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A three-component domino reaction of 2-tetralone, hydroxylamine and acetylene: a one-pot, highly regioselective synthesis of 4,5-dihydrobenz[*e*]indoles

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ABSTRACT

2-Tetralone, hydroxylamine and acetylene react in the system MOH/DMSO to give 4,5-dihydrobenz[*e*]indole and its *N*-vinyl derivatives in up to 41% and 75% (in the case of excess acetylene) yields, respectively. The amount of the alternative regioisomer, *N*-vinyl-4,9-dihydrobenz[*f*]indole, does not exceed 2% (GLC–MS), while the corresponding regioisomer of 4,5-dihydrobenz[*e*]indole is not detectable.

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Derivatives of *e*-, *f*- and *g*-isomers of benzindoles are potential drug precursors[1] possessing antiarrhythmic, central nervous system depressant, anti-inflammatory and antihypertensive activity.[1c] The chemistry of benzindoles has been developed significantly due to the discovery of indole antibiotics (CC-1065 and duocarmycins), which are strong cytotoxins and potential anti-cancer drugs.[2] Among them, benz[*e*]indole isomers are more stable and pharmacologically active.[3] Recently, carbocyanine and 4,4-difluoro-4-boro-3a,4a-diaza-*s*-indacene (BODIPY) dyes with benz[*e*]indole[4] and benz[*g*]indole[5] moieties, showing fluorescence in the near-infrared spectral region, have been synthesized for bio-monitoring. 1*H*-Benz[*f*]indole and its 3-methyl derivatives fluoresce with a high quantum yield (0.8), and in the presence of protein functional groups, fluorescence quenching does not occur. Such benzindoles can be successfully applied for the investigation of peptide–protein and protein–protein interactions.[6]

Unsubstituted *e*- and *g*-isomers of benzindoles have been synthesized by the oxidation of hydroxynaphthopiperidines (in 27% and 30% yields, respectively).[7] The *e*- and *g*-isomers of benzindoles were also obtained by the cyclization of pyruvic acid 1- and 2-naphthylhydrazones under acidic conditions followed by decarboxylation (for the *e*- and *g*-isomers, the yields were 26% and 55%, respectively).[8] Synthesis of the *f*-isomer was accomplished by the reduction of *N*-acetylbenz[*f*]indoxyl with $NaBH_4$ and subsequent hydrolysis of the *N*-acetyl group (26% yield, five steps).[9]

Substituted and annelated 3*H*-benz[*e*]indoles were synthesized from 2-benzylamino-1,4-naphthoquinone by successive treatment with vinylmagnesium bromide and mesityl chloride in the presence of triethylamine (yield 58%).[10] These compounds were also prepared (in 46–48% yield) by photostimulated condensation of 1-bromo(iodo)-2-naphthylamine with ketone enolates in DMSO.[11]

Thus, the synthesis of benzindole derivatives still represents a challenge and the search for expedient methods for their preparation remains of particular importance.

A promising approach to the synthesis of 4,5-dihydrobenz [*g*]indoles from 1-tetralone oxime and acetylene,[12] or its synthetic equivalent vinyl chloride,[13] was described without experimental details (in one page Letters) and was not further developed. This reaction (Trofimov reaction[14]) was also successfully employed for the preparation of 4,5-dihydrobenz[*g*]indoles[5] using the LiOH/DMSO catalytic system instead of KOH/DMSO which was utilized in the previous work. Recently, 4,5-dihydrobenz[*g*]indoles were reported among pyrroles synthesized in a one-pot procedure from ketones and acetylene.[15]

Herein, for the first time, we report on the synthesis of 4,5-dihydrobenz[*e*]indoles **2a,b** via the three-component reaction of 2-tetralone **1**, hydroxylamine and acetylene in an MOH/DMSO system. The isolated yields of indoles **2a** and **2b** reach 41% and 75% (when a large excess of acetylene was used) (Scheme 1).

