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

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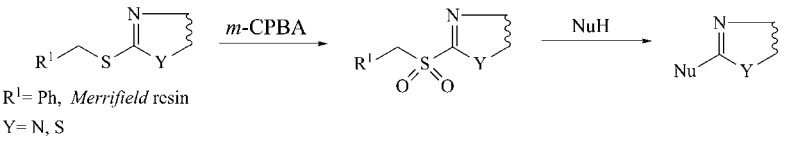
The synthesis of novel triazolo[1,5-*a*]triazin-7-ones is presented. Starting from 3-amino-5-sulfanyl-1,2,4-triazole, the synthetic sequence involved alkylation with benzyl bromide, reaction with *p*-nitrophenyl chloroformate followed by treatment with a primary amine, and condensation with diethoxymethyl 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*).

Scheme 1



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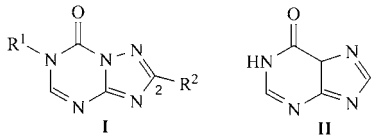
Within this context, an investigation was undertaken to expand the scope of this methodology and its potential application in the synthesis of more-elaborate heterocyclic scaffolds based on the [1,2,4]triazole nucleus. Triazoles are important pharmacophores in different therapeutic areas, and many biologically 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.



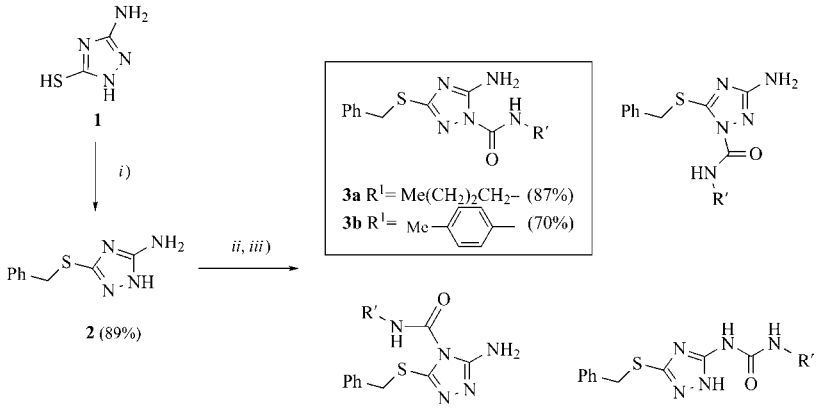
I **II**

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 $PhCH_2Br$ 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 triazolotriazinones **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 CH_2Cl_2 led to the sulfone derivatives **5a** and **5b**, respectively, in good yields (70–89%).

Scheme 2



i) $PhCH_2Br$ (1.1 equiv.), Et_3N (1.1 equiv.), DMF, r.t., 5 h. *ii*) *p*-Nitrophenyl chloroformate (1.1 equiv.), pyridine (1.1 equiv.), 1,4-dioxane, r.t., 1 h. *iii*) $R'NH_2$ (2.5 equiv.), 4 h.

