Synthesis of Substituted 2-Amino-3-(alkyl or aryl)sulfonylpyrroles

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A general route for the synthesis of 2-amino-3-(alkyl or aryl)sulfonyl pyrroles is reported.

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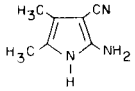
In 1961, Gewald (1) first reported the synthesis of 2-amino-3-cyano-4,5-dimethylpyrrole (I) by the base catalyzed condensation of 3-amino-2-butanone with malononitrile. This technology was extended to the synthesis of 2-amino-3-cyanopyrroles with varying 4 and 5 substituents by a group of Soviet researchers (2) and also in the authors' laboratory (3). 1-Alkyl-2-amino-3-cyanopyrroles have been produced by direct synthesis (4) and by alkylation of the corresponding N,H pyrroles (5).



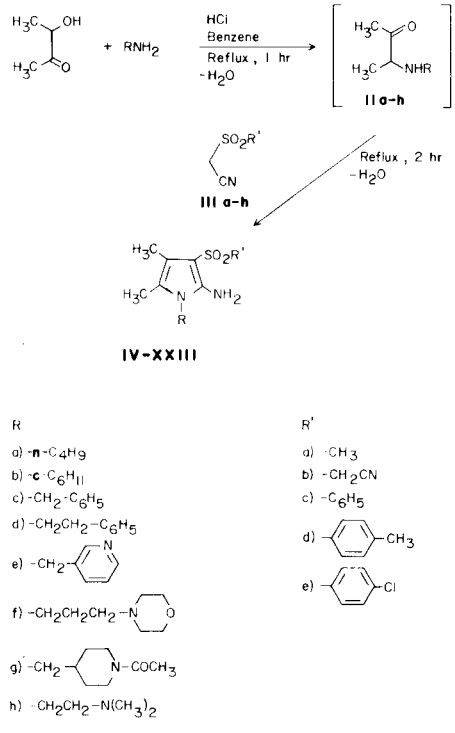
I

In our laboratory, we are concerned with the synthesis of derivatives of 2-aminopyrroles as potential medicinal agents. Such compounds have been reported to possess antiallergic (6), local anesthetic/antiarrhythmic (7,8), hypotensive (9), and anticonvulsant (10,11) properties. The desire to expand the scope of the synthetic possibilities has led us to investigate the synthesis of 2-aminopyrroles with varying 3 substituents.

We now wish to report a facile method (Scheme I) for the synthesis of 1,4,5-trialkyl-2-amino-3-(alkyl or aryl)-sulfonylpyrroles (IV-XXIII). The intermediate alkylamino ketones (IIa-h) were prepared *in situ* by the acid catalyzed reaction of the corresponding amine with acetoin. Addition of the alkyl- or arylsulfonylacetonitrile (IIIa-e) (12-15) to the reaction mixture and further refluxing gave the 2-amino-3-(alkyl or aryl)sulfonylpyrroles (IV-XXIII) in yields from 34.2 to 95.7% (Table I).

The pyrroles (IV-XXIII) were crystallized from either methanol or methanol/water and gave microanalyses, tlc, and spectral data consistent with their structures. The ir spectra showed characteristic absorptions at 3500-3300 cm^{-1} ($-NH_2$); 1640-1610, 1550-1530, and 1500-1465 cm^{-1} (pyrrole ring); and 1305-1265 and 1100-1075 cm^{-1} ($-SO_2-$). The nmr spectra (deuteriochloroform) showed absorptions at δ 1.85-2.02 and 1.89-2.10 for the C4 and C5 methyl groups, and at δ 3.6-5.8 for the amino group. The methylsulfones (IV-VIII) gave a 3-proton singlet at δ 2.9-3.0, and the cyanomethylsulfones (IX and X) gave a 2-proton singlet at δ 3.9. The synthesis of VI is given in the experimental as a general procedure for compounds IV-XXIII.

SCHEME I



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Varian EM360A nmr spectrometer using tetramethylsilane as an internal standard and deuteriochloroform 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. Tlc were performed on Eastman Chromatogram Sheet, type 6060 (silica gel).

1-Benzyl-2-amino-3-methylsulfonyl-4,5-dimethylpyrrole (VI).

A mixture of acetoin (4.15 g. of an 85% aqueous solution, 0.04 mole), benzylamine (4.29 g., 0.04 mole), and aqueous hydrochloric acid (0.2 ml.) in benzene (50 ml.) was stirred and refluxed under a Dean-Stark trap for 1 hour with the evolution of water (0.9 ml.). The mixture was cooled, methyl sulfonylacetonitrile (13) (4.77 g., 0.04 mole) was added, and the mixture then refluxed for 2 hours. The benzene was removed *in vacuo* and the residue recrystallized twice from methanol/water (4:1) to give a white powder (8.4 g., 75.5%, homogeneous on tlc - ethyl acetate, R_f =

