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Studies on Protection of Oxindoles[§]

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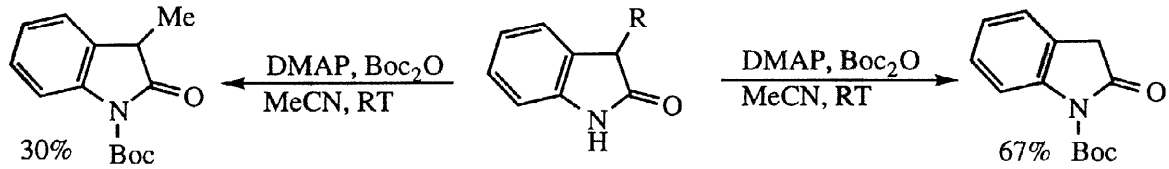
Abstract: Protection of amide nitrogen of oxindole and methyloxindole using Boc and Z-groups has been described. Sodium carbonate was found to be an effective base for these protections.

In continuation of our earlier report[1] on the protection of oxindoles, we now would like to report an extension of this work involving other versatile protecting groups like Boc and benzyloxycarbonyl (Z) groups. These groups are widely used in peptide chemistry for the protection of amino groups. Boc protection of indoles and amides were carried[2,3] out using Boc-anhydride and DMAP in acetonitrile. Application of this procedure to oxindole **1a** yielded N-Boc-oxindole **2a** in 67% yield. But, treatment of 3-methyloxindole **1b** with Boc_2O and DMAP in acetonitrile at room temperature, under the same condition, yielded a complex mixture of mono and diacylated derivatives from which N-Boc-3-methyloxindole **2b** was isolated in 30% yield (Scheme 1).



2b **1** **2a**

a) R=H; b) R=Me

Scheme 1

The above reaction with 3-methyloxindole was not clean and isolation of the desired N-Boc-3-methyloxindole required a careful and tedious chromatographic separation. Our attempts to protect the amide nitrogen of oxindole **1a** using benzyl chloroformate and triethylamine in THF gave only the N- and O-acylated di-Z-derivative **3a**, irrespective of the ratio of the reagents used (Scheme 2 and Table). When 3-methyloxindole **1b** was subjected to the same treatment it gave only a trace amount of **3b**; however, treatment of **1b** with benzyl chloroformate and DMAP gave the N- and C-acylated di-Z-derivative **4** in 43% yield (Table).

[§] Dedicated to the late Dr. Louis A. Cohen on his 72nd birth anniversary.
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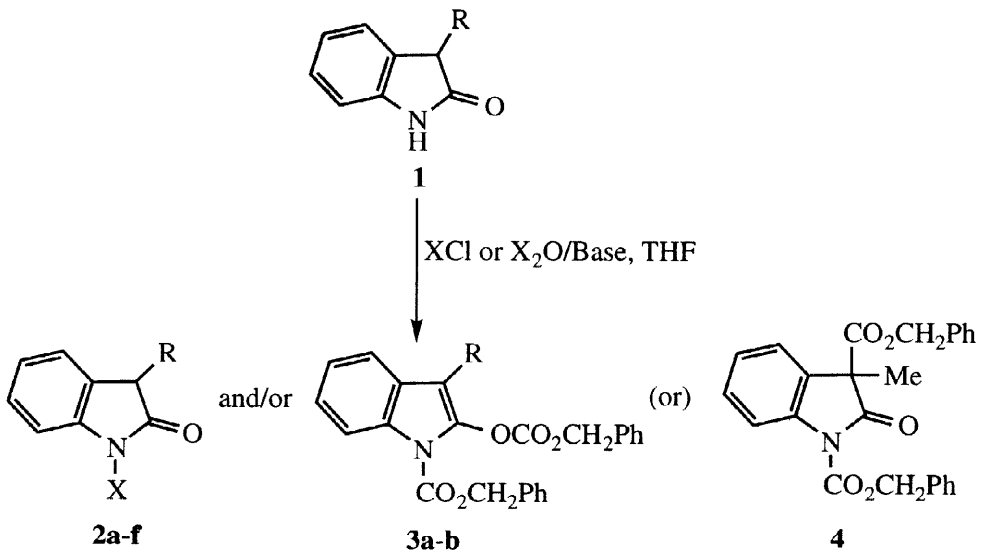

Scheme 2

Table:

