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UTILITY OF POLYFUNCTIONALLY SUBSTITUTED HETEROCYCLIC COMPOUNDS IN THE SYNTHESIS OF NEW PYRAZOLOPYRIMIDINES AND THEIR ANNELATED DERIVATIVES

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ABSTRACT

3,5-Diamino-4-arylazopyrazole derivatives Ia,b were treated with 1,1-dicyanoprop-1-ene to yield pyrazolo [5,1-b] pyrimidines IIa,b. Compound II was treated with α-substituted cinnamonitriles gave fused pyrazole derivatives IV and V. Thieno compounds VIa, b were obtained via the reaction of II with sulfur. The latter compounds were treated with benzoyl and acetyl isothiocyanates to afford the thiourea derivatives VII and VIII, respectively. Compound VI underwent dipolar cycloaddition reaction with N-phenylmaleimide and acrylonitrile to yield the corresponding fused pyrazole derivatives IX and X, respectively. Nitration and bromination of the thieno compound VI afforded the corresponding nitro and bromo derivatives.All structures were established on the basis of elemental analyses and spectral data.

INTRODUCTION

Pyrazolo [5,1-b] pyrimidine derivatives are biologically interesting and have recently received considerable attention due to their ability to inhibit 3', 5'-cyclic AMP phosphodiesterase and cardiotropic properties[1,2]. Antipyretic, anti-inflammatory and anticancer activities have also been reported for many pyrazolo [5,1-b] pyrimidine derivatives [3,4].

As a part of our research program directed towards the synthesis of potential anti-schistozomal agents [5], we report here the synthesis of new pyrazolo [5,1-b] pyrimidines and their annelated derivatives.

RESULTS AND DISCUSSION

Compounds Ia,b were treated with a-cyanocrotononitrile in pyridine to yield IIa,b. Structure II was suggested for the product on the basis of elemental analysis and spectral data. The IR spectrum of IIa, revealed an absorption band at 2220 cm^{-1} for the cyano group. The ^{1}HNMR spectrum showed a singlet at d 1.7 ppm coresponding to the protons of a methyl group attached to an aromatic system. The reaction is assumed to proceed via Michael addition of the ring nitrogen proton to the double bond of a-cyanocrotononitrile followed by cyclization and spontaneous aromatization to afford the final product [6-8].

Compounds IIa,b were treated with phenyl isothiocyanate to afford the thiourea derivatives IIIa,b. The appearance of absorption bands due to the cyano groups in the IR spectrum of compounds IIIa,b confirmed the formation of acyclic thiourea derivatives. Compounds IIa,b also reacted with a-cyanocinnamonitrile and ethyl a-cyanocinnamate (in ethanol containing a catalytic amount of piperidine) to afford pyrazolo [5,1-b] quinazoline derivatives IVa,b and Va & b, respectively. Structures IV and V were established on the basis of elemental analysis and spectral data. The reaction

is assumed to proceed via Michael addition of the methyl protons to the double bond in a-substituted cinnamonitrile followed by cyclization involving the ortho-cyano group [9].

On the other hand, compounds IIa,b were treated with elemental sulfur (in pyridine) to afford thieno derivatives VIa,b. Structure VI was established on the basis of elemental analysis and spectral data. The IR spectrum of compound VIa showed no absorption due to the cyano group. Also, ^{1}H NMR spectrum of VIa indicated the absence of any signals due to the methyl protons. The formation of the thieno derivatives is assumed to proceed via Gewald reaction [10].

Compounds VIa,b on treatment with benzoyl and acetyl isothiocyanates (in dry acetone) afforded the thiocarbonyl derivatives VII and VIII, respectively.

Compound VIa,b underwent cycloaddition reactions with dipolarophiles such as N-phenylmaleimide and acrylonitrile to afford pyrazolo [5,1-b] quinazoline derivatives. The formation of these derivatives is assumed to proceed via [4+2] cycloaddition followed by aromatization via loss of hydrogen sulfide[6]. Nitration and bromination of compounds VIa,b have takenplace readily to afford compounds XIa,b and XIIa in high yields.

EXPERIMENTAL

All m.ps were determined on a Gallenkamp melting point apparatus. IR spectra (KBr disc) were recorded on a Shemadzu Spectra 200-91506 spectrophotometer. ^{1}H NMR spectra were obtained in DMSO-d_6 on a Varian 90 MHz, and TMS as the internal reference. Elemental analyses were carried out by the Microanalytical Center at Cairo University.

