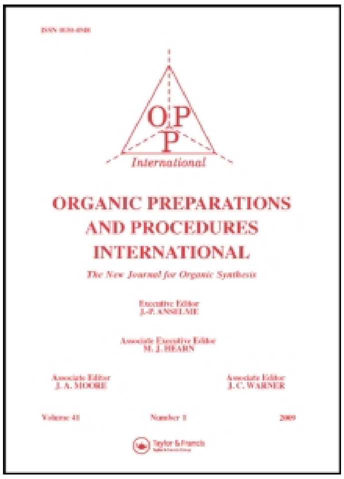

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NEW HETEROCYCLES FORMING REACTIONS OF ACYL THIOFORMANILIDES

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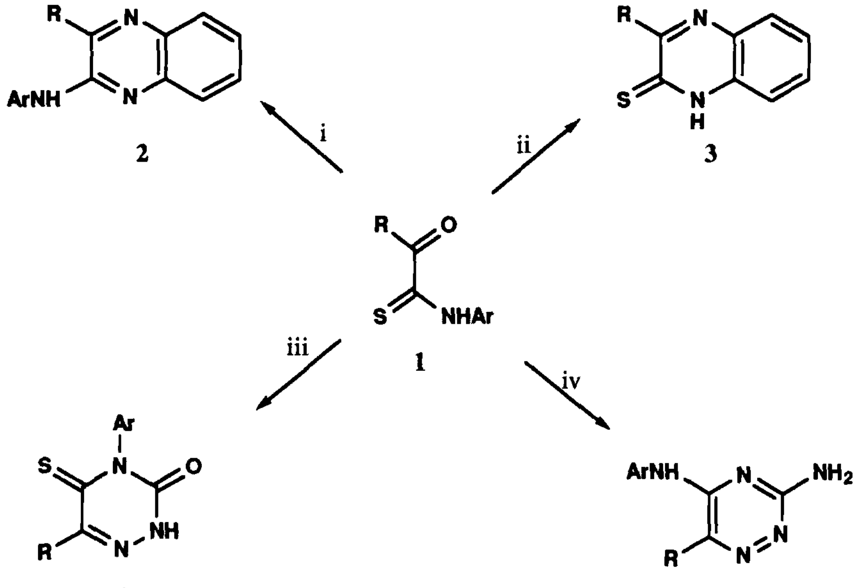
Acyl thioformanilides (**1**)[1,2] have two possible sites for nucleophilic attack. The present communication describes new reactions of **1** with *o*-phenylenediamine, semicarbazide and aminoguanidine (Scheme 1). The acyl thioformanilides (**1**) were synthesized by the method of Adiwidjaja.[2]



Scheme 1

i) *o*-phenylenediamine, pyridine, 114° ii) *o*-phenylenediamine, MeOH, RT, under N_2
iii) 1. semicarbazide, EtOH, 78° 2. pyridine, 114° iv) 1. aminoguanidine dihydrochloride, EtOH, 78°
2. 10% NaOH (pH = 8-9), EtOH, 78°

a) R = Ph, Ar = Ph
b) R = Ph, Ar = *p*-$CH_3OC_6H_4$
c) R = Ph, Ar = *p*-$CH_3C_6H_4$
d) R = Ph, Ar = *p*-ClC_6H_4
e) R = Ph, Ar = *p*-$NO_2C_6H_4$
f) R = Ph, Ar = *o*-$CH_3C_6H_4$
g) R = Ph, Ar = *o*-BrC_6H_4
h) R = *t*-Bu, Ar = Ph
i) R = Ph, Ar = *p*-BrC_6H_4
j) R = Ph, Ar = *p*-FC_6H_4

It is interesting to note that compounds **2a-2g** were obtained at reflux in pyridine or ethanol while compound **3a** was formed in methanol at room temperature. The reaction with semicarbazide gave the semicarbazones (condensation at carbonyl group), which were cyclized at reflux in pyridine to give the 1,2,4-triazines (**4**). It was also found that **1a** condensed with aminoguanidine hydrochloride to yield **5a**.

EXPERIMENTAL SECTION

Melting points are uncorrected. The elemental analysis for C H N were performed on a Carlo Erba 1106 elemental analyzer. The following instruments were used for structure analysis. The infrared spectra were determined using Mattson Alpha-Centauri FT-IR spectrometer. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer. The mass spectra were measured on a Finegan 4021 mass spectrometer.

