Synthesis of 2*H*-Pyrazolo[3,4-*b*]pyridin-3-oles *via* Cyclization of Pyrazolacrylonitriles

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The reaction of 1-acyl-3-amino-5-pyrazolones **1** with ethyl ethoxymethylenecyanoacetate and ethoxymethylenemalononitrile **2** is described. Thermal cyclization in phenyl ether of the obtained pyrazolacrylonitriles **3** provides good yields of pyrazolopyridin-3-ol derivatives **4**.

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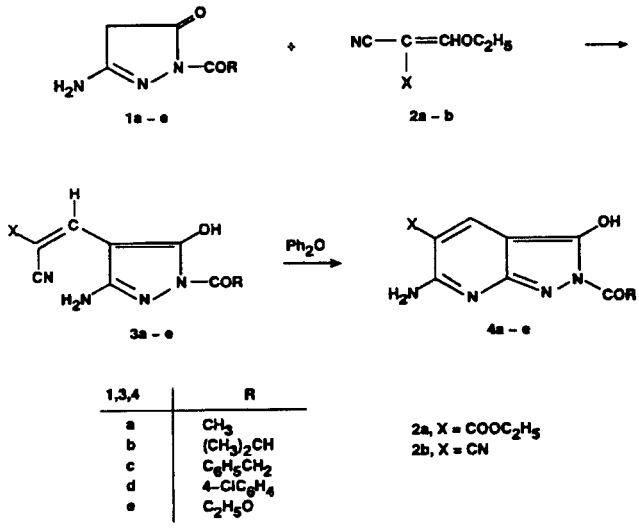
The N^1-acyl-2-ethoxycarbonylacetamidrazones are versatile intermediates for the preparation of polyfunctionally substituted heterocycles.

In previous studies, we have found that, under mild conditions, these intermediates react with *N*-[bis-(methylthio)methylene]cyanamide to afford polysubstituted pyrimidines [1] and with enol ethers to give pyridine derivatives [2].

We have recently reported the cyclization of N^1-acyl-2-ethoxycarbonylacetamidrazones under strongly basic conditions to give 1-acyl-3-amino-5-pyrazolones [3]. The 3-amino-5-pyrazolones have acquired importance in organic synthesis as precursors to pyrazole derivatives condensed to six-membered rings with interesting pharmacological activity [4-7]. The 1-alkyl or aryl-3-amino-5-pyrazolones are known to react with functionally substituted double bond systems and with polyfunctional electrophiles to give pyranopyrazoles and pyrazolopyridines [8-10].

We now wish to report the reaction between 1-acyl-3-amino-5-pyrazolones **1** and enol ethers such as ethyl ethoxymethylenecyanoacetate **2a** and ethoxymethylenemalononitrile **2b** under different reaction conditions.

SCHEME



Treatment of **1** with an equimolecular amount of enol ethers **2** in dimethyl sulfoxide at 70-80° for 3 hours furnished the pyrazolacrylonitriles **3** in good yields (Table 1).

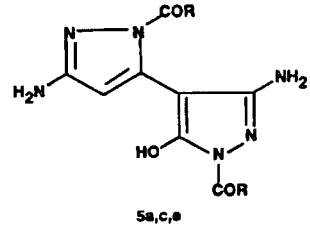
The structure of these adducts was established by means of spectral data and microanalyses. The ir spectra show several bands between 3480 and 3150 cm^{-1} due to the absorptions of the NH_2 and OH groups.

The ^1H nmr display one single olefinic signal at 7.58-7.90 ppm and the signals of NH_2 and OH groups (deuterium oxide exchangeable) at 7.63-7.80 and 11.82-12.40 ppm, respectively (Table 2).

The structure of adducts **3** showed that the reaction proceeds only by attack of the enol ether at the C-4 position of heterocyclic ring, without competition for the other nucleophilic sites.

When the reaction between compounds **1** and the enol ethers **2** was carried out in ethanol under reflux, the adducts **3** were obtained in low yields (20-25%). In some cases, besides compounds **3**, the 4,5'-bipyrazoles **5** were isolated. Their formation could be rationalized assuming that the H-4 protons of pyrazolone **1** are acid enough to react with the enolic form of another molecule.

