SYNTHESES OF 3-SUBSTITUTED 3,4-DIHYDROISOCHROMEN-1-ONES

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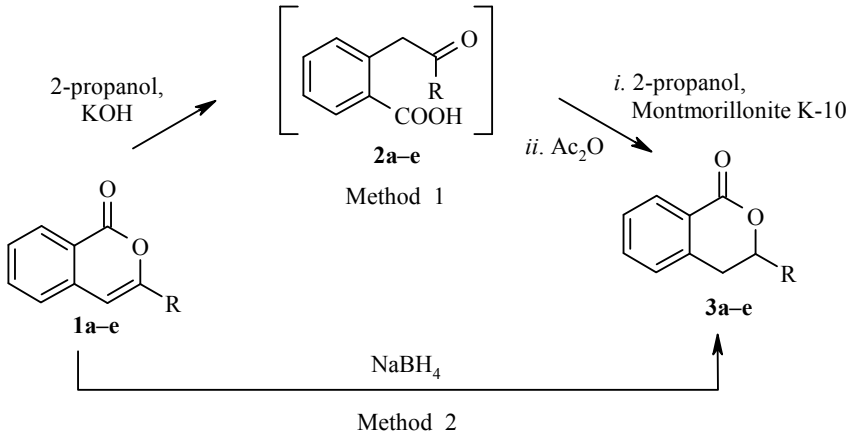
The isochromen-1-one skeleton is found in a variety of natural products [1]. Isocoumarins and their derivatives, such as dihydroisocoumarins, are secondary metabolites of a wide variety of microbial, plant, and insect sources and are used in the synthesis of other medicinal compounds [2-4]. Most methods available for the construction of 3-substituted 3,4-dihydroisochromen-1-one nucleus suffer from one or more drawbacks, such as the multistep procedure [5] and use of expensive and hazardous reagents and solvents. Many studies on isocoumarin synthesis, including cyclization of keto acids and electrophilic cyclization of alkynylbenzoic acid derivatives, have been reported [6, 7]. Finding an efficient method for the synthesis of 3,4-dihydroisochromen-1-one is still a challenge.



1–3 a R = Ph, **b** R = cyclohexyl, **c** R = 4-$MeOC_6H_4$, **d** R = Me, **e** R = thiophen-3-yl

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In continuation of our interest in the synthesis of heterocyclic compounds [8-12], we have developed a new method for the synthesis of 3-substituted 3,4-dihydroisochromen-1-ones from 3-substituted isocoumarins obtained by the treatment of homophthalic acid with acid chlorides [13].

The ^{1}H and ^{13}C NMR spectra were taken on a Bruker AVANCE III spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ with TMS as an internal reference. LC/MS analyses were performed with an LCMS-Agilent-1100 series Ion Trap. GC/MS analyses were performed with the Agilent GCMS-5973 Inert MSD series.

General procedures.

Isocoumarins **1a-e** used in our reaction were prepared as reported previously [13].

Method 1. 3-Substituted isocoumarins **1a-e** (1 mmol) were dissolved in 2-propanol, KOH (0.5 g) pellets were added, and the solution was refluxed for 1 h. After the completion of the reaction, 2-propanol was removed, and water was added to the reaction mixture. The solution was acidified with diluted HCl and extracted with ether. To the keto acid, a clay catalyst, montmorillonite K-10, was added. The mixture was refluxed in 2-propanol for 2 h, and then the solvent was removed under reduced pressure to give solid products **2a-e**. The product was treated with acetic anhydride and refluxed for 1 h, then cold water was added to the mixture and stirred overnight, and the resulting solution was extracted with ether. The ether layer was evaporated under vacuum to yield compounds **3a-e**.

Method 2. 3-Substituted isocoumarins **1a-e** (1 mmol) and sodium borohydride (4 mmol) in methanol were stirred overnight. After that, the solvent was removed under reduced pressure, and then ammonium chloride solution was added to remove the excess sodium borohydride. This mixture was filtered off and dried to give solid 3-substituted 3,4-dihydroisochromen-1-ones **3a**–**e**.

