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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/gpss20

REACTIONS WITH HYDRAZONOYL HALIDES. PART 27^[1]: SYNTHESIS OF SOME NEW TRIAZOLO[4,3a]BENZIMIDAZOLE AND UNSYMMETRICAL AZINE DERIVATIVES

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To cite this article: Abdou O. Abdelhamid , Hussien F. Zohdi , M. M. M. Sallam & Nagla A. Ahmed (2000) REACTIONS WITH HYDRAZONOYL HALIDES. PART 27^[1]: SYNTHESIS OF SOME NEW TRIAZOLO[4,3-a]BENZIMIDAZOLE AND UNSYMMETRICAL AZINE DERIVATIVES, Phosphorus, Sulfur, and Silicon and the Related Elements, 164:1, 181-188, DOI: 10.1080/10426500008045244

To link to this article: http://dx.doi.org/10.1080/10426500008045244

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REACTIONS WITH HYDRAZONOYL HALIDES. PART 27^[1]: SYNTHESIS OF SOME NEW TRIAZOLO[4,3-*a*]BENZIMIDAZOLE AND UNSYMMETRICAL AZINE DERIVATIVES

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(Received March 06, 2000; In final form April 14, 2000)

Triazolo[4,3-*a*]benzimidazole, unsymmetrical azine containing pyrazole moiety were synthesised via reactions of C-pyrazolôyl-N-p-chlorophenylhydrazonoyl bromide with each 2-(methylthio)benzimidazole and carbodithioates, respectively. Newly synthesised compounds were confirmed on the basis of elemental analysis, spectral data, and alternative route whenever possible.

INTRODUCTION

Extensive studies of the chemistry of hydrazonoyl halides have established the value of these compounds as versatile precursors for the synthesis of heterocycles^[2–5]. In continuation of our interest in the synthesis of heterocyclic systems containing pyrazole moiety^[6–10], we report herein a facile synthesis of triazolo[4,3-a]benzimidazole and unsymmetrical azines.

RESULTS AND DISCUSSION

The reaction of equimolar ammounts of C-pyrazoloyl-N-p-chlorophenylhydrazonoyl bromide^[1] (1) with 2-(methylthio)benzimidazole (2) in boiling

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ethanolic triethylamine solution furnished exclusively the corresponding 2-p-chlorophenyl-1-[3'-ethoxycarbonyl-5'-methyl-4'-(p-tolyl)] pyrazoloyl-triazolo[4,3-a]benzimidazole (5) in excellent yield. Structure 5 was elucidated on the basis of analytical and spectral data. ¹H NMR spectrum showed signals at $\delta = 1.01$ (t, 3H), 2.46 (s, 3H), 2.55 (s, 3H), 4.08 (q, 2H) and 7.26–8.56 (m, 12H). The formation of 5 can be explained by a stepwise path involving substitution to give amidrazone 3, which readily cyclized to give intermediate 4. The latter converted to 5 via elimination of methyl mercaptan (cf. Scheme 1).



SCHEME 1

Compound 1 readily reacted with methyl phenylethylenehydrazinecarbodithioate (**6a**), in ethanol to afford a product, which analyzed correctly for $C_{31}H_{27}ClN_6O_3S$ (**9a**). Structure **9** was inferred on the basis of spectral data and alternative synthesis. Thus ¹H NMR spectrum of **9a** showed signals at $\delta = 1.14$ (t, 3H); 2.39 (s, 3H); 2.43 (s, 3H); 2.46 (s, 3H); 4.12 (q, 2H) and 7.26–8.04 (m, 13H). Structure of **9a** was further confirmed by the reaction of hydrazonoyl bromide **1** with ethyl phenylethylenehydrazinecarbodithioate (**10a**) in ethanolic triethylamine solution, which afforded a product identical in all respects (mp., mixed mp. and spectra) with **9a** (cf. Scheme 2). The formation of **9a** can be explained via elimination of methyl mercaptan (or ethyl mercaptan) from the cycloadduct **8**, which is assumed to be formed from the 1,3-dipolar cycloaddition of the nitrile imide **11** (prepared in situ from **1** with triethylamine) to the C=S double bond of **6a** (cf. Scheme 2). Alternatively the formation of the product **9a** can also be explained by a stepwise path involving substitution, to give acyclic hydrazone 7, which transferred to the cyclic intermediate 8. Elimination of methyl (or ethyl) mercaptan from 8 afforded the final isolable product 9a (cf. Scheme 2). All attempts to isolate either the intermediate cycloadduct 8 or the open hydrazone 7were unsuccessful.



Similarly, the hydrazinecarbodithioate derivatives **6b-d** reacted with the hydrazonoyl bromide **1** to give the corresponding 2,3-dihydro-1,3,4-thia-diazoles **9b-d**, respectively.

Analogy, the hydrazonoyl bromide 1 reacted with the appropriate carbodithioate 12a-c(or 13a-c) in ethanolic triethylamine solution, to afford 2,3-dihydrothiadiazoles 14a-c (cf. Scheme 2).

