Synthesis of 2-Amino-3-ethoxycarbonylpyrroles

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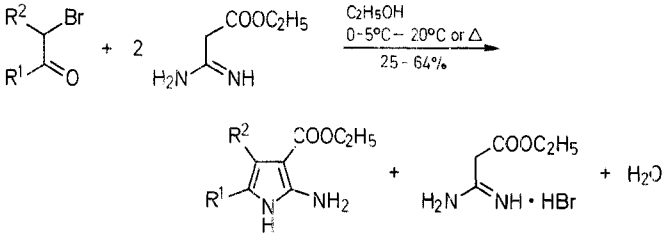
Condensation of ethoxycarbonylacetamidine with α-bromoketones affords a versatile route to 2-amino-3-ethoxycarbonylpyrroles. Selective *N*-methylation is achieved under phase-transfer conditions.

The condensation of acetylaminoacetone with *t*-butyl cyanoacetate was reported to yield 2-amino-3-*t*-butoxycarbonyl-4-methylpyrrole.[1] Following the same approach, a series of α-aminoketones were condensed with *t*-butyl cyanoacetate to give 1-substituted-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrroles.[2] We now wish to report that the condensation of ethoxycarbonylacetamidine with various α-bromoketones[3] provides a versatile route to 2-amino-3-ethoxycarbonylpyrroles (Scheme **A**). Alkyl or aryl substituents can be introduced in position 4 and 5 by properly choosing the starting α-bromoketone. Cyclic α-bromoketones can also be used (Table 1). The α-bromoketones were stirred in absolute ethanol with two equivalents of ethoxycarbonylacetamidine, obtained *in situ* from the hydrochloride[4] and sodium ethoxide, up to the disappearance of the halide component. Pure 2-amino-3-ethoxycarbonylpyrroles were obtained in yields ranging from 25 to 64% after chromatography on a silica gel column and recrystallization from appropriate solvent (Table 1). They are rather unstable at room temperature when dissolved in organic solvents, giving rise to unidentified by-products (TLC). In the case of compound **7** we were unable to isolate in a pure state the corresponding 2-amino-3-ethoxycarbonyl-4,5-dihydro-1*H*-benz[*g*]indole, even by operating under an inert atmosphere. Thus the crude reaction mixture was eventually treated with palladium on carbon in refluxing xylene to convert the 4,5-dihydro derivative to **7**. Similary, we cannot exclude the presence of the dehydro-2-amino-3-ethoxycarbonylindeno[1,2-*b*]pyrrole in the crude reaction mixture of compound **6**.



