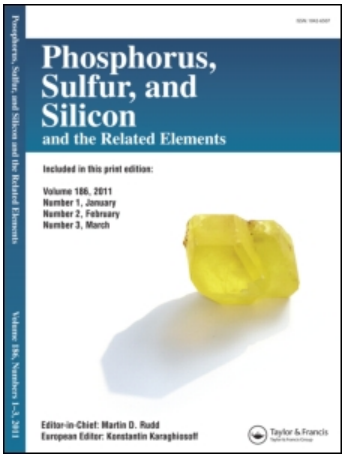

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Reactions of Hydrazidoyl Halides: Synthesis of Imidazo[2,1-b]thiazole, Thiazolo[2,3-c]-as-Triazole and Heterocyclic Enaminonitriles

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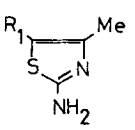
Arylazo derivatives of imidazo[2,1-b]thiazoles could be obtained via reaction of hydrazidoyl halides with 2-aminothiazole. Thiazolo[2,3-c]-as-triazole and heterocyclic enaminonitriles were obtained in good yields from hydrazidoyl halides and triethylamine and from malonitrile, respectively. Pyrazolo[3,4-d]pyrimidines and pyrazolo[3,4-d]pyridazines were obtained via reaction of heterocyclic enaminonitriles with formic acid and hydrazine hydrate, respectively. The structures of the products were assigned and confirmed on the basis of their elemental analyses and spectral data.

Key words: Imidazo[2,1-b]thiazole, Thiazolo[2,3-c]-as-triazole, Heterocyclic Enaminonitriles, Pyrazolo[3,4-d]pyridazine, Pyrazolo[3,4-d]pyrimidine.

The reaction of several hydrazidoyl halides with benzamidines has been investigated [1–5] and was found to lead to the formation of heterocyclic derivatives depending on the nature of the hydrazidoyl halides employed. In connection with our research about the use of hydrazidoyl halides in the synthesis of fused heterocyclic systems and some of their arylazo derivatives, it was of interest to examine the reaction of α-ketohydrazidoyl halides with 2-aminothiazoles, triethylamine and malonitrile. The products of the reactions are expected to be of commercial and biological interest [6–9].

Thus, it has been found that the hydrazidoyl bromide **1** reacted with 2-aminothiazole **4** in refluxing ethanolic triethylamine to yield 6-phenylazoimidazo[2,1-b]thiazole **6** in good yield (90%). Similarly **2** and **3** reacted to give **7** and **8** respectively (cf. Chart 1 and Experimental). The analytical and spectroscopic (IR and ^{1}H-NMR) data of the products **6–8** are consistent with their structure assignments. Thus, the Ir spectra of the compounds in the series **6**, **7** revealed bands for CO(ester) groups and the absence of NH bands. In case of **8**, the Ir spectrum showed bands near 1720, 1700 and 3350 cm^{-1} due to the presence of two carbonyl and NH groups. The ^{1}H-NMR spectrum of **8a** revealed the presence of one ethoxycarbonyl group. Although these data cannot distinguish between the isomeric structures **8** and **8A**, the latter structure and structures **6A** and **7A** were rejected because 2-aminothiazoles react with α-haloketones and α-haloesters to give 5-substituted and 5-oxo derivatives of imidazo [2,1-b]thiazole [9]. The reactions of hydrazidoyl halides **1–3** with 2-aminobenzthiazole **5** yielded, similarly, **9** and **10**, respectively (cf. Experimental).

