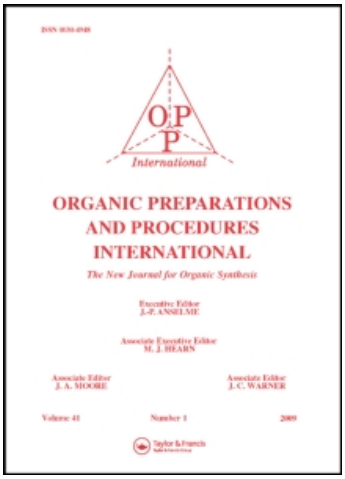

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF 4-AROYL-[(5-PHENYL-2(2H)-TETRAZOLYL)-1-OXOETHYL]- THIOSEMICARBAZIDES AND 4-AROYL-5-[(5-PHENYL-2(2H)-TETRAZOLYL)METHYL)-1,2,4-(4H)-TRIAZOLE-3-THIONE

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To cite this Article Xiaorning, Feng , Rong, Chen and Shaoyin, Cai(1992) 'SYNTHESIS OF 4-AROYL-[(5-PHENYL-2(2H)-TETRAZOLYL)-1-OXOETHYL]- THIOSEMICARBAZIDES AND 4-AROYL-5-[(5-PHENYL-2(2H)-TETRAZOLYL)METHYL)-1,2,4-(4H)-TRIAZOLE-3-THIONE', Organic Preparations and Procedures International, 24: 4, 492 — 496
To link to this Article: DOI: 10.1080/00304949209356234
URL: http://dx.doi.org/10.1080/00304949209356234

D. Lampe and B. V. L. Potter, *Chem. Commun.*, 1500 (1990); (i) G. R. Baker, D. C. Billington and D. Gani, *Tetrahedron*, **47**, 3895 (1991).

9. The cylindrical reservoir is a 22x25 cm chromatography developing chamber purchased from Fisher Scientific.

10. The bath temperature was 52°.

11. Analysis of the insoluble material by mass spectrometry (70 eV) indicated that the compound (*m/z*= 256) has a fragmentation pattern identical to that observed with elemental sulfur (S_8).

12. (a) M. McKibben and E. W. McClelland, *J. Chem. Soc.*, 170 (1923); (b) S. Smiles and E. E. McClelland, *ibid.*, 86 (**1922**).

13. The reaction rates were monitored by thin-layer chromatography ($CHCl_3$) until the presence of the slow-moving thiosulfinate **3** (R_f= 0.27) was negligible (less than 5%).

14. Peroxides were qualitatively measured with Quantofix test sticks purchased from Aldrich Chemical Co.

15. The solid reagent can be stored indefinitely, at ambient temperature, in amber glass containers. Alternatively, a 0.05 M solution of **4** in acetonitrile can be kept for at least one month at 20° in a properly cleaned and "siliconized" bottle.[1b]

16. A. G. Hortmann, A. J. Aron and A. K. Bhattacharya, *J. Org. Chem.*, **43**, 3374 (1978).

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SYNTHESIS OF 4-AROYL-[(5-PHENYL-2(2H)-TETRAZOLYL)-1-OXOETHYL]-THIOSEMICARBAZIDES AND 4-AROYL-5-[(5-PHENYL-2(2H)-TETRAZOLYL)METHYL)-1,2,4-(4H)-TRIAZOLE-3-THIONE

Submitted by (09/13/91)

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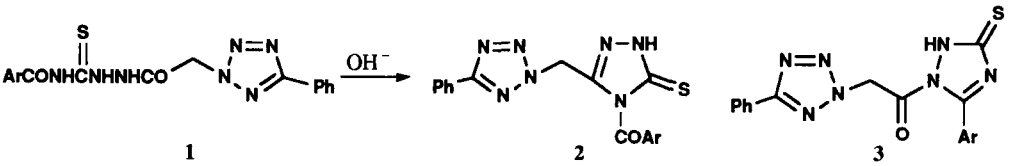
Acylthiosemicarbazides have been reported to possess physiological activity.[1-3] We had previously prepared acylthiosemicarbazides and related heterocyclic derivatives by reaction of cyanoacetylhydrazine[4] and α-phenylcyanoacetylhydrazine[5] with aroylisothiocyanates and observed that they promote growth of wheat plumules at low concentrations. A number of 5-aryl-2H-tetra-

