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Pyridazine, Oxazine, Pyrrole, and Pyrrolo[1,2-*a*]quinazoline Derivatives from Malononitrile Dimer

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ABSTRACT: *2-Amino-1,1,3-tricyano-3-bromopropene was obtained from bromination of 2-amino-1,1,3-tricyanopropene (malononitrile dimer) with N-bromosuccinimide. This bromo derivative reacts with hydrazine hydrate, phenyl hydrazine, and hydroxylamine hydrochloride to afford pyridazine and oxazine derivatives, respectively. In base-catalyzed reactions with primary aromatic amines and anthranilic acid derivatives, it produces N-aryl pyrrol-3,5-dicarbonitrile and pyrrolo[1,2-*a*]quinazolin-5-imine, or pyrrolo[1,2-*a*]quinazolin-5-one derivatives, respectively. The structures of the newly synthesized heterocycles were established on the basis of elemental analyses and spectral data.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:612–616, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10199

INTRODUCTION

Synthesis of pyrroles and fused pyrroles is known [1,2]. In the last few years we have been involved in a program aiming to develop azoles and their fused derivatives of anticipated activity as biodegradable agrochemicals [3–7]. In the context of this program, some new functionally substituted pyridazines, polysubstituted pyrrole, and pyrrolo-fused derivatives were required. 2-Amino-1,1,3-tricyano-3-bromopropene (**3**) seemed a good candidate to fulfill this objective via its reaction with the hydrazine hydrate, phenyl hydrazine, hydroxylamine hydrochloride, and aromatic amines **10** to produce pyridazines, oxazine, *N*-aryl pyrrole, and pyrrolo[1,2-*a*]quinazoline derivatives. This prompted us to investigate the reaction of 2-amino-1,1,3-tricyanopropene (**1**) [8,9] with bromine, aiming to obtain the monosubstituted product **3**. An aqueous suspension of 1 mol of **1** reacted readily with 2 mol of bromine to yield the substitution product 2-amino-1,1,3-tricyano-3,3-dibromopropene (**2**) (Scheme 1, Table 1), the same behavior of **1** with bromine has been reported [8]. The desired product **3** could be obtained by treating **1** with *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) at room temperature in 68% yield (Scheme 1, Tables 1 and 2).

The ^{1}H NMR spectrum of **3** showed a singlet for NH_2 at $\delta = 4.20$ and two singlets at $\delta = 4.82$ and 4.92 ppm which integrated for 1H. The appearance of two singlets for this proton may be explained by the presence of two geometrical isomers. It can be suggested that the bromination took place on the methylene group of **1** to produce **3a**, which is tautomeric to **3b** via the ion pair **3c**. Mass spectral measurements, ^{13}C NMR, and analytical data are in complete agreement with the substitution product **3** (Tables 1 and 2).

Compound **3** has been utilized in a number of transformations. For example, the reaction of compound **3** with hydrazine hydrate, phenyl hydrazine,

