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Synthesis of New Pyrazolo[1,5-*a*]-s-triazine, Pyrazolo[5,1-*c*]-as-triazines, Pyrazolo[1′,5′:1,2]imidazo[4,5-*b*]quinoxaline, and Pyrazolo[1,5-*a*]pyrimidines

M. A. Zahran,[a] *A. A. Hassanien,*[b] *H. A. Emam,*[a] *M. Z. El-Said,*[c] *and Y. A. Ammar*[a,*]

[a]*Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt*

[b]*Chemistry Department, Faculty of Education, Suez Canal University, Al-Arish, Egypt*

[c]*National Research Center, Dokki, Cairo, Egypt*

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Novel pyrazolo[1,5-*a*]-s-triazine, pyrazolo[1,5-*c*]-as-triazine, pyrazolo[1′,5′:1,2]imidazo[4,5-*b*]quinoxaline and pyrazolo[1,5-*a*]pyrimidines have been prepared using 5-aminopyrazoles as starting materials.

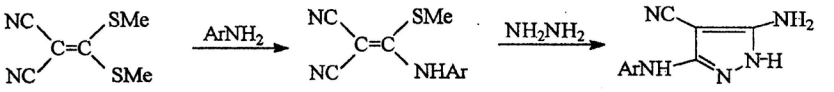
INTRODUCTION

Polyfunctionally substituted heterocyclic compounds are biologically interesting molecules and their synthesis has recently received considerable attention.[1–4] In continuation of our interest in the synthesis of condensed pyrazolo derivatives,[5,6] we report here a variety of synthetic routes to pyrazolo[1,5-*a*]-s-triazines, pyrazolo[5,1-*c*]-as-triazines, pyrazolo[1′,5′:1,2]imidazo-[4,5-*b*]quinoxaline and pyrazolo[1,5-*a*]pyrimidines. This work has led to some procedures for the synthesis of heterocyclic systems from 5-aminopyrazoles in good yields and under milder conditions.

* Author to whom correspondence should be addressed.

RESULTS AND DISCUSSION

The starting materials, 5-amino-2-(3-arylamino)pyrazole-4-carbonitrile **3a,b**, were synthesized by the reaction of hydrazine with [arylamino(methylsulfanyl)methylidene]malononitriles **2a,b** [prepared *via* the displacement reaction of [bis(methylsulfanyl)methylidine]malononitrile **1** with aromatic amines] (Scheme 1).