3-Phenyl-3,4-dihydroisocoumarin (3a). Method 1. 85% yield; mp 143°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.13–3.37 (2H, m, CH_2); 5.56-5.60 (1H, m, CH); 7.29 (1H, d, *J* = 7.1, H Ar); 7.31-7.65 (7H, m, H Ar); 8.14 (1H, d, *J* = 7.2, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.4, 79.9, 124.9 (2C), 127.2, 127.8, 128.1, 128.5, 128.6, 130.2 (2C), 133.9, 138.4, 138.8, 164.7. GC/MS, *m/z*: 224.11 $[M]^+$. Found, %: C 80.23; H 5.46; O 14.21. $C_{15}H_{12}O_2$. Calculated, %: C 80.34; H 5.39; O 14.27.

3-Cyclohexyl-3,4-dihydroisochromen-1-one (3b). Method 1. 82% yield; oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.90–0.94 (1H, m, cyclohexyl); 1.18–1.21 (3H, m, cyclohexyl); 1.30–1.83 (6H, m, cyclohexyl); 2.02 (1H, m, cyclohexyl); 2.85-3.03 (2H, m, CH_2); 4.28–4.31 (1H, m, CH); 7.24-7.27 (1H, m, H Ar); 7.37-7.40 (1H, m, H Ar); 7.51–7.55 (1H, m, H Ar); 8.08 (1H, s, H Ar). LC/MS, *m/z*: 231.2 $[M+1]^+$; 232.2 $[M+2]^+$. Found, %: C 78.35; H 7.79; O 13.86. $C_{15}H_{18}O_2$. Calculated, %: C 78.23; H 7.88; O 13.89.

3-(4'-Methoxyphenyl)-3,4-dihydroisochromen-1-one (3c). Method 1. 89% yield; oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10-3.35 (2H, m, CH_2); 3.82 (3H, s, CH_3); 5.51 (1H, m, CH); 6.92 (2H, d, *J* = 8.0, H Ar); 7.28 (1H, d, *J* = 7.0, H Ar); 7.39 (2H, d, *J* = 8.0, H Ar); 7.42 (1H, m, H Ar); 7.54 (1H, m, H Ar); 8.15 (1H, d, *J* = 7.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 35.4, 55.3, 79.8, 114.2, 125.7, 127.1, 127.3, 127.8 (2C), 130.4 (2C), 130.6, 133.8, 139.0, 159.8, 165.5. LC/MS, *m/z*: 255.4 $[M+1]^+$. Found, %: C 75.44; H 5.62; O 18.74. $C_{16}H_{14}O_3$. Calculated, %: C 75.57; H 5.55; O 18.88.

3-Methyl-3,4-dihydroisochromen-1-one (3d). Method 1. 92% yield; oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (3H, d, *J* = 7.0, CH_3); 2.87–3.04 (2H, m, CH_2); 4.62–4.75 (1H, m, CH); 7.24-8.10 (4H, m, H Ar). GC/MS, *m/z*: 162.01 $[M]^+$. Found, %: C 74.14; H 6.17; O 19.69. $C_{10}H_{10}O_2$. Calculated, %: C 74.06; H 6.21; O 19.73.

3-(Thiophen-3-yl)-3,4-dihydroisochromen-1-one (3e). Method 1. 87% yield; oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.28-3.53 (2H, m, CH_2); 5.82-5.85 (1H, m, CH); 7.01–7.04 (1H, m, H Ar); 7.04-7.17 (1H, m, H Ar); 7.27-7.35 (1H, m, H Ar); 7.42-7.61 (1H, m, H Ar); 7.65–7.67 (1H, m, H Ar); 7.90-7.92 (1H, m, H Ar); 8.14 (1H, d, *J* = 7.2, H Ar). GC/MS, *m/z*: 231 $[M+1]^+$. Found, %: C 67.72; H 4.44; O 13.96. $C_{13}H_{10}O_2S$. Calculated, %: C 67.80; H 4.38; O 13.90; S 13.92.

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