

Synthesis of Triazolo[1,5-*a*]triazin-7-one Derivatives and Highly Functionalized [1,2,4]Triazoles

by Montserrat Heras^{*a)}, David Font^{a)}, Anthony Linden^{b)}, and José M. Villalgordo^{*a)}¹⁾

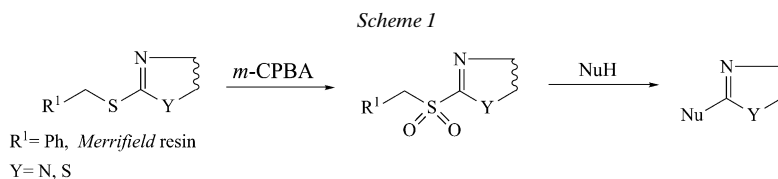
^{a)} Departament de Química, Facultat de Ciències, Universitat de Girona, Campus de Montilivi, E-17071 Girona

^{b)} Organisch-Chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich (phone: 34-972-418-274; fax: 34-972-418-150; e-mail: montserrat.heras@udg.es)

The synthesis of novel triazolo[1,5-*a*]triazin-7-ones is presented. Starting from 3-amino-5-sulfanyl-1,2,4-triazole, the synthetic sequence involved alkylation with benzyl bromide, reaction with *p*-nitrophenyl chloroformate followed by treatment with a primary amine, and condensation with diethoxymethyl acetate. Final oxidation of the thioether moiety with 3-chloroperbenzoic acid provided 2-(benzylsulfonyl)[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-ones **5a** and **5b** in good overall yields. Treatment of **5a** and **5b** with secondary amines provided highly functionalized [1,2,4]triazoles through an unexpected triazinone ring opening. A mechanism for this transformation is proposed.

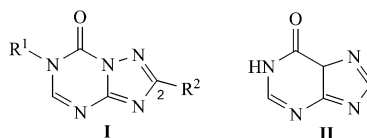
Introduction. – Heteroaromatic nucleophilic addition/elimination reactions are commonly recognized in many electron-deficient heterocycles [1]. However, analogous reactions with electron-rich heterocycles are rather uncommon [2]. On the other hand, alkyl- or arylsulfinyl, or alkyl- or arylsulfonyl substituents as leaving groups in electron-deficient heteroaromatic systems have been reported to have reactivities equivalent to or greater than that of a Cl group, and many examples that demonstrate the reactivity of electron-deficient azines bearing alkylsulfinyl and sulfonyl groups with a wide variety of simple nucleophiles have been reported [3].

During the last few years, we have been engaged in a research program focused on the development of efficient methodologies that could be readily adapted for the combinatorial and/or parallel synthesis of relevant core structures in solution or on solid support [4]. We have recently described the synthesis of novel 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles [5][6] and 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones [7][8]. The method has a nucleophilic *ipso*-substitution of the corresponding activated sulfones as one of the key steps for introducing molecular diversity (*Scheme 1*).



¹⁾ Present address: Roviall Química S.L., Polígono Industrial Oeste, Parcela 22/2 Módulo L, E-30169, San Ginés, Murcia.

Within this context, an investigation was undertaken to expand the scope of this methodology and its potential application in the synthesis of more-elaborate heterocyclic scaffolds based on the [1,2,4]triazole nucleus. Triazoles are important pharmacophores in different therapeutic areas, and many biologically active compounds have this moiety incorporated into their structures. Particularly interesting are triazolo[1,5-*a*]triazin-7-ones of type **I**, which are 5-aza analogues of hypoxanthine **II** with potential therapeutic interest [9][10]. In particular, inhibition of xanthine oxidase [11] and eosinophilia [12] has been studied. The results of this investigation are disclosed herein.



Results and Discussion. – Our objective in this study was to develop a synthetic protocol, which, starting from 3-amino-5-sulfanyl-1,2,4-triazole, would effectively afford a variety of molecularly diverse triazolo[1,5-*a*]triazin-7-ones of type **I** with different substitution patterns, especially at the C(2) position, which are the less studied derivatives.

Several strategies have been reported for the synthesis of triazolo[1,5-*a*]triazin-7-ones [13]. One of these approaches involves reaction of 1*H*-[1,2,4]triazol-3-amine with an isocyanate followed by condensation with diethoxymethyl acetate (DEMA) [9]. However, this method has some limitations due to the lack of availability of the corresponding isocyanates. This limitation prevents the introduction of a high degree of molecular diversity over the C(2) position in these derivatives. To circumvent this problem, an alternative approach would be the use of a chloroformate followed by treatment with a primary amine. Moreover, the presence of the thiol group in 3-amino-5-sulfanyl-1,2,4-triazole would also serve as an efficient means to introduce molecular diversity through thioether formation, oxidation, and nucleophilic displacement of the corresponding activated sulfone.

Thus, synthesis of triazolo[1,5-*a*]triazin-7-ones was carried out as depicted in *Schemes 2* and *3*. Alkylation of 3-amino-5-sulfanyl-1,2,4-triazole **1** with PhCH₂Br bromide in DMF afforded **2**. When **2** was allowed to react in 1,4-dioxane with *p*-nitrophenyl chloroformate in the presence of pyridine followed by treatment with the corresponding primary amine, carboxamides **3a** and **3b** were isolated in good yields (70–87%). The structure elucidation of compounds **3** was accomplished by the usual spectroscopic methods. In agreement with the literature [9][10], only one of the four possible monosubstituted isomers was detected (*Scheme 2*). In addition, **3a** was subjected to an X-ray crystal-structure analysis, which unambiguously confirmed the structure (*Figure*). Condensation of **3a** and **3b** with DEMA provided triazolo-triazinones **4a** and **4b**, respectively in 65–67% yield (*Scheme 3*). Oxidation of the thioether moiety with 3 equiv., of 3-chloroperbenzoic acid (*m*-CPBA) in CH₂Cl₂ led to the sulfone derivatives **5a** and **5b**, respectively, in good yields (70–89%).

