Journal of the Chinese Chemical Society, **1996**, *43*, 493-496

Reactions with Hydrazidoyl Halides XII[1] Synthesis of Pyrazolo[5,1-*c*]-1,2,4-triazine, Selenadiazolo[3,2-*a*]quinazolones, Selenadiazoline, Thiadiazoline and Thiazole Derivatives

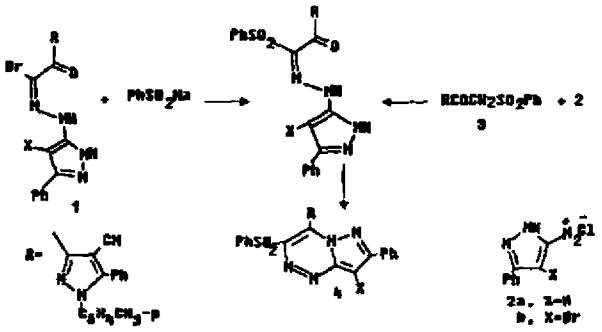
Nabil M. Hassan, Abdelgawad A. Fahmi, Fouad F. Abd-El-Mageid and Abdou O. Abdelhamid*
Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Several new pyrazolo[5,1-*c*]triazine, selenadiazoline, thiadiazoline, selenadiazolo[3,2-*a*]quinazolone, and arylazothiazole derivatives were synthesised by the reaction of hydrazonoyl halides with different reagents. The structure of new heterocycles were assigned on the basis of their elemental analysis, spectral data, and alternate synthesis whenever possible.

INTRODUCTION

Several pyrazoles,[2-5] 1,2,4-triazines,[6,7] selenadiazolines,[8] and thiadiazolines[9] are reported to have different biological activity as analgesic, antipyretic, antiinflammatory and antibacterial agents. This paper describes the synthesis of several new heterocycles via reactions of hydrazidoyl bromide **1** with some reagents.

Scheme I



RESULTS AND DISCUSSION

Treatment of hydrazidoyl bromide **1a** with sodium benzenesulfinate in boiling ethanol afforded a product which gave analytical and spectral data in accord with its formulation as 3-phenylsulfonyl-4(4-cyano-5-phenyl-1-*p*-tolylpyrazol-3-yl)-7-phenylpyrazolo[5,1-*c*]-1,2,4-triazine (**4a**). Its IR spectrum attested to the absence of CO and NH groups. The ^{1}H-NMR spectrum of **4a** showed signals at δ 2.3 (s, 3 H, $CH_3C_6H_4$-p), 6.4 (s, 1 H, pyrazole H-4) and 7.1-8.0 (m, 19 H, ArH's) ppm. These results suggest that cyclization[10-15] occurred as soon as intermediate hydrazone was formed to afford the corresponding pyrazolotriazine derivative **4a**. In support of this fact **4a** was also obtained by treatment of diazotized 3-amino-5-phenylpyrazole (**2a**) with ketosulfone **3** in ethanolic sodium acetate solution at 0-5 °C (cf Scheme I).

Treatment of **6a-c** with potassium selenocyanate (or potassium thiocyanate) in ethanol at room temperature gave only one spot on a thin-layer chromatogram. The IR spectra of these products showed the absence of the band due to the selenocyanate (or thiocyanate) group, and new imino absorptions were observed in the region of 3320-3350 cm^{-1}. The ^{1}H NMR spectrum of **9a** showed signals at δ (ppm) 2.3 (s, 3 H, 4-$CH_3C_6H_4$) and 7.2-8.4 (m, 15 H, ArH's and NH). Upon shaking with D_2O, a new singlet appeared at 4.3 ppm assignable to a DOH proton and 7.1-8.4 (m, 14 H, ArH's). The results indicate that the hydrazone **8** was not the end product of this reaction. The structures of **9** and **10** were further elucidated by independent synthesis. Thus, treatment of each of **5a** and **5b** with arenediazonium chlorides **7a-c** in ethanolic sodium acetate solution gave products **9a-c** and **10a-c**, respectively (cf Scheme II).

