChrospher 100 RP-18 (12.5 x 0.40 cm), acetonitrile:methanol:10 *mM* octanesulfonic acid in 0.1% aqueous phosphoric acid = 3:1:6, Tr = 4.7 minutes (98%); ir (potassium bromide): 3470, 3133, 1697, 1450, 1350; ^{1}H nmr: δ 2.62 (m, 2H), 3.20 (m, 2 H), 6.65 (s, 1 H), 7.37 (s, 1 H), 7.51 (t, J = 7.7, 1 H), 7.58 (d, J = 7.7, 1 H), 7.68 (t, J = 7.5, 1 H), 7.99 (t, J = 6.9, 1 H), 9.14 (s, 2 H); ^{13}C nmr: δ 24.7 (d, J = 3.1), 33.8 (q, J = 27.6), 127.4, 131.2, 131.9, 134.1, 137.1, 137.9, 149.6, 154.7, 127.0 (q, J = 277.0).

Anal. Calcd. for $C_{11}H_{12}F_3N_3O_4S$: C, 38.94; H, 3.56; N, 12.38. Found: C, 38.77; H, 3.55; N, 12.37

N-[[[[(Aminocarbonyl)amino]carbonyl]amino]carbonyl]-2-(3,3,3-trifluoropropyl)benzenesulfonamide (**3**).

Compound **4** (2.65 g, 7.82 mmoles) was suspended in acetonitrile (20 ml). To this suspension was added dropwise chlorosulfonylisocyanate (1.9 g, 13.7 mmoles) in acetonitrile (5 ml). After 1.5 hours, water (10 ml) was added dropwise. The mixture was then heated to 40° for 15 minutes. The acetonitrile was removed under reduced pressure. The product (3.1 g) was filtered and washed with ice water. Purification was by trituration with ether to afford **3** as a white solid (2.4 g, 83%), mp 186-189° dec; ms: (MW = 382.32), m/z 381, 338, 295, 252, 237, 205; hplc: YMC packed column AQ-303 S-5 ODS acetonitrile:10 *mM* hexanesulfonic acid in 0.1% aqueous phosphoric acid = 1:1, Tr = 4.7 minutes, (99%); ir (potassium bromide): 3447, 3339, 3142, 1734, 756; ^{1}H nmr: δ 2.60 (m, 2H), 3.21 (m, 2H), 6.82 (bs, 1 H), 7.35 (bs, 1H), 7.51 (m, 2H), 7.66 (m, 1H), 8.00 (t, J = 7.3, 1H), 9.63 (s, 1H), 10.20 (bs, 1H); ^{13}C nmr: δ 24.8, 33.2 (q, J = 27.6), 127.2, 130.7, 131.8, 134.1, 137.1, 138.1, 148.8, 151.8, 153.9, 127.0 (q, J = 277.0).

Anal. Calcd for $C_{12}H_{13}F_3N_4O_5S$: C, 37.66; H, 3.40; N, 14.63. Found C, 37.48, H; 3.57; N, 14.49.

REFERENCES AND NOTES

[1] Presented in part at the Eighth IUPAC International Congress of Pesticide Chemistry, July, 1994.

[2] Low use rate usually implies 2-75 g/ha.

[3] G. Levitt, Belgian Patent 853,374 (1977); *Chem. Abstr.*, **88**, 6935x (1978).

[4] The isolation and identification of isolates were accomplished by Ciba Plant Protection Environmental Fate Group and will be published at a latter date. A biological screen on compound **2** at an application rate of 2 kg/ha demonstrated no activity towards grasses and broadleaf weeds.

[5] R. W. Reiser, A. C. Barefoot, R. F. Dietrich, A. J. Fogiel, W. R. Johnson, and M. T. Scott, *J. Chromatogr.*, **91**, 554 (1991).

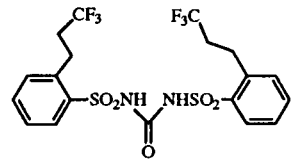
[6] M. L. Montgomery and V. H. Freed, *J. Ag. Food Chem.*, **12**, 11 (1964).

[7] R. Badon, J. Bastide, and J. Sabadie, *Chemosphere*, **21**, 289 (1990).

[8] W. Meyer and K. Oertle, Ciba-Geigy A.-G., European Patent Appl. EP 120,814 (1983); *Chem. Abstr.*, **102**, 62281a (1985).

[9] Farbwerke Hoechst, British Patent 1,230,473 (1968); *Chem. Abstr.*, **72**, 89756h (1970).

[10] This compound was identified by mass spectral analysis and ^{1}H nmr as the following dimer:



^{1}H nmr (deuteriochloroform): δ 2.44 (m, 4H), 3.15 (m, 4H), 7.37 (d, J = 7.7), 7.39 (t, J = 7.8), 7.59 (t, J = 7.5), 8.01 (d, J = 8.1), 8.98 (bs, 2H); ms: (chemical ionization, methane and ammonia, direct insertion probe, MW = 532.47), M+H$^+$ (533), 280, 260, 234, 188, 172, 152, 109.