Synthesis and transformations of 1,4-diethynyl-2-nitrobenzene

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Heating 2-nitro-1,4-bis(1,3,3-trimethylindolin-2-ylideneacetyl)benzene with $POCl_3$ followed by treatment with an aqueous solution of NaOH gave 2-nitro-1,4-diethynylbenzene. Some transformations involving this product were considered. 2-Acetylamino-1,4-diethynylbenzene and its dimorpholinomethyl derivative underwent heterocyclization, resulting in the terminal and methine carbon-substituted indolylacetylenes.

Key words: acetylene fragmentation, indoline enaminoketones, Fischer base, 2-nitro-1,4-diethynylbenzene, aminomethylation, heterocyclization, 6-ethynylindole.

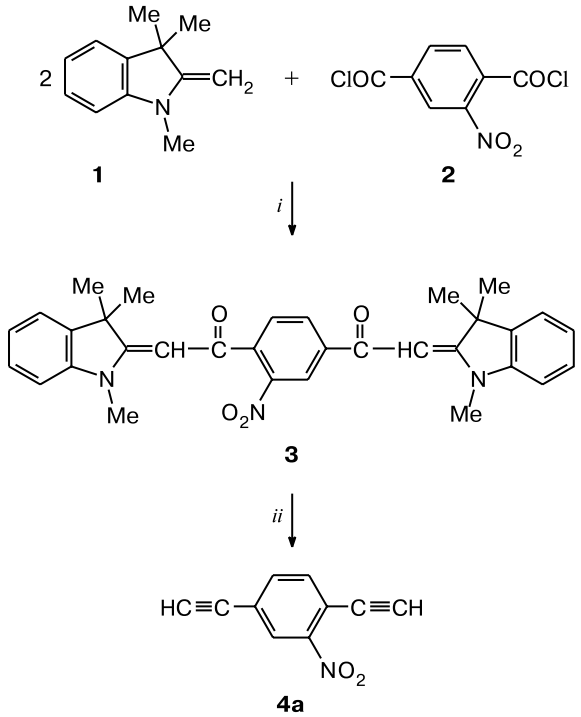
Previously, we have shown[1,2] that the acetylene fragmentation of indoline enaminoketones is a versatile method for the synthesis of various terminal aryl- and hetarylacetylenes irrespective of the electronic properties or the number of substituents in the nucleus. The method involves treatment of enaminoketones, formed in good yields upon condensation of carboxylic acid chlorides with Fischer bases (**1**), with phosphorus oxychloride in hot dioxane and the subsequent cleavage of the resulting indoleninium salts with aqueous alkali. The scope of this method for the synthesis of ethynyl derivatives is restricted only by availability of the starting acids, as the Fischer base, 1,3,3-trimethyl-2-methyleneindoline (**1**), is commercially available.

Similarly, treatment of the Fischer base **1** with nitroterephthalic dichloride (**2**) resulted in the synthesis of diketone **3**, which was converted into 2-nitro-1,4-diethynylbenzene (**4a**) in ~80% yield (Scheme 1).

Condensation of 1,4-diethynyl-2-nitrobenzene (**4a**) with formaldehyde and secondary amines, *e.g.*, morpholine, piperidine, *N*-(2-furoyl)piperazine, in dioxane at 80—90 °C in the presence of CuCl yielded diaminomethyl derivatives **4b—d*** (Scheme 2).

Treatment of nitrodiacetylenes **4a,b** with zinc dust in aqueous ammonia results in amines **5a,b**; one is an oil rapidly darkening in air, while the other is a crystalline solid quite stable in air. These amines react with acetic anhydride in benzene, giving rise to compounds **6a,b** (Scheme 3).

Scheme 1



Reagents and conditions: *i*. Benzene, 24 h; *ii*. (1) $POCl_3$, (2) NaOH.

* Bases **4c,d** could be isolated and characterized only as dihydrochlorides.