Scheme II

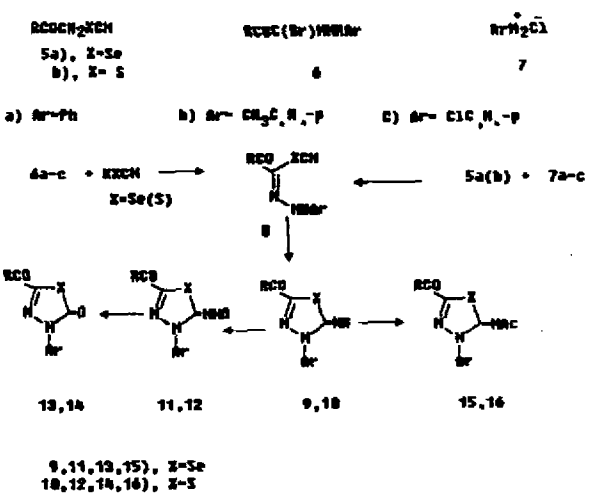


Table 1. Characterization of the Newly Synthesized Derivatives

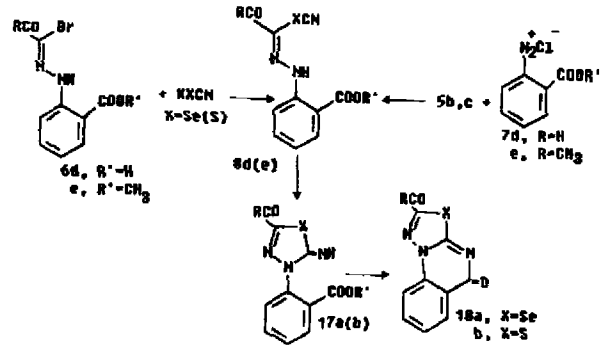
Comp.	Mp. °C	Yield (%)	Mol. For. Mol. Wt.	Calcd./Found C	H	N	S
1	182	72	$C_{28}H_{19}BrN_7O$	61.21	3.48	17.84	
			(549.42)	61.00	3.20	17.70	
4a	248	82	$C_{34}H_{23}N_7SO_2$	68.78	3.90	16.51	5.40
			(593.66)	68.80	3.70	16.70	5.50
4b	284	76	$C_{34}H_{22}BrN_7SO_2$	60.71	3.29	14.57	4.76
			(672.58)	60.60	3.40	14.40	4.60
5a	138	85	$C_{20}H_{14}N_4Se$	59.26	3.48	13.82	
			(405.32)	59.40	3.30	13.60	
6b	212	77	$C_{26}H_{20}BrN_5O$	62.65	4.04	14.05	
			(498.39)	62.50	3.90	14.10	
6c	201	72	$C_{25}H_{17}BrClN_5O$	57.88	3.30	13.50	
			(518.73)	57.70	3.20	13.60	
6d	265	70	$C_{26}H_{18}BrN_5O_3$	59.10	3.43	13.25	
			(528.38)	59.00	3.30	13.40	
6e	221	73	$C_{27}H_{20}BrN_5O_3$	59.78	3.71	12.91	
			(542.41)	59.60	3.50	13.00	
9a	153	89	$C_{26}H_{18}N_6SeO$	61.30	3.56	16.49	
			(509.43)	61.40	3.60	16.60	
9b	164	84	$C_{27}H_{20}N_6SeO$	61.95	3.84	16.05	
			(523.45)	61.80	4.00	16.10	
9c	168	82	$C_{26}H_{17}ClN_6SeO$	57.41	3.15	15.54	
			(543.88)	57.30	3.30	15.50	
10b	160	72	$C_{27}H_{20}N_6SO$	68.05	4.23	17.63	6.72
			(476.54)	68.10	4.30	17.50	6.60
10c	184	68	$C_{26}H_{17}ClN_6SO$	62.96	3.45	16.94	7.14
			(495.97)	62.80	3.50	17.10	7.30
11a	149	71	$C_{26}H_{17}N_7SeO_2$	57.99	3.18	18.12	
			(538.43)	57.80	3.20	18.30	
11b	144	68	$C_{27}H_{19}N_7SeO_2$	58.70	3.46	10.19	
			(552.42)	58.80	3.30	10.00	
11c	146	64	$C_{26}H_{16}ClN_7SeO_2$	54.51	2.81	17.11	
			(572.87)	54.40	2.70	17.20	
12b	126	66	$C_{27}H_{19}N_7SO_2$	64.14	3.78	19.34	6.34
			(505.56)	64.00	3.80	19.40	6.40
12c	128	61	$C_{26}H_{16}ClN_7SO_2$	59.37	3.06	18.64	6.09
			(525.98)	59.50	2.90	18.50	6.00
13a	206	59	$C_{26}H_{17}N_5SeO_2$	61.18	5.83	14.27	
			(510.41)	61.20	5.70	14.40	
13b	192	64	$C_{27}H_{19}N_5SeO_2$	61.83	5.22	14.27	
			(524.44)	61.90	5.30	14.40	
14b	187	67	$C_{27}H_{19}N_5SO_2$	67.91	4.40	14.66	
			(477.53)	67.80	4.20	14.40	
15a	295	84	$C_{26}H_{20}N_6SeO_2$	60.98	3.65	15.23	
			(551.47)	60.80	3.50	15.30	
15b	265	88	$C_{29}H_{22}N_6SeO_2$	61.59	3.92	14.68	
			(565.51)	61.60	4.00	14.70	
16b	225	80	$C_{29}H_{22}N_6SO_2$	67.16	4.26	16.21	
			(518.60)	67.20	4.40	16.40	
18a	325	76	$C_{27}H_{16}N_6SeO_2$	60.56	3.01	15.59	
			(535.42)	60.60	3.00	15.60	
18b	310	82	$C_{27}H_{16}N_6SO_2$	66.38	3.30	17.20	6.55
			(488.51)	66.30	3.20	17.30	6.50
20	242	79	$C_{27}H_{21}N_7S$	68.18	4.45	20.61	6.74
			(464.56)	68.20	4.60	20.20	6.90