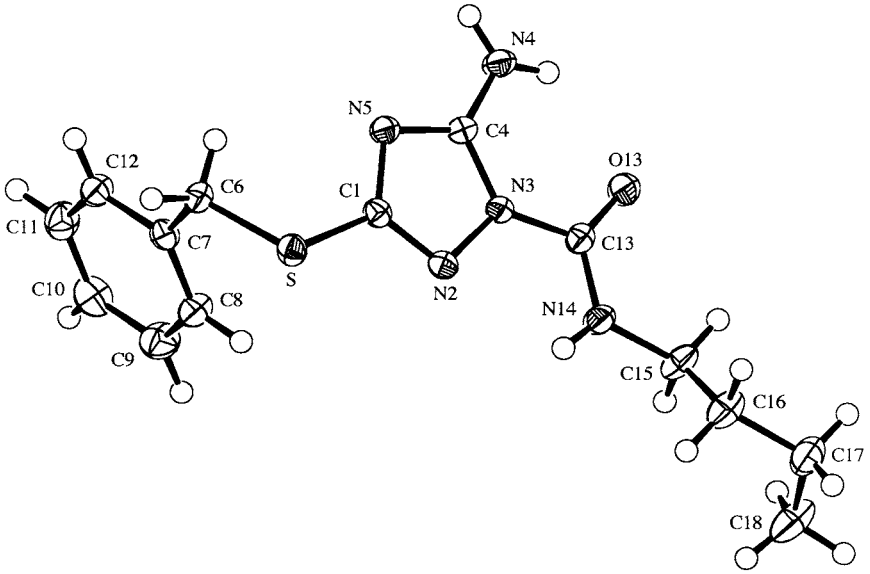
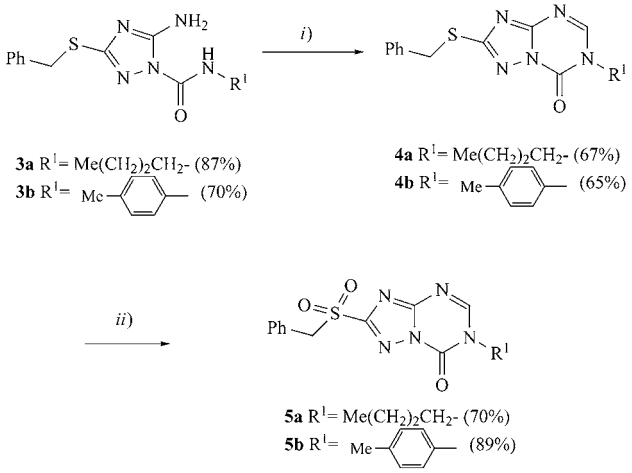


Figure. *ORTEPII* [14] *View of the molecular structure of compound* **3a**, *showing the labelling of the non-H-atoms* (ellipsoids drawn at the 50% probability level)

We then examined the nucleophilic *ipso*-substitution of the $PhCH_2SO_2$ 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

