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Stille carbonylation of *N*-protected bromomethylindoles

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Abstract—A variety of *N*-protected indolylmethylbromides are carbonylated using 5 mol % $Pd(PPh_3)_2Cl_2$ under Stille conditions in the presence of an alcohol to afford the corresponding methyl/ethyl esters.

Indole and its myriad of derivatives are important fragments of a large number of natural products of both marine and terrestrial origin, and hence continue to capture the attention of synthetic organic chemists. Recently, Gribble has extensively reviewed[1] the various developments involved in the synthesis of indoles.

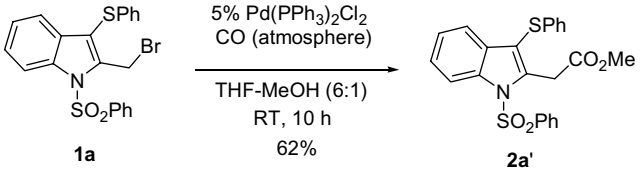
In general, most substituted indoles are prepared through lithiation protocols.[2] The fact that *N*-protected methylindole can be easily allyl brominated using NBS led to the syntheses of a variety of substituted indoles. In particular, the synthetic elaboration of bromomethylindoles has been thoroughly exploited in order to prepare different types of indole-based natural products.[3–5] The bromomethylindoles can be smoothly displaced by a variety of nucleophiles such as CN, OH, $(EtO)_3P$, PPh_3, SPh, NR_2, N_3, etc.[6] They can also be easily displaced by stabilized carbanions derived from diethylmalonate, ethyl acetoacetate, phenylacetonitrile, etc.[7] Srinivasan and co-workers have reported $PdCl_2$-mediated arylation of bromomethylindoles.[8] Bromomethylindoles have also been used to synthesize β and γ-carboline derivatives.[9]

In an ongoing project, we required several 2-indolylmethyl esters as starting materials. To our surprise, there were only a few reports which described the synthesis of indolylmethyl acetates.[10] All these methods involved multi-step procedures and gave only low yields. Since numerous bromomethylindoles were easily available, we decided to investigate the carbonylation of bromomethylindoles under Stille conditions[11] using a Pd catalyst.

As a model study, bromo compound **1a** was carbonylated using 5% $Pd(PPh_3)_2Cl_2$ as a catalyst under CO atmosphere at room temperature.

Workup followed by column chromatographic purification afforded methyl ester **2a′** in 62% yield (Scheme 1). The carbonylation reaction was then tested with a variety of bromomethylindoles, **1a–l** and the results are presented in Table 1.

The bromo compound **1a** was also converted into the corresponding ethyl ester (entry 2) without any appreciable change in yield. During the carbonylation of bromomethylindole **1b** (entry 3), both bromides underwent simultaneous carbonylation to afford bisester **2b**. The bis(dibromomethyl)indole **1l** afforded the corresponding bisester **2l** (entry 13) in a reasonable yield. The carbonylations of bromomethylindoles **1f–h** containing a vinyl ester moiety led to the respective products in diminished yields (entries 7–9). The relatively unexplored bromomethylindoles **1i** and **1j** were also carbonylated to afford the corresponding esters **2i** and **2j** in 77% and 52% yields, respectively.



Scheme 1.

Keywords: Bromomethylindoles; Stille carbonylation; Pd catalyst; Indolylmethyl esters.
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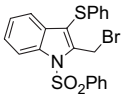
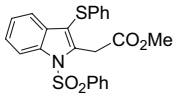
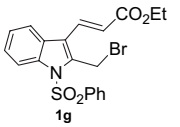
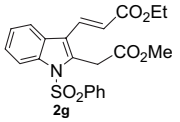
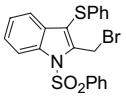
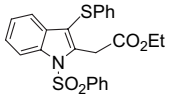
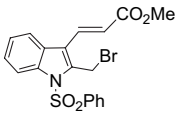
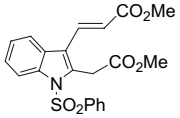
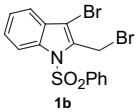
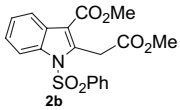
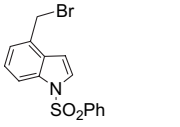
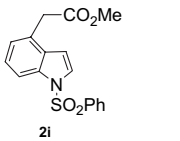
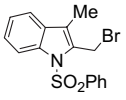
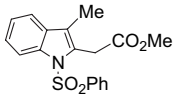
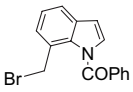
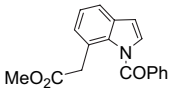
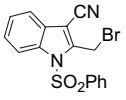
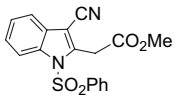
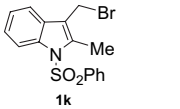
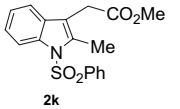
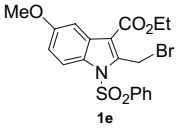
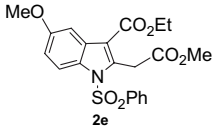
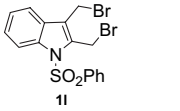
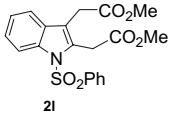
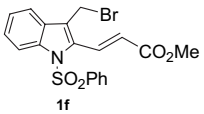
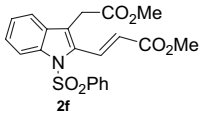
Table 1. Preparation of indolylmethyl esters via Stille carbonylation