Preparation of Compounds 2. Typical Procedure.- A solution of benzoylthioformanilide (**1a**) (1.2 g, 5 mmol) and *o*-phenylenediamine (0.65 g, 6 mmol) in 15 mL of dry pyridine was refluxed for 10 hrs. The reaction mixture was cooled and diluted with 40 mL of water. The brown precipitate was collected and dissolved in conc. hydrochloric acid. The insoluble material was removed and the filtrate was neutralized to give the crude product which was recrystallized from ethanol to provide **2** (Tables 1 and 2).

TABLE 1. Yields and Physical Constants of Quinoxalines **2**

Cmpd. No	mp. (°C)	Yield (%)	Time (hrs)	Elemental Analysis (Found) C	H	N
2a	112-113	81	10	80.78 (81.05)	5.08 (5.13)	14.13 (14.33)
2b	100-101	83	14	77.04 (77.24)	5.23 (5.21)	12.83 (12.81)
2c	126-127	71	14	81.00 (81.30)	5.50 (5.54)	13.49 (13.61)
2d	142-143	83	5	72.40 (72.12)	4.25 (4.18)	12.66 (12.79)
2e	228-229	83	2.5	70.17 (70.28)	4.12 (4.07)	16.36 (16.54)
2f	119-120	77	8	81.00 (81.02)	5.30 (5.51)	13.49 (13.67)
2g	141-145	64	14	63.85 (64.03)	3.75 (3.76)	11.17 (11.42)
2h	110-111	72	20	77.94 (77.80)	6.90 (6.99)	15.15 (15.32)

TABLE 2. Spectral data for Compounds **2**

Cmpd. No	^{1}H NMR (ppm CDCl$_3$)	IR (cm^{-1}) NH	Heterocyclic Ring			MS (M$^+$)
2a	7.0-8.0 (m, 14H)	3380	1600 1440	1570 1410	1500 1340	297
2b	3.7 (s, 3H), 6.7-7.8 (m, 13H)	3405	1600 1460	1560 1420	1505 1330	327
2c	2.3 (s, 3H), 7.1-8.0 (m, 13H)	3410	1600 1430	1560 1410	1470 1330	311
2d	7.0-8.0 (m, 13H)	3410	1600 1440	1560 1410	1490 1330	331
2e	7.1-8.3 (m, 13H)	3380	1600 1440	1560 1410	1500 1325	342
2f	2.2(s, 3H), 7.1-7.8 (m, 13H)	3405	1600 1460	1560 1420	1505 1330	311
2g	7.2-8.1 (m, 13H)	3440	1600 1430	1560 1405	1490 1350	375
2h	1.8 (s, 9H), 6.9-8.0 (m, 9H)	3480	1600 1435	1570 1410	1500 1330	277

Preparation of Compound 3.- A solution of benzoylthioformanilide (**1a**) (2.0 g, 8.2 mmol) and *o*-phenylenediamine (1.1 g, 10 mmol) in 40 mL absolute methanol to which was added acetic acid

(0.5 mL) was allowed to stand at room temperature for 3 days under nitrogen. The precipitated solid was collected and recrystallized from acetonitrile to yield 0.8 g (46%) of the **3a**, mp. 200° (dec.).

Anal. Calcd. for $C_{14}N_{10}N_2S$: C, 70.28; H, 4.23; N, 11.75; S, 13.45

Found: C, 70.28; H, 4.19; N, 11.77; S, 13.45

IR (KBr): 3410, 3040, 2960, 1605, 1560, 1450, 1360, 1260, 1120, 1100, 840, 740, 690, 590 cm^{-1}. MS (m/z): 238 (M$^+$)

Preparation of Compounds 4. Typical Procedure.- To a solution of benzoylthioformanilide (0.7 g, 2.9 mmol) in ethanol (6 mL) were added semicarbazide hydrochloride (0.66 g, 6 mmol), anhydrous sodium acetate (0.49 g, 6 mmol), water (3 mL) and acetic acid (1.2 mL). The mixture was refluxed for 30 min. It was cooled to give the semicarbazone (Table 3).

A solution of the semicarbazone in pyridine (15 mL) was refluxed for 15 hrs. Upon addition 50 mL of water to the reaction mixture, a red precipitate was obtained. The crude product was purified by silica-gel column chromatography using chloroform-petroleum ether (1:1) as eluent to afford **4a** (Tables 4 and 5).