Synthesis of pyrazolo [5,1-b] pyrimidine derivatives IIa,b :

A solution (0.01 mole) of Ia or Ib, in 10 ml pyridine was added to a mixture (0.01 mole each) of malononitrile and acetaldehyde in 25 ml pyridine. The reaction mixture was refluxed for 3 h, allowed to cool and then poured over ice-cold water containing HCl. The so formed solid was collected by filtration, washed with water and crystallized from ethanol to afford compounds IIa,b.

Synthesis of the thiourea derivatives IIIa,b :

A solution of IIa,b (0.01 mole) and phenyl isothiocyanate (0.01 mole), in 20 ml pyridine was refluxed for 3 h, cooled, and then poured over ice-cold water containing HCl. The so formed solid was collected by filtration washed with water and crystallized from dioxane to afford IIIa,b.

Reaction of IIa,b with a-substituted cinnamonitrile derivaties :

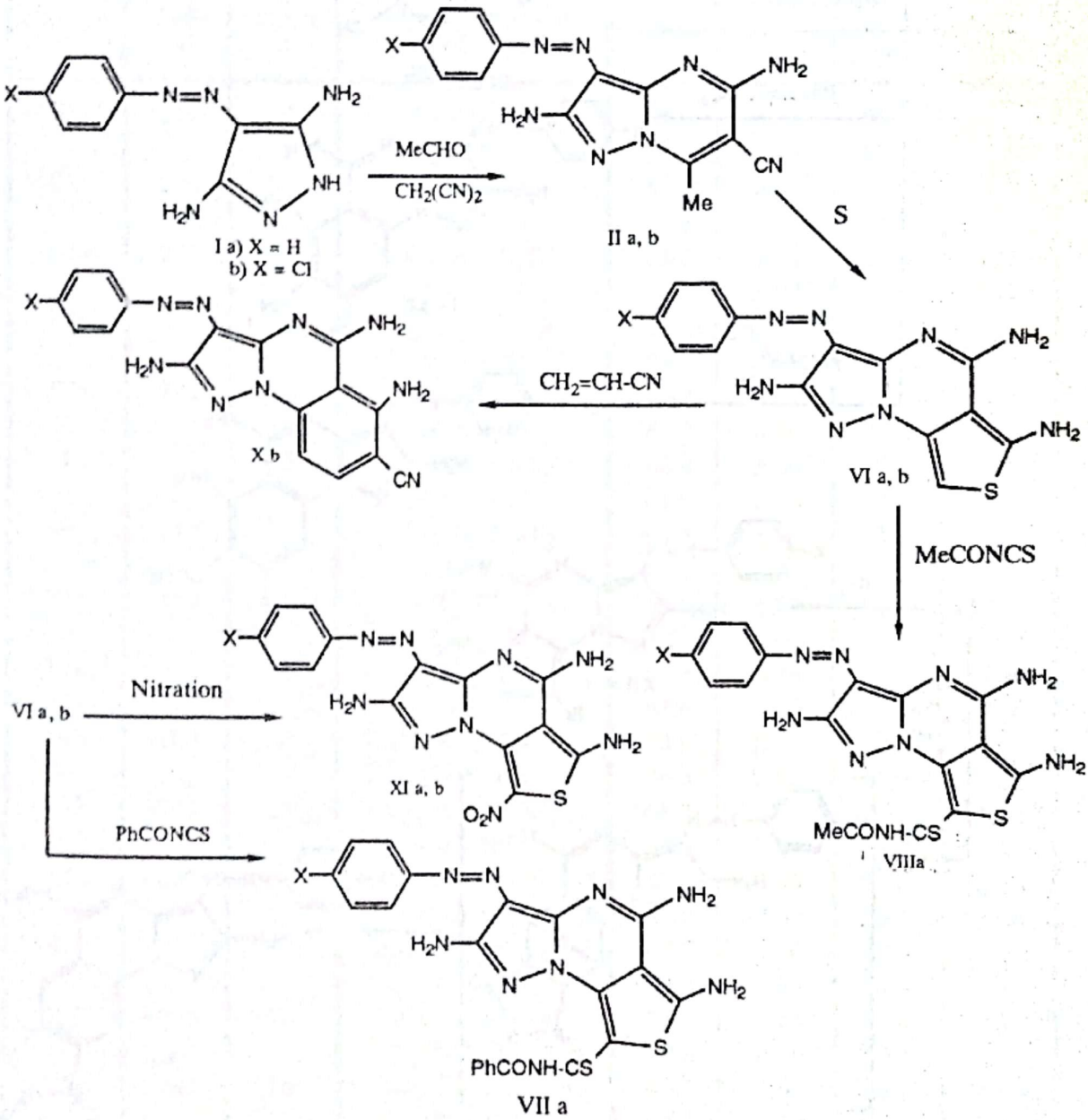
To a solution of IIa,b (0.01 mole) in 25 ml ethanol containing equimolecular amounts of triethylamine, was added the a-cyanocinnamonitrile or a-ethoxycarbonylcinnamonitrile (0.01 mole). The reaction mixture was refluxed for 3 h and allowed to cool. The formed precipitate was collected by filtration and crystallized from ethanol to afford pyrazolo [5,1-b] quinoline derivatives IVa,b and Va & b, respectively.

