REACTIONS OF TRIETHYL(1-METHYL-2-INDOLYL)BORATE WITH N-CARBOPHENOXYPYRIDINIUM DERIVATIVES

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Abstract —— The reaction of triethyl(1-methyl-2-indolyl)borate with several N-carbophenoxypyridinium derivatives afforded 3-substituted 2-ethyl-1-methylindoles in the absence of copper(I) ion, while 3-substituted 1-methylindoles were obtained in the presence of copper(I) ion.

Trialkyl(1-methyl-2-indolyl)borates appear to be promising synthetic intermediates as evidenced by a novel conversion of them to 2,3-dialkyl-1-methylindoles *via* a simple alkylation reported by Levy.[1] In the context of our continuing studies on heteroarylborane compounds,[2a] it was previously reported that copper(I) ion played a critical role in the reaction of tributyl(1-methyl-2-indolyl)borate with allyl bromide leading to regioselective allylation at the 2-position of the indole ring, proceeded probably *via* displacement process,[3] to afford 2-allyl-1-methylindole.[2b] In this paper, we wish to report the reaction of triethyl(1-methyl-2-indolyl)-borate (1) with N-carbophenoxypyridinium derivatives (2) without copper(I) ion, and the reaction in the presence of copper(I) ion which reveals a mechanistic alternative to the previous results.[2b]

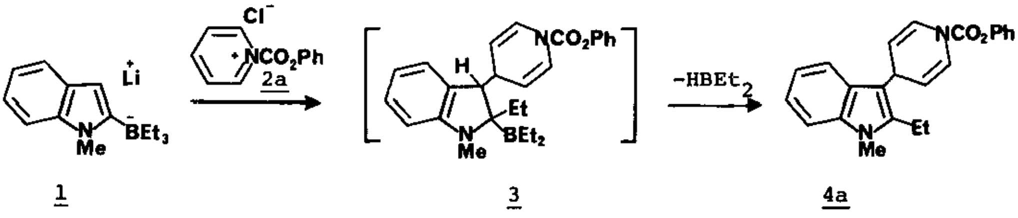


Chart 1

When 1 was reacted with N-carbophenoxypyridinium chloride (2a) in tetrahydrofuran without copper(I) ion, formation of 2,3-disubstituted indole (4a) was observed as was expected by known path (Chart 1). Additional results of the reaction of 1 and N-carbophenoxypyridinium derivatives (2b, 2c and 2d) were also summarized in Table 1. Stable crystalline compound (4b) bearing Et_2B group, intermediary compound in the addition step, was isolated from 1 with 2b. An attempted reaction of 1 with 2d resulted in a complex mixture.

On the other hand, the reaction of 1 with 2a in the presence of copper(I) ion afforded unexpected 3-substituted indole (6a) as a sole isolable product, which may be assumed to be formed through quite different reaction mode from that of the previous result.[2b] Structural assignment of 6a was made on the basis of spectral data (ir, nmr, Mass) (Table 2) as well as comparison with those of an authentic sample (6a)[4] prepared from indole and 2a according to usual methods.[5] The results of the same type of the reaction of 1 were illustrated in Table 1.