zolylalkanoic acids and certain hydrazine derivatives are known to be good antiinflamatory agents[6-8] and plant growth regulators.[9] With this in mind, we synthesized fifteen 4-aroyl-1-[(5-phenyl-2(2H)-tetrazolyl)-1-oxoethyl]thiosemicarbazides (**1**) by the condensation of acid hydrazides and aroylisothiocyanates. Compounds **1** on treatent with NaOH yielded 4-aroyl-5-[(5-phenyl-2-(2H)-tetrazolyl)methyl]-1,2,4-(4H)-trizole-3-thione (**2**).

Structures **1** and **2** were supported by their elemental analytical data, IR, ^{1}H NMR (Table 1) and MS spectra.



1 2 3

a) Ar = C_6H_5 b) Ar = *p*-FC_6H_4 c) Ar = *m*-FC_6H_4 d) Ar = *o*-FC_6H_4 e) Ar = *p*-ClC_6H_4
f) Ar = *o*-ClC_6H_4 g) Ar = *o*-BrC_6H_4 h) Ar = *p*-$O_2NC_6H_4$ i) Ar = *m*-$O_2NC_6H_4$
j) Ar = *o*-$O_2NC_6H_4$ k) Ar = *m*-MeC_6H_4 l) Ar = *p*-MeC_6H_4 m) Ar = C_6H_5CH=CH
n) Ar = 2-Furyl o) Ar = α-$C_{10}H_7CH_2$

TABLE 1. IR and ^{1}H NMR Data of **1a,e** and **2a,e**

No.	IR(cm^{-1})	^{1}H NMR (δ ppm)
1a	1258(C=S), 3184, 1307(NH), 1673(C=O)	7.40-7.90 (m, 10H, Ar-H, 6.70 (s, 2H, CH_2) 3.50 (br, 2H, N_2H_2),[a] 4.30 (br, 1H, NH)[a]
1e	1244(C=S), 3170, 1286(NH), 1616(C=O)	7.32-7.87 (m, 9H, Ar-H, 5.60 (s, 2H, CH_2) 3.40 (br, 2H, N_2H_2),[a] 4.50 (br, 1H, NH)[a]
2a	1285(C=S), 3143, 1365(NH), 1674(C=O)	7.40-7.95 (m, 10H, Ar-H, 6.40 (s, 2H, CH_2) 4.25 (br, 1H, NH)[a]
2e	1268(C=S), 3144, 1427(NH), 1687(C=O)	7.30-7.92 (m, 9H, Ar-H, 6.15 (s, 2H, CH_2) 4.90 (br, 1H, NH)[a]

a) Exchangeable with D_2O.

The results of analyses show that ring-closure products are 1,2,4-triazole ring systems which possess NCSN. Since compounds **1** have two carbonyl groups at 1,4-positions, ring-closure could have occurred in two directions to give **2** or **3**. Structure **2** was confirmed by mass spectrometry. The fragmentation patterns of all compounds **2** are similar, with the fragment (ArCO), whose relative intensity is 10-99%. Fragment (ArCO) supported the structure of compounds **2**. The MS spectra have the rearrangement fragment (ArNCO). We found the isotope ion peak of (A+2) when compounds **1** possesses Cl or Br.

Compounds **1** and **2** were screened for their antifungal activity against *Escherichia Coli* and *Bacillus Subtilis* at 1.0 x 10^{-4} mol/L. The results showed that all the compounds have strong inhibiting effects.

EXPERIMENTAL SECTION

All the compounds were analyzed by PE-2400CHN-Model elemental analyzer. Melting points were determined on XSP-1 model microscopic melting point apparatus with partial immersion thermometer and are uncorrected. IR spectra were recorded on NIC-5-DX spectrometer as KBr pellets. ^{1}H NMR spectra were obtained on EM-360L spectrometer using DMSO-d_6 as solvent and HMDS0 as internal standard. MS spectra were run on VG7070-E model mass spectrometer (EI, at 70 ev).