Treatment of **9a-c** and **10b,c** with sodium nitrite in acetic acid at room temperature gave the nitrosoimino derivatives **11** and **12** as red to brownish red solids in good yield (Table 1). The IR spectra of **11a-c** and **12b,c** showed no NH absorption, but displayed a peak for a cyano group at 2220 cm^{-1} and a carbonyl absorption at 1650 cm^{-1}. The structures of the 3-aryl-5-(4-cyano-5-phenyl-1-*p*-tolylpyrazol-3-oyl)-2-nitrosoimino-2,3-dihydro-1,3,4-selenadiazoles (**11**) and 3-aryl-5-(4-cyano-5-phenyl-1-*p*-tolylpyrazol-3-oyl)-2-nitrosoimino-2,3-dihydro-1,3,4-thiadiazoles (**12**) were also supported by ^1H NMR, analytical data and chemical reactions. Compounds **11a,b** and **12b** decomposed to selenadiazolones **13a,b** and thiadiazolones **14b** upon reflux in xylene solutions. The IR spectra of **13a,b** and **14b** revealed cyano group at 2220 and two carbonyl absorption bands near 1650 and 1705 cm^{-1}. The ^1H NMR spectrum of **13a** showed signals at δ 2.4 (s, 3 H, p-$CH_3C_6H_4$) and 7.1-7.6 (m, 14 H, ArH's) ppm. Acetylation of **9a,b** and **10b** with acetic anhydride afforded the corresponding *N*-acetyl derivatives **15a,b** and **16b**, respectively. The IR (cm^{-1}) spectra of **15a,b** and **16b** revealed bands at 2220 (CN), 1660 (CO) and 1630 (CH_3CO=). The ^1H NMR spectrum of **15a** showed signals at δ (ppm) 2.3 (s, 3 H, CH_3CON=), 2.4 (s, 3 H, 4-$CH_3C_6H_4$) and 7.2-7.8 (m, 14 H, ArH's).

Treatment of hydrazidoyl halide **6d** or **6e** with KSeCN or KSCN in ethanol at room temperature gave the 1,3,4-selenadiazolo[3,2-*a*]quinazolone **18a** and 1,3,4-thiadiazolo[3,2-*a*]quinazolone **18b**, respectively. The structure of **18** was inferred from elemental analysis and spectral data. The IR spectra of **18a,b** showed the absence of bands due to SeCN (SCN), NH and OH groups and the presence of two carbonyl absorption bands at 1680 and 1640 cm^{-1}. The ^1H NMR spectra of **18a,b** showed signals at δ (ppm) 2.4 (s, 3 H, 4-$CH_3C_6H_4$) and 7.1-7.8 (m, 13 H, ArH's). To account for the formation of **18a,b**, it is suggested that the reaction of **6d** or **6e** with KSeCN or KSCN leads to the formation of hydrazone **8d** or **8e**. The hydrazone **8** undergoes spontaneous cycloaddition[16,17] to give the imino-1,3,4-selenadiazoline **17a** or thiadiazoline analoge **17b** which complete the reaction by loss of water (or loss of methanol) to give the final isolable **18a,b** (Scheme III). The structure of **18** was further elucidated by independent synthesis. Thus, treatment of each of **5a** and **5b** with **7d** or **7e** in ethanolic sodium acetate solution at 0-5 °C yielded a product identical to **18a** and **18b**, respectively.

