ADDITION-CYCLIZATION OF 2-HYDROXY-2,3-DIHYDROINDOL-3-ONES WITH ACETYLENECARBOXYLATES: PREPARATION OF FURO[2,3-*b*]INDOLES

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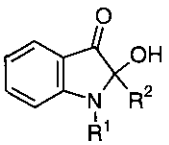
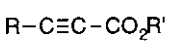
Abstract ——— The reaction of 2-hydroxyindol-3-ones (**1**) with dimethyl acetylenedicarboxylate (**2a**, DMAD) in the presence of base (triethylamine or sodium carbonate) underwent Michael addition followed by cyclization to produce 3a-hydroxyfuro[2,3-*b*]indoles (**3**).

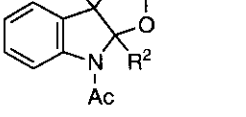
Compounds possessing furo[2,3-*b*]indole skeleton are of interest in connection with their possible biological activities, represented by the Calabar bean alkaloid physovenine[1] and the akuammiline alkaloid aspidodasycarpine.[2] A number of approaches to this skeleton are known: electrophilic addition-cyclization of tryptopholes,[3] reductive cyclization of oxindole-ethanols and -acetates,[4] Baeyer-Villiger oxidation of indolobutanone,[5] reaction of indolylmagnesium bromides with ethylene oxide,[6] reaction of 2-indolyl sulfoxide with ketene,[7] reaction of indoles with dimethyl acetylenedicarboxylate (DMAD),[8] copper catalyzed reaction of isatin-3-hydrazone with DMAD,[9] Knoevenagel reaction-cyclization of isatin,[10] and others.[11-13] The reaction of α-hydroxy ketones with acetylene compounds affords furan compounds.[14] In connection with our studies on the chemistry of indol-3-ones,[15] we here report the reactions of 2-hydroxyindol-3-ones (**1**) with acetylene compounds (**2**) by means of the addition-cyclization of **1a**, **b** with DMAD (**2a**) giving furo[2,3-*b*]indole derivatives (**3**).



1 **a** : R^1= Ac, R^2 = Ph
b : R^1= Ac, R^2 = Me
c : R^1= Ac, R^2 = H
d : R^1= H, R^2 = $CH_2CH{=}CH_2$

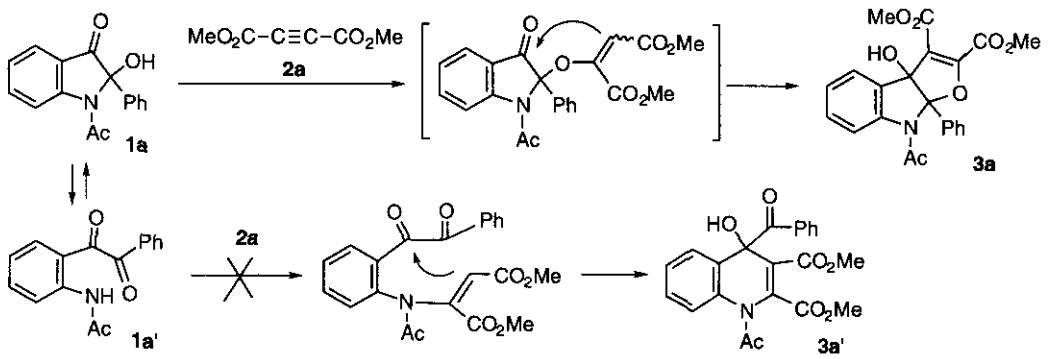


2 **a** : R = CO_2Me, R'= Me
b : R = H, R'= Et
c : R = Me, R'= Et

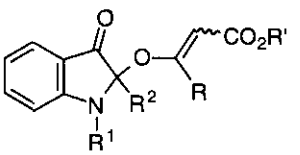


3 **a** : R^2 = Ph
b : R^2 = Me

Initially we examined the reaction of 2-hydroxyindol-3-ones (**1**) with DMAD (**2a**) following the reported procedure.[14a, c] Thus, when 2-phenylindol-3-one (**1a**) was treated with **2a** in the presence of sodium carbonate at room temperature for 44 h, 3a-hydroxyfuro[2,3-*b*]indole (**3a**) was obtained in 44% yield. The structure of **3a** was assigned on the basis of its analytical and spectral data. 2-Hydroxyindol-3-one (**1a**) exists in equilibrium with its open-chain tautomer (**1a'**).[16] However, the isomeric structure (**3a'**) derived from **1a'** was easily ruled out by the appearance of the signals due to 3a-C (δ 91.1 ppm) and 8a-C (δ 113.0) and the lack of the signal due to the koto carbon (δ near 200). The reaction of 2-methylindol-3-one (**1b**)



