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Note

Utility of hydrazidoyl halides in heterocyclic chemistry: Synthesis of pyrazol-5-yl-1, 2, 4-triazole, pyrazol-5-yl-thiadiazole and pyrrazol-5-yl-triazolo[4, 5-*b*]triazine derivatives

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Reaction of 3-arylpyrazol-5-ylhydrazonyl chlorides **1a-f** with phenyl isothiocyanate, acetyl isothiocyanate, ethoxycarbonyl isothiocyanate, carbon disulfide and cyanamide affords pyrazol-5-yl-thiadiazole derivatives **2-5** and pyrazol-5-yl-1, 2, 4-triazole derivatives **6** respectively. The triazoles **6** react with acetic anhydride, ethyl chloroformate, benzoyl isothiocyanate acetyl isothiocyanate to give the products **7-10** respectively. Similarly, hydrazonyl chlorides **11g-i** react with cyanamide to afford the triazole derivatives **12g-i** which on reaction with benzoyl isothiocyanate, benzenesulphonyl chloride and phenyl isocyanate afford **13, 14** and **15**, respectively. All structures have been established on the basis of elemental analyses and spectral data.

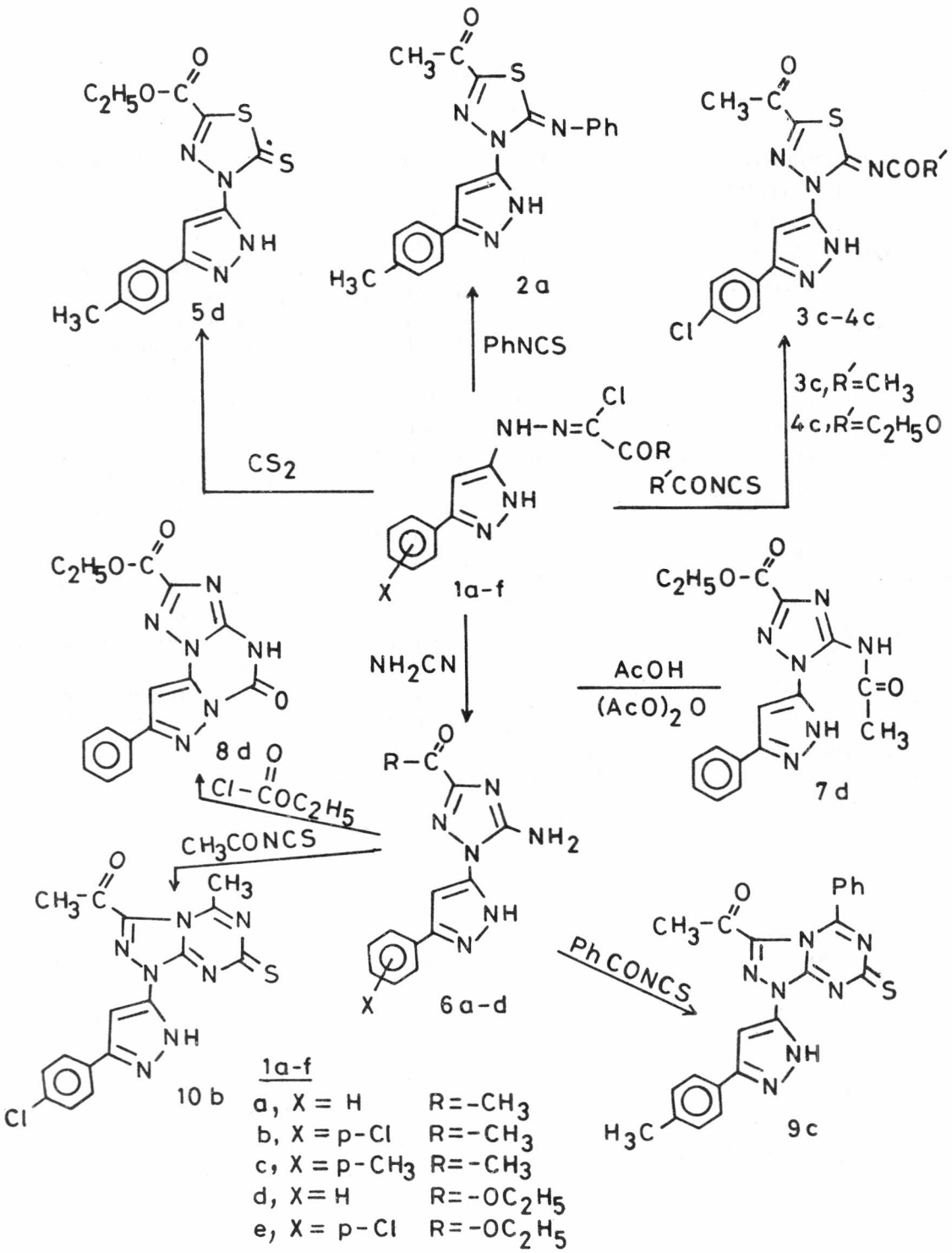
Pyrazoles and triazines have been extensively studied as many drugs include these rings. Many pyrazole derivatives show various biological activities[1]. For example, the common sulpha drug, Orisul has a prolonged bacteriostatic action *in vivo*. Similarly, a number of *s*-triazine derivatives exhibit various biological activities[2], such as antibacterial activity[3]. In continuation of our programme directed toward the synthesis of new compounds with expected antibacterial activity utilizing hydrazidoyl halides as starting materials[4-8], we report herein the synthesis of new derivatives of pyrazol-5-yl-1, 2, 4-triazole, pyrazol-5-yl-thiadiazole and pyrazol-5-yltriazolo[5, 1-*b*]-*s*-triazinthione.

