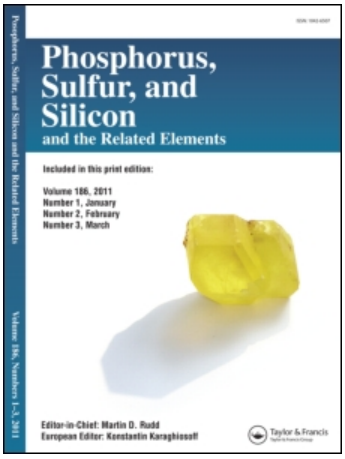

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UTILITY OF HYDRAZIDOYL HALIDES IN HETEROCYCLES: A NEW ROUTE FOR THE SYNTHESIS OF ALKYLMERCAPTOHETEROCYCLIC COMPOUNDS

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UTILITY OF HYDRAZIDOYL HALIDES IN HETEROCYCLES: A NEW ROUTE FOR THE SYNTHESIS OF ALKYLMERCAPTOHETEROCYCLIC COMPOUNDS

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The reaction of hydrazidoyl chloride (**I**) with ethyl mercaptan afforded the thioether derivative **II**. Compound **II** was converted to the pyridazine derivative **III** by fusion with ethyl cyanoacetate. Compound **III** was converted to the corresponding dioxide derivative **IV**. Compound **III** was utilized to synthesize a variety of heterocyclic compounds such as phthalazine and thieno[2,3-*d*] pyridazine derivatives, **VIIIa–e** and **XI**, respectively. Compound **XI** underwent chemical transformations to afford several new heterocyclic compounds. All structures were established on the basis of elemental analyses and spectral data.

Key words: Hydrazidoyl halides; heterocycles; IR; NMR; mercaptans.

Hydrazidoyl chlorides have received considerable attention in the synthesis of heterocyclic compounds.[1] In continuation of our interest in utilizing hydrazidoyl halides for the synthesis of azoles and fused azoles,[2–7] with anticipated biological activities, we report herein the results of our investigation on the reaction of hydrazidoyl halides with ethyl mercaptan.

Thus, compound **I** reacted with ethyl mercaptan, in presence of sodium ethoxide, to give the corresponding ethylthio ether derivative **II**, which upon heating with ethyl cyanoacetate afforded the corresponding ethylthiopyridazine derivative **III**. The IR spectrum of compound **III** revealed absorption bands at 2220 and 1700 cm^{-1} corresponding to the cyano and carbonyl groups, respectively. Oxidation of compound **III** with hydrogen peroxide in acetic acid,[8,9] gave the corresponding ethylsulfone derivative **IV**. Compound **III** also reacted with *a*-substituted cinnamonitriles **Va–e**, in basic medium, to give the corresponding ethyl mercaptophthalazine **VIIIa–e**. The formation of **VIII** is assumed to proceed via Michael additional[10,11] to afford intermediate **VI** which cyclizes to **VII**, which in turn loses hydrogen cyanide to afford the final product **VIII**. Structure **VIII** was established on the basis of elemental analysis, spectral data (Tables I and II). Alternatively, compound **VIIIa** was prepared via the reaction of **III** with benzaldehyde to afford compound **IX**, which upon reaction with malononitrile afforded **VIIIa**. Compounds **VIIIa–e** underwent oxidation, with hydrogen peroxide in acetic acid, to give the corresponding sulfone derivatives **Xa–e**. Alternatively, compound **Xa** was obtained via the reaction of **IV** with α-substituted cinnamonitrile **Va** (Scheme I).

