Generation of 6,7-Dihydro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyridines — Unexpected Products in the Reaction of 5-Ethylthio-1,3,4-thiadiazole-2-amine and 3-(Dimethylamino)propiophenones

Jairo Quiroga*[a], Braulio Insuasty[a], Pedro Hernandez[a], Rodolfo Moreno[a], Regina H. de Almeida[b], and Herbert Meier[c]

Department of Chemistry, Universidad del Valle[a],
A.A. 25360 Cali, Colombia

Instituto de Quimica de Sao Carlos[b],
USP CP. 780 Sao Carlos, Brasil

Institut für Organische Chemie, Universität Mainz[c],
J.-J.-Becherweg 18−22, D-55099 Mainz, Germany

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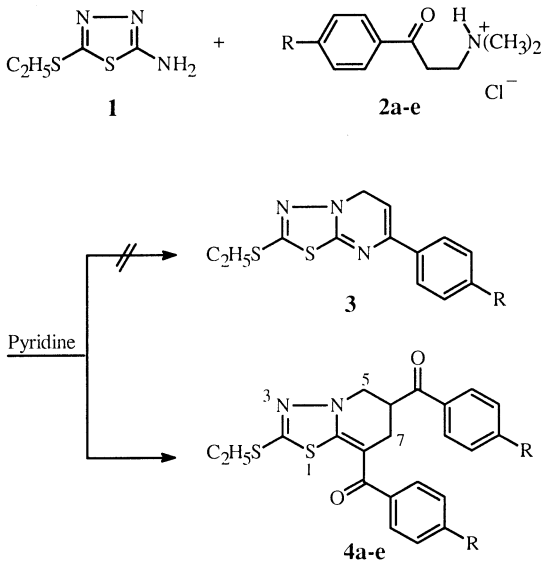
A series of 6,8-diaroyl-6,7-dihydro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyridines **4a**–**e** was prepared by the reaction of 5-ethylthio-1,3,4-thiadiazole-2-amine (**1**) and *p*-substituted 3-(dimethylamino)propiophenones **2a**–**e** in pyridine. The unexpected cyclization process was established by NMR and X-ray diffraction measurements.

1,3,4-Thiadiazoles find a variety of applications as antibiotic, antiinflammatory or bacteriostatic agents and as pesticides[1][2]. These biological activities have stimulated us to synthesize and investigate a new class of fused 1,3,4-thiadiazoles. Based on our experience[3][4][5][6] with the reaction of aminoazoles and α,β-unsaturated ketones (chalcones) or their precursors, the 3-(dimethylamino)propiophenones, we studied the reaction of 5-ethylthio-1,3,4-thiadiazole-2-amine (**1**) with the hydrochlorides of *p*-substituted 3-(dimethylamino)propiophenones **2a**−**e** in boiling pyridine.

Scheme 1



4	R	m.p. [°C]	Yield [%]
a	H	111	42
b	OCH_3	136	45
c	Cl	155	50
d	Br	147	52
e	NO_2	155	65

Although a condensation reaction of the amine **1** and the ketone followed by a cyclization to 5*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidines **3** seemed to be likely, we isolated 1:2-adducts which have the structure of 6,8-diaroyl-6,7-dihydro-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyridines **4a**−**e**.

It is well-known that 3-aminopropiophenones are easily cleaved to aryl vinyl ketones which then can react with 3-aminopropiophenone in the sense of a Michael addition[7].

Scheme 2

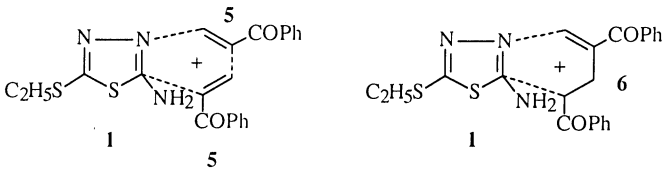


Table 1. ^{1}H-NMR data of the compounds **4a**−**e** (δ values in CD_3SOCD_3, TMS as the internal standard)

Comp. 4	5-H dd / dd	6-H m	7-H dd / dd	6-Aroyl m	8-Aroyl m	CH_2 q	CH_3 t
a	4.44 / 4.34	4.21	2.91 / 2.84	7.25−7.98	7.25−7.98	3.19	1.36
b	4.41 / 4.27	4.24	2.93 / 2.87	6.84−7.42	6.98−7.97	3.17	1.35
c	4.46 / 4.32	4.17	2.90 / 2.81	7.35−7.40	7.53−7.98	3.18	1.35[a]
d	4.45 / 4.30	4.17	2.89 / 2.80	7.29−7.52	7.68−7.90	3.18	1.35
e	4.53 / 4.38	4.28	2.92 / 2.79	7.58−8.15	8.15−8.27	3.21	1.37