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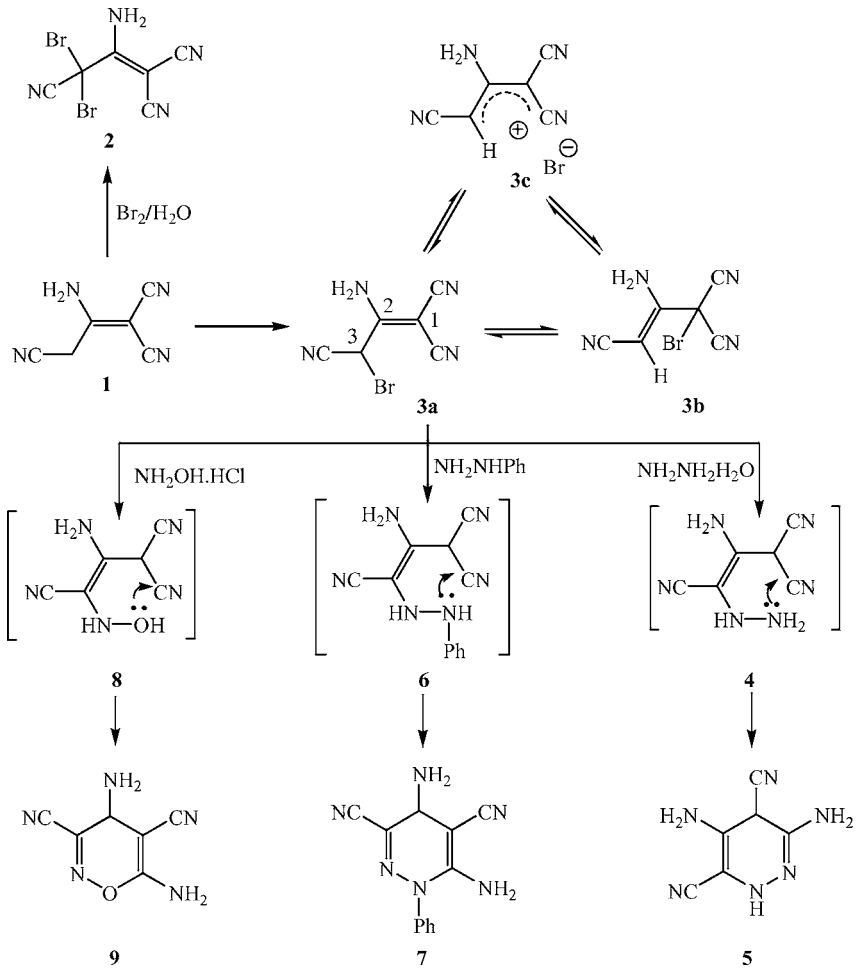


SCHEME 1

and hydroxylamine hydrochloride afforded solid products for which structures **5, 7**, and **9**, respectively, were assigned (Scheme 1) on the basis of analytical and spectral data (Tables 1 and 2). Their formation is assumed to proceed via the acyclic intermediates **4, 6**, and **8**, respectively [10].

Compound **3** was also found to be useful for the synthesis of pyrrole and pyrrolo-fused derivatives. Thus, **3** reacts with the aromatic amines **10a–d** (aniline, *p*-anisidine, *p*-toluidine, and *p*-chloroaniline, respectively) in refluxing ethanol catalyzed by potassium carbonate to afford solid products **12a–d**. The

TABLE 1 Physical and Analytical Data of the Newly Prepared Compounds

	mp (°C) (Solvent)	*Yield (%)*	*Mol. Formula (Mol. Wt.)*	*m/e*	*Analysis: Calcd. (Found) (%)*			
					C	*H*	*N*	*X*
2	152–154 (Aq. EtOH)	85	$C_6H_2Br_2N_4$ (289.92)		24.86 (24.90)	0.70 (0.90)	19.33 (19.50)	55.12 (55.20)
3	125–127 (EtOH)	68	$C_6H_3BrN_4$ (211.02)	210, 212	34.15 (34.10)	1.43 (1.50)	26.55 (26.50)	37.87 (38.00)
5	190–192 (EtOH)	70	$C_6H_6N_6$ (162.15)		44.44 (44.60)	3.73 (3.80)	51.83 (52.00)	
7	225–227 (EtOH/DMF)	75	$C_{12}H_{10}N_6$ (238.25)	238	60.50 (60.70)	4.23 (4.30)	35.27 (35.20)	
9	159–161 (EtOH)	62	$C_6H_5N_5O$ (163.14)	163	44.17 (44.10)	3.09 (3.20)	42.93 (43.10)	
12a	162 (EtOH)	60	$C_{12}H_9N_5$ (223.23)	223	64.56 (64.70)	4.06 (4.10)	31.37 (31.30)	
12b	204 (EtOH)	65	$C_{13}H_{11}N_5O$ (253.26)	253	61.65 (61.60)	4.38 (4.40)	27.65 (27.50)	
12c	215 (EtOH)	58	$C_{13}H_{11}N_5$ (237.26)		65.81 (65.90)	4.67 (4.70)	29.52 (29.40)	
12d	232 (EtOH/DMF)	60	$C_{12}H_8ClN_5$ (257.68)		55.93 (56.10)	3.13 (3.00)	27.18 (27.30)	13.76 (13.70)
13	228 (EtOH/DMF)	59	$C_{13}H_8N_6$ (248.24)	248	62.90 (63.10)	3.25 (3.10)	33.85 (33.90)	
14	202 (EtOH)	64	$C_{13}H_7N_5O$ (249.23)		62.65 (62.60)	2.85 (3.00)	28.10 (28.00)	

