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Ethynylation of indoles with 1-benzoyl-2-bromoacetylene on Al_2O_3

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Abstract—Indoles are cross-coupled with 1-benzoyl-2-bromoacetylene on Al_2O_3 at room temperature under base and solvent-free conditions to afford 3-(2-benzoylethynyl)indoles in 22–76% yields, thus representing the first examples of direct ethynylation of the indole nucleus.

Indoles are important molecules, which exhibit a wide spectrum of biological activity.[1] Many naturally occurring products contain the indole skeleton as a backbone of their structural frameworks.[2] The biological and pharmacological activity of natural and synthetic indole derivatives has led to the extensive development of diverse methodologies for their synthesis. In particular, highly potent indole building blocks are those with acetylenic moieties. They are currently used in the design of numerous indole structures[2b,3] due to the rich chemistry of the acetylene function.

Different syntheses of indolylacetylenes are known, including the Stephans–Castro reaction (reaction of iodoindoles with copper acetylenes),[4] cross-coupling of iodoindoles with terminal acetylenes in the presence of palladium(0,II) complexes, copper halides and bases,[5] palladium mediated cross-coupling reactions[6] and titanium induced indole formation (reductive cyclization of an oxo-amide).[7]

Also effective are palladium catalyzed cross-coupling reactions of 2-stannylindole with methyl bromopropiolate in DMF and $Pd(PPh_3)_4$ as catalyst,[5b] and the zinc chloride derivative of methyl propiolate with iodoindole.[5b] However, all the known methods for *C*-ethynylation of indoles require either halo (iodo) or metal substituted (Sn) indoles as reactants. To the best of our knowledge, there are no methods for introduction of an acetylenic moiety in place of a CH–indole hydrogen.

Recently,[8] we succeeded in developing a novel cross-coupling employing non-halogenated pyrroles and readily available haloacetylenes. The reaction proceeded in the presence of Al_2O_3 at room temperature requiring no palladium, copper, base or solvent. Consequently, we were intrigued by the prospect of applying this methodology to the synthesis of acetylenic indole derivatives.

Our efforts to reach this goal have led us to the finding that indoles **1a**,**b** can be reacted smoothly under the same conditions with 1-benzoyl-2-bromoacetylene (**2**) to give 3-(2-benzoylethynyl)indoles **3a**,**b** chemo- and regioselectively in 72% and 76% yields, respectively (Scheme 1).[9]

The reaction occurred at room temperature (1 h), when the reactants were ground with a 10-fold mass excess of Al_2O_3 under solvent-free conditions. In the absence of Al_2O_3, the ethynylation did not take place (~1% of a mixture of unidentified products was obtained).

The only side products of the reaction were 1,1-di(indol-3-yl)-2-benzoylethenes **4a**,**b**, detectable in all cases (^{1}H NMR) in small amounts (5–8%). The isolated yield of **4b** was 6%. The adducts **4a**,**b** were most probably

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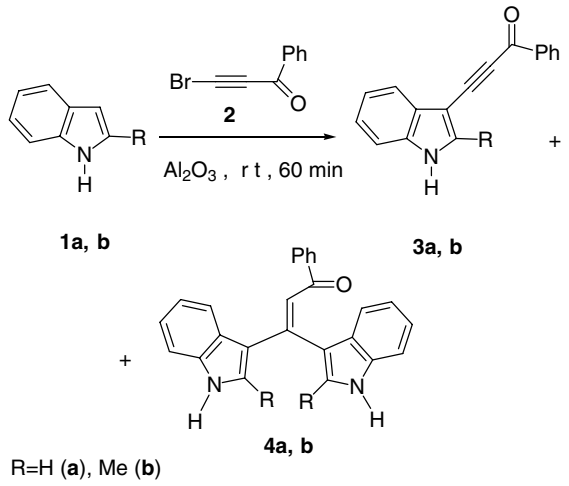


