Sci. J. Fac. Sci. Monoufia Univ. Vol. VIII (1994). 153-162

SYNTHESIS OF FUSED PYRAZOLO-[3,4-b]-PYRIDINE HETEROCYCLIC COMPOUNDS.

A.F. Khattab, S.M. Yassin, I.A. El-Sakka* and Farag El-Essawy

Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

ABSTRACT

*The aminopyrazolopyridine derivative **1** reacted with phenacyl bromide, chloroacetyl chloride and oxalyl chloride to give the tricyclic derivatives **2, 3a** and **4**, respectively. The reaction of diazotized **1** with 1-phenyl-3-methylpyrazol-5-one gave the corresponding hydrazone **6**. On the other hand **1** condensed with triethylorthoformate or urethane to afford the ylidenes **7** and **8**, respectively. The structure of **8** was confirmed through its reaction with malononitryl, ethyl cyanoacetate or hydrazine hydrate to give the tricyclic derivatives **10, 11** and **12**, respectively.*

INTRODUCTION

Pyrazoles are interesting compounds due to their high biological activities, for example, they have analgesic, antiinflammatory and antipyretic effects, moreover, in recent years, fused pyrazole derivatives have shown potential biological activities[1-3]. 5-(1H)-Aminopyrazole has also been known to react with bifunctional reagents to yield pyrazolopyrimidine derivatives[4-7].

* For correspondence.

DISCUSSION

In the present work, it was found that interaction of the aminopyrazolopyridine derivative **1** with active methylene reagents, namely, phenacyl bromide, chloroacetyl chloride and oxalyl chloride gave the tricyclic compounds **2, 3a** and **4**, respectively. The structure of compounds **2-4** was confirmed by their correct elemental and spectral analyses. Thus, the IR spectrum of **2** showed a band at 3270 cm^{-1} for (NH). The MS spectrum showed the molecular ion peak at m/z 262 (M^+, 75). The IR spectrum of **3a** showed a band at 3190 cm^{-1} for (NH) and 1750 cm^{-1} for (C=O). Structure **3b** was excluded since amide CO must appear at 1650-1690 cm^{-1}. The MS spectrum of compound **3a** showed the molecular ion peak at m/z 238 (M^+, 70). The IR spectrum of **4** showed a band at 3320 cm for (NH): two bands in the region of 1740-1720 cm^{-1} for (CO-CO).

On the other hand, it has been found that diazotization of **1** in presence of concentrated nitric acid afforded the diazonium salt **5**. This coupled with 1-phenyl-3-methyl-5-pyrazolone in presence of sodium acetate to give the corresponding hydrazone **6** in a good yield. The structure of **6** was elucidated by correct elemental and spectral analyses. Thus, the IR spectrum of **6** showed a band at 3150 cm^{-1} for *(NH) and 1700 cm^{-1} for (C=O).* The ^{1}H-NMR *spectrum in* DMSO showed signals at δ = 2.4, 2.63, 2.8 (3s, 9H $3CH_3$), 6.85 (s, 1H C-5), 7.35 (m, 5H Ph), 7.43 (s, 1H NH), 7.99 (s, 1H NH). The MS spectrum showed the molecular ion peak at m/z 347 (M^+, 100).

On the other hand **1** condensed with triethylorthoformate to afford **7**. The structure of **7** was confirmed by the correct elemental and spectral analyses. The IR spectrum of **7** showed a band at 3130 cm^{-1}

for (NH). The MS spectrum showed the fragment peak at m/z 173 ($M^+ - OC_2H_5$, 6).

Compound **1** condensed also with urethane to give **8** and not **9**. The structure **9** was excluded based on elemental and spectral analyses. Thus, the IR spectrum of **8** showed a band at 3250-3200 cm^{-1} for (NH_2 and NH). The MS spectrum showed the fragment peak at 190 ($M^+ - CH_2=C-\overset{+}{O}H$, 60). ^{13}C-NMR spectrum in DMSO showed signals at 14.65, 16.39, 24.04, 60.14 and 111.98 (aliphatic carbons), 123.09, 125.95, 139.44, 142.39, 155.18 and 160.84 (aromatic carbons).