with **2a** under the same conditions took place slowly to give a low yield (18%) of **3b**. Instead of sodium carbonate, using triethylamine as a base in these reactions resulted in improvement of yields of products (**3a**, **b**): namely heating (110 ℃) of **1a** and **1b** with **2a** in toluene for 30 min gave 79 and 84% yields of **3a** and **3b**, respectively. In the case of 2-hydroxyindol-3-ones (**1c**), however, the desired cyclization did not occur at all to afford Michael adduct (**4c**) (28%). On prolonged heating of **4c** in the presence of triethylamine, no cyclization product was obtained. The reaction of *N*-deacetyl derivative (**1d**) with DMAD (**2a**) also gave the adduct (**4d**) as a mixture (1 : 1) of *E*- and *Z*-isomers in 81% yield. When **1b** was treated with ethyl propiolate (**2b**) under the same conditions, the addition reaction proceeded smoothly to give *Z*-olefin (**4e**) (94%) without a cyclized product (**3**). The reaction of **1b** with ethyl 2-butynoate (**2c**) did not occur at all. Finally, we also attempted the reaction of **1** with the olefinic Michael acceptors dimethyl fumarate and 1,4-diphenyl-2-butene-1,4-dione, but were unsuccessful.



4 c : R^1= Ac, R^2 = H, R = CO_2Me, R'= Me
d : R^1= H, R^2 = $CH_2CH{=}CH_2$, R = CO_2Me, R'= Me
e : R^1= Ac, R^2 = Me, R = H, R'= Et

EXPERIMENTAL

All mps are uncorrected, and were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded with a Hitachi 270-30 or a Shimadzu FTIR-8100 spectrophotometer. NMR spectra were determined with a JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard. MS spectra were obtained with a JEOL JMS-DX302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., 100-200 mesh and Merck, 400 mesh). 1-Acetyl-2,3-dihydro-2-hydroxyindol-3-ones (**1**) were prepared by the reported procedures,[17] respectively. All reactions were carried out under argon.

*Reaction of 1-acetyl-2,3-dihydro-2-hydroxy-2-phenylindol-3-one (**1a**) with dimethyl acetylene-dicarboxylate (**2a**, DMAD)*

a) In the presence of sodium carbonate: A suspension of **1a** (134 mg, 0.5 mmol), **2a** (85 mg, 0.6 mmol) and sodium carbonate (70 mg, 0.7 mmol) in dry acetone (1.5 mL) was stirred at rt for 44 h. The reaction mixture was diluted with dichloromethane. After removal of solids, the filtrate was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (1 : 1) to give dimethyl 8-acetyl-3a-hydroxy-3a,8a-dihydro-8a-phenylfuro[2,3-*b*]indole-2,3-dicarboxylate (**3a**) (90 mg, 44%); mp 220-221 ℃ (ethyl acetate-hexane). Anal. Calcd for $C_{22}H_{19}NO_7$; C, 64.54; H, 4.68; N, 3.42. Found: C, 64.45; H, 4.73; N, 3.35. IR ν ($CHCl_3$); 1753, 1659 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 1.97 (3H, s, Ac), 3.78 (3H, s, OMe), 3.95 (3H, s, OMe), 7.15 (1H, t, *J*=7 Hz, Ar-H), 7.3-7.55 (7H, m, Ar-H), 7.62 (1H, d, *J*=7 Hz, Ar-H), 8.49 (1H, d, *J*=7 Hz, Ar-H). ^{13}C-NMR δ ($CDCl_3$); 25.1, 52.1, 53.3, 91.1, 111.1, 113.0, 116.7, 124.9, 125.0, 126.0, 128.8, 129.0, 129.9, 130.5, 133.7, 143.3, 155.1, 160.0, 162.4, 171.0. MS *m/z*; 409 (M^+, 17%), 367 (18), 322 (15), 280 (59), 248 (100), 208 (16), 105 (23).

b) In the presence of triethylamine: A toluene solution (10 mL) of **1a** (50 mg, 0.19 mmol), **2a** (52 mg, 0.37 mmol), and triethylamine (37 mg, 0.37 mmol) was heated under reflux for 40 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (1 : 2) to give **9a** (61 mg, 79%).

*Reaction of 1-acetyl-2,3-dihydro-2-hydroxy-2-methylindol-3-one (**1b**) with DMAD (**2a**) in the presence of triethylamine* A solution of **1b** (50 mg, 0.24 mmol), **2a** (70 mg, 0.49 mmol) and triethylamine (50 mg, 0.49 mmol) in dry toluene (1 mL) was heated under reflux for 30 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (1 : 1) to give dimethyl 8-acetyl-3a-hydroxy-3a,8a-dihydro-8a-methylfuro[2,3-*b*]indole-2,3-dicarboxylate (**3b**) (71 mg, 84%); mp 108-109 ℃ (ethyl acetate-hexane). Anal. Calcd for

$C_{17}H_{17}NO_7$; C, 58.79; H, 4.93; N, 4.03. Found: C, 58.85; H, 5.00; N, 4.08. IR ν ($CHCl_3$); 1753, 1714, 1655 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 1.93 (3H, s, Me), 2.48 (3H, s, Ac), 3.76 (3H, s, OMe), 3.87 (3H, s, OMe), 4.19 (1H, s, OH), 7.10 (1H, t, *J*=7.5 Hz, Ar-H), 7.28 (1H, t, *J*=7.5 Hz, Ar-H), 7.60 (1H, d, *J*=7.5 Hz, Ar-H), 8.12 (1H, d, *J*=7.5 Hz, Ar-H). ^{13}C-NMR δ ($CDCl_3$); 18.9, 24.7, 52.0, 53.1, 89.5, 109.0, 113.0, 116.9, 124.4, 124.6, 129.0, 130.0, 141.9, 154.3, 159.9, 162.9, 169.9. MS *m/z*; 347 (M^+, 32%), 305 (8), 288 (9), 260 (25), 218 (66), 186 (100), 146 (29).

