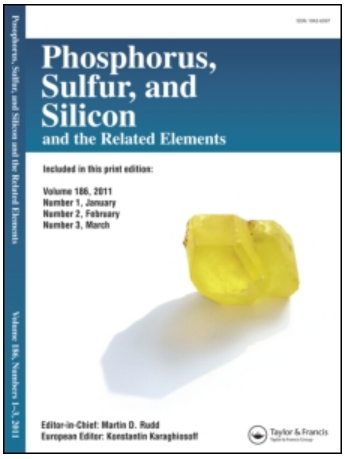

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Reactions with Maleimides XI: 1 Dipolar Cycloaddition Reactions with Thiazolonylarylhydrazones: A New Route for the Synthesis of Several New Thiazolonylpyrazoles of Expected Biological Activities

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REACTIONS WITH MALEIMIDES XI:[1] DIPOLAR CYCLOADDITION REACTIONS WITH THIAZOLONYLARYLHYDRAZONES: A NEW ROUTE FOR THE SYNTHESIS OF SEVERAL NEW THIAZOLONYLPYRAZOLES OF EXPECTED BIOLOGICAL ACTIVITIES

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Several new pyrrolopyrazoles were synthesised via the reaction of thiazolonylarylhydrazones with N-arylmaleimides followed by partial dehydrogenation using bromobenzene and complete aromatization using nitrobenzene. Structures were elucidated by elemental analyses and spectral data studies.

Keywords: Dipolar cycloaddition reactions; N-arylmaleimides; pyrrolopyrazoles; thiazolones

INTRODUCTION

Pyrazoles and annelated pyrazoles have long been known to exhibit diverse biological activities.[1] Among these activities include their use as CAMP phosphodiesterase inhibitors,[2] antipyretic,[3] antitumor,[4] hypnotic,[5] and herbicidal[6] agents. Moreover, thiazoles are also reported to be used in several pharmaceutical and medicinal preparations.[7,8] It was of value to combine the two moieties in a series of derivatives with the objective of investigating their expected biological activities. The reactions of thiazolonylarylhydrazones with N-arylmaleimides seemed to be an easy, logical and unique route for the synthesis of the desired heterocyclic derivatives. This reaction was first reported from this laboratory.[9]

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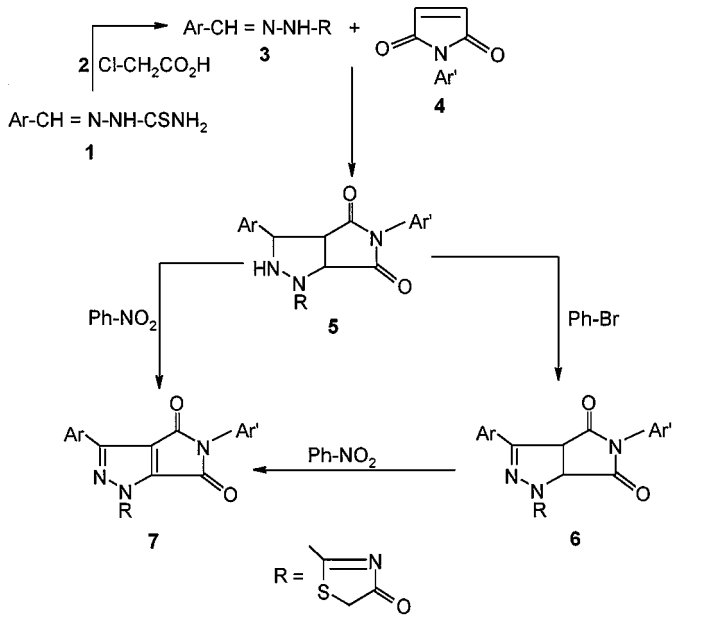
RESULTS AND DISCUSSION

