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Synthesis of 3-Pyrrol-3'-yloxindoles with a Carbamate Function

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Abstract—By the reaction of methyl {4(3)-[2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetyl]phenyl} carbamates with ethyl 3-aminocrotonate at boiling in the mixture toluene–anhydrous ethanol, 2 : 1, ethyl 5-{3(4)-[(methoxycarbonyl)amino]phenyl}-2-methyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylates were obtained. The condensation of methyl {3(4)-[2-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)acetyl] phenyl}carbamates with ethyl acetoacetate in the presence of ammonium acetate and 20 mol% of 1-methyl-3-butylimidazolium chloride or 1-methyl-3-octylimidazolium tetrafluoroborate at boiling in anhydrous ethanol led to the formation of the corresponding 3-pyrrol-3'-yloxindoles with a carbamate function.

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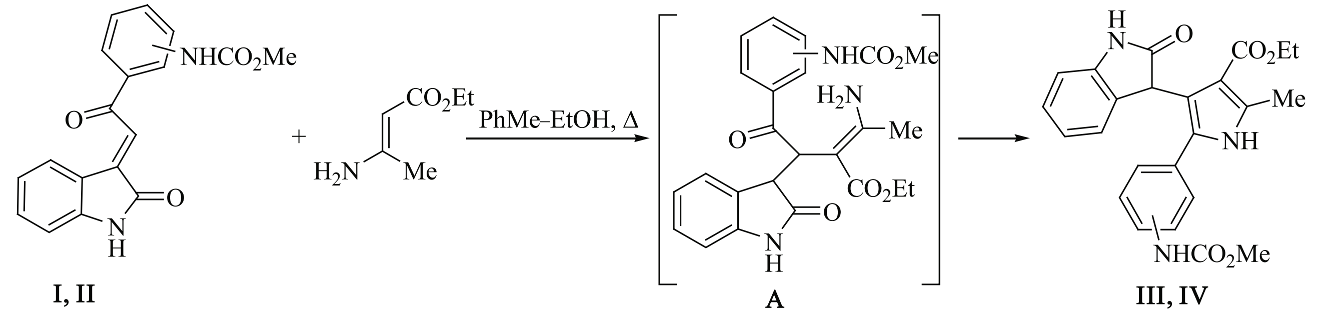
α,β-Unsaturated ketones are widely used in the synthesis of diverse heterocyclic compounds [1–3].

Aiming at the synthesis of new biologically active compounds possessing a carbamate function we studied the reactions of methyl {4(3)-[2-(2-oxo-1,2-dihydro-1*H*-indol-3-ylidene)acetyl]phenyl}carbamates (**I, II**) with ethyl 3-aminocrotonate. The process was performed by boiling over 5 h of equimolar amounts of the reagents in the mixture toluene–anhydrous ethanol, 2 : 1, v/v. The study of the structure of the reaction products by IR, ^{1}H NMR spectroscopy, and mass spectrometry established that the reaction products were ethyl 5-[3(4)-methoxycarbonylaminophenyl]-2-methyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylates (**III, IV**) formed in 88–91% yield.

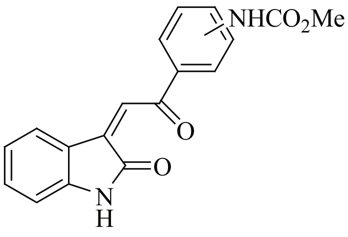


The formation of 3-pyrrole-3'-yloxindoles **III, IV** occurred apparently as a result of the primary attack of the electron-excessive β-carbon atom of the enamine on the electron-deficient carbon atom of compound **I, II** leading to the formation of intermediate compounds **A** further suffering the heterocyclization.

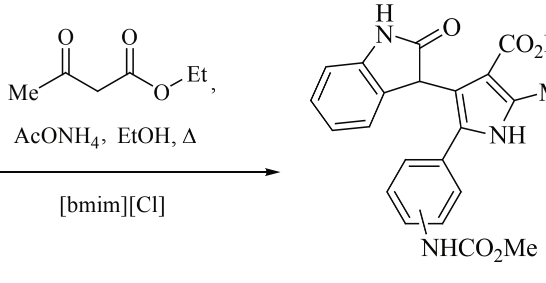
The 3-acetonylideneoxindole is known to react with methyl(ethyl) 3-amino-, methyl 3-(methyl-amino) crotonates with the formation of pyrroloindoles which according to the ^{1}H NMR data exist as keto-enol tautomers [4].