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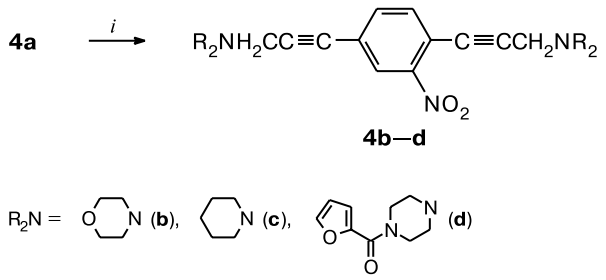
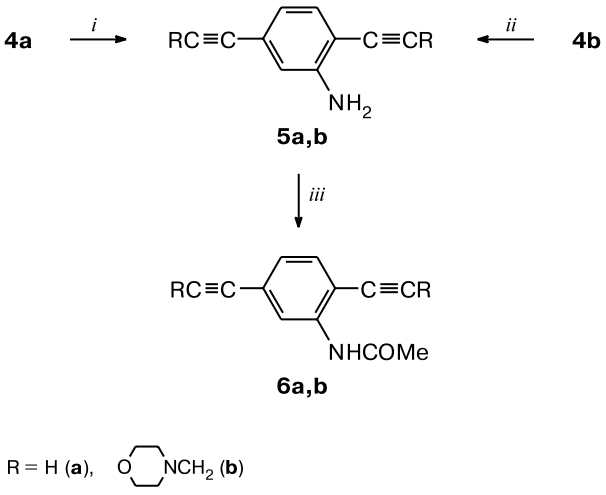
Scheme 2



Reagents and conditions: *i*. R_2NH, CH_2O, CuCl, dioxane, 80—90 °C, 1 h.

Scheme 3



Reagents, conditions, and yields: *i*. Zn, NH_4OH, 20 °C, 48 h; *ii*. Zn, NH_4OH, 70—80 °C, 3 h; *iii*. Ac_2O, benzene, reflux, 2—4 h; yields 30% (**6a**) and 92% (**6b**).

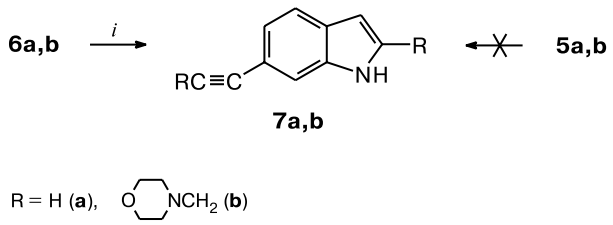
Heating of acetamides **6a,b** with sodium hydride in freshly distilled DMF with subsequent keeping of the reaction mixture for 12 h at room temperature induced heterocyclization accompanied by the removal of the acetyl protective group to give 6-ethynylindole (**7a**) and bis-morpholinomethyl derivative (**7b**). All attempts to carry out cyclization directly of amines **5a** and **5b** in a similar way failed. Our search for other cyclization conditions for these compounds has been unsuccessful either (Scheme 4).

The Mannich base **7b** enters into electrophilic substitution typical of indole. For example, it reacts with morpholine and formaldehyde in glacial acetic acid giving rise to tris(aminomethyl) derivative **8**, which was isolated and characterized as the trihydrochloride (Scheme 5).

The structure of all the synthesized compounds was confirmed by elemental analysis and spectroscopy.

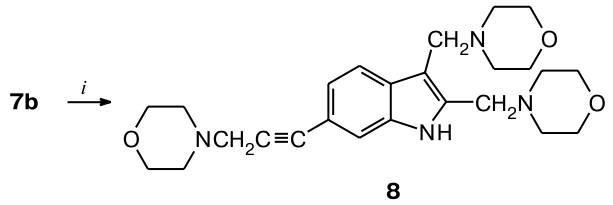
Note also that heterocyclization of 2-acetylamino-1,4-diethynylbenzene (**6a**) to 6-ethynylindole (**7a**) can be considered to be a new method for the synthesis of terminal alkynes of the indole series, because all known methods for the preparation of ethynylindoles consist of transformation of structural fragments linked directly to the indole nucleus.[3—11]

Scheme 4



Reagents, conditions, and yields: *i*. NaH, DMF, 1 h at 80—85 °C and 12 h at ~20 °C; yields 45% (**7a**) and 50% (**7b**).

Scheme 5



Reagents and conditions: *i*. CH_2O, AcOH, O NH, 85 °C, 1 h.