Synthesis of the thieno-derivative 4 :

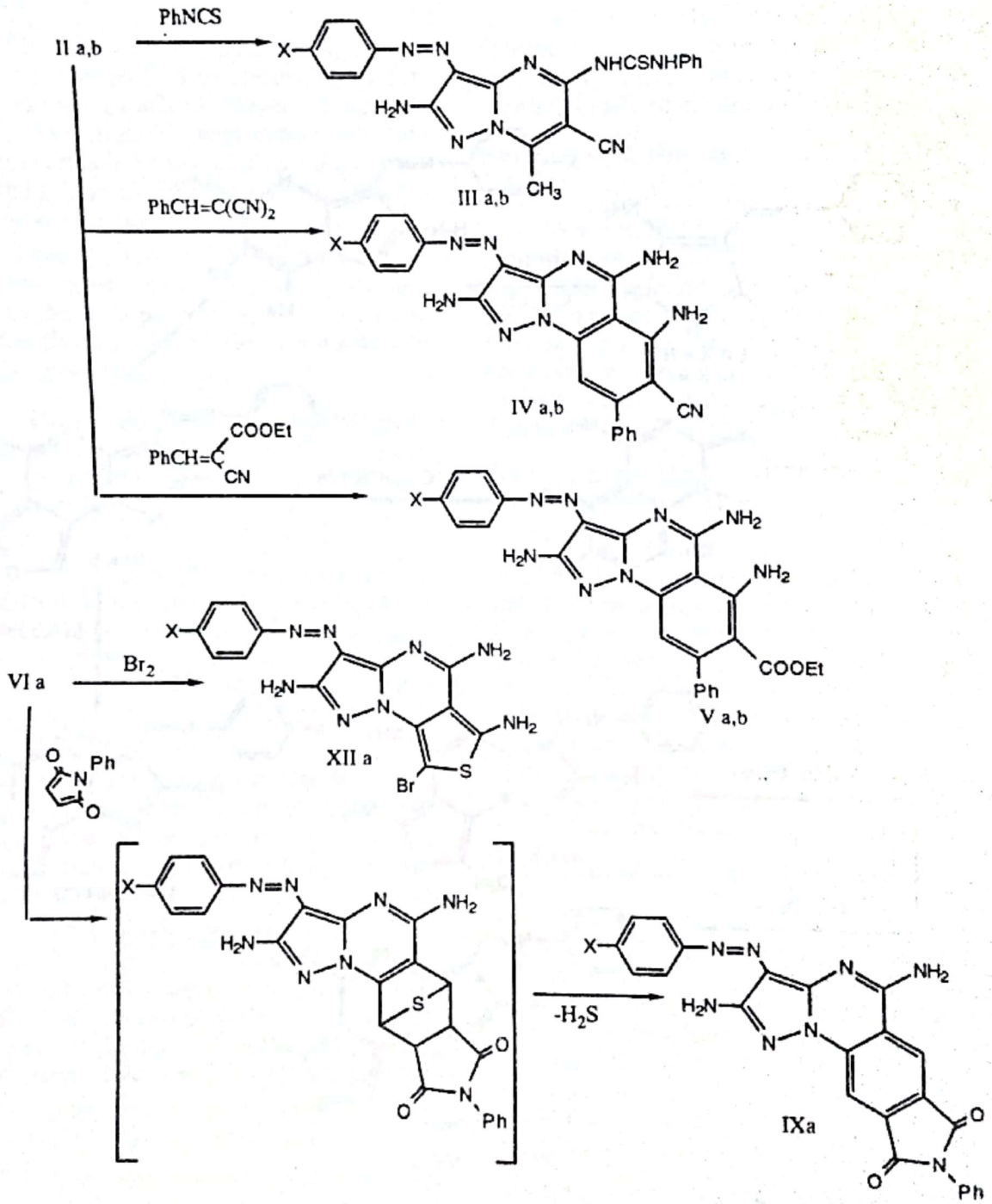
Compounds IIa,b (0.01 mole each) were added to a suspension of 0.01 mole of elemental sulfer in 30 ml pyridine. The reaction mixture was refluxed for 3 h, cooled, poured over ice-cold water and acidified with HCl. The so formed solid was collected by filtration, washed with water and crystallized from ethanol/DMF to afford compounds VIa,b.