Yet the ^{1}H NMR data showed that 3-pyrrole-3’-yloxindoles **III, IV** existed in the keto form apparently due to the π-stacking between the oxindole and the phenyl ring [5]. In the keto form the atom $C^{3'}$ is sp^3-hybridized thus permitting the rotation of the phenyl ring in the direction of the oxindole providing the possibility of π-stacking. In the enol form the atom $C^{3'}$ becomes sp^2-hybridized favoring the location of the indole and pyrrole rings in the same plane with this atom. This molecular geometry increases strains ant reduces the possibility of π-stacking between the phenyl ring and the oxindole.

The appearance of a singlet signal in the ^{1}H NMR spectra in the region of 4.53–4.55 ppm belonging to the proton $H^{3'}$, and the presence in the IR spectrum of the absorption band of the amide carbonyl group confirm the structure of compounds **III, IV**.



I, II



III, IV

Recently an information appeared on a successful reaction between ethyl acetoacetate and chalcones in the presence of ammonium acetate and 10 mol% of ionic liquid, 1-methyl-3-cyanomethylimidazolium chloride [6, 7].

We investigated the reactions of chalcones **I, II** with ethyl acetoacetate, ammonium acetate in the presence of 10–30 mol% 1-methyl-3-butylimidazolium chloride or 1-methyl-3-octylimidazolium tetrafluoroborate. The process was carried out by boiling the reagents in anhydrous ethanol.

It was found that the shortest process (3 h) and the highest yields of 3-pyrrole-3'-yloxindoles (**III, IV**) were observed at the use of 20 mol% of 1-methyl-3-butylimidazolium chloride. The use of 1-methyl-3-octylimidazolium tetrafluoroborate in these reactions also provides pyrroloindoles **III**, **IV** in high yields (88, 89% respectively), but the required reaction time increased to 4 h. The increase in the ionic liquid concentration to 30 mol% did not result in higher yield or shorter reaction time.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian VXR-500 (500.13 MHz) in DMSO-d_6, internal reference TMS. IR spectra were recorded on a spectrophotometer Specord M82 in the frequency range 4000–400 cm^{-1} from pellets with KBr. Mass spectra were measured on an instrument Finnigan MAT INCOS 50 at the ionizing electrons energy 70 eV. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates.

Methyl {3-[2-(2-oxo-1,2-dihydro-1*H*-indol-3-ylidene)acetyl]phenyl}carbamate (II) was obtained by isatin condensation with methyl N-(3-acetylphenyl) carbamate by procedure [8]. Yield 1.35 g (84%), red-orange crystals, mp 227–229°C (from dioxane). IR spectrum, ν, cm^{-1}: 3410–3340 (NH), 1710 (C=O), 1620, 1575, 1550 (C−C$_{\text{arom}}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, NHCO$_2\underline{\text{Me}}$), 6.89 d (1H$_{\text{arom}}$, *J* 7.5 Hz), 6.96 t (1H$_{\text{arom}}$, *J* 7.5 Hz), 7.35 t (1H$_{\text{arom}}$, *J* 7.5 Hz), 7.52 t (1H$_{\text{arom}}$, *J* 8.0 Hz), 7.67 s (1H, CH), 7.70 d (1H$_{\text{arom}}$, *J* 8.0 Hz), 7.79 d (1H$_{\text{arom}}$, *J* 8.0 Hz), 8.01 d (1H$_{\text{arom}}$, *J* 7.5 Hz), 8.21 s (1H$_{\text{arom}}$), 9.93 br.s (1H, N$\underline{\text{H}}$CO$_2$Me), 10.80 br.s (1H, NHCO). Mass spectrum, *m/z* (I_{rel}, %): 323 (11) $[M + 1]^{+\cdot}$, 322 (83) $[M]^{+\cdot}$, 294 (43), 261 (25), 234 (35), 220 (22), 200 (1.7), 178 (23), 172 (44), 150 (10), 144 (78), 135 (34), 116 (100), 89 (43), 77 (13). Found, %: C 66.85; H 4.32; N 8.57. $C_{18}H_{14}N_2O_4$. Calculated, %: C 67.08; H 4.35; N 8.70.