Thus, we synthesized 2-nitro-1,4-diethynylbenzene (**4a**) and studied some of its transformations. It was also shown that *N*-acetyl derivatives **6a,b** cyclize on heating with sodium hydride to give ethynylindoles with simultaneous removal of the acetyl protection. Alkyne **7b** was found to undergo 3-aminomethylation.

Experimental

^1H NMR spectra were recorded on a Bruker WP-200 spectrometer (operation frequency 200 MHz) in $CDCl_3$, DMSO-d_6, acetone-d_6, or DMF-d_7 relative to internal Me_4Si. IR spectra were measured on a UR-20 instrument in mineral oil for compounds **4a—d**, **5b**, **6a—b**, and **7a** and as KBr pellets for compound **7b**. Thin layer chromatography was carried out on Silufol UV-254 plates, which were visualized using a UV lamp. Preparative chromatography was performed on columns with silica gel (100—160 mesh, Kavalier).

2-Nitro-1,4-bis(1,3,3-trimethylindolin-2-ylidenacetyl)benzene (3). A mixture of nitroterephthalic acid (45.1 g, 0.21 mol), thionyl chloride (151 g, 1.27 mol) and DMF (1 mL) in anhydrous benzene (200 mL) was refluxed until dissolution of the starting acid was complete, cooled, and concentrated on a rotary evaporator. To remove excess thionyl chloride, the residue was shaken with petroleum ether (60 mL), which was then evaporated. The resulting dichloride **2** was dissolved in anhydrous

benzene (100 mL) and this solution was added with stirring and water cooling to a solution of Fischer base (**1**) (90 g, 0.52 mol) and triethylamine (52.3 g, 0.52 mol) in anhydrous benzene (400 mL). The reaction mixture was kept for 24 h at room temperature, the precipitate was filtered off, washed on a filter successively with 3% hydrochloric acid, water, 10% aqueous Na_2CO_3, and Pr^iOH, and dried. Yield 84 g (75%), m.p. 246—247 °C (from AcOH). Found (%): C, 73.83; H, 5.77; N, 7.95. $C_{32}H_{31}N_3O_4$. Calculated (%): C, 73.68; H, 5.99; N, 8.06. ^{1}H NMR ($CDCl_3$), δ: 1.86 (s, 12 H, H 2 *gem*-CMe_2); 3.21, 3.35 (both s, 3 H each, NMe); 5.43, 5.93 (both s, 1 H each, =CH); 6.79—8.46 (m, 11 H, H_{arom}).

1,4-Diethynyl-2-nitrobenzene (4a). Compound **3** (23.5 g, 0.14 mol) was heated with phosphorus oxychloride (15.16 mL, 0.17 mol) in dioxane (100 mL) for 6 h at 90 °C. The reaction mixture was cooled, poured into a stirred 10% solution of NaOH (670 mL), and filtered. The filtrate was extracted with chloroform (3×200 mL) and the precipitate on the filter was washed with chloroform (100 mL). The chloroform extracts were combined and dried with sodium sulfate, the solvent was evaporated, and the residue was chromatpgraphed on a column eluting with carbon tetrachloride. Yield 5 g (78%), m.p. 127—128 °C (from EtOH). Found (%): C, 69.93; H, 3.05; N, 8.13. $C_{10}H_5NO_2$. Calculated (%): C, 70.18; H, 2.94; N, 8.18. IR, ν/cm^{-1}: 1350, 1530 (NO_2); 2105 (C≡C); 3270 (≡CH). ^{1}H NMR ($CDCl_3$), δ: 3.32, 3.61 (both s, 1 H each, ≡CH); 7.66 (s, 2 H, H_{arom}); 8.14 (s, 1 H, H_{arom}).