0022-152X/80/081793-03$02.25

Table I

Substituted 2-Amino-3-(alkyl or aryl)sulfonylpyrroles

Compound No.	R	R'	Yield (%)	M.p. (°C)	R_f	Recrystallization Solvent	Formula		Analysis (%) Calcd.	Found
IV	a	a	51.1	59-61	.60	methanol/water (5:1)	$C_{11}H_{20}N_2O_2S$	C	54.06	54.11
								H	8.25	8.25
								N	11.47	11.46
								S	13.12	13.08
V	b	a	80.6	142-143	.73 (b)	methanol	$C_{13}H_{22}N_2O_2S$	C	57.74	57.77
								H	8.20	8.24
								N	10.36	10.33
								S	11.86	11.81
VI	c	a	75.5	108-110	.61	methanol	$C_{14}H_{18}N_2O_2S$	C	60.40	60.31
								H	6.52	6.55
								N	10.07	10.02
								S	11.52	11.43
VII	f	a	67.3	132-133	.31	methanol/water (5:1)	$C_{14}H_{25}N_3O_3S$	C	53.30	53.20
								H	7.99	8.00
								N	13.32	13.29
								S	10.17	10.16
VIII	g	a	58.0	180-181	.55 (b)	methanol	$C_{15}H_{25}N_3O_3S$	C	55.02	55.11
								H	7.70	7.79
								N	12.83	12.78
								S	9.79	9.72
IX	b	b	68.5	117-118	.69	methanol	$C_{14}H_{21}N_3O_2S$	C	56.92	57.00
								H	7.17	7.17
								N	14.23	14.25
								S	10.85	10.83
X	c	b	49.4	101-102	.51	methanol	$C_{15}H_{17}N_3O_2S$	C	59.38	59.31
								H	5.65	5.68
								N	13.85	13.81
								S	10.57	10.55
XI	a	c	77.4	121-122	.66 (b)	methanol	$C_{16}H_{22}N_2O_2S$	C	62.71	62.77
								H	7.24	7.27
								N	9.14	9.11
								S	10.46	10.42
XII	b	c	68.3	154-155	.59	methanol	$C_{18}H_{24}N_2O_2S$	C	65.02	64.93
								H	7.27	7.31
								N	8.43	8.37
								S	9.63	9.61
XIII	c	c	70.1	174.5-175.5	.70 (b)	methanol	$C_{19}H_{20}N_2O_2S$	C	67.03	67.12
								H	5.92	5.97
								N	8.23	8.19
								S	9.42	9.38
XIV	a	d	57.3	106-107	.64	methanol/water (10:1)	$C_{17}H_{24}N_2O_2S$	C	63.71	63.75
								H	7.55	7.55
								N	8.74	8.71
								S	10.00	10.02
XV	b	d	72.2	137-138	.94 (b)	methanol	$C_{19}H_{26}N_2O_2S$	C	65.86	65.87
								H	7.56	7.57
								N	8.09	8.10
								S	9.25	9.20
XVI	c	d	67.7	178-179	.67	methanol	$C_{20}H_{22}N_2O_2S$	C	67.76	67.79
								H	6.26	6.28
								N	7.90	7.90
								S	9.05	9.01

Table I continued

Compound No.	R	R'	Yield (%)	M.p. (°C)	R_f	Recrystallization Solvent	Formula		Analysis (%) Calcd.	Found
XVII	d	d	62.4	92-93.5	.64	methanol/water (8:1)	$C_{21}H_{24}N_2O_2S$	C	68.44	68.55
								H	6.57	6.62
								N	7.60	7.58
								S	8.70	8.65
XVIII	e	d	95.7	176-178.5	.36	methanol	$C_{19}H_{21}N_3O_2S$	C	64.20	64.20
								H	5.96	5.99
								N	11.82	11.80
								S	9.02	8.99
XIX	f	d	71.5	140.5-141.5	.44	methanol	$C_{20}H_{29}N_3O_3S$	C	61.35	61.37
								H	7.46	7.49
								N	10.73	10.71
								S	8.19	8.17
XX	a	e	34.2	103-104	.65	methanol/water (10:1)	$C_{16}H_{21}ClN_2O_2S$	C	56.37	56.44
								H	6.21	6.21
								Cl	10.40	10.33
								N	8.22	8.24
								S	9.41	9.42
XXI	b	e	54.5	121-122	.91 (b)	methanol	$C_{16}H_{23}ClN_2O_2S$	C	58.92	58.89
								H	6.32	6.35
								Cl	9.66	9.66
								N	7.64	7.61
								S	8.74	8.73
XXII	c	e	66.7	168-169	.63	methanol	$C_{19}H_{19}ClN_2O_2S$	C	60.87	60.95
								H	5.11	5.11
								Cl	9.46	9.46
								N	7.47	7.46
								S	8.55	8.48
XXIII (a)	h	e	91.7	150-151	.42 (b)	water	$C_{16}H_{22}ClN_3O_2S \cdot HCl$	C	49.98	49.04
								H	5.91	5.92
								Cl	18.07	17.95
								N	10.71	10.68
								S	8.17	8.13

(a) Characterized as the hydrochloride salt. (b) Acetone, all others determined in ethyl actate.

0.61), m.p. 108-110°; ir (potassium bromide): 3450, 3350, 1630, 1550, 1485, 1280, 1090, 945 cm^{-1}; nmr (deuteriochloroform): δ 1.96 (s, 3H, $-CH_3$ at C_4 or C_5), 2.10 (s, 3H, $-CH_3$ at C_4 or C_5), 2.95 (s, 3H, $-SO_2-CH_3$), 4.45 (broad s, 2H, $-NH_2$), 4.83 (s, 2H, $-CH_2-C_6H_5$), 6.8-7.3 (m, 5H-, C_6H_5).

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