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The Paal-Knorr Condensation of Acetonylacetone with 5-Aminopyrazoles

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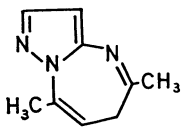
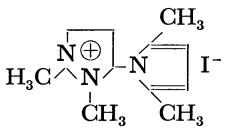
There are very few reports on the Paal-Knorr condensation using heterocyclic amine. The reaction was undertaken with the expectation of formation of pyrazolo-1,3-diazepine ring, but it gave rise to only normal condensation.



This paper deals with the condensation of acetonylacetone with several 5-aminopyrazoles (**1**, **2a**,**b** and **3**) in the presence of acetic acid to form a new series of 1-(pyrazol-5-yl)-2,5-dimethylpyrroles (**4**, **5a**,**b** and **6**). 1,4-Disubstituted 5-aminopyrazole such as **2c** and **2d** could not be condensed under these conditions, due perhaps to steric requirements.

The structure of **4** obtained from 1,2-unsubstituted 5-aminopyrazole (**1**) was confirmed by means of NMR spectral data and chemical evidence. All NMR spectra of **4**, **5**, and **6** show two sharp singlets in the ranges δ 1.92—2.05(6H) and 5.61—5.90(2H) corresponding to the α-methyl protons and β-protons of pyrrole nucleus, respectively. Methylation of **4a**—**d** with methyl iodide gave the corresponding 1-(1-methylpyrazol-5-yl)-2,5-dimethylpyrroles (**5**). Support for the structures **5c** and **5d** was provided by NMR spectra, in which the *N*-methyl protons are located at high magnetic field than that of the corresponding 1-(2-methylpyrazol-5-yl)-2,5-dimethylpyrroles (**6**) similar to other cases. Furthermore, with two moles of methyl iodide, **4a** reacted to give methiodide (**7**), which could be also derived from either **5a** or **6a** by similar methylation.



7

1	2	3	4	5	6	R	R′
1a	**2a**	**3a**	**4a**	**5a**	**6a**	H	H
1b	**2b**	**3b**	**4b**	**5b**	**6b**	CH_3	H
1c	**2c**	**3c**	**4c**	(**5c**)	**6c**	H	$COOC_2H_5$
1d	**2d**	**3d**	**4d**	(**5d**)	**6d**	CH_3	$COOC_2H_5$
1e			**4e**			C_6H_5	H

Experimental

All melting points and boiling points are uncorrected. The NMR spectra were taken with a JNM-C-60 high-resolution NMR spectrometer, using TMS as an internal standard.

5-Aminopyrazoles. 1,2-Unsubstituted 5-aminopyrazoles (**1a**–**d**) were prepared by the use of a method described in a previous paper.[1] 3-Phenyl-5-aminopyrazole (**1e**) was obtained as described in literature.[2] *N*-Methyl-5-aminopyrazoles (**2a,b** and **3a,b**) were obtained by hydrolysis of 4-ethoxycarbonyl derivatives (**2c,d** and **3c,d**), prepared by

1) H. Baba, I. Hori, T. Hayashi and H. Midorikawa, This Bulletin, **42**, 1653 (1969).

2) A. Takamizawa and Y. Hamashima, *Yakugaku Zasshi*, **84**, 1113 (1964).

Table 1. Physical properties, yields, analytical and NMR data of 1-(pyrazol-5-yl)-2,5-dimethylpyrroles