Boiling in ethanolic-triethylamine resulted in the cyclization of the hydrazidoyl chloride **11** to the thiazolo[2,3-c]-as-triazole derivative **12**. On the other hand, **11**



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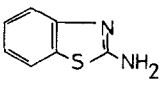

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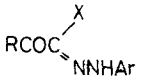
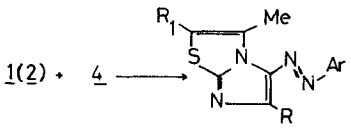
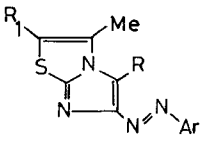


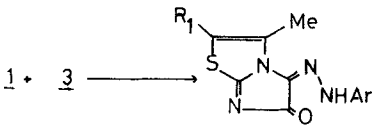
1, R = C_6H_5; X = Br
2, R = Me; X = Cl
3, R = OEt; X = Cl



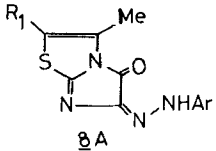
6, R = Ph
7, R = Me



6A
7A

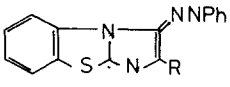


8



8A

Comp.	R	R_1	Ar
6	Ph	COOEt	Ph
7	Me	COOEt	$C_6H_4NO_2$-p
8a	-	COOEt	$C_6H_4NO_2$-p
8b	-	Ac	$C_6H_4NO_2$-p
8c	-	Bz	$C_6H_4NO_2$-p



9a, R = Ph
9b, R = Me

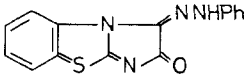


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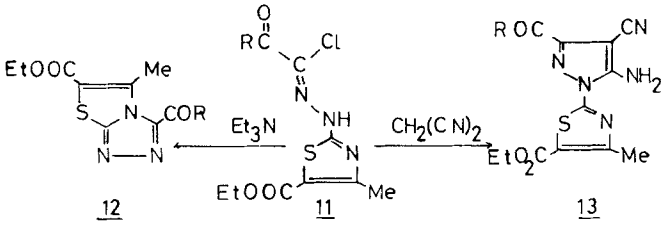
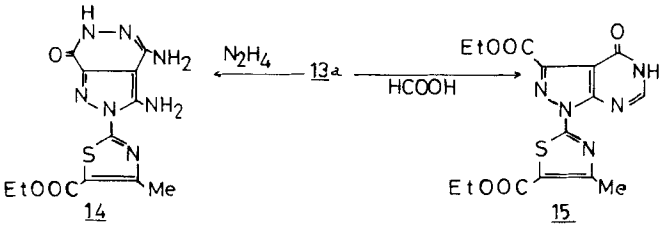
Chart 1



12 11 13

11 - 13a, R = OEt
b, R = Me



14 15

Chart 2

was treated with malononitrile in the presence of sodium ethoxide or aqueous sodium hydroxide to afford the heterocyclic enaminonitrile **13**. Compound **13a** reacted with hydrazine hydrate to yield the pyrazolo[3,4-d]pyridazine derivative **14**. The pyrazolo[3,4-d]pyrimidine derivative **15** could be obtained by refluxing compound **13a** with formic acid (cf. Chart 2).

In conclusion, the results described here indicate that the reaction of α-ketohydrazidoyl halides with 2-aminothiazoles, triethylamine and malononitrile appears to be an efficient route for imidazo[2,1-b]thiazole, thiazolo[2,3-c]-as-triazole and heterocyclic enaminonitrile derivatives. The latter could be converted easily to give pyrazolo[3,4-d]pyridazine and pyrazolo[3,4-d]pyrimidine derivatives.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Beckman spectrophotometer. ^{1}H-NMR on a Varian EM-390-90 MHz spectrometer using TMS as internal indicator and chemical shifts are expressed as δ ppm. The microanalytical were performed by the microanalytical Centre at Cairo University. Hydrazidoyl halides **1–3** were prepared according to literature procedures [10–13]. Compound **11** is newly synthesized by the authors [14].

Synthesis of Imidazo[2,1-b]thiazole derivatives **6–10**. *General procedure.* Equimolecular amounts of each of the hydrazidoyl halides **1–3**, 2-aminothiazole **4** or **5** (0.005 mole) and triethylamine (0.006 mole) in ethanol (25 ml) were refluxed for 3 hours and then cooled. The solid formed was collected and washed with water. Compounds **6–10** were obtained in almost quantitative yields.