TABLE 3. Yields and Physical Constants of Semicarbazones 

$$R-\overset{\overset{\displaystyle NNHCONH_2}{\|}}{C}-CSNHAr$$

R	Ar	mp.(°C) (dec.)	Yield (%)	Elemental Analysis (Found) C	H	N
Ph	Ph	199	84	60.38 (60.59)	4.72 (4.74)	18.78 (18.75)
Ph	*p*-MeOC$_6$H$_4$	207	83	58.52 (58.58)	4.91 (4.89)	17.06 (17.26)
Ph	*p*-MeC$_6$H$_4$	205	81	61.52 (61.35)	5.16 (5.12)	17.93 (17.89)
Ph	*p*-ClC$_6$H$_4$	210	83	54.14 (53.85)	3.94 (3.88)	16.84 (16.84)
Ph	*p*-BrC$_6$H$_4$	200	81	47.76 (47.84)	3.47 (3.45)	14.85 (14.99)
Ph	*p*-FC$_6$H$_4$	201	87	56.95 (57.18)	4.14 (4.14)	17.71 (17.86)
t-Bu	Ph	179	83	56.09 (56.36)	6.52 (6.58)	20.13 (19.83)

TABLE 4. Yields and Physical Constants of 1,2,4-triazines 4

Cmpd. No.	mp. (°C)	Yield (%)	Time (hrs)	Elemental Analysis (Found) C	H	N
4a	199-200	76	20	64.04 (64.17)	3.94 (3.98)	14.94 (15.07)
4b	211-212	69	25	61.72 (61.59)	4.20 (4.18)	13.50 (13.70)
4c	217-218	80	25	65.07 (65.29)	4.44 (4.60)	14.23 (14.26)
4d	184-185	64	30	57.05 (57.05)	3.19 (3.09)	13.31 (13.26)
4h	196-197	87[a]	20	59.76 (59.88)	5.78 (5.74)	16.08 (16.28)
4i	192-193	86	30	50.01 (49.81)	2.78 (2.74)	11.66 (11.66)
4j	182-183	68	20	60.19 (59.87)	3.36 (3.26)	14.04 (14.25)

a) Dimethoxyethane as solvent.

TABLE 5. Spectral Data for Compounds 4

Cmpd. No.	^{1}H NMR (δ ppm, $CDCl_3$)	IR (cm^{-1}) NH	C=O	C=S	MS (M$^+$)
4a	6.8-7.3 (m, 10H), 9.9 (s, 1H)	3200	1680	1090	281
4b	3.8 (s, 3H), 6.9-7.7 (m, 9H), 10.2 (s, 1H)	3200	1690	1095	311
4c	2.3 (s, 3H), 6.9-7.4 (m, 9H), 10.0 (s, 1H)	3200	1705	1095	295
4d	7.1-7.7 (m, 9H), 10.1 (s, 1H)	3220	1700	1090	315
4h	1.4 (s, 9H), 6.9-7.5 (m, 5H), 10.0 (s, 1H)	3200	1705	1070	261
4i	7.0-7.8 (m, 9H), 10.1 (s, 1H)	3200	1700	1090	359
4j	7.2-7.8 (m, 9H), 10.2 (s, 1H)	3180	1685	1095	299

Preparation of Compound 5a.- A solution of benzoylthioformanilide (**1a**, 0.5 g, 2.1 mmol) and aminoguanidine dihydrochloride (0.35 g, 2.4 mmol) in 14 mL of ethanol was refluxed for 5 hrs. After evaporation of the solvent, the solid obtained was dissolved in 10% sodium hydroxide, the solution was filtered and the filtrate was neutralized with conc. HCl to give 64% yield of guanylhydrazone hydrochloride, mp. 197-198°.

Anal. Calcd. for $C_{15}H_{16}ClN_5S$: C, 53.96; H, 4.80; N 20.97. Found: C, 53.90; H, 4.72; N, 21.20

A solution of the guanylhydrazone hydrochloride in 10 mL absolute ethanol (the pH of the solution was adjusted to 8-9) was refluxed for 5 hrs. The solution was filtered hot and evaporated. The solid obtained was purified by chromatography on silica-gel using acetone-petroleum ether (1:1) as eluent to give 0.3 g (64%) of **5a**, mp. 186-187°.

Anal. Calcd. for $C_{15}H_{13}N_5$: C, 68.44; H, 4.94; N, 26.62. Found: C, 68.58; H, 5.51; N, 26.75

IR (KBr): 3480, 3320, 3200, 3050, 2920, 1630, 1560, 1520, 1470. 1440. 1400, 1140, 1030, 780, 710 cm^{-1}, ^{1}H NMR ($CDCl_3$) 7.0-7.6 (m, 10H). 5.5 (s, 2H). MS (m/z): 263 (M$^+$).

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