Compd.	Mp °C (Bp °C/mmHg)	Yield %	Formula	Analysis Found (Calcd) C%	H%	N%	NMR (CCl_4) δ ppm Pyrazole nucleus R	R′	N–CH_3	Pyrrole nucleus α-2CH_3	β-2H
4a	205—208	87.6	$C_9H_{11}N_3$	67.13 (67.05	6.60 6.88	26.02 26.07)	[6.27$_d$(H) (J=2.4 Hz)	7.89$_d$(H)		2.22	6.08][a]
4b	140—142	48.5	$C_{10}H_{13}N_3$	68.81 (68.54	7.39 7.48	24.08 23.98)	1.76 (CH_3)	5.83 (H)		2.05	5.62
4c	136	78.5	$C_{12}H_{15}O_2N_3$	61.57 (61.78	6.49 6.48	18.19 18.02)	7.16 (H)	1.19, 4.12 ($COOC_2H_5$)		2.00	5.90
4d	102—105 (205—208/5.5)	85.0	$C_{13}H_{17}O_2N_3$	63.31 (63.14	6.86 6.93	17.09 16.99)	1.98 (CH_3)	1.02, 4.00 ($COOC_2H_5$)		2.00	5.72
							[2.68 (CH_3)	1.06, 4.15 ($COOC_2H_5$)		2.18	6.03][a]
4e	150—152	62.3	$C_{15}H_{15}N_3$	75.83 (75.92	6.79 6.37	18.01 17.71)	7.24$_m$(C_6H_5)	6.37 (H)		2.02	5.67
5a	(95—99/15)	63.8	$C_{10}H_{13}N_3$	68.92 (68.54	7.49 7.48	24.40 23.98)	[6.21$_d$(H) (J=1.8 Hz)	7.54$_d$(H)	3.48	1.97	5.91][b]
5b	(75/2)	78.0	$C_{11}H_{15}N_3$	69.39 (69.81	7.49 7.99	22.42 22.20)	2.21 (CH_3)	5.88 (H)	3.33	1.94	5.74
5c	(115—116/2)		$C_{13}H_{17}O_2N_3$	62.78 (63.14	6.88 6.93	17.22 16.99)	7.83 (H)	1.12, 4.06 ($COOC_2H_5$)	3.50	1.92	5.80
5d	(105—111/10)		$C_{14}H_{19}O_2N_3$	63.68 (64.34	7.58 7.33	16.23 16.08)	2.42 (CH_3)	1.05, 4.01 ($COOC_2H_5$)	3.44	1.92	5.76
6a	62—63 (135—137/9.5)	66.5	$C_{10}H_{13}N_3$	68.17 (68.54	7.50 7.48	23.85 23.98)	[6.14$_d$(H) (J=2.1 Hz)	7.36$_d$(H)	3.89	2.10	5.85][b]
6b	67—69	92.3	$C_{11}H_{15}N_3$	69.37 (69.81	7.91 7.99	22.57 22.20)	2.27 (CH_3)	5.80 (H)	3.72	2.03	5.61
6c	(140—145/2)	58.5	$C_{13}H_{17}O_2N_3$	62.84 (63.14	6.74 6.93	16.96 16.99)	7.97 (H)	1.11, 4.08 ($COOC_2H_5$)	3.73	1.97	5.71
6d	65—68	37.6	$C_{14}H_{19}O_2N_3$	63.49 (64.34	7.25 7.33	16.52 16.08)	2.55 (CH_3)	1.02, 4.00 ($COOC_2H_5$)	3.77	1.93	5.63

a) in C_5H_5N b) in $CDCl_3$

the procedure of Schimdt *et al.*.[3] **1a**: bp 140—142°C/7 mmHg (lit[4] 115—116°C/1.5 mmHg, mp 38—40°C). **1b**[1]: mp 47—48°C, bp 146.5—147°C/4 mmHg. **1c**: mp 104.5—105.5°C (lit[5] 102—103°C). **1d**[1]: mp 109—110°C. **1e**: mp 127—128°C). (lit.[2] 120—122°C). **2a**: mp 71—73°C (lit[6] 67°C, bp 110°C/4 mmHg). **2b**: mp 77—78°C (lit[7] 78—79°C). **2c**: mp 99—101°C (lit[3] 101°C, bp 121°C/0.05 mmHg). **2d**: mp 108—109°C (Found: C, 52.63; H, 6.98; N, 23.14%. Calcd for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94%). **3a**: bp 95—100°C/10 mmHg (lit[6] 92—98°C/9 mmHg). **3b**: mp 66—67°C (Found: C, 54.26; H, 7.98; N, 37.85%. Calcd for $C_5H_9N_3$: C, 54.03; H, 8.16; N, 37.81%). **3c**: mp 88—90°C (lit[3] 92—93°C). **3d**: mp 101—103°C (Found: C, 52.35; H, 7.13; N, 22.87%. Calcd for $C_8H_{13}O_2N_3$: C, 52.44; H, 7.15; N, 22.94%).