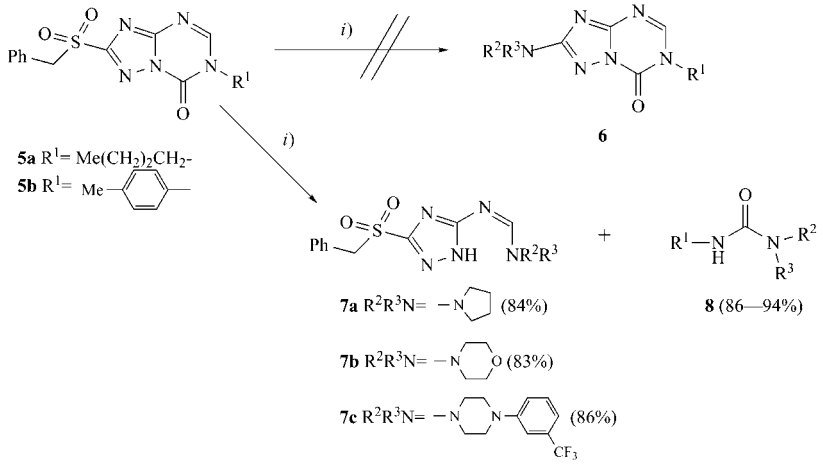
Scheme 3



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

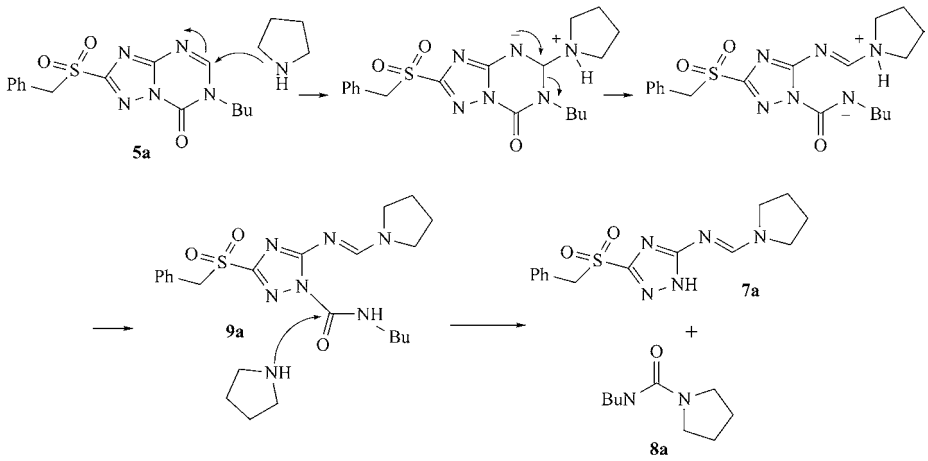


i) R^2R^3NH (3 equiv.), 1,4-dioxane, r.t.

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

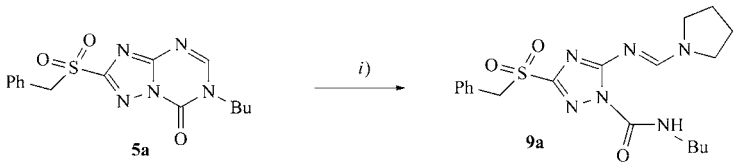
at the carbonyl atom of **9**, with ultimate loss of the corresponding urea **8**, would afford the triazole derivative **7** (*Scheme 5*).

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

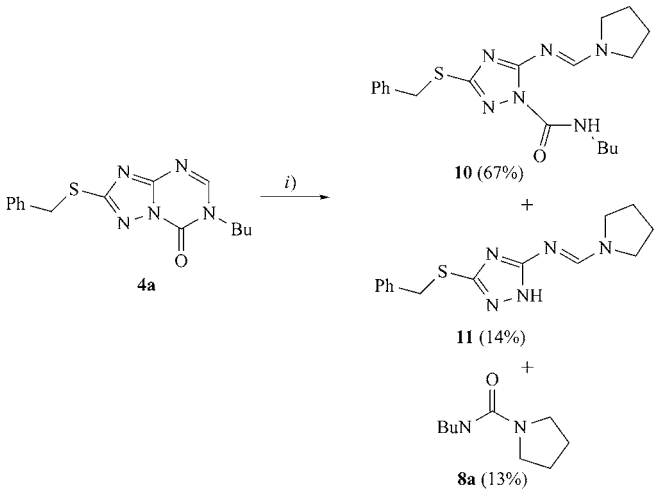


i) Pyrrolidine (1 equiv.), 1,4-dioxane, r.t.

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 N_2. M.p.: *Electrothermal* digital melting-point apparatus *IA 91000*, uncorrected. Anal. TLC: precoated TLC plates, silica gel *60* F_{254} (*Merck*). Flash chromatography (FC): silica gel 60 (230–400 mesh, *Merck*). IR Spectra: *Mattson-Galaxy Satellite FT-IR*; ν in cm^{-1}. ^1H- and ^{13}C-NMR (200 and 50 MHz, resp.): *Bruker DPX-200 Advance* instrument: δ in ppm rel. to $SiMe_4$ 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)-1*H*-[1,2,4]-triazol-3-amine* (**2**). Et_3N (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 N_2 at r.t. for 15–20 min. Next, benzyl bromide (4.05 ml, 34.1 mmol) was added, and the mixture was stirred under N_2 at r.t. for 4 h. The soln. was evaporated to dryness, and the resulting residue was partitioned between AcOEt (150 ml) and H_2O (100 ml). The org. layer was washed with brine (50 ml), dried ($MgSO_4$), 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): 3412*s*, 3323*m*, 3227*m*, 3206*m*, 3174*w*, 3061*m*, 2981*m*, 2882*m*, 2767*m*, 2730*m*, 2579*m*, 2366*m*, 2340*w*, 1622*s*, 1546*s*, 1495*m*, 1452*m*, 1339*m*, 1294*m*, 1238*m*, 1140*w*, 1086*m*, 1022*m*, 920*w*, 857*w*, 751*m*, 704*m*, 659*w*. ^1H-NMR ($CDCl_3$, 50°): 7.38–7.22 (*m*, 5 arom. H); 5.8 (br. *s*, 3 H, NH_2, NH); 4.32 (*s*, CH_2S). ^{13}C-NMR ($CDCl_3$, 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 N_2 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 N_2 at r.t. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (50 ml), washed with aq. sat. $NaHCO_3$ soln. (3 × 10 ml) and brine (10 ml). The org. layer was dried ($MgSO_4$), filtered, and concentrated. The resulting crude material was purified by FC (hexane/AcOEt).

