One Step Synthesis of 6,7-Dimethyl-2-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*][1,3]pyrimidines

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A one-step synthesis of substituted pyrrolo[1,2-*a*][1,3]pyrimidines from acetyl methyl carbinol, 3-aminopropionic acid, and substituted acetonitriles is reported.

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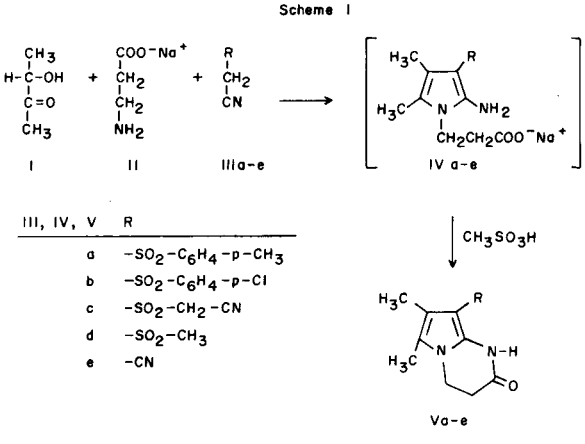
In 1975, Roth and Eger [1] reported the synthesis of 1-alkyl-2-amino-3-cyanopyrroles from acetyl methyl carbinol, primary amines, and malononitrile. This technology was recently extended to the synthesis [2] of 1-alkyl-2-amino-3-(alkyl or aryl)sulfonylpyrroles.

We now wish to report a facile one-step synthesis of pyrrolo[1,2-*a*][1,3]pyrimidines from acetyl methyl carbinol (I), 3-aminopropionic acid (II), and substituted acetonitriles (IIIa-e) (Scheme I). In this procedure, acetyl methyl carbinol was condensed with sodium 3-aminopropionate to yield the corresponding α-amino ketone. Addition of the substituted acetonitriles IIIa-e [3-6] to the reaction mixture and further refluxing under a Dean-Stark trap gave the proposed substituted 2-aminopyrroles IVa-e. The pyrrolo[1,2-*a*][1,3]pyrimidines Va-e were obtained in yields from 30-89% (Table I) upon treating IVa-e with methane sulfonic acid.

Scheme I



The structural assignments of these pyrrolo[1,2-*a*][1,3]-pyrimidines were made on the basis of elemental analysis,

Table I

Compound No	Mp °C	Yield (%)	Molecular Formula		Analysis (%) Calcd.	Found
Va	243-245 dec	82.0	$C_{16}H_{18}N_2O_3S$	C	60.35	60.34
				H	5.70	5.73
				N	8.80	8.78
				S	10.07	10.40
Vb	218-220 dec	87.1	$C_{15}H_{15}ClN_2O_3S$	C	53.17	53.01
				H	4.46	4.50
				N	8.27	8.22
				Cl	10.47	10.52
				S	9.46	9.50
Vc	232-233 dec	50.5	$C_{11}H_{13}N_3O_3S$	C	49.42	49.36
				H	4.90	4.94
				N	15.72	15.67
				S	12.00	11.95
Vd	201-203 dec	89.1	$C_{10}H_{14}N_2O_3S$	C	49.57	49.60
				H	5.82	5.84
				N	11.56	11.52
				S	13.23	13.29
Ve	259-261 dec	30.1	$C_{10}H_{11}N_3O$	C	63.47	63.51
				H	5.86	5.87
				N	22.21	22.19

infrared spectra, and nmr spectra. These data are presented in the Experimental and Table I.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The spectra were determined on a Varian EM360A NMR Spectrometer using tetramethylsilane as an internal standard and deuteriochloroform or DMSO-d_6 as the solvent. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. The tlc were performed on Eastman Chromatogram Sheets, type 6060 (silica gel).

6,7-Dimethyl-8-(*p*-toluenesulfonyl)-2-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-[1,3]pyrimidine (Va).

