Synthesis of Heterocyclic Sulfonylureas

Werner Löwe* and Norbert Matzanke

Institut für Pharmazie der Freien Universität Berlin,
Königin-Luise-Str. 2+4,
D-14195 Berlin, Germany
Received December 29, 1995

Dedicated to the memory of Professor Nicholas Alexandrou

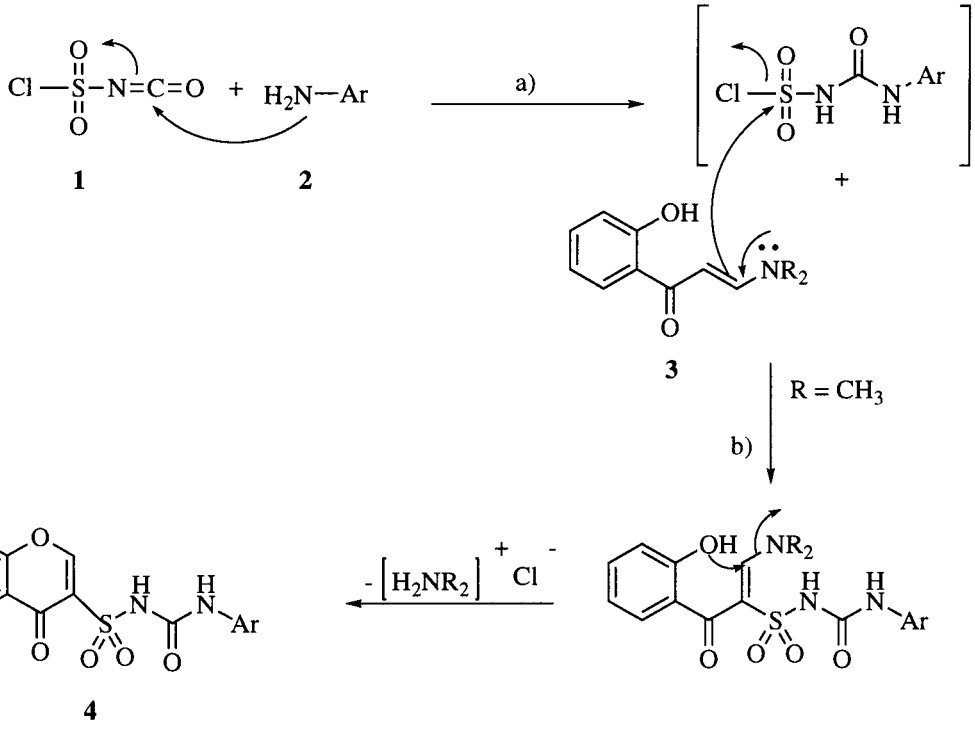
We examined the scope of the previously reported one-pot synthesis [1] of chromone-3-sulfonylureas. Different anilines and heterocyclic amines were thereby reacted with chlorosulfonyl isocyanate-derived chlorosulfonylureas. These were treated with different enaminones and enamines to provide the title compounds.

J. Heterocyclic Chem., **33**, 763 (1996).

Previously, we reported a new and simple synthetic method for preparing hitherto unknown chromone-3-sulfonylureas [1]. The chlorosulfonylureas are provided by adding 4-chloroaniline **2** (Ar = 4-Cl-C_6H_4) to chlorosulfonyl isocyanate **1**. The remaining electrophilic centre of the sulfur atom reacted with enaminones **3** derived from 2-hydroxyacetophenones and *N,N*-dimethylformamide dimethyl acetal [2] to provide the chromone-3-sulfonylureas **4** (Scheme 1). We have found that this reaction is widely applicable for the preparation of different substituted heterocyclic sulfonylureas.

In a first series of reactions different anilines with electron-withdrawing groups, sterically obstructed anilines (*e.g.* 2,6-difluoroaniline) and heterocyclic amines (*e.g.* 2-amino-4,6-dimethylpyrimidine) were added to a solution containing equimolar amounts of chlorosulfonyl isocyanate. The intermediates gave a moderate to good yield of the chromone derivatives without prior isolation by reacting with 3-dimethylamino-(2-hydroxyphenyl)-2-propenone (Table 1). Unsubstituted anilines, anilines with electron-donating groups and aliphatic amines decreased the yields due to the basicity of the amines. In this case,

Scheme 1



a) dioxane/ether, 1 hour 0°C; b) 60°C

no selective enhancement of the isocyanate moity of chlorosulfonyl isocyanate was possible [3].

