SYNTHESIS OF N-SUBSTITUTED PYRROLES FROM 1-R-3-R^1-3,4-DICHLOROBUTANONES

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Reaction of acyl chlorides or methallyl chlorides in the present of aluminum chloride gives 1-R-3-R^1-3,4-dichlorobutanones which give 1,2- and 1,2,4-substituted pyrroles with ethanolamine. The dichlorobutanones react with glycine and a-alanine to give the N-pyrrolyl derivatives of acetic and propionic acids.

The five-membered pyrrole aromatic system is one of the most frequently encountered components of natural compounds and the chemistry of pyrrole is probably one of the most studied aspects of synthetic organic chemistry [1].

TABLE 1. Parameters for II, III

Compound	Empirical formula	R*	bp, °C (mm Hg) or mp, °C	n_D^{20}	Yield, %
IIa	$C_9H_{15}NO$	C_3H_7	118 ... 120 (8)	1,5075	78
IIb	$C_9H_{15}NO$	i-C_3H_7	112 ... 114 (8)	1,5060	76
IIc	$C_{10}H_{17}NO$	C_4H_9	120 ... 122 (5)	1,5045	72
IId	$C_{11}H_{19}NO$	C_5H_{11}	128 ... 130 (5)	1,5010	74
IIe	$C_{11}H_{17}NO$	C_5H_9	133 ... 134 (5)	1,5260	55
IIf	$C_{12}H_{19}NO$	C_6H_{11}	153 ... 155 (5)	1,5245	62
IIg	$C_{13}H_{21}NO$	2-$CH_3C_6H_{10}$	160 ... 162 (3)	1,5185	48
IIh	$C_{11}H_{16}ClNO$	1-ClC_5H_8	148 ... 150 (2)	1,5395	52
IIi	$C_{12}H_{18}ClNO$	1-ClC_6H_{10}	174 ... 176 (2)	1,5375	56
IIj	$C_{12}H_{18}ClNO$	4-ClC_6H_{10}	170 ... 172 (2)	1,5380	60
IIk	$C_{10}H_{17}NO$	C_3H_7	115 ... 117 (4)	1,5025	65
IIl	$C_{10}H_{17}NO$	i-C_3H_7	110 ... 112 (4)	1,5010	60
IIm	$C_{11}H_{19}NO$	C_4H_9	121 ... 123 (4)	1,5020	71
IIn	$C_{12}H_{21}NO$	C_5H_{11}	131 ... 133 (3)	1,5015	68
IIo	$C_{12}H_{19}NO$	C_5H_9	121 ... 122 (1)	1,5230	54
IIp	$C_{13}H_{21}NO$	C_6H_{11}	134 ... 136 (1)	1,5205	67
IIq	$C_{14}H_{23}NO$	2-$CH_3C_6H_{10}$	141 ... 143 (1)	1,5145	52
IIr	$C_{13}H_{20}ClNO$	4-ClC_6H_{10}	164 ... 167 (1)	1,5345	55
IIIa	$C_{12}H_{17}NO_2$	C_6H_{11}	124 ... 125 (EtOH—H_2O)	—	55
IIIb	$C_{13}H_{19}NO_2$	C_6H_{11}	128 ... 130 (EtOH)	—	50
IIIc	$C_{13}H_{19}NO_2$	2-$CH_3C_6H_{10}$	132 ... 134 (2)	1,5070	52
IIId	$C_{14}H_{21}NO_2$	2-$CH_3C_6H_{10}$	137 ... 140 (2)	1,5045	51
IIIe	$C_{13}H_{19}NO_2$	C_6H_{11}	152 ... 155 (3)	1,5180	47
IIIf	$C_{14}H_{21}NO_2$	C_6H_{11}	158 ... 160 (3)	1,5145	45
IIIg	$C_{14}H_{21}NO_2$	2-$CH_3C_6H_{10}$	138 ... 141 (2)	1,5060	35
IIIh	$C_{15}H_{23}NO_2$	2-$CH_3C_6H_{10}$	132 ... 134 (MeOH)	—	39

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*I, IIa-j, IIIa, c, e, g: $R^1 = H$; I, IIk-r, IIIb, d, f, h $R^1 = CH_3$; IIIa-d $R^2 = H$; IIIe-h $R^2 = CH_3$.