Scheme 2

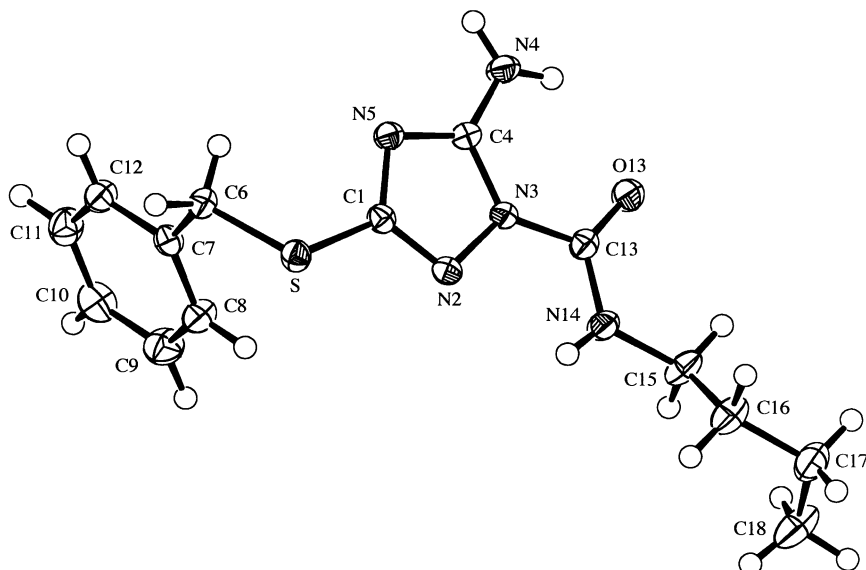
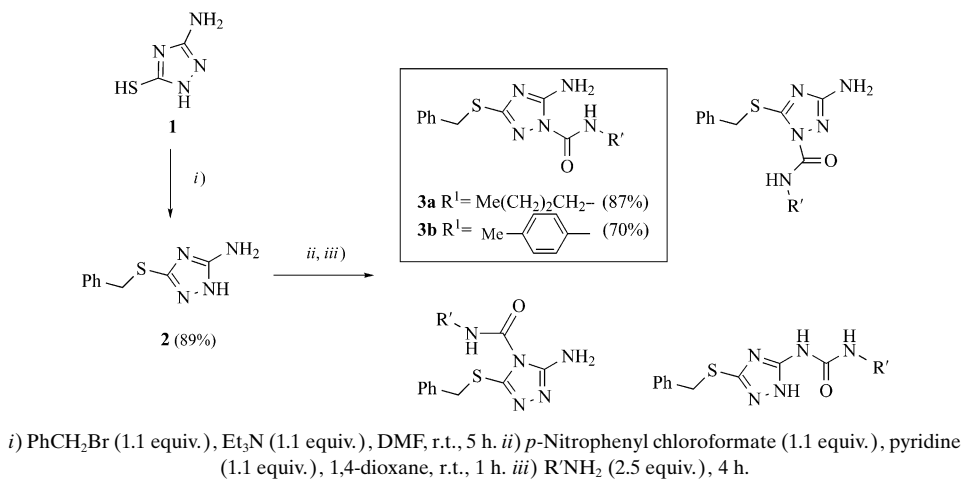
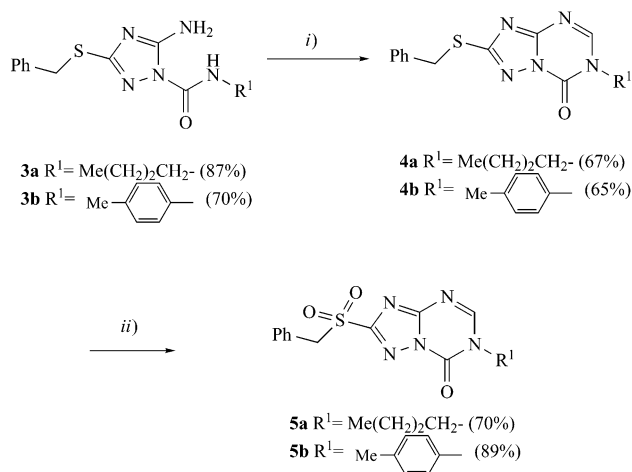


Figure. ORTEP [14] View of the molecular structure of compound **3a**, showing the labelling of the non-H-atoms (ellipsoids drawn at the 50% probability level)

We then examined the nucleophilic *ipso*-substitution of the PhCH₂SO₂ group (Scheme 4). Unexpectedly, treatment of either sulfone **5a** or **5b** with 3 equiv. of the corresponding secondary amine led to the formation of the same triazole derivatives **7a–c**, which were isolated in excellent yields (83–86%), together with ureas **8** (86–94%). The corresponding triazolotriazinones **6** were not obtained. The structure

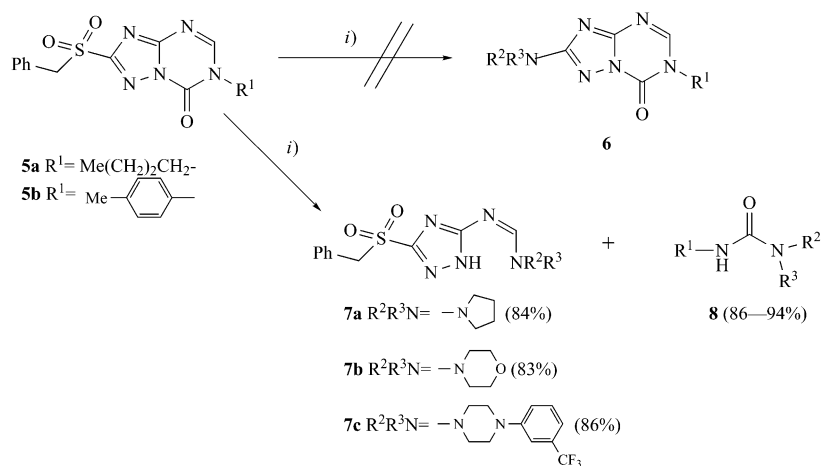
Scheme 3



i) DEMA (2 equiv.), DMF, 120°, 4 h. ii) *m*-CPBA (3 equiv.), CH_2Cl_2 , r.t., overnight.

elucidation of the novel triazole derivatives **7a–c** was accomplished by the usual spectroscopic methods.

