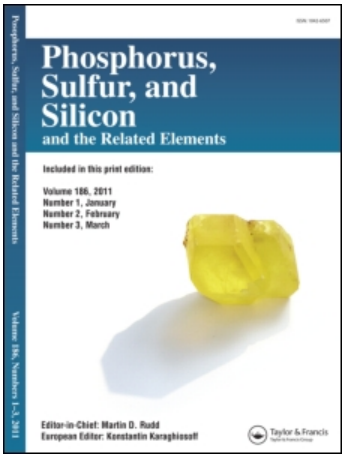

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HETEROCYCLIC SYNTHESIS WITH NITRILES: SYNTHESIS OF SOME NOVEL PYRROLE, PYRROLO[1,2-a]QUINAZOLINE AND PYRROLO[1,2-a]TRIAZINE DERIVATIVES

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HETEROCYCLIC SYNTHESIS WITH NITRILES: SYNTHESIS OF SOME NOVEL PYRROLE, PYRROLO[1,2-a]QUINAZOLINE AND PYRROLO[1,2-a]TRIAZINE DERIVATIVES

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α-(Bromothiocyanatomethyl) benzylidenemalononitrile 1 undergoes base catalysed reactions with primary aromatic amines, anthranilic acid derivatives and urea derivatives in refluxing ethanol to afford N-arylpyrrole-3-carbonitrile, pyrrolo[1,2-a]quinazolin-5-imine, pyrrolo[1,2-a]quinazolin-5-one and pyrrolo[1,2-a]triazine derivatives respectively.

Keywords: α-(bromothiocyanatomethyl) benzylidenemalononitrile; N-arylpyrroles; Pyrrolo[1,2-a]quinazolines; pyrrolo[1,2-a]triazines

Pyrroles and fused pyrrole derivatives have recently received considerable attention due to their synthetic and pharmaceutical importance and different approaches for their synthesis have been developed[1,2]. In the last few years we have reported several syntheses of pyrrole derivatives[3,5] as a part of a program aiming to develop new simple routes for synthesis of functionally substituted heterocycles of anticipated biological activity that can be used as potential biodegradable agrochemicals[4]. In continuation of this work we have recently reported[6] the synthesis and some reactions of α-(bromothiocyanatomethyl) benzylidenemalononitrile 1 (Scheme 1). In the present work we explore the synthetic potentialities of 1 to obtain some novel poly-substituted pyrroles and

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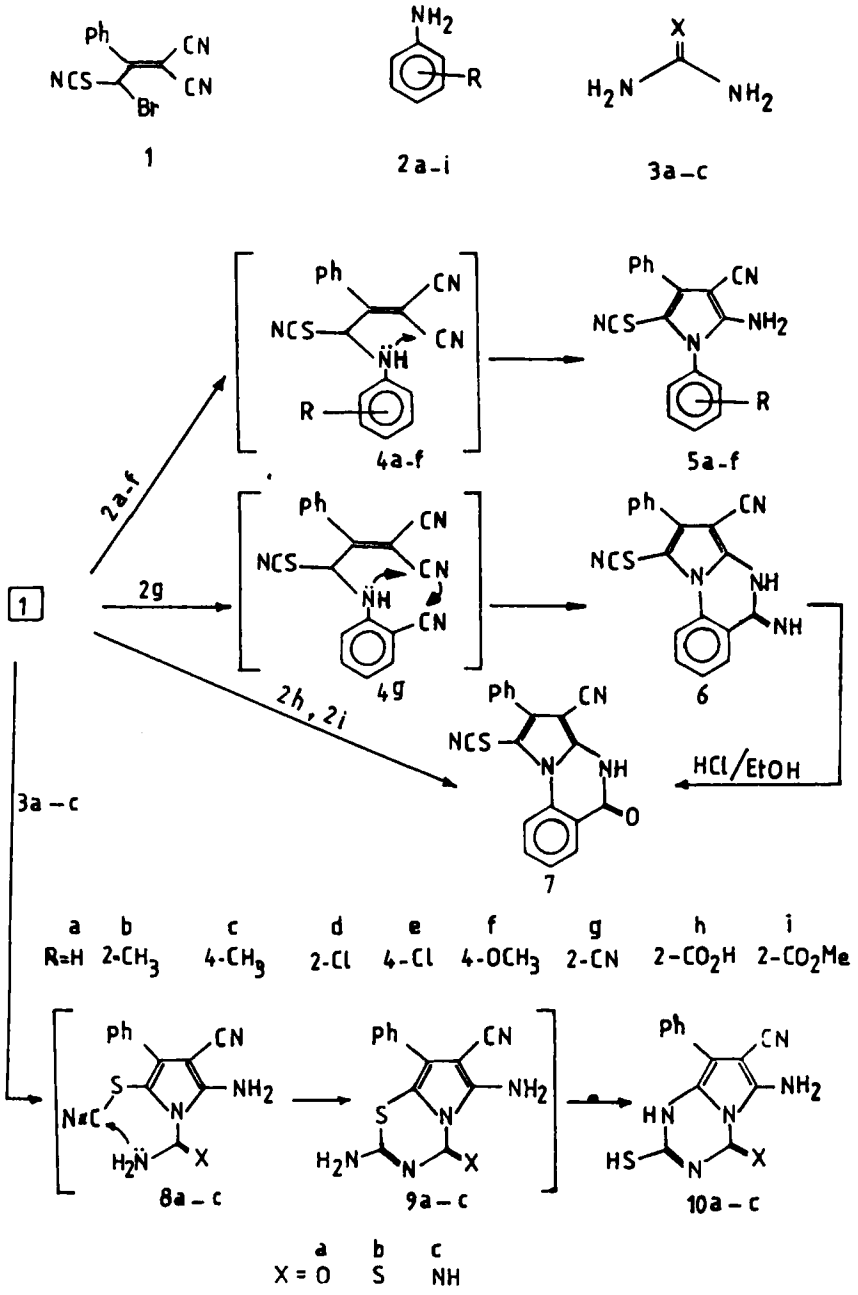