TABLE 2. MS Data of Compounds **2**

No.	M/Z (related Intensity) (%)
2a	363 (M^+, 5.0); 306 (4.0); 259 (3.1); 185 (4.2); 146 (12.6); 145 (10.1); 119 (17.2); 117 (5.2); 105 (74.2); 103 (42.1); 91 (7.1); 89 (7.2); 77 (63.1); 65 (11.1); 58 (100)
2c	381 (M^+. 2.3); 380 (1.4); 351 (7.8); 325 (4.0); 323 (2.5); 309 (61.0); 308 (71.2); 281 (37.4); 280 (44.3); 259 (13.1); 186 (10.2); 185 (14.3); 15 (99.1); 149 (100); 145 (8.4); 123 (35.0); 120 (27.4); 117 (11.0); 10 (32.4); 104 (82.3); 95 (22.1); 77 (41.4); 76 (54.3)
2d	381 (M^+, 1.2); 259(8.1); 185 (20.7); 177 (7.2); 176 (10.1); 161 (7.2); 14 (7.2); 145 (14.2); 132 (48.3); 131 (52.4); 123 (52.4); 117 (4.3); 104 (92.4); 103 (18.4); 95 (22.1); 77 (89.2); 76 (42.5); 58 (100)
2e	397 (M^+, 5.0); 259 (24.2); 256 (23.4); 192 (11.2); 191 (9.8); 185 (15.7) 160 (97.2); 158 (98.4); 145 (17.2); 141 (99.3); 139 (49.2); 117 (16.9); 113 (76.4); 111 (100); 103 (18.4); 75 (82.3)
2g	441 (M^+, 2.6); 259 (15.7); 205 (21.4); 185 (19.6); 183 (20.1); 176 (51.7); 160 (3.2l; 157 (4.5); 155 (6.4); 145 (7.4); 131 (99.3); 117 (13.8); 104 (99.2); 103 (89.2); 89 (14.3); 77 (99.5); 76 (100)
2i	408 (M^+,3.4); 346 (38.3); 259 (24.8); 255 (8.5); 225 (28.9); 185 (7.2); 149 (100); 145 (7.8); 131 (5.4); 122 (8.5); 117 (18.6); 104 (63.8); 103 (75.6); 89 (3.4); 77 (23.5); 76 (42.9)
2j	408 (M^+, 2.1); 407 (3.2); 259 (23.7); 185 (20.4); 176 (12.1); 150 (14.3); 145 (25.4); 131 (64.7); 122 (18.3); 117 (25.8); 104 (98.4); 103 (51.6); 77(100)
2k	377 (M^+, 5.3); 376 (2.4); 350 (4.5); 321 (4.7); 259 (31.4); 185 (20.9); 161 (65.9); 160 (15.6); 159 (3.2); 145 (19.1); 131 (12.8); 119 (99.4); 118 (97.7); 117 (23.5); 104 (61.5); 103 (74.5); 91 (100); 89 (67.4); 77 (53.8); 76 (38.4)
2l	393 (M^+, 2.7); 392 (3.2); 365 (4.3); 333 (42.1); 259 (34.8); 244 (2.8); 206 (100); 185 (4.2); 184 (26.8); 173 (11.2); 149 (5.9); 145 (19.4); 135 (18.7); 117 (3.6); 103 (12.6); 89 (5.6); 7 7(4.2); 76 (4.9)
2m	389 (M^+, 2.3); 259 (14.2); 206 (23.5); 185 (16.9); 176 (99.4); 160 (4.8); 146 (84.3); 145 (8.6); 131 (99.5); 117 (20.4); 103 (98.4); 89 (74.3); 77 (99.2); 75 (100)
2o	427 (M^+, 1.2); 426 (10.1); 259 (16.2); 185 (3.6); 169 (41.2); 168 (60.7); 145 (25.8); 141 (100); 127 (2.5); 117 (18.31; 103 (2.4); 89 (4.6)

(5-Phenyl-2H-tetrazolyl-2-yl)acethydrazide were prepared according to reference to a literature[10] procedure, and aroylisothiocyanates were obtained according to reference 5.