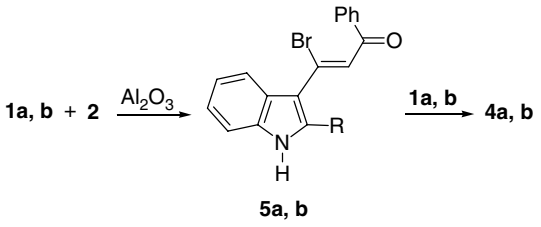
Scheme 1.

formed by substitution of bromine in the intermediates of this reaction, namely the 3-(2-benzoyl-1-bromoethenyl)indoles **5a**,**b** since ethynylindoles **3a**,**b** cannot add indoles **1a**,**b** under the reaction conditions (Scheme 2).

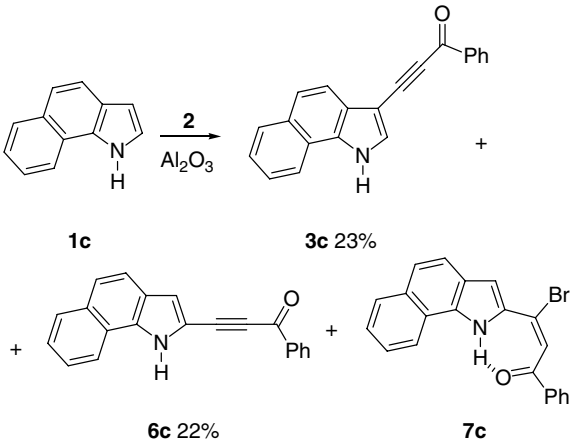
The condensed indole, benz[*g*]indole (**1c**), under the same conditions, was coupled with acetylene **2** to furnish a mixture of 3-(**3c**) and 2-ethynylindole **6c** in a 45% overall yield (based on **1c** consumed, the conversion was 66%) (Scheme 3). In this case, 2-(2-benzoyl-1-bromoethenyl)-benz[*g*]indole (**7c**), stabilized by strong intramolecular H-bonding between the NH and C=O groups (δ NH 14.59 ppm), was also observed.

In accordance with our previous results,[8] 4,5-dihydrobenz[*g*]indole (**1d**), being actually a pyrrole, on reaction with bromobenzoylacetylene **2** on alumina was readily converted to the corresponding 2-ethynylated derivative **3d** in 68% yield (Scheme 4). A side product of the coupling, 2-benzoyl-1,1-di(4,5-dihydrobenz[*g*]indol-2-yl)-ethene (**4d**), was isolated in 9% yield (Scheme 4).

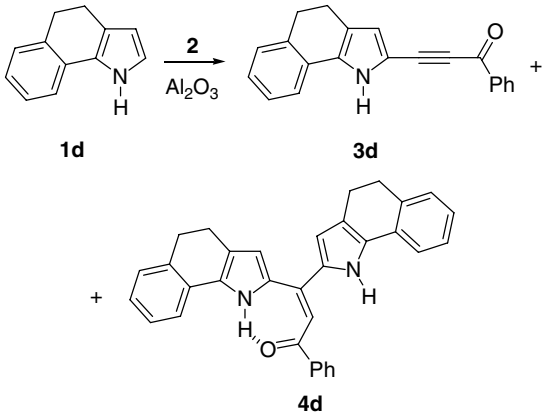
In summary, for the first time, a facile direct regio- and chemoselective ethynylation of indoles with bromobenzoylacetylene on Al_2O_3 has been developed. This new method requires no palladium, copper, base or solvent. The benzoylethynylindoles, thus synthesized, are actually prospective protected ethynylindoles since the benzoyl moiety can be eliminated through its conversion to a tertiary alcohol moiety followed by elimination of the alcohol. The synthetic importance of this ethynylation looks even more attractive taking into account



Scheme 2.



Scheme 3.



Scheme 4.

that standard Sonogashira coupling often fails with electrophilic acetylenes.