It has been found that the thiosemicarbazones of aromatic aldehydes **1a–1c** reacted with chloroacetic acid (**2**) to give the N-[2-thiazolin-4-on-2-yl)arylhydrazones **3a–3c** which were taken as the starting materials for the present study (Figure 1). Thus, it was found that **3a** reacted with N-phenylmaleimide (**4a**) to yield a reaction product of molecular formula $C_{20}H_{16}N_4O_3S$ resulting from equimolecular addition of **3a** to **4a**. The IR spectrum of this reaction product showed the presence of CO—NAr—CO,[10] NH, a ring-CO, and saturated CH and CH_2 groups. Its ^{1}H NMR spectrum revealed the signals at δ 3.9 (t, pyrrolidine H-3), δ 4.3 (d, pyrrolidine H-4), δ 4.9 (d, pyrazolidine H-3), δ 5.8 (s, thiazolonyl-CH_2), and δ 4.5 (s, br, NH), in addition to aromatic protons at δ 7.1–7.8 (m, 10H). In the light of the above findings, this reaction product was formulated as the 5-thiazolonylpyrrolidino[3,4-d]pyrazolidine-2,6-dione derivative **5a** (cf. Experimental Part).



5-7a, Ar = Ar' = C_6H_5
b, Ar = C_6H_5; Ar' = C_6H_4-Cl-p
c, Ar = C_6H_5; Ar' = C_6H_4-CH_3-p
d, Ar = C_6H_4-Cl-p; Ar' = C_6H_5
e, Ar = Ar' = C_6H_4-Cl-p
5-7f, Ar = C_6H_4-Cl-p; Ar' = C_6H_4-CH_3-p
g, Ar = C_6H_4-OCH_3-p; Ar' = C_6H_5
h, Ar = C_6H_4-OCH_3-p; Ar' = C_6H_4-Cl-p
i, Ar = C_6H_4-OCH_3-p; Ar' = C_6H_4-CH_3-p

FIGURE 1

Analogously, **3a** reacted with N-p-chlorophenylmaleimide (**4b**) and with N-p-methylphenylmaleimide (**4c**) to give the corresponding 5-thiazolonylpyrrolidino[3,4-d]pyrazolidine-2,6-dione derivatives **5b** and **5c** respectively. Structures of **5b**, **5c** were also established based on correct elemental analyses and spectral data (cf. Experimental Part).

On the other hand, the arylhydrazone **3b** cycloadded to each of **4a–4c** to give good yields of the pyrrolidino[3,4-d]pyrazolidine-2,6-dione derivatives **5d–5f** respectively. IR and ^{1}H NMR spectral data, in addition to elemental analysis, were used for establishment of the structure of **5d–5f** as for **5a–5c** respectively cited (cf. Experimental Part).

Moreover, compounds **5g–5i** could also be obtained on cycloaddition of the arylhydrazone derivative **3c** to each of the maleimides **4a–4c**. Again, compounds **5g–5i** were confirmed by elemental analyses and spectral data which were in a good agreement with the assigned structures (cf. Experimental Part).

The course of dehydrogenation of compound **5** was taken as an additional evidence for their assigned structure. Thus, partial dehydrogenation of **5a–5i** using bromobenzene resulted in the formation of products with two hydrogens less than the corresponding startings **5a–5i** in each case. The absorption band of the NH group was entirely absent in the IR spectra of these reaction products. Moreover, their ^{1}H NMR spectra did not reveal neither NH nor pyrazolidine H-3 protons in each case. Based on the above results, these reaction products could be formulated as the 5-thiazolonylpyrrolidino[3,4-d]-Δ^2-pyrazoline-2,6-dione derivatives **6a–6i**, respectively (cf. Experimental Part).

On the other hand, complete dehydrogenation of **6a–6i** was achieved via boiling their solutions in nitrobenzene to give the corresponding 5-thiazolonylpyrrolo[3,4-d]pyrazole-2,6-dione derivatives **7a–7i**, respectively. ^{1}H NMR spectra of **7a–7i** did not reveal any signals of pyrrolidine or pyrazolidine or NH protons, thus supporting the assigned structures. A further proof of the structure of **7a–7i** came from their alternative synthesis via direct dehydrogenation of the corresponding **5a–5i** by boiling their solutions in nitrobenzene. Compounds **7a–7i** prepared via this route were found completely identical with **7a–7i** prepared via the first route (cf. Experimental Part). The biological activity of **5–7** is now being carried out.

EXPERIMENTAL

All melting points were uncorrected. IR (KBr discs) spectra were recorded on Perkin Elmer FT-IR type 4 spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer in

$CDCl_3$ using TMS as an internal standard. Chemical shifts are expressed as δ units. Microanalyses were performed at the Microanalytical center of Cairo University. Compounds **3**[11] and **4**[12] were prepared according to literature procedures.