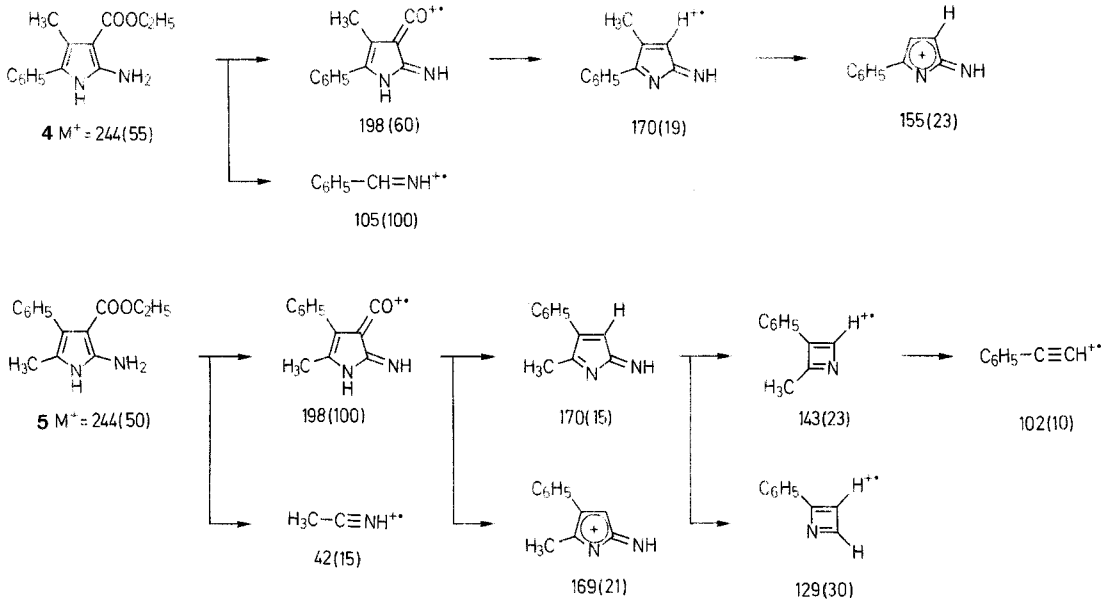
1-7

Scheme **A**

The IR and ^{1}H-NMR spectra confirm the structure of the new 2-aminopyrroles **1–7** (Table 2). All compounds show three strong infrared bands characteristic of the β-enaminoester group[1] at 1660–1630, 1620–1600 and 1570–1510 cm^{-1}, and the stretching bands of NH_2 and NH at 3500–3200 cm^{-1}. Three deuterium exchangeable protons are observed in the ^{1}H-NMR spectrum in deuterochloroform: the NH appears as a broad singlet at $\delta = 7.80–10.84$ ppm and the NH_2 at $\delta = 5.07–5.95$ ppm.

When the substituents in position 4 and 5 are different (compounds **1, 4, 5**) and in the cases of compounds **6** and **7**, two isomers could in principle be obtained as a consequence of the competition between C-alkylation and *N*-alkylation of the ethoxycarbonylacetamidine which preceeds the final ring closure. The demonstration that the C-alkylation is the favoured first step of the condensation comes from the mass spectra of isomers **4** and **5** (Scheme **B**). The fragment with $m/e = 105$ (100%) attributed to $C_6H_5-CH=NH^+$ for compound **4** and the fragment with $m/e = 42$(15%) attributed to $CH_3-C\equiv NH^+$ for compound **5**, confirm the structure shown in Scheme **A**. An additional and definite confirmation comes from the ^{13}C-NMR spectrum of compound **5** (Table 2, footnote h). Shift correlation by long-range coupling experiment ("CALOC") shows couplings of the carbon in position five with the methyl group and NH. It is worth mentioning that the same competition has been observed in the Hantzsch pyrrole synthesis which involves the alkylation of an intermediate enamine by the α-halo carbonyl component.[5] Obviously, the reaction of amidines with α-haloketones, when the C-alkylation is not possible, gives imidazoles.[6]

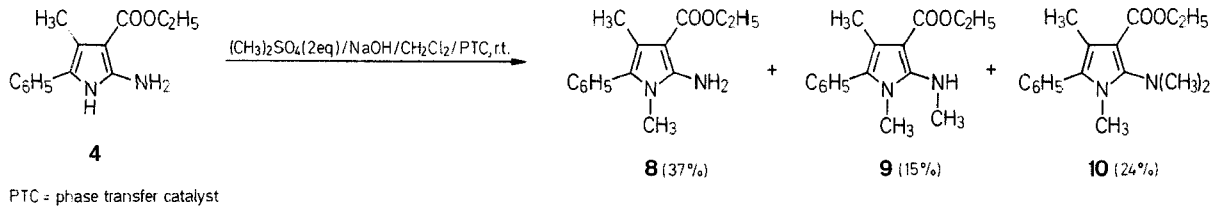
The use of sodium hydride and dimethyl sulfate in tetrahydrofuran was reported to afford selective *N*-methylation of 2-Aminopyrroles.[7] We observed the same selectivity by operating under phase-transfer conditions, already employed for the alkylation of simple pyrroles.[8,9] For instance, methylation of compound **4** by 1.1 equivalents of dimethyl sulfate gives only



Scheme **B**

compound **8** in 67% yield. However, when two equivalents of dimethyl sulfate are employed, compounds **8**, **9** and **10** are simultaneously obtained in 37%, 15% and 24% yield respectively (Scheme **C**).

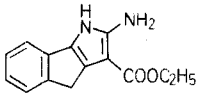
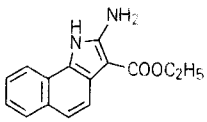
The condensation of ethoxycarbonylacetamidine with bromoacetone and chloroacetaldehyde and the synthesis of a series of 4,7-dihydro-4-oxo-1 *H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acids has been recently reported.[10]