TABLE 2 IR, ^{1}H, and ^{13}C NMR Data of the Newly Prepared Compounds

	IR (cm^{-1})	*^{1}H, ^{13}C NMR (DMSO-d_6)*
3	3430–3250 (NH_2), 2220, 2205, 2195 (CN)	4.20 (s, 2H, NH_2, D_2O-exchangeable), 4.82, 4.92 (2s, 1H) δC; 34.44 (C-3), 115.24, 116.45, 117.11 (CN), 135.45 (C-1), 159.28 (C-2)
5	3540–3290 (NH, NH_2), 2220, 2215 (CN)	2.95 (s, 2H, NH_2), 4.10 (s, 1H, H-5), 4.47 (s, 2H, NH_2) 7.81–8.05 (b, 1H, NH)
7	3450–3200 (NH_2), 2220, 2210 (CN)	2.70 (s, 2H, NH_2, D_2O-exchangeable), 4.30 (s, 2H, NH_2, D_2O-exchangeable), 7.01–7.32 (m, 6H, Ar–H, H-4)
9	3400–3200 (NH_2), 2222, 2212 (CN)	3.10 (s, 2H, NH_2), 4.70 (s, 2H, NH_2), 5.20 (s, 1H, H-4)
12a	3390–3210 (NH_2), 2220, 2205 (CN)	2.90 (s, 2H, NH_2, D_2O-exchangeable), 4.75 (s, 2H, NH_2, D_2O-exchangeable), 7.15–7.84 (m, 5H, Ar–H)
12b	3380–3250 (NH_2), 2215, 2205 (CN)	3.12 (s, 2H, NH_2, D_2O-exchangeable), 3.75 (s, 3H, OCH_3), 4.55 (s, 2H, NH_2, D_2O-exchangeable), 7.15–7.75 (m, 4H, Ar–H) δC; 54.83 (OCH_3), 115.92, 117.07 (CN), 118.25, 122.05, 131.48, 145.59 (C-arom), 129.22 (C-3), 134.66 (C-4), 144.76 (C-2), 150.34 (C-5)
12c	3350–3240 (NH_2), 2222, 2206 (CN)	3.25 (s, 2H, NH_2, D_2O-exchangeable), 2.38 (s, 3H, CH_3), 4.85 (s, 2H, NH_2, D_2O-exchangeable), 7.18–7.65 (m, 4H, Ar–H)
12d	3380–3260 (NH_2), 2215, 2205 (CN)	3.18 (s, 2H, NH_2, D_2O-exchangeable), 4.40 (s, 2H, NH_2, D_2O-exchangeable), 7.20–7.55 (m, 4H, Ar–H)
13	3445–3185 (NH, NH_2), 2225, 2210 (CN)	4.45 (s, 2H, NH_2), 7.10 (s, 1H, NH), 7.25–7.68 (m, 4H, Ar–H), 9.88 (s, 1H, NH)
14	3460–3240 (NH, NH_2), 2225, 2207 (CN), 1685 (CO)	4.65 (s, 2H, NH_2), 7.35–8.10 (m, 4H, Ar–H), 10.15 (s, 1H, NH) δC; 116.10, 118.25 (CN), 120.60 (C-9), 125.95 (C-7), 126.38 (C-5a), 127.34 (C-6), 129.65 (C-2), 133.20 (C-8), 135.75 (C-3), 140.05 (C-9a), 145.45 (C-1), 153.12 (C-3a), 168.48 (C-5)