Entry	Substrate **1** R	Reagent	Conditions	Product(s)	Yield (%)
1	H	$ClCO_2CH_2Ph$	Et_3N/rt, 10h	**3a** (R=H; X=CO_2CH_2Ph)	65
2	Me	$ClCO_2CH_2Ph$	Et_3N/rt, 10h	**3b** (R=Me; X=CO_2CH_2Ph)	<1
3	Me	$ClCO_2CH_2Ph$	DMAP/rt, 10h	**4**	43
4	H	Boc_2O	Na_2CO_3/rt, 20h	**2a** (R=H; X=Boc)	76
5	Me	Boc_2O	Na_2CO_3/rt, 20h	**2b** (R=Me; X=Boc)	61
6	H	$(PhCH_2OCO)_2O$	Na_2CO_3/rt, 10h	(i) **2c** (R=H; X=CO_2CH_2Ph)	67
				(ii) **3a** (R=H)	15
7	Me	$(PhCH_2OCO)_2O$	Na_2CO_3/rt, 10h	(i) **2d** (R=Me; X=CO_2CH_2Ph)	57
				(ii) **3b** (R=Me)	14
8	H	Ac_2O	Na_2CO_3/rt, 20h	**2e** (R=H; X=Ac)	74
9	Me	Ac_2O	Na_2CO_3/rt, 20h	**2f** (R=Me; X=Ac)	58

So oxindole **1a** and 3-methyloxindole **1b** have differing reactivity even under almost similar conditions. It was our interest to devise a general method for protecting the amide nitrogen of oxindoles by Boc and Z groups.

After several unsuccessful experiments to effect the desired N-protection, we decided to carry out the reaction under milder condition using an organic solvent insoluble base like sodium carbonate. Accordingly, oxindole **1a** and 3-methyloxindole **1b** were treated with Boc-anhydride and sodium bicarbonate or sodium carbonate in THF at room temperature to yield N-Boc-oxindoles **2a** and **b** in 76% and 61% yields, respectively. Protection under this condition was smooth and isolation of the product was very simple when compared to the condition described in scheme 1. The choice of base, sodium carbonate or sodium bicarbonate, did not appreciably affect the yield of the reaction; however, C- and O- acylations were observed when potassium carbonate was used as a base.

Benzyloxycarbonylation of oxindoles **1a** and **b** was carried out using dibenzyl dicarbonate and sodium carbonate in THF at room temperature. Besides the major Z-protected oxindoles **2c** and **d**, di-Z-oxindoles **3a** and **b** were also isolated as side products (Table). To further test the applicability of this method, acetylation of oxindoles **1a** and **b** was carried out with excess acetic anhydride and sodium carbonate in THF at room temperature to yield N-acetyloxindoles **2e** and **f** in 74% and 58% yield, respectively (Table). So, our simple two-phase reaction offers a viable route for protection of oxindoles.

The oxindole carbonyl, in N-Boc-oxindoles, is more vulnerable to nucleophilic attack than the carbonyl of the Boc-group which is sterically less accessible. Thus the oxindole carbonyl of N-Boc-oxindoles could be elaborated by nucleophilic addition to 2-substituted indole derivatives which have been the subject of intensive research.[4-7] N-Boc-oxindole was also a potential precursor for 2-azido and 2-fluoroindoles.[1] The chemistry of N-Boc-oxindoles will be investigated in the future.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Gemini-300 (300 MHz) or Bruker (300 MHz) spectrometer. Elemental analyses were done at Atlantic Microlab, Norcross, GA. Melting points were recorded on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Silica gel 60 (230-400 mesh) was used for column chromatography.

***N-Bocoxindoles* 2a** *and 2b:* **Method** *1*: To a solution of oxindole **1a** or 3-methyloxindole **1b** (2 mmole) in MeCN (25 ml) at room temperature were added DMAP (30 mg) and $(t\text{-Boc})_2O$ (0.48 g, 2.2 mmole). The resulting solution was stirred at room temperature for 6h. Then the solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (25 ml). The organic layer was washed with 10% $KHSO_4$ solution (20 ml), saturated solution of $NaHCO_3$ (20 ml) and water (2x25 ml). Then it was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was applied on a column of silica gel. (Eluent: 1:50 EtOAc/hexane).