[a] OCH_3 singlets at δ = 3.73 and 3.80

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Table 2. ^{13}C-NMR data of the compounds **4a−e** (δ values in CD_3SOCD_3, TMS as the internal standard)

4	C-2 / C-8a	C-5	C-6	C-7	C-8	6-CO	8-CO	CH_2	CH_3	CH	C_q
A	151.7 / 154.1	50.4	38.2	27.8	84.0	199.7	183.5	27.6	14.7	127.2, 127.9, 128.3, 128.8, 129.3, 133.5	135.1, 139.6
b	151.2 / 154.1	50.5	37.8	28.5	84.3	197.9	182.4	27.6	14.7[a]	113.2, 114.0, 129.3, 130.7	127.9, 131.7, 160.2, 163.4
c	152.0 / 154.7	50.4	38.3	27.2	94.0	198.6	181.8	27.6	14.6	127.9, 128.9, 129.2, 130.2	133.7, 134.1, 138.1, 138.5
d	152.0 / 154.7	50.4	38.3	27.6	93.9	198.9	181.9	27.6	14.7	129.4, 130.3, 130.9, 131.9	122.8, 127.7, 134.0, 138.5
e	152.8 / 155.1	50.4	38.9	27.7	93.9	198.9	180.8	27.2	14.6	123.1, 123.8, 128.5, 129.7	139.7, 145.5, 147.5, 150.0

[a] OCH_3 signals at δ = 51.5 and 55.5

In the present case ketone **5** or its dimer **6** could be responsible for the anellation of a piperidine ring to the 1,3,4-thiadiazole ring. Extrusion of ammonia could then lead to the obtained compound **4**. However, it was not possible to find an experimental proof for the assumed intermediates under the reaction conditions used. Moreover, when we subjected equimolar amounts of **1** and **6** [7b] to the reaction conditions used, product **4** was not formed. Thus, the mechanism for the unexpected process **1** + **2** → **4** remains still unknown.

The structures of the compounds **4a−e** were established by ^{1}H- and ^{13}C-NMR measurements. Additionally, a crystal structure analysis was performed for **4b**. The tables 1 and 2 summarize the ^{1}H and ^{13}C chemical shifts. The assignment of the signals was supported by ^{1}H,^{1}H COSY and ^{1}H,^{13}C shift correlation spectra. The protons on the pyri-

Figure 1. X-ray crystal structure of compound **4b**[11]