Entry	Bromo compounds[12]	Esters[13]	Yield (%), mp (°C)	Entry	Bromo compounds[12]	Esters[13]	Yield (%), mp (°C)
1	 **1a**	 **2a'**	62 (114–116)	8	 **1g**	 **2g**	45 (142)
2	 **1a**	 **2a"**	61 (90)	9	 **1h**	 **2h**	45 (150)
3	 **1b**	 **2b**	58 (122–124)	10	 **1i**	 **2i**	77 (88)
4	 **1c**	 **2c**	58 (120–122)	11	 **1j**	 **2j**	52 (88–90)
5	 **1d**	 **2d**	47 (96)	12	 **1k**	 **2k**	58 (70)
6	 **1e**	 **2e**	50 (118)	13	 **1l**	 **2l**	58 (138)
7	 **1f**	 **2f**	42 (150)				

In summary, we have synthesized several indolylmethyl esters involving hitherto unexplored Stille carbonylation of the corresponding *N*-protected bromomethylindoles. The synthetic utility of these esters will be explored in due course.

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12. The required bromocompounds **1a**–**l** were prepared via the allylic bromination of the corresponding methylindoles using NBS in the presence of a catalytic amount of benzoyl peroxide in CCl_4 under reflux.
13. All the esters gave satisfactory spectral and analytical data.
Typical experimental procedure for **2a′**: A two-necked flask containing bromo compound **1a** (0.5 g, 1.09 mmol), $PdCl_2(PPh_3)_2$ (40 mg, 0.06 mmol), and K_2CO_3 (0.16 g, 1.16 mmol) was evacuated. To this, dry THF (30 mL) and MeOH (5 mL) were added via syringe. The reaction mixture was then purged with dry carbon monoxide gas for 5 min, then stirred under a carbon monoxide atmosphere at room temperature for 10 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2×20 mL). The combined extract was washed with water (10 mL) and dried (Na_2SO_4). Removal of the solvent followed by column chromatographic purification (silica gel, EtOAc–hexane 1:5) afforded **2a′** as a colorless solid (0.42 g, 62%); mp 114–116 °C; IR (KBr) ν_{max}: 1740, 1365, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58 (s, 3H), 4.30 (s, 2H), 6.98–7.03 (m, 3H), 7.06–7.15 (m, 3H), 7.24 (t, J = 7.36 Hz, 1H), 7.37–7.40 (m, 3H), 7.50 (t, J = 6.3 Hz, 1H), 7.80 (t, J = 8.3 Hz, 2H), 7.98 (d, J = 8.3 Hz, 1H). MS (EI) *m*/*z* (%): 437 (M^+, 28%), 378 (42), 237 (100). Elemental anal. calcd for $C_{23}H_{19}NO_4S_2$: C, 63.14; H, 4.38; N, 3.20; S, 14.66. Found: C, 63.08; H, 4.52; N, 3.17; S, 14.53.
Data for **2b**: mp 122–124 °C; IR (KBr) ν_{max}: 1739, 1712, 1384, 1195 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.93 (s, 3H), 4.74 (s, 2H), 7.30–7.33 (m, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.53–7.55 (t, J = 7.3 Hz, 1H), 7.89 (d, J = 7.4 Hz, 2H), 8.02–8.09 (m, 2H). ^{13}C NMR (75.5 Mz, $CDCl_3$): δ 32.87, 51.62, 52.29, 113.42, 114.05, 122.15, 124.42, 125.35, 126.83, 129.37, 134.06, 138.43, 140.49, 164.84, 169.77. MS (EI) *m*/*z* (%): 388 (M+1, 40%), 329 (23). Elemental anal. calcd for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.42; N, 3.62; S, 8.28. Found: C, 59.11; H, 4.57; N, 3.58; S, 8.32.
Data for **2g**: mp 142 °C; IR (KBr) ν_{max}: 1743, 1712, 1369, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.36 Hz, 3H), 3.72 (s, 3H), 4.23–4.28 (m, 4H), 6.52 (d, J = 16.1 Hz, 1H), 7.29–7.33 (m, 3H), 7.41–7.44 (m, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 16.1 Hz, 1H), 7.77–7.79 (m, 1H), 7.83 (d, J = 7.3 Hz, 1H), 8.02 (d, J = 6.8 Hz, 1H). MS (EI) *m*/*z* (%): 427 (M^+, 13%), 286 (77), 182 (36), 154 (95). Elemental anal. calcd for $C_{22}H_{21}NO_6S$: C, 61.81; H, 4.95; N, 3.28; S, 7.50. Found: C, 61.73; H, 5.02; N, 3.22; S, 7.58.