2-Ethoxycarbonyl-3-methyl-6-phenylazo-5-phenylimidazo[2,1-b]thiazole (**6**). Yellow crystals, yield 90%, m.p. 212°C (AcOH). IR: 1720 (CO); 1620 (C=N) and 1600 (C=C). ^{1}H-NMR: 1.2 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3); 4.2 (q, 2H, $\underline{CH_2}CH_3$) and 7.1–7.8 (m, 10 H, ArH's). $C_{21}H_{18}N_4SO_2$ (390.4). Calcd: C, 64.6; H, 4.6; N, 14.3; S, 8.2. Found: C, 64.5; H, 4.7; N, 14.4; S, 8.1.

2-Ethoxycarbonyl-3,5-dimethyl-6-(4'-nitrophenyl)azoimidazo[2,1-b]thiazole (**7**). Yellow crystals, yield 92%, m.p. 220°C (EtOH). IR: 1715 (CO); 1620 (C=N); 1600 (C=C) and 1500–1400 (NO_2). ^{1}H-NMR: 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.2 (s, 3H, CH_3); 2.4 (s, 3H, CH_3); 4.1 (q, 2H, $CH_2\underline{CH_3}$) and 7.3–7.8 (m, 4H, ArH's). $C_{16}H_{15}N_5SO_4$ (373). Calcd: C, 51.5; H, 4.0; N, 18.8; S, 8.6. Found: C, 51.6; H, 4.1; N, 18.8; S, 8.4.

2-Ethoxycarbonyl-3-methyl-5-oxo-6-(4'-nitrophenyl)hydrazinoimidazo[2,1-b]thiazole (**8a**). Yellow powder, yield 83%, m.p. 158°C (EtOH). IR: 1720, 1700 (CO); 3350 (NH); 1620 (C=N); 1600 (C=C) and 1500–1400 (NO_2). ^{1}H-NMR: 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3); 4.2 (q, 2H, $\underline{CH_2}CH_3$) and 7.3–8.2 (m, 5H, ArH's and NH). $C_{15}H_{13}N_5SO_5$ (375.3). Calcd.: C, 48.0; H, 3.5: N, 18.1: S, 8.5. Found: C, 47.9, H, 3.6, N, 17.9, S, 8.6.

2-Acetyl-3-methyl-5-oxo-6-(4'-nitrophenyl)hydrazinoimidazo[2,1-b]thiazole (**8b**). Yellow powder, yield 80%, m.p. 182°C (EtOH). IR: 3360 (NH); 1690, 1670 (CO); 1630 (C=N); 1600 (C=C) and 1500–1400 (NO_2). ^{1}H-NMR: 2.2 (s, 3H, CH_3); 2.4 (s, 3H, CH_3) and 7.3–8.3 (m, 5H, ArH's and NH). $C_{14}H_{11}N_5SO_4$ (245.3). Calcd.: C, 48.7; H, 3.2; N, 20.3; S, 9.3. Found: C, 48.6; H, 3.1; N, 20.5; S, 9.3.

2-Benzoyl-3-methyl-5-oxo-6-(4'-nitrophenyl)hydrazinoimidazo[2,1-b]thiazole (**8c**). Yellow powder, yield 75%, m.p. 135°C (EtOH). IR: 3350 (NH); 1690, 1660 (CO); 1630 (C=N); 1600 (C=C) and 1500–1400 (NO_2). ^{1}H-NMR: 2.4 (s, 3H, CH_3) and 7.1–8.5 (m, 10 H, ArH's and NH). $C_{19}H_{13}N_5SO_4$ (407.4). Calcd.: C, 56.0; H, 3.2; N, 17.2; S, 7.9. Found: C, 55.8; H, 3.3; N, 17.3; S, 7.8.

