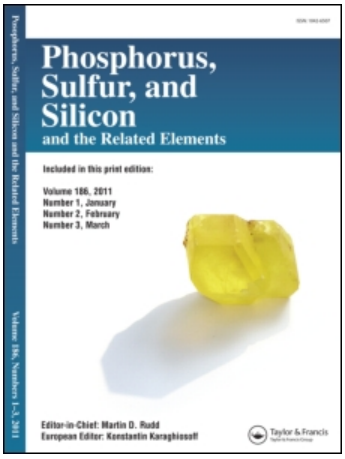

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1,3,4-THIADIAZOLES. REGIOSELECTIVE *O*-DEMETHYLATION ON DEHYDRATIVE CYCLIZATION OF 1-(3,4,5-TRIMETHOXYBENZOYL)4-SUBSTITUTED THIOSEMICARBAZIDES WITH SULPHURIC ACID

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1,3,4-THIADIAZOLES. REGIOSELECTIVE *O*-DEMETHYLATION ON DEHYDRATIVE CYCLIZATION OF 1-(3,4,5-TRIMETHOXYBENZOYL)-4-SUBSTITUTED THIOSEMICARBAZIDES WITH SULPHURIC ACID

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Cyclization of 1-(3,4,5-trimethoxybenzoyl)-4-substituted thiosemicarbazides ***2a–g*** *with sulphuric acid at ambient temperature afforded the selectively demethylated products 2-(4-hydroxy-3,5-dimethoxyphenyl)-5-substituted amino-1,3,4-thiadiazoles* ***4a–g****. Meanwhile, dehydrative cyclization of 1-(3,4,5-trimethoxybenzoyl)-4-(benzyl or* t*-butyl)thiosemicarbazides* ***2h,i*** *with sulphuric acid yielded 2-(4-hydroxy-3,5-dimethoxyphenyl)-5-amino-1,3,4-thiadiazole* ***5****. On the other hand, dehydration of* ***2h,i*** *by heating with phosphorus oxychloride yielded 2-(3,4,5-trimethoxyphenyl)-5-amino-1,3,4-thiadiazole* ***6****.*

Keywords: 1,3,4-Thiadiazoles; *N*-debenzylation; *N*-(*t*-debutylation); selective *O*-demethylation

INTRODUCTION

1,3,4-thiadiazole nucleus constitutes the active part of several biologically active compounds, including antibacterial,[1–4] antimycotic,[5,6] antiviral,[7,8] carbonic anhydrase inhibitor,[9–11] and anti-inflammatory[12,13] activities. In view of these findings, and in continuation to our interest in the synthesis of 2-substituted-5-amino-1,3,4-thiadiazoles,[14] we report our observations on the dehydrative cyclization of 1-(3,4,5-trimethoxybenzoyl)-4-substituted thiosemicarbazides with sulphuric acid and phosphorus oxychloride.