It has been found that hydrazonyl chloride **1c** reacts with phenyl isothiocyanate to afford pyrazol-5-yl-thiadiazole derivative **2a** (Scheme I). This reaction was discussed in the previous work and the pyrazol-5-yl-thiadiazole structure was established and not the isomeric pyrazol-5-yl-1, 2, 4-triazole-5-thione.This reaction was investigated further to obtain new compounds in good yields. Acetyl isothiocyanate, ethoxycarbonyl isothiocyanate and carbon disulfide as polarophiles reacted in a similar way with hydrazonyl halides **1b,f** to afford the corresponding pyrazol-5-yl-thiadiazole derivatives **3c, 4c** and **5d** respectively (Scheme I). The formation of these products is assumed to proceed *via* dipolar cycloaddition of the polarophiles with the nitrilimine which is generated from hydrazonyl halide **1** in basic medium. The regioselectivity of this reaction on C=S or C=N has been reported[9], and cycloaddition reaction occurs on C=S to yield the thiadiazole structure and not the isothermic structure 1, 2, 4-triazole.

Compounds **1a-d** reacted with cyanamide in pyridine to give pyrazol-5-yl-1, 2, 4-triazole derivatives **6a-d**. The formation of compound **6d** is assumed to proceed via dipolar cycloaddition of nitrileimine to the cyano group to give the corresponding aminotrizole derivatives **6a-d**. Compound **6d** reacted with acetic anhydride and ethyl chloroformate to give **7d** and **8d**, respectively and the formation of **8d** is assumed to proceed via acylation followed by cyclization *via* loss of ethanol to give pyrazolo[5, 1-*a*]triazolo[3, 2-*c*]-*s*-triazine **8d**. The structures **7d** and **8d** were established on the basis of ^{1}H NMR data (cf. Table I).

On the other hand, compounds **6a-d** reacted with benzoyl isothiocyanate and acetyl isothiocyanate in pyridine to afford the corresponding pyrazol-5-yl-1, 2, 4-triazolo[5, 1-*b*]triazin-5-thione derivatives **9c** and **10b** respectively. The formation of these compounds is assumed to proceed *via* the addition of the amino group to C=S of the isothiocyanate derivative to afford the corresponding thiourea **9c** and **10b** respectively. Structures **2-10** were established on the basis of elemental analyses and spectral data (cf. Scheme I, Table I).