The reaction was carried out as follows: a mixture of ketone **1**, $NH_2OH{\cdot}HCl$ and $NaHCO_3$ in the molar ratio 1:1.2:1.2 in DMSO was stirred at 70 °C for 0.5 h, and after degassing with argon (to remove CO_2) and adding 1.1–1.7 mol equiv (with respect to **1**) of MOH, the

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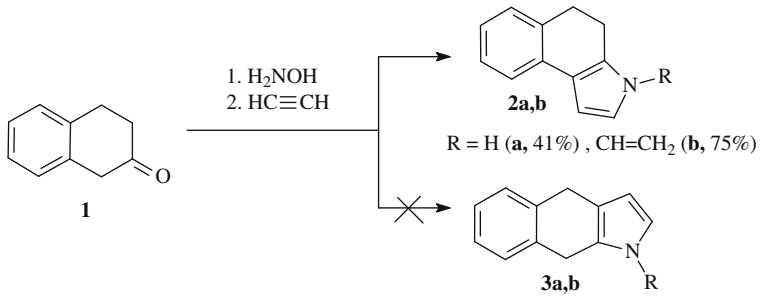


Scheme 1.

Table 1
The yields and ratios of 4,5-dihydrobenz[*e*]indoles obtained under different conditions

Molar ratio **1**:MOH:DMSO	M	Temperature (°C)	Time (h)	Total yield of **2a** + **2b** (%)	Ratio **2a**:**2b**
0.035:0.038:1.397	K	110[a]	3	75	**2b** only
0.035:0.038:1.397	Na	100–110[a]	3	73	3:7
0.007:0.012:0.699	Na	90[b]	1	53	7:3

[a] Initial acetylene pressure = 14 atm.
[b] Initial acetylene pressure = 4 atm.

mixture was heated (90–110 °C) with compressed acetylene for 1–3 h.[16]

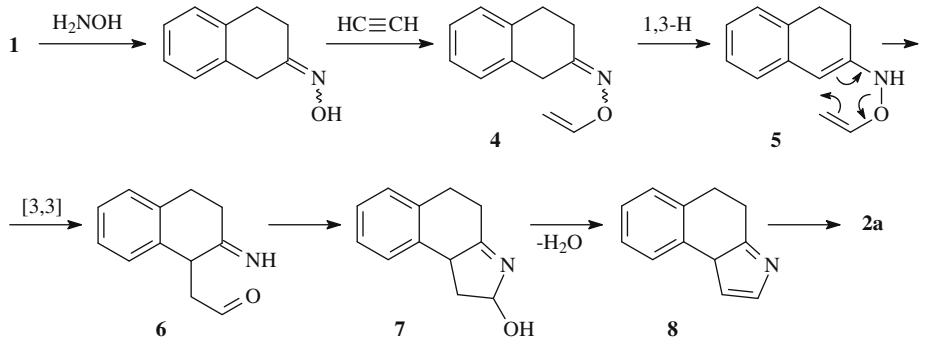
The reaction could in principle involve either 1-CH_2 or the 3-CH_2 groups to deliver a mixture of the *e*-isomers (**2a,b**) and *f*-isomers (**3a,b**) (Scheme 1). In fact, under the conditions studied, the reaction proves to be strictly regioselective to produce *e*-isomers **2a,b** almost exclusively.

In a sample of *N*-vinyl-4,5-dihydrobenz[*e*]indole (**2b**) (Table 1), only 2% of the *f*-isomer **3b** was detected (GLC–MS), while in the non-vinylated *e*-indole **2a**, no other isomeric dihydrobenz[*f*]indoles were discernible.

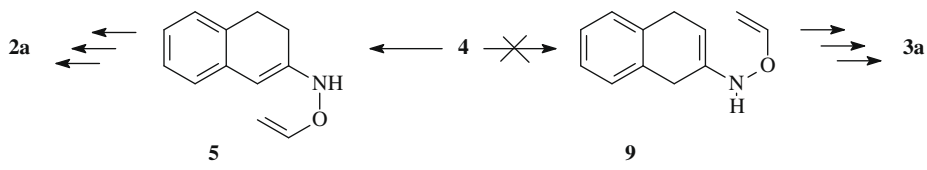
As can be seen from the Table 1, *N*-vinyl-4,5-dihydrobenz[*e*]indole (**2b**) was obtained in 75% yield when the KOH/DMSO catalytic system was used (110 °C, 3 h, initial acetylene pressure = 14 atm). At lower temperature (90–100 °C) in the NaOH/DMSO system, the crude represents a mixture of indoles **2a** and **2b** in a ratio of 3:7–7:3. Pure indole **2a** was isolated by column chromatography (Al_2O_3) in 41% yield.

