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Reactions of monothiodiacylamines or *N*-aroylthioimidates with 3-aminopyrazoles gave pyrazolo[1,5-*a*]-1,3,5-triazines in good yields.

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Recently, we reported a modified Einhorn-Brunner reaction for the synthesis of 1,2,4-triazoles **1** and 1,2,4-oxadiazoles **2** by the condensation of monothiodiacylamines **3** with hydrazines and hydroxylamine [3]. The regioselectivity of this reaction is attributed to a fast and selective reaction of the thioacyl group with hydrazines and hydroxylamine, which is followed by a facile rate-determining intramolecular cyclization. We now report an extension of this reaction to a new synthesis of 2,4-dialkyl(or diaryl)pyrazolo[1,5-*a*]-1,3,5-triazines **5**.

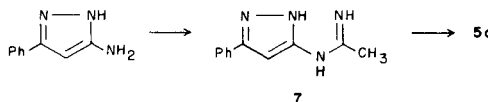
Results and Discussion.

Monothiodiacylamines **3a-e** (in Table I) were prepared either by reactions of thioamides with acyl chlorides (Method A) [3,4] or acylamidines with hydrogen sulfide (Method B) [5]. Condensations of monothiodiacylamines **3a-d** (R = R' = aryl or alkyl) with 3-aminopyrazoles in ethanol gave pyrazolo[1,5-*a*]-1,3,5-triazines **5a-g** (in Table II) in good yields (51-93%). However, the monothiodiacylamine **3e** (R = 4-ClC₆H₄, R' = CH₃) under the same reaction conditions condensed with 3-amino-5-phenylpyrazole to give the open-chained product **6** which cyclized in acetonitrile in the presence of potassium carbonate to give the pyrazolo[1,5-*a*]-1,3,5-triazine **5o** in 81% overall yield. *N*-Aroylthioimidates **4a-b** (in Table I) were prepared by reactions of monothiodiacylamines **3a-b** with iodoethane in

acetonitrile in the presence of potassium carbonate (Method C) [5]. Condensations of *N*-aroylthioimidates **4a-b** with 3-aminopyrazoles also gave pyrazolo[1,5-*a*]-1,3,5-triazines **5e-n** (in Table II) in good yields (65-81%).

The structure of the pyrazolo[1,5-*a*]-1,3,5-triazine **5g** was determined by single crystal x-ray analysis, and the structures of the other pyrazolo[1,5-*a*]-1,3,5-triazines were all supported by nmr, ir and elemental analysis data.

The synthesis of 2,4-dialkyl-pyrazolo[1,5-*a*]-1,3,5-triazines was first reported in 1973 [6,7]. The pyrazolo[1,5-*a*]-1,3,5-triazines **5c** were synthesized by the reaction of 3-amino-5-phenylpyrazole with ethyl acetimidate followed by the reaction of the resulting *N*-(pyrazol-3-yl)acetimidine **7** with triethyl orthoacetate [8]. Since every conceivable monothiodiacylamine and *N*-acylthioimidate can be prepared from reported methods [5,9], the present method provides a new and convenient regioselective synthesis of 2,4-dialkyl(or diaryl)-pyrazolo[1,5-*a*]-1,3,5-triazines.



EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried over phosphorus pentoxide under high vacuum for 1-10 hours. Infrared spectra were measured on a Perkin-Elmer spectrophotometer (Model 21). The nmr spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were recorded on A.E.I. MS 902. Monothiodiacylamines **3a-e** and *N*-aroylthioimidate **4a-b** were prepared by reported methods [3,4,5].

7-Methyl-2-phenyl-4-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]-1,3,5-triazine **5g**. Typical Procedure for **5a-n**.

Monothiodiacylamines **3a-d** and *N*-aroylthioimidates **4a-b** reacted with 3-aminopyrazoles under the same reaction conditions to give pyrazolo[1,5-*a*]-1,3,5-triazines **5a-n**. A mixture of 3.09 g (0.010 mole) of *N*-(phenylthioxomethyl)-4-(trifluoromethyl)benzamide (**3a**) and 1.07 g (0.011 mole) of 3-amino-5-methylpyrazole in 10 ml of ethanol was stirred at 60° for 24 hours (yellow crystals precipitated out from the reaction mixture in one hour). After being kept in refrigerator overnight the reaction mixture deposited 1.8 g (51%) of **5g** as yellow crystals, mp 145-146°; ms: m/e 354 (M⁺); nmr (deuteriochloroform): δ 2.60 (s, 3H), 6.52 (s, 1H), 7.55 (m, 3H), 7.88 (d, J = 8.5 Hz, 2H), 8.58 (m, 2H), 9.04 (d, J = 8.5 Hz, 2H); ir (potassium bromide): 1610, 1600, 1520, 1495, 1470, 1380, 1330, 1240, 1165, 1120, 1070, 1020, 850, 690 cm⁻¹.

