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Synthesis of 3-alkylidene-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one derivatives in the THF–H_2O system

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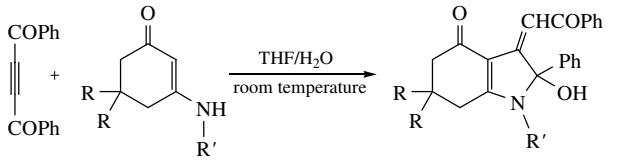
The reactions of dibenzoylacetylene with cyclic enaminocarbonyls in the THF–H_2O system lead to 3-alkylidene-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one derivatives in high yields.

Enaminones are used in the preparation of pyrrole derivatives.[1] The conjugate addition of alkyl 3-aminocrotonates to (*E*)-1,2-dibenzoylethylene leads to polysubstituted pyrroles.[2] As a part of our studies on the development of new routes to heterocyclic systems,[3] we report the reactions of cyclic enaminocarbonyls with dibenzoylacetylene **1** in the THF–H_2O (1:1) system. These reactions are compared with those carried out in CH_2Cl_2. The reaction of **1** with enaminones derived from cyclohexane-1,3-dione or 5,5-dimethylcyclohexane-1,3-dione in the THF–H_2O system leads to 3-alkylidene-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one derivatives **3** (Scheme 1) in high yields.†



1

	R	R′
2a	H	Benzyl
2b	Me	Me
2c	Me	Allyl
2d	Me	Benzyl

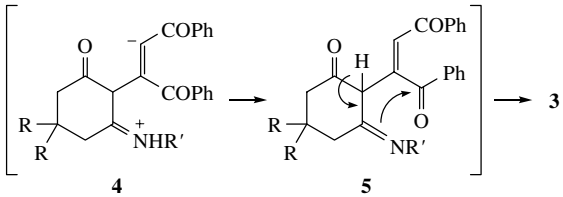
	R	R′	Yield (%)
3a	H	Benzyl	95
3b	Me	Me	95
3c	Me	Allyl	96
3d	Me	Benzyl	92

Scheme 1

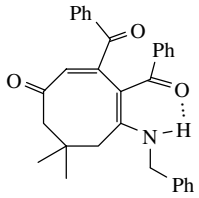
The structures of **3a–d** were deduced from their elemental analyses and IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds are similar and display molecular ion peaks at appropriate *m*/*z* values. The ^{1}H NMR spectrum of **3b** exhibits three singlets identified as two methyl groups (δ 1.18 and 1.19 ppm), N–Me (δ 2.84 ppm) and olefinic protons (δ 8.13 ppm). The OH proton resonance at δ 8.52 ppm disappeared after addition of D_2O to a $CDCl_3$ solution of **3b**. The methylene protons appear as two AB quartets at δ 2.39 and 2.43 ppm, and the protons of aromatic rings exhibit complex multiplets in the aromatic region. The proton-decoupled ^{13}C NMR spectrum of **3b** showed 21 distinct resonances, in agreement with the proposed structure.

Although the mechanism of the reaction between **1** and enaminone **2** is unknown, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of enaminones,[4] it is reasonable to assume that **3** results from initial addition of **2** to the acetylenic ketone and subsequent cyclization of iminoketone intermediate **5** to yield **3**.

Compounds **3a**–**d** were obtained in lower yields (45–80%) when the reactions were carried out in CH_2Cl_2. When the reaction of enaminone **2d** was carried out in CH_2Cl_2, a nearly 1:1 mixture of **3d** and **6** was obtained. The product is the result of a [2+2] cycloaddition reaction between **1** and **2d**, followed by cycloreversion to stable product **6**. Compound **6** was identified from its ^{1}H and ^{13}C NMR spectra. The NH proton signal of **6** appears at 13.27 ppm as a result of strong hydrogen bonding with the vicinal carbonyl group.



Scheme 2



6

Since products **3a**–**d** are insoluble in water, they were easily separated by filtration and washed with distilled water. The simple experimental and workup conditions of presented reactions combined with high yields of products are expected to contribute to the development of a green strategy for the synthesis of 3-alkylidene-1,2,3,5,6,7-hexahydro-4*H*-indol-2-ol derivatives.