Scheme 4

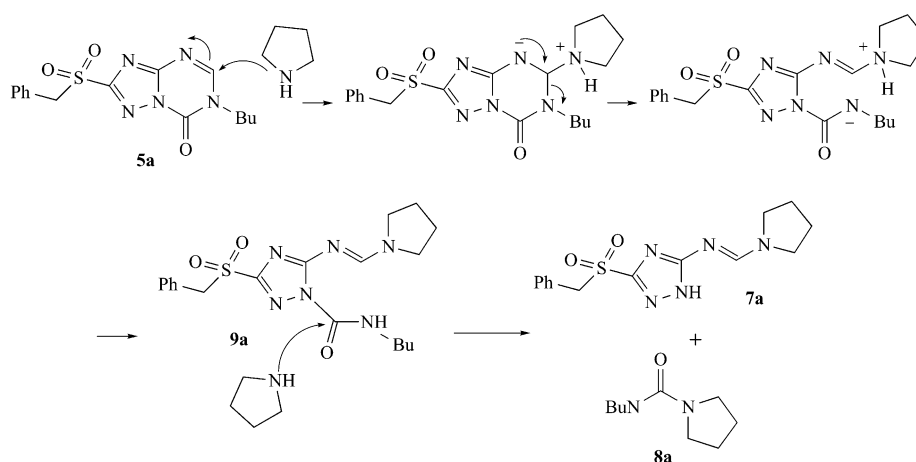


i) $R^2R^3\text{NH}$ (3 equiv.), 1,4-dioxane, r.t.

Formation of triazoles **7** could be rationalized in terms of an initial attack of the secondary amine at C(5) of the triazolo-triazinone **5** followed by triazinone ring opening to give the triazole-carboxamide **9**. It should be noted that this nucleophilic attack is favored, since the negative charge formed at N(4) is stabilized by delocalization in the triazole ring. Subsequent attack of a second molecule of amine

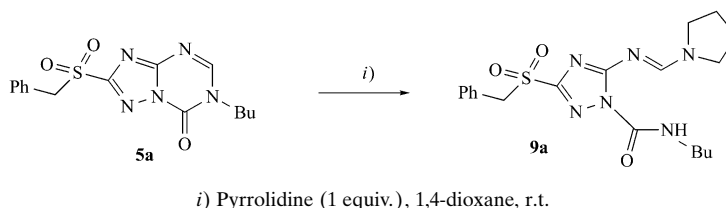
at the carbonyl atom of **9**, with ultimate loss of the corresponding urea **8**, would afford the triazole derivative **7** (Scheme 5).

Scheme 5



In good agreement with this mechanism, when sulfone **5a** was treated with 1 equiv. of pyrrolidine at room temperature, carboxamide **9** was obtained exclusively in 87% yield (Scheme 6).

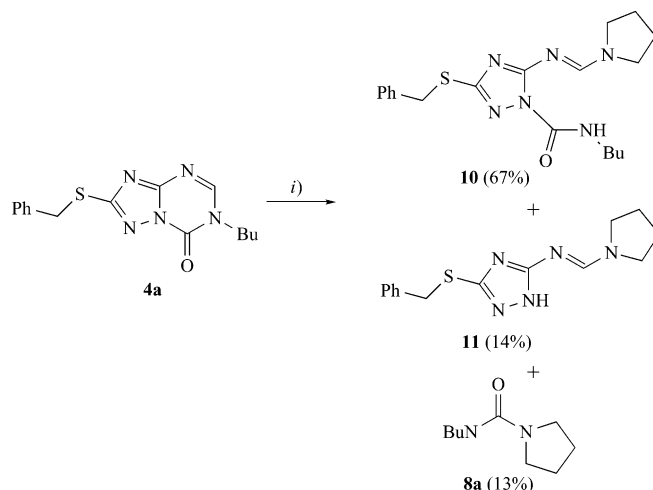
Scheme 6



In addition, we examined whether triazolo-triazinones **4** behave similarly. Treatment of **4a** with 3 equiv. of pyrrolidine afforded carboxamide **10**, triazole **11**, and urea **8a** in 67%, 14%, and 13% yields, respectively (Scheme 7).

Conclusions. – An efficient synthetic strategy to prepare novel 2-(benzylsulfonyl)[1,2,4]triazolo[1,5-*a*]triazin-7-ones has been described. Attempts to replace the benzylsulfonyl group by treatment with secondary amines were unsuccessful, instead, highly functionalized [1,2,4]triazoles were obtained in excellent yields. To the best of our knowledge, there are no prior reports of this transformation performed under such mild conditions.

Scheme 7



i) Pyrrolidine (3 equiv.), 1,4-dioxane, r.t., 2 h.

Experimental Part

General. All commercially available chemicals were used as purchased. DMF and 1,4-dioxane were dried over activated molecular sieves (4 Å). All reactions were carried out under dry N₂. M.p.: *Electrothermal* digital melting-point apparatus *IA 91000*, uncorrected. Anal. TLC: precoated TLC plates, silica gel 60 *F₂₅₄* (*Merck*). Flash chromatography (FC): silica gel 60 (230–400 mesh, *Merck*). IR Spectra: *Mattson-Galaxy Satellite FT-IR*; ν in cm⁻¹. ¹H- and ¹³C-NMR (200 and 50 MHz, resp.): *Bruker DPX-200 Advance* instrument; δ in ppm rel. to SiMe₄ as int. standard, *J* in Hz. MS: *VG Quattro* instrument in the pos. ion FAB mode, 3-NBA or 1-thioglycerol as matrix, *m/z* (rel. %).