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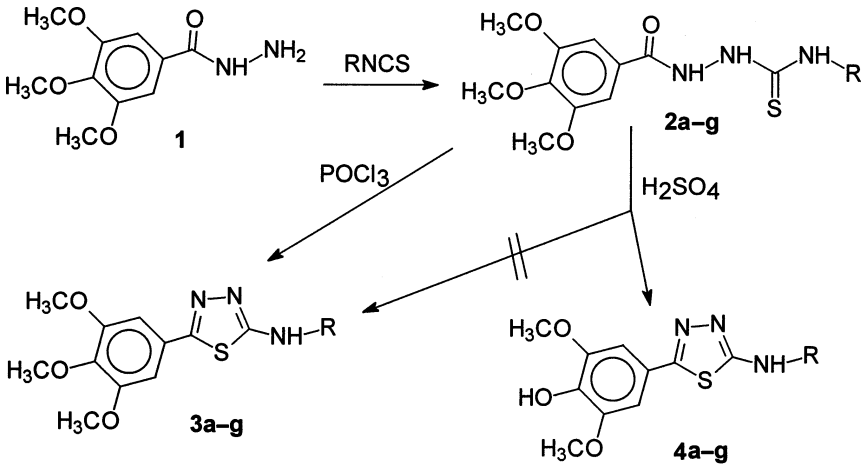
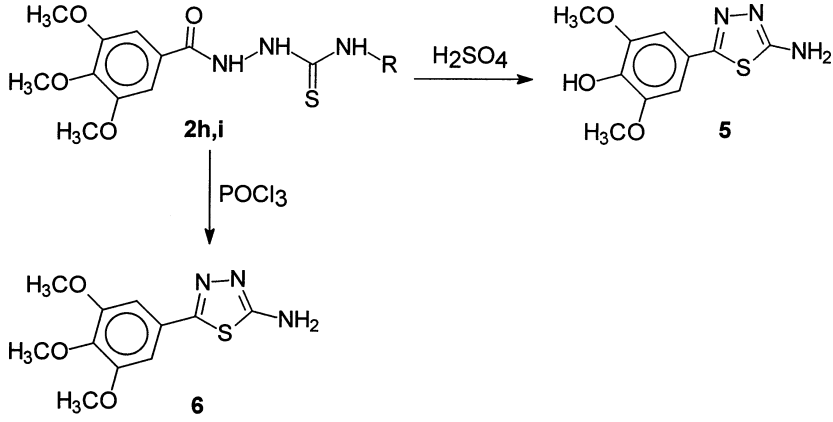
RESULTS AND DISCUSSION

The reaction of 3,4,5-trimethoxybenzoic acid hydrazide **1** with certain alkyl or arylisothiocyanates in ethanol yielded the corresponding 1-(trimethoxybenzoyl)-4-substituted thiosemicarbazides **2a–i** in high yields. Several procedures were reported for dehydrative cyclization of 1,4-disubstituted thiosemicarbazides to their substituted amino-1,3,4-thiadiazole analogues utilizing a variety of dehydrating agents, including sulphuric acid,[5,14,15] phosphorus oxychloride,[14,16] polyphosphoric acid,[17] and methane sulphonic acid.[13] Attempted cyclization of compounds **2a–g** via stirring with sulphuric acid at ambient temperature for 24 h did not yield the expected 2-(3,4,5-trimethoxyphenyl)-5-substituted amino-1,3,4-thiadiazoles **3a–g**; the *O*-demethylated products **4a–g** were obtained instead. On the other hand, compounds **3a–g** were successfully obtained by cyclization of **2a–g** via heating with phosphorus oxychloride (Scheme 1).



SCHEME 1

Dehydrative cyclization of 1-(trimethoxybenzoyl)-4-benzyl or *t*-butyl-thiosemicarbazides **2h**, **2i** using sulphuric acid yielded the *O*-demethylated, *N*-debenzylated or de(*t*-butylated) product **5**. Meanwhile, heating compound **2h** or **2i** with phosphorus oxychloride yielded the *N*-debenzylated or de(*t*-butylated) product **6** (Scheme 2). The structures of the *O*-demethylated and the *N*-debenzylated or de(*t*-butylated) products were confirmed by the correct elemental analyses, mass spectra, and NMR data. Although the literature are enriched



SCHEME 2

with several reports on the *O*- and *N*-dealkylation and debenzylation under the influence of various reagents, to our knowledge the described regioselective *O*-demethylation via the action of suphuric acid is unusual and previously unreported. Nonselective *O*-demethylation was reported to be conducted via the action of aqueous hydrobromic acid,[18] boron tribromide in dichloromethane,[19,20] sodium ethanethiolate in dimethylformamide,[21–23] and oxidative demethylation with silver(II)oxide in the presence of nitric acid[24] or cobalt trifluoride in dioxane-water.[25] Selective *O*-demethylation was achieved by the action of diisobutylaluminium[26] and magnesium iodide etherate.[27] The cleavage of *N*-benzyl and alkyl bond has been reported to take place via the action of catalytic hydrogenation,[28] sodium or lithium and ammonia,[29,30] *tert*-butyllithium in tetrahydrofuran,[31] aqueous hydrobromic acid,[32] 95% formic acid,[33] phenol and orthophosphoric acid,[34] trifluoroacetic acid,[35,36] and diethyl azodicarboxylate.[37]

