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A palladium- and copper-free cross-coupling of ethyl 3-halo-2-propynoates with 4,5,6,7-tetrahydroindoles on alumina

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Abstract—Ethyl 3-halo-2-propynoates undergo facile (no heating, no base, no solvent) palladium- and copper-free cross-coupling with 4,5,6,7-tetrahydroindoles on alumina to afford the corresponding 4,5,6,7-tetrahydroindole-2-propynoates in 46% and 71% yields. The yield of the by-products [ethyl 3,3-di(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylates] under appropriate conditions can reach 79%.

Efficient methodologies for the regioselective functionalization of pyrroles and indoles are of great importance, since these ring systems occur as structural motifs in numerous biologically active natural products and pharmaceuticals.[1] Among these heterocycles, ethynyl derivatives attract major attention due to the rich chemistry of the triple bond.[2] As a result, considerable efforts have been devoted to the development of new methodologies for efficient synthesis of ethynylpyrroles and ethynylindoles.[3]

However, almost all the known methods for the *C*-ethynylation of pyrroles and indoles require either functionalized pyrroles or indoles as reactants.[3b,e–g]

Recently, a facile direct regio- and chemoselective ethynylation of pyrroles and indoles with acylbromoacetylenes on Al_2O_3 has been developed.[4] This new approach requires no palladium, copper, base, solvent or a prior functionalization step, making the target chemical transformation highly efficient experimentally.

Consequently, we were intrigued by the prospect of applying this methodology to the synthesis of 4,5,6,7-tetrahydroindole-2-propynoates. These compounds are promising protected ethynylpyrroles, since the ester moiety can be easily removed through conventional decarboxylation procedures.[5] Furthermore, 4,5,6,7-tetrahydroindole-2-propynoates undergo easy catalytic dehydrogenation[6] to yield 2-substituted indoles, which are potential intermediates for many alkaloids and pharmacologically important substances.[7]

Although methods for the preparation of 3-substituted indoles are well established, there is a need for easier access to 2-substituted indoles: compared with the corresponding 3-substituted compounds, 2-ethynylindoles still remain difficult to access since most electrophilic aromatic substitution reactions of indoles occur at the 3-position.

In this Letter, we report the results of our studies on cross-coupling of 1*H*- and 1-vinyl-4,5,6,7-tetrahydroindoles with ethyl bromo- and iodopropynoates to give 2-(ethynyl)-4,5,6,7-tetrahydroindoles.

The reaction proceeds at room temperature, rapidly (0.5 h) and is slightly exothermic. Experimentally, the reactants are ground with an excess of Al_2O_3 under solvent-free conditions. The synthesis was monitored by NMR (^1H) of $CDCl_3$ extracts of the reaction mixture.

In contrast to benzoylbromoacetylene, which with 4,5,6,7-tetrahydroindole **1** [Al_2O_3, pH 7.4, 10-fold

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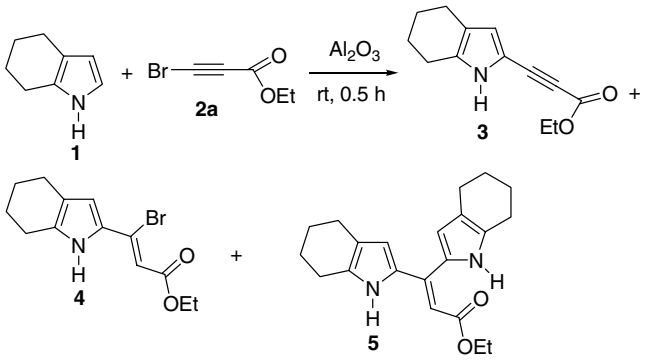


Scheme 1.

amount (by weight), room temperature, 0.5 h] formed mainly 2-(benzoylethynyl)-4,5,6,7-tetrahydroindole,[4a] ethyl bromopropynoate **2a** under similar conditions, reacted with **1** to form a mixture of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoate **3** (20%), 3-bromo-3-(4,5,6,7-tetrahydroindol-2-yl)-2-propenoate **4** (62%) and 3,3-di(4,5,6,7-tetrahydroindol-2-yl)acrylate **5** (14%) (Scheme 1).