SCHEME 1

pyrrolo-fused heterocycles via the reaction of 1 with aromatic amines 2 and urea derivatives 3.

Thus, compound 1 reacts with the aromatic amines 2a–f in refluxing ethanol catalysed by potassium carbonate to afford coloured solid products. The IR spectra of these products showed in each case, absorption bands at ν 3380-3260, 2205 and 2178 cm^{-1} corresponding to NH_2, CN, and SCN groups respectively. Structures 5a–f were assigned to these products on the basis of the spectral as well as analytical data (Tables I & II). The ^{1}H-NMR spectra of compounds 5a, d, e revealed a broad singlet at δ 5.5 (2H) and a multiplet at δ 7.2–8.1 ppm assignable to NH_2 and aromatic protons while the spectra of 5b, c, f showed in addition a methyl or methoxy singlet at 1.9 or 3.75 ppm respectively. Compounds 5a–f are assumed to be formed from 1 and aromatic amines by elimination of HBr to afford the acyclic intermediates 4a–f which then undergo internal Michael addition of the NH group to one of the CN groups to afford the final isolable products 5a–f. A similar behaviour of bromo derivatives with aromatic amines has been reported[7].

TABLE I Elemental analyses data of the novel compounds

Compd No.	*Yield %*	*mp°C Solvent*	*Mol.F. Mol.Wt.*	*Calcd Found*	*Analysis %*		
					C	*H*	*N*
5a	55	142	$C_{18}H_{12}N_4S$		68.33	3.82	17.71
		EtOH	316.39		68.5	3.6	17.6
5b	49	192	$C_{19}H_{14}N_4S$		69.07	4.27	16.96
		EtOH	330.41		69.0	4.3	17.0
5c	52	197	$C_{19}H_{14}N_4S$		69.07	4.27	16.96
		EtOH	330.41		69.1	4.4	16.9
5d	58	202	$C_{18}H_{11}N_4SCl$		61.62	3.16	15.97
		EtOH	350.83		61.5	3.2	16.1
5e	62	214	$C_{18}H_{11}N_4SCl$		61.62	3.16	15.97
		EtOH	350.83		61.7	3.1	16.0
5f	60	200	$C_{19}H_{14}N_4OS$		65.88	4.07	16.17
		EtOH	346.41		65.8	4.0	16.3
6	60	205	$C_{19}H_{11}N_5S$		66.85	3.25	20.51
		EtOH	341.40		66.5	3.3	21.0
7	63	185	$C_{19}H_{10}N_4OS$		66.65	2.94	16.36
		EtOH	342.38		66.4	3.2	16.7
10a	59	225	$C_{13}H_9N_5OS$		55.11	3.20	24.72
		EtOH/DMF	283.31		55.0	3.3	24.8
10b	58	218	$C_{13}H_9N_5S_2$		52.16	3.03	23.39
		EtOH/DMF	299.38		52.2	3.0	23.7
10c	61	236	$C_{13}H_{10}N_6S$		55.31	3.57	29.77
		EtOH/DMF	282.33		55.6	4.0	30.0