PTC = phase transfer catalyst

Scheme **C**

Table 1. Synthesis of compounds **1–7**

Product No.	α-Bromoketone[a]	R^1	R^2	Reaction Conditions Time (h)	Reaction Conditions Temp. (°C)	Yield (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c]
1	2-Bromoacetophenone	C_6H_5	H	20 0.33	20+ 60	52	121–122 (cyclohexane)	$C_{13}H_{14}N_2O_2$ (230.3)
2	3-Bromo-2-butanone	CH_3	CH_3	2 2	20+ 60	25	127–129 (*t*-$C_4H_9OCH_3$)	$C_9H_{14}N_2O_2$ (182.2)
3	2-Bromo-2-phenyl acetophenone	C_6H_5	C_6H_5	1 0.5	60+ reflux	64	220–222 (C_2H_5OH)	$C_{19}H_{18}N_2O_2$ (306.4)
4	2-Bromopropiophenone	C_6H_5	CH_3	24	20	52	135–136 (*t*-$C_4H_9OCH_3$)	$C_{14}H_{16}N_2O_2$ (244.3)
5	1-Bromo-1-phenyl acetone	CH_3	C_6H_5	1 2	20+ 60	53	155–156 (*t*-$C_4H_9OCH_3$)	$C_{14}H_{16}N_2O_2$ (244.3)
6	2-Bromo-1-indanone			6 6	60+ 80	41	167–169 (*t*-$C_4H_9OCH_3$)	$C_{14}H_{14}N_2O_2$ (242.3)
7	2-Bromo-1-tetralone			2 4	60+ 110[d]	39	182 (dec.) (C_2H_5OH/H_2O)	$C_{15}H_{14}N_2O_2$ (254.3)

[a] See Ref. 3.
[b] Melting points were determined on a Büchi SMP-510 capillary apparatus and are uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.34, H ±0.3, N ±0.4.
[d] Followed by 30 min reflux in xylene with 10% palladium on carbon.

Table 2. Spectrometric Data of Compounds **1–7**

Product No.	IR (Nujol) ν (cm^{-1})[a] NH_2 and NH	$-CO-C=C-N$	^{1}H-NMR ($CDCl_3$) δ (ppm)[b] CH_3CH_2[c]	CH_3CH_2[d]	NH_2	NH[e]	CH_3[f]	aromatic[g] and other protons
1	3500, 3300	1650, 1600, 1560	1.31	4.27	5.22 (s)	8.84	–	7.1–7.4 (5H); 6.62 (d, 1H, J = 2 Hz, 4-H)
2	3450, 3310	1640, 1600, 1510	1.32	4.24	5.09 (br s)	7.80	2.02; 2.08	–
3	3500, 3350	1640, 1600, 1550	0.98	4.02	5.47 (s)	10.02	–	7.0–7.3 (10H)
4	3500, 3450, 3400	1660, 1600, 1570	1.25	4.13	5.22 (s)	8.33	2.28	7.20 (5H)
5[h]	3500, 3330, 3250	1630, 1600, 1550	1.06	4.09	5.07 (br s)	7.89	2.02	7.31 (5H)
6	3450, 3350, 3200	1630, 1600, 1530	1.37	4.29	5.47 (s)	9.95	–	7.0–7.4 (4H); 3.56 (s, 2H, CH_2)
7	3500, 3400, 3300	1660, 1620, 1540	1.47	4.40	5.95 (br s)	10.84	–	7.32 (ddd, J = 8 Hz, 1 Hz, 7-H); 7.44 (ddd, J = 8 Hz, 1 Hz, 8-H); 7.55 (d, J = 9 Hz, 4-H); 7.88 (dd, J = 8 Hz, 9-H); 7.93 (d, J = 9 Hz, 5-H); 8.04 (dd, J = 8 Hz, 6-H)

[a] Recorded on a Perkin-Elmer 157 spectrometer.
[b] Recorded on a Brüker WH-270 spectrometer. A few drops of DMSO-d_6 were added to $CDCl_3$ to aid dissolution of compounds **3** and **7**.
[c] Triplet, 3H, J = 7 Hz.
[d] Quartet, 2H, J = 7 Hz.
[e] Broad singlet.
[f] Singlet.
[g] Multiplet.
[h] ^{13}C-NMR (DMSO-d_6/TMS): δ = 11.03 (CH_3); 14.23 (CH_3CH_2); 57.72 (CH_3CH_2); 90.82 (C-2); 117.31 (C-5); 117.71 (C-4); 124.98, 126.75, 130.36, 136.39 (arom); 146.95 (C-3); 165.61 ppm (CO). Recorded on a Bruker AM-250 spectrometer.