Condensation of Acetonylacetone with 5-Aminopyrazoles. To a solution of acetonylacetone (0.02 mol) and 5-aminopyrazole (0.02 mol) dissolved in benzene (50 m*l*), acetic acid (0.5 m*l*) was added, and the mixture was refluxed with a water-separator until the formation of water ceased. After the reaction mixture had been evaporated on a rotary evaporator at 50°C, the residue was purified by washing or recrystallization from an appropriate solvent or by distillation under reduced pressure to give 1-(pyrazol-5-yl)-2,5-dimethylpyrroles (**4, 5a, b** and **6**).

Both **2c** and **2d** did not react and were quantitatively recovered. The results along with the NMR data are summarized in Table 1.

Methylation of 4a–d with Methyl Iodide. A mixture of **4** (5.0 mmol) and methyl iodide (5.0 mmol) in methanol (5 m*l*) was heated in a sealed tube at 100°C for 5 hr. After cooling the reaction mixture was evaporated on a rotary evaporator at 40°C. The dark-reddish residue was distillated under reduced pressure to give mono-methylated products as colorless oil.

The products thus obtained from **4a** and **4b** were identical with the corresponding **5** prepared by the above condensation (yields 40.0 and 32.5%, respectively). The products obtained from **4c** and **4d** were inferred to be the corresponding **5** from NMR spectral study (yields 36.6 and 38.0% respectively). The physical properties, analyses and NMR data are shown in Table 1.

Formation of Methiodide (7). *a)* From **4a**: A mixture of **4a** (0.40 g, 2.5 mmol) and methyl iodide (0.71 g, 5.0 mmol) in methanol (3 ml) was heated in a sealed tube at 100°C for 12 hr. After cooling the reaction mixture was evaporated on a rotary evaporator at 40°C. The dark-reddish residue was triturated with ether-methanol to yield brown crystals. Gel filtration (Sephadex LH-20) with methanol gave the methiodide (**7**) (0.55 g, 70.0%) as nearly colorless needles; mp 159—161°C (dec). NMR (CD_3COCD_3): δ 2.08(s, 6H), 4.03(s, 3H), 4.56(s, 3H), 5.96(s, 2H), 7.04(d, J=3 Hz, 1H),

3) P. Schmidt, K. Eichenberger, M. Wilhelm, and J. Druey, *Helv. Chim. Acta*, **42**, 349 (1959).

4) H. Reimlinger, A. V. Overstreten, and H. G. Viehe, *Chem. Ber.*, **94**, 1036 (1961).

5) J. Druey and P. Schmidt, Ger. 1065421 (1959); *Chem. Abstr.*, **55**, P18786c (1961).

6) S. Hayashi, *Yakugaku Zasshi*, **85**, 442 (1965).

7) C. F. Boehringer and Soehne G.m.b.H., Brit. 863060 (1961); *Chem. Abstr.*, **55**, P18776a (1961).

8.89(d, J=3 Hz, 1H). Found: C, 41.50; H, 5.07; N, 13.57; I, 39.93%. Calcd $C_{11}H_{16}N_3I$: C, 41.66; H, 5.08; N, 13.25; I, 40.01%.

b) From ***5a*** *or* ***6a***. A mixture of **5a** or **6a** (2.5 mmol) and methyl iodide (2.5 mmol) in methanol (2 m*l*) was worked up by the method mentioned above. Both products thus obtained were identical with **7** (yields 56.5 and 52.7%, respectively).

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