5-(Benzylsulfanyl)-1H-[1,2,4]-triazol-3-amine (2). Et₃N (4.39 ml, 34.1 mmol) was added dropwise to a suspension of 3-amino-5-sulfanyl-1,2,4-triazole **1** (3.6 g, 31.0 mmol) in dry DMF (50 ml), and the mixture was stirred under N₂ at r.t. for 15–20 min. Next, benzyl bromide (4.05 ml, 34.1 mmol) was added, and the mixture was stirred under N₂ at r.t. for 4 h. The soln. was evaporated to dryness, and the resulting residue was partitioned between AcOEt (150 ml) and H₂O (100 ml). The org. layer was washed with brine (50 ml), dried (MgSO₄), and concentrated under reduced pressure. FC (AcOEt) provided **2** (5.69 g, 89%). Colorless solid. M.p. 107–108°. TLC (hexane/AcOEt 1:3): *R_f* 0.26. IR (KBr): 3412s, 3323m, 3227m, 3206m, 3174w, 3061m, 2981m, 2882m, 2767m, 2730m, 2579m, 2366m, 2340w, 1622s, 1546s, 1495m, 1452m, 1339m, 1294m, 1238m, 1140w, 1086m, 1022m, 920w, 857w, 751m, 704m, 659w. ¹H-NMR (CDCl₃, 50°): 7.38–7.22 (*m*, 5 arom. H); 5.8 (br. s, 3 H, NH₂, NH); 4.32 (*s*, CH₂S). ¹³C-NMR (CDCl₃, 50°): 158.8 (*s*, C(5)); 155.5 (*s*, C(3)); 137.3 (*s*); 128.8, 128.7, 127.5 (3*d*), 37.5 (*t*).

Synthesis of Carboxamides 3a and 3b. General Procedure 1 (GP 1). A mixture containing **2** (619 mg, 3.0 mmol, 1 equiv.), *p*-nitrophenyl chloroformate (665 mg, 3.3 mmol, 1.1 equiv.), and pyridine (0.26 ml, 3.3 mmol, 1.1 equiv.) in dry 1,4-dioxane was stirred under N₂ at r.t. for 1 h. Next, the corresponding amine (7.5 mmol, 2.5 equiv.) was added in one portion, and the resulting mixture was stirred under N₂ at r.t. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (50 ml), washed with aq. sat. NaHCO₃ soln. (3 × 10 ml) and brine (10 ml). The org. layer was dried (MgSO₄), filtered, and concentrated. The resulting crude material was purified by FC (hexane/AcOEt).

5-Amino-N-3-(benzylsulfanyl)-butyl-1H-[1,2,4]triazole-1-carboxamide (3a). According to GP 1, the reaction between **2** and butylamine (0.4 ml, 7.5 mmol, 2.5 equiv.) afforded **3a** (796 mg, 87%). Colorless solid. M.p. 52–53°. TLC (hexane/AcOEt 2:1): *R_f* 0.38. IR (KBr): 3415m, 3355m, 2957m, 2989m, 2869w, 1715s, 1626s, 1530s, 1487s, 1307s, 1274s, 1187m, 1073w, 989w, 857w, 752m, 700m. ¹H-NMR (CDCl₃): 7.32–7.18 (*m*, 5 arom. H);

6.65 (*t*, *J* = 5.8, NH); 6.5 (br. *s*, NH₂); 4.2 (*s*, CH₂S); 3.25 (*q*, *J* = 6.6, CH₂NH); 1.53–1.18 (*m*, 4 H); 0.85 (*t*, *J* = 7.2, Me). ¹³C-NMR (CDCl₃): 159.4 (*s*, C=O); 156.5 (*s*, C(5)); 150.6 (*s*, C(3)); 136.9 (*s*, 1 arom. C); 128.8, 128.5, 127.4 (3*d*, 5 arom. C–H); 39.6 (*t*, CH₂NH); 35.5 (*t*, CH₂S); 31.5, 19.8 (*t*, 2 CH₂); 13.6 (*q*, Me). FAB-MS: 306 (45, [M + 1]⁺), 305 (14, M⁺), 208 (12), 207 (100), 206 (37).

5-Amino-N-3-(benzylsulfanyl)-(4-methylphenyl)-1H-[1,2,4]-triazole-1-carboxamide (3b). According to GP 1, the reaction between **2** and *p*-toluidine (810 mg, 7.5 mmol, 2.5 equiv) afforded **3b** (712 mg, 70%). Colorless solid. M.p. 165–166°. TLC (hexane/AcOEt 2 : 1): *R*_f 0.44. IR (KBr): 3429*m*, 3360*m*, 3288*w*, 3122*w*, 1732*s*, 1640*m*, 1597*m*, 1539*s*, 1491*s*, 1312*m*, 1098*w*, 811*w*, 624*w*. ¹H-NMR ((D₆)DMSO): 9.82 (*s*, NH); 7.56–7.06 (*m*, 9 arom. H, NH₂); 4.42 (*s*, CH₂S); 2.29 (*s*, Me). ¹³C-NMR ((D₆)DMSO): 158.8 (*s*, C(5)); 157.1 (*s*, C=O); 152.6 (*s*, C(3)); 137.9, 134.5, 133.5 (*s*, 3 arom. C); 129, 128.8, 128.3, 127.2, 121.2 (5*d*, 9 arom. CH); 34.4 (*t*, CH₂S); 13.6 (*q*, Me). FAB-MS: 340 (40, [M + 1]⁺), 339 (9, M⁺), 241 (22), 242 (15), 207 (100).

Synthesis of Triazolo-triazinones 4a and 4b. General Procedure 2 (GP 2). Diethoxymethyl acetate (0.65 ml, 4 mmol, 2 equiv.) was added in one portion to a soln. of the corresponding carboxamide (2 mmol, 1 equiv.) **3a**, **b** in dry DMF (6 ml). The resulting mixture was then stirred under N₂ at 120°. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure, and the resulting residue was purified by FC (hexane/AcOEt).