Compound 1 reacted with sodium benzenesulfinate to afford the corresponding hydrazone 16c in acceptable yield (cf. Scheme 3). IR (cm⁻¹) spectrum of 16c revealed two bands at 1314 and 1140 assignable to the asymmetric and symmetric vibrations of SO₂ group. The ¹H NMR spectrum of 16c is in good agreement with its structures. Oxidation of the sulfide 17 (prepared by reaction of 1c with sodium thiophenolate) with hydrogen peroxide in acetic acid^[11] yielded product identical in all respects (mp., mixed mp. and spectra) with 16c. Structure 16 was confirmed by the alternative synthesis via the reaction of diazotized anilines with ketosulfone 18 [prepared by the reaction of 4-(2-bromoacetyl)-3-ethoxycarbonyl-5-methyl-1-p-tolylpyrazole with sodium benzenesulfinate] in ethanolic sodium acetate solution.



EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ¹H NMR spectra were recorded in CDCl₃ and (CD₃)₂SO on a Varian Gemini 200 MHz spectrometer and chemical shifts were expressed in δ units using TMS as internal reference. Elemental analyses were carried out at the Microanalytical Center of the University of Cairo, Giza, Egypt. Alkyl carbodthioates^[12–14] were prepared as previously reported.

Synthesis of 2-p-chlorophenyl-1-[3'-ethoxycarbonyl-5'-methyl-4'-(p-tolyl)]pyrazol-oyltriazolo[4,3-a]benzimidazole (5)

A mixture of hydrazonoyl bromide 1(2.5g, 0.005 mol), 2-methylsulfanylbenzimidazole (0.89g, 0.005 mol), and triethylamine (0.75 ml, 5 mmol) in ethanol (20 ml) was refluxed for 3h. The resulting solid, which precipitated, was collected, washed with water and crystallized from ethanol gave 5 (cf. Tables I and II).

% Analyses, Calcd. /Found							
Compd no.	M.P., °C colour	Mol.Formula Mol.Wt.	Yield %	с	H	N	s
5	240-242	C29H23CIN6O3	83	64.62	4.30	15.59	
	Yellow	539.00		64.60	4.10	15.70	
9a	178-80	C31H27CIN6O3S	92	62.15	4.54	14.03	5.35
	Yellow	599.12		62.30	4.40	13.90	5.20
9b	19092	C ₂₉ H ₂₅ CIN ₆ O ₄ S	89	59.13	4.28	14.27	5.44
	Yellow	589.08		59.20	4.40	14.10	5.40
9c	197–200	C30H26CIN7O3S	89	60.06	4.37	16.34	5.34
	Yellow	600.10		60.10	4.30	16.40	5.34
9d	192194	$C_{29}H_{25}CIN_6O_3S_2$	90	57.56	4.16	13.89	10.60
	Yellow	605.14		57.80	4.00	14.10	10.50
14a	148-50	C28H27CIN6O3S	94	59.73	4.83	14.93	5.69
	Yellow	563.08		59.80	4.90	15.10	5.80
14b	280-82	C29H29CIN6O3S	93	60.36	5.07	14.56	5.56
	Orange	577.11		60.10	5.00	14.60	5.60
14c	232-234	C33H29CIN6O3S	95	63.40	4.68	13.44	5.13
	Orange	625.15		63.20	4.80	14.30	5.20
16a	200203	C ₂₈ H ₂₆ N ₄ O ₅ S	77	63.38	4.94	10.56	6.04
	Yellow	530.61		63.20	4.80	10.60	5.80
16b	160-163	C ₂₉ H ₂₈ N ₄ O ₅ S	78	63.96	5.18	10.29	5.89
	Yellow	544.63		64.10	5.30	10.40	5.90
16c	139–140	C28H25 ClN4O5S	82	59.52	4.46	9.92	5.67
	Yellow	565.05		59.70	4.30	9.80	5.80
17c	197-200	C ₂₈ H ₂₅ ClN ₄ O ₃ S	65	63.09	4.73	10.51	6.02
	Yellow	533.05		63.20	4.90	10.70	5.90
18	88–90	C ₂₂ H ₂₂ N ₂ O ₅ S	72	61.96	5.20	6.57	7.52
	colorless	426.50		61.80	5.00	6.70	7.40