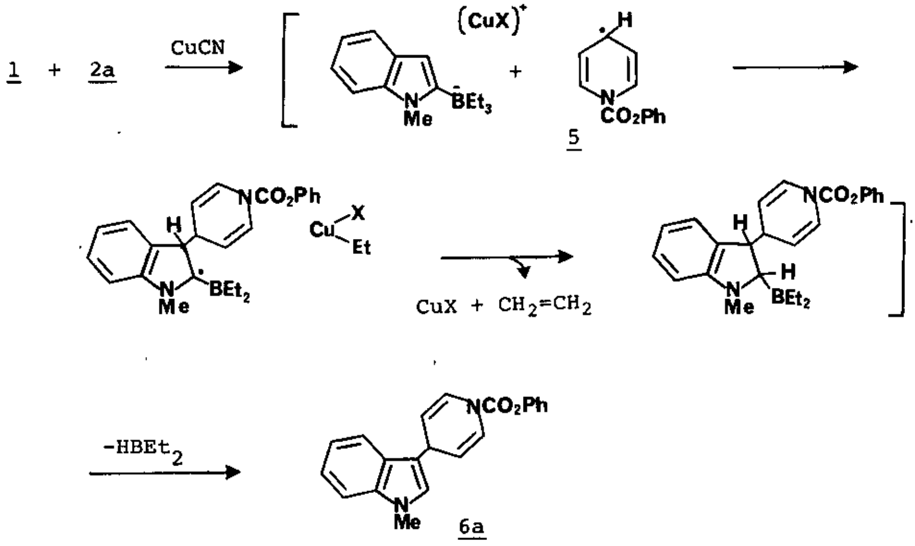


Chart 2

Mechanistic process for the formation of 4a may be rationalized in common with the earlier results,[1,2] i.e., nucleophilic addition of 1 to 2a and the subsequent ethyl migration from boron to carbon (1 ⟹ 3), followed by an oxidation sequence (3 ⟹ 4a) (Chart 1).

Taking into account that 2a is an efficient electron acceptor,[6] the reaction of 1 with 2a in the presence of copper(I) ion might involve single electron transfer leading to pyridylradical (5) prior to C-C bond formation.[7] Plausible sequences leading to 6a were interpreted as outlined in Chart 2, though the details have not yet been clear.

Further studies in progress are aimed at elucidating the mechanistic details.

EXPERIMENTAL

Infrared spectra were recorded with a Hitachi 270-30 spectrometer, and proton (^{1}H-nmr) and carbon-13 nuclear magnetic resonance (^{13}C-nmr) spectra were determined with a JEOL FX-90Q, a JEOL JNM GX-270 and a JEOL GX-400 spectrometers. Tetramethylsilane (in ^{1}H-nmr) and the $CDCl_3$ resonance at 77.1 ppm (in ^{13}C-nmr) were used as internal references. Chemical shifts are given in δ-value downfield from tetramethylsilane. Coupling constants are reported in hertz and splitting patterns are designated as follows; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on a JEOL JMS-D300 and a JEOL JMS-QH100 spectrometers. Flash chromatography was performed on a silica gel 230-40 mesh ASTM obtained from Merck. Tetrahydrofuran was distilled from sodium benzophenone ketyl before use. All melting points were determined with a Yanagimoto micro melting point apparatus, and are uncorrected.

Typical Procedure: Formation of 3-(1-Carbophenoxy-1,4-dihydro-4-pyridyl)-2-ethyl-1-methylindole (4a)

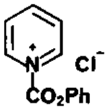
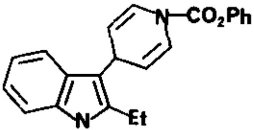
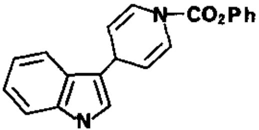
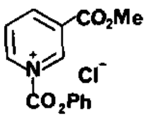
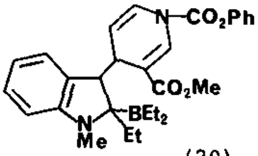
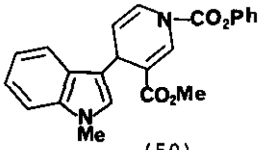
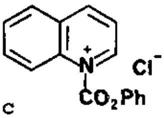
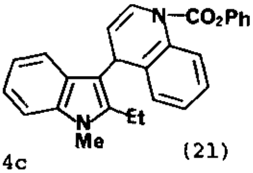
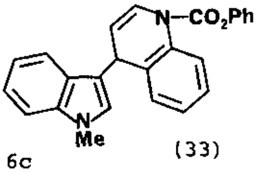
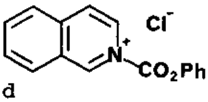
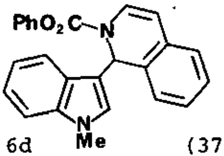
A mixture of 1-methylindole (262 mg, 2 mmol) and butyllithium (1.5M solution in hexane, 2 ml, 3 mmol) in tetrahydrofuran (10 ml) was refluxed for 5 h under an argon atmosphere, then cooled to -20°C. Triethylborane (1M solution in hexane, 3 ml, 3 mmol) was added. After stirring for 30 min, the resulted pale yellow solution was added to a suspension of 2a, derived from pyridine (237 mg, 3 mmol) and phenyl chlorocarbonate (468 mg, 3 mmol), in tetrahydrofuran (10 ml) at -20°C under an argon atmosphere. The mixture was gradually warmed to room temperature and stirred overnight. After treatment with 10% aqueous sodium hydroxide (5 ml) and 30% aqueous hydrogen peroxide (2 ml) solutions at 0°C, the mixture was extracted with ethyl acetate (60 ml). The extract was washed with brine (30 ml), and dried over magnesium sulfate. The solvent was removed, and the residue was subjected to flash chromatography with ethyl acetate:hexane=1:20 to give 260 mg (36% yield) of 4a. Other products (4b, 4c) were obtained from 1 with 2b and 2c, respectively, in a similar manner as above, and spectral data of the products (4a, 4b, 4c) were summarized in Table 2.