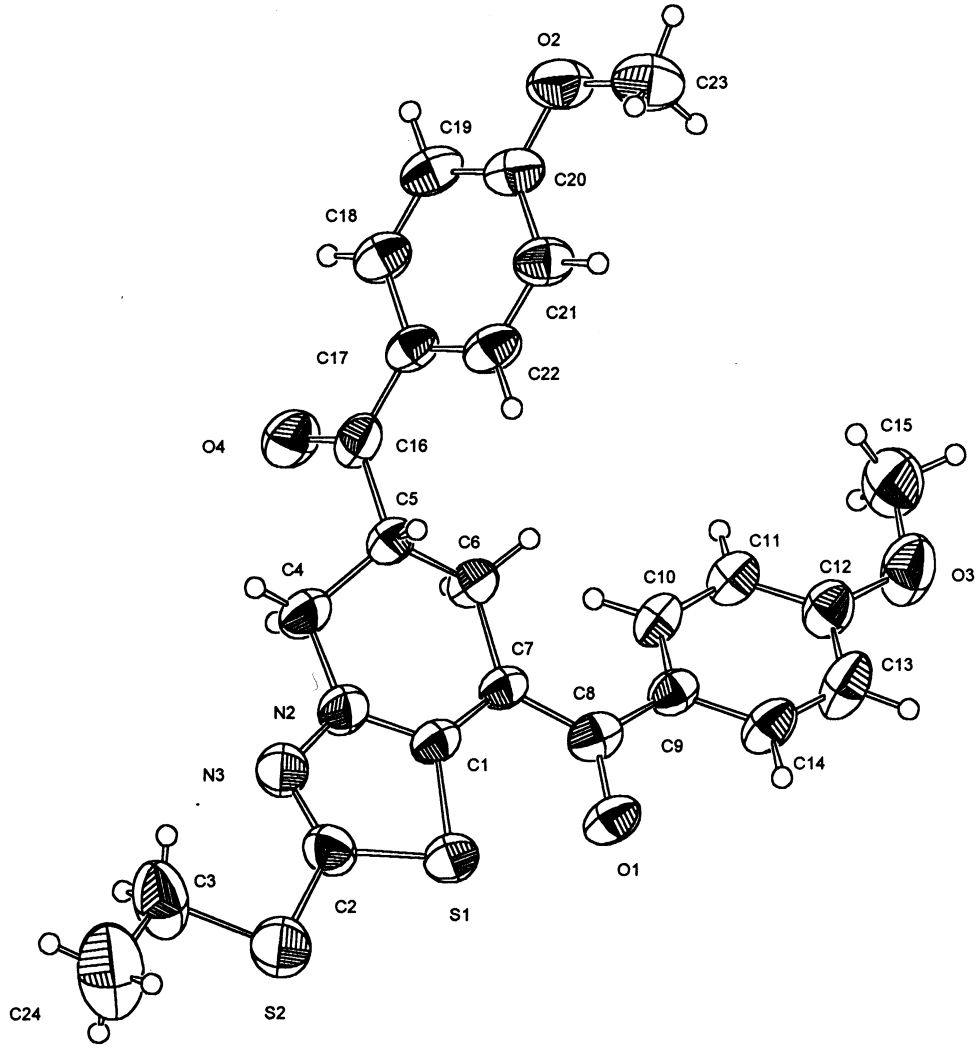

Table 3. Selected bond lengths [Å] bond angles [°] and torsional angles [°] of compound **4b** (The numbering corresponds to Figure 1 and not to the nomenclature)

S(1)−C(1)	1.738(3)	C(1)−S(1)−C(2)	88.1(2)
S(1)−C(2)	1.749(4)	N(3)−C(2)−S(1)	116.6(3)
S(2)−C(2)	1.743(3)	C(2)−N(3)−N(2)	108.3(3)
N(2)−C(1)	1.349(4)	C(1)−N(2)−N(3)	118.4(3)
N(2)−C(4)	1.464(4)	N(2)−C(1)−S(1)	108.6(2)
N(2)−N(3)	1.378(4)	N(2)−C(1)−C(7)	123.9(3)
N(3)−C(2)	1.288(4)	C(1)−C(7)−C(6)	117.0(3)
C(1)−C(7)	1.380(4)	C(7)−C(6)−C(5)	111.1(3)
C(6)−C(7)	1.516(4)	C(4)−C(5)−C(6)	110.8(3)
C(5)−C(6)	1.530(4)	N(2)−C(4)−C(5)	107.4(3)
C(4)−C(5)	1.514(4)	C(3)−S(2)−C(2)− N(3)	−2.5(4)
		C(4)−C(5)−C(16)−O(4)	−30.3(5)
		C(1)−C(7)−C(8)−O(1)	−5.0(5)
		C(4)−N(2)−C(1)−S(1)	−179.6(3)
		N(3)−N(2)−C(1)−C(7)	−179.6(3)

dine ring show a typical ABCDE pattern for the building block 5-CH_2−6-CH−7-CH_2. The geminal couplings ^2J amount to (−12.5 ± 0.3) Hz for 5-CH_2 (AB) and to (−14.5 ± 0.3) Hz for 7-CH_2 (DE). The vicinal coupling constants are: ^3J(AC) = 7.6 ± 0.3 Hz and ^3J(CD) = 8.3 ± 0.3 Hz for the *trans* and ^3J(BC) = 3.7 ± 0.2 Hz and ^3J(CE) = 4.2 ± 0.2 Hz for the *cis* arranged protons. The integration of the four doublet of doublets (A, B, D, E) and the multiplet (C) corresponds to 1:1:1:1:1.

Figure 1 shows an X-ray crystal structure of compound **4b**; the most important geometric data of this novel type of heterobicyclic system[8][9][10] are listed in table 3. The torsional angles reveal that the anellation of the two rings does not deviate much from planarity; the same statement can be made for the carbonyl group on C-8, which is cisoid and almost coplaner to the double bond between C-8 and C-8a.

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Experimental Section

Melting points were taken on a Büchi melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were run on a Bruker AM 400 in D_3CSOCD_3. The mass spectra were recorded on a Varian MAT 711 or a Finnigan M 95 operating at 70 eV. The elemental analyses were obtained by using a LEGO CHNS - 900 equipment.

General Procedure for the Preparation of the 6,7-Dihydro-5H-1,3,4-thiadiazolo[3,2-a]pyridines **4a**−**e**: A solution of 5-ethylthio-1,3,4-thiadiazole-2-amine (**1**) (81 mg, 0.5 mmol) and 1.0 mmol of the corresponding 3-(dimethylamino)propiophenone hydrochloride (**2a**−**e**) in 4 ml of pyridine was heated for 20 min to reflux. The reaction products **4a**−**e** crystallized on cooling, were washed with cold ethanol and purified by column chromatography (2.5 x 40 cm silica gel) with petroleum ether (50−80 / ethyl acetate (1:1).