Similarly, hydrazonyl chlorides[10] **11g-i** reacted with cyanamide to give pyrazol-5-yl-1, 2, 4-triazole derivatives **12g-i**. Compound **12g** reacted with benzoyl isothiocyanate to give the cyclised product **13g** which is a pyrazol-5-yl-1, 2, 4-triazol[5, 1-*b*]-*s*-triazine-7-thione derivative. Compound **12i** reacted with benzene-sulfonyl chloride in pyridine to afford the N-benzenesulfonyl derivative **14i**, and **12h** reacted with phenyl isocyanate in acetic acid to afford the urea derivative **15h** in-



Scheme I

stead of the cyclised product **16h** as indicated by the elemental analysis, IR and ^{1}H NMR spectra (cf Scheme II, Table I).

Experimental Section

M.ps were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded in KBr discs using a Shemadzu 200-91506 spectrophotometer. ^{1}H NMR spectra were recorded in [^{2}H] DMSO on a Varian 90 MHz instrument with TMS as internal reference. Elemental analyses were carried out by the

Table I—Characterization data for the newly synthesized compounds

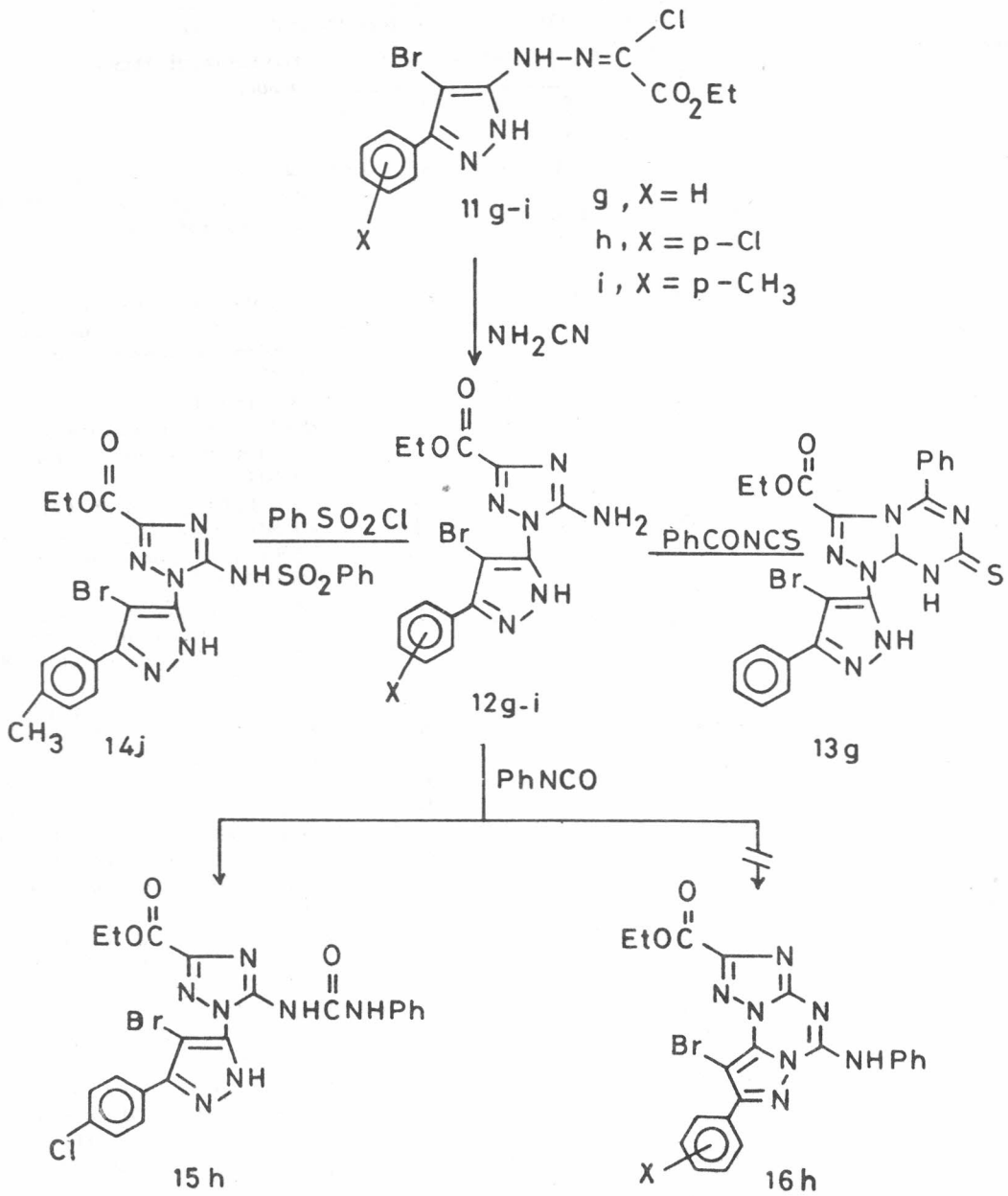
Compd	m.p. °C	Yield (%)	Mol. formula (mol. Wt.)	Found (%) (Calcd.)				^{1}H NMR in [^{2}H]DMSO (δ, ppm)
				C	H	N	S	
2a	195	80	$C_{20}H_{17}N_5OS$ (375.454)	63.8 (64.0	4.3 4.56	18.5 18.7	8.6 8.54)	2.2(s, 3H, CH_3), 2.7(s, 3H, CH_3CO), 6.4(s, 1H, pyrazole proton), 7.2-8.0(m, 9H, aromatic protons), 9.8(s, 1H, NH)
3c	125	61	$C_{15}H_{12}ClN_5O_2S$ (361.811)	49.9 (49.79	3.4 3.34	19.0 19.36	8.6 8.86)	2.5, 2.7(2s, 6H, 2 × CH_3), 6.4(s, 1H, pyrazole proton), 7.3-8.1(m, 4H, aromatic protons), 8.9(s, 1H, NH).
4c	170	65	$C_{16}H_{14}ClN_5O_3S$ (391.837)	48.8 (49.0	3.7 3.60	18.0 17.87	8.3 8.18)	1.4(t, 3H, CH_3), 2.3(s, 3H, CH_3), 4.3(q, 2H, CH_2), 6.4(s, 1H, pyrazole proton), 7.2-8.0(m, 4H, aromatic protons), 9.2(s, 1H, NH).
