

Convenient synthesis of methyl indol-2-ylpropiolate

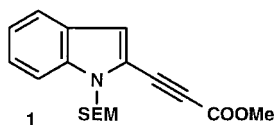
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Received (in Cambridge, UK) 26th July 1999, Accepted 31st August 1999

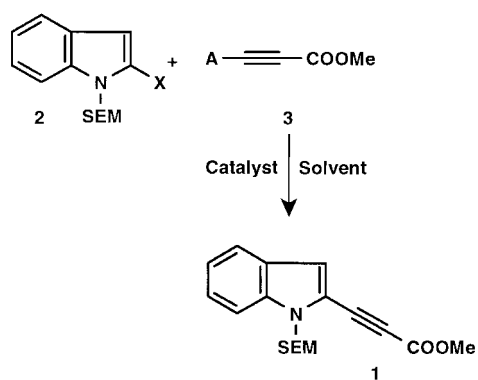
Methyl indol-2-ylpropiolate **1** is synthesized by using a catalyst system of $\text{PPh}_3\text{-CuI}$ in the presence of K_2CO_3 as base. The procedure appears convenient if compared with Pd-catalyzed cross-coupling reactions. The interest is increased by the use of an alk-1-yne containing an electron-withdrawing group.

The biological and pharmacological activity of natural and synthetic indole derivatives has led to the extensive development of synthetic methodologies. Recently indol-2-yl derivatives have attracted particular attention¹ due to their usefulness in the total synthesis of polyfunctional complex molecules. We reported² in a previous article the preparation of 5-(indol-2'-yl)pyridin-2-one and 5-(indol-2'-yl)pyran-2-one to be used as electron-poor dienes, together with electron-rich enes, in [4+2] π cycloaddition reactions. Within the context and in connection with our ongoing studies of indole alkaloid synthesis by [4+2]- π cycloadditions, we wanted to explore the possibility of using indol-2-ylacetylenes as ene partners in [4+2] π cycloaddition reactions with electron-rich and electron-poor dienes. For this reason we required a convenient method for the preparation of electron-poor ene methyl indol-2-ylpropiolate **1**. Moreover, this compound could be useful in designing processes for the construction of indole derivatives, by exploiting the rich chemistry of the acetylene function.



Different syntheses of indol-2-ylacetylenes have been described in the literature, and these are based on the Stephens–Castro reaction,^{3a–f} Pd-mediated cross-coupling reaction^{3g} and titanium induced indole formation.^{3h} Our first choice was the application of palladium-catalyzed cross-coupling reactions to 2-stannyindole **2a** and methyl bromopropynoate **3b**⁴ in DMF at 110 °C and $\text{Pd}(\text{PPh}_3)_4$ as catalyst, according to Palmisano (Scheme 1).⁵ The desired product **1** was obtained in 45% yield (Table 1, entry 1) and although this was acceptable, the toxicity of the tin derivatives forced us to consider other methodologies. Thus we investigated Pd-mediated cross-coupling reactions⁶ of the zinc chloride 3-derivative of methyl propiolate **3c**⁷ with 2-iodo-1-[2-(trimethylsilyl)ethoxymethyl]indole **2b** (2-trimethylsilyl)ethoxymethyl = SEM).⁸ The reaction was carried out in THF at room temperature for 24 h and product **1** was obtained in 35% yield (entry 2).⁹

In an attempt to improve the reaction yield, we shifted our attention to the Stephens–Castro coupling reaction of copper(I) arylacetylenes with iodoarenes^{10a} or iodoalkenes.^{10b} Although this method is widely used for the synthesis of acetylenes, its scope is limited by the harsh reaction conditions needed and difficulty in preparing cuprous acetylides. For this reason, we investigated the preparation of **1** by the Sonogashira reaction¹¹ that permits coupling between alk-1-ynes and aryl or vinyl halides in the presence of a base, a palladium (0 or II) catalyst and cuprous iodide under mild conditions.



Scheme 1

The reaction of *N*-SEM-2-iodoindole **2b** with methyl propiolate in Et_2NH , Et_3N or DMPA as base and in the presence of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ did not give the desired product. The use of Et_3N as base and CH_3CN as solvent in the presence of $\text{Pd}(\text{PPh}_3)_4$ and PPh_3 at 40 °C gave **1**, though only in 35% yield (entry 3).

We then elected to use an inorganic base applying the Miura modification¹² of the Sonogashira reaction. The reaction of *N*-SEM-2-iodoindole **2b** with methyl propynoate **3a** was carried out in DMF at 120 °C in the presence of a catalytic amount of CuI using K_2CO_3 as a base, and gave **1** in 53% yield (entry 4). This reaction is of great interest as it did not require the expensive palladium catalyst,¹³ nor is there any need to convert the methyl propynoate into the corresponding 3-bromo derivative. Although the Sonogashira reaction has been reported to fail in the case of alk-1-ynes containing an electron-withdrawing group directly attached to the ethynyl carbon atom,¹⁴ we successfully realized the reaction between indol-2-yl iodide and methyl propynoate.

