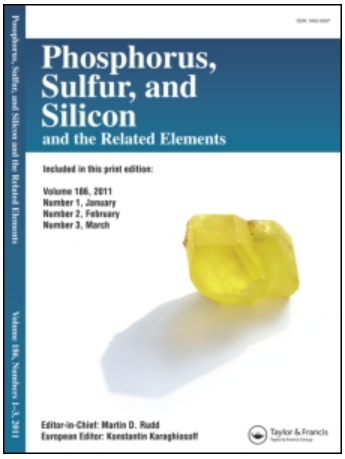

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Dipolar Cycloaddition Reactions with Thiazolonylhydrazones: A New Route for the Synthesis of Several New Thienyl- and Furyl-Thiazolonylpyrrolopyrazole Derivatives of Expected Biological Activities

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DIPOLAR CYCLOADDITION REACTIONS WITH THIAZOLONYLHYDRAZONES: A NEW ROUTE FOR THE SYNTHESIS OF SEVERAL NEW THIENYL- AND FURYL-THIAZOLONYLPYRROLOPYRAZOLE DERIVATIVES OF EXPECTED BIOLOGICAL ACTIVITIES

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Several new pyrrolopyrazoles were synthesized via the reactions of each of 2-thiophenecarboxaldehyde thiazolonylhydrazone or 2-furaldehyde thiazolonylhydrazone with N*-substituted maleimides followed by partial dehydogenation using bromobenzene and complete aromatization using nitrobenzene. Structures were established on the basis of elemental analyses and spectroscopic data studies.*

Keywords: Cycloaddition reactions; furans; *N*-substituted maleimides; pyrrolopyrazoles; thiazolinones; thiophenes

INTRODUCTION

Pyrazoles and their annelated derivatives have been widely investigated for therapeutic uses, especially as antipyretic[1,2] and active CNS regulants;[3,4] they also were reported to have hyptonic[5] and herbicidal[6] activities. Moreover, the thiophene, furan, and thiazolinone moieties also are reported to be used in several pharmaceutical and medicinal preparations.[7–12] In view of these versatile benefits, it was important to

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incorporate these moieties with the pyrazole ring in a series of derivatives. This would allow us obtain some new heterocyclic compounds with expected wide spectrum of potential applications that were extensively required for our medicinal chemistry program.[13–16] The reactions of each of 2-thiophenecarboxaldehyde thiazolonylhydrazone or 2-furaldehyde thiazolonylhydrazone with a variety of *N*-substituted maleimides seemed to be an easy, logical, and unique route for using hydrazones and thiosemicarbazones of certain aldehydes as four-electron three-atomic centers in dipolar cycloaddition reactions to synthesize the desired heterocyclic derivatives.

RESULTS AND DISCUSSION

It has been found that the thiosemicarbazones of 2-thiophenecarboxaldehyde and 2-furaldehyde **1a,b** reacted with chloroacetic acid to give the corresponding hydrazone derivatives **2a,b**, which were taken as the starting materials for the present study. Thus, it has been found that 2-thiophenecarboxaldehyde *N*-(2-thiazolin-4-on-2-yl)hydrazone (**2a**) reacted with *N*-phenylmaleimide (**3a**) to yield a reaction product of molecular formula $C_{18}H_{14}N_4O_3S_2$ resulting from equimolecular addition of **2a** to **3a**. The IR spectrum of this reaction product showed the presence of NH, CO—NR′—CO,[17] ring—CO, and saturated CH and CH_2 groups. Its ^{1}H NMR spectrum (δ ppm) revealed the signals at 3.49 (t, pyrrolidine H-4), 3.71 (s, thiazolonyl—CH_2), 3.98 (d, pyrrolidine H-3), 4.21 (d, pyrazolidine H-3), 4.58 (br, s, NH, D_2O-exchangeable), 6.55–6.92 (m, 3H, thiophene) in addition to aromatic protons 7.16–7.77 (m, 5H, ArHs). In the light of the above findings, this reaction product could be formulated as the 1-phenyl-5-thiazolonyl-3-(2-thienyl)-pyrrolidino[3,4-*c*]pyrazolidin-2,6-dione derivative **4a** (cf. Experimental).

Analogously, **2a** reacted with each of *N*-*p*-chlorophenylmaleimide (**3b**), *N*-*p*-methylphenylmaleimide (**3c**), or *N*-ethylmaleimide (**3d**) to give the corresponding 5-thiazolonyl-3-(2-thienyl)pyrrolidino[3,4-*c*]pyrazolidin-2,6-dione derivatives **4b–d** respectively. Structure of **4b–d** also was established based on correct elemental analyses and spectral data (cf. Experimental).