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9. *Preparative procedure illustrating the preparation of 3-(2-benzoylethynl)indoles* **3a**–**c**, **6c** *and 2-(2-benzoylethynyl)-4,5-dihydrobenz[g]indole* **3d**. Equimolar amounts of indoles **1a**–**c** or pyrrole **1d** (0.5–1.0 mmol) and 1-benzoyl-2-bromoacetylene (**2**) were ground together at rt with a 10-fold amount (by weight) of Al_2O_3 (chromatography grade, Merck, pH 6.8–7.8) in a china mortar for 1–2 min. The reaction mixture self-heated (5–8 °C) and within 10 min turned from yellow to orange-brown. After 60 min, the reaction products were extracted sequentially with *n*-hexane (10–15 mL), *n*-hexane–Et_2O (2:1–1:2) (40–50 mL) and Et_2O (15–20 mL). The fractions were further chromatographed on a column or by thin layer (Al_2O_3) to yield indoles **3a**–**c**, **6c** or pyrrole **3d** as yellow-orange or red crystals (after recrystallization from benzene) and 1,1-di(indolyl)-2-benzoylethenes **4b**,**d**.

3-(2-Benzoylethynyl)indole (**3a**). Yield 72%. Yellow crystals, mp 178–179 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.75 (br s, 1H, NH), 8.29 (m, 2H, H_o, Ph), 7.86 (m, 1H, H-4), 7.75 (d, $J = 2.4$ Hz, 1H, H-2), 7.62 (m, 1H, H_p, Ph), 7.53 (m, 2H, H_m, Ph), 7.45 (m, 1H, H-7), 7.30 (m, 2H, H-5, H-6). ^{13}C NMR (101.6 MHz, $CDCl_3$): δ 178.2 (C=O), 137.4 (C_i), 135.4 (C-7a), 133.8 (C_p, Ph), 133.0 (C-2), 129.6 (C_o, Ph), 128.7 (C_m, Ph), 128.6 (C-3a), 124.0 (C-6), 122.0 (C-5), 120.2 (C-4), 112.1 (C-7), 96.2 (C-3), 92.0 (≡C), 90.6 (C≡). IR (KBr): 3396 (NH), 2173 (C≡C), 1626 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71. Found: C, 83.59; H, 4.38; N, 5.90.

3-(2-Benzoylethynyl)-2-methylindole (**3b**). Yield 76%. Orange crystals, mp 167–168 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.83 (br s, 1H, NH), 8.30 (m, 2H, H_o, Ph), 7.72 (m, 1H, H-4), 7.62 (m, 1H, H_p, Ph), 7.53 (m, 2H, H_m, Ph), 7.35 (m, 1H, H-7), 7.25 (m, 2H, H-5, H-6), 2.62 (s, 3H, Me). ^{13}C NMR (101.6 MHz, $CDCl_3$): δ 178.0 (C=O), 145.7 (C-2), 137.6 (C_i), 135.0 (C-7a), 133.6 (C_p, Ph), 129.4 (C_o, Ph), 129.3 (C-3a), 128.6 (C_m, Ph), 123.2 (C-6), 121.8 (C-5), 119.6 (C-4), 111.2 (C-7), 94.7 (≡C), 94.2 (C-3), 91.7 (C≡), 13.3 (Me). IR (KBr): 3273 (NH), 2161 (C≡C), 1627 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{13}NO$: C, 83.38; H, 5.05; N, 5.40. Found: C, 83.13; H, 5.29; N, 5.44.