† *A typical procedure for the preparation of 1-benzyl-2-hydroxy-3-(2-oxo-2-phenylethylidene)-2-phenyl-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one* **3a**: to a stirred solution of 0.47 g of **1** (2 mmol) in 10 ml of THF and 10 ml of H_2O was added 0.20 g of 3-(benzalamino)-2-cyclohexen-1-one **2a** (2 mmol) at room temperature. The reaction mixture was stirred for 12 h. The precipitate was filtered off and washed with Et_2O. Compound **3a** was obtained as yellow powder, mp 185–187 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.90–2.55 (m, 6H, 3CH_2), 4.45 (q, AB system, 2H, N–CH_2, J_{AB} 16.5 Hz, $\Delta\nu_{AB}$ 180 Hz), 7.12–7.89 (m, 15H, 3Ph), 8.21 (s, 1H, C=CH), 8.67 (br. s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 21.4 (CH_2), 24.6 (CH_2), 37.5 (CH_2), 46.2 (N–CH_2), 96.4 (C–OH), 108.7 (N–C=*C*), 110.2 (CH), 125.7 (CH), 127.2 (CH), 127.7 (CH_{para}), 128.2 (2CH), 128.3 (2CH), 128.7 (2CH), 128.8 (2CH), 128.9 (CH_{para}), 132.5 (CH_{para}), 136.2 (C_{ipso}), 138.6 (C_{ipso}), 139.3 (C_{ipso}), 163.2 (C), 174.4 (N–*C*=C), 191.3 (C=O), 192.5 (C=O). IR (KBr, ν/cm^{-1}): 3410 (OH), 1652 and 1629 (C=O). EIMS, *m*/*z*: 435 (M$^+$), 330, 105, 91, 77.

*For 2-hydroxy-1,6,6-trimethyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one* **3b**: yellow powder, mp 187–189 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.18 (s, 3H, Me), 1.19 (s, 3H, Me), 2.39 (q, AB system, 2H, CH_2, J_{AB} 16.0 Hz, $\Delta\nu_{AB}$ 3 Hz), 2.43 (q, AB system, 2H, CH_2, J_{AB} 17.5 Hz, $\Delta\nu_{AB}$ 42 Hz), 2.84 (s, 3H, N–Me), 7.19–7.88 (m, 10H, 2Ph), 8.13 (s, 1H, C=CH), 8.61 (br. s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 27.8 (N–Me), 28.5 (Me), 29.3 (Me), 33.4 (CH_2), 37.4 (CH_2), 51.7 (*C*Me$_2$), 96.6 (C–OH), 107.4 (N–C=*C*), 109.3 (CH), 125.5 (2CH), 128.1 (2CH), 128.3 (2CH), 128.6 (2CH), 128.6 (CH_{para}), 132.4 (CH_{para}), 138.6 (C_{ipso}), 138.7 (C_{ipso}), 163.1 (3C), 172.6 (N–*C*=C), 190.2 (C=O), 192.4 (C=O). IR (KBr, ν/cm^{-1}): 3420 (OH), 1658 and 1633 (C=O). EIMS, *m*/*z*: 387 (M$^+$), 370, 354, 282, 105, 77.

*For allyl-2-hydroxy-6,6-dimethyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one* **3c**: pale yellow crystals, mp 177–179 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.15 (s, 3H, Me), 1.16 (s, 3H, Me), 2.38 (q, AB system, 2H, CH_2, J_{AB} 16.0 Hz, $\Delta\nu_{AB}$ 3 Hz), 2.46 (q, AB system, 2H, CH_2, J_{AB} 17.5 Hz, $\Delta\nu_{AB}$ 36 Hz), 3.90 (ABX system, 2H, CH_2N, J_{AB} 17.0 Hz, $J_{AX} = J_{BX}$ = 5.5 Hz), 5.01 (d, 1H, CH, $^3J_{HH}$ 10.5 Hz), 5.04 (d, 1H, CH, $^3J_{HH}$ 16.0 Hz), 5.36 (m, 1H, CH), 7.21–7.88 (m, 10H, 2Ph), 8.14 (s, 1H, C=CH), 8.56 (br. s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.5 (Me), 29.0 (Me), 33.6 (CH_2), 37.5 (CH_2), 44.7 (N–CH_2), 51.7 (*C*Me$_2$), 96.8 (C–OH), 107.4 (N–C=*C*), 109.6 (CH), 117.7 (CH), 125.6 (2CH), 128.1 (2CH), 128.2 (2CH), 128.6 (2CH), 128.7 (CH_{para}), 132.4 (CH_{para}), 133.0 (CH_2), 138.6 (C_{ipso}), 139.2 (C_{ipso}), 163.0 (C), 173.2 (N–*C*=C), 190.3 (C=O), 192.4 (C=O). IR (KBr, ν/cm^{-1}): 3410 (OH), 1656 and 1634 (C=O). EIMS, *m*/*z*: 413 (M$^+$), 394, 308, 238, 105, 77.