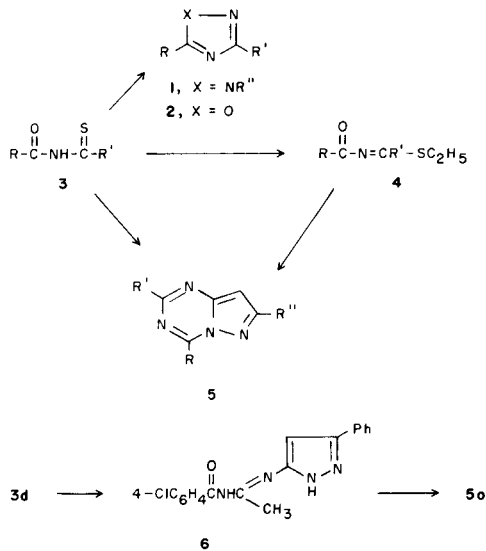


Table I

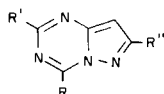
Monothiodiacylamines **3** and *N*-Aroylthioimidates **4**

Compound	R	R'	Method	Yield, %	Mp, °C	Formula [d]
3a	4-CF ₃ C ₆ H ₄	C ₆ H ₅	A	31	127-129 [a]	C ₁₅ H ₁₀ F ₃ NOS
3b	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	A	27	154-155	C ₁₅ H ₉ ClF ₃ NOS
3c	4-CF ₃ C ₆ H ₄	4-FC ₆ H ₄	A	17	132-133	C ₁₅ H ₉ F ₄ NOS
3d	CH ₃	CH ₃	A	56	60-61 [c]	C ₄ H ₇ NOS
3e	4-ClC ₆ H ₄	CH ₃	B	93	101-103 [b]	C ₉ H ₆ ClNOS
4a	4-CF ₃ C ₆ H ₄	C ₆ H ₅	C	90	46-48	C ₁₇ H ₁₄ F ₃ NOS
4b	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	C	94	105-106	C ₁₇ H ₁₃ ClF ₃ NOS

[a] Lit mp 127-129° [3]. [b] Lit mp 101-103° [4]. [c] Lit mp 62° [5]. [d] See Table III for the analytical data of all new compounds.

Table II

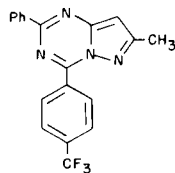
Pyrzolo[1,5-a]-1,3,5-triazines



5

Compound	R	R'	R''	Yield, %		Mp, °C	Formula [b]
				From 3	From 4		
5a	4-CF ₃ C ₆ H ₄	4-FC ₆ H ₄	2-C ₄ H ₉ S	93	—	228-230	C ₂₂ H ₁₂ F ₄ N ₄ S
5b	4-CF ₃ C ₆ H ₄	4-FC ₆ H ₄	3-(CH ₃ O)C ₆ H ₄	65	—	204-206	C ₂₅ H ₁₆ F ₄ N ₄ O
5c	CH ₃	CH ₃	C ₆ H ₅	82	—	168-170 [a]	C ₁₃ H ₁₂ N ₄
5d	CH ₃	CH ₃	2-C ₄ H ₉ O	62	—	148-150	C ₁₁ H ₁₀ N ₄ O
5e	4-CF ₃ C ₆ H ₄	C ₆ H ₅	C ₆ H ₅	61	67	204-205	C ₂₄ H ₁₅ F ₃ N ₄
5f	4-CF ₃ C ₆ H ₄	C ₆ H ₅	H	55	65	124-126	C ₁₆ H ₁₁ F ₃ N ₄
5g	4-CF ₃ C ₆ H ₄	C ₆ H ₅	CH ₃	51	73	145-146	C ₁₉ H ₁₃ F ₃ N ₄
5h	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	CH ₃	—	70	176-177	C ₁₉ H ₁₂ ClF ₃ N ₄
5i	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	H	—	78	183-185	C ₁₈ H ₁₀ ClF ₃ N ₄
5j	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	C ₆ H ₅	—	81	225-227	C ₂₆ H ₁₄ ClF ₃ N ₄
5k	4-CF ₃ C ₆ H ₄	4-ClC ₆ H ₄	2-C ₄ H ₉ O	—	69	206-208	C ₂₂ H ₁₂ ClF ₃ N ₄ O
5l	4-CF ₃ C ₆ H ₄	C ₆ H ₅	2-C ₄ H ₉ S	—	79	222-224	C ₂₂ H ₁₃ F ₃ N ₄ S
5m	4-CF ₃ C ₆ H ₄	C ₆ H ₅	2-C ₄ H ₉ O	—	79	212-213	C ₂₂ H ₁₃ F ₃ N ₄ O
5n	4-CF ₃ C ₆ H ₄	C ₆ H ₅	3-(CH ₃ O)C ₆ H ₄	—	72	170-171	C ₂₅ H ₁₇ F ₃ N ₄ O
5o	4-ClC ₆ H ₄	CH ₃	C ₆ H ₅	81	—	220-221	C ₁₈ H ₁₃ ClN ₄