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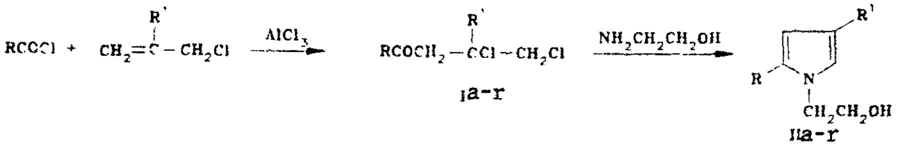
TABLE 2. IR Spectra of IIa-r, IIIa-h

Compound	$\delta(\nu)$, cm^{-1}		
	$\delta_{=C-H}$ & $\nu_{=C-H}$	$\nu_{C=C}$ & $\nu_{C=O}$	ν_{OH} or ν_{COOH}
IIa	780, 890, 3071, 3116	1541, 1614	3210...3500
IIb	786, 879, 3076, 3112, 3141	1535, 1600	3200...3550
IIc	770, 889, 3124, 3142	1538, 1604	3220...3600
IId	785, 881, 3080, 3126	1530, 1604	3200...3450
IIe	781, 880, 3090, 3135	1545, 1605	3200...3550
IIf	785, 865, 3075, 3105	1530, 1610	3200...3550
IIg	724, 785, 865, 3075, 3105	1530, 1600	3200...3600
IIh	770, 885, 3032, 3122	1540, 1595	3200...3500
IIi	780, 894, 3031, 3122	1502, 1550, 1580	3250...3550
IIj	801, 884, 3025, 3095	1542, 1602	3220...3500
IIk	785, 890, 3030, 3125	1510, 1580	3200...3550
IIl	790, 889, 3005, 3141	1540, 1605	3200...3600
IIm	881, 895, 3041, 3125	1512, 1598	3300...3600
IIn	792, 887, 3005, 3112, 3144	1505, 1584	3200...3500
IIo	800, 896, 3015, 3136	1532, 1608	3250...3550
IIp	781, 890, 3122, 3144	1527, 1594	3200...3550
IIq	789, 860, 3080, 3108	1562, 1605	3200...3600
IIr	780, 870, 3060, 3125	1505, 1595	3250...3600
IIIa	780, 890, 3085, 3125	1500, 1570, 1728	2500...3000
IIIb	781, 896, 3072, 3130	1502, 1582, 1730	2500...3000
IIIc	750, 885, 3085, 3115	1548, 1610, 1730	2600...3200
IIId	740, 880, 3090, 3120	1535, 1605, 1730	2500...3000
IIIe	750, 875, 3090, 3105	1535, 1605, 1730	2500...3000
IIIf	745, 880, 3075, 3095	1540, 1595, 1725	2500...3000
IIIg	740, 875, 3085, 3120	1540, 1600, 1728	2500...3000
IIIh	735, 870, 3080, 3110	1555, 1605, 1725	2500...3200

We have previously shown that electrophilic addition of carboxylic acid chlorides to allyl or methallyl chloride in the presence of aluminum chloride under Kondakov–Krapivin conditions [2] gives rise to 1-R-3-R^1-3,4-dichlorobutanones Ia-r. These are convenient starting materials for constructing five-membered heterocyclic systems with one hetero atom and can be used successfully for obtaining furans [3-6]. Treatment of dichloroketones I with phosphorus pentasulfide in DMF leads to 2- and 2,4-substituted thiophenes [6-8] and reaction of I with primary amines in ether to pyrroles [6, 9-11]. There is interest in using this reaction for synthesis of N-substituted pyrroles since compounds of this type cannot always be obtained by traditional methods [1]. With this in mind we have studied the reaction of some dichloroketones I with ethanolamine, glycine, and α-alanine.