TABLE I

Characterization data for the newly synthesized compounds

Compd.	m.p. °C	Solvent Yield %	Mol.Formula (Mol. Wt.)	Calc. /required C	H	N	S
III	123	EtOH	$C_{14}H_{13}N_3OS$	62.0	4.79	15.5	11.8
		70	(271.33)	62.3	5.0	15.3	12.0
IV	165	EtOH	$C_{14}H_{13}N_3O_3S$	55.4	4.28	13.85	10.6
		63	(303.33)	55.2	4.5	14.1	10.4
VIIIa	245	EtOH/DMF	$C_{23}H_{16}N_4OS$	69.3	4.51	14.1	8.04
		72	(398.48)	69.5	4.3	14.4	7.7
VIIIb	268	EtOH/DMF	$C_{23}H_{17}ClN_4OS$	63.8	3.92	12.9	7.40
		75	(432.93)	64.1	4.1	12.6	7.7
VIIIc	215	EtOH/DMF	$C_{24}H_{20}N_4O_2S$	67.3	4.66	13.1	7.48
		70	(425.51)	67.6	4.5	13.4	7.1
VIIId	185	EtOH/DMF	$C_{29}H_{23}N_3O_2S$	72.9	4.81	8.79	6.71
		70	(477.58)	73.1	4.5	9.0	6.9
VIIIe	150	EtOH	$C_{25}H_{23}N_3O_3S$	67.4	5.16	9.43	7.19
		65	(445.53)	67.2	5.3	9.4	7.0
Xa	280	EtOH/DMF	$C_{23}H_{18}N_4O_3S$	64.2	4.18	13.0	7.44
		50	(430.48)	64.1	4.3	12.8	7.5
XI	212	EtOH/DMF	$C_{14}H_{13}N_3OS_2$	55.4	4.28	13.8	21.1
		80	(303.40)	55.5	4.5	14.1	21.1
XIIa	275	EtOH/DMF	$C_{16}H_{15}N_3O_2S_2$	55.6	4.30	12.2	18.6
		55	(345.44)	55.7	4.2	12.0	18.8
XIIb	230	EtOH	$C_{21}H_{17}N_3O_2S_2$	61.9	4.17	10.3	15.7
		60	(407.51)	62.1	4.0	10.5	15.8
XIIIa	165	EtOH/DMF	$C_{17}H_{16}N_4O_2S_3$	50.5	3.65	13.8	23.8
		60	(404.53)	50.3	3.5	13.5	23.5
XIIIb	260	EtOH/DMF	$C_{21}H_{18}N_4OS_3$	57.5	4.10	12.8	21.9
		58	(438.59)	57.5	4.4	13.0	22.0
XV	235	EtOH/DMF	$C_{14}H_{12}BrN_3OS_2$	44.0	3.13	11.0	16.8
		70	(382.30)	44.2	3.0	10.8	16.5
XVI	220	EtOH	$C_{14}H_{13}N_3O_3S_2$	50.1	3.87	12.5	19.1
		45	(335.40)	50.3	4.0	12.5	19.3
XIX	208	EtOH/DMF	$C_{17}H_{14}N_4OS$	63.3	4.34	17.4	9.93
		61	(322.39)	63.0	4.5	17.4	9.7
XXIa	285	EtOH/DMF	$C_{18}H_{13}N_3O_4S$	58.8	3.53	11.4	8.72
		65	(367.38)	58.5	3.7	11.6	8.7
XXIb	275	EtOH/DMF	$C_{24}H_{18}N_4O_3S$	65.1	4.06	12.7	7.24
		60	(442.49)	65.0	4.1	12.5	7.3