EXPERIMENTAL

Melting points (°C, uncorrected) were recorded on a Fisher-Johns melting point apparatus. NMR spectra were recorded on a Bruker A 250 FT instrument at 250 MHz for ^{1}H NMR and 62.9 MHz for ^{13}C NMR using tetramethylsilane (TMS) as an internal standard and dimethylsulfoxide (DMSO)-d_6 as solvent (Chemical shifts in δ ppm). Silica gel plates 60 F_{254} (Merck, Darmstadt, Germany) were used for monitoring the reaction. Mass spectra were obtained on a Kratos MS 50-spectrometer at 70 eV. Analytical data (C, H, N, S) were within $\pm$0.4% of the theoretical values.

1-(3,4,5-Trimethoxybenzoyl)-4-substituted Thiosemicarbazides 2a–i

A mixture of 3,4,5-trimethoxybenzoic acid hydrazide (2.26 g, 0.01 mol) and the appropriate alkyl or arylisothiocyanate (0.01 mol) in ethanol (20 ml) was heated under reflux for 1 h. On cooling, the precipitated crystalline solid was filtered, washed with cold ethanol, and dried to yield compounds **2a–i** in 90–97% yields. The products were pure enough to be used in the next step without further purification (Table I).

2a: ^{1}H NMR: 2.87 (d, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.88 (s, 6H, OCH_3), 7.25 (s, 2H, Ar—H), 8.0 (s, 1H, NH, D_2O-exchang.), 9.31 (s, 1H, NH, D_2O-exchang.), 10.28 (s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 31(CH_3), 56 (2 × OCH_3), 61 (OCH_3), 106, 128, 152, 140, 167 (Ar—C, C=O & C=S).

2b: ^{1}H NMR: 1.06 (t, 3H, CH_3), 3.46 (q, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 7.26 (s, 2H, Ar—H), 8.06 (s, 1H, NH, D_2O-exchang.), 9.25 (s, 1H, NH, D_2O-exchang.), 10.26 (s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 13 (CH_3), 36 (CH_2), 56 (2 × OCH_3), 60 (OCH_3), 105, 128, 153,140, 166 (Ar—C, C=O, & C=S).

2c: ^{1}H NMR: 0.86 (t, 3H, CH_3), 1.24 (q, 2H, CH_2), 1.47 (q, 2H, CH_2), 3.34 (q, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 7.26 (s, 2H, Ar—H), 8.03 (s, 1H, NH, D_2O-exchang.), 9.23 (s, 1H, NH, D_2O-exchang.), 10.25 (s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 14 (CH_3), 20 (CH_2), 31 (CH_2), 43 (CH_2), 56 (2 × OCH_3), 59 (OCH_3), 105, 127, 152, 140, 166 (Ar—C, C=O & C=S).

2d: ^{1}H NMR: 3.72 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.14–7.42 (m, 7H, Ar—H), 9.76 (br s, 2H, NH, D_2O-exchang.), 10.50 (s, 1H, NH, D_2O-exchang.).

TABLE I Melting Points, Yield Percentages, Molecular Formulae, and Molecular Weights of Compounds **2a–i**

Comp. no.	R	m.p. (°C)	Yield (%)	Molecular formula (mol. weight)
2a	CH_3	210–212	94	$C_{12}H_{17}N_3O_4S$ (299.34)
2b	C_2H_5	205–207	90	$C_{13}H_{19}N_3O_4S$ (313.37)
2c	$C_4H_9(n)$	188–190	90	$C_{15}H_{23}N_3O_4S$ (341.42)
2d	C_6H_5	185–187	95	$C_{17}H_{19}N_3O_4S$ (361.41)
2e	4-FC_6H_4	210–212	94	$C_{17}H_{18}FN_3O_4S$ (379.40)
2f	4-ClC_6H_4	204–206	96	$C_{17}H_{18}ClN_3O_4S$ (395.86)
2g	4-BrC_6H_4	234–236	97	$C_{17}H_{18}BrN_3O_4S$ (440.31)
2h	$C_6H_5CH_2$	200–202	92	$C_{18}H_{21}N_3O_4S$ (375.44)
2i	$(CH_3)_3C$	160–162	90	$C_{15}H_{23}N_3O_4S$ (341.42)

2e: ^{1}H NMR: 3.72 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.14 (s, 2H, Ar—H), 7.30 (d, 2H, Ar—H), 7.43 (d, 2H, Ar—H), 9.75 (br s, 2H, NH, D_2O-exchang.), 10.49 (s, 1H, NH, D_2O-exchang.).