With an increased alumina ratio (50-fold), product **4** was not formed and the only reaction products were indoles **3** (38%) and **5** (62%). A similar result was observed when a more basic sample of alumina (pH 9.5, 50-fold amount) was employed.

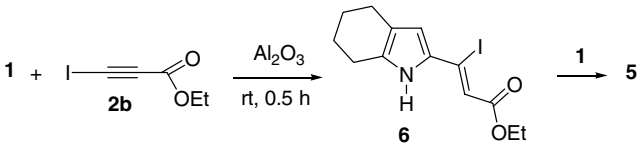
When K_2CO_3 (10% relative to alumina) was added to the reaction mixture with 50-fold amount of alumina (pH 9.5) the proportion of indolylpropynoate **3** in the reaction mixture increased to 58% (preparative yield 46%, Table 1),[8] while the content of di(indolyl)acrylate **5** dropped to 34%.

Unlike ethyl bromopropynoate **2a**, ethyl iodopropynoate **2b** reacted with 4,5,6,7-tetrahydroindole **1** (ratios of **1:2b**, 1:1, 2:1) on alumina of different pH values (7.4 and 9.5) and with different quantities (10- and 50-fold excess) to afford chemospecifically, di(indolyl)acrylate **5** (yield 79%, Table 1) (Scheme 2).[9]

Table 1. Cross-coupling of 4,5,6,7-tetrahydroindoles **1** and **10** with ethyl-3-halo-2-propynoates **2a**,**b** on alumina

Reagents		Al_2O_3		Product	Yield (%)
Indole	Propynoate	pH	Amount		
1	**2a**	9.5	50-fold[a]	**3**	46
				5	24
1	**2b**	9.5	50-fold	**3**	0
				5	79
10	**2a**	7.4	50-fold	**11**	71
				12	0
10	**2b**	9.5	5-fold	**11**	24
				12	31

[a] K_2CO_3 (10% relative to alumina) was used.



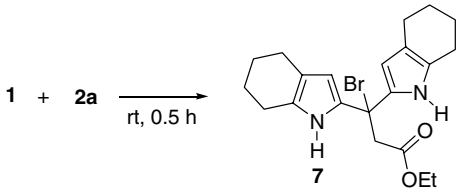
Scheme 2.

Upon mixing of equimolar quantities of indole **1** and ethyl bromopropynoate **2a** without alumina, strong self-heating occurred and bright violet colouration was observed. A caramel coloured reaction product consisted of di(indolyl)propanoate **7** and propynoate **2a** (Scheme 3).

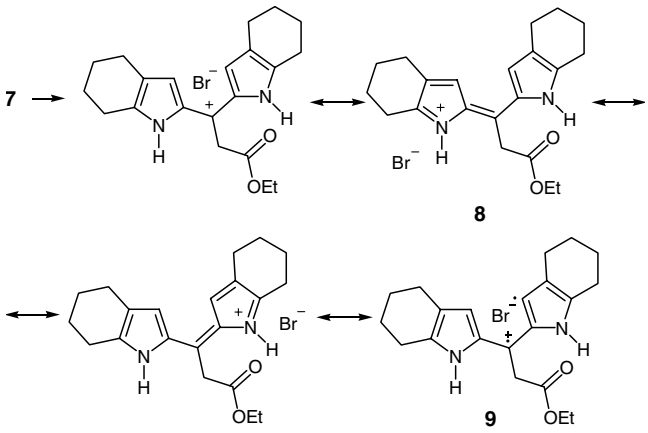
With 2 mol equivalents of indole **1** per 1 mol equivalent of ethyl bromopropynoate **2a**, the reaction furnished propanoate **7**, though accompanied by resinification. An attempt to isolate this product by chromatography (Al_2O_3 or SiO_2, diethyl ether–*n*-hexane, 1:1) failed and so it was characterized only by spectral methods.[10]