FIGURE

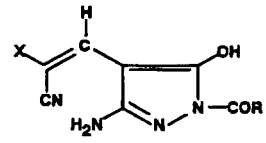


The ^1H nmr spectra of compounds **5** showed the proton signal of H-4 (7.28-7.40 ppm) and two broad bands (exchangeable) at 6.90 and 7.90 ppm, respectively, due to the two NH_2 groups.

The intermediates **3**, by heating in phenyl ether at 200°, underwent cyclization to give good yields of pyrazolo[3,4-*b*]pyridines **4** (Table 3). The reaction was rapid

Table 1

Physical and Analytical Data of Compounds 3



Compound	R	X	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N
3a	CH_3	CN	335-340 [a]	90	$C_9H_7N_5O_2$	49.77 49.69	3.25 3.23	32.25 32.19
3b	$(CH_3)_2CH$	CN	193-195[b]	60	$C_{11}H_{11}N_5O_2$	53.87 53.82	4.52 4.53	28.56 28.50
3c	$C_6H_5CH_2$	CN	255-256[c]	88	$C_{15}H_{11}N_5O_2$	61.43 61.39	3.78 3.76	23.88 23.92
3d	4-$ClC_6H_4CH_2$	CN	269-270[d]	90	$C_{15}H_{10}ClN_5O_2$	54.97 55.02	3.07 3.06	21.37 21.34
3e	C_2H_5O	CN	199-200 [d]	95	$C_{10}H_9N_5O_3$	48.58 48.64	3.65 3.63	28.33 28.28
3f	CH_3	$COOC_2H_5$	228-229 [d]	66	$C_{11}H_{12}N_4O_4$	50.00 50.07	4.58 4.59	21.20 21.17
3g	$(CH_3)_2$ CH	$COOC_2H_5$	179-180 [c]	77	$C_{13}H_{16}N_4O_4$	53.42 53.38	5.52 5.50	19.17 19.14
3h	$C_6H_5CH_2$	$COOC_2H_5$	175-176 [c]	83	$C_{17}H_{16}N_4O_4$	59.99 60.03	4.74 4.75	16.46 16.43
3i	4-$ClC_6H_4CH_2$	$COOC_2H_5$	215-216 [d]	75	$C_{17}H_{15}ClN_4O_4$	54.48 54.42	4.03 4.04	14.95 14.92
3j	C_2H_5O	$COOC_2H_5$	189-190 [d]	55	$C_{12}H_{14}N_4O_5$	48.98 49.02	4.80 4.87	19.04 18.99

[a] From ethanol. [b] From ethyl acetate. [c] From 2-propanol. [d] From acetonitrile.