N-(tert-butoxycarbonyl)indol-2-one ***2a*** : Yield: 0.31 g (67%); mp 67 °C (hexane); IR ($CHCl_3$): 1791, 1761 and 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65 (s, 9H, t-Bu), 3.65 (s, 2H, CH_2), 7.11-7.35 (m, 3H, arom) and 7.81 (d, 1H, J = 8.3 Hz, arom); MS (CI, NH_3): 234 (M+1)); analysis calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.0; found: C, 66.84; H, 6.46; N, 5.96.

N-(tert-butoxycarbonyl)-3-methylindol-2-one **2b** : Yield: 0.15 g (30%); gum; IR ($CHCl_3$): 1789, 1761 and 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H, J = 7.6 Hz, Me), 1.67 (s, 9H, t-Bu), 3.58 (q, 1H, J = 7.6 Hz, 3-CH), 7.15-7.35 (m, 3H, arom) and 7.84 (d, 1H, J = 8.2 Hz, arom); MS (CI, NH_3): 248 (M+1); analysis calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93; N, 5.66; found: C, 67.90; H, 6.96; N, 5.61.

Method 2 : A solution of **1a** or **b** (2 mmole) and $(t\text{-Boc})_2O$ (1.1 g, 5 mmole) in THF (30 ml) was stirred with $NaHCO_3$ or Na_2CO_3 (1.5g) for 20h at room temperature. The solid was filtered and washed with THF (10 ml). The filtrates were combined and the solvent was removed under reduced pressure. The residue was applied on a column of silica gel. **2a** (1:50 EtOAc/hexane), Yield: 0.35g (76%); **2b** (1:50 EtOAc/hexane), Yield: 0.3 g (61%).

Carbobenzyloxylation of oxindole with benzyl chloroformate : To a solution of **1a** (0.67 g, 5 mmole) and benzyl chloroformate (2.1 ml, 15 mmole) in THF (60 ml) at room temperature was added Et_3N (2.1 ml, 15 mmole) and the solution was stirred for 10h. Then the solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (50 ml). The organic layer was washed with water (3x25 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was applied on a column of silica gel. N-Carbobenzyloxy-2-oxycarbobenzyloxyindole **3a** : (1:50 EtOAc/hexane), Yield: 1.3 g (65%); mp 86-88 °C (EtOAc/hexane); IR ($CHCl_3$): 1777, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.05 (s, 2H, CH_2), 5.32 (s, 2H, CH_2), 6.31 (s, 1H, indole-3H), 7.21-7.52 (m, 13H, arom) and 8.09 (d, 1H, J = 8.4 Hz, indole-7H); MS (CI, NH_3): 419 (M+18); analysis calcd. for $C_{24}H_{19}NO_5$: C, 71.81; H, 4.77; N, 3.49; found: C, 71.96; H, 4.81; N, 3.52.

Carbobenzyloxylation of methyloxindole with benzyl chloroformate : To a solution of **1b** (0.3 g, 2 mmole) and benzyl chloroformate (0.6 ml, 4.2 mmole) in THF (30 ml) at room temperature was added DMAP (0.49 g, 4 mmole) and the solution was stirred for 10h. Then the solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (30 ml). The organic layer was washed with 10% $KHSO_4$ solution (20 ml), saturated solution of $NaHCO_3$ (20 ml) and water (2x25 ml). Then it was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure and the residue was applied on a column of silica gel. 1,3-Bis-(carbobenzyloxy)-3-methylindol-2-one **4** : (1:10 EtOAc/hexane), Yield: 0.36 g (43%); mp 84 °C (benzene/hexane); IR ($CHCl_3$): 1798, 1775, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.75 (s, 3H, Me), 5.14 (s, 2H, CH_2), 5.48 (s, 2H, CH_2), 7.05-7.55 (m, 13H, arom) and 7.95 (d, 1H, J = 8 Hz, indole-7H); MS (CI, NH_3): 433 (M+18); analysis calcd. for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.1; N, 3.37; found: C, 72.43; H, 5.17; N, 3.30.

Carbobenzyloxylation of oxindoles with dibenzyl dicarbonate : To a solution of **1a** or **1b** (1 mmole) and dibenzyl dicarbonate (0.31g, 1.1 mmole) in THF (25 ml) at room temperature was added Na_2CO_3 (0.5g). The reaction mixture was stirred for 10h. Then the solid was filtered and washed with THF (10 ml). The filtrates were combined and concentrated under reduced pressure. The concentrated solution was applied on a column of silica gel.