Typical Procedure: Formation of 3-(1-Carbophenoxy-1,4-dihydro-4-pyridyl)-1-methylindole (6a)

A mixture of 1-methylindole (262 mg, 2 mmol) and butyllithium (1.5M solution in hexane, 2 ml, 3 mmol) in tetrahydrofuran (10 ml) was refluxed for 5 h under an argon atmosphere, then cooled to -20°C. Triethylborane (1M solution in hexane, 3 ml, 3 mmol) was added. After stirring for 30 min, copper(I) cyanide (294 mg, 3.3 mmol) was added, and the mixture was stirred for 20 min. The resulted dark-brown solution was added to a suspension of 2a, derived from pyridine (237 mg, 3 mmol) and phenyl chlorocarbonate (468 mg, 3 mmol) in tetrahydrofuran (10 ml), at -20°C under an argon atmosphere. The mixture was gradually warmed to room temperature, and stirred overnight. After treatment with 10% aqueous sodium hydroxide (5 ml) and 30% aqueous hydrogen peroxide (2 ml) solutions, the mixture was diluted with ethyl acetate (80 ml), washed with brine (40 ml), and dried over magnesium sulfate. The solvent was removed, and the residue was subjected to flash chromatography with ethyl acetate:hexane=1:20 to give 265 mg (40% yield) of 6a.

Other products (6b, 6c, 6d) were produced from 1 with 2b, 2c, and 2d, respectively, in a similar manner as above, and spectral data of the products (6a, 6b, 6c, 6d) were summarized in Table 2.

Table 1 Reactions of 1 with N-carbophenoxypyridinium derivatives[a)]

N-Carbophenoxy-pyridinium derivatives	Product in the absence of CuCN (yield %)	Product in the presence of CuCN (yield %)
 2a	 4a (36) mp 138-141°C[b)]	 6a (40) syrup
 2b	 4b (20) mp 130-132°C[c)]	 6b (50) syrup
 2c	 4c (21) syrup	 6c (33) syrup
 2d	———— d)	 6d (37) mp 164-166°C[e)]

a) Yields are based on 1-methylindole b) Attempted recrystallization was unsuccessful because of their instability c) Recrystallized from hexane-ethyl acetate; Anal. Calcd for $C_{29}H_{35}BN_2O_4$: C, 71.61; H, 7.25; N, 5.76. Found: C, 71.75; H, 7.42; N, 5.64. d) Complex mixture e) Recrystallized from hexane-ethyl acetate ; Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.92; H, 5.30; N, 7.36. Found: C, 78.95; H, 5.25; N, 7.48.