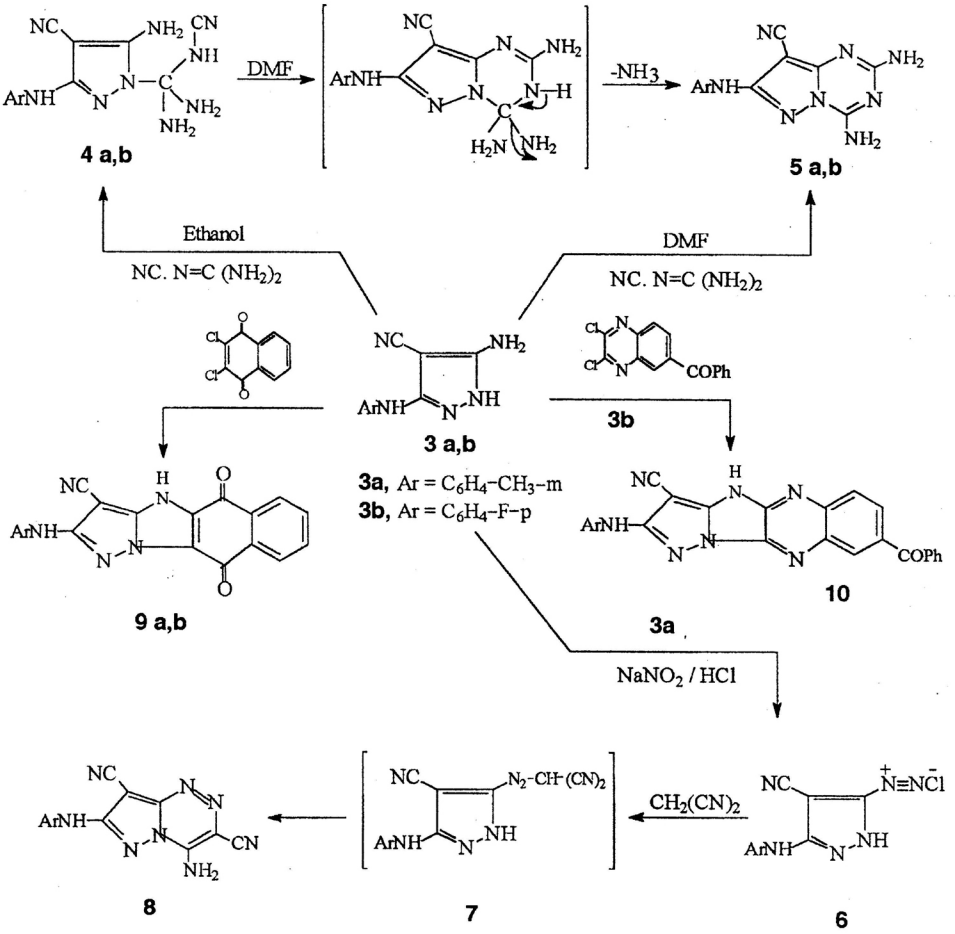


1 **2a**, Ar = C_6H_4–CH_3-m; **2b**, Ar = C_6H_4–F-p **3 a,b**

Scheme 1.

Now we wish to describe the cyclocondesation of 5-aminopyrazole **3a,b** with different reagents. It has been reported that 5-aminopyrazoles condensed with dicyandiamide to give 2,4-diaminopyrazolo-[1,4-*a*]-1,3,5-triazines. It has been found that the product of 5-aminopyrazoles **3a,b** with dicyandiamide depends on the applied reaction conditions. Thus, the interaction of 5-aminopyrazoles **3a,b** with dicyandiamide (cyanoguanidine) in ethanol yielded a product for which structure **4a,b** was suggested based on analytical and spectral data, while refluxing **3a,b** with dicyandiamide in DMF affected cyclization to give pyrazolo[1,5-*a*]-s-triazines **5a,b**, which was supported by spectral data and independent synthesis of the same product through refluxing of **3a,b** in DMF (Scheme 2). We assumed that **3a,b** was added to dicyandiamide to give **4a,b**, which cyclized in DMF and aromatized with elimination of NH_3 to yield **5a,b**. Compound **3a** was also diazotized to give the diazonium chloride **6** which underwent coupling with malononitrile to furnish the corresponding pyrazolo-5-yl hydrazine **7** as intermediate, which spontaneously cyclized to give the pyrazolo[5,1-*c*]-as-triazine derivative **8**.

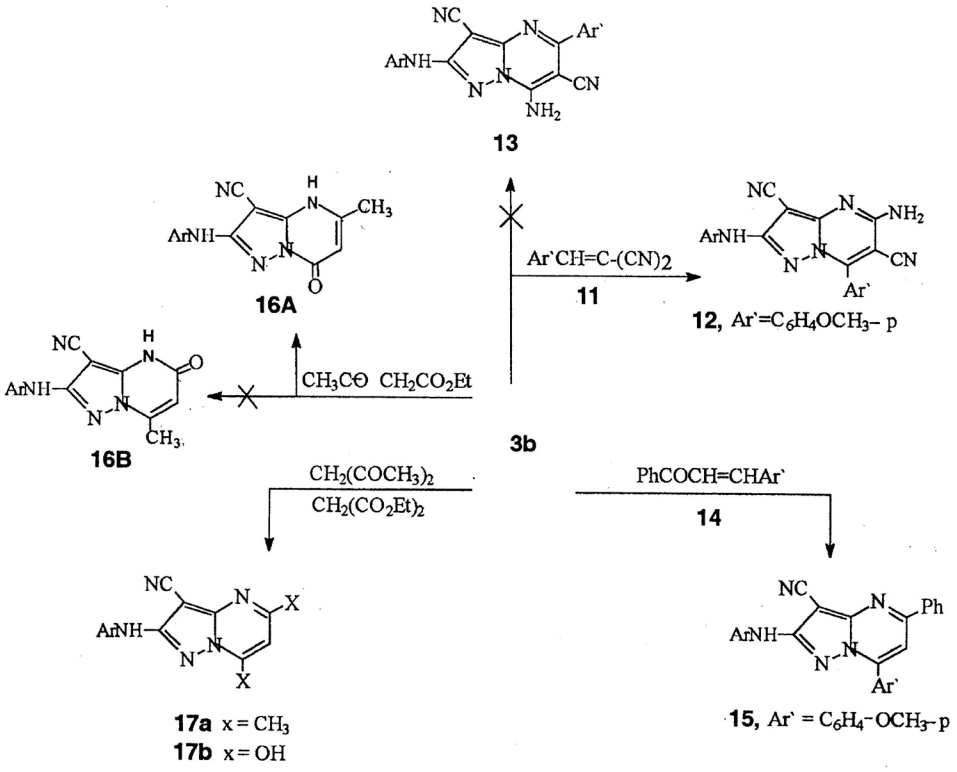
As an extension of this synthetic route, the behaviour of **3a,b** towards dichlorinated compounds was investigated. Thus, condensation of **3a,b** with 2,3-dichloronaphthoquinone led to a doubly fused compound and gave naphthoimidazopyrazole **9a,b** through elimination of two molecules of HCl. Similarly, condensation of **3b** with 6-benzoyl-2,3-dichloroquinoxaline produced pyrazolo[1′,5′:1,2]imidazo[4,5-*b*]quinoxaline **10** (Scheme 2). Also, we report here the synthesis of some fluorinated compounds containing pyrazolo[1,5-*a*]pyrimidines. It has been found that compound **3b** reacts with *p*-methoxybenzylidenemalononitrile **11** to yield a product with the molecular formula $C_{21}H_{14}N_7OF$ at *m*/*z* 399 (M^+ 100%). Two isomeric structures **12** and