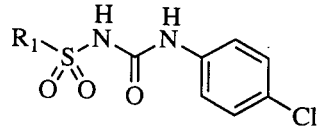
In a second series of reactions, we altered the enaminone compounds **3** to evaluate the scope of the reaction. No limits were observed when the chlorosulfonylurea was reacted with different enaminones, as is depicted in Table 2. The heterocyclic enaminones **3i** and **3j** [4] were transformed in the same manner. This reaction is not limited to enaminones. The cyclic enamine *N*-methylindole gave the indole-3-sulfonylurea **4k** in this procedure.

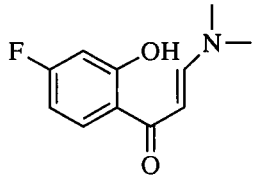
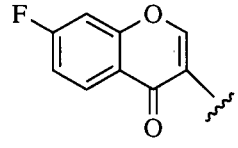
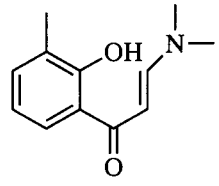
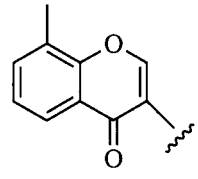
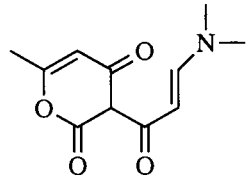
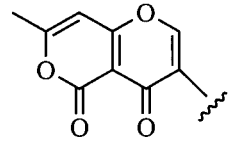
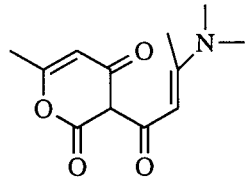
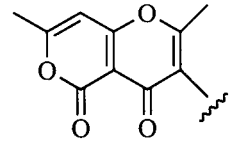
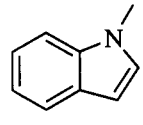
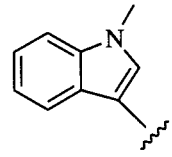
Preliminary experiments had indicated that chromone sulfonylureas are unstable in bases. This is due to their chromone C-2 electrophilic center, which is part of acyl-vinyl-sulfonyl structure. The addition of acid resulted in cleavage to sulfonamides, which can be used as precursors for further sulfonamide derivatives.

Table 1

Compound	Ar =	mp °C
4	4-chlorophenyl	255
4a	4-fluorophenyl	265
4b	2,4-dichlorophenyl	210
4c	2,6-difluorophenyl	150
4d	4,6-dimethyl-2-pyrimidyl	209
4e	4,6-dichloro-2-pyrimidyl	217
4f	4-methoxy-6-methyl-2-triazinyl	187

Table 2



Compound	Enaminones/Enamine	Compound	R_1	mp °C	Yield (%)
3g		**4g**		197	24
3h		**4h**		203	77
3i		**4i**		209-210	61
3j		**4j**		204	69
3k		**4k**		203	75

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were determined with a Bruker AC 300 (300 MHz) spectrometer with TMS as internal standard. Infrared spectra were determined with a Perkin-Elmer 297 spectrophotometer. Mass spectra were obtained on a CH-7A-Varian MAT (70 eV) instrument, FAB mass spectra on a CH-5-DF-MAT-Varian (80 eV) spectrometer. Microanalyses were performed with a Perkin-Elmer 240 B and C analyzer. Thin layer chromatography was performed on Merck precoated tlc plates with silica gel 60-F254. Column (flash) chromatography was performed with Merck silica gel 60 (230-400 mesh).

Chromone-3-sulfonylureas, **4-4k.**

General Procedure.

The solution of the corresponding amine (7 mmoles) in 10 ml of anhydrous 1,4-dioxane was added to a stirred solution of 991 mg (7 mmoles) chlorosulfonyl isocyanate in a mixture of 50 ml of anhydrous 1,4-dioxane and 10 ml of anhydrous ether over a 20 minute period and was then cooled in an ice bath. The solution was stirred for a further 60 minutes at 20°C and was then treated with 7 mmoles of the enaminone/enamine. The mixture was stirred for 60 minutes at 60°C, cooled to room temperature and then placed on 300 g of crushed ice. The precipitate was collected, washed with brine (200 ml) and dried. The crude residue was purified either by washing with hot methanol or by flash chromatography with chloroform/methanol (9+1) to provide the title compounds as white solids.

3-(4-Chlorophenyl)-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4**.