2-Amino-3-ethoxycarbonylpyrroles 1–7; General Procedure:
To a solution of ethoxycarbonylacetamidine hydrochloride[4] (3.33 g, 20 mmol) in anhydrous ethanol (25 ml) maintained at 0–5°C is added 95% sodium ethoxide (1.43 g, 20 mmol). After stirring for 10 min, the appropriate α-bromoketone[3] (10 mmol) is added to the mixture which is stirred for the time and at the temperature shown in Table 1. The ethanol is evaporated under reduced pressure, the residue triturated with ethyl acetate and filtered to removed both the sodium chloride and the hydrobromide of ethoxycarbonylacetamidine. The filtrate is evaporated under reduced pressure and the residue is chromatographed on a silica gel column eluting with 30% ethyl acetate in cyclohexane. Compounds **1–7** so obtained are recrystallized from the solvent given in Table 1. The yields are not optimized. It is subsequently found that a substantial improvement is obtained by operating under argon. In the case of compound **7** it is more expedient to remove the sodium chloride and the hydrobromide of ethoxycarbonylacetamidine by trituration of the crude reaction mixture with water and collect compound **7** by filtration.

Methylation of 2-Amino-3-ethoxycarbonyl-4-methyl-5-phenylpyrrole (4):
To a vigorously stirred solution of compound **4** (4.88 g, 20 mmol), benzyltributylammonium bromide (7.12 g, 20 mmol) and dimethyl sulfate (2.1 ml, 22 mmol) in dichloromethane (50 ml), is added 50% sodium hydroxide (10 ml, 120 mmol) while maintaining the temperature at 0°C. The mixture is stirred for 4 h at room temperature, diluted with dichloromethane (50 ml), the organic phase is separated, washed with 10% aqueous ammonium acetate (2 × 30 ml), dried with magnesium sulfate and evaporated. The residue is chromatographed on a silica gel column eluting with 20% ethyl acetate in cyclohexane to give **8**: yield: 3.5 g (67%). An analytical sample is obtained by recrystallization from t-butyl methyl ether; m.p. 96–97°C.

$C_{15}H_{18}N_2O_2$	calc.	C 69.74	H 7.02	N 10.84
(258.3)	found	69.80	7.09	10.86

^{1}H-NMR ($CDCl_3$): δ = 1.34 (t, 3H, J = 7 Hz, CH_2CH_3); 2.16 (s, 3H, 4-CH_3); 3.22 (s, 3H, NCH_3); 4.29 (q, 2H, CH_2CH_3, J = 7 Hz); 5.09 (br s, 2H, NH_2); 7.2–7.5 ppm (m, 5H_{arom}).

If two equivalents of dimethyl sulfate are added to the solution of compound **4**, tetrabutylammonium hydrogensulfate and 50% sodium hydroxide in dichloromethane (same molar ratios as described above), compound **8** is obtained in a 37% yield together with the dimethylated derivative **9** (15%) and the trimethylated derivative **10** (24%). The three compounds can be separated by chromatography on a silica gel column eluting with 10% ethyl acetate in cyclohexane. Compound **9** is recrystallized from t-butyl methyl ether; m.p. 88–90°C.

$C_{16}H_{20}N_2O_2$	calc.	C 70.56	H 7.40	N 10.28
(272.4)	found	70.57	7.54	10.25

^{1}H-NMR ($CDCl_3$): δ = 1.36 (t, 3H, J = 7 Hz, CH_2CH_3); 2.18 (s, 3H, 4-CH_3); 2.88 (br d, 3H, $NHCH_3$); 3.31 (s, 3H, NCH_3); 4.29 (q, 2H, CH_2CH_3, J = 7 Hz); 5.84 (br, s, 1H, NH); 7.2–7.5 ppm (m, 5H_{arom}).

Compound **10** is an oil; b.p. 125°C/0.05 mbar.

$C_{17}H_{22}N_2O_2$	calc.	C 71.30	H 7.74	N 9.78
(286.4)	found	71.42	7.44	9.86

^{1}H-NMR ($CDCl_3$): δ = 1.37 (t, 3H, J = 7 Hz, CH_2CH_3); 2.13 (s, 3H, 4-CH_3); 2.83 (s, 6H, $N(CH_3)_2$); 3.30 (s, 3H, NCH_3); 4.30 (q, 2H, CH_2CH_3, J = 7 Hz); 7.27 ppm (m, 5H_{arom}).

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