3-(2-Benzoylethynyl)benz[g]indole (**3c**). Yield 23%. Yellow crystals, mp 226–227 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.46 (br s, 1H, NH), 8.31 (m, 2H, H_o, Ph), 8.03 (m, 1H, H-9), 7.96 (m, 1H, H-6), 7.91 (d, $J = 8.7$ Hz, 1H, H-4), 7.80 (d, $J = 2.7$ Hz, 1H, H-2), 7.68 (d, $J = 8.7$ Hz, 1H, H-5), 7.62 (m, 1H, H_p, Ph), 7.56 (m, 1H, H-8), 7.54 (m, 2H, H_m, Ph), 7.49 (m, 1H, H-7). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 178.2 (C=O), 137.4 (C_i), 133.8 (C_p, Ph), 131.3 (C-5a), 130.5 (C-2), 130.5 (C-9b), 129.6 (C_o, Ph), 129.3 (C-6), 128.7 (C_m, Ph), 126.4 (C-8), 125.1 (C-7), 125.1 (C-3a), 123.0 (C-5), 121.7 (C-9a), 119.4 (C-9), 119.3 (C-4), 98.0 (C-3), 91.9 (≡C), 90.1 (C≡). IR (KBr): 3192 (NH), 2174 (C≡C), 1611 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{13}NO$: C, 85.40; H, 4.44; N, 4.74. Found: C, 85.65; H, 4.23; N, 5.09.

2-(2-Benzoylethynyl)benz[g]indole (**6c**). Yield 22%. Pale yellow crystals, mp 215–216 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.40 (br s, 1H, NH), 8.21 (m, 2H, H_o, Ph), 8.03 (m, 1H, H-9), 7.88 (m, 1H, H-6), 7.62 (m, 1H, H_p, Ph), 7.61 (d, $J = 8.3$ Hz, 1H, H-4), 7.56 (m, 1H, H-8), 7.52 (m, 2H, H_m, Ph), 7.49 (m, 1H, H-7), 7.50 (d, $J = 8.3$ Hz, 1H, H-5), 7.24 (d, $J = 2.2$ Hz, 1H, H-3). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 177.0 (C=O), 136.9 (C_i), 133.9 (C_p, Ph), 133.3 (C-9b), 131.9 (C-5a), 129.6 (C_o, Ph), 129.2 (C-6), 128.7 (C_m, Ph), 126.3 (C-8), 125.9 (C-7), 123.7 (C-3a), 122.6 (C-5), 121.3 (C-9a), 120.5 (C-4), 120.3 (C-9), 115.6 (C-3), 113.5 (C-2), 92.0 (≡C), 87.2 (C≡). IR (KBr): 3285 (NH), 2175 (C≡C), 1623 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{13}NO$: C, 85.40; H, 4.44; N, 4.74. Found: C, 85.72; H, 4.28; N, 4.82.

2-(2-Benzoylethynyl)-4,5-dihydrobenz[g]indole (**3d**). Yield 68%. Red crystals, mp 178 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 9.57 (br s, 1H, NH), 8.15 (m, 2H, H_o, Ph), 7.53 (m, 1H, H_p, Ph), 7.44 (m, 2H, H_m, Ph), 7.40 (m, 1H, H-9), 7.23 (m, 1H, H-7), 7.20 (m, 2H, H-6, H-8), 6.68 (d, $J = 2.2$ Hz, 1H, H-3), 2.95 (m, 2H, H-5), 2.75 (m, 2H, H-4). ^{13}C NMR (101.61 MHz, $CDCl_3$): δ 177.4 (C=O), 137.3 (C_i), 133.7 (C_p, Ph), 129.6 (C_o, Ph), 128.6 (C_m, Ph), 127.0 (C-8), 110.1 (C-2), 120.4 (C-9), 128.8 (C-6), 127.3 (C-7), 120.0 (C-3), 94.2 (≡C), 90.7 (C≡), 29.8 (C-5), 21.7 (C-4). IR (KBr): 3270 (NH), 2159 (C≡C), 1620 (C=O) cm^{-1}. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 85.24; H, 4.98; N, 5.03.