Refluxing the dichloroketones Ia-r with a threefold excess of ethanolamine in absolute ether gives the corresponding 1-(2-hydroxyethyl)-2-R-4-R^1-pyrroles (IIa-r) (Table 1).



R and R^1 are the same for I and II, and are given in Table 1.

The structures for pyrroles IIa-r were confirmed by IR and PMR spectroscopy. The IR spectra of II (Table 2) showed broad hydroxyl group absorption at 3200-3600 cm^{-1} and pyrrole ring multiple bond stretching at 1500-1614 cm^{-1}. The PMR spectra (Table 3) showed a broad singlet for the hydroxyl protons (2.95-3.1 ppm), two hydroxyethyl triplets with spin-spin coupling of 7 Hz (3.11-3.31 and 3.85-3.97 ppm), and characteristic pyrrole ring proton multiplets at 5.5-6.9 ppm.

Pyrrole ring formation was also observed when the dichlorobutanone I was treated with glycine of α-alanine to give the corresponding N-pyrrolyl acetic or propionic acids in satisfactory yield (35-55%). The reaction takes place in aqueous alkaline solution of the amino acid (twofold excess of NaOH) at 0 to –5°C with subsequent heating to 60-65°C (Table 1).

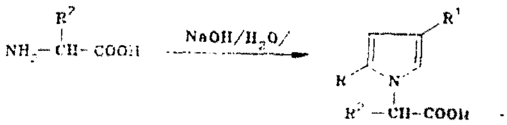


TABLE 3. PMR Spectra of Pyrroles IIb, f, g, i, *l*, p, q, IIIa-h

Compound	σ, ppm (SSCC, J, Hz)						
	3-H, m	5-H, m	R	R'	CH (2H t, J=7 Hz	OCH or CHR	OH or COOH (1H, s)
IIb	6,04	6,78	1,12 (6H, d, J=7); 2,51 (1H, m)	6,21 (1H,m)	3,24	3,91 (2H,t, J=7)	3,08 br.s
IIf	5,51	6,28	1,16 ... 2,21 (11H, m)	5,75 (1H,m)	3,16	3,86 (2H,t, J=7)	3,05 br.s
IIg	5,48	6,27	0,85 (3H, d, J=8); 1,15 ... 2,24 (10H, m)	5,75 (1H, m)	3,18	3,88 (2H,t, J=7)	2,95 br.s
IIi	6,14	6,86	1,21 ... 2,34 (10H, m)	6,32 (1H, m)	3,31	3,97 (2H,t, J=7)	3,1 br.s
IIl	5,98	6,73	1,21 (6H, d, J=7); 2,83 (1H, m)	1,96 (3H, s)	3,11	3,86 (2H,t, J=7)	3,01 br.s
IIp	5,43	6,12	1,1 ... 2,23 (11H, m)	1,94 (3H, s)	3,15	3,85 (2H,t, J=7)	3,05 br.s
IIq	5,50	5,72	0,87 (3H, d, J=8); 1,11 ... 2,26 (10H, m)	1,95 (3H, m)	3,15	3,87 (2H,t, J=7)	3,05 br.s
IIIa	5,61	6,41	1,12 ... 2,34 (11H, m)	5,83 (1H, s)	—	4,26 (2H, s)	11,6
IIIb	5,57	6,30	1,1 ... 2,3 (11H, m)	1,94 (3H, s)	—	4,25 (2H, s)	11,5
IIIc	5,58	6,35	0,85 (3H, d, J=8); 1,2 ... 2,4 (10H, m)	5,76 (1H, m)	—	4,3 (2H, s)	11,5
IIId	5,54	6,30	0,86 (3H, d, J=8); 1,1 ... 2,3 (10H, m)	1,92 (3H, s)	—	4,31 (2H, s)	11,8
IIIe	5,58	6,30	1,1 ... 2,4 (11H, m)	5,8 (1H, m)	—	1,26 (3H, d, J=7,5); 4,58 (1H, q, J=7,5)	10,8
IIIf	5,61	6,28	1,1 ... 2,4 (11H, m)	1,93 (3H, s)	—	1,25 (3H, d, J=7,5); 4,55 (1H, q, J=7,5)	10,6
IIIg	5,55	6,33	0,85 (3H, d, J=8); 1,1 ... 2,3 (10H, m)	5,78 (1H, m)	—	1,23 (3H, d, J=7); 4,57 (1H, q, J=7)	10,8
IIIh	5,58	6,35	0,86 (3H, d, J=8); 1,1 ... 2,3 (11H, m)	1,92 (3H s)	—	1,25 (3H, d, J=7); 4,55 (1H, q, J=7)	10,6