5d	220	80	$C_{14}H_{12}N_4OS_2$ (316.405)	53.0 (53.2	3.5 3.82	17.5 17.7	20.1 20.3)	1.3(t, 3H, CH_3), 2.7(s, 3H, CH_3), 4.3(q,)H, CH_2), 6.5(s, 1H, pyrazole proton), 7.3-8.1(m, 4H, aromatic protons), 9.5(s, 1H, NH)
6d	115	82	$C_{14}H_{14}N_6O_2$ (298.306)	56.1 (56.4	4.3 4.73	27.9 28.2	— —)	1.3(t, 3H, CH_3), 4.2(q, 2H, CH_2), 5.4(s, 2H, NH_2), 6.3(s, 1H, pyrazole proton), 7.3-8.1(m, 5H, aromatic protons), 8.9(d, 1H, NH).
7d	210	58	$C_{16}H_{16}N_6O_3$ (340.343)	56.3 (56.5	4.4 4.74	24.5 24.7	— —)	1.3(t, 3H, CH_3), 2.6(s, 3H, CH_3), 4.3(q, 2H, CH_2), 6.4(s, 1H, pyrazole proton), 7.2-8.0(m, 5H, aromatic protons), 8.7, 9.3(2s, 2H, 2 NH).
8d	> 300	56	$C_{15}H_{12}N_6O_3$ (324.300)	55.9 (55.6	4.0 3.73	26.1 25.9	— —)	1.3(t, 3H, CH_3), 4.3(q, 2H, CH_2), 6.4(s, 1H, pyrazole proton), 7.2-8.0(m, 5H, aromatic protons), 11.3(s, 1H, NH).
9c	175	60	$C_{22}H_{17}N_7OS$ (427.490)	61.5 (61.8	3.8 4.01	22.6 22.9	7.4 7.50)	2.1(s, 3H, CH_3), 2.7(s, 3H, CH_3CO), 6.4(s, 1H, pyrazole proton), 7.2-8.1(m, 9H, aromatic protons), 9.8(s, 1H, NH).
10b	> 300	65	$C_{16}H_{12}ClN_7OS$ (386.837)	49.4 (49.81	3.1 3.14	25.6 25.4	8.3 8.31)	2.2(s, 3H, CH_3), 2.7(s, 3H, CH_3CO), 6.3(s, 1H, pyrazole proton), 7.3-8.0(m, 4H, aromatic protons), 8.9(s, 1H, NH)
12g	130	80	$C_{14}H_{13}BrN_6O_2$ (377.207)	44.2 (44.6	3.2 3.47	21.9 22.3	— —)	1.3(t, 3H, CH_3), 4.3(q, 2H, CH_2), 5.1(s, br, 2H, NH_2), 7.4-7.8(m, 5H, aromatic protons), 9.3(s, 1H, NH).
13g	215	63	$C_{22}H_{17}BrN_7O_2S$ (523.398)	50.4 (50.49	3.4 3.27	18.4 18.73	6.0 6.13)	1.3(t, 3H, CH_3), 4.2(q, 2H, CH_2), 7.3-8.1(m, 10H, aromatic protons), 9.0, 9.6(2s, 2H, 2 NH).
14i	120	72	$C_{21}H_{19}BrN_6O_4S$ (531.394)	47.2 (47.5	3.2 3.60	15.6 15.8	5.8 6.03)	1.3(t, 3H, CH_3), 2.2(s, 3H, CH_3), 4.2(q, 2H, CH_2), 7.2-8.1(m, 9H, aromatic protons), 9.3, 11.1(2s, 2H, 2 NH).
15h	240	66	$C_{21}H_{17}BrClNO_3$ (531.275)	47.5 (47.4	3.5 3.2	18.5 18.4	— —)	1.3(t, 3H, CH_3), 4.3(q, 2H, CH_2), 4.8, 5.3(2s, br, 2H, 2NH), 7.2-8.0(m, 9H, aromatic protons), 9.4(s, 1H, NH).