TABLE II IR and ^{1}H-NMR data of the novel compound

Compd. No.	*IR ν cm^{-1} (Selected bands)*	*^{1}H-NMR δ ppm DMSO-d_6/TMS*
5a	3380–3250(NH_2),2205(CN),2178(SCN).	5.5(s,2H,NH_2);7.28–8.0(m,10H,arom.H).
5b	3360–3240(NH_2),2210(CN),2182(SCN).	1.9(s,3H,CH_3);5.4(s,2H,NH_2);7.3–8.0(m,9H,arom.H).
5c	3350–3240(NH_2),2210(CN),2180(SCN).	1.95(s,3H,CH_3);5.43(s,2H,NH_2);7.3–7.9(m,9H,arom.H).
5d	3360–3250(NH_2),2207(CN),2175(SCN).	5.52(s,2H,NH_2);7.3–8.1(m,9H,arom.H).
5e	3370–3255(NH_2),2215(CN),2185(SCN).	5.54(s,2H,NH_2);7.3–8.05(m,9H,arom.H).
5f	3365–3245(NH_2),2205(CN),2175(SCN).	3.75(s,3H,CH_3);5.3(s,2H,NH_2);7.35–7.85(m,9H,arom.H).
6	3430–3320(NH),2220(CN),2180(SCN).	7.2(s,1H,NH);7.3–8.0(m,9H,arom.H);10.2(s,1H,NH).
7	3450–3350(NH),2225(CN),2190(SCN), 1680(CO).	7.3–8.15(m,9H,arom.H);10.35(s,1H,NH).
10a	3430–3250(NH&NH_2),2220(CN),1670(CO).	5.52(s,2H,NH_2);6.4(s,1H,SH);7.3–7.65(m,5H,arom.H);10.2(s,1H,NH).
10b	3440–3240(NH&NH_2),2220(CN).	5.53(s,2H,NH_2);6.3(s,1H,SH);7.28–7.68(m,5H,arom.H);9.8(s,1H,NH).
10c	3450–3245(NH&NH_2),2218(CN).	5.52(s,2H,NH_2);6.25(s,1H,SH);7.3–7.7(m,5H,arom.H);8.1(s,1H,NH); 9.9(s,1H,NH).

Compound 1 reacts with anthranilonitrile 2g in refluxing ethanol in the presence of triethylamine to afford the dihydropyrrolo[1,2-a]quinazolin-5-imine derivative 6 presumably via the acyclic intermediate 4g which is assumed to undergo a double internal Michael addition of the NH group to the neighbouring CN group. The IR spectrum of 6 exhibits absorption bands at ν 3430-3320, 2220 and 2180 cm^{-1} corresponding to NH, CN and SCN groups respectively. The ^{1}H-NMR spectrum of 6 revealed two broad singlets at δ 7.2 and 10.2 ppm besides an aromatic multiplet (9H) at 7.35–7.85 ppm. The elemental analysis is in complete agreement with structure 6 (Tables I&II).

Under similar conditions compound 1 reacts with anthranilic acid 2h or methyl anthranilate 2i to afford the dihydropyrrolo[1,2-a]quinazolin-5-one derivative 7 apparently via loss of water or methanol respectively. The IR spectrum of 7 showed absorption bands at ν 3450-3350, 2225, 2190 and 1680 cm^{-1} which are assignable to NH, CN, SCN and CO groups respectively. The ^{1}H-NMR spectrum of 7 revealed only one singlet (1H) at δ 10.35 ppm besides an aromatic multiplet (9H) at δ 7.3–8.15 ppm. Compound 7 could be obtained quantitatively upon refluxing 6 in ethanolic HCl. The two products were shown to be identical by TLC analysis and an undepressed mixture melting point.