2-(Benzylsulfanyl)-6-butyl-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-one (4a). According to GP 2, starting with carboxamide **3a** (610 mg, 2 mmol, 1 equiv.), **4a** (422 mg, 67%) was obtained as a colorless solid. M.p. 94–95°. TLC (hexane/AcOEt 1 : 1): *R*_f 0.35. IR (KBr): 3060*w*, 2958*w*, 2929*w*, 2865*w*, 1735*s*, 1595*s*, 1545*s*, 1454*w*, 1429*m*, 1388*m*, 1333*w*, 1270*m*, 1246*s*, 1194*w*, 1152*w*, 736*w*, 708*m*. ¹H-NMR ((D₆)DMSO): 8.64 (*s*, H–C(7)); 7.5–7.24 (*m*, 5 arom. H); 4.49 (*s*, CH₂S); 3.98 (*t*, *J* = 7.2, CH₂N); 1.78–1.27 (*m*, 4 H); 0.93 (*t*, *J* = 7.0, Me). ¹³C-NMR ((D₆)DMSO): 164.9 (*s*, C=O); 157.7 (*s*, C(3a)); 153.5 (*d*, C(5)); 143.1 (*s*, C(2)); 137.3 (*s*, 1 arom. C); 128.8, 128.4, 127.3 (3*d*, 5 arom. CH); 46.9 (*t*, CH₂N); 34.4 (*t*, CH₂S); 30.2, 18.9 (*t*, 2 aliph. CH₂); 13.4 (*q*, Me). FAB-MS: 316 (100, [M + 1]⁺).

2-(Benzylsulfanyl)-6,7-dihydro-6-(4-methylphenyl)-[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-one (4b). According to GP 2, starting with carboxamide **3b** (679 mg, 2 mmol, 1 equiv.), **4b** (454 mg, 65%) was obtained as a colorless solid. M.p. 192–193°. TLC (hexane/AcOEt 1 : 1): *R*_f 0.48. IR (KBr): 3067*w*, 2926*w*, 1762*s*, 1640*m*, 1590*s*, 1503*w*, 1441*w*, 1334*s*, 1268*w*, 1222*w*, 1144*m*, 1025*w*, 771*m*, 639*w*. ¹H-NMR ((D₆)DMSO): 8.62 (*s*, H–C(5)); 7.51–7.31 (*m*, 9 arom. H); 4.52 (*s*, CH₂S); 2.42 (*s*, Me). ¹³C-NMR ((D₆)DMSO): 165.1 (*s*, C=O); 157.7 (*s*, C(3a)); 153.2 (*d*, C(5)); 142.9 (*s*, C(2)); 139.4, 137.3, 133.1 (*s*, 3 arom. C); 129.8, 129.1, 128.8, 127.3, 127.2 (5*d*, 9 arom. CH); 34.4 (*t*, CH₂S); 20.7 (*q*, Me). FAB-MS: 350 (100, [M + 1]⁺); 349 (9, M⁺).

Oxidation of 2-(Benzylsulfanyl)triazolo-triazinones 4a and 4b to the Corresponding Sulfones 5a and 5b. General Procedure 3 (GP 3). *m*-CPBA (1.4 g, 4.5 mmol, 3 equiv.) was added in small portions to cooled solns. (0°) of **4a** and **4b** (1.5 mmol, 1 equiv.) in CH₂Cl₂ (15 ml). The resulting mixture was then stirred overnight as the temp. was increased from 0° to r.t. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the resulting residue was purified by FC (hexane/AcOEt).

2-(Benzylsulfonyl)-6-butyl-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-one (5a). According to GP 3, starting with **4a** (473 mg, 1.5 mmol, 1 equiv.), **5a** (364 mg, 70%) was obtained as a colorless solid. M.p. 152–153°. TLC (hexane/AcOEt 1 : 2): *R*_f 0.49. IR (KBr): 3058*w*, 2963*w*, 2927*w*, 2862*w*, 1766*s*, 1601*s*, 1548*m*, 1459*w*, 1432*m*, 1390*m*, 1340*m*, 1234*w*, 1200*w*, 1148*m*, 1107*w*, 836*w*, 771*m*, 696*m*. ¹H-NMR ((D₆)DMSO): 8.82 (*s*, H–C(5)); 7.39 (*s*, 5 arom. H); 4.97 (*s*, CH₂SO₂); 4.05 (*t*, *J* = 7.0, CH₂N); 1.81–1.29 (*m*, 4 H); 0.94 (*t*, *J* = 7.0, Me). ¹³C-NMR ((D₆)DMSO): 163.2 (*s*, C=O); 158.5 (*s*, C(3a)); 155.4 (*d*, C(5)); 144.2 (*s*, C(2)); 131.9, 129.2, 128.9 (3*d*, 5 arom. CH); 127.1 (*s*, 1 arom. C); 59.5 (*t*, CH₂SO₂); 47.9 (*t*, CH₂N); 30.5, 19.4 (*t*, 2 CH₂); 13.9 (*q*, Me). FAB-MS: 348 (100, [M + 1]⁺); 155 (16); 154 (53); 138 (20); 137 (41); 136 (39).