Scheme 2.

13 are considered. Structure **12** appears more likely than **13** since the ring nitrogen is the most nucleophilic center in the molecule. Based on the analogy to the behaviour of 5-aminopyrazole towards acrylonitrile and cyanocinnamonitriles,[7] the ^{1}H-NMR spectrum indicates clearly that the two ortho protons of the *p*-anisyl group appear in the lower field (7.9–8.4 ppm). If this product was **13**, the aromatic protons should appear in the higher field. The formation of **12** is assumed to proceed *via* addition of the ring nitrogen to the double bond, followed by intramolecular cyclization, which then aromatizes to the final isolable product **12** as 5-amino-7-(4-methoxyphenyl)-3,6-dicyano-2-(4-fluoroanilino)pyrazolo[1,5-*a*]pyrimidine **12**.

In a similar manner, compound **3b** reacted with chalcone **14** to produce 3-cyano-5,7-diaryl-2-(4-fluoroanilino)pyrazolo[1,5-*a*]pyrimidine **15**. Mass spectrum of **15** gave *m*/*z* 435 (M^+, 100%), ^{1}H-NMR indicates that the aromatic protons including pyrimidinyl H-5 appear in the lower field of 7.8–8.5 ppm, as previously stated. The formation of **15** is assumed to proceed *via* an initial addition, which undergoes intramolecular cyclocondensation followed by aromatization. Furthermore, condensation of **3b** with ethyl acetoacetate in acetic acid caused cyclization *via* water and ethanol elimination to give 5-methyl-7-oxo-2-(4-fluoroanilino(-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **16A**. Structure **16A** was proposed on the basis of analytical data. If this product was the other possible isomer **16B**, the methyl group next to the bridgehead nitrogen atom shoud appear as a doublet, and the adjacent proton as a quartet in ^{1}H-NMR spectrum. Also, reaction of **3b** with acetylacetone or diethyl malonate produced the pyrazolo[1,5-*a*]pyrimidine derivatives **17a,b**, respectively (Scheme 3).



Scheme 3.

EXPERIMENTAL

Mps are uncorrected. Elemental analyses were carried out in the microanalytical laboratories of the Faculty of Science, Cairo University. IR spectra (KBr) were measured on a Shimadzu IR 440 spectrophotometer, ^{1}H-NMR spectra on a JEOL FX 90 Q (90 Mhz) spectrophotometer and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer using the direct-inlet system. 5-Amino-2-(4- fluoroanilino)pyrazolo-4-carbonitrile **36** was prepared according to the reported method.[4]

*Formation of **4a,b***

A suspension of **3a,b** (0.01 mol) and dicyandiamide (0.01 mol) in ethanol (20 ml) was refluxed for 4 h. The obtained product was recrystallized from ethanol to give **4a,b** (65–70%) **4a** *m/z*: 297 (M^+, 13%) 283 (10.0), 213 (6.2), 168 (13.4), 149 (51.8) 129 (19.5) and 84 (100).