On the other hand, compound 1 reacts with urea 3a, thiourea 3b or guanidine 3c in refluxing ethanol catalysed by triethylamine to afford coloured solid products. Elemental analyses of these species showed the absence of bromine and moreover that they are 1:1 adducts through elimination of HBr. In addition the novel compounds all contain sulphur. The IR spectra did not show absorption bands due to the SCN group at ν 2170–2220 cm^{-1}. Structures 10a–c were thus assigned to these reaction products. The ^{1}H-NMR spectra confirmed these structures. The spectra revealed in all cases a singlet at δ 6.3 ppm assignable to the SH group. In addition the signals expected for such structures were also present (Table II). The formation of compounds 10a–c is assumed to proceed via elimination of HBr and cyclization to afford the intermediate pyrrole derivatives 8a–c which then undergo cyclization by attack of the NH_2 group on the SCN moiety to yield the intermediate pyrrolothiadiazines 9a–c. These latter intermediates rearrange via ring opening and recyclization to afford the final isolable pyrrolotriazine derivatives 10a–c. The rearrangement of 2-amino thiadiazines into mercaptotriazines has been reported earlier[8,9].

Thus, some new polysubstituted pyrroles and pyrrolo-fused heterocycles are now available from cheap and easily obtainable starting materials. The reaction procedures, the separation and purification techniques are rather simple. Further extension of this work is being developed.

EXPERIMENTAL

All melting points are uncorrected and taken on a Gallenkamp melting point apparatus. IR spectra were recorded in KBr pellets on a Pye-Unicam SP-1100 spectrophotometer. ^{1}H-NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer in DMSO-d_6 using TMS as internal standard and expressed in δ ppm. Microanalyses were performed by the Microanalytical Center of Cairo University.

2-Amino-1-aryl-4-phenyl-5-thiocyanatopyrrole-3-carbonitrile derivatives 5a–f: General Procedure

To a solution of α-(bromothiocyanatomethyl)benzylidenemalononitrile 1(3.04g; 0.01 mole) in 30 ml of ethanol was added 0.01 mole of the appropriate primary aromatic amine (2a–f) and stirred until complete solution was observed, when a solution of potassium carbonate was added dropwise (1.38g; 0.01 mole, dissolved in the least amount of water) while stirring. After complete addition the

reaction mixture was refluxed for 2h, left to cool to room temperature, poured on cold water, and neutralized with HCl. The precipitated solids were filtered off, washed with water and recrystallized from the proper solvent (Table I).

The Reaction of 1 with the Anthranilic Acid Derivatives 2g–i

To a solution of 1 (3.04g; 0.01 mole) in 30 ml of ethanol was added 0.01 mole of either of anthranilonitrile 2g, anthranilic acid 2h, or methyl anthranilate 2i and 0.01 mole of triethylamine. The reaction mixture was refluxed for 5–7h(TLC control) and then left to cool overnight. The mixture was then poured on cold water and neutralized with HCl. The respective precipitates were separated by filtration and recrystallized to afford 3-cyano-2-phenyl-1-thiocyanato-4,5-dihydropyrrolo[1,2-a]quinazolin-5-imine 6 and 3-cyano-2-phenyl-1-thiocyanato-4,5-dihydropyrrolo[1,2-a] quinazolin-5-one 7 respectively.

Transformation of 3-cyana-2-phenyl-1-thiocyanato-4,5-dihydropyrrolo[1,2-a]quinazolin-5-imine 6 into 3-cyano-2-phenyl-1-thiocyanato-4,5-dihydropyrrolo[1,2-a]quinazolin-5-one 7

To a solution of 6 (3.41g; 0.01 mole) in 30 ml of ethanol was added 5 ml of concd HCl and refluxed for 1h. After cooling to room temperature the reaction mixture was diluted with cold water and neutralized with ammonia. The precipitate was collected by filtration and recrystallized to afford a product which is identical to 7 in all respects.

The Reaction of 1 with Urea Derivatives 3a–c

To a solution of 1(3.04g; 0.01 mole) in 30 ml of DMF was added 0.01 mole of either urea 3a, thiourea 3b, or guanidine nitrate 3c followed by a catalytic amount of triethylamine (in case of 3a or 3b) or by 0.01 mole of the same reagent in case of 3c. The respective reaction mixtures were refluxed for 3h, left to cool, poured on cold water and neutralized with HCl. The precipitates were filtered off and recrystallized to afford 1-amino-2-cyano-5-mercapto-4,7-dihydropyrrolo[1,2-a]1,3,5-triazine-7-one (thione or imine) 10a–c respectively.

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