Table 2 Spectral data of 4 and 6

Compd.	ir cm^{-1}	^{1}H-nmr($CDCl_3$) δ	^{13}C-nmr($CDCl_3$) δ	Mass (m/z) Formula Calcd (Found)
4a	1712, 1686, 1632[a]	1.21(t, 3H, J=8Hz), 2.83(q, 2H, J=8Hz), 3.69 (s, 3H), 4.50-4.70(m, 1H), 4.90-5.20(m, 2H), 6.90-7.80(m, 10H), 7.63(dd, 1H, J=2, 6Hz)	15.0(q), 17.7(t), 29.4(q), 29.9(d), 108.9(d), 111.0(d), 111.5(d), 112.9(s), 118.8(d), 119.0(d), 120.9(d), 121.6(d), 121.8(d), 125.9(d), 127.1(s), 129.5(d), 136.9(s), 138.7(s), 150.2(s), 150.8(s)	$C_{23}H_{22}N_2O_2$ 358.16809 (358.16699)
6a	1728, 1690, 1632, 1614[b]	3.76(s, 3H), 4.40-4.60(m, 1H), 5.05-5.40(m, 2H), 6.90(s, 1H), 6.90-7.60(m, 10H), 7.67(dd, 1H, J=2, 6Hz)	30.1(d), 32.7(q), 109.5(d), 111.0(d), 115.5(s), 119.0(d), 119.1(d), 121.6(d), 121.9(d), 125.9(d), 126.5(s), 126.7(d), 129.5(d), 137.4(s), 150.1(s), 150.9(s)	$C_{21}H_{18}N_2O_2$ 330.13681 (330.13791)
4b	1744, 1704, 1680, 1622[a]	0.69(t, 3H, J=8Hz), 1.05-1.15(m, 8H), 1.19 (q, 2H, J=8Hz), 1.76(dq, 1H, J=7, 15Hz), 2.06(dq, 1H, J=7, 14Hz), 2.55(d, 1H, J=3Hz), 3.04(s, 3H), 3.73(dd, 1H, J=3, 5Hz), 3.84(s, 3H), 4.99(m, 1H), 6.44(d, 1H, J=8Hz), 6.73 (dd, 1H, J=1.5, 7.5Hz), 6.83-6.95(m, 2H), 6.99(dd, 1H, J=1.5, 8.5Hz), 7.18(ddd, 1H, J=1.5, 7.5, 8Hz), 7.25(d, 1H, J=7Hz), 7.37 (dd, 1H, J=7, 8.5Hz), 7.78(s, 1H)	5.8(q), 9.3(q), 10.7(q), 21.8(t), 26.0(t), 34.2 (q), 35.0(d), 51.7(q), 52.0(d), 110.1(d), 112.1(s), 114.0(d), 120.5(s), 121.2(d), 121.6(d), 126.1(d), 127.1(d), 128.2(s), 129.4(d), 132.0(d), 134.9(d), 144.7(s), 149.0(s), 150.4(s), 167.2(s)	455 and 456 (M^+-30) 258(base)
6b	1742, 1710, 1626[b]	3.61(s, 3H), 3.71(s, 3H), 4.79(d, 1H, J=4Hz), 5.35(dd, 1H, J=4, 8Hz), 6.90-7.50(m, 9H), 6.91(s, 1H), 7.65(dd, 1H, J=2, 6Hz), 8.16(d, 1H, J=2Hz)	29.6(d), 32.5(q), 51.3(q), 109.3(d), 112.6(s), 113.1(d), 119.0(d), 119.2(d), 120.0(d), 121.3(d), 121.5(d), 126.2(d), 126.5(s), 127.5(d), 129.5(d), 130.9(d), 137.1(s), 149.7(s), 150.4(s), 166.9(s)	$C_{23}H_{20}N_2O_4$ 388.14238 (388.14278)

Table 2 (continued)

Compd.	ir cm^{-1}	^1H-nmr ($CDCl_3$) δ	^{13}C-nmr ($CDCl_3$) δ	Mass (m/z) Formula Calcd (Found)
<u>4c</u>	1728, 1680, $1594^{b)}$	1.17(t, 3H, J=7Hz), 2.80(q, 2H, J=7Hz), 3.73 (s, 3H), 4.90-5.10(m, 1H), 5.45(dd, 1H, J=3, 7Hz), 6.90-7.70(m, 13H), 8.13(d, 1H, J=8Hz)	14.7(q), 17.8(t), 29.5(q), 33.9(d), 108.9(d), 112.1(s), 115.4(d), 116.2(d), 119.1(d), 121.0(d), 121.3(d), 121.8(d), 125.1(d), 125.3(d), 125.9(d), 126.4(d), 126.8(s), 128.6(d), 129.5(d), 131.5(s), 135.7(s), 137.1(s), 139.7(s), 150.9(s), 151.4(s)	$C_{27}H_{24}N_2O_4$ 408.18372 (408.18252)
<u>6c</u>	1730, 1672, $1614^{b)}$	3.72(s, 3H), 4.95(d, 1H, J=4Hz), 5.64(dd, 1H, J=4, 7Hz), 6.78(s, 1H), 7.00-7.70(m, 13H), 8.15(d, 1H, J=6Hz)	32.7(q), 34.8(d), 109.5(d), 115.0(d), 117.6(s), 119.2(d), 119.4(d), 121.4(d), 121.8(d), 125.3(d), 125.9(d), 126.5(d), 126.7(s), 127.0(d), 128.8(d), 129.5(d), 131.3(s), 135.8(s), 137.5(s), 150.9(s), 151.2(s)	$C_{25}H_{20}N_2O_2$ 380.15242 (380.15142)
<u>6d</u>	1712, $1626^{a)}$	3.64(s, 3H), 6.11(d, 1H, J=7.5Hz), 6.59 (br s, 1H), 6.89(s, 1H), 6.95-7.50(m, 13H), 7.86(dd, 1H, J=2, 6Hz)	32.8(q), 52.0(d), 109.2(d), 110.4(d), 115.7(s), 119.7(d), 120.5(d), 121.8(d), 125.0(d), 125.7(d), 126.1(s), 127.0(d), 127.5(d), 127.7(d), 129.4(d), 130.2(s), 132.7(s), 137.0(s), 151.2(s)	$C_{25}H_{20}N_2O_2$ 380.15242 (380.15380)