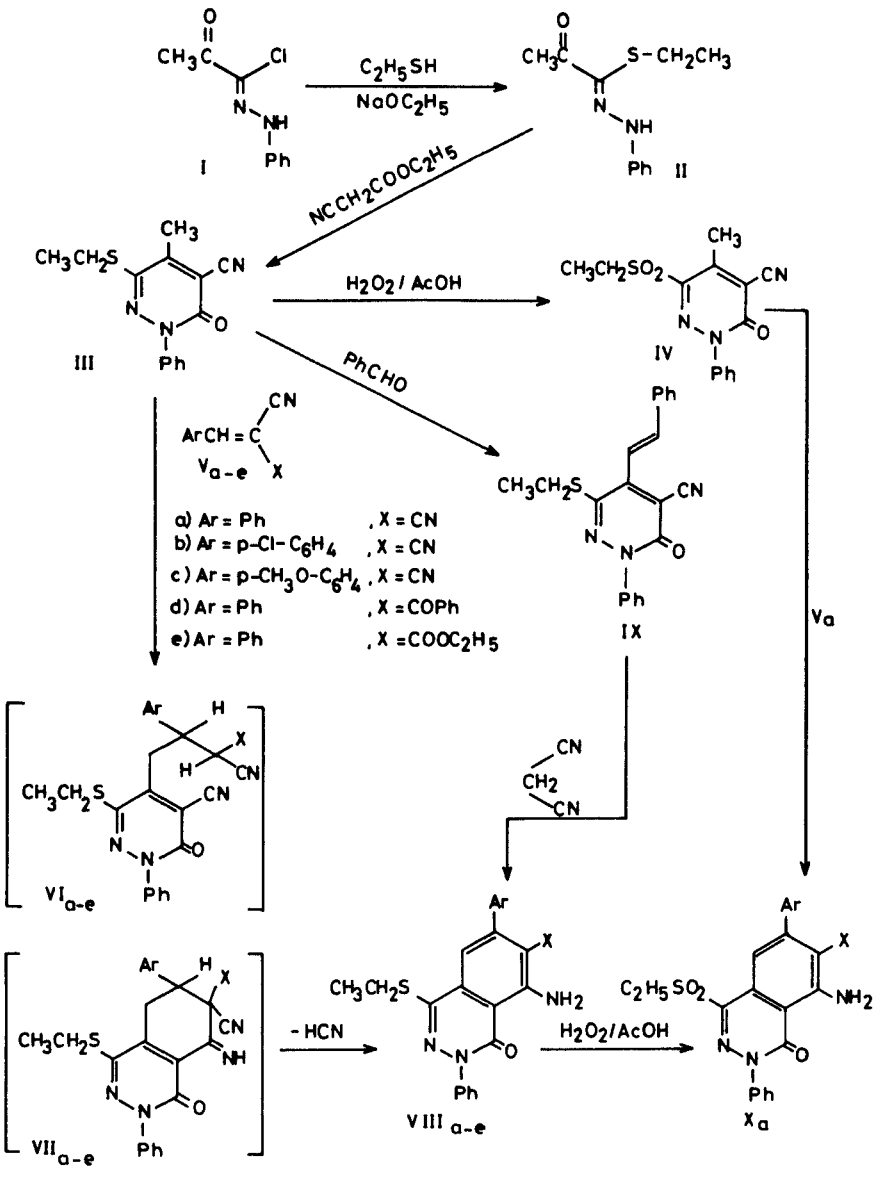
Compound **III** reacted with elemental sulfur to afford the corresponding ethylmercaptothieno[3,4-*d*]pyridazine derivative **XI**. Structure **XI** was confirmed on the basis of elemental analysis and spectral data. The IR spectrum of compound **XI** revealed absorption bands at 3400–3300 and 1700 cm^{-1} for the amino and carbonyl groups, respectively; and no cyano group absorption was observed in the region 2300–2100 cm^{-1}. The reaction mechanism was discussed previously.[10,11]