[a] Lit mp 164.5-165° [8]. [b] See Table III for the analytical data of all new compounds.

**5g**X-Ray data for **5g**

Crystal Data.

A crystal of **5g**, C₁₉H₁₃F₃N₄, was found to be triclinic, space group P1-bar, $a = 10.368(1)$, $b = 17.982(3)$, $c = 4.425(1)\text{Å}$, $\alpha = 94.54(1)^\circ$, $\beta = 101.48(1)^\circ$; $v = 803.5\text{Å}^3$. For $Z = 2$ and $FW = 354.4$ the calculated density (D_c) is 1.46gcm^{-3} . Cell constants and an orientation matrix were obtained from least squares refinement, using the setting angles of 25 re-

flections on the range $13 < \theta < 41^\circ$, measured by the computer controlled diagonal slit method of centering. The yellow platelike crystal had approximate dimensions of $0.20 \times 0.25 \times 0.05\text{mm}$. Data collection and preliminary examination were performed with CuK α radiation ($\lambda = 1.54184\text{Å}$ at $23 \pm 1^\circ$), μ (CuK α) = 10.0cm^{-1} and $F(000) = 364$.

Data Collection and Processing.

Three-dimensional intensity data were measured on a computer controlled Enraf-Nonius CAD-4 Kappa axis diffractometer equipped with a graphite crystal, incident beam monochromator. The take-off angle was 2.8° . The data were collected at a temperature of $23 \pm 1^\circ$ using the $W-\theta$ scan technique. The scan rate was $2-20^\circ\text{mm}^{-1}$ (in omega) with a scan width of $0.7 + 0.300 \tan \theta$ deg. Data were collected to a maximum 2θ of 150.0° . A total of 3431 reflections were collected, of which 3306 were unique. As a check on crystal and electronic stability 3 representative reflections were measured every 41 minutes. The slope of the least squares line through a plot of intensity versus time was $-155 \pm 59\text{counts/hour}$

Table III
Analytical Data of All New Compounds Reported

Compound	C		H		N		S		F		Cl	
	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3b	52.4	52.8	2.64	2.64	4.08	4.01	9.33	9.25	16.6	16.8	10.3	10.2
3c	55.0	55.2	2.77	2.77	4.28	4.07	9.80	9.74	23.2	23.0	—	—
4a	60.5	60.5	4.18	4.32	4.15	3.94	9.51	9.88	16.9	16.8	—	—
4b	54.9	54.9	3.52	3.33	3.77	3.66	8.62	8.78	15.3	15.4	9.54	9.58
5a	59.9	60.0	2.97	2.71	12.7	12.7	7.26	7.68	17.2	17.0	—	—
5b	64.6	64.4	3.47	3.32	12.1	12.0	—	—	16.4	16.8	—	—
5d	61.7	61.8	4.71	4.66	26.2	26.3	—	—	—	—	—	—
5e	69.2	69.0	3.63	3.36	13.4	13.7	—	—	13.7	13.5	—	—
5f	63.5	63.5	3.26	3.02	16.5	16.6	—	—	16.7	16.7	—	—
5g	64.4	64.6	3.70	3.79	15.8	15.8	—	—	16.1	16.5	—	—
5h	58.7	58.4	3.11	3.16	14.4	14.6	—	—	14.7	14.4	9.12	9.16
5i	57.7	57.7	2.69	2.69	15.0	15.2	—	—	15.2	14.9	9.46	9.62
5j	63.9	64.0	3.13	3.16	12.4	12.6	—	—	12.6	12.4	7.86	7.90
5k	59.9	59.5	2.75	2.55	12.7	12.5	—	—	12.9	12.7	8.04	7.96
5l	62.6	62.5	3.10	3.11	13.3	13.3	7.59	7.95	13.5	13.2	—	—
5m	65.0	64.6	3.22	3.14	13.8	14.1	—	—	14.0	14.0	—	—
5n	67.0	66.6	3.84	3.58	12.6	12.6	—	—	12.8	12.9	—	—
5o	67.4	67.4	4.08	4.09	17.5	17.6	—	—	—	—	11.0	11.1

which corresponds to a total loss in intensity of 2.9%. A linear decay correction was applied. The correction factors on I ranged from 1.00 to 1.03 with an average value of 1.01. Lorentz and polarisation corrections were applied to this data. No absorption correction was made. A secondary extinction correction was applied. The final coefficient, refined in least squares, was 0.0000067 (in absolute values).