The three-component reaction involves the formation of *O*-vinyloxime **4** (Scheme 2). According to the established mechanism of the Trofimov reaction,[17] the intermediate **4** undergoes domino transformations (Scheme 2): a 1,3-prototropic shift gives *O*-vinyl hydroxylamine **5** which is further converted (via a 3,3-sigmatropic shift) into imino ketone **6**. The latter cyclizes to hydroxypyrroline **7**, which after dehydration, and aromatization of 3*H*-pyrrole **8** gives the final product **2a**.

The reaction selectivity can be explained based on the consideration of the two intermediates **5** and **9** (Scheme 3). The latter which might lead to *f*-isomer **3a** is obviously less stable (compared to the intermediate **5**) due to the absence of conjugation with the adjacent benzene ring, whereas such conjugation stabilizes intermediate **5**. Unlike their alternative isomers **3a**,**b**, 4,5-dihydrobenz[*e*]indoles **2a**,**b** are conjugated and thus should contribute thermodynamically to the reaction selectivity.



Scheme 2.



Scheme 3.

In conclusion, a short route to hitherto unknown 4,5-dihydrobenz[*e*]indole derivatives, as potential precursors of drugs and optoelectronic materials, from readily available starting materials (2-tetralone, hydroxylamine and acetylene) has been developed. Such dihydrobenzindoles are easily aromatized over NiS/Al_2O_3[18] into the corresponding benzindoles. An apparent advantage of this reaction is the possibility of the selective one-pot preparation of *N*-vinyl-4,5-dihydrobenz[*e*]indole, a potent monomer and intermediate for the synthesis of diverse benz[*e*]indole derivatives by exploring the rich reactivity[17a,19] of the *N*-vinyl group.