TABLE II

Spectroscopic data for the newly synthesized compounds

Compd.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
III	2220 (CN); 1700 (CO).	1.2(t, 3H, CH_3); 2.4(s, 3H, CH_3); 4.4(q, 2H, CH_2); 7.4-7.9(m, 5H, aromatic protons).
IV	2220 (CN); 1700 (CO).	
VIIIa	3400-3200 (NH_2); 2210 (CN); 1690 (CO).	1.3(t, 3H, CH_3); 3.5(s, 1H, CH); 4.5(q, 2H CH_2); 7.0-7.8(m, 10H, aromatic protons); 11.2(s, br, 2H, NH_2).
VIIIb	3370-3200 (NH_2); 2220 (CN); 1660 (CO).	
VIIIc	3380-3200 (NH_2); 2220 (CN); 1700 (CO).	1.2(t, 3H, CH_3); 3.4(s, 3H, CH_3); 4.2(q, 2H, CH_2); 7.2-7.7(m, 10H, aromatic protons); 10.9(s, br, 2H, NH_2).
VIIId	3400-3220 (NH_2); 1710 (CO).	1.3(t, 3H, CH_3), 4.4(q, 2H, CH_2); 7.1-8.0(m, 15H, aromatic protons); 11.0(s, br, 2H, NH_2).
VIIIe	3400-3100 (NH_2); 1725, 1690 (two CO).	
Xa	3350-3120 (NH_2); 2220, (CN); 1700 (CO).	
XI	3330-3080 (NH_2); 1690 (CO).	1.4(t, 3H, CH_3), 4.4(q, 2H, CH_2); 7.0(s, 1H, thieno proton); 7.2-8.3(m, 7H, aromatic and amino protons).
XIIa	3150 (NH); 1700, 1660 (two CO).	
XIIb	3180 (NH); 1690, 1670 (two CO).	
XIIIa	3300-3120 (NH, NH_2); 1700, 1680 (two CO).	1.3(t, 3H, CH_3); 2.7(s, 3H, CH_3CO); 4.4(q, 2H, CH_2); 6.9-7.4(m, 6H, aromatic and NH protons); 8.7(s, br, 2H, NH_2).
XIIIb	3400-3200 (NH, NH_2); 1700 (CO).	1.4(t, 3H, CH_3); 4.3(q, 2H, CH_2); 7.0-7.7(m, 11H, aromatic and NH protons); 8.8(s, br, 2H, NH_2).
XV	3370-3100 (NH_2); 1700 (CO).	1.3(t, 3H, CH_3); 4.4(q, 2H, CH_2); 7.3-8.3(m, 7H, aromatic and NH_2 protons).
XVI	3400-3100 (NH_2); 1700 (CO).	
XIX	3390-3120 (NH_2); 2220 (CN).	1.3(t, 3H, CH_3); 4.4(q, 2H, CH_2); 7.0(d, 2H, aromatic protons); 7.4-8.3(m, 7H, aromatic and NH_2 protons).
XXIa	3250-3080 (NH_2); 1730-1690 (three CO).	
XXIb	3300-3100 (NH_2); 1730-1700 (three CO).	

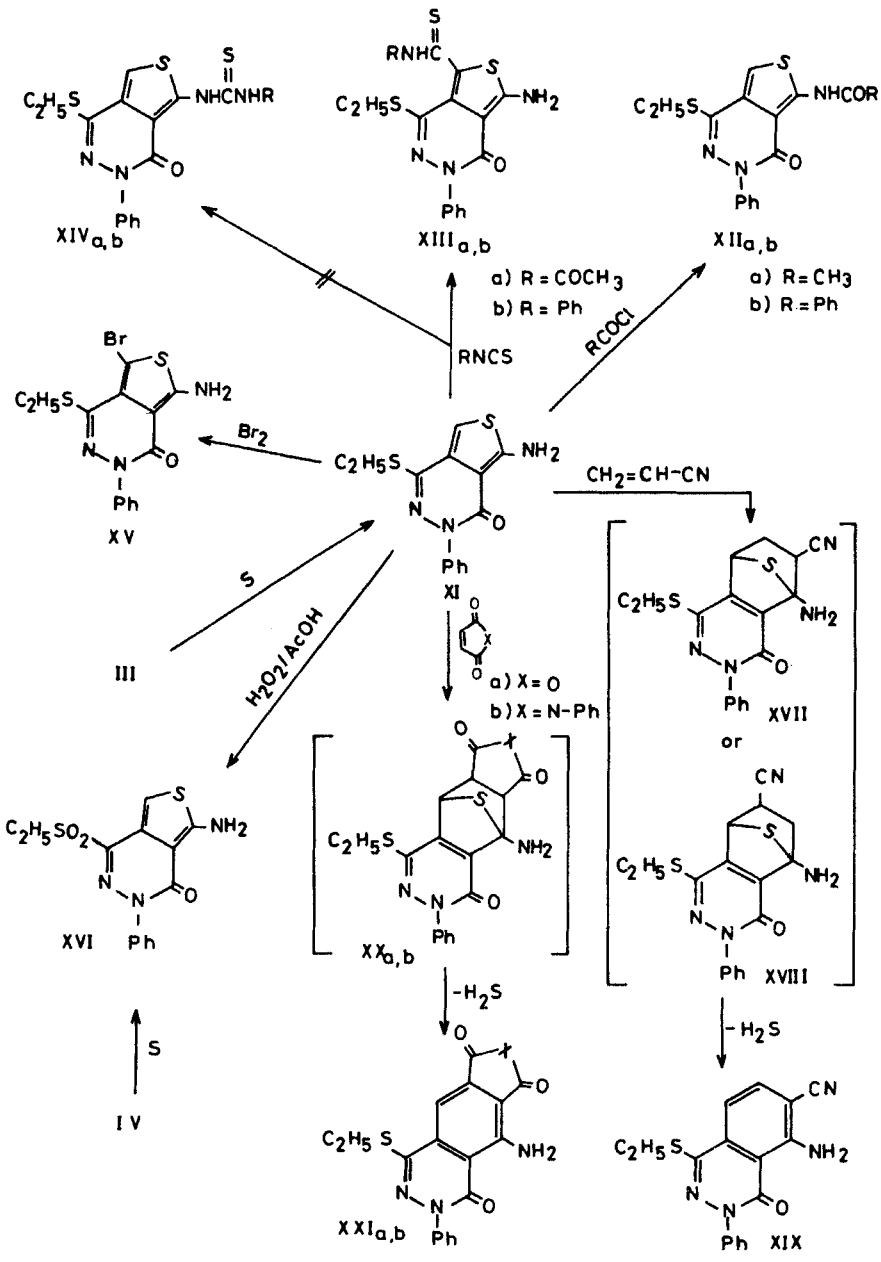
Compound **XI** was acylated to afford the N-acyl derivatives **IIIa,b**. Compound **XI**, also reacted with acetyl isothiocyanate and phenyl isothiocyanate to afford 1:1 adducts. Two possible isomeric structures, **XIII** and **XIV**, were considered. Structure **XIII** was established for the reaction product based on the absence of a thieno-proton signal in the ^{1}H NMR spectrum of compounds **XIIIa,b**. Oxidation of **XI**, with hydrogen peroxide in acetic acid, afforded the corresponding sulfone derivative