A further support for the given structure of **8** was obtained when compound **8** was allowed to interact with active methylene compounds such as malononitrile and ethyl cyanoacetate to give the corresponding tricyclic compounds **10** and **11**, respectively. Similarly **8** reacted with hydrazine hydrate to give **12**. The structure of **10-12** was confirmed by the correct elemental and spectral analyses. Thus, the IR spectrum of **10** showed bands at 3300-3250 cm^{-1} for (NH_2) and 2220 cm^{-1} for (C≡N). The MS spectrum showed the molecular ion peak at m/z 253 (M^+, 60). The IR spectrum of **11** showed a band at 3400-3220 cm^{-1} for (NH_2, NH), 1640 cm^{-1} for (C=O) and 2225 cm^{-1} for (C≡N). The IR spectrum of **12** showed a band at 3350-3300 cm^{-1} for (NH_2, NH). The MS spectrum showed the molecular ion peak at m/z 202 (M^+, 1).

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on Perkin Elmer 1720 FT and Pye-Unicam sp-1000 spectrophotometer. The ^{1}H-NMR spectra were measured on a Bruker AC 250 FT and a Varian EM 360/390 NMR spectrometer using TMS as internal

standard and chemical shifts were expressed as ppm. The ^{13}C-NMR spectra were recorded on a Bruker AC. The microanalyses were performed by the microanalytical unit at Cairo University.

6,8-Dimethyl-3-phenyl-1H-imidazolo-[2,3-b]-pyrazolo-[3'-4'-b] pyridine 2:

To a suspension of **1** (1.6 g; 0.01 mol) in 10 ml ethanol, phenacyl bromide (2.1 g; 0.01 mol) and 2-3 drops of piperidine were added. The reaction mixture was heated under reflux for 24 h. The solid product, formed upon partial evaporation was collected by filtration and crystallized from the proper solvent (cf. Table 1).

6,8-Dimethyl-1H-imidazolo-[2,3-b]-pyrazolo-[3',4'-b]-pyridine-3-one hydrochloride 3a:

To a stirred suspension of **1** (1.6 g; 0.01 mol) in 10 ml dry benzene, chloroacetyl chloride (1.1 g; 0.01 mol) was added dropwise at room temperature. Stirring was continued for 48 h. The formed solid product was collected by filtration and crystallized from the proper solvent (cf. Table 1).

6,8-Dimethyl-1H-imidazolo-[2,3-b]-pyrazolo-[3'-4'-b]-pyridine-2,3-dione hydrochloride 4:

The same experimental procedure described for the synthesis of **3a** was carried out except for the use of oxalyl chloride instead of chloracetyl chloride and time of stirring was reduced to 24 h.

4,6-Dimethyl-3-[4,5-dihydro-3-methyl-5-oxo-1-phenylpyrazolo-4-yl)-azo]-1H-pyrazolo-[3,4-b]-pyridine 6:

To a solution of 1-phenyl-3-methyl-5-pyrazolone (1.7 g; 0.01 mol) in ethanol (30 ml) containing sodium acetate (1.5 g; 0.01 mol), the diazonium salt **5** [prepared by adding sodium nitrite solution (0.7 g; 0.01 mol) to a cold mixture of **1** (1.6 g; 0.01 mol) in 70% nitric acid (3 ml)] was added with continuous stirring. The reaction mixture was kept at 0°C with stirring until precipitation was completed (about 3 h). The solid product, so formed, was collected by filtration and crystallized from the proper solvent (cf. Table 1).

4,6-Dimethyl-3-(ethoxylideneamino)-1H-pyrazolo-[3,4-b]-pyridine 7:

A mixture of **1** (1.6 g; 0.01 mol) and triethylorthoformate (1.5 g; 0.01 mol) in 10 ml ethanol was heated under refluxed for 24 h. After cooling, the solid product was filtered off, dried and then recrystallized from the proper solvent (cf. Table 1).

4,6-Dimethyl-3-(aminoethoxylideneamino)-1H-pyrazolo-[3,4-b]-pyridine 8:

To a suspension of **1** (3.2 g; 0.02 mol) in 10 ml 1,4-dioxane, urethane (1.9 g; 0.02 mol) and 2-3 drops piperidine were added. The reaction mixture was heated under reflux for 18 h and the solid product formed, after partial evaporation, was collected by filtration and crystallized from the proper solvent (cf. Table 1).

2,4-Diamino-6,8-dimethylpyrido-[3,4-b]-pyrazolo-[2',3'-b]-pyrimidine-3-carbonitrile 10:

To a suspension of **8** (2.3 g; 0.01 mol) in 20 ml ethanol, malononitrile (0.7 g; 0.01 mol) and 2-3 drops of piperidine were added. The reaction mixture was refluxed for 72 h. The solid product formed, after partial evaporation, was collected by filtration and crystallized from the proper solvent (cf. Table 1).