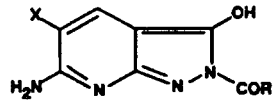
Table 2

IR and ^1H NMR Spectral Data of Compounds 3

Compound	IR (cm^{-1})	^1H NMR (DMSO-d_6) δ (ppm)
3a	3400, 3340, 3240, 2240, 2220 1715, 1650, 1610	2.39 (s, 3H, CH_3), 7.61 (s, 1H, =CH), 7.63 (br s, 2H, NH_2), 12.40 (br s, 1H, OH)
3b	3420, 3340, 3220, 2240, 2220 1720, 1660, 1600	1.05 (d, 6H, $2CH_3$), 3.60 (m, 1H, CH), 7.62 (s, 1H, =CH), 7.70 (br s, 2H, NH_2)
3c	3410, 3330, 3150, 2220, 1710 1680, 1660, 1620	4.22 (s, 2H, CH_2), 7.25 (m, 5H, Ar), 7.65 (s, 1H, =CH), 7.74 (br s, 2H, NH_2)
3d	3410, 3330, 3150, 2220, 1710 1680, 1660, 1620	4.22 (s, 2H, CH_2), 7.26 (m, 4H, Ar), 7.65 (s, 1H, =CH), 7.76 (br s, 2H, NH_2)
3e	3480, 3380, 3180, 2240, 2220 1770, 1650, 1610	1.23 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 7.58 (s, 1H, =CH), 7.80 (br s, 2H, NH_2)
3f	3420, 3320, 3170, 2220, 1730 1670, 1650	1.22 (t, 3H, CH_3), 2.40 (s, 3H, CH_3), 4.17 (q, 2H, CH_2), 7.68 (s, 2H, NH_2), 7.88 (s, 1H, =CH), 11.94 (br s, 1H, OH)
3g	3370, 3210, 2220, 1725, 1660	1.06 (d, 6H, $2CH_3$), 1.20 (t, 3H, CH_3), 3.65 (m, 1H, CH), 4.17 (q, 2H, CH_2), 7.68 (s, 2H, NH_2), 7.88 (s, 1H, =CH), 11.82 (br s, 1H, OH)
3h	3425, 3320, 3210, 2215, 1715 1690, 1640	1.20 (t, 3H, CH_3), 4.17 (q, 2H, CH_2), 4.23 (s, 2H, CH_2), 7.25 (m, 5H, Ar), 7.72 (s, 2H, NH_2), 7.90 (s, 1H, =CH), 11.89 (br s, 1H, OH)
3i	3440, 3340, 3160, 2210, 1730 1710, 1670, 1640	1.21 (t, 3H, CH_3), 4.17 (q, 2H, CH_2), 4.24 (s, 2H, CH_2). 7.32 (m, 4H, Ar), 7.75 (s, 2H, NH_2), 7.90 (s, 1H, =CH), 11.93 (br s, 1H, OH)
3j	3370, 3320, 3250, 3200, 2220 1745, 1720, 1680, 1650	1.21 (m, 6H, $2CH_3$), 4.12-4.26 (m, 4H, $2CH_2$), 7.78 (br s, 2H, NH_2), 7.85 (s, 1H, =CH)

Table 3

Physical and Analytical Data of Compounds 4



Compound	R	X	Mp (°C)	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N
4a	CH_3	CN	268-270 [a]	76	$C_9H_7N_5O_2$	49.77	3.25	32.25
						49.71	3.27	32.22
4b	$(CH_3)_2CH$	CN	268-270 [b]	80	$C_{11}H_{11}N_5O_2$	53.87	4.52	28.56
						53.90	4.50	28.53
4c	$C_6H_5CH_2$	CN	268-270 [b]	81	$C_{15}H_{11}N_5O_2$	61.43	3.78	23.88
						61.39	3.76	23.85
4d	4-$ClC_6H_4CH_2$	CN	278-280 [b]	74	$C_{15}H_{10}ClN_5O_2$	54.97	3.07	21.37
						54.94	3.05	21.34
4e	C_2H_5O	CN	266-268 [b]	84	$C_{10}H_9N_5O_3$	48.58	3.65	28.33
						48.54	3.67	28.36
4f	CH_3	$COOC_2H_5$	254-256 [c]	80	$C_{11}H_{12}N_4O_4$	50.00	4.58	21.20
						49.96	4.55	21.17
4g	$(CH_3)_2CH$	$COOC_2H_5$	242-244 [d]	50	$C_{13}H_{16}N_4O_4$	53.42	5.52	19.17
						53.39	5.50	19.20
4h	$C_6H_5CH_2$	$COOC_2H_5$	246-248 [c]	76	$C_{17}H_{16}N_4O_4$	59.99	4.74	16.46
						60.03	4.71	16.41
4i	4-$ClC_6H_4CH_2$	$COOC_2H_5$	238-240 [c]	68	$C_{17}H_{15}ClN_4O_4$	54.47	4.03	14.95
						54.43	4.00	14.92
4j	C_2H_5O	$COOC_2H_5$	172-174 [e]	70	$C_{12}H_{14}N_4O_5$	48.98	4.80	19.04
						48.95	4.77	19.00

[a] From dimethyl sulfoxide. [b] From dioxane. [c] From 2-ethoxyethanol. [d] From acetonitrile. [e] From ethanol.