Signal broadening in the ^1H NMR spectra of adduct **7**, atypical chemical shifts of the C–Br (133.4 ppm), C-5 (157.7 ppm) and C-2 (129.9 ppm) carbon atoms in the ^{13}C NMR spectra suggest that this adduct is capable of dissociation to cation **8** or radical **9**, which are stabilized by the two adjacent indole systems and, probably, by the ester group (Scheme 4).

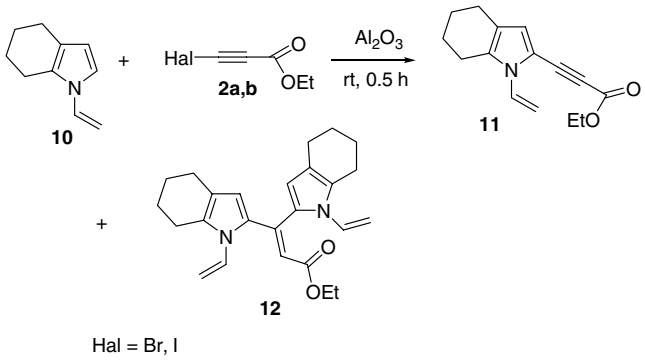
Recently,[11] it was shown that 1-vinyl-4,5,6,7-tetrahydroindole **10** reacts with benzoylbromoacetylene (Al_2O_3, pH 7.4, 10-fold amount) selectively to give the corresponding ethynylindole in 70% yield. Under similar



Scheme 3.



Scheme 4.



Scheme 5.

conditions, indole **10** and ethyl bromopropynoate **2a** formed (0.5 h) di(indolyl)acrylate **12** (23%) along with indolylpropynoate **11** (77%) (^{1}H NMR).

At a higher content of Al_2O_3 (50-fold amount) the selectivity of the reaction was greater and in 0.5 h the ratio of **11**:**12** reached 92:8 (preparative yield of indolylpropynoate **11** in this case was 71%, Table 1) (Scheme 5).[12]

In the case of ethyl iodopropynoate **2b**, indole **10** reacted slowly and in contrast to indole **1**, with no selectivity: in 0.5 h (Al_2O_3, 10-fold amount) the starting material **10** still remained (46%) with the ratio of **11**:**12** at 40:14.

To isolate di(indolyl)acrylate **12** we carried out the reaction with **10** and iodopropynoate **2b** (ratio of **10**:**2b**, 1:1) on alumina (pH 9.5, 5-fold amount) for 1 h. In this case, the reaction gave indolylpropynoate **11** (53%) and di(indolyl)acrylate **12** (47%), the preparative yield of the latter was 31% (Table 1).[13]

Thus the results obtained represent a new concise and experimentally simple route to the 4,5,6,7-tetrahydroindole-2-propynoate and its vinyl derivative.

Acknowledgement

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8. Equimolar amounts of indole **1** (1 mmol) and ethyl bromopropynoate **2a** were ground together at rt with 50-fold amount (by weight) of Al_2O_3 (pH 9.5), containing K_2CO_3 (10% relative to alumina) in a China mortar for 5–10 min. After 0.5 h the yellow reaction mixture was washed with *n*-hexane. After removing the solvent, the residue was purified by chromatography on a column or by thin layer (Al_2O_3, eluent—*n*-hexane) to yield ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoate **3** (46%) as yellow crystals, mp 114–115 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 8.15 (br s, 1H, NH), 6.49 (d, $J = 2.0$ Hz, 1H, H-3), 4.25 (q, $J = 7.1$ Hz, 2H, OCH_2), 2.55 (m, 2H, CH_2-7), 2.46 (m, 2H, CH_2-4), 1.79 (m, 2H, CH_2-5), 1.73 (m, 2H, CH_2-6), 1.32 (t, $J = 7.1$ Hz, 3H, Me). ^{13}C NMR (100.13 MHz, $CDCl_3$) δ 154.7 (C=O), 133.3 (C-5), 119.6 (C-3), 119.6 (C-4), 107.5 (C-2), 85.1 (≡C), 82.5 (C≡), 61.7 (OCH_2), 23.5 (CH_2-6), 23.1 (CH_2-7), 23.0 (CH_2-5), 22.7 (CH_2-4), 14.3 (Me). IR (KBr) ν 3334 (NH), 2175 (C≡C), 1677 (C=O). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H,