It should be pointed out that the result represents a short and convenient route, experimentally simple, to the direct synthesis of esters of indol-2-ylpropiolate.

Experimental¹⁵

Methyl [*N*-(2-trimethylsilyloxyethyl)indol-2-yl]propiolate (**1**)

Method A. 2-(Tributylstannyl)-1-SEM-indole (253 mg, 0.47 mmol) was dissolved in DMF (2.4 ml). 3-Bromo methyl propiolate (100 mg, 0.61 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (6 mg, 0.0047 mmol) were added to the solution. The mixture was warmed at 110 °C and stirred for 1 h. It was then allowed to cool at room temp., poured into water and extracted with AcOEt. The crude was purified by flash chromatography (hexane–AcOEt 15:1). Yield: 45%.

Method B. Methyl propiolate (15 μl , 0.17 mmol) were dissolved in THF (0.5 ml). The solution was cooled to –78 °C;

Table 1

Entry	X	A	Catalyst	Solvent/base	T/°C	Yield (%)		
1	2a	SnBu ₃	3b	Br	Pd(PPh ₃) ₄	DMF	110	45
2	2b	l	3c	ZnCl	Pd(PPh ₃) ₄	THF	room temp.	35
3	2b	l	3a	H	Pd(PPh ₃) ₄ -PPh ₃ -CuI	CH ₃ CN/Et ₃ N	40	35
4	2b	l	3a	H	PPh ₃ -CuI	DMF/K ₂ CO ₃	110	53

BuLi (0.109 ml, 0.17 mmol, 1.6 M solution) was added dropwise. The mixture was stirred for 1 h. A solution of ZnCl₂ (24 mg, 0.18 mmol), previously dried by melting under vacuum, in THF (0.6 ml) was added slowly. The mixture was then stirred for 1 h at 0 °C. A solution of 2-iodo-*N*-SEM-indole (67 mg, 0.18 mmol) and Pd(PPh₃)₄ (17 mg, 0.015 mmol) in THF (0.4 ml) was added. The mixture was stirred at room temperature for 24 h. It was then poured into aqueous NH₄Cl and extracted with AcOEt. The product was isolated by flash chromatography. Yield: 35%.

Method C. 2-Iodo-*N*-SEM-indole (460 mg, 1.2 mmol) was dissolved in CH₃CN (10 ml). CuI (10 mg, 0.053 mmol), Pd(PPh₃)₄ (32 mg, 0.028 mmol), methyl propiolate (0.12 ml, 1.4 mmol) and Et₃N (1.5 ml) were added. The solution was stirred for 6 h at 40 °C and for 12 h at room temperature. The mixture was poured into a saturated NaCl solution and extracted with AcOEt. The product was isolated by flash chromatography. Yield: 35%.

Method D. CuI (15 mg, 0.073 mmol), PPh₃ (28 mg, 0.11 mmol) and K₂CO₃ (220 mg, 1.7 mmol) were dissolved in DMF (6 ml). Methyl propiolate (0.15 ml, 1.7 mmol) and a solution of 2-iodo-*N*-SEM-indole (400 mg, 1.1 mmol) in DMF (4 ml) was added. The mixture was warmed at 110 °C and stirred for 36 h. The mixture was poured into brine and extracted with Et₂O. After flash chromatography purification (CH₂Cl₂-hexane 1:1) **1** was obtained in 53% yield. Yellow oil, *R*_f 0.44 (hexane-AcOEt 15:1). IR (CHCl₃)/cm⁻¹ 3060, 2200, 1700, 1250; ¹H-NMR (CDCl₃) δ 7.65 (1H, d), 7.50 (1H, d), 7.35 (1H, t), 7.20 (1H, t), 7.10 (1H, s), 5.70 (2H, s), 3.80 (3H, s), 3.55 (2H, t), 0.90 (2H, t), 0.00 (9H, s). ¹³C-NMR (CDCl₃) δ 154.1, 137.7, 127.1, 125.3, 121.7, 121.5, 118.1, 114.1, 110.7, 87.4, 78.7, 73.1, 65.9, 52.7, 17.6, -1.6 (3C); Anal. Calcd for C₁₈H₂₃NO₃Si: C 65.62, H 7.04, N 4.25. Found: C 65.70, H 7.11, N 4.31%.

Acknowledgements

This work was supported by Ministero dell'Educazione e della Ricerca Scientifica e Tecnologica (MURST).

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Communication 9/06023E