2-(Benzylsulfonyl)-6-(4-methylphenyl)-6,7-dihydro[1,2,4]triazolo[1,5-*a*][1,3,5]triazin-7-one (5b). According to GP 3, starting with **4b** (524 mg, 1.5 mmol, 1 equiv.), **5b** (509 mg, 89%) was obtained as a colorless solid. M.p. 191–192°. TLC (hexane/AcOEt 1 : 1): *R*_f 0.13. IR (KBr): 3054*w*, 3041*w*, 2967*w*, 2906*w*, 1777*s*, 1595*s*, 1555*m*, 1521*m*, 1434*m*, 1360*s*, 1326*s*, 1272*m*, 1232*m*, 1144*s*, 1077*w*, 929*w*, 828*w*, 768*m*, 700*m*, 633*m*. ¹H-NMR ((D₆)DMSO): 8.84 (*s*, H–C(5)); 7.47–7.41 (*m*, 9 arom. H); 5.03 (*s*, CH₂SO₂); 2.43 (*s*, Me). ¹³C-NMR ((D₆)DMSO): 163.0 (*s*, C=O); 158.0 (*s*, C(3a)); 154.8 (*d*, C(5)); 143.6 (*s*, C(2)); 139.7, 132.8 (*s*, 2 arom. C); 131.4, 129.9, 128.7, 128.5, 127.1 (5*d*, 9 arom. CH); 126.7 (*s*, 1 arom. C); 58.9 (*t*, CH₂SO₂); 20.7 (*q*, Me). FAB-MS: 382 (100, [M + 1]⁺); 228 (15); 201 (18).

Reaction of Sulfone Derivatives 5a and 5b with Amines. Synthesis of Triazoles 7 and 9. General Procedure 4 (GP 4). To a soln. of **5a** and **5b** (0.5 mmol, 1 equiv.) in dry 1,4-dioxane (2 ml), the corresponding amine (1.5 mmol, 3 equiv.) was added at r.t. The mixture was stirred under N₂ at r.t. Upon completion of the reaction

(TLC monitoring), the solvent was removed under reduced pressure and the resulting residue was purified by FC (hexane/AcOEt) to provide triazoles **7** together with the corresponding ureas **8** or the triazoles **9**.

3-(Benzylsulfonyl)-5-[(pyrrolidin-1-yl)methylidene]amino]-1H-[1,2,4]triazole (**7a**). According to GP 4, treatment of **5a** (187 mg, 0.5 mmol, 1 equiv.) or **5b** (190 mg, 0.5 mmol, 1 equiv.) with pyrrolidine (0.12 ml, 1.5 mmol, 3 equiv.) afforded **7a** (130 mg, 84%) as a colorless solid. M.p. 194–195°. TLC (hexane/AcOEt 1:5): R_f 0.21. IR (KBr): 3198w, 3081w, 2969w, 2926w, 2870w, 1618s, 1566s, 1461w, 1408m, 1324m, 1244w, 1127m, 1051w, 729w, 701w. $^1\text{H-NMR}$ ((D₆)DMSO): 13.76 (s, NH); 8.66 (s, CH); 7.38–7.25 (m, 5 arom. H); 4.70 (s, CH₂SO₂); 3.36 (t, J = 6.0, CH₂N); 3.44 (t, J = 6.0, CH₂N); 2.01–1.79 (m, 4 H). $^{13}\text{C-NMR}$ ((D₆)DMSO): 161.9 (s, triaz. C); 158.2 (s, triaz. C); 155.2 (d, CH); 131.1, 128.4, 128.3 (3d, 5 arom. CH); 127.7 (s, 1 arom. C); 59.2 (t, CH₂SO₂); 48.9 (t, CH₂N); 45.5 (t, CH₂N); 24.5, 24.0 (t, 2 CH₂). FAB-MS: 320 (73, $[M+1]^+$), 171 (100), 154 (32), 149 (21), 147 (28), 138 (25), 137 (52), 136 (59), 135 (25), 133 (23), 125 (26).

3-(Benzylsulfonyl)-5-[(morpholin-4-yl)methylidene]amino]-1H-[1,2,4]triazole (**7b**). According to GP 4, treatment of **5a** (187 mg, 0.5 mmol, 1 equiv.) or **5b** (190 mg, 0.5 mmol, 1 equiv.) with morpholine (0.13 ml, 1.5 mmol, 3 equiv.) afforded **7b** (139 mg, 83%). Colorless solid. M.p. 154–155°. TLC (hexane/AcOEt 1:2): R_f 0.10. IR (KBr): 3167w, 3077w, 2970w, 2924w, 2861w, 1614s, 1569s, 1437m, 1412m, 1356m, 1321m, 1263w, 1236w, 1152m, 1115m, 1068w, 997w, 875w, 785w, 697w. $^1\text{H-NMR}$ ((D₆)DMSO): 13.81 (s, NH); 8.56 (s, CH); 7.39–7.25 (m, 5 arom. H); 4.70 (s, CH₂SO₂); 3.69–3.60 (m, 8 H). $^{13}\text{C-NMR}$ ((D₆)DMSO): 162.1, 158.7 (2s, triaz. C); 157.6 (d, CH); 131.6, 128.9, 128.7 (3d, 5 arom. CH); 127.1 (s, 1 arom. C); 66.9 (t, CH₂O); 65.8 (t, CH₂O); 59.7 (t, CH₂SO₂); 49.5 (t, CH₂N); 43.3 (t, CH₂N). FAB-MS: 336 (100, $[M+1]^+$), 187 (18), 154 (38), 149 (48), 141 (26), 140 (72), 139 (19), 138 (32), 137 (52), 136 (65), 135 (19), 125 (18).