This compound had mp 255°C, yield 1.86 g (70%); ir (potassium bromide): ν 3330, 3068 (NH), 1720, 1661 (C=O), 1380, 1160 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.30 (d, J = 8.9 Hz, 2H, 2'-H, 6'-H), 7.38 (d, J = 8.9 Hz, 2H, 3'-H, 5'-H), 7.62 (t, J = 7.4 Hz, 1H, 6-H), 7.81 (d, J = 8.4 Hz, 1H, 8-H), 7.94 (t, J = 7.2 Hz, 1H, 7-H), 8.13 (d, J = 7.9 Hz, 1H, 5-H), 8.92 (s, 1H, NH-3), 9.19 (s, 1H, 2-H), 11.01 (s, 1H, NH-1); ms: (FAB positive (dimethyl sulfoxide/glyerol) m/z = 379 ([M+H]$^+$, 8%, ^{35}Cl); FAB negative (dimethyl sulfoxide/glyerol) m/z = 377 ([M-H]$^-$, 100%, ^{35}Cl).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_5S$: C, 50.73; H, 2.93; N, 7.40. Found C, 50.47; H, 2.63; N, 7.61.

3-(4-Fluorophenyl)-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4a**.

This compound had mp 265°C; yield 0.61 g (24%); ir (potassium bromide): ν 3354, 3251, 3075 (NH), 1722, 1658 (C=O), 1376, 1160 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.09 (t, J = 8.9 Hz, 2H, 3'-H, 5'-H), 7.35 (t, J = 4.9 Hz, 2H, 2'-H, 6'-H), 7.62 (t, J = 7.7 Hz, 1H, 7-H), 7.81 (d, J = 8.3 Hz, 1H, 8-H), 7.94 (t, J = 8.6 Hz, 1H, 6-H), 8.14 (d, J = 6.7 Hz, 1H, 5-H), 8.81 (s, 1H, NH-3), 9.17 (s, 1H, 2-H), 10.93 (s, 1H, NH-1); ms: (70 eV) m/z = 362 (M$^{+\cdot}$, 1%), 251 (54%), 225 (4%), 137 (13%), 111 (100%).

Anal. Calcd. for $C_{16}H_{11}FN_2O_5S$: C, 53.04; H, 3.06; N, 7.73. Found: C, 52.82; H, 2.90; N, 7.83.

3-(2,4-Dichlorophenyl)-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4b**.

This compound had mp 210°C, yield 0.36 g (25%); ir (potassium bromide): ν 3332, 3069 (NH), 1721, 1660 (C=O), 1380, 1163 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.33 (dd, J = 2.2/6.7 Hz, 1H, 5'-H), 7.60-7.64 (m, 2H, aromatic), 7.81 (d, J = 8.4 Hz, 1H, 8-H), 7.92-7.96 (m, 2H, aromatic), 8.14 (d, J = 7.9 Hz, 1H, 5-H), 8.58 (s, 1H, NH-3), 9.21 (s, 1H, 2-H), 11.61 (br, 1H, NH-1); ms: (70 eV) m/z = 412 (M$^{+\cdot}$, 1%, ^{35}Cl), 251 (44%), 225 (8%), 187 (12%), 161 (75%).

Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_5S$:C, 46.50; H, 2.44; N, 6.78. Found: C, 46.11; H, 2.20; N, 6.85.

3-(2,6-Difluorophenyl)-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)-urea **4c**.

This compound had mp 150°C, yield 0.89 g (34%); ir (potassium bromide): ν 3293, 3063 (NH), 1728, 1653 (C=O), 1376, 1161 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.09 (t, J = 8.1 Hz, 2H, 3'-H, 5'-H); 7.32 (dt, J = 6.4/8.4 Hz, 1H, 4'-H), 7.17 (t, J = 7.2 Hz, 1H, 7-H), 7.81 (d, J = 8.2 Hz, 1H, 8-H), 7.94 (dt, J = 1.6/7.0 Hz, 1H, 6-H), 8.17 (dd, J = 1.5/6.5 Hz, 1H, 5-H), 8.23 (s, 1H, NH-3), 9.13 (s, 1H, 2-H), 11.53 (br, 1H, NH-1); ms: (70 eV) m/z = 251 (24%), 225 (100%), 155 (34%), 129 (38%).

Anal. Calcd. for $C_{16}H_{10}F_2N_2O_5S$: C, 50.53; H, 2.65; N, 7.37. Found: C, 50.13; H, 2.85; N, 7.30.

3-[2-(4,6-Dimethylpyrimidyl)]-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4d**.

