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SHORT COMMUNICATIONS

Synthesis of 3-Phenylisoindolinones by Reaction of 2-Carboxybenzophenone and 2-Methoxycarbonylbenzophenone with Ureas in Formic Acid

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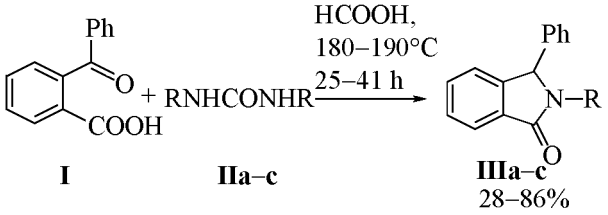
3-Phenylisoindolinone (**IIIa**) was formerly obtained by reaction of 2-carboxybenzophenone (**I**) with formamide in formic acid [1] or stepwise through a preliminary preparation of 3-formamido-3-phenylisoindolinone followed by reduction of the latter with formic acid [2]. Examples are known of compound **IIIa** synthesis by reduction of 2-carboxybenzophenone oxime [3] or by ammonolysis of 3-phenylphthalide [4].

We showed in the preceding studies that benzophenones with ureas in formic acid readily form the corresponding *N*-benzhydrylformamides [5] whereas

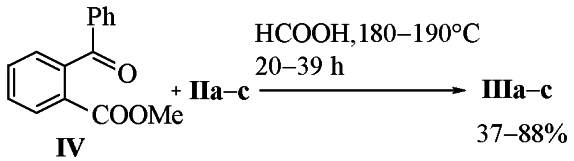


I **IIa–c** **IIIa–c**
28–86%

R=H, Me, Ph.

2-aminobenzophenones under similar conditions afford phenazoline derivatives [6]. In extension of this research [5, 6] we report here on reaction between 2-carboxybenzophenone (**I**) with ureas **IIa–c** in formic acid that was established to be a convenient one-stage synthesis of 3-phenylisoindolin-1-ones (**IIIa–c**).

In order to reveal the preparative opportunities of this convenient reaction we at the early stage of the study prepared by conventional method [7] ester **IV** which with ureas **IIa–c** in formic acid also readily yielded compounds **IIIa–c**.

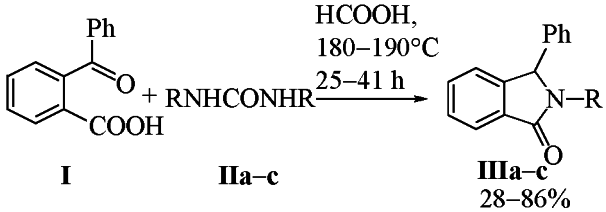


IV

From ester **IV** 3-phenylisoindolinones **IIIa–c** form faster and with higher yield in general agreement with the fact that in nucleophilic substitution the methoxy group is a better leaving group than OH group.

The problem whether the aminating reagent in these reactions is the corresponding amine or isocyanate (the products of ureas **IIa–c** decomposition) is not yet clear. However the sufficiently long time required for formation of products **IIIa–c** suggests that the limiting stage of the reaction is the dissociation of ureas **IIa–c** since the 1,3-disubstituted ureas are known to be less prone to decomposition than urea proper or its N-monosubstituted derivatives [8]. By an example of the synthesis of 3-phenylisoindolinone (**IIIa**) we revealed that under continuous removing of water all the other conditions being the same compound **IIIa** formed 5 times faster. This fact shows that water notably inhibits formation of compounds **IIIa–c** under the chosen conditions.

The additional reductive function of the formic acid in the synthesis of compounds **IIIa–c** was proved by special experiments. For instance, from 2-carboxybenzophenone (**I**) and urea **IIa** in boiling glacial



I **IIa–c** **IIIa–c**
28–86%

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acetic acid within 17 h 3-acetoxy-3-phenyldihydroisoindolinone (**V**) was obtained that in boiling formic acid within 5 h was transformed into compound **IIIa** in 92% yield.

Thus we demonstrated that 2-carboxybenzophenone (**I**) and its methyl ester **IV** cleanly reacted with ureas **IIa–c** in formic acid giving rise to 3-phenylisoindolinones **IIIa–c** which may serve as excellent synthons for preparation of new biologically active compounds.