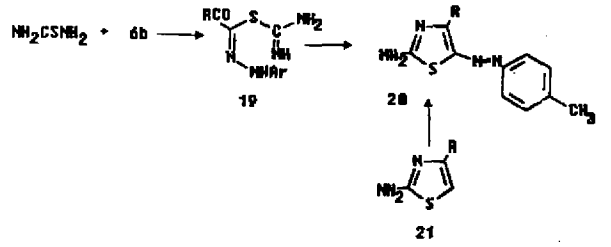
Treatment of **6b** with thiourea in ethanol gave a red product which was identified as 5-arylazo-4(4-cyano-5-phenyl-1-*p*-tolypyrazol-3-yl)-2-aminothiazole (**20**). The structure of the latter was inferred from its spectral and elemental analyses. The ^1H NMR spectrum of **20** showed sig-

Scheme III



nals at δ (ppm) 2.3 (s, 6 H, $2CH_3C_6H_3$-p), 5.9 (s, br., 2 H, NH_2) and 7.1-7.8 (m, 13 H, ArH's). Upon shaking with D_2O the signal at 5.9 ppm disappeared and a new singlet appeared at 4.5 ppm. The formation of **20** is assumed to proceed the intermediacy of the acyclic tautomeric intermediate **19** which then cyclizes under the expermintal conditions with loss one molecule of water to afford **20** Unequivocal support of the structure of **20** was achieved by its independent synthesis through another route. Thus, **7b** reacted with thiazole **21** in ethanolic sodium acetate solution at 0-5 °C (Scheme IV).

Scheme IV



EXPERIMENTAL

All melting points are uncorrected and were determined on a Gallenkamp melting point apparatus. The infrared spectra in KBr were recorded on a Perkin Elmer model 1430 Ratio Recording Spectrophotometer. ^{1}H NMR spectra were obtained on Varian Gemini 200 MHz spectrometer. Elemental analyses were carried out by the Microanalytical Center at Cairo University. Compounds **3**, **5a**, **6a** and **21** were prepared according to literature procedures.[1]

Synthesis of 1

An aqueous solution of diazotized 3-amino-5-phenylpyrazole (**2a**) (1.6 g, 0.01 mol) was added to a stirred solution of 4-cyano-5-phenyl-1-*p*-tolylpyrazoloyl-3-methane dimethylsulfonium bromide[1] (0.01 mol) in ethanol (20 mL) containing sodium acetate (1 g) at room temperature. After stirring for 30 min, the separated solid was collected and crystallized from ethanol to give **1** (Table 1).

Synthesis of Selenocyanate 5a

A mixture of KSeCN (1.4 g, 0.01 nmol) and 3-bromoacetyl-5-phenyl-1-*p*-tolylpyrazole-4-carbonitrile[1] (0.01 mol) in ethanol (20 mL) was stirred at room temperature for 30 min. It was filtered while still boiling. The filtrate was diluted to turbidity, which upon cooling, the filtrate deposited yellow-tan crystals of 3-selenocyanatoacetylpyrazole **5a**. IR (cm^{-1}): 1680 (CO), 2160 (SeCN) and 2225 (CN); ^{1}H NMR δ (ppm) 2.4 (s, 3 H, 4-$CH_3C_6H_4$), 3.6 (s, 2 H, CH_2) and 7.1-7.4 (m, 9H, ArH's) (Table 1).

Synthesis of Pyrazolo[5,1-*c*]-1,2,4-triazines 4

Method A

A mixture of hydrazidoyl bromide **1** (0.01 mol) and sodium benzenesulfinate (1.6 g, 0.01 mol) in ethanol (20 mL) was refluxed for **1h**. The solid formed collected by filtration, and crystallization from acetic acid gave **4** (Table 1).

Method B

A stirred mixture of ketosulfone **3** (4.4 g, 0.01 mol) and sodium acetate trihydrate (1.3 g, 0.01 mol) in ethanol (50 mL) was treated with the appropriate diazonium chloride **2** (0.01 mol) at room temperature for 1 h. The solid formed was collected, washed with water, and then crystallized from acetic acid to give **4a** and **4b**, respectively. The product **4a** was found identical (IR, ^{1}H NMR, mp and mixed mp) with a sample of **4a** prepared as above.

Synthesis of 6b-d

A mixture of dimethylsulfonium bromide[1] (0.1 mol) and the appropriate *N*-nitroso substituted acetanilide (0.12 mol) in ethanol (100 mL) was stirred at room temperature for 2 h. The yellow solid formed was collected, washed with water, and then, crystallized from acetic acid to give **6b-d** (Table 1).

Synthesis of 9a-c, 10b,c, 18a,b and 20

Method A

A mixture of the appropriate **6a-d** (0.01 mol) and KSeCN (1.4 g, 0.01 mol) or KSN (1 g, 0.01 mol) or thiourea (1.4 g, 0.02 mol) in ethanol (50 mL) was stirred at room temperature for 4 h or at reflux in the case of thiourea. The reaction mixture was diluted with water, and the solid formed was, collected by filtration. Crystallization from ethanol

gave **9a-c**, **10b,c**, **18a,b**, and **20**, respectively (Table 1).