A solution of 3-aminopropionic acid (9.89 g, 0.11 mole) and sodium methylate (5.40 g, 0.10 mole) in ethanol (80 ml) was refluxed for 5 minutes. Toluene (10 ml) and acetyl methyl carbinol (10.4 g of an 85% aqueous solution, 0.10 mole) were added and the mixture refluxed with stirring until 30 ml of distillate was collected *via* a Dean-Stark trap. After cooling, *p*-toluenesulfonylacetonitrile (19.5 g, 0.10 mole) was added and the mixture was refluxed for one hour after collecting another 30 ml of distillate. The reaction mixture was cooled in an ice-bath while a mixture of methane sulfonic acid (9.61 g, 0.10 mole) and ethanol (10 ml) was added dropwise. After the addition was complete, the reaction mixture was refluxed for 30 minutes then allowed to stand overnight at room temperature. The reaction mixture was diluted with water (200 ml), the precipitate was collected, and washed with water. The solid was suspended in methanol (100 ml), collected, and air dried. The product (26.1 g, 82%) was recrystallized from methanol to give white crystals, mp 243-245°; ir (potassium bromide): 3300 (NH), 1685 (C=O), 1290 and 1120 (SO_2); nmr (deuteriochloroform): δ 1.92 (s, 3H, C-7 Me), 2.0 (s, 3H, C-6 Me), 2.37 (s, 3H, toluene ring Me), 2.78 (t, 2H, C-3 methylene), 3.92 (t, 2H, C-4 methylene), 6.94-7.82 (m, 4H, ArH), 9.0 (broad s, 1H, amide NH) ppm.

6,7-Dimethyl-8-(*p*-chlorophenylsulfonyl)-2-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*][1,3]pyrimidine (Vb).

This compound had ir (potassium bromide): 3290 (NH), 1690 (C=O), 1290, 1130 (SO_2); nmr (deuteriochloroform): δ 1.95 (s, 3H, C-7 Me), 1.98 (s, 3H, C-6 Me), 2.78 (t, 2H, C-3 methylene), 3.92 (t, 2H, C-4 methylene), 7.16-7.85 (m, 4H, ArH), 8.94 (broad s, 1H, amide NH) ppm.

6,7-Dimethyl-8-(cyanomethylsulfonyl)-2-oxo-1,2,3,4-tetrahydropyrrolo-[1,2-*a*][1,3]pyrimidine (Vc).

This compound had ir (potassium bromide): 3280 (NH), 2245 (CN), 1300, 1100 (SO_2); nmr (deuteriochloroform): δ 2.30 (s, 6H, C-6 and C-7 Me), 2.68 (t, 2H, C-3 methylene), 3.97 (t, 2H, C-4 methylene), 4.82 (s, 2H, C-8 sulfone methylene), 9.08 (broad s, 1H, amide NH) ppm.

6,7-Dimethyl-8-(methylsulfonyl)-2-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]-[1,3]pyrimidine (Vd).

This compound had ir (potassium bromide): 3370 (NH), 1675 (C=O), 1250, 1150 (SO_2); nmr (DMSO-d_6): δ 2.01 (s, 6H, C-6 and C-7 Me), 2.68 (t, 2H, C-3 methylene), 3.01 (s, 3H, C-8 sulfone Me), 3.96 (t, 2H, C-4 methylene), 8.84 (broad s, 1H, amide NH) ppm.

6,7-Dimethyl-8-cyano-2-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*][1,3]pyrimidine (Ve).

This compound had ir (potassium bromide): 3150 (NH), 2205 (CN), 1715 (C=O); nmr (DMSO-d_6): δ 1.92 (s, 3H, C-7 Me), 2.01 (s, 3H, C-6 Me), 2.63 (t, 2H, C-3 methylene), 3.90 (t, 2H, C-4 methylene), 10.92 (broad s, 1H, amide NH) ppm.

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