Table 4

IR and ^1H NMR Spectral Data of Compounds 4

Compound	IR (cm^{-1})	^1H NMR δ (ppm)
4a	3380, 3330, 3240, 3170, 3040 2230, 1725, 1695, 1660	2.57 (s, 3H, CH_3), 7.63 (br s, 2H, NH_2), 8.35 (s, 1H, H-4), 12.06 (br s, 1H, OH)
4b	3440, 3380, 3290, 3250, 3170 3040, 2220, 1730, 1690, 1660	1.10 (d, 6H, $2CH_3$), 3.70 (m, 1H, CH), 7.68 (br s, 2H, NH_2), 8.30 (s, 1H, H-4), 11.95 (br s, 1H, OH)
4c	3390, 3330, 3230, 3170, 3040 2220, 1720, 1685, 1650	4.31 (s, 2H, CH_2), 7.27 (m, 5H, Ar), 7.74 (br s, 2H, NH_2), 8.35 (s, 1H, H-4), 12.20 (br s, 1H, OH)
4d	3400, 3330, 3230, 3050, 2230 1720, 1690, 1630	4.32 (s, 2H, CH_2), 7.36 (m, 4H, Ar), 7.75 (br s, 2H, NH_2), 8.36 (s, 1H, H-4), 12.20 (br s, 1H, OH)
4e	3350, 3220, 3200, 3120, 3020 2220, 1710, 1655	1.25 (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 7.69 (br s, 2H, NH_2), 8.27 (s, 1H, H-4), 11.80 (br s, 1H, OH)
4f	3380, 3290, 3120, 1715, 1690 1640	1.29 (t, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.24 (q, 2H, CH_2), 8.05 (br s, 2H, NH_2), 8.34 (s, 1H, H-4), 12.06 (br s, 1H, OH)
4g	3400, 3320, 3190, 3080, 1700, 1670, 1630	1.11 (d, 6H, $2CH_3$), 1.28 (t, 3H, CH_3), 3.74 (m, 1H, CH), 4.22 (q, 2H, CH_2), 8.02, 8.06 (s, 2H, NH_2), 8.33 (s, 1H, H-4), 11.98 (br s, 1H, OH)
4h	3330, 3200, 3080, 1710, 1690 1670, 1650	1.29 (t, 3H, CH_3), 4.24 (q, 2H, CH_2), 4.32 (s, 2H, CH_2), 7.28 (m, 5H, Ar), 8.07, 8.11 (s, 2H, NH_2), 8.37 (s, 1H, H-4), 11.10 (br s, 1H, OH)
4i	3350, 3210, 3090, 1710, 1690 1670, 1650	1.28 (t, 3H, CH_3), 4.23 (q, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.34 (m, 4H, Ar), 8.06, 8.11 (s, 2H, NH_2), 8.36 (s, 1H, H-4), 12.02 (br s, 1H, OH)
4j	3410, 3290, 3190, 1695, 1635	1.29 (m, 6H, $2CH_3$), 4.25 (m, 4H, $2CH_2$), 7.35 (br s, 2H, NH_2), 8.30 (s, 1H, H-4), 11.25 (br s, 1H, OH)

and we did not observe any competition from the intramolecular condensation of pyranopyrazoles [10].

Of particular note, the ^{1}H nmr spectra of **4** displayed one proton singlet at 8.27-8.37 ppm that could be assigned to the H-4, while the OH group gives rise to a broad singlet downfield (11.10-12.20 ppm) (Table 4).

EXPERIMENTAL

Melting points were determined on Köfler hot stage and are uncorrected. The ir spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded for hexadeuteriodimethyl sulfoxide solution with a Varian Unity 300 spectrometer; chemical shifts are reported in ppm from hexamethyldisiloxane as an internal standard and are given in δ units. The elemental analyses (C, H, N) were carried out with a Carlo Erba Model 1106 Elemental Analyzer. The 1-acyl-3-amino-5-pyrazolones **1a,c-e** were obtained by a previously described procedure [3].

3-Amino-1-isobutyryl-5-pyrazolone (**1b**).