2f: ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.29 (s, 2H, Ar—H), 7.37 (d, 2H, Ar—H), 7.49 (d, 2H, Ar—H), 9.82 (s, 2H, NH, D_2O-exchang.), 10.50 (s, 1H, NH, D_2O-exchang.).

2g: ^{1}H NMR: 3.72 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.29 (s, 2H, Ar—H), 7.45 (d, 2H, Ar—H), 7.50 (d, 2H, Ar—H), 9.83 (s, 2H, NH, D_2O-exchang.), 10.51 (s, 1H, NH, D_2O-exchang.).

2h: ^{1}H NMR: 3.70 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 4.73 (d, 2H, CH_2), 7.24–7.31 (m, 7H, Ar—H), 8.62 (s, 1H, NH, D_2O-exchang.), 9.45 (s, 1H, NH, D_2O-exchang.), 10.36 (s, 1H, NH, D_2O-exchang.).

2i: ^{1}H NMR: 1.46 (s, 9H, CH_3), 3.72 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 7.24 (s, 2H, Ar—H), 8.21 (s, 1H, NH, D_2O-exchang.), 9.12 (s, 1H, NH, D_2O-exchang.), 10.25 (s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 29 ($3 \times CH_3$), 53 ($C(CH_3)_3$), 56 ($2 \times OCH_3$), 60 (OCH_3), 105, 128, 131, 141, 153, 165 (Ar—C, C=O & C=S).

2-(3,4,5-Trimethoxyphenyl)-5-substituted Amino-1,3,4-thiadiazoles 3a–g

A mixture of the substituted thiosemicarbazide **2a–g** (1.0 g) and phosphorus oxychloride (10 ml) was heated under reflux for 1 h, and the mixture was then evaporated under reduced pressure. The resulting residue was washed with saturated sodium hydrogen carbonate solution, then with water, dried and crystallized to yield compounds **3a–g** (Table II).

3a: ^{1}H NMR: 2.91 (t, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.81 (s, 6H, OCH_3), 7.01 (s, 2H, Ar—H), 7.85 (br s, 1H, NH, D_2O-exchang.). MS, m/z (Rel. Int.): 281 (M^+, 22), 267 (23), 266 (100), 194 (19), 180 (14), 88 (49), 74 (26).

TABLE II Melting Points, Yield Percentages, Crystallization Solvents, Molecular Formulae, and Molecular Weights of Compounds **3a–g**

Comp. no.	R	Cryst. solv.	m.p. (°C)	Yield (%)	Molecular formula (mol. weight)
3a	CH_3	EtOH	218–220	68	$C_{12}H_{15}N_3O_3S$ (281.32)
3b	C_2H_5	EtOH	219–220	65	$C_{13}H_{17}N_3O_3S$ (295.35)
3c	$C_4H_9(n)$	EtOH	193–195	64	$C_{15}H_{21}N_3O_3S$ (323.41)
3d	C_6H_5	$CHCl_3$/EtOH	233–235	73	$C_{17}H_{17}N_3O_3S$ (343.40)
3e	4-FC_6H_4	$CHCl_3$/EtOH	228–230	71	$C_{17}H_{16}FN_3O_3S$ (361.39)
3f	4-ClC_6H_4	$CHCl_3$/EtOH	265–267	77	$C_{17}H_{16}ClN_3O_3S$ (377.84)
3g	4-BrC_6H_4	$CHCl_3$/EtOH	258–260	70	$C_{17}H_{16}BrN_3O_3S$ (422.29)

3b: ^{1}H NMR: 1.19 (t, 3H, CH_3), 3.33 (q, 2H, CH_2), 3.69 (s, 3H, OCH_3), 3.83 (s, 6H, OCH_3), 7.0 (s, 2H, Ar—H), 7.82 (br s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 14 (CH_3), 41 (CH_2), 55 (2 × OCH_3), 61 (OCH_3), 103, 126, 138, 144, 154, 169 (Ar—C & Thiadiazole-C). MS, m/z (Rel. Int.): 295 (M^+, 8), 281 (12), 280 (100), 266 (25), 253 (9), 197 (18), 179 (64), 69 (46), 44 (58).