SCHEME I

XVI. Alternatively, compound **XVI** was obtained via the reaction of **IV** with elemental sulfur.

Compound **XI** underwent dipolar-cycloaddition reactions, with acrylonitrile, maleic anhydride and N-phenyl maleimide to afford the corresponding phthalazine derivatives **XIX** and **XIXa,b**, respectively. The reaction mechanism was previously discussed.[10,12] Structures **XIX** and **XXI** were established on the basis of elemental analyses and spectral data (Tables I and II).



SCHEME II

EXPERIMENTAL

M.p.s. were determined on a Gallenkamp melting point apparatus. IR spectra were recorded for KBr discs usinga Shemadzu Spectra 200-91506 spectrophotometer. ^{1}H NMR spectra were obtained in [^{2}H]DMSO on a Varian 90 MHz, with TMS as the internal reference. Elemental analyses were carried out by the Microanalytical Center at Cairo University. All physical and elemental data of the products are listed in Tables I and II.

Synthesis of acetylphenylhydrazidoyl ethyl mercaptan (**II**). Acetylphenylhydrazidoyl chloride (0.01 mole) was added to a solution of ethyl mercaptan (0.01 mole) in 20 ml absolute ethanol containing 0.01 mole of sodium. The reaction mixture was stirred for 3 hrs at room temperature and left overnight. It was then poured over crushed ice; and the formed product was collected by filtration, washed with water and crystallized from ethanol to afford compound **II**.

Synthesis of the pyridazine derivative **III**. A mixture of compound **II** (0.01 mole), ethyl cyanoacetate (0.01 mole) and ammonium acetate (0.02 mole) was heated for 2 hrs at 140°C. The reaction mixture was then poured over crushed ice and the solid product was collected by filtration, washed with water and crystallized from ethanol-dioxane mixture to afford compound **III**.

Synthesis of the ethyl sulfone derivative **IV**. To a solution of compound **III** (2 g) in 30 ml acetic acid; was added 50 ml hydrogen peroxide solution portion-wise with continuous stirring. The reaction mixture was warmed for 2 hrs and then poured over crushed ice. The so formed solid was collected by filtration and crystallized ethanol to afford compound **IV**.