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16. *Synthesis of 4,5-dihydrobenz[e]indole* (**2a**). A mixture of $NH_2OH{\cdot}HCl$ (0.59 g, 8.5 mmol), $NaHCO_3$ (0.71 g, 8.5 mmol) and 2-tetralone (1.00 g, 7 mmol) in DMSO (50 mL) was stirred at 70 °C for 30 min, then degassed with argon, and NaOH (0.5 g, 12 mmol) was added. The mixture was placed in a 0.5 L steel rotating autoclave. The autoclave was fed with acetylene at a pressure of 4 atm and then the autoclave was decompressed to atmospheric pressure to remove air. The autoclave was fed with acetylene again at a pressure of 4 atm and heated (90 °C) whilst rotating for 1 h. The reaction mixture, after cooling to room temperature, was diluted with water (150 mL) and extracted with diethyl ether (20 mL × 6). The combined extract was washed with cold water (30 mL × 3) and dried (K_2CO_3) overnight. After removal of the solvent, a crude residue was obtained. Column chromatography (basic Al_2O_3, benzene/hexane 1:3) gave 0.17 g (13%) of **2b** and 0.47 g (41% yield) of **2a** as yellow crystals. Mp 121–122 °C. IR (KBr) ν_{max}: 3405, 3059, 3020, 2932, 2890, 2834, 1606, 1558, 1449, 1426, 1391, 1356, 1310, 1293, 1277, 1245, 1191, 1155, 1110, 1083, 1065, 1035, 1017, 993, 966, 936, 901, 877, 840, 837, 762, 718, 691, 679, 648, 633, 551, 479, 458. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.97 (br. s, 1 H, NH), 7.41 (d, 1 H, H-9, $^3J_{8-9}$ = 7.4 Hz), 7.20 (m, 2 H, H-6, H-8), 7.05 (dd, 1 H, H-7, $^3J_{6-7}$ = 7.4 Hz, $^3J_{7-8}$ = 7.4 Hz), 6.71 (m, 1 H, H-1), 6.50 (m, 1 H, H-2), 3.04 (t, 2 H, H-4, ^3J = 7.8 Hz). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 132.95 (C-5a), 132.53 (C-9a), 128.70 (C-3a), 127.51 (C-6), 126.30 (C-8), 123.99 (C-7), 121.20 (C-9), 118.03 (C-9b), 116.62 (C-2), 103.26 (C-1), 29.32 (C-5), 21.46 (C-4). GLS-MS **2a**, *m/z*: 168 $[M-H]^+$ (100%), 139 $[M-2Me]^+$ (34%), 115 (22%), 97 (85%). Anal. Calcd for $C_{12}H_{11}N$ (169.23): C, 85.17; H, 6.55; N, 8.28. Found: C, 85.14; H, 6.57; N, 8.29.
Synthesis of N-vinyl-4,5-dihydrobenz[e]indole (**2b**). A mixture of $NH_2OH{\cdot}HCl$ (2.92 g, 42 mmol), $NaHCO_3$ (3.53 g, 42 mmol) and 2-tetralone (5.00 g, 35 mmol) in DMSO (100 mL) was stirred at 70 °C for 30 min, then degassed with argon, and $KOH{\cdot}0.5H_2O$ (2.5 g, 38 mmol) was added. The mixture was placed in a 0.5 L steel rotating autoclave. The autoclave was fed with acetylene at a pressure of 4 atm and then the autoclave was decompressed to atmospheric pressure to remove air. The autoclave was fed with acetylene again at a pressure of 14 atm and heated (110 °C) whilst rotating for 3 h. The reaction mixture, after cooling to room temperature, was diluted with water (250 mL) and extracted with diethyl ether (35 mL × 6). The combined extract was washed with cold water (50 mL × 3) and dried (K_2CO_3) overnight. After removal of the solvent, a crude residue was obtained which was purified by flash chromatography (basic Al_2O_3, benzene) to give 5.02 g (75% yield) of **2b** as a yellow-orange oily liquid. IR (KBr) ν_{max}: 3060, 3043, 3013, 2982, 2932, 2889, 2833, 1642, 1606, 1584, 1556, 1505, 1483, 1446, 1425, 1393, 1377, 1360, 1305, 1248, 1219, 1156, 1121, 1080, 1035, 959, 946, 908, 863, 803, 761, 744, 725, 706, 684, 665, 649, 622, 596, 580, 553, 526, 473, 444. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.39 (d, 1 H, H-9, $^3J_{8-9}$ = 7.4 Hz), 7.22 (m, 2 H, H-6, H-8), 7.08 (dd, 1 H, H-7, $^3J_{6-7}$ = 7.4 Hz, $^3J_{7-8}$ = 7.4 Hz), 7.00 (d, 1 H, H-2, $^3J_{1-2}$ = 3.0 Hz), 6.90 (dd, 1 H, H_X, $^3J_{B-X}$ = 15.6 Hz, $^3J_{A-X}$ = 8.9 Hz), 6.57 (d, 1 H, H-1, $^3J_{1-2}$ = 3.0 Hz), 5.15 (d, 1 H, H_A, $^3J_{A-X}$ = 8.9 Hz), 4.75 (d, 1 H, H_B, $^3J_{B-X}$ = 15.6 Hz), 3.04 (t, 2 H, H-4, ^3J = 7.8 Hz). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 132.91 (C-5a), 132.85 (C-9a), 130.18 (C_α), 129.53 (C-3a), 127.89 (C-6), 126.78 (C-8), 124.98 (C-7), 121.74 (C-9), 120.20 (C-9b), 117.12 (C-2), 105.41 (C-1), 98.21 (C_β), 29.44 (C-5), 20.48 (C-4). GLS–MS **2b**, *m/z*: 194 $[M-H]^+$ (100%), 180 $[M-Me]^+$ (37%), 167 $[M-CH{=}CH_2]$ (32%), 152 (28%), 139 (27%), 115 (20%), 97 (45%). GLS–MS **3b**, *m/z*: 195 $[M]^+$ (50%), 180 $[M-Me]^+$ (100%), 167 (7%), 152 (18%), 139 (67%), 115 (20%), 97 (12%). **2b**:**3b** = 98:2. Anal. Calcd for $C_{14}H_{13}N$ (195.27): C, 86.12; H, 6.71; N, 7.17. Found: C, 86.16; H, 6.70; N, 7.14.
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