Structure Analysis and Refinement.

The structure was solved by direct methods. Using 275 reflections for which $E \geq 1.73$ and 2075 relationships, a total of 16 phase sets were obtained. The 26 non-hydrogen atoms were located from an E-map prepared from the phase set with probability statistics: absolute figure of merit = 1.12, residual = 0.09, and psi zero = 0.980. Hydrogen atoms were located and their positions and isotropic thermal parameters were refined. The structure was refined in full-matrix least squares where the function minimized was $\Sigma w(|F_o| - |F_c|)^2$ and the weight w is defined as $w = 4F_o^2/\sigma^2(F_o^2)$. The standard deviation on intensities, $\sigma(F_o^2)$, is defined as follows: $\sigma^2(F_o^2) = [S^2(C + R^2B) + (pF_o^2)^2]/Lp^2$ where S = scan rate, C = total integrated peak count, R = ratio of scan time to background counting time, B = total background count, Lp is the Lorentz-polarisation factor, and the parameter p is a factor introduced to downweight intense reflections. Here p was set to 0.060.

Scattering factors were taken from Cromer and Waber [10]. Anomalous dispersion effects were included in F_c^2 [11]; the values of $\Delta F'$ and $\Delta F''$ were those of Cromer [12]. Only the 2183 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 288 variable parameters and converged (largest parameter shift was 0.29 times its esd) with unweighted and weighted agreement factors of $R_1 = \Sigma |F_o| - |F_c| / \Sigma |F_o| = 0.066$; $R_2 = (\Sigma w(|F_o| - |F_c|)^2 / \Sigma w F_o^2)^{1/2} = 0.101$.

The standard deviation of an observation of unit weight was 2.50. The highest peak in the final difference fourier had a height of $0.47 e/\text{\AA}^3$ with an estimated error based on ΔF [13] of 0.06. Plots of $\Sigma (|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$, and various classes of indices showed no unusual trends.

All calculations were performed on a PDP-11/60 based TEXRAY [14] system which includes the Enraf-Nonius SDP and proprietary crystallographic software of Molecular Structure Corporation.

4-Chloro-*N*-[1-[(5-phenyl-1*H*-pyrazolo-3-yl)imino]ethyl]benzamide (6).

To a stirred solution of 3.50 g (0.022 mole) of 3-amino-5-phenylpyrazole in 20 ml of ethanol at 60° was added 4.27 g (0.020 mole) of *N*-thioacetyl-4-chlorobenzamide (3e). Although the product immediately precipitated out, the reaction mixture was kept at 60° for one hour. After cooling, the reaction mixture deposited 6.0 g (89%) of 6 as off-white crystals, mp 189-190°; ms: m/e 338 (M^+); nmr (DMSO- d_6): δ 2.32 (s, 3H), 6.6-8.4 (m, 11H), 10.56 (bs, 0.5H), 13.02 (bs, 0.5H); ir (potassium bromide): 1715, 1635, 1590, 1565, 1480, 1470, 1450, 1420, 1390, 1320, 1300, 1250, 1090, 940, 910, 750 cm^{-1} .

4-(4-Chlorophenyl)-2-methyl-7-phenylpyrazolo[1,5-a]-1,3,5-triazine (5o).

A mixture of 3.0 g (0.0089 mole) of 4-chloro-*N*-[1-[(5-phenyl-1*H*-pyrazolo-3-yl)imino]ethyl]benzamide (6) and 6.0 g (0.043 mole) of potassium carbonate in 150 ml of acetonitrile was stirred at 80° for 3.5 hours and then diluted with 550 ml of chloroform. The chloroform solution was washed with 2×100 ml of water and dried over sodium sulfate. After being concentrated down to ca. 20 ml, the solution deposited 2.6 g (91%) of 5o as yellow crystals, mp 220-221°; ms: m/e 320 (M^+); nmr (deuteriochloroform): δ 2.77 (s, 3H), 6.88 (s, 1H), 7.4-7.7 (m, 3H), 7.60 (d, $J = 9$ Hz, 2H), 7.9-8.3 (m, 2H), 8.94 (d, $J = 9$ Hz, 2H); ir (potassium bromide): 1600, 1480, 1230, 1190, 1100, 760, 680 cm^{-1} .

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