3c: ^{1}H NMR: 1.12 (t, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.53 (m, 2H, CH_2), 3.45 (q, 2H, $NHCH_2$), 3.70 (s, 3H, OCH_3), 3.87 (s, 6H, OCH_3), 7.0 (s, 2H, Ar—H), 8.22 (s, 1H, NH, D_2O-exchang.).

3d: ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.86 (s, 6H, OCH_3), 6.99–7.35 (s, 7H, Ar—H), 7.81 (s, 1H, NH, D_2O-exchang.).

3e: ^{1}H NMR: 3.70 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 7.07 (s, 2H, Ar—H), 7.20 (d, 2H, Ar—H), 7.66 (d, 2H, Ar—H). 8.02 (s, 1H, NH, D_2O-exchang.). ^{13}C NMR: 55 (2 × OCH_3), 60 (OCH_3), 104, 115, 119, 125, 137, 139, 148, 156, 164 (Ar—C & Thiadiazole-C). MS, m/z (Rel. Int.): 362 ($M^+ + 1$, 11), 361 (M^+, 58), 347 (13), 346 (22), 208 (5), 194 (7), 193 (16), 168 (15), 95 (16), 69 (65), 45 (100).

3f: ^{1}H NMR: 3.71 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 7.01 (s, 2H, Ar—H), 7.34 (d, 2H, Ar—H), 7.44 (d, 2H, Ar—H). 8.05 (s, 1H, NH, D_2O-exchang.).

3g: ^{1}H NMR: 3.72 (s, 3H, OCH_3), 3.85 (s, 6H, OCH_3), 7.11 (s, 2H, Ar—H), 7.51 (d, 2H, Ar—H), 7.61 (d, 2H, Ar—H). 8.46 (s, 1H, NH, D_2O-exchang.). MS, m/z (Rel. Int.): 423 ($M^+ + 2$, 43), 422 ($M^+ + 1$, 12), 421 (M^+, 45), 409 (86), 407 (88), 393 (11), 377 (14), 363 (9), 228 (50), 230 (51), 194 (72), 179 (100), 45 (94).

2-(4-Hydroxy-3,5-dimethoxyphenyl)-5-substituted Amino-1,3,4-thiadiazoles 4a–g

98% Sulphuric acid (6 ml) was added dropwise to the appropriate substituted thiosemicarbazide **2a–g** (1.0 g), and the mixture was stirred at ambient temperature for 24 h. The resulting homogenous mixture was poured onto crushed ice (100 g), neutralized with ammonium hydroxide solution, and the separated yellowish orange precipitate was filtered, washed with water, dried, and crystallized to yield compounds **4a–g** (Table III).

4a: ^{1}H NMR: 2.92 (d, 3H, CH_3), 3.82 (s, 6H, OCH_3), 7.01 (s, 2H, Ar—H), 7.86 (s, 1H, NH, D_2O-exchang.), 8.81 (br s, 1H, OH, D_2O-exchang.). MS, m/z (Rel. Int.): 268 ($M^+ + 1$, 21), 267 (M^+, 100), 252 (9), 194 (22), 179 (38), 88 (69).

4b: ^{1}H NMR: 1.18 (t, 3H, CH_3), 3.70 (q, 2H, CH_2), 3.82 (s, 6H, OCH_3), 6.97 (s, 2H, Ar—H), 7.85 (s, 1H, NH, D_2O-exchang.), 8.82 (br s, 1H, OH, D_2O-exchang.). ^{13}C NMR: 14 (CH_3), 40 (CH_2), 56 (2 × OCH_3), 103, 121, 126, 148, 156, 168 (Ar—C & Thiadiazole-C). MS, m/z (Rel.