This compound had mp 209°C, yield 0.52 g (20%); ir (potassium bromide): ν 3416, 3065 (NH), 1717, 1661 (C=O), 1374, 1177 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.44 (s, 6H, CH_3), 7.05 (s, 1H, 5'-H), 7.60 (t, J = 7.4 Hz, 1H, 7-H), 7.81 (d, J = 8.3 Hz, 1H, 8-H), 7.93 (t, J = 8.1 Hz, 1H, 6-H), 8.09 (d, J = 7.8 Hz, 1H, 5-H), 9.23 (s, 1H, 2-H), 10.62 (s, 1H, NH-3), 13.42 (br, 1H, NH-1); ms: (70 eV) m/z = 251 (44%), 225 (18%), 149 (27%), 123 (100%).

Anal. Calcd. for $C_{16}H_{14}N_4O_5S$: C, 51.33; H, 3.77; N, 14.97. Found: C, 51.09; H, 3.55; N, 15.01.

3-(2-(4,6-Dichloropyrimidyl))-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4e**.

This compound had mp 217°C, yield 0.58 g (20%); ir (potassium bromide): ν 3402, 3261, 3105 (NH), 1725, 1659 (C=O), 1374, 1170 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.62 (t, J = 7.5 Hz, 1H, 7-H), 7.68 (s, 1H, 5'-H), 7.82 (d, J = 8.4 Hz, 1H, 8-H), 7.94 (t, J = 7.4 Hz, 1H, 6-H), 8.13 (d, J = 7.7 Hz, 1H, 5-H), 9.24 (s, 1H, 2-H), 10.67 (s, 1H, NH-3), 11.46 (br, 1H, NH-1); ms: (70 eV) m/z = 251 (77%), 225 (13%), 189 (17%), 163 (60%).

Anal. Calcd. for $C_{14}H_8Cl_2N_4O_5S$: C, 40.50; H, 1.94; N, 13.49. Found: C, 40.53; H, 1.75; N, 13.27.

3-[2-(4-Methoxy-6-methyl-1,3,5-triazinyl)]-1-(4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4f**.

This compound had mp 187°C, yield 0.30 g (11%); ir (potassium bromide): ν 3420, 3030 (NH), 1729, 1663 (C=O), 1362, 1169 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.48 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 7.62 (t, J = 7.5 Hz, 1H, 6-H), 7.82 (d, J = 8.4 Hz, 1H, 8-H), 7.94 (t, J = 7.6 Hz, 1H, 7-H), 8.11 (d, J = 7.6 Hz, 1H, 5-H), 9.26 (s, 1H, 2-H), 11.03 (s, 1H, NH-3), 12.60 (br, 1H, NH-1); ms: (70 eV) m/z = 251 (68%), 225 (12%), 166 (12%), 140 (56%).

Anal. Calcd. for $C_{15}H_{13}N_5O_6S$: C, 46.03; H, 3.35; N, 17.90. Found: C, 46.10; H, 3.25; N, 17.69.

3-(4-Chlorophenyl)-1-(7-fluoro-4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4g**.

This compound had mp 197°C, yield 0.68 g (24%); ir (potassium bromide): ν 3349, 3079 (NH),1726, 1645, 1615 (C=O), 1349, 1160 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 7.31 (d, J = 8.6 Hz, 2H, 2'-H, 6'-H), 7.38 (d, J = 7.4 Hz, 2H, 3'-H, 5'-H), 7.50 (t, J = 8.5 Hz, 1H, 6-H), 7.83 (d, J = 9.3 Hz, 1H, 8-H), 8.20 (t, J = 7.7 Hz, 1H, 5-H), 8.91 (s, 1H, NH-3), 9.19 (s, 1H, 2-H), 11.05 (br, 1H, NH-1); ms: (70 eV) m/z = 396 ($M^{+\cdot}$, 2%, ^{35}Cl).

Anal. Calcd. for $C_{16}H_{10}ClFN_2O_5S$: C, 48.43; H, 2.54; N, 7.06. Found: C, 48.62; H, 2.70; N, 7.09.

3-(4-Chlorophenyl)-1-(8-methyl-4-oxo-4*H*-1-benzopyran-3-sulfonyl)urea **4h**.

This compound had mp 203°C, yield 1.06 g (77%); ir (potassium bromide): ν 3353, 3064 (NH), 1721, 1656 (C=O), 1377, 1159 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.54 (s, 3H, CH_3), 7.30 (d, J = 8.9 Hz, 2H, 2'-H, 6'-H), 7.38 (d, J = 8.9 Hz, 2H, 3'-H, 5'-H), 7.50 (t, J = 7.6 Hz, 1H, 6-H), 7.79 (d, J = 7.1 Hz, 1H, 7-H), 7.96 (d, J = 7.7 Hz, 1H, 5-H), 8.91 (s, 1H, NH-3), 9.19 (s, 1H, 2-H), 11.00 (br, 1H, NH-1); ms: (70 eV) m/z = 265 (52%), 239 (8%), 153 (14%), 127 (100%).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_5S$: C, 51.98; H, 3.34; N, 7.13. Found: C, 52.17; H, 3.43; N, 7.23.