*Reaction of 1-acetyl-2,3-dihydro-2-hydroxyindol-3-one (**1c**) with DMAD (**2a**) in the presence of triethylamine* A solution of **1c** (50 mg, 0.26 mmol), **2a** (70 mg, 0.49 mmol) and triethylamine (50 mg, 0.49 mmol) in dry toluene (1 mL) was heated under reflux for 15 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (1 : 1) to give dimethyl 1-acetyl-3-oxo-2,3-dihydroindol-2-yloxyfumarate (**4c**) (24 mg, 28%); a viscous oil. IR ν ($CHCl_3$); 1740, 1706, 1640 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.39 (3H, s, Ac), 3.76 (3H, s, OMe), 3.88 (3H, s, OMe), 5.75 (1H, s, OCH), 6.07 (1H, s, =CH-), 7.26 (1H, t, *J*=7.5 Hz, Ar-H), 7.70 (1H, t, *J*=7.5 Hz, Ar-H), 7.74 (1H, d, *J*=7.5 Hz, Ar-H), 8.48 (1H, d, *J*=7.5 Hz, Ar-H). ^{13}C-NMR δ ($CDCl_3$); 23.6, 52.0, 53.2, 84.7, 100.1, 118.1, 121.3, 125.0, 125.1, 138.65, 153.0, 157.1, 165.5, 169.0, 190.8.

*Reaction of 1-acetyl-2-allyl-2,3-dihydro-2-hydroxyindol-3-one (**1d**) with DMAD (**2a**) in the presence of triethylamine* A solution of **1d** (50 mg, 0.26 mmol), **2a** (76 mg, 0.53 mmol) and triethylamine (53 mg, 0.53 mmol) in dry toluene (1 mL) was heated under reflux for 10 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (2 : 3) to give a mixture (1 : 1) of dimethyl 1-acetyl-2-allyl-3-oxo-2,3-dihydroindol-2-yloxy-maleate and -fumarate (**4d**) (71 mg, 81%); a viscous oil. HRMS; Found: M^+331.1057, $C_{22}H_{19}NO_7$ requires M 331.1055. IR ν ($CHCl_3$); 1741, 1636 cm^{-1}. MS *m/z*; 311 (M^+, 31%), 313 (25), 290 (77), 262 (57), 258 (56), 230 (81), 202 (57), 170 (40), 158 (100). Further purification of the mixture of **4d** by column chromatography gave an isomer ;^{1}H-NMR δ ($CDCl_3$); 2.66 (1H, dd, *J*=8.2, 13.2 Hz, C<u>H</u>-CH=), 2.74 (1H, dd, *J*=6.6, 13.2 Hz, C<u>H</u>-CH=), 3.16 (1H, s, NH), 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 5.11 (1H, dd, *J*=1.6, 17.6 Hz, -CH=), 5.12 (1H, dd, *J*=1.6, 11.6 Hz, =CH-), 5.6 (1H, dddd, *J*=6.6, 8.2, 11.6, 17.6 Hz, -CH=), 6.44 (1H, s, =CH-), 6.99 (1H, d, *J*=7.5 Hz, Ar-H), 7.18 (1H, t, *J*=7.5 Hz, Ar-H), 7.33 (1H, t, *J*=7.5 Hz, Ar-H), 7.44 (1H, d, *J*=7.5 Hz, Ar-H).

*Reaction of the indol-3-one (**1b**) with ethyl* propiolate *(**2b**) in the presence of triethylamine* A solution of **1b** (50 mg, 0.24 mmol), **2b** (48 mg, 0.49 mmol) and triethylamine (49 mg, 0.49 mmol) in dry toluene (1 mL) was heated under reflux for 10 min. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-hexane (1 : 2) to give dimethyl (Z)-1-acetyl-2-allyl-3-oxo-2,3-dihydroindol-2-yloxyacrylate (**4e**) (70 mg, 94%); mp 113-115 ℃ (ethyl acetate-hexane). IR ν ($CHCl_3$); 1736, 1713, 1686, 1653 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 1.21 (3H, t, *J*=7.3 Hz, Me), 1.86 (3H, s, Me), 2.44 (3H, s, Ac), 5.54 (1H, d, *J*=11.8 Hz, =CH-), 7.03 (1H, s, *J*=11.8 Hz, =CH-), 7.29 (1H, t, *J*=7.5 Hz, Ar-H), 7.74 (1H, t, *J*=7.5 Hz, Ar-H), 7.74 (1H, d, *J*=7.5 Hz, Ar-H), 8.60 (1H, d, *J*=7.5 Hz, Ar-H). MS *m/z*; 303 (M^+, 1%), 188 (44), 146 (100).

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