*5,7-Diamino-2-(3-tolylamino or 4-fluoroanilino) pyrazolo [1,5-a]-s-triazine-3-carbonitriles **5a,b***

A mixture of **3a,b** (0.01 mol) and dicyandiamide (0.01 mol) in DMF (20 ml) was refluxed for 4 h. The obtained solid was recrystallized from DMF to give **5a,b** (67–70%) (Table I); ν_{max}/cm^{-1}: 3490, 3430, 3360, 3100 (NH_2-NH), 2208 (CN); **5a** *m/z:* 280 (M^+, 100%), 257 (40.0), 198 (12.0), 170 (3.0), 155 (2.5), 91 (40.0).

*7-Amino-2-(3-tolylamino)pyrazolo [5,1-c]-as-triazine-3,6 dicarbonitrile **8***

To a solution of malonitrile (0.01 mol) in ethanol (40 ml) and sod. acetate (2 g), diazonium chloride **6** (0.01 mol) [prepared from 0.01 mol of **3a** and nitrous acid 0.01

TABLE I

Characterization data for newly synthesized compounds

Comp. no.	m.p. (*T*/°C)	Formula	Found (Required) / %	
			C	H
3b	220	$C_{10}H_8N_5F$	55.60 (55.30)	3.40 (3.68)
4a	197	$C_{13}H_{15}N_9$	52.10 (52.52)	5.40 (5.05)
4b	240	$C_{12}H_{12}N_9F$	48.20 (47.84)	4.10 (3.99)
5a	>300	$C_{13}H_{12}N_8$	55.70 (55.71)	4.30 (4.28)
5b	>300	$C_{12}H_9N_8F$	50.60 (50.70)	3.00 (3.16)
8	>300	$C_{14}H_{10}N_8$	57.70 (57.95)	3.40 (3.44)
9a	165	$C_{21}H_{13}N_5O_2$	68.50 (68.66)	3.50 (3.54)
9b	155	$C_{20}H_{10}N_5O_2F$	64.70 (64.96)	2.80 (2.70)
10	355	$C_{25}H_{14}N_7OF$	67.00 (67.11)	3.40 (3.13)
12	>300	$C_{21}H_{14}N_7OF$	63.30 (63.16)	3.20 (3.51)
15	290	$C_{26}H_{18}N_5OF$	71.50 (71.72)	4.30 (4.14)
16A	300	$C_{14}H_{10}N_5OF$	59.60 (59.36)	3.70 (3.53)
17a	270	$C_{15}H_{12}N_5F$	64.30 (64.06)	4.10 (4.27)
17b	252	$C_{13}H_8N_5O_2F$	54.90 (53.74)	2.60 (2.81)

mol at 0 °C] was added under stirring. The solid product obtained on standing was collected by filteration and washed several times with water and recrystallized from ethanol to give **8** (75%) (Table I); *m/z*: 290 (M^+, 79.8%) 289 (100), 261 (4.0), 237 (4.8), 213 (1.2), 197 (7.2), 157 (2.3), 131 (2.2), 106 (5.3), 89 (5.4).

*Condensation of **3a,b** with 2,3-dichloronaphthoquinone and 6-benzoyl-2,3-dichloroquinoxaline*

A mixture of **3a,b** (0.01 mol) and 2,3-dichloronaphthoquinone or 6-benzoyl-2,3-dichloroquinoxaline (0.01 mol) in DMF (20 ml) was refluxed for 4 h, the obtained product was recrystallized from ethanol to give **9a,b**, **10** (70–75%) (Table I).