The structure of these pyrroles was also confirmed by IR (Table 2) and PMR (Table 3) spectroscopy. The IR spectra of III showed hydroxyl group absorption at 2500-3200 cm^{-1}, pyrrole ring stretching at 1500-1615 cm^{-1}, and carboxyl group carbonyl absorption at 1725-1730 cm^{-1}. The PMR spectra of IIIa-h showed N-methylene (methine) group proton signals at 4.25-4.58 ppm, characteristic pyrrole ring signals at 5.5-6.4 ppm, and low field signals for the acidic protons at 10.6-11.8 ppm.

Thus, pyrroles II and III may be prepared by this method without separation and purification of the dichlorobutanones I which are synthesized from the acid chloride and allyl or methallyl chloride. The synthesis represents a convenient preparation of N-substituted pyrroles.

EXPERIMENTAL

IR spectra were taken as thin layers or Vaseline mulls on a UR-20 instrument. Proton magnetic resonance spectra were recorded on a Tesla BS-467 (60 MHz) instrument with CCl_4 solvent and TMS internal standard. The purity of the reaction products was monitored by TLC using Silufol UV-254 plates.

Elemental analytical data for C, H, N, and Cl for IIa-r and IIIa-h agreed with that calculated.

General Synthesis of N-Hydroxyethylpyrroles IIa-r. A mixture of aluminum chloride (14.7 g, 0.11 mole) and dry dichloroethane (70 ml) was cooled to –20°C and the acid chloride (0.1 mole) and allyl or methallyl chloride (0.11 mole) added in turn. The reaction mixture was stirred for 1 h at 20°C, decomposed with hydrochloric acid (0.5%), the organic layer separated, and the aqueous extracted with ether (3 × 100 ml). The combined organic extracts were washed successively with water, aqueous $NaHCO_3$ (5%), and water and dried ($CaCl_2$). Solvent was distilled off in vacuo and the residue dissolved in absolute ether (100 ml). Ethanolamine (18.3 g, 0.3 mole) in ether (30 ml) was added slowly to the solution which had been cooled to –10°C. The reaction mixture was refluxed for 4 h on a water bath, cooled, washed with water, 10% aqueous Na_2CO_3, and water and again dried with Na_2SO_4. Solvent was evaporated off and the residue distilled in vacuo or recrystallized.

General Synthesis of 2-(N-Pyrrolyl)acetic and Propionic Acids (IIIa-h). Dichloroketone I (0.1 mole) was added to an aqueous solution of NaOH (8 g, 0.2 mole) and the α-amino acid 0.1 mole) at 0 to –5°C. The temperature was increased to 60-65°C, held for a further 2 h, cooled, diluted with HCl (10%, 100 ml), and extracted with methylene chloride (3 × 100 ml). The combined extracts were washed with water and dried with Na_2SO_4. Solvent was evaporated off and the residue distilled in vacuo or recrystallized.

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