6.96; N, 6.45. Found: C, 71.67; H, 7.12; N, 6.23, and ethyl 3,3-di(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate **5** (yield 24%) as brown crystals, mp 140 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 12.28 (br s, 1H, NH), 8.05 (br s, 1H, NH′), 6.41 (s, 1H, H-3), 6.29 (s, 1H, H-3′), 5.55 (s, 1H, CH=), 4.14 (q, $J = 6.8$ Hz, 2H, OCH_2), 2.67 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.49 (m, 4H, CH_2), 1.80 (m, 4H, CH_2), 1.73 (m, 4H, CH_2), 1.17 (t, $J = 6.8$ Hz, 3H, Me). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3 (C=O), 139.9 (C=), 133.3 (C-5), 130.5 (C-2′), 129.8 (C-5′), 126.9 (C-2), 119.6 (C-4), 118.9 (C-4′), 116.8 (C-3), 111.5 (C-3′), 102.6 (=*C*HCO), 60.2 (OCH_2), 23.8, 23.4, 23.3, 23.0, 22.9 [2(CH_2)$_4$], 14.5 (Me). IR (KBr) ν 3374 (NH), 1668 (C=O). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.37; H, 7.64; N, 8.15.

9. Indole **1** (2 mmol) and ethyl iodopropynoate **2b** (1 mmol) were ground together at rt with 50-fold amount (by weight) of Al_2O_3 (pH 9.5) in a China mortar for 5–10 min. After 0.5 h the reaction products were extracted with *n*-hexane. The residue after removing the solvent was purified by chromatography on a column or by thin layer (Al_2O_3, eluent—*n*-hexane) to yield di(indolyl)acrylate **5** (79%).
10. Indole **1** (2 mmol) and ethyl bromopropynoate **2a** (1 mmol) were mixed without alumina at rt in a China mortar for 2–3 min. The reaction mixture self-heated (30 °C) and within 10 min turned to a bright violet caramel-like mass consisting of ethyl 3-bromo-3,3-di(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propanoate **7**. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 12.65 (br s, 2H, NH), 7.06 (s, 2H, H-3), 4.15 (q, $J = 7.5$ Hz, 2H, OCH_2), 3.90 (br s, 2H, CH_2), 3.20 (m, 4H, CH_2-7), 2.55 (m, 4H, CH_2-4), 1.77 (m, 8H, CH_2-5,6), 1.22 (t, $J = 7.5$ Hz, 3H, Me). ^{13}C NMR (100.6, $CDCl_3$) δ 169.1 (C=O), 157.7 (C-5), 133.4 (C–Br), 129.9 (C-2), 128.6 (C-4), 127.5 (C-3), 61.9 (OCH_2), 39.2 (*C*H_2CO), 25.1 (CH_2-7), 23.3 (CH_2-6), 23.0 (CH_2-5), 21.9 (CH_2-4), 13.6 (Me). IR (KBr) ν 3423 (NH), 1734 (C=O).
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12. Equimolar amounts of indole **10** (1 mmol) and ethyl bromopropynoate **2a** were ground together at rt with 50-fold amount (by weight) of Al_2O_3 (pH 7.4) in a China mortar for 5–10 min. After 0.5 h the yellow reaction mixture was washed with *n*-hexane. The residue after removing the solvent was purified by chromatography on a column or by thin