IR spectra showed in each case, absorptions at 3390–3210, 2220, and 2205 cm^{-1} attributed to NH_2 and CN groups, respectively (Tables 1 and 2). The ^{1}H NMR spectra of compounds **12a–d** showed two broad D_2O-exchangeable NH_2 proton singlets at $\delta = 2.90$–4.75 ppm and a multiplet at $\delta = 7.15$–7.84 ppm for the aromatic protons. **12a–d** are assumed to be formed via elimination of HBr to afford the intermediates **11a–d**, followed by cyclization to afford the final products **12a–d** (Scheme 2). A similar behavior of bromo derivatives with aromatic amines has been reported [11,12].

Compound **3** reacts with anthranilonitrile **10e** in refluxing ethanol in the presence of triethylamine to afford the dihydropyrrolo[1,2-*a*]quinazolin-5-imine **13** presumably via the acyclic intermediate **11e**, which is assumed to undergo an addition of NH group to CN group (Tables 1 and 2). Under similar reaction conditions, compound **3** reacts with anthranilic acid (**10f**) or methyl anthranilate (**10g**) to produce the dihydropyrrolo[1,2-*a*]quinazolin-5-one **14** apparently via loss of water or methanol respectively. ^{13}C NMR data agree with structure **14** (Table 2). Compound **14** could be obtained quantitatively from **13** upon refluxing the latter in ethanolic HCl. TLC matched the two products and no depression of melting point was obtained on admixture with **14** prepared by the present method [4,5].

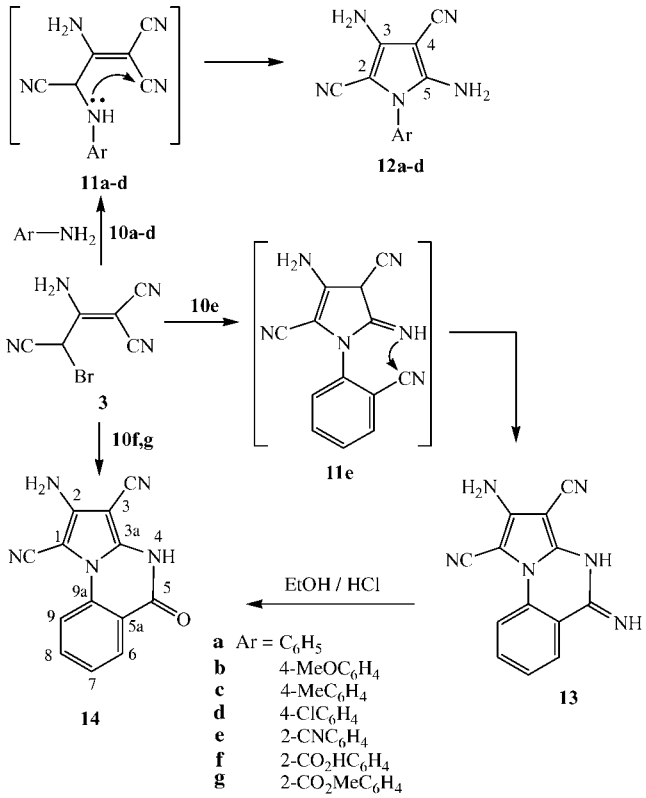
In summary, we have demonstrated the simple routes for the synthesis of new polysubstituted pyridazines, oxazines, pyrroles, and pyrrolo-fused heterocycles from easily obtainable starting materials. Research along this direction is in progress.

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a Perkin-Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a VXR 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out by the Microanalytical Center at Cairo University. 2-Amino-1,1,3-tricycanopropene (**1**) was prepared as described [8,9].

*2-Amino-1,1,3-tricyano-3,3-dibromopropene (**2**)*

To a suspension of 6.6 g (0.05 mol) of **1** in 75 ml of water was added slowly 16 g (5.15 ml; 0.1 mol) of bromine with shaking. The solid was collected by filtration, washed with water, and dried. The yield was 85% (12.32 g); crystallization from EtOH–water; mp 152–154°C [lit. 155°C] [8].