N-Carbobenzyloxy-2-oxycarbobenzyloxyindole 3a : (1:50 EtOAc/hexane), Yield: 0.06 g (15%).

N-Carbobenzyloxyindol-2-one 2c : (1:10 EtOAc/hexane), Yield: 0.18 g (67%); mp 109-10 °C (EtOAc/hexane); IR ($CHCl_3$): 1796, 1763, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.66 (s, 2H, 3-CH_2), 5.45 (s, 2H, CH_2), 7.12-7.55 (m, 8H, arom) and 7.87 (d, 1H, J = 8.3 Hz, indole-7H); MS (CI, NH_3): 268 (M+1); analysis calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.9; N, 5.24; found: C, 71.85; H, 4.93; N, 5.18.

N-Carbobenzyloxy-3-methyl-2-oxycarbobenzyloxyindole 3b : (1:50 EtOAc/hexane), Yield: 0.06 g (14%); mp 70 °C (benzene/hexane); IR ($CHCl_3$): 1774, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, Me), 5.09 (s, 2H, CH_2), 5.29 (s, 2H, CH_2), 7.2-7.47 (m, 13H, arom) and 8.07 (d, 1H, J = 8 Hz, indole-7H); MS (CI, NH_3): 433 (M+18); analysis calcd. for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.1; N, 3.37; found: C, 72.27; H, 5.11; N, 3.33.

N-Carbobenzyloxy-3-methylindol-2-one 2d : (1:10 EtOAc/hexane), Yield: 0.16 g (57%); mp 64 °C (benzene/hexane); IR ($CHCl_3$): 1793, 1767, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H, J = 7.5 Hz, Me), 3.61 (q, 1H, J = 7.5 Hz), 5.45 (s, 2H, CH_2), 7.15-7.58 (m, 8H, arom) and 7.89 (d, 1H, J = 8.2 Hz, indole-7H); MS (CI, NH_3): 282 (M+1); analysis calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; found: C, 72.56; H, 5.43; N, 4.96.

Acetylation of oxindoles : To a suspension of Na_2CO_3 (0.7 g) in THF (20 ml) were added oxindole **1a** or 3-methyloxindole **1b** (1 mmole) and Ac_2O (0.6 ml, 6 mmole). The reaction mixture was stirred for 20h at room temperature and the solid was filtered and washed with THF (10 ml). The filtrates were combined and concentrated. The concentrated crude product was chromatographed on a column of silica gel.

N-Acetylindol-2-one 2e : (1:20 EtOAc/hexane), Yield: 0.13 g (74%); mp 125-26 °C (benzene/hexane) (Lit.[8] 126 °C); ^1H NMR ($CDCl_3$): δ 2.7 (s, 3H, Me), 3.75 (s, 2H, 3-CH_2), 7.16-7.37 (m, 3H, arom) and 8.24 (d, 1H, J = 8 Hz, indole-7H).

N-Acetyl-3-methylindol-2-one 2f: (1:20 EtOAc/hexane), Yield: 0.11 g (58%); mp 78-79 °C (benzene/hexane) (Lit.[9] 69-72 °C); ^1H NMR ($CDCl_3$): δ 1.56 (d, 3H, J = 7.5 Hz, Me), 2.7 (s, 3H, Me), 3.65 (q, 1H, J = 7.5 Hz), 7.20-7.36 (m, 3H, arom) and 8.25 (d, 1H, J = 8.2 Hz, indole-7H).

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REFERENCES

1. Rajeswaran, W.G.; Cohen, L.A. *Tetrahedron Lett.* **1997**, *38*, 7813.
2. Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 296.
3. Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, *48*, 2424.
4. Rajeswaran, W.G.; Srinivasan, P.C. *Synthesis* **1992**, 835.
5. Nagarathnam, D. *Synthesis* **1992**, 743.
6. Nagarathnam, D. *J. Heterocycl. Chem.* **1992**, *29*, 1371.
7. Sadanandan, E.V.; Srinivasan, P.C. *Synthesis* **1992**, 648.
8. Holt, S.J.; Kellie, A.E.; O'Sullivan, D.G.; Sadler, P.W. *J. Chem. Soc.* **1958**, 1217.
9. Chien, C-S.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 1843.