*For 1-benzyl-2-hydroxy-6,6-dimethyl-3-(2-oxo-2-phenylethylidene)-2-phenyl-1,2,3,5,6,7-hexahydro-4*H*-indol-4-one* **3d**: pale yellow crystals, mp 167–169 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.01 (s, 3H, Me), 1.09 (s, 3H, Me), 2.22 (q, AB system, 2H, CH_2, J_{AB} 17.5 Hz, $\Delta\nu_{AB}$ 40 Hz), 2.34 (q, AB system, 2H, CH_2, J_{AB} 16.0 Hz, $\Delta\nu_{AB}$ 5 Hz), 4.45 (q, AB system, 2H, NCH_2, J_{AB} 16.5 Hz, $\Delta\nu_{AB}$ 90 Hz), 7.14–7.88 (m, 15H, 3Ph), 8.19 (s, 1H, C=CH), 8.71 (br. s, 1H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.4 (Me), 28.8 (Me), 33.6 (CH_2), 37.9 (CH_2), 46.1 (N–CH_2), 51.7 (*C*Me$_2$), 97.0 (C–OH), 107.6 (N–C=*C*), 109.8, (CH), 125.6 (2CH), 126.9 (2CH), 127.6 (CH_{para}), 128.2 (2CH), 128.3 (2CH), 128.6 (2CH), 128.7 (2CH), 128.9 (CH_{para}), 132.5 (CH_{para}), 136.4 (C_{ipso}), 138.6 (C_{ipso}), 139.4 (C_{ipso}), 162.9 (C), 173.5 (N–*C*=C), 190.4 (C=O), 192.5 (C=O). IR (KBr, ν/cm^{-1}): 3435 (OH), 1655 and 1630 (C=O). EIMS, *m*/*z*: 463 (M$^+$), 358, 105, 91, 77.

For 3,4-dibenzoyl-5-(benzylamino)-7,7-dimethyl-2,4-cyclooctadien-1-one **6**: pale yellow crystals, mp 180–182 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 1.14 (s, 3H, Me), 1.32 (s, 3H, Me), 2.32 (d, 1H, CH_2, $^2J_{AX}$ 11.5 Hz), 2.47 (d, 1H, CH_2, $^2J_{AX}$ 13.5 Hz), 2.71 (d, 1H, CH_2, $^2J_{AX}$ 13.5 Hz), 3.48 (d, 1H, CH_2, $^2J_{AX}$ 11.5 Hz), 4.78 (ABX system, 2H, N–CH_2, J_{AB} 15.5 Hz, J_{AX} 5.5 Hz, $\Delta\nu_{AB}$ 36 Hz), 6.28 (s, 1H, C=CH), 7.19–7.45 (m, 15H, 3Ph), 13.27 (br. s, 1H, N–H···O=C). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 28.8 (Me), 29.5 (Me), 38.9 (CH_2), 39.2 (CH_2), 48.3 (N–CH_2), 52.7 (*C*Me$_2$), 105.6 (N–C=*C*), 127.0 (2CH), 127.7 (2CH), 128.1 (CH), 128.3 (2CH), 129.0 (2CH), 129.2 (2CH), 129.7 (2CH), 130.3 (CH_{para}), 132.1 (CH_{para}), 132.2 (CH_{para}), 136.1 (C_{ipso}), 136.6 (C_{ipso}), 142.5 (C_{ipso}), 150.5 (C), 167.8 (N–*C*=C), 195.2 (C=O), 198.5 (C=O), 200.7 (C=O). IR (KBr, ν/cm^{-1}): 3360 (NH), 1716, 1660 and 1648 (C=O). EIMS, *m*/*z*: 463 (M$^+$), 358, 149, 105, 91, 57.

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