5-Amino-N*-3-(benzylsulfanyl)-butyl-1*H*-[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): 3415*m*, 3355*m*, 2957*m*, 2989*m*, 2869*w*, 1715*s*, 1626*s*, 1530*s*, 1487*s*, 1307*s*, 1274*s*, 1187*m*, 1073*w*, 989*w*, 857*w*, 752*m*, 700*m*. ^1H-NMR ($CDCl_3$): 7.32–7.18 (*m*, 5 arom. H);

6.65 (*t*, *J* = 5.8, NH); 6.5 (br. *s*, NH_2); 4.2 (*s*, CH_2S); 3.25 (*q*, *J* = 6.6, CH_2NH); 1.53–1.18 (*m*, 4 H); 0.85 (*t*, *J* = 7.2, Me). ^{13}C-NMR ($CDCl_3$): 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 (*3d*, 5 arom. C–H); 39.6 (*t*, CH_2NH); 35.5 (*t*, CH_2S); 31.5, 19.8 (*t*, 2 CH_2); 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)-1*H*-[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*. ^{1}H-NMR ((D_6)DMSO): 9.82 (*s*, NH); 7.56–7.06 (*m*, 9 arom. H, NH_2); 4.42 (*s*, CH_2S); 2.29 (*s*, Me). ^{13}C-NMR ((D_6)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 (*5d*, 9 arom. CH); 34.4 (*t*, CH_2S); 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 N_2 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*. ^{1}H-NMR ((D_6)DMSO): 8.64 (*s*, H–C(7)); 7.5–7.24 (*m*, 5 arom. H); 4.49 (*s*, CH_2S); 3.98 (*t*, *J* = 7.2, CH_2N); 1.78–1.27 (*m*, 4 H); 0.93 (*t*, *J* = 7.0, Me). ^{13}C-NMR ((D_6)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 (*3d*, 5 arom. CH); 46.9 (*t*, *C*H_2N); 34.4 (*t*, CH_2S); 30.2, 18.9 (*t*, 2 aliph. CH_2); 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*. ^{1}H-NMR ((D_6)DMSO): 8.62 (*s*, H–C(5)); 7.51–7.31 (*m*, 9 arom. H); 4.52 (*s*, CH_2S); 2.42 (*s*, Me). ^{13}C-NMR ((D_6)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*, CH_2S); 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 CH_2Cl_2 (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*. ^{1}H-NMR ((D_6)DMSO): 8.82 (*s*, H–C(5)); 7.39 (*s*, 5 arom. H);); 4.97 (*s*, CH_2SO_2); 4.05 (*t*, *J* = 7.0, CH_2N); 1.81–1.29 (*m*, 4 H); 0.94 (*t*, *J* = 7.0, Me). ^{13}C-NMR ((D_6)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 (*3d*, 5 arom. CH); 127.1 (*s*, 1 arom. C); 59.5 (*t*, CH_2SO_2); 47.9 (*t*, CH_2N); 30.5, 19.4 (*t*, 2 CH_2); 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*, 1077w, 929*w*, 828*w*, 768*m*, 700*m*, 633*m*. ^{1}H-NMR ((D_6)DMSO): 8.84 (*s*, H–C(5)); 7.47–7.41 (*m*, 9 arom. H); 5.03 (*s*, CH_2SO_2); 2.43 (*s*, Me). ^{13}C-NMR ((D_6)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*, CH_2SO_2); 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 N_2 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]-1*H-*[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): 3198*w*, 3081*w*, 2969*w*, 2926*w*, 2870*w*, 1618*s*, 1566*s*, 1461*w*, 