Reaction of VIa with benzoyl and acetyl isothiocyanates :

To a solution of VIa (0.01 mole) in 20 ml dry acetone, was added benzoyl or acetyl isothiocyanate (0.01 mole). The reaction mixture was refluxed for 3 h, and allowed to cool. The so formed solid


MeCHO
$CH_2(CN)_2$
I a) X = H
b) X = Cl
II a, b
S
CH_2=CH-CN
X b
VI a, b
MeCONCS
Nitration
VI a, b
XI a, b
PhCONCS
MeCONH-CS
VIIIa
PhCONH-CS
VII a

Scheme 1


PhNCS
II a,b
X
N=N
NHCSNHPh
H_2N
N
CN
CH_3
III a,b
$PhCH=C(CN)_2$
NH_2
IV a,b
Ph
COOEt
$PhCH=C$
CN
V a,b
VI a
Br_2
XII a
Br
S
O
N
Ph
$-H_2S$
IXa

Scheme 2

Table (1): Characterization data for the newly synthesized compounds.

Compd.	m.p. °C	Yield %	Mole. Formula (Mole. Wt.)	Calcd./required			
				C	H	N	S
IIa	210	80	$C_{14}H_{12}N_8$	57.5	4.14	38.3	
			(292.306)	57.3	3.90	38.1	
IIb	235	61	$C_{14}H_{11}ClN_8$	51.4	3.39	34.3	
			(326.351)	51.5	3.20	34.1	
IIIa	255	65	$C_{21}H_{17}N_9S$	59.0	4.01	29.5	7.50
			(427.494)	58.8	3.90	29.2	7.60
IIIb	225	80	$C_{21}H_{16}ClN_9S$	54.6	3.49	27.3	6.94
			(461.939)	54.3	3.30	27.5	7.10
IVa	202	82	$C_{23}H_{17}N_9$	65.9	4.09	30.1	
			(419.452)	65.7	3.80	29.8	
IVb	230	75	$C_{23}H_{16}ClN_9$	60.9	3.55	27.8	
			(453.897)	61.0	3.30	27.6	
Va	142	73	$C_{25}H_{22}N_8O_2$	64.4	4.75	24.0	
			(466.505)	64.2	4.50	23.7	
Vb	168	65	$C_{23}H_{21}ClN_8O_2$	59.9	4.23	22.3	
			(500.950)	60.1	4.00	22.1	
VIa	>300	58	$C_{14}H_{12}N_8S$	51.8	3.73	34.5	9.89
			(324.370)	51.6	3.50	34.2	10.00
VIb	>300	56	$C_{14}H_{11}ClN_8S$	46.9	3.09	31.2	8.90
			(358.815)	46.9	2.80	31.0	9.00
VII	>300	60	$C_{22}H_{17}N_9OS_2$	54.2	3.50	25.9	13.20
			(487.568)	54.0	3.30	26.0	12.80
VIII	>300	65	$C_{17}H_{15}N_9OS_2$	48.0	3.55	29.6	15.10
			(425.497)	47.7	3.30	29.7	14.70
IX	>300	80	$C_{24}H_{16}N_8O_2$	64.3	3.60	25.0	
			(448.446)	64.0	3.60	24.9	
X	>300	70	$C_{17}H_{12}ClN_9$	54.0	3.20	33.4	
			(377.799)	53.9	3.30	33.1	
XIa	>300	75	$C_{14}H_{11}N_9O_2S$	45.5	3.00	34.1	8.62
			(369.367)	45.7	3.10	33.8	8.50
XIb	>300	63	$C_{14}H_{10}ClN_9O_2S$	41.6	2.50	31.2	7.94
			(403.812)	41.5	2.70	31.0	8.10
XIIa	>300	72	$C_{14}H_{11}BrN_8S$	41.7	2.75	27.8	7.95
			(403.271)	41.5	3.00	27.8	7.70