4-Amino-6,8-dimethylpyrido-[3,4-d]-pyrazolo-[2',3'-b]-pyrimidin-4-one-3-carbonitrile 11:

To a suspension of **8** (2.3 g; 0.01 mol) in 20 ml ethanol, ethyl cyanoacetate (1.1 g; 0.01 mol) and 2-3 drops of piperidine were added. The reaction mixture was heated under reflux for 50 h. The solid product formed from the solution, after its partial evaporation, was collected by filtration and crystallized from the proper solvent (cf. Table 1).

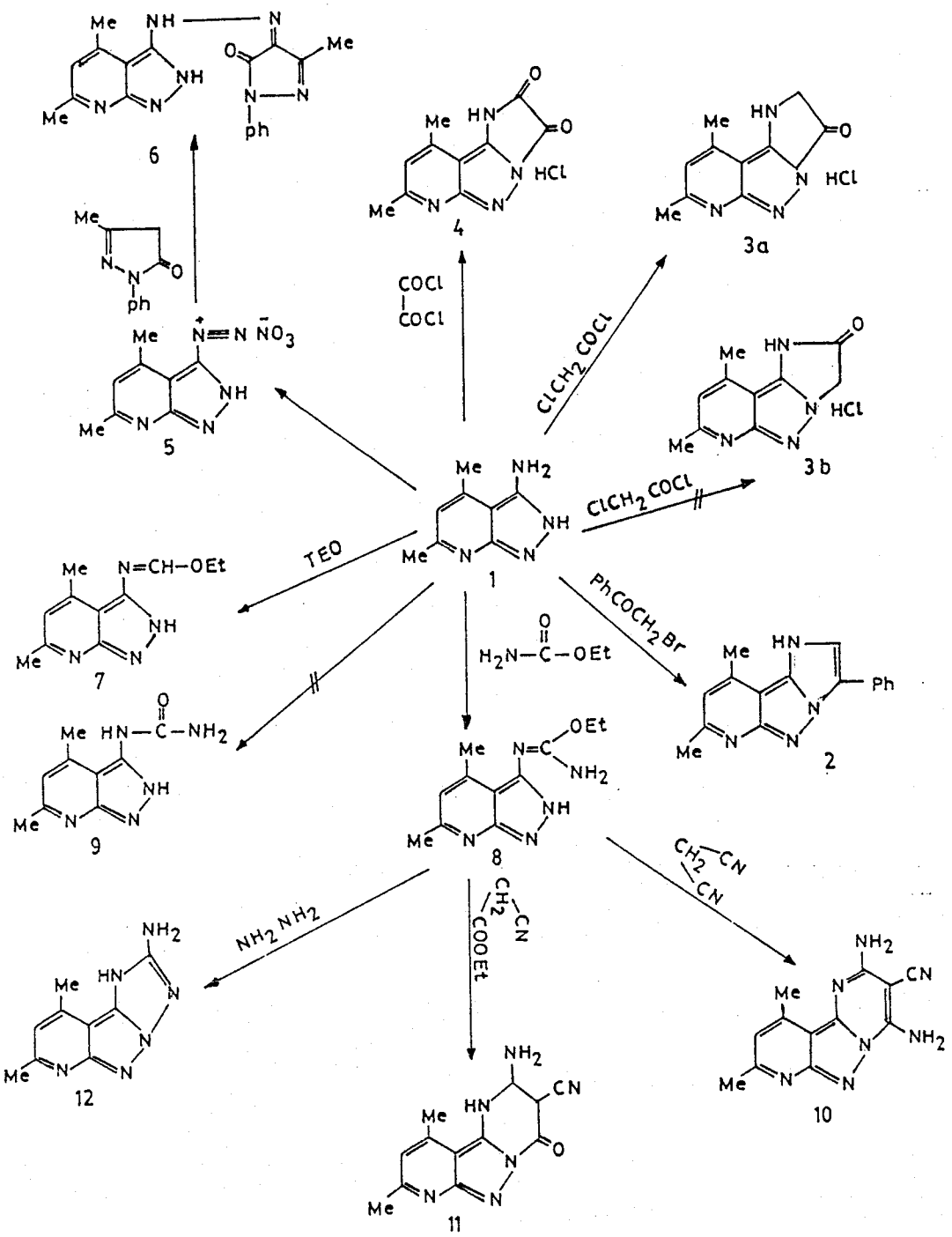
2-Amino-6,8-dimethyl-1H-triazolo-[2,3-b]-pyrazolo-[3',4'-b]-pyridine 12:

A mixture of **9** (2.3 g; 0.01 mol) and hydrazine hydrate (10 ml) was refluxed for 4 h. After cooling, the formed solid product was filtered off, washed with methanol, dried and then crystallized from the proper solvent (cf. Table 1).