layer (Al_2O_3, eluent—*n*-hexane) to yield ethyl 3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoate **11** in 71% yield as yellowish crystals, mp 26–27 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.91 (dd, $J = 16.1$, 9.3 Hz, 1H, H_x), 6.56 (s, 1H, H-3), 5.37 (dd, $J = 16.1$, 1.2 Hz, 1H, H_B), 4.92 (dd, $J = 9.4$, 1.2 Hz, 1H, H_A), 4.24 (q, $J = 7.1$ Hz, 2H, CH_2), 2.62 (m, 2H, CH_2-7), 2.45 (m, 2H, CH_2-4), 1.79 (m, 2H, CH_2-5), 1.70 (m, 2H, CH_2-6), 1.31 (t, $J = 7.1$ Hz, 3H, Me). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.6 (C=O), 134.1 (C-5), 129.9 (HC=), 121.2 (C-3), 120.7 (C-4), 110.0 (C-2), 103.9 (=CH_2), 87.9 (≡C), 81.3 (C≡), 61.7 (OCH_2), 24.1 (CH_2-7), 23.1 (CH_2-4), 22.9 (CH_2-5,6), 14.1 (Me). IR (KBr) ν 2192 (C ≡ C), 1702 (C=O), 1644 (C=C). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.26; H, 7.04; N, 5.90.
13. Equimolar amounts of indole **10** (1 mmol) and ethyl iodopropynoate **2b** were ground together at rt with 5-fold amount (by weight) of Al_2O_3 (pH 9.5) in a China mortar for 5–10 min. After 1 h the yellow reaction mixture was washed with *n*-hexane. The residue after removing the solvent was purified by chromatography on a column or by thin layer (Al_2O_3, eluent—*n*-hexane) to yield ethyl 3-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2-propynoate **11** (24%) and ethyl 3,3-di(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate **12** (31%) as a yellow oil. Data for **12**: ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 6.54 (dd, $J = 15.9$, 8.8 Hz, 1H, H_x), 6.52 (dd, $J = 16.1$, 9.1 Hz, 1H, $H_{x'}$), 6.07 (s, 1H, H-3), 5.98 (s, 1H, H-3′), 5.88 (s, 1H, CH=), 4.96 (d, $J = 15.9$ Hz, 1H, H_B), 4.87 (d, $J = 16.1$ Hz, 1H, $H_{B'}$), 4.86 (d, $J = 8.8$ Hz, 1H, H_A), 4.56 (d, $J = 9.1$ Hz, 1H, $H_{A'}$), 4.02 (q, $J = 7.1$ Hz, 2H, OCH_2), 2.65 (m, 2H, CH_2-7′), 2.60 (m, 2H, CH_2-7), 2.46 (m, 2H, CH_2-4′), 2.43 (m, 2H, CH_2-4), 1.80 (m, 4H, CH_2-6,6′), 1.71 (m, 4H, CH_2-5,5′), 1.11 (t, $J = 7.1$ Hz, 3H, Me). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.5 (C=O), 138.0 (C=), 134.2 (C-5), 132.6 (C-2, $J_{CH} = 5.5$ Hz), 131.9 (HC=), 130.8 (C-5′), 130.5 (HC′=), 128.5 (C-2′, $J_{CH} = 9.4$ Hz), 120.0 (C-4), 119.3 (C-4′), 116. 1 (C-3), 113.5 (C-3′), 112.9 (=*C*HCO), 106.8 (=CH_2), 102.6 (=$CH_{2'}$), 59.7 (OCH_2), 24.4 (CH_2-7), 24.2 (CH_2-7′), 23.5, 23.4, 23.2, 23.1, 23.0, 22.9 [2(CH_2)$_3$], 14.3 (Me). IR (KBr) ν 1710 (C=O), 1641 (C=C). Anal. Calcd for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.56; H, 7.61; N, 7.31.