Ethyl 5-(4-methoxycarbonylaminophenyl)-2-methyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (III). (a) A mixture of 1.61 g (5 mmol) of compound **I**, 0.64 ml (5 mmol) of ethyl 3-aminocrotonate in 15 ml of a mixture toluene–anhydrous ethanol, 2:1, was boiled for 5 h. On cooling the separated crystals were filtered off, washed on the filter with ethyl ether (5 ml), and recrystallized from dioxane. Yield 1.8 g (85%), colorless crystals, mp 194–195°C. IR spectrum, ν, cm^{-1}: 3400–3320 (NH), 1715, 1687 (C=O), 1620, 1560, 1555 (C−C$_{\text{arom}}$). ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, CO$_2$CH$_2$C$\underline{\text{H}}_3$, *J* 7.0 Hz), 2.42 s (3H, CH$_3$), 3.75 q (2H, OC$\underline{\text{H}}_2$CH$_3$, *J* 7.0 Hz), 3.65 s (3H,

$NHCO_2\underline{Me}$), 4.53 s (1H, $H^{3'}$), 6.80–6.84 m ($3H_{arom}$), 7.10–7.14 m ($1H_{arom}$), 7.43 d ($2H_{arom}$, *J* 8.5 Hz), 7.54 d ($2H_{arom}$, *J* 8.5 Hz), 9.75 br.s (1H, $N\underline{H}CO_2Me$), 10.30 br.s (1H, NH), 11.52 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 434 (0.5) $[M+1]^{+\cdot}$, 433 (10) $[M]^{+\cdot}$, 387 (80), 355 (60), 328 (40), 300 (20), 285 (21), 272 (15), 257 (18), 194 (15), 154 (16), 128 (10), 77 (8). Found, %: C 66.27; H 5.27; N 9.53. $C_{24}H_{23}N_3O_5$. Calculated, %: C 66.51; H 5.31; N 9.70.

(b) A mixture of 0.6 g (1.86 mmol) of compound **I**, 0.24 ml (1.86 mmol) of ethyl acetoacetate, 0.14 g (1.86 mmol) of ammonium acetate, 20 mol% of 1-methyl-3-butylimidazolium chloride in 15 ml anhydrous ethanol was boiled for 3 h, the reaction mixture was cooled and poured into 50 ml of distilled water, the separated precipitate was filtered off, washed with water on the filter (20 ml), dried in air, and recrystallized from dioxane. Yield 0.74 g (92%), colorless crystals, mp 194–195°C. Found, %: C 66.33; H 5.20; N 9.47. $C_{24}H_{23}N_3O_5$. Calculated, %: C 66.51; H 5.31; N 9.70.

Ethyl 5-(3-methoxycarbonylaminophenyl)-2-methyl-4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-1*H*-pyrrole-3-carboxylate (IV) was obtained by procedure *a* reacting 5 mmol of compound **II** with 5 mmol of ethyl 3-aminocrotonate. Yield 1.86 g (86%), colorless crystals, mp 214–215°C (from dioxane). IR spectrum, ν, cm^{-1}: 3410–3300 (NH), 1710, 1690 (C=O), 1610, 1565, 1550 ($C-C_{arom}$). ^1H NMR spectrum, δ, ppm: 1.06 t (3H, $CO_2CH_2C\underline{H}_3$, *J* 7.0 Hz), 2.43 s (3H, CH_3), 3.73 q (2H, $OC\underline{H}_2CH_3$, *J* 7.0 Hz), 3.65 s (3H, $NHCO_2\underline{Me}$), 4.55 s (1H, $H^{3'}$), 6.82 t ($2H_{arom}$, *J* 8.0 Hz), 7.10–7.16 m ($3H_{arom}$), 7.19–7.44 m ($2H_{arom}$), 7.62 s ($1H_{arom}$), 9.75 br.s (1H, $N\underline{H}CO_2Me$), 10.31 br.s (1H, NH), 11.60 br.s (1H, NH). Found, %: C 66.35; H 5.41; N 9.44. $C_{24}H_{23}N_3O_5$. Calculated, %: C 66.51; H 5.31; N 9.70.

Compound **IV** was obtained by method *b* reacting 1.86 mmol of compound **II**, 1.86 mmol of ethyl acetoacetate, 1.86 mmol of ammonium acetate, in the presence of 20 mol% of 1-methyl-3-butylimidazolium chloride. Yield 0.73 g (91%), co;orless crystals, mp 214–215°C (from dioxane). Found, %: C 66.42; H 5.27; N 10.04. $C_{24}H_{23}N_3O_5$. Calculated, %: C 66.51; H 5.31; N 9.70.

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