Table 1: Experimental data for the synthesized compounds.

Comp. No.	Yield %	M.P./ °C*	Formula	Found (required) %		
				C	H	N
2	22	> 300 [a]	$C_{16}H_{14}N_4$	73.33 (73.26)	5.28 (5.38)	21.29 (21.36)
3	76	270-271 [b]	$C_{10}H_{11}ClN_4O$	50.23 (50.31)	4.65 (4.65)	23.26 (23.47)
4	50	> 300 [b]	$C_{10}H_9ClN_4O_2$	47.50 (47.53)	3.53 (3.59)	22.13 (22.17)
6	85	250-251 [a]	$C_{18}H_{17}N_7O$	61.24 (62.23)	5.82 (5.93)	28.16 (28.23)
7	20	> 300 [a]	$C_{11}H_{14}N_4O$	60.44 (60.53)	6.41 (6.47)	25.66 (25.67)
8	50	269-270 [c]	$C_{11}H_{15}N_5O$	56.54 (56.63)	6.41 (6.48)	30.02 (30.03)
10	86	> 300 [a]	$C_{12}H_{11}N_7$	56.90 (56.91)	4.60 (4.38)	38.63 (38.72)
11	33	285-286 [c]	$C_{12}H_{10}N_6O$	56.58 (56.69)	3.87 (3.96)	33.03 (33.06)
12	54	> 300 [b]	$C_9H_{10}N_6$	53.35 (53.45)	4.85 (4.98)	41.55 (41.56)

* Crystallized from a = DMF, b = methanol
c = acetone, d = acetic acid.


6
4
3a
5
3b
1
7
2
9
8
12
11
10
TEO
PhCOCH2Br
NH2NH2

REFERENCES

1- H.S. El-Khashef, K.U. Sadek, H.H. Elnima and M.H. Elnagdi, J. Chem. and Engineering data, **27**, 103 (1982).

2- H.R. Synder, U.S. Patent, 1967, 3293261, C.A. **66**, 464240 (1967).

3- A. Vogel and F. Troxler, Helv. Chem. Acta., **58**, 761 (1975).

4- M.R.H. Elmoghayar, M.K. Ibrahim, I.A. El-Sakka and M.H. Elnagdi, Arch. Pharm. (Weinheim), **316**, 697 (1983).

5- M.H. Elnagdi, E.M. Kandeel, E.M. Zayed and Z.E. Kandeel, J. Heterocycl. Chem., **14**, 155 (1977).

6- M.H. Elnagdi, M.R. Elmoghayar and E.M. Kandeel, Z. Naturforch., **33**, 307 (1977).

7- S. Checchi and M. Ridi, Gazz. Chim. Ital., **87**, 597 (1957).

تخليق مركبات بيرازولو-(4,3-b)-بيريدين الملتحمة لمركبات عضوية غير متجانسة

د. أحمد خطاب ، د. صلاح محمد ياسين ، د. إبراهيم السقا

قسم الكيمياء – كلية العلوم – جامعة المنوفية

تتفاعل مشتقات الأمينوبيرازولوبيريدين 1 مع فيناسيل بروميد ، كلورو أسيتيل كلوريد وأوكزاليل كلوريد لتعطى المشتقات ثلاثية الحلقة 2 ، 3 و 4 على الترتيب . بتفاعل المركب 1 المدستز مع ١-فينيل-٣-ميثيل بيرازول-٥-أون ينتج الهيدرازون المقابل 6 ومن ناحية أخرى يتكاثف 1 مع تراى إيثيل أورثو فورمات أو اليوريثان ليعطى البيليدينات 8 ، 7 على الترتيب . وقد تم إثبات صحة تركيب المركب 8 من خلال تفاعله مع المالونونيتريل ، الإيثيل سيانو أسيتات أو هيدرات الهيدرازين معطيا المشتقات ثلاثية الحلقة 10 ، 11 ، 12 على الترتيب .

ولقد تم إثبات صحة التركيبات الناتجة بواسطة إستخدام الرنين النووى المغناطيسى للبروتون ومطياف الكتلة والأشعة دون الحمراء علاوة على التحليل الكمى للعناصر .