Microanalytical Center at Cairo University. All physical and elemental data of the products are listed in Table I.

Compounds **1a-f** and **11g-i** were prepared as reported[7,10].

Reaction of 1a-f with several polarophiles: General procedure. A suspension of **1a-f** (0.01 mole) in dry acetone and phenyl isothiocyanate, acetyl isothiocyanate, ethoxycarbonyl isothiocyanate or carbon disulfide in dry pyridine was refluxed for 3 hr. The solvent was evaporated, the residue acidified with hydrochloric acid and crystallized from ethanol to afford compounds **2a, 3c, 4c** and **5d** respectively.

Reaction of cyanamide with compounds 1a-f and 11g-i. A suspension of cyanamide (0.01 mole) and any of **1a-f** or **11g-i** (0.01 mole) in 20 mL pyridine was refluxed for 3 hr. The reaction mixture was cooled and poured over ice/HCl mixture. The resulting solid was collected by filtration and crystallized from ethanol to yield compounds **6d** and **12g** respectively.



Scheme II

Reaction of 6b, c and 12g with benzoyl and acetyl isothiocyanates. The reactions of **6c** and **12g** with benzoyl isothiocyanate and **6b** with acetyl isothiocyanate were carried out, as described above for the synthesis of compounds **2a-5d**, to yield **9c, 13g** and **10b**, respectively; all of which were crystallized from ethanol.

Reaction of 6d with acetic anhydride and ethyl chloroformate. The reaction of compound **6d** with acetic anhydride and ethyl chloroformate, was carried out as reported[10], affording **7d** and **8d**, respectively which were crystallized from ethanol.

Reaction of 12i with benzenesulphonyl chloride. To a suspension of **12i** (0.01 mole) in 10 mL pyridine, was added benzenesulphonyl chloride (0.012 mole). The reaction mixture was refluxed for 5 hr and then poured over ice/HCl mixture. The resulting solid was collected by filtration and crystallized from ethanol to afford **14i** (cf Scheme II).

Reaction of 12h with phenyl isocyanate. A su-

spension of **12h** (0.01 mole) and phenyl isocyanate in 20 mL acetic acid was well shaken and left for 1 hr at room temperature. The pale yellow solid was collected by filtration and crystallized from ethanol to afford the urea derivative **15h**.

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