3-(4-Chlorophenyl)-1-(7-methyl-4,5-dioxo-4,5-dihydropyrano[4,3-*b*]pyran-3-sulfonyl)urea **4i**.

This compound had mp 209-210°C, yield 1.75 g (61%); ir (potassium bromide): ν 3314, 3091 (NH), 1747, 1632, 1605, 1548 (C=O), 1358, 1176 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.33 (s, 3H, CH_3), 6.74 (s, 1H, 8-H), 7.33 (d, J = 8.9 Hz, 2H, 2'-H, 6'-H), 7.40 (d, J = 9.0 Hz, 2H, 3'-H, 5'-H), 8.93 (s, 1H, NH-3), 9.02 (s, 1H, 2-H), 11.06 (br, 1H, NH-1); ms: FAB positive (dimethyl sulfoxide/glycerol) m/z = 411 ($[M+H]^+$, 9%, ^{35}Cl), FAB negative (dimethyl sulfoxide/glycerol) m/z = 409 ($[M-H]^-$, 60%, ^{35}Cl).

Anal. Calcd. for $C_{16}H_{11}ClN_2O_7S$: C, 46.78; H, 2.70; N, 6.82. Found: C, 46.80; H, 3.01; N, 6.66.

3-(4-Chlorophenyl)-1-(2,7-dimethyl-4,5-dioxo-4,5-dihydropyrano[4,3-*b*]pyran-3-sulfonyl)urea **4j**.

This compound had mp 204°C, yield 2.04 g (69%); ir (potassium bromide): ν 3310, 3097 (NH), 1753, 1641, 1605, 1549 (C=O), 1358, 1176 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 2.31 (s, 3H, 7-CH_3), 2.76 (s, 3H, 2-CH_3), 6.66 (s, 1H, 8-H), 7.33 (d, J = 8.8 Hz, 2H, 2'-H, 6'-H), 7.40 (d, J = 8.8 Hz, 2H, 3'-H, 5'-H), 8.97 (s, 1H, NH-3), 10.74 (br, 1H, NH-1); ms: FAB positive (dimethyl sulfoxide/glycerol) m/z = 425 ($[M+H]^+$, 23%, ^{35}Cl); FAB negative (dimethyl sulfoxide/glycerol) m/z 423 ($[M-H]^-$, 28%, ^{35}Cl).

Anal. Calcd. for $C_{17}H_{13}ClN_2O_7S$: C, 48.06; H, 3.08; N, 6.59. Found: C, 47.89; H, 2.79; N, 6.53.

3-(4-Chlorophenyl)-1-(1-methylindole-3-sulfonyl)urea **4k**.

This compound had mp 203°C, yield 1.90 g (75%); ir (potassium bromide): ν 3338, 3118 (NH), 2891 (CH-aliphat.), 1681, 1596 (C=O), 1340, 1179 (SO_2NR_2) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide): δ 3.89 (s, 3H, CH_3), 7.27-7.36 (m, 6H, 6-H, 7-H, 2'-H, 3'-H, 5'-H, 6'-H), 7.59 (d, J = 8.1 Hz, 1H, 7-H), 7.88 (d, J = 7.7 Hz, 1H, 4-H), 8.18 (s, 1H, 2-H), 8.76 (s, 1H, NH-3), 10.66 (br, 1H, NH-1); ms: FAB positive (dimethyl sulfoxide/glycerol) m/z = 364 ($[M+H]^+$, 10%, ^{35}Cl); FAB negative (dimethyl sulfoxide/glycerol) m/z = 362 ($[M-H]^-$, 47%, ^{35}Cl).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S$: C, 52.82; H, 3.88; N, 11.55. Found: C, 52.97; H, 3.99; N, 11.36.

REFERENCES AND NOTES

[1] W. Löwe and N. Matzanke and T. Rütjes, *Arch. Pharm. (Weinheim)*, **327**, 819 (1994).

[2] B. Föhlisch, *Chem. Ber.*, **104**, 348 (1971).

[3] R. Graf, *Angew. Chem.*, **80**, 179 (1968).

[4] W. Löwe, *J. Heterocyclic Chem.*, **14**, 931 (1977); B. Müller, Dissertation, Freie Universität Berlin (1982).