a) KBr b) film

REFERENCES AND NOTES

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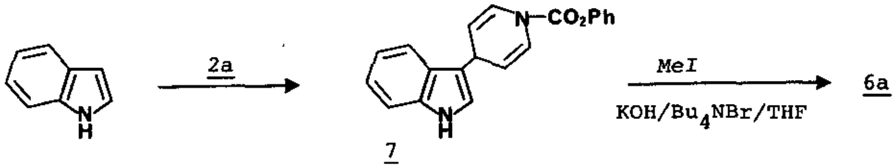
2. a) M. Ishikura, T. Ohta, and M. Terashima, Heterocycles, 1986, 24, 2793; M. Ishikura, I. Oda, M. Kamada, and M. Terashima, Synth. Comm., 1987, 17, 959. b) M. Ishikura, M. Kamada, I. Oda, T. Ohta, and M. Terashima, J. Heterocyclic Chem., 1987, 24, 377.
3. K. Uchida, K. Utimoto, and H. Nozaki, J. Org. Chem., 1976, 41, 2941; K. Uchida, K. Utimoto, and H. Nozaki, Tetrahedron, 1977, 33, 2987; J. B. Campbell, Jr. and H. C. Brown, J. Org. Chem., 1980, 45, 549; H. C. Brown and J. B. Campbell, Jr., J. Org. Chem., 1980, 45, 550; H. C. Brown and G. A. Molander, J. Org. Chem., 1981, 46, 645.

4. Compound (6a) was alternatively prepared as follows:



A mixture of indole (580 mg, 5 mmol), pyridine (20 ml), and phenyl chlorocarbonate (780 mg, 5 mmol) was stirred for 2 days at room temperature. The mixture was concentrated on a rotary evaporator, and the residue was extracted with ether (100 ml). The extract was washed with 10% aqueous hydrochloric acid solution (20 ml), and water (40 ml), and dried over magnesium sulfate. The solvent was removed, and the residue was subjected to flash chromatography with ethyl acetate:hexane=5:1 to give 630 mg (40% yield) of 7 as very unstable crystals, which were used in the next step without further purification.
mp 159-162°C (from ethyl acetate-hexane); ir(KBr) : 3440, 1720, 1688, 1632 cm^{-1}; ^{1}H-nmr(CDCl$_3$) δ : 4.40-4.60(m, 1H), 5.00-5.50(m, 2H), 6.80-7.70(m, 12H), 8.05(br s, 1H); Mass m/z: Calcd for $C_{20}H_{16}N_2O_2$ 316.12128. Found 316.12312.

Iodomethane (1 ml) was added to a mixture of 7 (200 mg, 0.63 mmol), powdered potassium hydroxide (112 mg, 2 mmol), and tetrabutylammonium bromide (64 mg, 0.2 mmol) in tetrahydrofuran (10 ml) at 0°C under an argon atmosphere, then the whole was stirred for 1 h at room temperature. The mixture was diluted with ethyl acetate (70 ml), washed with brine (40 ml), and dried over magnesium sulfate. The solvent was removed, and the residue was subjected to flash chromatography with ethyl acetate:hexane=1:20 to give 166 mg (80% yield) of 6a, whose spectral data (ir, nmr, Mass) was identical with those of 6a derived from 1 and 2a in the presence of copper(I) cyanide.

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6. A. N. Kost and S. I. Suminov, "Iminium Salts in Organic Chemistry," ed. by H. Böhme and H. G. Viehe, John Wiley & Sons, New York (1979), Vol. 2, p.573.

7. A. K. Sheinkman and Yu. N. Il'ina, Khim. Geterotsikl. Soedin., 1971, 7, 568 [Chem. Abstr., 1972, 76, 25046b]; N. Miyaura, M. Itoh, and A. Suzuki, Tetrahedron Lett., 1976, 255; N. Miyaura, M. Itoh, and A. Suzuki, Synthesis, 1976, 618.

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