1,4-Bis(3-morpholinoprop-1-ynyl)-2-nitrobenzene (4b). Diacetylene **4a** (3 g, 18 mmol) was dissolved in dioxane (150 mL), and CuCl (0.18 g, 1.8 mmol), 40% formalin (5.4 mL), and morpholine (6.26 mL, 72 mmol) were added to the solution. The reaction mixture was stirred for 1 h at 90 °C and cooled, the solvent was evaporated, ether (5 mL) was added to the resulting oil, and the precipitated crystals were filtered off and washed with ether on the filter. Yield 5.6 g (87%), m.p. 98—99 °C (from EtOH). Found (%): C, 64.85; H, 6.34; N, 11.61. $C_{20}H_{23}N_3O_4$. Calculated (%): C, 65.03; H, 6.28; N, 11.37. IR, ν/cm^{-1}: 2240 ($CH_2C{\equiv}CCH_2$). ^{1}H NMR ($CDCl_3$), δ: 2.61—2.69 (m, 4 H each, CH_2NCH_2, H of both morpholine rings); 3.53, 3.56 (both s, 2 H each, CCH_2), 3.75—3.80 (m, 4 H each, CH_2OCH_2, H of both morpholine rings); 7.56 (s, 2 H, H_{arom}); 8.07 (s, 1 H, H_{arom}).

2-Nitro-1,4-bis(3-piperidinoprop-1-ynyl)benzene dihydrochloride (4c). A mixture of CuCl (0.53 g, 5.3 mmol), formalin (3.95 mL), and piperidine (5.2 mL, 53 mmol) in dioxane (50 mL) was added with stirring to a solution of diacetylene **4a** (3 g, 18 mmol) in dioxane (50 mL). The reaction mixture was stirred for 1 h at 80 °C and cooled, the solvent was evaporated, the residue was dissolved in benzene and washed with a 10% aqueous solution of ammonia and water, and dried with sodium sulfate. The solvent was removed and the resulting oil was dissolved in chloroform and acidified with an ethanol solution of HCl. The precipitate was filtered off and washed with chloroform on the filter. Yield 1.2 g (16%), m.p. 220—225 °C (with dec.). Found (%): C, 60.45; H, 6.89; Cl, 16.47; N, 9.78. $C_{22}H_{27}N_3O_2 \cdot 2HCl$. Calculated (%): C, 60.27; H, 6.67; Cl, 16.19; N, 9.56. ^{1}H NMR (DMSO-d_6), δ: 1.43—1.85 (m, 10 H each, $CH_2CH_2CH_2$, CH_2NCH_2, H of both piperidine rings); 4.32, 4.39 (both s, 2 H each, CCH_2), 7.92—8.34 (m, 4 H each, CH_2OCH_2, H of both piperidine rings); 7.92—8.37 (m, 3 H, H_{arom}); 11.63 (br.s, 2 H, NHCl).

1,4-Bis{3-[4-(2-furoyl)piperazino]prop-1-ynyl}-2-nitrobenzene dihydrochloride (4d). Diacetylene **4a** (1 g, 6 mmol), formalin (1.8 mL), *N*-(2-furoyl)piperazine (2.6 g, 14.5 mmol), and CuCl (0.12 g, 1.2 mmol) were mixed in dioxane (20 mL). The reaction mixture was stirred for 1 h at 80 °C, cooled, and filtered, the filtrate was evaporated, and the residue was dissolved in chloroform. The solution was washed with 10% aqueous ammonia and water and dried with sodium sulfate. The solvent was removed and the resulting oil was dissolved in chloroform and acidified with an ethanol solution of HCl. The resulting oil was covered with acetone and kept for 12 h at room temperature. The precipitate was filtered off, washed on the filter with acetone, dried in a desiccator over $CaCl_2$ and paraffin, and recrystallized from anhydrous EtOH. Yield 1.4 g (37%), m.p. 199—202 °C. Found (%): C, 57.50; H, 5.03; Cl, 11.70; N, 11.20. $C_{30}H_{29}N_5O_6 \cdot 2HCl$. Calculated (%): C, 57.33; H, 4.97; Cl, 11.28; N, 11.14. ^{1}H NMR (DMF-d_7), δ: 3.60 (s, 8 H, H of both piperazine rings); 4.54, 4.58 (both s, 2 H each, CCH_2); 6.68—7.89 (m, 3 H each, H of both furan rings); 7.89—8.37 (m, 3 H, H_{arom}).