Table (2): IR and ^1H NMR data for compounds listed in Table 1

Compd.	ν max/cm^{-1}	δ values
IIa	3430-3100 (NH_2); 2220 (CN)	1.7 (s, 3H, CH_3); 6.8-8.0 (m, 9H, aromatic and NH_2 protons)
IIIa	3400-3100 (NH, NH_2); 2230 (CN)	
IIIb	3390-3120 (NH, NH_2); 2220 (CN)	
IVa	3500-3180 (NH_2); 2220 (CN)	
IVb	3480-3190 (NH_2); 2210 (CN)	
Va	3500-3100 (NH_2)	1.3 (t, 3H, CH_3); 4.3 (q, 2H, CH_2); 6.7-8.5 (m, 17H, aromatic and NH_2 protons)
VIa	3500-3000 (NH_2)	6.1 (s, 1H, thieno proton); 6.5 (s, 2H, NH_2); 6.9-7.9 (m, 9H, aromatic and NH_2 protons).
VIII	3400-3120 (NH, NH_2)	2.7 (s, 3H, CH_3); 6.4 (s, 2H, NH_2); 7.0-8.1 (m, 9H, aromatic and NH_2 protons); 9.8 (s br, 1H, NH).
IX	3420-3100 (NH_2);1710,1690 (two CO)	
X	3500-3100 (NH_2); 2210 (CN)	
XIa	3500-3200 (NH_2)	6.6 (s br, 2H, NH_2); 6.9-8.0 (m, 9H, aromatic and NH_2 protons)
XIIa	3480-3120 (NH_2)	6.5 (s br, 2H, NH_2); 7.0-7.9 (m, 9H, aromatic and NH_2 protons)

was collected by filtration and crystallized from ethanol to afford compounds VII and VIII, respectively.

Reaction of Va,b with dienophiles :

Each of compounds VIa and VIb (0.01 mole) was added to a solution (0.01 mole each) of N-phenylmaleimide, or acrylonitrile in 20 ml pyridine. The reaction mixtures were refluxed for 3 h, cooled and poured over ice/HCl mixture. The so formed solids were collected by filtration, washed with water and crystallized from ethanol/DMF to afford compounds XI and X, respectively.

Nitration of compounds VIa,b :

Compounds VIa,b were treated with 5 ml of conc. HNO_3 and H_2SO_4 (3:1) at 0°C. The reaction mixture was kept at room temperature for 2 h and then poured onto ice. The solid product was collected by filtration, washed with water and crystallized from dioxane to afford compounds IXa,b.

Bromination of compound VIa :

To a solution of VIa (0.01 mole) in 30 ml chloroform, was gradually added 0.01 mole of bromine in 10 ml chloroform. The reaction mixture was stirred at room temperature for 3 h. The solid product was collected by filtration and crystallized from ethanol/DMF to afford compound XII.

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استخدام المركبات الغير متجانسة عديدة الوظائف فى تخليق مركبات البيرازولوبيريميدين ومشتقاتها الحلقية الجديدة

أحمد حافظ حسين الغندور

قسم الكيمياء - كلية العلوم - جامعة القاهرة - فرع بنى سويف

بمعالجة مشتقات ٣ر٥ - ثنائى أمينو -٤- أريل أزوبيرازول مع ١ر١-ثنائى سيانو -١-بروبين للحصول على بيرازولو [٥ر١-ب] بيراميدين II وكذلك بتفاعل II مع مستبدلات ألفا ساموئيتريل أعطى مشتقات البيرازول الملتحمة IX و X بالتوالى.

وقد تم التأكد من التركيب الكيميائى للمركبات بواسطة التحليل الدقيق للعناصر وتحاليل الطيف النورى المغناطيسى والأشعة تحت الحمراء المختلفة