2-Benzoyl-1,1-di[(2-methyl)indol-3-yl]ethene (**4b**). Yield 6%. Yellow crystals, mp 146–148 °C (ethanol). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.20 (br s, 1H, NH), 8.15 (br s, 1H, NH′), 7.82 (m, 2H, H_o, Ph), 7.54 (m, 1H, H-4), 7.28 (m, 1H, H_p, Ph), 7.24 (m, 1H, H-7), 7.18 (m, 2H, H_m, Ph), 7.10 (m, 1H, H-6), 7.10 (s, 1H, =CH), 7.07 (m, 1H, H-7′), 7.02 (m, 1H, H-5), 7.02 (m, 1H, H-4′), 6.96 (m, 1H, H-6′), 6.82 (m, 1H, H-5′), 2.00 (s, 3H, Me′), 1.98 (s, 3H, Me). ^{13}C NMR (101.6 MHz, $CDCl_3$): δ 192.9 (C=O), 144.6 (C=), 140.3 (C_i), 137.1 (C-2), 136.1 (C-2′), 135.7 (C-7a′), 135.5 (C-7a), 131.3 (C_p, Ph), 128.4 (C-3a), 128.2 (C-3a′), 128.1 (C_o, Ph), 127.8 (C_m, Ph), 122.1 (=CH), 122.0 (C-6), 121.4 (C-6′), 120.7 (C-5), 119.9 (C-5′), 119.7 (C-4), 119.6 (C-4′), 115.4 (C-3), 114.4 (C-3′), 110.6 (C-7), 110.1 (C-7′), 13.3 (Me), 13.1 (Me′). IR (KBr): 3386, 3278 (NH), 1627 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{22}N_2O$: C, 83.05; H, 5.68; N, 7.17. Found: C, 83.12; H, 5.63; N, 7.19.

2-Benzoyl-1,1-[di-4,5-dihydrobenz[g]indol-2-yl]ethene (**4d**). Yield 9%. Red crystals, mp 223–224 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 15.02 (br s, 1H, NH), 9.35 (br s, 1H, NH′), 8.03 (m, 2H, H_o, Ph), 7.66 (m, 1H, H-9), 7.48 (m, 1H, H-9′), 7.40 (m, 2H, H_m, Ph), 7.35 (m, 1H, H_p, Ph), 7.25 (m, 1H, H-6′), 7.20 (m, 1H, H-6), 7.18 (m, 1H, H-7), 7.18 (m, 1H, H-8′), 7.16 (m, 1H, H-7′), 7.14 (m, 1H, H-8), 6.77 (s, 1H, =CH), 6.69 (d, $J = 2.0$ Hz, 1H, H-3), 6.56 (d, $J = 2.2$ Hz, 1H, H-3′), 2.95 (m, 2H, H-5), 2.79 (m, 2H, H-4′), 2.75 (m, 2H, H-4), 2.74 (m, 2H, H-5′). ^{13}C NMR (101.6 MHz, $CDCl_3$): δ 188.2 (C=O), 141.7 (C_i), 140.8 (C=), 136.7 (C-5a), 135.6 (C-5a′), 134.3 (C-9b), 133.9 (C-2′), 131.5 (C_p, Ph), 131.2 (C-9b′), 131.1 (C-2), 128.8 (C-6), 128.7 (C-6′), 128.4 (C-8), 128.4 (C-8′), 128.1 (C_o, Ph), 127.8 (C_m, Ph), 127.2 (C-7), 126.3 (C-7′), 124.3 (C-3a), 122.2 (C-3a′), 121.7 (C-9), 120.3 (C-9a′), 120.0 (C-9a), 119.7(C-9′), 118.3 (C-3), 112.9 (C-3′), 109.6 (=C), 30.1 (C-5), 29.9 (C-5′), 22.0 (C-4), 22.0 (C-4′). IR (KBr): 3317, 3279 (NH) cm^{-1}. Anal. Calcd for $C_{33}H_{26}N_2O$: C, 84.95; H, 5.62; N, 6.00. Found: C, 84.72; H, 5.47; N, 5.64.