TABLE III Melting Points, Yield Percentages, Crystallization Solvents, Molecular Formulae, and Molecular Weights of Compounds **4a–g**

Comp. no.	R	Cryst. solv.	m.p. (°C)	Yield (%)	Molecular formula (mol. weight)
4a	CH_3	EtOH/H_2O	139–140	52	$C_{11}H_{13}N_3O_3S$ (267.30)
4b	C_2H_5	EtOH/H_2O	152–154	53	$C_{12}H_{15}N_3O_3S$ (281.32)
4c	$C_4H_9(n)$	MeOH	133–135	50	$C_{14}H_{19}N_3O_3S$ (309.38)
4d	C_6H_5	EtOH	218–220	68	$C_{16}H_{15}N_3O_3S$ (329.37)
4e	4-FC_6H_4	EtOH	215–217	62	$C_{16}H_{14}FN_3O_3S$ (347.36)
4f	4-ClC_6H_4	EtOH	220–222	70	$C_{16}H_{14}ClN_3O_3S$ (363.81)
4g	4-BrC_6H_4	EtOH	207–209	74	$C_{16}H_{14}BrN_3O_3S$ (408.26)

Int.): 282 ($M^+ + 1$, 20), 281 (M^+, 100), 266 (16), 253 (18), 197 (20), 179 (64).

4c: ^{1}H NMR: 0.91 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 3.40 (q, 2H, $NHCH_2$), 3.85 (s, 6H, OCH_3), 6.99 (s, 2H, Ar—H), 7.77 (br s, 1H, NH, D_2O-exchang.), 8,66 (br s, 1H, OH, D_2O-exchang.).

4d: ^{1}H NMR: 3.85 (s, 6H, OCH_3), 7.05–7.24 (s, 7H, Ar—H), 7.75 (br s, 1H, NH, D_2O-exchang.), 9.88 (br s, 1H, OH, D_2O-exchang.).

4e: ^{1}H NMR: 3.87 (s, 6H, OCH_3), 7.07 (s, 2H, Ar—H), 7.19 (d, 2H, Ar—H), 7.62 (d, 2H, Ar—H), 7.88 (br s, 1H, NH, D_2O-exchang.), 10.53 (s, 1H, OH, D_2O-exchang.). ^{13}C NMR: 56 (2 × OCH_3), 105, 115, 119, 125, 137, 139, 148, 153, 158, 164 (Ar—C & Thiadiazole-C). MS, m/z (Rel. Int.): 347 ($M^+ + 1$, 28), 346 (M^+, 47), 328 (9), 208 (11), 193 (33), 168 (32), 95 (35), 69 (100).

4f: ^{1}H NMR: 3.86 (s, 6H, OCH_3), 7.06 (s, 2H, Ar—H), 7.41 (d, 2H, Ar—H), 7.72 (d, 2H, Ar—H), 7.95 (s, 1H, NH, D_2O-exchang.), 10.34 (s, 1H, NH, D_2O-exchang.). MS, m/z (Rel. Int.): 356 ($M^+ + 2$, 41), 364 ($M^+ + 1$, 23), 363 (92), 349 (8), 195 (47), 184 (49), 179 (55), 69 (54), 45 (100).

4g: ^{1}H NMR: 3.85 (s, 6H, OCH_3), 7.08 (s, 2H, Ar—H), 7.52 (d, 2H, Ar—H), 7.61 (d, 2H, Ar—H), 8.90 (s, 1H, NH, D_2O-exchang.), 10.51 (s, 1H, OH, D_2O-exchang.). MS, m/z (Rel. Int.): 409 ($M^+ + 2$, 97), 408 ($M^+ + 1$, 30), 407 (M^+, 97), 393 (6), 377 (7), 363 (19), 329 (4), 231 (48), 229 (47), 194 (82), 179 (100), 45 (98).