Synthesis of 5a–5i

A solution of each of **3a–3c** (0.01 mmol) in acetic acid (20 mL) was treated with the appropriate **4a–4c** (0.01 mmol), and the reaction mixture was then heated under reflux for 4 h. Removal of the solvent gave a residue which was crystallized from glacial acetic acid and identified as **5a–5i** respectively (cf. Tables I and II).

TABLE I Characterization Data of the Newly Synthesized Compounds

Comp.	m.p. (°C) (color)	Yield (%)	Molecular formula	% Analysis calcd./found				
				C	H	N	S	Cl
5a	251-2	90	$C_{20}H_{16}N_4O_3S$	61.21	4.11	14.27	8.17	—
	Yellow			61.40	4.30	14.50	8.40	—
5b	253-4	95	$C_{20}H_{15}N_4O_3SCl$	56.27	3.54	13.12	7.51	8.30
	Yellow			56.40	3.60	13.40	7.70	8.50
5c	237-9	97	$C_{21}H_{18}N_4O_3S$	62.05	4.46	13.78	7.89	—
	P. Yellow			62.30	4.70	13.90	7.70	—
5d	293-4	91	$C_{20}H_{15}N_4O_3SCl$	56.27	3.54	13.12	7.51	8.30
	Yellow			56.40	3.70	13.40	7.80	8.20
5e	280-1	89	$C_{20}H_{14}N_4O_3SCl_2$	52.07	3.06	12.14	6.95	15.37
	White			52.20	3.30	12.40	6.80	15.50
5f	268-9	88	$C_{21}H_{17}N_4O_3SCl$	57.20	3.88	12.70	7.27	8.04
	Yellow			57.40	3.70	12.50	7.10	8.20
5g	262-3	93	$C_{21}H_{18}N_4O_4S$	59.71	4.26	13.27	7.58	—
	Yellow			59.90	4.30	13.10	7.40	—
5h	252-3	94	$C_{21}H_{17}N_4O_4SCl$	55.20	3.72	12.26	7.00	7.77
	Yellow			55.40	3.90	12.10	7.20	7.50
5i	298-9	92	$C_{22}H_{20}N_4O_4S$	60.55	4.58	12.84	7.33	—
	Yellow			60.70	4.40	12.60	7.50	—
6a	255-6	90	$C_{20}H_{14}N_4O_3S$	61.52	3.61	14.35	8.21	—
	Yellow			61.70	3.50	14.60	8.00	—
6b	256-7	88	$C_{20}H_{13}N_4O_3SCl$	56.54	3.08	13.18	7.54	8.34
	Yellow			56.70	3.30	13.40	7.20	8.10
6c	244-6	81	$C_{21}H_{16}N_4O_3S$	62.36	3.98	13.85	7.92	—
	Yellow			62.50	3.70	13.60	7.70	—
6d	286-7	87	$C_{20}H_{13}N_4O_3SCl$	56.54	3.08	13.18	7.54	8.34
	Yellow			56.80	3.20	13.20	7.70	8.50
6e	285-6	89	$C_{20}H_{12}N_4O_3SCl_2$	52.30	2.63	12.20	6.98	15.43
	Yellow			52.10	2.40	12.00	6.80	15.30