On the other hand, the 2-furaldehyde *N*-(2-thiazolin-4-on-2-yl)hydrazone (**2b**) cycloadded to each of **3a–d** to give good yields of the pyrrolidino[3,4-*c*]pyrazolidin-2,6-dione derivatives **4e–h** respectively. IR and ^{1}H NMR spectral data in addition to elemental analyses were used to establish the structure of **4e–h** as for **4a–d** previously reported (cf. Experimental).

The course of dehydrogenation of compounds **4a–h** was taken as an additional evidence for their assigned structure.

Thus, partial dehydrogenation of **4a–h** using bromobenzene resulted in the formation of products with two hydrogens less than the corresponding startings **4a–h** 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 NH nor pyrazolidine H-3 protons. Based on the above results, these reaction products could be formulated as the 5-thiazolonylpyrrolidino[3,4-*c*]-Δ^2-pyrazolin-2,6-dione derivatives **5a–h** respectively (cf. Experimental).

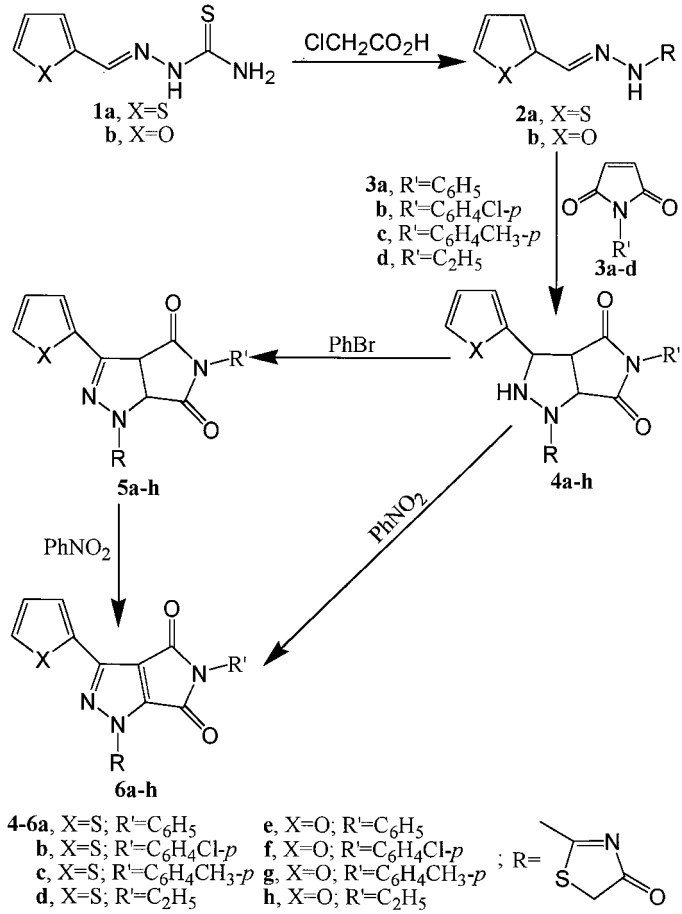

CHART 1

On the other hand, complete dehydrogenation of **5a–h** was achieved via boiling their solutions in nitrobenzene to give the corresponding 5-thiazolonylpyrrolo[3,4-*c*]pyrazol-2,6-dione derivatives **6a–h** respectively. ^{1}H NMR spectra of **6a–h** did not reveal any signals of pyrrolidine or pyrazolidine or NH protons, thus supporting the assigned structure. A further proof for the structure of **6a–h** came from their alternative syntheses via direct dehydrogenation of the corresponding **4a–h** by boiling their solutions in nitrobenzene. Compounds **6a–h** prepared via this route were found completely identical with **6a–h** prepared via the first route (cf. Experimental). The bioresponses of the newly synthesized compounds are now under investigation.

EXPERIMENTAL

All melting points are uncorrected. IR (KBr discs) spectra were recorded on Perkin Elmer FT-IR type 4 spectrophotometer. ^{1}H NMR spectra were recorded on Gemini 200 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Microanalyses were performed at the Microanalytical Center of Cairo University.

Compounds **2a**,[18] **2b**,[19] and **3**[20] were prepared according to literature procedures.