2-(4-Hydroxy-3,5-dimethoxyphenyl)-5-amino-1,3,4-thiadiazole 5

Sulphuric acid (98%, 5 ml) was added to compound **2h** or **2i** (0.01 mol), and the mixture was stirred at ambient temperature for 24 h. The obtained yellowish green syrupy solution was then added cautiously to crushed ice (100 g), neutralized with saturated sodium hydrogen

carbonate solution, and stirred for 1 h. The separated yellowish white precipitate was filtered, washed with water, dried, and crystallized from ethanol to yield 1.04 g (41%) or 1.75 g (69%) of compound **5** in cases of compounds **2h** and **2i**, respectively, m.p. 128–130°C. ^{1}H NMR: 3.82 (s, 6H, OCH_3), 6.97 (s, 2H, Ar—H), 7.46 (s, 2H, NH_2, D_2O-exchang.), 9.45 (br. s, 1H, OH, D_2O-exchang.). ^{13}C NMR: 56 (OCH_3), 104, 121, 137, 148, 157, 168 (Ar—C & Thiadiazole-C). MS, m/z (Rel. Int.), $C_{10}H_{11}N_3O_3S$ (253.27): 254 ($M^+ + 1$, 13.9), 253 (M^+, 100), 238 (11.6), 194 (4.1), 180 (29.1), 164 (14.8), 153 (5.9), 74 (29.1), 45 (36.2).

2-(3,4,5-Trimethoxyphenyl)-5-amino-1,3,4-thiadiazole 6

A mixture of phosphorus oxychloride (10 ml) and compound **2h** or **2i** (0.01 mol) was heated under reflux for 2 h. The mixture was evaporated in vacuo, and the residue was washed with diluted ammonia solution and then with water, dried, and crystallized from $CHCl_3$/EtOH to yield 0.91 g (34%) or 1.9 g (71%) of compound **6** in the cases of compounds **2h** and **2i**, respectively, m.p. 122–124°C. ^{1}H NMR: δ 3.79 (s, 3H, OCH_3), 3.81 (s, 6H, OCH_3), 6.95 (s, 2H, Ar—H), 7.55 (s, 2H, NH_2, D_2O-exchang.). ^{13}C NMR: 56 ($2 \times OCH_3$), 60 (OCH_3) 104, 107, 138, 147, 153, 169 (Ar—C & Thiadiazole-C). MS, m/z (Rel. Int.), $C_{11}H_{13}N_3O_3S$ (267.30): 268 ($M^+ + 1$, 11.3), 267 (M^+, 56.9), 252 (18.24), 224 (9.51), 179 (6.10), 164 (5.39), 152 (6.74), 135 (12.22), 95 (18.25), 69 (85.03), 45 (100).

REFERENCES

[1] A. Foroumadi, S. Mansouri, Z. Kiani, and A. Rahmani, *Eur. J. Med. Chem.*, **38,** 851 (2003).
[2] L. M. Thomasco, R. C. Gadwood, E. A. Weaver, J. M. Ochoada, C. W. Ford, G. E. Zurenko, J. C. Hamel, D. Stapert, J. K. Moerman, R. D. Schaadt, and B. H. Yagi, *Bioorg. Med. Chem. Lett.*, **13,** 4193 (2003).
[3] S. Rollas, S. Karakus, B. B. Durgun, M. Kiraz, and H. Erdiniz, *Il Farmaco*, **51,** 811 (1996).
[4] A. Foroumadi, A. Asadipou, M. Mirzaei, J. Karimi, and S. Emami, *Il Farmaco*, **57,** 765 (2002).
[5] H. N. Dogan, A. Duran, S. Rollas, G. Sener, M. K. Uysal, and D. Gülen, *Bioorg. Med. Chem.*, **10,** 2893 (2002).
[6] M. G. Mamolo, L. Vio, and E. Banfi, *Il Farmaco*, **51,** 71 (1996).
[7] M. Tonew and E. Klimke, *Chemotherapy*, **20,** 350 (1974).
[8] L. Bonina, A. Arena, R. A. Merendino, and P. Mastroeni, *Drugs Exp. Clin. Res.*, **9,** 577 (1983).
[9] C. T. Supuran and B. W. Clare, *Eur. J. Med. Chem.*, **34,** 41 (1999).
[10] D. W. Christianson and J. D. Cox, *Annu. Rev. Biochem.*, **68,** 33 (1999).
[11] A. Casini, A. Scozzafava, F. Mincione, L. Menabuoni, M. Starnotti, and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, **13,** 2867 (2003).