TABLE I Characterization Data of the Newly Synthesized Compounds *(Continued)*

Comp.	m.p. (°C) (color)	Yield (%)	Molecular formula	% Analysis calcd./found				
				C	H	N	S	Cl
6f	278-9	92	$C_{21}H_{15}N_4O_3SCl$	57.47	3.44	12.76	7.30	8.07
	Yellow			57.70	3.70	12.50	7.10	8.30
6g	264-5	87	$C_{21}H_{16}N_4O_4S$	60.00	3.80	13.33	7.61	—
	Yellow			60.20	4.00	13.20	7.80	—
6h	262-4	92	$C_{21}H_{15}N_4O_4SCl$	55.44	3.30	12.32	7.04	7.81
	Yellow			55.20	3.50	12.20	6.80	8.00
6i	256-7	90	$C_{22}H_{18}N_4O_4S$	60.82	4.14	12.90	7.37	—
	Yellow			61.10	4.30	12.70	7.20	—
7a	296-8	79	$C_{20}H_{12}N_4O_3S$	61.84	3.11	14.42	8.25	—
	Brown			61.60	3.40	14.20	8.40	—
7b	258-6	85	$C_{20}H_{11}N_4O_3SCl$	56.81	2.62	13.25	7.58	8.38
	Brown			56.70	2.80	13.40	7.70	8.20
7c	280-2	79	$C_{21}H_{14}N_4O_3S$	62.67	3.50	13.92	7.96	—
	Brown			62.90	3.20	14.10	7.70	—
7d	>300	75	$C_{20}H_{11}N_4O_3SCl$	56.81	2.62	13.25	7.58	8.38
	Brown			56.60	2.90	13.50	7.40	8.10
7e	>300	80	$C_{20}H_{10}N_4O_3SCl_2$	52.53	2.20	12.25	7.01	15.50
	Brown			52.70	2.50	12.40	7.30	15.20
7f	>300	83	$C_{21}H_{13}N_4O_3SCl$	57.73	3.00	12.82	7.34	8.11
	Brown			57.60	3.30	13.00	6.70	8.40
7g	>300	84	$C_{21}H_{14}N_4O_4S$	60.28	3.34	13.39	7.65	—
	Brown			60.40	3.50	13.20	7.40	—
7h	>300	80	$C_{21}H_{13}N_4O_4SCl$	55.69	2.87	12.37	7.07	7.84
	Brown			55.50	2.70	12.20	7.20	7.70
7i	>300	79	$C_{22}H_{16}N_4O_4S$	61.11	3.70	12.96	7.40	—
	Brown			61.30	3.90	13.10	7.20	—

Partial Dehydrogenation of 5a–5i

A solution of each of **5a–5i** (1.0 g) in bromobenzene (15 mL) was heated under reflux for 3 h. Removal of the solvent left behind a residue which was crystallized from glacial acetic acid and identified as **6a–6i**, respectively (cf. Tables I and II).

Complete Dehydrogenation of 5a–5i or 6a–6i

A solution of each of **5a–5i** or **6a–6i** in nitrobenzene (15 mL) was heated under reflux for 3 h. The solvent was steam-distilled, and the residue obtained was triturated several times with cold ethanol. Crystallization from ethanol gave **7a–7i** respectively (cf. Tables I and II).

TABLE II IR and ^{1}H NMR Data of the Synthesized Compounds

Comp.	IR [KBr, cm^{-1}]	^{1}H NMR [$CDCl_3/\delta$]
5a	3300 (NH); 2980 (sat. CH and CH_2); 1780,1710 (CONArCO) and 1680 (ring-CO)	3.9 (t, 1H, pyrrolidine H-3); 4.3 (d, 1H, pyrrolidine H-4); 4.5 (s, br, 1H, NH); 4.9 (d, 1H, pyrrolidine H-3); 5.8 (s, 2H, thiazolonyl-CH_2) and 7.1–7.8 (m, 10H, ArH'S)
5b	3330 (NH); 2985 (sat. CH and CH_2); 1770,1700 (CONArCO) and 1670 (ring-CO)	
5c	3350 (NH); 2975 (sat. CH and CH_2); 1780,1700 (CONArCO) and 1680 (ring-CO)	1.6 (s, 3H, CH_3); 3.92 (t, 1H, pyrrolidine H-3); 4.25 (d, 1H, pyrrolidine H-4); 4.7 (s, br, 1H, NH); 4.95 (d, 1H, pyrrolidine H-3); 5.9 (s, 2H, thiazolonyl-CH_2) and 7.1–7.7 (m, 9H, ArH'S)
5d	3300 (NH); 2980 (sat. CH and CH_2); 1770,1720 (CONArCO) and 1680 (ring-CO)	
5e	3350 (NH); 2985 (sat. CH and CH_2); 1770,1715 (CONArCO) and 1680 (ring-CO)	
5f	3330 (NH); 2975 (sat. CH and CH_2); 1770,1710 (CONArCO) and 1675 (ring-CO)	
5g	3300 (NH); 2975 (sat. CH and CH_2); 1770,1710 (CONArCO) and 1675 (ring-CO)	3.8 (s, 3H, OCH_3); 3.95 (t, 1H, pyrrolidine H-3); 4.3 (d, 1H, pyrrolidine H-4); 4.85 (s, br, 1H, NH); 5.1 (d, 1H, pyrrolidine H-3); 5.85 (s, 2H, thiazolonyl-CH_2) and 7.1–7.6 (m, 9H, ArH'S).
5h	3350 (NH); 2980 (sat. CH and CH_2); 1770,1710 (CONArCO) and 1680 (ring-CO)	
5i	3330 (NH); 2980 (sat. CH and CH_2); 1780,1715 (CONArCO) and 1680 (ring-CO)	1.59 (s, 3H, CH_3); 3.0 (S, 3H, OCH_3); 3.7 (t, 1H, pyrrolidine H-3); 4.25 (d, 1H, pyrrolidine H-4); 4.82 (s, br, 1H, NH); 4.92 (d, 1H, pyrrolidine H-3); 5.8 (s, 2H, thiazolonyl-CH_2) and 7.1–7.7 (m, 8H, ArH'S)
6a	2980 (sat. CH and CH_2); 1770,1710 (CONArCO) and 1680 (ring-CO)	
6b	2985 (sat. CH and CH_2); 1780,1715 (CONArCO) and 1685 (ring-CO)	
6c	2980 (sat. CH and CH_2); 1770,1700 (CONArCO) and 1670 (ring-CO)	1.6 (s, 3H, CH_3); 3.95 (d, 1H, pyrrolidine H-3); 4.7 (d, 1H, pyrrolidine H-4); 5.8 (s, 2H, thiazolonyl-CH_2) and 7.0–7.7 (m, 9H, ArH'S)