7-Phenylazo-8-phenylimidazo[2,1-b]benzthiazole (**9a**). Yellow crystals, yield 83%, m.p. 196°C (AcOH). IR: 1620 (C=N) and 1600 (C=C). ^{1}H-NMR: 7.1–7.6 (m, ArH's). $C_{21}H_{14}N_4S$ (354.4). Calcd: C, 71.2; H, 4.0; N, 15.8; S, 9.0. Found: C, 71.1; H, 4.0; N, 15.9; S, 8.9.

8-Methyl-7-phenylazoimidazo[2,1-b]benzthiazole (**9b**). Yellow crystals, yield 85%; m.p. 220°C

(AcOH). IR: 1630 (C=N) and 1600 (C=C). ^{1}H-NMR: 2.3 (s, 3H, CH_3) and 7.2–7.6 (m, 9H, ArH's). $C_{16}H_{12}N_4S$ (292.3). Calcd.: C, 65.7; H, 4.1; N, 19.1; S, 10.9. Found; C, 65.5; H, 4.0; N, 19.3; S, 11.1.

8-Oxo-7-phenylhydrazinoimidazo[2,1-b]thiazole (**10**). Yellow crystals, yield 87%, m.p. 230°C (AcOH). IR: 3360 (NH), 1690 (CO), 1630 (C=N) and 1600 (C=C). ^{1}H-NMR: 7.3–8.5 (m, ArH's and NH). $C_{15}H_{10}N_4SO$ (294.3). Calcd.: C, 61.2; H, 3.4; N, 19.0; S, 10.9. Found: C, 61.2; H, 3.3; N, 18.9; S, 11.0.

Synthesis of Thiazolo[2,3-c]-as-triazole (**12a,b**). A solution of each of the appropriate hydrazidoyl chloride **11a,b** (2.0 g) in ethanol (20 ml) was treated with triethylamine (5 ml). The reaction mixture was refluxed for 3 hours and then evaporated under reduced pressure. The remaining solid product was collected by filtration and crystallized from ethanol to give the thiazolo[2,3-c]-as-triazole (**12a, b**).

4,6-Diethoxycarbonyl-5-methylthiazolo[2,3-c]-as-triazole (**12a**). Pale yellow crystals, yield 60%, 197°C (EtOH). IR: 1720, 1710 (CO) and 1630 (C=N). ^{1}H-NMR: 1.1 (t, 3H, $CH_2\underline{CH_3}$); 1.3 (t, 3H, $CH_2\underline{CH_3}$), 2.4 (s, 3H, CH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$) and 4.3 (q, 2H, $\underline{CH_2}CH_3$). $C_{11}H_{13}N_3SO_4$ (283.3). Calcd.: C, 46.6; H, 4.6; N, 14.8; S, 11.3. Found: C, 46.6; H, 4.5; N, 14.7; S, 11.4.

4-Acetyl-6-ethoxycarbonyl-5-methylthiazolo[2,3-c]-as-triazole (**12b**). Colorless crystals, yield 55%, m.p. 282 (EtOH) IR: 1720, 1670 (CO) and 1630 (C=N). ^{1}H-NMR: 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.2 (s, 3H, CH_3); 2.4 (s, 3H, CH_3) and 4.2 (q, 2H, $\underline{CH_2}CH_3$). $C_{10}H_{11}N_3SO_3$ (253.3). Calcd.: C, 47.4; H, 4.4; N, 16.6; S, 12.7. Found: C, 47.3; H, 4.5; N, 16.6; S, 12.6.

Synthesis of Heterocyclic enaminonitriles (**13a, b**). Malononitrile (0.33 g, 0.005 mole) was added with stirring to an ethanolic solution of sodium ethoxide obtained by dissolving sodium metal (0.11 g, 0.005 g-atom) in ethanol (20 ml). The appropriate hydrazidoyl chloride **11** (0.005 mole) was added to the resulting solution and stirring was continued for additional 3 hours at room temperature. The solid which precipitated was collected and crystallized from ethanol to give the pyrazole derivatives **13a, b**.