Reaction of compound **III** *with benzaldehyde*. Benzaldehyde (0.01 mole) was added to a solution of compound **III** (0.01 mole) in 20 ml ethanol, containing 3 drops of piperidine. The reaction mixture was refluxed for 3 hrs and the solvent was evaporated. The so formed solid product was collected and crystallized from ethanol mixture to afford compound **IX**.

Synthesis of phthalazine derivative **VIII**

Method A: To a solution of compound **IX** (0.01 mole) in 20 ml ethanol containing 2 drops of piperidine, was added malononitrile (0.01 mole). The reaction mixture was refluxed for 3 hrs, cooled and poured over ice/HCl mixture. The precipitated product was collected by filtration, washed with water and crystallized from ethanol to afford compound **VIIIa**.

Method B: A solution of compound **III** (0.01 mole) and cinnamonitrile derivatives (0.01 mole), in 30 ml ethanol containing two drops of piperidine was refluxed for 3 hrs and allowed to cool. The reaction mixture was then poured over ice/HCl mixture and the collected product was crystallized from ethanol to afford a product (in case of α-cyanocinnamonitrile) identical in all aspects (elemental analysis, m.p. and spectral data) to that obtained from method A.

Reaction of compound **VIII** *with hydrogen peroxide*. To a warm solution of compound **VIII** (0.01 mole) in 30 ml acetic acid, was added 50 ml of hydrogen peroxide in small portions over a period of two hours. The reaction mixture was then poured over crushed ice and the so formed solid was collected by filtration and crystallized to afford a product identical in all aspects (elemental analysis, m.p. and spectral data) to that obtained from the reaction of compound **IV** with cinnamonitrile derivatives **Va–e**.

Synthesis of the thienopyridazine derivative **XI**. Compound **III** (0.01 mole) was added to a suspension of sulfur powder (0.01 mole) in 30 ml ethanol containing triethyl amine (0.01 mole). The reaction mixture was refluxed for 3 hrs, cooled and poured over ice/HCl mixture. The produced solid was collected by filtration, washed with water and crystallized from ethanol-dioxane mixture to afford compound **XI**.

Acylation of compound **XI**. Compound **XI** (0.01 mole) was added to a solution of 0.01 mole of acetyl chloride or benzoyl chloride in 30 ml pyridine. The reaction mixture was refluxed for 3 hrs, cooled and poured over ice/HCl mixture. The solid product was collected by filtration, washed with water and crystallized from ethanol to afford compounds **XIIa,b**.

Synthesis of compound **XIIIa,b**. Compound **XI** (0.01 mole) was added to a solution of 0.01 mole of acetyl isothiocyanate and phenyl isothiocyanate in dry pyridine. The reaction mixture was refluxed for 3 hrs, cooled and poured over ice/HCl mixture. The solid product so formed was collected by filtration, washed with water and crystallized to afford compounds **XIIIa,b**.

Bromination of compound **XI**. To a solution of **XI** (0.01 mole) in 30 ml chloroform, was added bromine (0.01 mole) in 10 ml chloroform. The reaction mixture was stirred at room temperature for 2 hrs and the chloroform was then evaporated. The solid product was triturated with alcohol and crystallized to afford compound **XV**.

Synthesis of the sulfone derivative **XVI**. To a warm solution of compound **XI** (0.01 mole) in 30 ml acetic acid, was added 5 ml hydrogen peroxide, in small portions with continuous stirring. The reaction

mixture was poured over ice. The solid product so formed was collected by filtration, and crystallized to afford a product identical in all aspects (elemental analysis, m.p. and spectral data) to that obtained from the reaction of compound **IV** with elemental sulfur in ethanol containing triethylamine (cf. synthesis of **XI**).

Reaction of **XI** *with dienophiles.* Compound **XI** (0.01 mole) was added to a solution of 0.01 mole of acrylonitrile, maleic anhydride or *N*-phenylmaleimide, in 20 ml pyridine. The reaction mixture was refluxed for 3 hrs, cooled and poured over ice/HCl mixture. The solid product was collected by filtration, washed with water and crystallized to afford compounds **XIX** and **XXIa,b**, respectively.

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