2-R-3-phenylisoindolin-1-ones (IIIa–c). General procedure. A mixture of 0.01 mol of 2-carboxybenzophenone (**I**) (method *a*) or 2-methoxycarbonylbenzophenone (**IV**) (method *b*), 0.03 mol of urea **IIa–c**, and 60 ml of 99.8% formic acid was heated for 1–2 h on a bath of temperature 120°C. Then within 1 h the bath temperature was raised to 180–190°C, and at this temperature the reaction mixture was maintained for 20–41 h. On cooling the reaction mixture was diluted with 120 ml of water, the separated precipitate was filtered off, washed with warm water, and recrystallized from alcohol.

3-Phenylisoindolin-1-one (IIIa). Reaction time 25 (method *a*) or 20 h (method *b*). Yield 86 (method *a*) or 88% (method *b*). mp 218–219°C, IR spectrum, ν, cm^{-1}: 1680 (C=O), 3215 br (NH). ^1H NMR spectrum, δ, ppm: 5.88 d (1H, C^3H), 7.50–7.93 m (9H, Harom), 8.94 d (1H, NH). ^{13}C NMR spectrum, δ, ppm: 59.63 (C^3H), 123.11–144.87 (C arom), 169.35 (C=O). Found, %: C 80.55; H 5.48; N 6.47. $C_{11}H_{11}NO$. Calculated, %: C 80.36; H 5.30; N 6.69.

(c) In 80 ml of boiling 99.8% formic acid was heated 2.67 g (0.01 mol) of compound **V** for 17 h. Then on cooling the reaction mixture was diluted with 160 ml of water, the separated precipitate was filtered off, washed with warm water, and recrystallized from alcohol. We obtained 1.92 g (92%) of compound **IIIa**. Its characteristics are in full agreement with those of the samples obtained by the previous procedures.

2-Methyl-3-phenylisoindolin-1-one (IIIb). Reaction time 32 (method *a*) or 27 h (method *b*). Yield 55 (method *a*) or 70% (method *b*). mp 97–98°C. IR spectrum, ν, cm^{-1}: 1675 (C=O). ^1H NMR spectrum, δ, ppm: 3.10 (3H, CH_3), 5.86 s (1H, C^3H), 7.35–8.03 m (9H, H arom). ^{13}C NMR spectrum, δ, ppm: 25.51 (NCH_3), 66.05 (C^3H), 127.53–142.58 (C arom), 177.50 (C=O). Found, %: C 80.80; H 6.01; N 6.19. $C_{14}H_{13}NO$. Calculated, %: C 80.69; H 5.87; N 6.27.

2,3-Diphenylisoindolin-1-one (IIIc). Reaction time 41 (method *a*) or 39 h (method *b*). Yield 28 (method *a*) or 37% (method *b*). mp 192–194°C. IR spectrum, ν, cm^{-1}: 1670 (C=O). ^1H NMR spectrum, δ, ppm: 6.85 s (1H, C^3H), 7.07–8.10 m (14H, H arom). ^{13}C NMR spectrum, δ, ppm: 62.20 (C^3H), 121.73–145.78 (C arom), 170.74 (C=O). Found, %: C 84.30; H 5.52; N 4.85. $C_{20}H_{15}NO$. Calculated, %: C 84.19; H 5.30; N 4.91.

(3-Oxo-1-phenyl-2,3-dihydro-1*H*-isoindol-1-yl)-acetate (V). A mixture of 2.26 g (0.01 mol) of 2-carboxybenzophenone (**I**), 1.80 g (0.03 mol) of urea **IIa**, and 60 ml of glacial acetic acid was maintained for 17 h on a bath heated to 180°C. On cooling the reaction mixture was diluted with 120 ml of water, the separated precipitate was filtered off, washed with warm water, and recrystallized from alcohol. We obtained 1.65 g (62%) of compound **V.** mp 245–246°C. ^1H NMR spectrum, δ, ppm: 1.83 (3H, CH_3), 6.87– 7.67 m (9H, H arom), 9.0 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.91 (CH_3), 72.43 (C^1), 120.89–146.52 (C arom), 166.56 (C=O), 168.20 (Me, C=O). Found, %: C 72.11; H 5.02; N 5.35. $C_{16}H_{13}NO_3$. Calculated, %: 71.90; H 4.90; N 5.24.

The reaction progress was monitored and the homogeneity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent benzene–ethanol, 4:1, spots visualized under UV irradiation. IR spectra were recorded on spectrophotometer UR-20 from mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on spectrometer Tesla BS 576A (operating frequencies 100 and 25.142 MHz respectively) from solutions in DMSO-d_6.

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