Synthesis of 4a–h

A solution of each of **2a,b** (0.01 mol) in acetic acid (20 ml) was treated with the appropriate **3a–d** (0.01 mol) 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 **4a–h** (cf. Tables I and II).

Partial Dehydrogenation of 4a–h

A solution of each of **4a-h** (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 the proper solvent and identified as **5a-h** respectively (cf. Tables I and II).

Complete Dehydrogenation of 4a–h or 5a–h

A solution of each of **4a–h** or **5a–h** in nitrobenzene (15 ml) was heated under reflux for 3 h. The solvent was evaporated to dryness under

TABLE I Characterization data of the Newly Synthesized Compounds

Comp. No.	m.p. °C Color	Yield (%)	M. Formula (M. wt.)	Calcd./(Found) C	H	N	S	Cl
4a	257–258	90	$C_{18}H_{14}N_4O_3S_2$	54.27	3.52	14.07	16.08	—
	Yellow			(54.4)	(3.6)	(14.2)	(16.1)	—
4b	230–231	85	$C_{18}H_{13}N_4O_3S_2Cl$	49.94	3.01	12.95	14.80	8.21
	Yellow			(50.0)	(3.1)	(13.1)	(14.7)	(8.2)
4c	209–210	87	$C_{19}H_{16}N_4O_3S_2$	55.34	3.88	13.59	15.53	—
	Pale yellow			(55.2)	(3.8)	(13.6)	(15.4)	—
4d	198–199	91	$C_{14}H_{14}N_4O_3S_2$	48.00	4.00	16.00	18.29	—
	Orange			(47.9)	(4.0)	(16.1)	(18.3)	—
4e	247–248	77	$C_{18}H_{14}N_4O_4S$	56.54	3.66	14.66	8.38	—
	Brown			(56.8)	(3.7)	(14.5)	(8.4)	—
4f	221–222	87	$C_{18}H_{13}N_4O_4SCl$	51.86	3.12	13.45	7.68	8.52
	Pale yellow			(52.0)	(3.1)	(13.6)	(7.7)	(8.4)
4g	203–204	93	$C_{19}H_{16}N_4O_4S$	57.58	4.04	14.14	8.08	—
	Pale yellow			(57.7)	(3.9)	(14.0)	(8.1)	—
4h	191–192	84	$C_{14}H_{14}N_4O_4S$	50.30	4.19	16.77	9.58	—
	Yellow			(50.4)	(4.2)	(16.9)	(9.5)	—
5a	251–252	76	$C_{18}H_{12}N_4O_3S_2$	54.55	3.03	14.14	16.16	—
	Pale brown			(54.7)	(3.0)	(14.2)	(16.2)	—
5b	262–263	73	$C_{18}H_{11}N_4O_3S_2Cl$	50.17	2.56	13.01	14.87	8.25
	Pale yellow			(50.4)	(2.6)	(13.2)	(14.7)	(8.2)
5c	283–284	81	$C_{19}H_{14}N_4O_3S_2$	55.61	3.41	13.66	15.61	—
	Yellow			(55.7)	(3.3)	(13.8)	(15.7)	—
5d	215–216	83	$C_{14}H_{12}N_4O_3S_2$	48.28	3.45	16.09	18.39	—
	Yellow			(48.1)	(3.4)	(16.2)	(18.5)	—
5e	236–237	74	$C_{18}H_{12}N_4O_4S$	56.84	3.16	14.74	8.42	—
	Pale brown			(56.8)	(3.3)	(14.6)	(8.5)	—
5f	266–267	82	$C_{18}H_{11}N_4O_4SCl$	52.11	2.65	13.51	7.72	8.56
	Brown			(52.1)	(2.4)	(13.6)	(7.8)	(8.6)
5g	242–243	89	$C_{19}H_{14}N_4O_4S$	57.87	3.55	14.21	8.12	—
	Yellow			(57.7)	(3.6)	(14.3)	(8.1)	—
5h	226–227	78	$C_{14}H_{12}N_4O_4S$	50.60	3.61	16.87	9.64	—
	Yellow			(50.8)	(3.6)	(16.9)	(9.5)	—
6a	>300	80	$C_{18}H_{10}N_4O_3S_2$	54.82	2.54	14.21	16.24	—
	Yellow			(55.0)	(2.4)	(14.2)	(16.4)	—
6b	>300	72	$C_{18}H_9N_4O_3S_2Cl$	50.41	2.10	13.07	14.94	8.28
	Pale yellow			(50.5)	(2.1)	(12.9)	(15.1)	(8.4)
6c	296–297	83	$C_{19}H_{12}N_4O_3S_2$	55.88	2.94	13.73	15.69	—
	Brown			(56.1)	(3.0)	(13.7)	(15.8)	—
6d	274–275	75	$C_{14}H_{10}N_4O_3S_2$	48.55	2.89	16.18	18.50	—
	Brown			(48.5)	(2.9)	(16.0)	(18.6)	—
6e	>300	79	$C_{18}H_{10}N_4O_4S$	57.14	2.65	14.81	8.47	—
	Orange			(57.4)	(2.5)	(14.9)	(8.4)	—
6f	289–290	77	$C_{18}H_9N_4O_4SCl$	52.36	2.18	13.58	7.76	8.61
	Brown			(52.5)	(2.2)	(13.4)	(7.8)	(8.6)
6g	>300	81	$C_{19}H_{12}N_4O_4S$	58.16	3.06	14.29	8.16	—
	Pale brown			(58.1)	(3.1)	(14.3)	(8.3)	—
6h	270–271	78	$C_{14}H_{10}N_4O_4S$	50.91	3.03	16.97	9.70	—
	Brown			(51.2)	(3.0)	(16.8)	(9.8)	—