Method B

A cold stirred solution (0-5 °C) of the appropriate **5a**, **5b** or thiazole **21** (0.01 mol) and sodium acetate (1.3 g) in ethanol (50 mL) was treated with the diazonium salt **7** (0.01 mol) and left in the refrigerator for 3 h. The solid formed was collected, washed with water, and then crystallized from ethanol to give **9a-c**, **10b,c**, **18a,b** and **20** which were identical in all respects (mp, mixed mp and spectra) with a samples prepared above.

Nitrosation of 9a-c and 10b,c

A solution of each of **9a-c** and **10b-c** (1 g) in acetic acid (30 mL) was treated with a saturated sodium nitrite solution with stirring for 30 min at 0-5 °C. The rosy coloured product which precippitated was collected, washed with water, and crystallized from ethanol to give the 2-nitroso derivatives **11a-c** and **12b** (Table 1).

Thermal Decomposition of 11a-c and 12b-c

The appropriate nitroso derivatives **11a-c** and **12b-c** (1 g) was refluxed in xylene (30 mL) for 15 min. The solvent was removed under vacuum. The residue was washed with pet-ether (40/60), and the solid formed was collected and crystallized from acetic acid to yield **13a-c** and **14b-c** (Table 1).

Acetylation of 9a-c and 10b-c

A solution of each of **9a-c** and **10b,c** (1 g) in acetic anhydride (15 mL) was stirred at room temperature for 10 min, and the crude solid was collected, washed with ethanol, and crystallized from acetic acid to give **15a-c** and **16b-c** (Table 1).

Received August 26, 1996.

REFERENCES

1. Part XI Abdelhamid, A. O.; Abd-El-Mageid, F. F.; Hassan, N. M.; Zohdi, H. F. *J. Chem. Res. (s)* **1995**, 492; *(M)* 303.
2. Jean Sice, "Centeral pharmacology" Saunders W. B. Company, **1962**, p. 824.
3. Izumi, K.; Kitamikado, T.; Sugiura, S.; Kato, K.; Hori, M. Fujimura, H. *J. Pharm. Soc. Japan* **1974**, *93*, 1349.
4. Sugiura, S.; Ohno, S.; Ohtani, O.; Izumi, K.; Kitamikado, T.; Asai, H.; Kato, K. *J. Med. Chem.* **1977**, *20*, 80.
5. Sugiura, S.; Kato, K.; Ohno, S.; Ohtani, O.; Wakayama, T. *J. Pharm. Soc. Japan* **1979**, *97*, 719.
6. Sen Gupta, A. K.; Rastogi, A.; Hajlela, K. *Indian J. Chem.* **1983**, *22B*, 1074.
7. Davidson, W. M.; Boykin, W. M. *J. Pharm. Sci.* **1978**, *65*, 737.
8. Shafiee, A.; Lalezari, I.; Yazdany, S.; Pournorouz, A. *J. Pharm. Sci.* **1973**, *62*, 839.
9. Sen Gupita, A. K.; Misra, H. K. *J. Antibact. Antifung. Agents*. **1980**, *8*, 17.
10. Abdelhamid, A. O.; Hassaneen, H. M.; Shawali, A. S. *J. Heterocycl Chem.* **1985**, *22*, 453.
11. Abdelhamid, A. O.; Attaby, F. A.; Khalifa, F. A.; Gabrial, S. S. *Arch. Pharm. Res.* **1992**, *15*, 14.
12. Tennant, G.; Vevers, R. J. S. *J. Chem. Soc. Perkin. Trans.* **1976**, *1*, 421.
13. Fortuna, D.; Stanovnik, B.; Tisler, M. *J. Org. Chem.* **1974**, *39*, 1833.
14. Bedford, G. R.; Cooper, F. C.; Partridge, M. W.; Stevens, M. F. G. *J. Chem. Soc.* **1963**, 5901.
15. Allmann, R.; Debaedemacker, T.; Grahn, W.; Reichardt, C. *Chem. Ber.* **1974**, *137*, 1555.
16. Wolkoff, P.; Nemeth, S. T.; Gibson, M. S. *Can. J. Chem.* **1975**, *53*, 3211.
17. Shawali, A. S.; Abdelhamid, A. O.; Hassaneen, H. M.; Shetta, A. *J. Heterocycl. Chem.* **1982**, *19*, 73.