1408*m*, 1324*m*, 1244*w*, 1127*m*, 1051*w*, 729*w*, 701*w*. ^{1}H-NMR ((D$_6$)DMSO): 13.76 (*s*, NH); 8.66 (*s*, CH); 7.38–7.25 (*m*, 5 arom. H); 4.70 (*s*, CH_2SO_2); 3.36 (*t*, J = 6.0, CH_2N); 3.44 (*t*, J = 6.0, CH_2N); 2.01–1.79 (*m*, 4 H). ^{13}C-NMR ((D$_6$)DMSO): 161.9 (*s*, triaz. C); 158.2 (*s*, triaz. C); 155.2 (*d*, *C*H); 131.1, 128.4, 128.3 (3*d*, 5 arom. CH); 127.7 (*s*, 1 arom. C); 59.2 (*t*, CH_2SO_2); 48.9 (*t*, CH_2N); 45.5 (*t*, CH_2N); 24.5, 24.0 (*t*, 2 CH_2). 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]-1*H-*[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): 3167*w*, 3077*w*, 2970w, 2924*w*, 2861*w*, 1614*s*, 1569*s*, 1437*m*, 1412*m*, 1356*m*, 1321*m*, 1263*w*, 1236*w*, 1152*m*, 1115*m*, 1068*w*, 997*w*, 875*w*, 785*w*, 697*w*. ^{1}H-NMR ((D$_6$)DMSO): 13.81 (*s*, NH); 8.56 (*s*, CH); 7.39–7.25 (*m*, 5 arom. H); 4.70 (*s*, CH_2SO_2); 3.69–3.60 (*m*, 8 H). ^{13}C-NMR ((D$_6$)DMSO): 162.1, 158.7 (2*s*, triaz. C); 157.6 (*d*, CH); 131.6, 128.9, 128.7 (3*d*, 5 arom. CH); 127.1 (*s*, 1 arom. C); 66.9 (*t*, *C*H_2O); 65.8 (*t*, CH_2O); 59.7 (*t*, CH_2SO_2); 49.5 (*t*, CH_2N); 43.3 (*t*, CH_2N). 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]-1*H-*[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): 3246*w*, 3067*w*, 2972*w*, 2860*w*, 1625*s*, 1560*s*, 1445*m*, 1324*m*, 1237*w*, 1123*m*, 944*w*, 865*w*, 783*w*, 696*w*. ^{1}H-NMR ((D$_6$)DMSO): 13.82 (*s*, NH); 8.63 (*s*, CH); 7.51–7.12 (*m*, 9 arom. H); 4.72 (*s*, CH_2SO_2); 3.81–3.75 (*m*, 4 H, CH_2N); 3.38 (br. *s*, 4 H, CH_2N). ^{13}C-NMR ((D$_6$)DMSO): 162.1, 158.7 (2*s*, triaz. C); 157.5 (*d*, CH); 151.2 (*s*, 1 arom. C); 131.6, (*d*, 2 arom. CH); 130.5 (*q*, J(C,F) = 31, 1 arom. C); 130.4, 128.7, 128.9 (3*d*, 4 arom. CH); 128.1 (*s*, 1 arom. C); 124.8 (*q*, J(C,F) = 270, CF_3); 119.7, 115.7, 112.1 (3*d*, 3 arom. CH); 59.7 (*t*, CH_2SO_2); 48.8 (*t*, CH_2N); 48.7 (*t*, CH_2N); 47.5 (*t*, CH_2N); 42.4 (*t*, CH_2N).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): 3341*w*, 2948*w*, 2922*m*, 2857*m*, 1620*s*, 1534*s*, 1482*m*, 1462*m*, 1436*m*, 1397*m*, 1362*m*, 1255*m*, 1228*m*, 1191*m*, 1147*m*, 765*m*. ^{1}H-NMR ((D$_6$)DMSO): 6.04 (br. *s*, NH); 3.31–3.24 (*m*, 4 H); 3.08 (*t*, J = 6.7, CH_2N); 1.93–1.83 (*m*, 4 H); 1.51–1.29 (*m*, 4 H); 0.96 (*t*, J = 6.7, Me). ^{13}C-NMR ((D$_6$)DMSO): 156.5 (*s*, C=O); 45.2 (*t*, CH_2N); 39.5 (*t*, CH_2N); 32.3, 24.9, 19.5 (3*t*, 3 CH_2); 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): 3316*w*, 3032*m*, 2969*m*, 2867*m*, 1645*s*, 1592*s*, 1525*s*, 1477*m*, 1447*m*, 1409*m*, 1380*m*, 1288*m*, 1245*m*, 1199*m*, 1115*m*, 809*m*, 754*m*. ^{1}H-NMR ((D$_6$)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}C-NMR ((D$_6$)DMSO): 153.9 (*s*, C=O); 138.0, 130.1 (2*s*, 2 arom. C); 128.6, 119.6 (2*d*, 4 arom. CH); 45.6 (*t*, CH_2N); 24.9 (*t*, 2 CH_2); 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]-1*H-*[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): 3463*w*, 3218*w*, 3082*w*, 2963*w*, 2876*w*, 1745*s*, 1634*s*, 1535*s*, 1464*w*, 1420*w*, 1340*m*, 1233*w*, 1140*m*, 917*w*, 704*w*. ^{1}H-NMR ((D$_6$)DMSO): 9.27 (*t*, J = 5.2, NH); 8.82 (*s*, CH); 7.40–7.35 (*s*, 5 arom. H); 4.79 (*s*, CH_2SO_2); 3.76 (*t*, J = 6.4, CH_2N); 3.53 (*t*, J = 6.2, CH_2N); 3.39–3.30 (*m*, CH_2N); 2.52–1.89 (*m*, 4 H); 1.63–1.25 (*m*, 4 H); 0.92 (*t*, J = 7.0, Me). ^{13}C-NMR ((D$_6$)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 (3*d*, 5 arom. CH); 122.6 (*s*, 1 arom. C); 54.4 (*t*, CH_2SO_2); 45.3 (*t*, CH_2N); 41.6 (*t*, CH_2N); 36.2 (*t*, CH_2N); 26.3, 20.0, 19.3, 14.9 (4*t*, 4 CH_2); 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 N_2 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-{[(pyrrolidin-1-yl)methylidene]amino}-1*H-*[1,2,4]triazole-1-carboxamide* (**10**). M.p. 106–107°. TLC (hexane/AcOEt 1:5): R_f 0.38. IR (KBr): 3437*w*, 3217*w*, 3051*w*, 2932*w*, 2870*w*, 1725*m*, 1630*s*, 1533*s*, 1462*m*, 1337*w*, 1277*m*, 704*w*. ^{1}H-NMR ((D$_6$)DMSO): 9.23 (*t*, *J* = 5.4, NH); 8.83 (*s*, C*H*); 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}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 (3*d*, 5 arom. *C*H); 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-{[(pyrrolidin-1-yl)methylidene]amino}-1*H-*[1,2,4]triazole* (**11**). M.p. 163–164°. TLC (hexane/AcOEt 1:5): R_f 0.18. IR (KBr): 3217*w*, 3061*w*, 2923w, 2871*w*, 1619*s*, 1564*s*, 1455*w*, 1402*w*, 1324*m*, 1260*w*, 1056*w*, 877*w*, 698*w*. ^{1}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}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 (3*d*, 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_2O/pentane
Empirical formula	$C_{14}H_{19}N_5OS$
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
μ(MoK_α) [mm^{-1}]	0.223
$2\theta_{(max)}$ [°]	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) × 10^{-6}
Final Δ_{max}/σ	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 ($\lambda = 0.71073$ Å) 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(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{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 $\Sigma w(|F_o| - |F_c|)^2$, where $w = [\sigma\ (F_o) + (0.005F_o)^2]^{-1}$. 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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