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

No.	IR (ν cm^{-1})	^{1}H NMR ($CDCl_3/\delta$ ppm)
4a	3340 (NH), 2985 (sat. CH and CH_2), 1780, 1700 (CONR'CO) and 1676 (ring-CO).	3.49 (t, 1H, pyrrolidine H-4), 3.71 (s, 2H, thiazolonyl-CH_2), 3.98 (d, 1H, pyrrolidine H-3), 4.21 (d, 1H, pyrazolidine H-3), 4.58 (br, s, 1H, NH, D_2O-exchangeable), 6.55–6.92 (m, 3H, thiophene) and 7.16–7.77 (m, 5H, ArHs).
4b	3330 (NH), 2980 (sat. CH and CH_2), 1770, 1705 (CONR'CO) and 1670 (ring-CO).	—
4c	3350 (NH), 2976 (sat. CH and CH_2), 1780, 1710 (CONR'CO) and 1680 (ring-CO).	2.26 (s, 3H, CH_3), 3.52 (t, 1H, pyrrolidine H-4), 3.65 (s, 2H, thiazolonyl-CH_2), 3.93 (d, 1H, pyrrolidine H-3), 4.17 (d, 1H, pyrazolidine H-3), 4.70 (br, s, 1H, NH, D_2O-exchangeable), 6.43–6.85 (m, 3H, thiophene) and 7.09–7.75 (m, 4H, ArHs).
4d	3332 (NH), 2980 (sat. CH and CH_2), 1772, 1715 (CONR'CO) and 1680 (ring-CO).	1.15 (t, 3H, CH_3), 3.41 (q, 2H, CH_2), 3.63 (t, 1H, pyrrolidine H-4), 3.74 (s, 2H, thiazolonyl-CH_2), 3.92 (d, 1H, pyrrolidine H-3), 4.15 (d, 1H, pyrazolidine H-3), 4.66 (br, s, 1H, NH, D_2O-exchangeable) and 6.69–7.04 (m, 3H, thiophene).
4e	3350 (NH), 2982 (sat. CH and CH_2), 1770, 1720 (CONR'CO) and 1680 (ring-CO).	—
4f	3330 (NH), 2985 (sat. CH and CH_2), 1780, 1712 (CONR'CO) and 1684 (ring-CO).	—
4g	3344 (NH), 2975 (sat. CH and CH_2), 1770, 1710 (CONR'CO) and 1675 (ring-CO).	2.28 (s, 3H, CH_3), 3.55 (t, 1H, pyrrolidine H-4), 3.71 (s, 2H, thiazolonyl-CH_2), 3.91 (d, 1H, pyrrolidine H-3), 4.16 (d, 1H, pyrazolidine H-3), 4.85 (br, s, 1H, NH, D_2O-exchangeable), 6.02–7.10 (m, 3H, furan) and 7.19–7.80 (m, 4H, ArHs).
4h	3300 (NH), 2980 (sat. CH and CH_2), 1780, 1716 (CONR'CO) and 1680 (ring-CO).	1.15 (t, 3H, CH_3), 3.43 (q, 2H, CH_2), 3.61 (t, 1H, pyrrolidine H-4), 3.75 (s, 2H, thiazolonyl-CH_2), 3.89 (d, 1H, pyrrolidine H-3), 4.20 (d, 1H, pyrazolidine H-3), 4.75 (br, s, 1H, NH, D_2O-exchangeable) and 6.12–7.20 (m, 3H, furan).
5a	2980 (sat. CH and CH_2), 1780, 1710 (CONR'CO) and 1682 (ring-CO).	—
5b	2985 (sat. CH and CH_2), 1775, 1710 (CONR'CO) and 1685 (ring-CO).	3.53 (d, 1H, pyrrolidine H-4), 3.70 (s, 2H, thiazolonyl-CH_2), 3.95 (d, 1H, pyrrolidine H-3), 6.49–6.86 (m, 3H, thiophene) and 7.15–7.70 (m, 4H, ArHs).