2-Amino-1,4-bis(3-morpholinoprop-1-ynyl)benzene (5b). Water (100 mL) was added to a mixture of diacetylene **4a** (5 g, 29.2 mmol), zinc dust (15 g, 230 mmol), and 25% aqueous ammonia (50 mL), the reaction mixture was stirred for 3 h at 70—80 °C and filtrered, the filtrate was extracted with chloroform, and the precipitate was also thoroughly washed with chloroform on the filter. The combined chloroform extracts were dried with sodium sulfate and the solvent was evaporated. Yield 3 g (65.5%), m.p. 125—127 °C (from Pr^iOH). Found (%): C, 69.97; H, 7.17; N, 12.49. $C_{20}H_{25}N_3O_2$. Calculated (%): C, 70.77; H, 7.42; N, 12.38. IR, ν/cm^{-1}: 2235 (C≡C); 3365—3470 (NH_2). ^{1}H NMR ($CDCl_3$), δ: 2.63—3.77 (m, 8 H each, CH_2NCH_2, CH_2OCH_2, H of both morpholine rings); 3.50, 3.58 (both s, 2 H each, $\equiv CCH_2$); 4.18 (br.s, 2 H, NH_2); 6.74 (d, 1 H, H_{arom}, J = 8.12 Hz); 6.77 (s, 1 H, H_{arom}); 7.20 (d, 1 H, H_{arom}, J = 8.12 Hz).

2-Acetylamino-1,4-diethynylbenzene (6a). A mixture of diacetylene **4a** (4.5 g, 26.3 mmol), zinc dust (10.45 g, 160 mmol), 25% aqueous ammonia (19 mL), and water (4.5 mL) was stirred at room temperature for 48 h and filtered. The filtrate was extracted with ether, and the precipitate was washed with ether on the filter. The combined ether extracts were dried with sodium sulfate, the solvent was evaporated, and the remaining oil was dissolved in benzene (50 mL). Acetic anhydride (15 mL) was added and the mixture was refluxed for 4 h. The solvent was evaporated, the residue was chromatographed on a column eluting with chloroform. Yield 1.42 g (30%, based on the starting nitrodiacetylene **4a**), m.p. 123—125 °C (from EtOH). Found (%): C, 78.87; H, 5.10; N, 7.76. $C_{12}H_9NO$. Calculated (%): C, 78.67; H, 4.95; N, 7.64. IR, ν/cm^{-1}: 1650 (MeC=O); 2090 (C≡C); 3200 (NH); 3300 (≡CH). ^{1}H NMR ($CDCl_3$), δ: 3.13, 3.55 (both s, 1 H each, ≡CH); 2.20 (s, 3 H, $COCH_3$); 7.10 (d, 1 H, H_{arom}, J = 7.6 Hz); 7.36 (d, 1 H, H_{arom}, J = 7.6 Hz); 7.86 (br.s, 1 H, H_{arom}); 8.50 (s, 1 H, N<u>H</u>COMe).

2-Acetylamino-1,4-bis(3-morpholinoprop-1-ynyl)benzene (6b). A mixture of amine **5b** (3 g, 8.84 mmol) and Ac_2O (1.8 mL) in benzene (50 mL) was refluxed for 2 h and cooled, the solvent was evaporated, and the residue was recrystallized from Pr^iOH. Yield 3.1 g (92%), m.p. 177—179 °C. Found (%): C, 69.96; H, 7.10; N, 10.89. $C_{22}H_{27}N_3O_3$. Calculated (%): C, 69.27; H, 7.13; N, 11.02. IR, ν/cm^{-1}: 1680 (MeC=O); 2210 (C≡C);

3310 (NH). ^{1}H NMR ($CDCl_3$), δ: 2.20 (s, 3 H, COMe); 2.60—2.66 (m, 4 H each, CH_2NCH_2, H of both morpholine rings); 3.48, 3.59 (both s, 2 H each, $\equiv CCH_2$); 3.69—3.80 (m, 4 H each, CH_2OCH_2, H of both morpholine rings); 7.04 (d, 1 H, H_{arom}, J = 7.9 Hz); 7.29 (d, 1 H, H_{arom}, J = 8.0 Hz); 7.79 (br.s, 1 H, H_{arom}); 8.40 (br.s, 1 H, NHCOMe).