SCHEME 2

*2-Amino-1,1,3-tricyano-3-bromopropene (**3**)*

To a solution of 13.2 g of **1** (0.1 mol) in 75 ml of dry DMF was added 17.8 g (0.1 mol) of NBS. The reaction mixture was stirred for 24 h at room temperature. The mixture was then poured on ice-cold water and acidified with a few drops of HCl, whereupon a precipitate appeared, which was filtered off and recrystallized from ethanol to afford **3** (14.35 g, 68%).

*4,6-Diamino-2,5-dihydropyridazine-3,5-dicarbonitrile (**5**)*

To a solution of 2.11 g (0.01 mol) of **3** in 25 ml of ethanol was added an excess of hydrazine hydrate (~2 ml), and the reaction mixture was refluxed for 3 h, after which it was left overnight. The solid precipitate was filtered off and crystallized from EtOH (1.14 g, 70%).

*4,6-Diamino-1-phenyl-1,4-dihydropyridazine-3,5-dicarbonitrile (**7**)*

A mixture of 2.11 g (0.01 mol) of **3** and 1.08 g (0.01 mol) of phenyl hydrazine in 30 ml of ethanol was refluxed for 3 h, whereupon a solid precipitate appeared. The reaction mixture was allowed to cool to room temperature and was then filtered. The solid product obtained was recrystallized from DMF/EtOH (2:1) (1.79 g, 75%).

*4,6-Diamino-4H-1,2-oxazine-3,5-dicarbonitrile (**9**)*

To a mixture of 2.11 g (0.01 mol) of **3** and 0.7 g (0.01 mol) of hydroxylamine hydrochloride in 30 ml of ethanol was added a solution of potassium carbonate (2.76 g; 0.02 mol in a minimum amount of water), and the reaction mixture was refluxed for 3 h. The mixture was left to cool to room temperature, and then poured on crushed ice and neutralized with HCl. The precipitate was filtered off and crystallized from EtOH (1.00 g, 62%).

*3,5-Diamino-1-aryl-1H-pyrrole-2,4-dicarbonitriles (**12a–d**): General Procedure*

To a solution of 2.11 g (0.01 mol) of **3** in 30 ml of ethanol was added 0.01 mol of the appropriate primary aromatic amines **10a–d**. The mixture was stirred until a complete solution was observed, and then a solution of potassium carbonate was added dropwise (1.38 g; 0.01 mol, dissolved in the least amount of water) while stirring. After complete addition the reaction mixture was refluxed for 2 h, left to cool to room temperature, poured on ice-cold water, and neutralized by HCl. The precipitated solids were filtered off, washed with water, and recrystallized from the proper solvent (Table 1).

*The Reaction of **3** with the Anthranilic Acid Derivatives **10e–g***

To a solution of 2.11 g (0.01 mol) of **3** in 30 ml of ethanol was added 0.01 mol of either anthranilonitrile (**10e**), anthranilic acid (**10f**), or methyl anthranilate (**10g**), and 0.01 mol of triethylamine. The reaction mixture was refluxed for 4–6 h (TLC control) and then left to cool overnight. The respective precipitates were filtered off, and recrystallized to afford 2-amino-1,3-dicyano-4,5-dihydro pyrrolo[1,2-*a*]quinazolin-5-imine (**13**, 1.46 g, 59%) and 2-amino-1,3-dicyano-4,5-dihydropyrrolo[1,2-*a*]quinazolin-5-one (**14**, 1.60 g, 64%), respectively.

*Transformation of **13** into **14***

To a solution of 2.48 g (0.01 mol) of **13** in 30 ml of ethanol was added 5 ml of concentrated HCl and the mixture was refluxed for 1 h. After cooling to room temperature the reaction mixture was diluted with cold water and neutralized with ammonia. The

precipitate was collected by filtration and crystallized to afford a product, which was identical to **14** in all respects.

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