Reaction of β-Aminocrotonamides with α-Haloketones and α-Hydroxyketones

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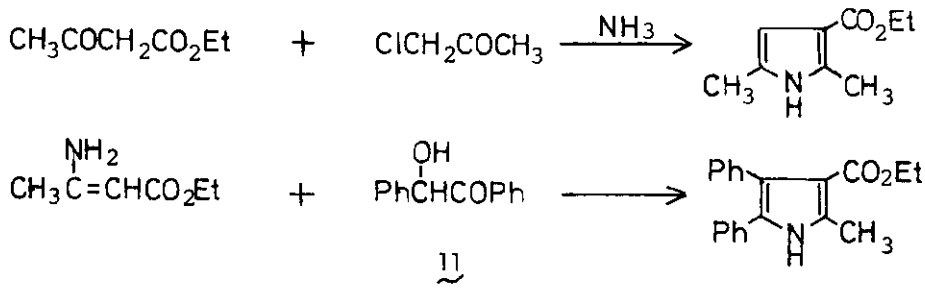
Reaction of bromoacetophenone (4) with β-aminocrotonamide (1) and β-aminocrotonanilide (2) gave 2-methyl-5-phenylpyrrole-3-carboxamide (6) and 2-methyl-5-phenylpyrrole-3-carboxanilide (7), respectively. Similarly, 2-chlorocyclohexanone (5) reacted with (1), (2) and β-amino-(N-methyl)crotonamide (3) to give 2-methyl-4,5,6,7-tetrahydroindole-3-carboxamide derivatives (8, 9 and 10).

Reactions of α-hydroxyketones such as benzoin (11) and acetoin (12) with (1), (2) and (3) afforded 2-methylpyrrole-3-carboxamide derivatives (13 — 18).

The classical Hantzsch pyrrole synthesis[1] proceeds from an α-chloroketone, ethyl acetoacetate, and ammonia. For the formation of the pyrrole derivatives, Hantzsch suggested the formation of ethyl β-aminocrotonate at the first stage, which has been confirmed by Feist[2] and Korschun.[3] On the other hand, pyrrole

derivatives were obtained by the reaction of ethyl β-aminocrotonate with α-hydroxyketones.[4,5,6] For instance, reaction of ethyl β-aminocrotonate with benzoin gave rise to ethyl 4,5-diphenyl-2-methylpyrrole-3-carboxylate.[4] During the course of the investigation of potential uses of diketene, an interest in our laboratory has been focused into the reaction of α-haloketones and α-hydroxyketones with β-aminocrotonamide derivatives, which are readily prepared from diketene[7]. In the present comunnication we wish to report a facile synthetic route of pyrrole derivatives.



A solution of β-aminocrotonamide (1) and bromoacetophenone (4) in ethanol was refluxed for 4 hr, and the reaction mixture was condensed to dryness. The residue was submitted to silica gel column chromatography using ethyl acetate as an eluant to give 2-methyl-5-phenylpyrrole-3-carboxamide (6) in 12% yield, yellow prisms, mp 221 - 222° (dec.).[8]

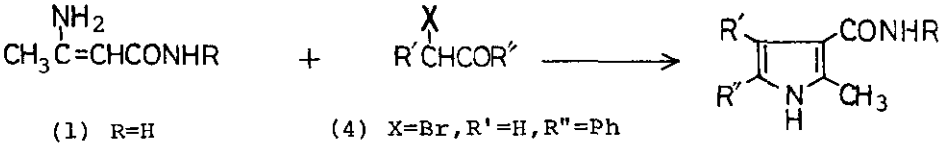
Similarly, bromoacetophenone (4) was allowed to react with β-aminocrotonanilide (2) giving 2-methyl-5-phenylpyrrole-3-carboxanilide (7) in 24% yield, needles (ethyl acetate), mp 249° (dec.).

Similar reaction of 2-chlorocyclohexanone (5) with (1) in ethanol did not proceed resulting in the recovery of starting materials. However, when this reaction was carried out in acetic acid in the presence of sodium acetate, 2-methyl-4,5,6,7-tetrahydroindole-3-carboxamide (8) was obtained in 5% yield, yellow needles (ethyl acetate), mp 193 - 194°.

A similar treatment of (5) with β-aminocrotonanilide (2) and β-amino-(N-methyl)crotonamide (3) gave a 15% yield of 2-methyl-4,5,6,7-tetrahydroindole-3-carboxanilide (9), needles (benzene), mp 195 - 196°, and a 16% yield of 2-methyl-4,5,6,7-tetrahydroindole-3-(N-methyl)carboxamide (10), needles (ethyl acetate), mp 156 - 157.5°, respectively.

A mixture of benzoin (11) and (1) in acetic acid was heated under reflux to give 4,5,-diphenyl-2-methylpyrrole-3-carboxamide (13) in 38% yield, yellow prisms (ethyl acetate), mp 215 - 216° (dec.). Similarly, (11) was allowed to react with (2) and (3) to give a 63% yield of 4,5-diphenyl-2-methylpyrrole-3-carboxanilide (14), needles (benzene-cyclohexane), mp 190 - 191°, and a 55% yield of 4,5-diphenyl-2-methylpyrrole-3-(N-methyl)carboxamide (15), prisms (benzene-cyclohexane), mp 199 - 200°, respectively.

Similar reactions of acetoin (12) with (1), (2) and (3) gave rise to a 31% yield of 2,4,5-trimethylpyrrole-3-carboxamide (16), yellow needles (ethyl acetate-methanol), mp 195°, a 41% yield of 2,4,5-trimethylpyrrole-3-carboxanilide (17), needles (benzene), mp 154.5 - 156°, and a 11% yield of 2,4,5-trimethylpyrrole-3-(N-methyl)carboxamide (18), needles (benzene), mp 170 - 170.5°, respectively.



(1) R=H
(2) R=Ph
(3) R=CH_3

(4) X=Br, R'=H, R"=Ph
(5) X=Cl, R'-R"=$-(CH_2)_4-$
(11) X=OH, R'=R"=Ph
(12) X=OH, R'=R"=CH_3

(6) R=H, R'=H, R"=Ph
(7) R=Ph, R'=H, R"=Ph
(8) R=H, R'-R"=$-(CH_2)_4-$
(9) R=Ph, R'-R"=$-(CH_2)_4-$
(10) R=CH_3, R'-R"=$-(CH_2)_4-$
(13) R=H, R'=R"=Ph
(14) R=Ph, R'=R"=Ph
(15) R=CH_3, R'=R"=Ph
(16) R=H, R'=R"=CH_3
(17) R=Ph, R'=R"=CH_3
(18) R=CH_3, R'=R"=CH_3

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8 All new compounds were characterized satisfactorily by elemental and spectroscopic analyses.

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