6,8-Dibenzoyl-2-ethylthio-6,7-dihydro-5H-1,3,4-thiadiazolo-[3,2-a]pyridine (**4a**): Yellow crystals, m.p. 111°C, yield: 86 mg (42%). − MS, *m/z* (%): 408 (34) [$M^{+\cdot}$], 304 (11), 303 (70), 105 (100) [$C_6H_5CO^+$]. − $C_{22}H_{20}N_2O_2S_2$ (408.6): calcd. C 64.68, H 4.93, N 6.86; found C 64.75, H 4.87, N 6.76.

2-Ethylthio-6,7-dihydro-6,8-bis(4-methoxybenzoyl)-5H-1,3,4-thiadiazolo[3,2-a]pyridine (**4b**): Yellow crystals, m.p. 136°C, yield: 105 mg (45%). − MS, *m/z* (%): 468 (32) [$M^{+\cdot}$], 334 (17), 333 (86), 135 (100) [$H_3CO-C_6H_4-CO^+$]. − $C_{24}H_{24}N_2O_4S_2$ (468.6): calcd. C 61.52, H 5.16, N 5.98; found C 61.65, H 5.07, N 5.86.

6,8-Bis(4-chlorobenzoyl)-2-ethylthio-6,7-dihydro-5H-1,3,4-thiadiazolo[3,2-a]pyridine (**4c**): Yellow crystals, m.p. 155°C, yield 119 mg (50%). − MS, *m/z* (%): 480 / 478 / 476 (4) [$M^{+\cdot}$, Cl_2 pattern], 339 (13), 337 (31), 141 (31), 139 (100) [$Cl-C_6H_4-CO^+$]. − $C_{22}H_{18}Cl_2N_2O_2S_2$ (477.5): calcd. C 55.34, H 3.80, N 4.95; found C 55.27, H 3.87, N 4.86.

6,8-Bis(4-bromobenzoyl)-2-ethylthio-6,7-dihydro-5H-1,3,4-thiadiazolo[3,2-a]pyridine (**4d**): Yellow crystals, m.p. 147°C, yield (147 mg) (52%). − MS, *m/z* (%): 568 / 566 / 564 (51) [$M^{+\cdot}$, Br_2 pattern], 384 (17), 383 (100), 382 (18), 381 (93), 202 (10), 185 / 183 (22) [$Br-C_6H_4-CO^+$]. − $C_{22}H_{18}Br_2N_2O_2S_2$ (566.4): calcd. C 46.66, H 3.20, N 4.95; found C 46.75, H 3.27, N 4.88.

2-Ethylthio-6,7-dihydro-6,8-bis(4-nitrobenzoyl)-5H-1,3,4-thiadiazolo[3,2-a]pyridine (**4e**): Pale orange crystals, m.p. 155°C, yield 162 mg (65%). − MS, *m/z* (%): 498 (18), [$M^{+\cdot}$], 437 (15), 404 (36), 392 (16), 380 (18), 348 (39), 270 (11), 154 (11), 150 (59) [$O_2N-C_6H_4-CO^+$], 122 (16), 120 (42), 104 (53), 92 (26), 87 (96), 64 (53), 59 (100). − $C_{22}H_{18}N_4O_6S_2$ (498.6): calcd. C 53.00, H 3.64, N 11.24; found C 53.05, H 3.57, N 10.99.

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[11] $C_{24}H_{24}N_2O_4S_2$, molecular mass 468.70; crystal size 0.20 × 0.18 × 0.12 mm; triclinic, space group *P*-1; unit cell dimensions: a = 8.665(2) A, b = 11.858(2) A, c = 12.709(2) A, α = 75.560(10)°, β = 70.000(10)°, γ = 71.210(10)°; V = 1147.4(4) A^3, Z = 2, d = 1.356 Mg/m^3; μ = 0.266 mm^{-1}, F(000) = 492; θ range between 2.71 and 26.29°; index ranges $0 \le h \le 10$, $-13 \le k \le 14$, $-14 \le l \le 15$; reflections collected 4940, independent reflections: 4625 [R(int) = 0.0367]; refinement: full-matrix least-squares on F^2; goodness-of-fit on F^2: 0.808; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0539, ω$R2$ = 0.0993; R indices (all data): $R1$ = 0.1627, ω$R2$ = 0.1170; extinction coefficient 0.0000(7); largest diff. peak and hole: 0.207 and −0.215 eA^{-3}. Further details of the structure investigation are available from the Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the depository number CSD-406082 the names of the authors, and the journal citation.

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