N^1-Isobutyryl-2-ethoxycarbonylacetamidrazone (2.15 g, 10 mmoles) was added to a cold stirred solution of sodium (0.01 g-atom) in absolute ethanol (10 ml). The mixture was stirred at room temperature for 12 hours, then diluted with water and rendered acidic by addition of acetic acid. The solid was filtered and washed with water, mp 164-165° (from acetonitrile), yield 80%; ir (nujol): 3400, 3330, 3200, 1670, 1620, 1570 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.00 (d, 6H, $2CH_3$), 3.75 (m, 1H, CH), 4.16 (s, 1H, H-4), 6.51 (s, 2H, NH_2).

Anal. Calcd. for $C_7H_{11}N_3O_2$: C, 49.69; H, 6.55; N, 24.84. Found: C, 49.63; H, 6.57; N, 24.86.

General Procedure for the Preparation of 1-Acyl-3-amino-5-hydroxy-1*H*-pyrazole-4-acrylonitrile Derivatives **3**.

Method A.

A solution of 1-acyl-3-amino-5-pyrazolone **1a-e** (5 mmoles) and the appropriate enol ether **2** (5 mmoles) in dimethyl sulfoxide (3 ml) was heated in a water bath at 70-80° for 3 hours. Water was then added and the formed precipitate was filtered, dried and recrystallized to give compounds **3**.

Method B.

A solution of **1a-e** (5 mmoles) and the appropriate enol ether **2** (5 mmoles) in anhydrous ethanol (10 ml) was refluxed for 1 hour. In some cases (**1a,c,e**) a precipitate was obtained that was identified as 5-hydroxy[4,5'-bipyrazole] **5**.

After concentration of the solution, compounds **3** were obtained in about 25% yields.

1,1'-Diacetyl-3,3'-diamino-5-hydroxy[4,5'-bipyrazole] (**5a**).

This compound was obtained in 20% yield; mp 348-350° dec; ir (nujol): 3350, 3220, 1730, 1660, 1610 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.38 (s, 6H, $2CH_3$), 6.90 (br s, 2H, NH_2), 7.36 (s, 1H, H-4'), 7.90 (br s, 2H, NH_2).

Anal. Calcd. for $C_{10}H_{12}N_6O_3$: C, 45.45; H, 4.58; N, 31.81. Found: C, 45.51; H, 4.56; N, 31.78.

3,3'-Diamino-1,1'-bis(phenylacetyl)-5-hydroxy[4,5'-bipyrazole] (**5c**)

This compound was obtained in 10% yield, mp 204-205°; ir (nujol): 3370, 3250, 1670, 1630, 1600 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.19 (s, 4H, $2CH_2$), 6.90 (br s, 2H, NH_2), 7.25 (m, 10H, Ar), 7.40 (s, 1H, H-4'), 7.90 (br s, 2H, NH_2).

Anal. Calcd. for $C_{22}H_{20}N_6O_3$: C, 63.45; H, 4.84; N, 20.18. Found: C, 63.39; H, 4.86; N, 20.15.

3,3'-Diamino-1,1'-bis(ethoxycarbonyl)-5-hydroxy[4,5'-bipyrazole] (**5e**)

This compound was obtained in 22% yield; mp 242-244° dec; ir (nujol): 3380, 3280, 3170, 1785, 1740, 1590 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.22 (m, 6H, $2CH_3$), 4.20 (m, 4H, $2CH_2$), 6.90 (br s, 2H, NH_2), 7.28 (s, 1H, H-4'), 7.90 (br s, 2H, NH_2).

Anal. Calcd. for $C_{12}H_{16}N_6O_5$: C, 44.44; H, 4.97; N, 25.92. Found: C, 44.49; H, 4.95; N, 25.89.

General Procedure for the Preparation of 3-Hydroxy-2*H*-pyra-zolo[3,4-*b*]pyridine Derivatives **4**.

A stirred mixture of **3** (5 mmoles) in phenyl ether (5 ml) was heated at 200° for 10 minutes. After cooling ethyl ether was added and the formed solid was collected by filtration and recrystallized from a suitable solvent to give compounds **4** in the yields reported in Table 3.

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