3-(Benzylsulfonyl)-5-[(4-[3-(trifluoromethyl)phenyl]piperazin-1-yl)methylidene]amino]-1H-[1,2,4]triazole (**7c**). According to GP 4, treatment of **5a** (187 mg, 0.5 mmol, 1 equiv.) or **5b** (190 mg, 0.5 mmol, 1 equiv.) with 1-(3-trifluoromethylphenyl) piperazine (0.28 ml, 1.5 mmol, 3 equiv.) afforded **7c** (205 mg, 86%) as a colorless solid. M.p. 198–199°. TLC (hexane/AcOEt 1:2): R_f 0.30. IR (KBr): 3246w, 3067w, 2972w, 2860w, 1625s, 1560s, 1445m, 1324m, 1237w, 1123m, 944w, 865w, 783w, 696w. $^1\text{H-NMR}$ ((D₆)DMSO): 13.82 (s, NH); 8.63 (s, CH); 7.51–7.12 (m, 9 arom. H); 4.72 (s, CH₂SO₂); 3.81–3.75 (m, 4 H, CH₂N); 3.38 (br. s, 4 H, CH₂N). $^{13}\text{C-NMR}$ ((D₆)DMSO): 162.1, 158.7 (2s, triaz. C); 157.5 (d, CH); 151.2 (s, 1 arom. C); 131.6, (d, 2 arom. CH); 130.5 (q, $J(\text{C,F})$ = 31, 1 arom. C); 130.4, 128.7, 128.9 (3d, 4 arom. CH); 128.1 (s, 1 arom. C); 124.8 (q, $J(\text{C,F})$ = 270, CF₃); 119.7, 115.7, 112.1 (3d, 3 arom. CH); 59.7 (t, CH₂SO₂); 48.8 (t, CH₂N); 48.7 (t, CH₂N); 47.5 (t, CH₂N); 42.4 (t, CH₂N). FAB-MS: 479 (100, $[M+1]^+$), 213 (52), 200 (60), 172 (48), 154 (40), 147 (40), 145 (45), 137 (64), 137 (52), 136 (77), 135 (38), 133 (47).

N-Butylpyrrolidine-1-carboxamide (**8a**). From **5a**: 80 mg (94%) colorless solid. M.p. 65–66°. TLC (hexane/AcOEt 1:5): R_f 0.25. IR (KBr): 3341w, 2948w, 2922m, 2857m, 1620s, 1534s, 1482m, 1462m, 1436m, 1397m, 1362m, 1255m, 1228m, 1191m, 1147m, 765m. $^1\text{H-NMR}$ ((D₆)DMSO): 6.04 (br. s, NH); 3.31–3.24 (m, 4 H); 3.08 (t, J = 6.7, CH₂N); 1.93–1.83 (m, 4 H); 1.51–1.29 (m, 4 H); 0.96 (t, J = 6.7, Me). $^{13}\text{C-NMR}$ ((D₆)DMSO): 156.5 (s, C=O); 45.2 (t, CH₂N); 39.5 (t, CH₂N); 32.3, 24.9, 19.5 (3t, 3 CH₂); 13.7 (q, Me). FAB-MS: 171 (100, $[M+1]^+$), 169 (14).

N-(4-Methylphenyl)pyrrolidine-1-carboxamide (**8b**). From **5b**: 92 mg (90%) colorless solid. M.p. 140–141°. TLC (hexane/AcOEt 1:5): R_f 0.38. IR (KBr): 3316w, 3032m, 2969m, 2867m, 1645s, 1592s, 1525s, 1477m, 1447m, 1409m, 1380m, 1288m, 1245m, 1199m, 1115m, 809m, 754m. $^1\text{H-NMR}$ ((D₆)DMSO): 7.97 (br. s, NH); 7.39 (d, J = 8.3, 2 arom. H); 7.03 (d, J = 8.3, 2 arom. H); 3.39–3.34 (m, 4 H); 2.24 (s, Me); 1.92–1.83 (m, 4 H). $^{13}\text{C-NMR}$ ((D₆)DMSO): 153.9 (s, C=O); 138.0, 130.1 (2s, 2 arom. C); 128.6, 119.6 (2d, 4 arom. CH); 45.6 (t, CH₂N); 24.9 (t, 2 CH₂); 20.3 (q, Me). FAB-MS: 205 (100, $[M+1]^+$), 204 (38, M^+), 203 (13).

3-(Benzylsulfonyl)-N-butyl-5-[(pyrrolidin-1-yl)methylidene]amino]-1H-[1,2,4]triazole-1-carboxamide (**9a**). According to GP 4, treatment of **5a** (187 mg, 0.5 mmol, 1 equiv.) with pyrrolidine (41 μl , 0.5 mmol, 1 equiv.) afforded **9a** (178 mg, 85%) as a colorless solid. M.p. 135–136°. TLC (hexane/AcOEt 1:5): R_f 0.28. IR (KBr): 3463w, 3218w, 3082w, 2963w, 2876w, 1745s, 1634s, 1535s, 1464w, 1420w, 1340m, 1233w, 1140m, 917w, 704w. $^1\text{H-NMR}$ ((D₆)DMSO): 9.27 (t, J = 5.2, NH); 8.82 (s, CH); 7.40–7.35 (s, 5 arom. H); 4.79 (s, CH₂SO₂); 3.76 (t, J = 6.4, CH₂N); 3.53 (t, J = 6.2, CH₂N); 3.39–3.30 (m, CH₂N); 2.52–1.89 (m, 4 H); 1.63–1.25 (m, 4 H); 0.92 (t, J = 7.0, Me). $^{13}\text{C-NMR}$ ((D₆)DMSO): 155.5 (s, C=O); 153.2 (s, triaz. C); 151.2 (d, CH); 143.4 (s, triaz. C); 126.8, 124.1, 123.9 (3d, 5 arom. CH); 122.6 (s, 1 arom. C); 54.4 (t, CH₂SO₂); 45.3 (t, CH₂N); 41.6 (t, CH₂N); 36.2 (t, CH₂N); 26.3, 20.0, 19.3, 14.9 (4t, 4 CH₂); 8.9 (q, Me). FAB-MS: 419 (10, $[M+1]^+$), 321 (18), 320 (100), 154 (19), 137 (26), 136 (36), 125 (18).

Reaction of Triazolo-triazinones **4a** and **4b** with Pyrrolidine. Synthesis of **10** and **11**. Pyrrolidine (0.12 ml, 1.5 mmol, 3 equiv.) was added to a soln. of triazolotriazinone **4a** (0.5 mmol, 1 equiv.) in dry 1,4-dioxane (2 ml). The mixture was stirred under N₂ at r.t. Upon completion of the reaction (TLC monitoring), the solvent was

removed under reduced pressure. FC of the resulting residue (hexane/AcOEt) provided **10** (124 mg, 67%), **11** (24 mg, 14%), and urea **8a** (11 mg, 13%) as colorless solids.