TABLE 3. Yield, mp and Elemental Analyses of Compounds **1** and **2**

Compd. No.	Yield[a] (%)	mp. (°C)	Elemental Analysis (Found) C	H	N
1a	83	196-197	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1b	63	244-245	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1c	90	205-206	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1d	60	200-202	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1e	66	229-232	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1f	56	199-201	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1g	47	217-218	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1h	64	210-211	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1i	66	210-211	47.89 (47.65)	3.31 (3.42)	26.28 (26.05)
1j	68	220-221	47.89 (47.76)	3.31 (3.49)	26.28 (26.46)
1k	63	169-170	54.67 (54.41)	4.33 (4.45)	24.79 (24.87)
1l	56	107-108	52.55 (52.62)	4.16 (3.98)	23.83 (23.67)
1m	64	210-211	56.01 (56.13)	4.21 (4.08)	24.06 (23.94)
1n	68	136-137	48.39 (48.48)	3.79 (3.84)	26.33 (26.29)
1o	69	215-216	59.31 (59.23)	4.30 (4.25)	22.01 (21.96)
2a	85	217-218	56.19 (56.01)	3.61 (3.58)	26.98 (26.82)
2b	73	175-177	53.54 (53.42)	3.17 (3.04)	25.71 (25.55)
2c	75	158-159	53.54 (53.69)	3.17 (3.25)	25.71 (25.49)
2d	79	164-166	53.54 (53.62)	3.17 (3.09)	25.71 (25.64)
2e	78	141-142	51.32 (51.17)	3.04 (3.14)	24.64 (24.51)
2f	69	145-146	51.32 (51.40)	3.04 (2.91)	24.64 (24.82)
2g	68	174-175	47.31 (47.25)	2.70 (2.84)	22.73 (22.62)
2h	78	166-167	45.00 (45.16)	2.96 (3.04)	27.44 (27.28)
2i	70	175-176	45.00 (44.89)	2.96 (3.15)	27.44 (27.35)
2j	92	160-161	45.00 (45.15)	2.96 (2.83)	27.44 (27.39)
2k	84	200-201	57.28 (57.13)	4.01 (3.87)	25.98 (26.15)
2l	71	141-143	51.95 (55.15)	3.84 (4.02)	24.92 (24.73)
2m	72	102-104	58.60 (58.54)	3.88 (3.75)	25.18 (25.09)
2n	65	133-134	50.84 (50.95)	3.41 (3.59)	27.67 (27.82)
2o	65	145-146	61.81 (61.81)	4.01 (3.87)	22.94 (22.73)

a) Yield of isolated product **1** and **2**. b) Found value is in parentheses.

4-Aroyl-2-[(5-phenyl-2(2H)-tetrazolyl)-1-oxoethyl]thiosemicarbazides 1.- Equimolar quantities of (5-phenyl-2H-tetrazol-2-yl)acethydrazide (0.01 mol) and the suitable aroylisothiocyanate (0.01 mol) were dissolved in absolute acetonitrile and was refluxed for 6 hrs. The reaction solution was poured

into cold water. The solid product was collected and washed with $NaHCO_3$-H_2O solution (5%), then with water. The crude product was recrystallized from DMF-H_2O (2:1).

4-Aroyl-5-[(5-phenyl-2(2H)-tetrazolyl)methyl]-1,2,4-(4H)-triazole-3-thione 2.- 4-Aroyl-1-[(5-phenyl-2(2H)-tetrazolyl)-1-oxoethyl]-thiosemicarbazide **1** (0.01 mol) and sodium hydroxide (2M, 50mL) were refluxed for 8 hrs to give a clear solution. The cooled solution was poured into cold water, and the precipitated solid was filtered off and washed with water. The filtrate was acidifed with cold 3M hydrochloric acid and the precipitate was collected, washed with water, and recrystallized from DMF-H_2O (3:1).

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