TABLE II IR and ^{1}H NMR Data of the Synthesized Compounds *(Continued)*

Comp.	IR [KBr, cm^{-1}]	^{1}H NMR [$CDCl_3/\delta$]
6d	2985 (sat. CH and CH_2); 1775,1705 (CONArCO) and 1670 (ring-CO)	
6e	2980 (sat. CH and CH_2); 1770,1705 (CONArCO) and 1680 (ring-CO)	
6f	2980 (sat. CH and CH_2); 1770,1710 (CONArCO) and 1675 (ring-CO)	1.55 (s, 3H, CH_3); 3.85 (d, 1H, pyrrolidine H-3); 4.8 (d, 1H, pyrrolidine H-4); 5.82 (s, 2H, thiazolonyl-CH_2) and 7.0–7.7 (m, 8H, ArH'S)
6g	2980 (sat. CH and CH_2); 1780,1710 (CONArCO) and 1680 (ring-CO)	
6h	2985 (sat. CH and CH_2); 1770,1705 (CONArCO) and 1670 (ring-CO)	
6i	2980 (sat. CH and CH_2); 1780,1710 (CONArCO) and 1675 (ring-CO)	
7a	2980 (sat. CH_2); 1770,1710 (CONArCO) and 1680 (ring-CO)	5.8 (s, 2H, thiazolonyl-CH_2) and 7.0–7.6 (m, 10H, ArH's)
7b	2985 (sat. CH_2); 1780,1705 (CONArCO) and 1675 (ring-CO)	
7c	2980 (sat. CH_2); 1770,1710 (CONArCO) and 1685 (ring-CO)	1.62 (s, 3H, CH_3); 5.82 (s, 2H, thiazolonyl-CH_2) and 7.1–7.7 (m, 9H, ArH's)
7d	2985 (sat. CH_2); 1750,1700 (CONArCO) and 1675 (ring-CO)	
7e	2975 (sat. CH_2); 1770,1705 (CONArCO) and 1670 (ring-CO)	
7f	2980 (sat. CH_2); 1775,1710 (CONArCO) and 1675 (ring-CO)	1.58 (s, 3H, CH_3); 5.9 (s, 2H, thiazolonyl-CH_2) and 7.0–7.6 (m, 8H, ArH's)
7g	2985 (sat. CH_2); 1780,1715 (CONArCO) and 1680 (ring-CO)	
7h	2985 (sat. CH_2); 1770,1705 (CONArCO) and 1675 (ring-CO)	
7i	2990 (sat. CH_2); 1770,1705 (CONArCO) and 1680 (ring-CO)	1.52 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 5.9 (s, 2H, thiazolonyl-CH_2) and 6.9–7.7 (m, 8H, ArH's)

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