3-(Benzylsulfanyl)-N-butyl-5-[[1-(pyrrolidin-1-yl)methylidene]amino]-1H-[1,2,4]triazole-1-carboxamide (10). M.p. 106–107°. TLC (hexane/AcOEt 1:5): R_f 0.38. IR (KBr): 3437w, 3217w, 3051w, 2932w, 2870w, 1725m, 1630s, 1533s, 1462m, 1337w, 1277m, 704w. $^1\text{H-NMR}$ ((D_6)DMSO): 9.23 (t, $J = 5.4$, NH); 8.83 (s, CH); 7.52–7.34 (s, 5 arom. H); 4.42 (s, CH_2S); 3.79 (t, $J = 6.4$, CH_2N); 3.56 (t, $J = 6.4$, CH_2N); 3.43–3.34 (m, CH_2N); 2.08–1.95 (m, 4 H); 1.66–1.33 (m, 4 H); 1.02 (t, $J = 7.2$, Me). $^{13}\text{C-NMR}$ ((D_6)DMSO): 159.6 (s, C=O); 157.7 (s, triaz. C); 155.5 (d, CH); 148.7 (s, triaz. C); 138.2 (s, 1 arom. C); 129.2, 128.7, 127.5 (3d, 5 arom. CH); 49.9 (t, CH_2N); 46.3 (t, CH_2N); 39.6 (t, CH_2N); 34.7 (t, CH_2S); 31.4, 24.9, 24.2, 19.9 (t, 4 CH_2); 13.9 (q, Me). FAB-MS: 387 (13, $[M + 1]^+$), 289 (18), 288 (100), 198 (37), 197 (19), 149 (11), 133 (18), 124 (26).

5-(Benzylsulfanyl)-5-[[1-(pyrrolidin-1-yl)methylidene]amino]-1H-[1,2,4]triazole (11). M.p. 163–164°. TLC (hexane/AcOEt 1:5): R_f 0.18. IR (KBr): 3217w, 3061w, 2923w, 2871w, 1619s, 1564s, 1455w, 1402w, 1324m, 1260w, 1056w, 877w, 698w. $^1\text{H-NMR}$ ((D_6)DMSO): 12.86 (s, NH); 8.66 (s, CH); 7.48–7.32 (s, 5 arom. H); 4.35 (s, CH_2S); 3.36 (t, $J = 6.0$, CH_2N); 3.47 (t, $J = 6.4$, CH_2N); 2.03–1.91 (m, 4 H). $^{13}\text{C-NMR}$ ((D_6)DMSO): 161.5 (s, triaz. C); 154.7 (d, CH); 144.7 (s, triaz. C); 138.7 (s, 1 arom. C); 129.1, 128.7, 127.3 (3d, 5 arom. CH); 49.1 (t, CH_2N); 45.7 (t, CH_2N); 35.2 (t, CH_2S); 24.9, 24.5 (t, 2 CH_2). FAB-MS: 289 (18), 288 (100, $[M + 1]^+$), 198 (23), 197 (13), 171 (21), 149 (23), 133 (19), 124 (13).

Table. Crystallographic Data of Compound **3a**

Crystallized from	Et ₂ O/pentane
Empirical formula	C ₁₄ H ₁₉ N ₅ OS
Formula weight [g mol ⁻¹]	305.40
Crystal color, habit	Colorless, prism
Crystal dimensions [mm]	0.23 × 0.42 × 0.43
Temperature [K]	173 (1)
Crystal system	Monoclinic
Space group	$P2_1/c$
Z	4
Reflections for cell determination	25
2θ range for cell determination [°]	37–40
Unit-cell parameters a [Å]	8.801 (2)
b [Å]	10.309 (2)
c [Å]	16.753 (2)
β [°]	99.49 (1)
V [Å ³]	1499.2 (5)
$F(000)$	648
D_x [g cm ⁻³]	1.353
$\mu(\text{MoK}\alpha)$ [mm ⁻¹]	0.223
$2\theta_{\text{max}}$ [°]	55
Total reflections measured	3875
Symmetry-independent reflections	3449
Reflections used [$I > 2\sigma(I)$]	2818
Parameters refined	203
Final $R(F)$	0.0409
$wR(F)$	0.0405
Goodness-of-fit	1.892
Secondary extinction coefficient	$1.18(9) \times 10^{-6}$
Final $\Delta_{\text{max}}/\sigma$	0.0004
$\Delta\rho$ (max; min) [e Å ⁻³]	0.30; –0.33

X-Ray Crystal-Structure Determination of 3a (see Table and Fig.)²⁾. All measurements were conducted at low temp. on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71073 \text{ \AA}$) and a 12-kW rotating-anode generator. The $\omega/2\theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. The space group was uniquely determined by the systematic absences. Equivalent reflections were merged. Data collection and refinement parameters are given in the Table, and a view of the molecule is shown in the Figure. The structure was solved by direct methods with SHELXS97 [15], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amine and amide H-atoms were placed in the positions indicated by a difference electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All of the remaining H-atoms were fixed in geometrically calculated positions [$d(\text{C-H}) = 0.95 \text{ \AA}$], and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{\text{eq}}$ of its parent C-atom. Refinement of the structure was carried out on F by means of full-matrix least-squares procedures, which minimized the function $\sum w(|F_o| - |F_c|)^2$, where $w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$. A correction for secondary extinction was applied. Neutral-atom scattering factors for non-H-atoms were taken from [16a], and the scattering factors for H-atoms were taken from [17]. Anomalous dispersion effects were included in F_c [18]; the values for f' and f'' were those of [16b]. The values of the mass-attenuation coefficients are those found in [16c]. All calculations were performed with the *teXsan* crystallographic software package [19].

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²⁾ Crystallographic data for this paper have been deposited with the *Cambridge Crystallographic Data Centre* (CCDC-202952). These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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