9a ν_{max}/cm^{-1}: 300, (NH) 2205 (CN), 1670, 1640 (CO); *m/z* 353 [M^+ (367)-CH_3 (15)],[8] 298 (2.3), 235 (100), 222 (31.4), 206 (16.8), 186 (10.6), 158 (16.9), 129 (29.9), 102 (26.0),

9b *m/z*: 371 (M^+, 2.6.%), 373 (M+2, 19.46%), 345 (3.76), 329 (11.84), 303 (6.99), 271 (7.15), 229 (4.59), 217 (100), 212 (15.52), 188 (11.31), 161 (10.08), 122 (6.59), 66 (5.7) and **10** *m/z*: 447 (M^+, 15.3%), 435 (7.35), 416 (6.2), 370 (35.18), 358 (22.15), 320 (85.21), 293 (100), 278 (32.07), 264 (66.09), 223 (10.32), 187 (13.37), 145 (10.16), 105 (21.57), 77 (26.11).

*Pyrazolo [1,5-a] pyramidines **12** and **15***

A mixture of **3b** (0.01 mol), cinnamonitrile **11** or chalcone **14** (0.01 mol) and piperidine (1 ml) in ethanol (30 ml) was refluxed for 4 h. The solvent was then evaporated and the obtained product was recrystallized from ethanol to give **12** and **15** (75–80%) (Table I).

12 ^{1}H-NMR (DMSO-d_6) δ/ppm: 4.2 (3H, s, OCH_3) 6.3 (2H, s. NH_2; cancelled with D_2O), 7.0–7.8, 7.9–8.8 (8H, m, Ar-H), 9.2 (1H, s, NH) cancelled with D_2O); *m/z*: 400 (M+1, 25%), 399 (M^+, 100), 398 (12.9), 373 (5.2), 356 (4.8), 329 (2.5), 291 (2.4), 250 (1.8), 225 (4.9), 200 (10.0), 183 (4.2), 157 (3.4), 134 (3.8), 114 (6.7), 95 (9.6).

15 ^{1}H-NMR (DMSO-d_6) δ/ppm: 4.1 (3H, s, OCH_3) 6.8-7.7, 7.8–8.6 (9H, m, 8H-Ar + 1H pyrimidinyl-6) & 9.4 ppm (1H, s, NH; cancelled with D_2O); *m/z*: 435 (M^+, 100%), 392 (1.26), 330 (7.26), 303 (2.65), 247 (5.44), 200 (4.43), 145 (2.19), 102 (1.68), 77 (4.14).

*5-Methyl-7-oxo-2-(4-fluoroanilino)-4,7-dihydropyrazolo[1,5-a] pyrimidine-3-carbonitrile **16A** and 5,7-dimethyl **17a** and 5,7-dihydroxy-2-(4-fluoroanilino)-pyrazolo[1,5-a]pyrimidine-3-carbonitrile **17b***

To a solution of **3b** (0.01 mol in acetic acid (20 ml), ethyl acetoacetate, acetylacetone or diethyl malonate (0.01 mol) was added. The solution was refluxed for 3 h. and the obtained product was recrystallized from ethanol to give **16A** or **17a,b** (70–75%) (Table I).

16A: IR ν_{max}/cm^{-1}: 3200 (NH), 2200 (CN) and 1650 (CO); ^{1}H-NMR (DMSO-d_6) δ/ppm: 2.4 (3H, s, CH_3), 6.8 (1H, s, CH), 7.4–8.0 (4H, AB system Ar-H) 8.8, 9.5 (2H, 2s, 2NH); *m/z* 284: (M+1, 26.5%), 283 (100), 254 (15.64), 240 (6.19), 203 (3.21), 187 (6.86), 160 (2.63), 134 (3.62), 95 (2.7).

17a δ_H: [$(CD_3)_2$ CO] 2.6, 2.8 (6H, s, 2s CH_3), 7.0 (1H, s, CH) 7.5–7.8 (4H, AB system Ar-H) 9.8 (1H, s, NH).

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SAŽETAK

Sinteza novih pirazolo[1,5-*a*]-2-triazina, pirazolo[5,1-*c*]-a-triazina, pirazolo[1′,5′:1,2]imidazo[4,5-*b*]kinoksalina, i pirazolo[1,5-*a*]pirimidina

M. A. Zahran, A. A. Hassanien, H. A. Emam, M. Z. El-Said i Y. A. Ammar

Polazeći of 5-aminopirazola priređeni su novi pirazolo[1,5-*a*]-s-triazin, pirazolo-[5,1-*c*]-s-triazini, pirazolo[1′,5′:1,2]imidazo[4,5-*b*]kinoksalin i pirazolo[1,5-*a*]pirimidini.