(Continued)

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

No.	IR (ν cm^{-1})	^{1}H NMR ($CDCl_3/\delta$ ppm)
5c	2985 (sat. CH and CH_2), 1774, 1705 (CONR'CO) and 1675 (ring-CO).	2.31 (s, 3H, CH_3), 3.53 (d, 1H, pyrrolidine H-4), 3.67 (s, 2H, thiazolonyl-CH_2), 4.00 (d, 1H, pyrrolidine H-3), 6.51–6.88 (m, 3H, thiophene) and 7.09–7.74 (m, 4H, ArHs).
5d	2980 (sat. CH and CH_2), 1776, 1700 (CONR'CO) and 1670 (ring-CO).	—
5e	2985 (sat. CH and CH_2), 1780, 1715 (CONR'CO) and 1686 (ring-CO).	3.50 (d, 1H, pyrrolidine H-4), 3.69 (s, 2H, thiazolonyl-CH_2), 3.88 (d, 1H, pyrrolidine H-3), 6.01–7.11 (m, 3H, furan) and 7.23–7.81 (m, 5H, ArHs).
5f	2975 (sat. CH and CH_2), 1780, 1710 (CONR'CO) and 1680 (ring-CO).	—
5g	2985 (sat. CH and CH_2), 1775, 1708 (CONR'CO) and 1670 (ring-CO).	—
5h	2980 (sat. CH and CH_2), 1780, 1710 (CONR'CO) and 1671 (ring-CO).	1.24 (t, 3H, CH_3), 3.49 (q, 2H, CH_2), 3.55 (d, 1H, pyrrolidine H-4), 3.75 (s, 2H, thiazolonyl-CH_2), 3.93 (d, 1H, pyrrolidine H-3) and 6.13–7.33 (m, 3H, furan).
6a	2980 (sat. CH_2), 1770, 1705 (CONR'CO) and 1680 (ring-CO).	—
6b	2985 (sat. CH_2), 1780, 1705 (CONR'CO) and 1685 (ring-CO).	3.80 (s, 2H, thiazolonyl-CH_2), 6.50–6.88 (m, 3H, thiophene) and 7.05–7.61 (m, 4H, ArHs).
6c	2985 (sat. CH_2), 1772, 1710 (CONR'CO) and 1670 (ring-CO).	—
6d	2985 (sat. CH_2), 1760, 1705 (CONR'CO) and 1675 (ring-CO).	1.31 (t, 3H, CH_3), 3.60 (q, 2H, CH_2), 3.82 (s, 2H, thiazolonyl-CH_2) and 6.63–7.00 (m, 3H, thiophene).
6e	2975 (sat. CH_2), 1770, 1705 (CONR'CO) and 1673 (ring-CO).	—
6f	2980 (sat. CH_2), 1750, 1700 (CONR'CO) and 1675 (ring-CO).	—
6g	2985 (sat. CH_2), 1782, 1714 (CONR'CO) and 1680 (ring-CO).	2.40 (s, 3H, CH_3), 3.75 (s, 2H, thiazolonyl-CH_2), 6.00–7.09 (m, 3H, furan) and 7.18–7.80 (m, 4H, ArHs).
6h	2991 (sat. CH_2), 1770, 1707 (CONR'CO) and 1675 (ring-CO).	1.33 (t, 3H, CH_3), 3.60 (q, 2H, CH_2), 3.82 (s, 2H, thiazolonyl-CH_2) and 6.11–7.32 (m, 3H, furan).

reduced pressure and the residue obtained was triturated several times with cold ethanol. Crystallization from the proper solvent gave **6a–h** respectively (cf. Tables I and II).

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