[12] M. Santagati, M. Modica, A. Santagati, F. Russo, and M. Amico-Roxas, *Pharmazie*, **49,** 880 (1994).
[13] E. Palaska, G. Sahin, P. Kelecin, N. T. Durlu, and G. Altinok, *Il Farmaco*, **57,** 101 (2002).
[14] A. A. El-Emam and J. Lehmann, *Monatsh. Chem.*, **125,** 587 (1994).
[15] S. Bahadur, M. K. Singh, and M. K. Shukla, *Arch. Pharm. (Weinheim)*, **315,** 17 (1982).
[16] J. Schwarz and H. Just, *Ger. Offen.*, 2,126,261 (1972); *Chem. Abstr.*, **76,** 99673a (1973).
[17] S. Leistner, M. Gutschow, and G. Wagner, *Synthesis*, 466 (1987).
[18] Y. Zeng, J. Yang, Z. Qiu, J. Cheng, C. Hu, and P. Zhen, *Tetrahedron Lett.*, **43,** 869 (2002).
[19] J. D. Spence, A. E. Raymond, and D. E. Norton, *Tetrahedron Lett.*, **44,** 849 (2003).
[20] J. W. Huffman, J. Lu, D. Dai, and A. Kitaygorodskiy, *Bioorg. Med. Chem.*, **8,** 439 (2000).
[21] K. Lal, S. Ghosh, and R. G. Salomon, *J. Org. Chem.*, **52,** 1072 (1987).
[22] J. A. Dodge, M. G. Stocksdale, D. J. Fahey, and C. D. Jones, *J. Org. Chem.*, **60,** 739 (1995).
[23] L. F. Frey, K. M. Marcantonio, C. Chen, D. J. Wallace, J. A. Murry, L. Tan, W. Chen, U. Dolling, and E. J. J. Grabowski, *Tetrahedron*, **59,** 6363 (2003).
[24] R. A. Tapia, Y. Prieto, F. Pautet, N. Walchshofer, H. Fillion, B. Fenet, and M. Sarciron, *Bioorg. Med. Chem.*, **11,** 3407 (2003).
[25] E. Pascual, C. Avendaño, and J. C. Menéndez, *Tetrahedron Lett.*, **44,** 6003 (2003).
[26] B. Roizel, J. Baltaze, and P. Sinay, *Tetrahedron Lett.*, **43,** 2371 (1999).
[27] S. Yamaguchi, M. Nedachi, H. Yokoyama, and Y. Hirai, *Tetrahedron Lett.*, **40,** 7363 (1999).
[28] E. Reimann, in *Methoden der Organischen Chemie, Reduktion I*, edited by E. Müller and O. Bayer (G. Thieme, Stuttgart, New York, 1980), Vol. 4, p. 400.
[29] T. Ohgi and S. H. Hecht, *J. Org. Chem.*, **46,** 1232 (1981).
[30] F. X. Webster, J. G. Millar, and R. M. Silverstein, *Tetrahedron Lett.*, **27,** 4941 (1986).
[31] R. M. Williams and E. Kwast, *Tetrahedron Lett.*, **30,** 451 (1989).
[32] E. G. Baggiolini, H. L. Lee, G. Pizzolato, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **104,** 6460 (1982).
[33] J. E. Semple, P. C. Wang, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.*, **102,** 7505 (1980).
[34] G. D. Field, W. J. Zally, L. H. Sternbach, and J. F. Blout, *J. Org. Chem.*, **41,** 3853 (1976).
[35] R. H. Schlessinger, G. R. Bebernitz, P. Lin, and Y. Y. Poss, *J. Am. Chem. Soc.*, **107,** 1777 (1985).
[36] P. Deshong, S. Ramesh, V. Elango, and J. J. Perez, *J. Am. Chem. Soc.*, **107,** 5219 (1987).
[37] A. Denis and C. Renou, *Tetrahedron Lett.*, **43,** 4171 (2002).