3-Ethoxycarbonyl-4-cyano-5-amino-3-(4'-methyl-5'-ethoxycarbonyl-2'-thiazolyl)pyrazole (**13a**). Pale yellow crystals, yield 75%, m.p. 209 (EtOH). IR: 3360, 3320, 3300 (NH_2), 2230 (CN) and 1720, 1710 (CO). ^{1}H-NMR: 1.1 (t, 3H, $CH_2\underline{CH_3}$); 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (q, 2H, $\underline{CH_2}CH_3$) and 6.0 (s, br, 2H, NH_2). $C_{14}H_{15}N_5SO_4$ (349.4). Calcd.: C, 48.1: H, 4.3; N, 20.0; S, 9.2. Found: C, 48.2, H, 4.3; N, 19.9; S, 9.2.

3-Acetyl-4-cyano-5-amino-3-(4'-methyl-5'-ethoxycarbonyl-2'-thiazolyl)pyrazole (**13b**). Pale yellow crystals, yield 80%, m.p. 160°C (EtOH). IR: 3360, 3270, 3180 (NH_2); 2220 (CN) and 1710, 1690 (CO) ^{1}H-NMR: 1.3 (t, 3H, $CH_2\underline{CH_3}$), 2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3); 4.2 (q, 2H, $\underline{CH_2}CH_3$) and 5.8 (s, br, 2H, NH_2). $C_{13}H_{13}N_5SO_3$ (319.3). Calcd.: C, 48.9; H, 4.1; N, 21.9; S, 10.0. Found: C, 49.0; H, 4.1; N, 22.0; S, 9.8.

Synthesis of 3,4-Diamino-7-oxo-2-(6'-ethoxycarbonyl-4'-methyl-2'-thiazolyl)pyrazolo[3,4-d]pyridazine (**14**). A mixture of the pyrazole derivative **13a** (2 g) and hydrazine hydrate (5 ml) was refluxed in ethanol (10 ml) for 4 hours. During this period, the pyrazole dissolved and the pyrazol[3,4-d]pyridazine (**14**) precipitated. The product was collected, wash with water and crystallized from dimethylformamide to give **14**, yellow crystals, yield 78%; m.p. 317°C. IR: 3420, 3350, 3300 (NH_2); 1710, 1680 (CO) and 1630 (C=N). ^{1}H-NMR: 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3); 4.2 (q, 2H, $\underline{CH_2}CH_3$); 6.0 (s, br, 4H, NH_2) and 9.1 (s, 1H, NH). $C_{12}H_{13}N_7SO_3$ (335.3). Calcd.: C, 43.0; H, 3.9; N, 29.2; S, 9.6. Found: C, 43.1; H, 3.8; N, 29.4; S, 9.8.

Synthesis of 5-Ethoxycarbonyl-3(H)-7-(5'-ethoxycarbonyl-4'-methyl-2'-thiazolyl)pyrazolo[3,4-d]-pyrimidin-4-one (**15**). The pyrazole **13a** (1.0 g) and formic acid (10 ml; 85%) were refluxed for 7 hours, then cooled. The solid so formed was collected, washed with water and crystallized from dimethylformamide to give **15**. Pale yellow crystals, yield 65%; m.p. 240°C. IR: 1720, 1700, 1680 (CO) and 1620 (C=N). ^{1}H-NMR: 1.1 (t, 3H, $CH_2\underline{CH_3}$); 1.3 (t, 3H, $CH_2\underline{CH_3}$); 2.4 (s, 3H, CH_3); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 4.3 (q, 2H, $\underline{CH_2}CH_3$) and 8.9 (s, br, 1H, NH). $C_{15}H_{14}N_5SO_4$ (376.3). Calcd.: C, 47.9; H, 3.7; N, 18.6; S, 8.5. Found: C, 47.9; H, 3.6; N, 19.0; S, 8.1.

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