TABLE I Characterization data of the newly synthesized compounds

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Comp no.	IR (cm ⁻¹)	¹ H NMR (δ ppm)		
9b	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 2.39(s, 3H, CH ₃); 2.43(s, 3H, CH ₃); 2.46(s, 3H, CH ₃); 4.12(q, 2H, CH ₂ CH ₃); and 7.26–8.04(m, 11H, ArH's).		
9с	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 2.39(s, 3H, CH ₃); 2.43(s, 3H, CH ₃); 2.46(s, 3H, CH ₃); 4.12(q, 2H, CH ₂ CH ₃); and 7.26–8.04(m, 12H, ArH's).		
9d	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 2.39(s, 3H, CH ₃); 2.43(s, 3H, CH ₃); 2.46(s, 3H, CH ₃); 4.12(q, 2H, CH ₂ CH ₃); and 7.26-8.04(m, 11H, ArH's).		
14a	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 1.81(m, 4H, 2CH ₂); 2.43(s, 3H, CH ₃); 2.50(s, 3H, CH ₃); 2.52(t, 4H, CH ₂); 4.12(q, 2H, CH ₂ CH ₃); and 7.26–8.04(m, 8H, ArH's).		
14b	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 1.81(m, 6H, 3CH ₂); 2.43(s, 3H, CH ₃); 2.50(s, 3H, CH ₃); 2.52(t, 4H, CH ₂); 4.12(q, 2H, CH ₂ CH ₃); and 7.26–8.04(m, 8H, ArH's).		
14c	1714,1651(CO's).	1.14(t, 3H, CH ₂ CH ₃); 1.81(m, 2H, CH ₂); 2.43(s, 3H, CH ₃); 2.50(s, 3H, CH ₃); 2.52(t, 4H, CH ₂); 4.12(q, 2H, CH ₂ CH ₃); and 7.26–8.04(m, 12H, ArH's)		
16a	3241(NH); 1720,1676(CO's); 1314,1140(SO ₂).	1.20(t, 3H, CH ₂ CH ₃); 2.27(s, 3H, CH ₃); 2.32(s, 3H, CH ₃); 4.28(q, 2H, CH ₂ CH ₃); 7.03–8.21(m, 14H, ArH's), and 12.38(s, br., 1H, NH).		
16b	3241(NH); 1720,1676(CO's); 1314,1140(SO ₂).	1.18(t, 3H, CH ₂ CH ₃); 2.27(s, 3H, CH ₃); 2.32(s, 3H, CH ₃); 2.40(s, 3H, CH ₃); 4.29(q, 2H, CH ₂ CH ₃); 7.03-8.21(m, 13H, ArH's), and 12.38(s, br., 1H, NH).		
17c	3450(NH); 1735,1659(CO's).	1.22(t, 3H, CH ₂ CH ₃); 2.29(s, 3H, CH ₃); 2.38(s, 3H, CH ₃); 4.11(q, 2H, CH ₂ CH ₃); 7.10–7.58(m, 13H, ArH's), and 8.61(s, br., 1H, NH).		
18	1726,1687(CO's); 1325,1043(SO ₂).	1.08(t, 3H, CH ₂ CH ₃); 2.27(s, 3H, CH ₃); 2.32(s, 3H, CH ₃); 4.12(q, 2H, CH ₂ CH ₃); 5.05(s, 2H, CH ₂); 7.28–7.85(m, 9H, ArH's).		

TABLE II IR and ¹H NMR spectra of some newly synthesized compounds

Synthesis of 2,3-dihydro-1,3,4-thiadiazoles 9b-d, and 14a-c. General Procedure

Triethylamine (0.7 ml, 0.005 mol) was added to a mixture of the appropriate dithiocarbazate **6a-d**, **10a-d**, **12a-c**, **13a-c** (0.005 mol) and hydrazonoyl bromide **1** (2.5g, 5 mol) in ethanol (20 ml), at room temperature with stirring. Stirring was continued for 2h, and the resulting solid was collected, washed with water and crystallized from acetic acid to give **9a-d** and **14a-c**, respectively. The compounds obtained are listed together with physical properties in tables I and II.

Synthesis of 1-benzenesulfonyl-2-[3'-ethoxycarbonyl-5'-methyl-4'-(p-tolyl)pyrazoloyl]ethane-2-one (18)

Equimolar quantities of 4-(2-bromoacetyl)-3-ethoxycarbonyl-5-methyl-1-p-tolylpyrazole¹⁵ and sodium benzenesulfinate (0.05 mol),in ethanol (50 ml) was refluxed 30 minutes. The reaction mixture wascooled, the solid, so formed, was collected and then crystallized from ethanol to give**18**(cf. Tables I and II).

Synthesis 16, 17

Method (A)- To a solution of sodium thiophenolate or sodium benzenesulfinate (0.005 mol) in ethanol (30 ml), a solution of hydrazonoyl bromide 1 (2.5g, 0.005 mol) was added while stirring. The reaction mixture was stirred for 4h. at room temperature. During this period, the material went into solution and new solid precipitated. The latter was collected, washed with water, and crystallized from ethanol to give corresponding 16c (77% yield) and 17 (65% yield), respectively (cf. Tables I and II).

Method (B)- The appropriate diazotized primary aromatic amines (0.01 mol) was added to a cold solution contains **18** (4.2g, 0.01 mol) and sodium acetate trihydrate (1.3g, 0.01 mol) in ethanol (50 ml). The reaction mixture stirred in ice chest for 8h and the resulting residue was collected, washed with water, and then crystallized from ethanol to give **16a-c** in 72–82 yields. Compound prepared by this method is identical in all respects (m.p., mixed m.p. and spectra) with those prepared above.

Oxidation of 17

To a solution of the appropriate sulfides 17 (1g) in glacial acetic acid (10 ml), hydrogen peroxide (7 ml, 30%) was added The reaction mixture was stirred for 48h at room temperature and then poured onto water (50 ml). The crude products were crystallized from ethanol to give 16c in

55% yield. The product prepared by this way proved identical in all respects with that prepared above.

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