6-Ethynylindole (7a). A mixture of acetamide **6a** (0.5 g, 2.73 mmol) and sodium hydride (0.01 g, 0.42 mmol) in freshly distilled DMF (20 mL) was heated for 80—85 °C and allowed to stand for 12 h at room temperature. The excess of sodium hydride was neutralized with a 10% aqueous solution of ammonium chloride, and water (100 mL) was added. The mixture was extracted with ether, the organic layer was washed with water, and dried with sodium sulfate, the solvent was evaporated, and the residue was subjected to TLC on silica gel plates (5—40 mesh, Kavalier), the product being eluted with benzene. Yield 0.17 g (45%), R_f 0.64 (chloroform), yellow oil. Found (%): C, 85.24; H, 5.12; N, 11.78. $C_{10}H_7N$. Calculated (%): C, 85.08; H, 5.00; N, 11.66. IR, ν/cm^{-1}: 2115 (C≡C); 3280 (≡CH); 3420 (NH). ^{1}H NMR ($CDCl_3$), δ: 3.04 (s, 1 H, ≡CH); 6.53—6.59, 7.20—7.26 (both m, 1 H each, $H(3)_{Ar}$, $H(2)_{Ar}$); 7.26—7.59 (m, 3 H, H_{arom}); 8.15 (br.s, 1 H, NH).

2-Morpholinomethyl-6-(3-morpholinoprop-1-ynyl)indole (7b). A mixture of acetamide **6b** (1.5 g, 3.93 mmol) and sodium hydride (0.288 g, 12 mmol) in 35 mL of freshly distilled DMF was stirred for 1 h at 80 °C and allowed to stand for 12 h at room temperature. The excess of sodium hydride was neutralized with a 25% aqueous solution of ammonium chloride. The mixture was extracted with methylene dichloride and the organic layer was dried with sodium sulfate. The solvent was evaporated and the residue was chromatographed on a column eluting with acetone. The resulting oil was treated with pentane and the precipitated crystals were filtered off and dried. Yield 0.7 g (50%), m.p. 121—123 °C (from Pr^iOH). Found (%): C, 71.28; H, 6.86; N, 11.97. $C_{20}H_{25}N_3O_2$. Calculated (%): C, 70.77; H, 7.42; N, 12.38. IR, ν/cm^{-1}: 2240 (C≡C); 3270 (NH). ^{1}H NMR ($CDCl_3$), δ: 2.54—2.71 (m, 4 each, CH_2NCH_2, H of both morpholine rings); 3.52 (s, 2 H, $C\equiv CCH_2$); 3.60—3.82 (m, 4 H each, CH_2OCH_2, H of both morpholine rings, 2 H, NCH_2); 6.30—6.39 (m, 1 H, $H(3)_{Ar}$); 7.06—7.43 (m, 3 H, H_{arom}); 9.07 (br.s, 1 H, NH).

2,3-Bis(morpholinomethyl)-6-(3-morpholinoprop-1-ynyl)indole trihydrochloride (8). A mixture of compound **7b** (0.5 g, 1.47 mmol), morpholine (0.19 mL, 2.18 mmol), and formalin (0.165 mL) in 10 mL of glacial AcOH was stirred for 1 h at 85 °C, diluted with cold water, neutralized with 10% aqueous NaOH, and extracted with chloroform. The organic layer was dried with sodium sulfate, the solvent was evaporated, and the residual oil was dissolved in an ethanol solution of HCl. Acetone was added to the resulting solution. The precipitated crystals were filtered off, washed with acetone on the filter, and dried. Yield 0.7 g (85%); hygroscopic crystals decomposing in air in about three weeks, m.p. 182—186 °C (with dec.). Found (%): C, 55.10; H, 6.92; Cl, 19.67; N, 10.35. $C_{25}H_{34}N_4O_3 \cdot 3HCl$. Calculated (%): C, 54.80; H, 6.81; Cl, 19.41; N, 10.22. ^{1}H NMR (DMF-d_7), δ: 3.55, 4.05 (both s, 12 H each, CH_2NCH_2, CH_2OCH_2, H of all morpholine rings); 4.47 (s, 1 H, $C\equiv CCH_2$), 4.99, 5.19 (both s, 2 H each, NCH_2); 7.32 (d, 1 H, H_{arom}, J = 8.77 Hz); 7.75 (s, 1 H, H_{arom}); 8.10 (d, 1 H, H_{arom}, J = 8.04 Hz); 12.81 (br.s, 1 H, NH).

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