A NOVEL SYNTHETIC METHOD OF PYRROLO[2,3-*b*]INDOLES AND ITS APPLICATION TO THE SYNTHESIS OF (±)-DEBROMOFLUSTRAMINE B[1]

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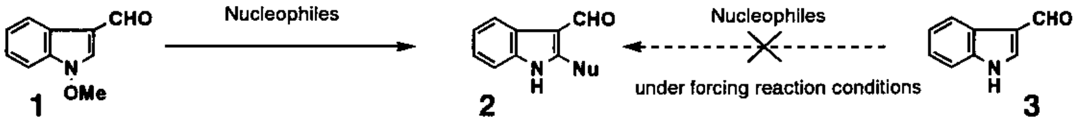
Abstract ———— 1-Methoxy-3-(2-nitrovinyl)indole (**4**) functions as an electrophile and reacted with various nucleophiles regioselectively at the 2-position. Employing allyl alkoxides as nucleophiles, a novel synthetic method of pyrrolo[2,3-*b*]indoles has been elaborated. Utilizing the method, the synthesis of (±)-debromoflustramine B (**10b**) was achieved.

Nucleophilic substitution reactions are rarely observed in the indole chemistry.[2-4] In our continuing project[1b,3,5] for developing our own reaction suitable for indole alkaloids syntheses, we have disclosed as shown in Scheme 1 that 1-methoxyindole-3-carbaldehyde[6] (**1**) undergoes nucleophilic substitution reactions[3] giving 2-substituted indole-3-carbaldehydes[7] (**2**) in sharp contrast with indole-3-carbaldehyde (**3**) which does not give **2** even under forcing reaction conditions. We now wish to report that 1-methoxy-3-(2-nitrovinyl)indole[6a] (**4**) can also react with nucleophiles regioselectively at the 2-position. Employing the reaction to allyl alkoxides as nucleophiles, a novel synthetic method of pyrrolo[2,3-*b*]indoles[8,9] has been elaborated and successfully applied for the synthesis of (±)-debromoflustramine B[10] (**10b**).

Scheme 1



***O*-Nucleophiles** (MeOH, EtOH, $HOCH_2CH_2OH$, etc.); ***N*-Nucleophiles** ($HNMe_2$, Pyrrole, Pyrrolidine, etc.); ***C*-Nucleophiles** (MeCOMe, $CH_2=CH\text{-}CH_2SiMe_3$, $Me_2C=CHCH_2SiMe_3$, MeCO-heteroaromatics, etc.)

The compound (**4**) was obtained in 91% yield by reacting **1** with nitromethane (Scheme 2). When **4** was treated with either NaOMe in MeOH or NaOPr in PrOH, **5a** and **5b** were obtained in 85 and 45% yields, respectively. Interestingly, the reaction of **4** with sodium allyl alkoxide in *N*-methylformamide (MFA) or *N,N*-dimethylformamide (DMF) afforded **5c**

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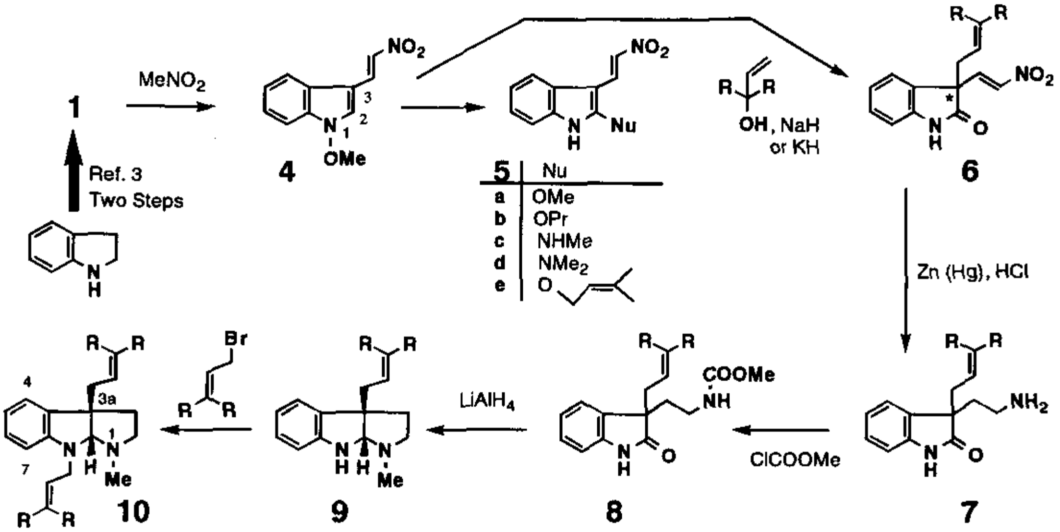
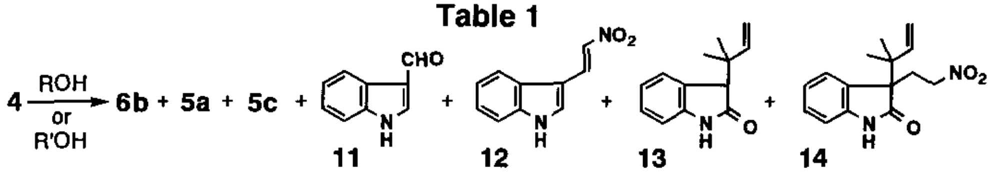
Scheme 2

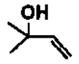
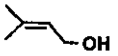


For compounds **6** through **10**: **a**) R = H; **b**) R = Me

Table 1



Entry	Reaction Conditions				Yield (%) of Products						
	Solvent	Base	Temp.(°C)	Time (h)	**6b**	**5a**	**5c**	**11**	**12**	**13**	**14**
1	ROH	NaH	99	1	0	16	0	7	0	0	0
2	ROH	KH	reflux	1.5	0	12	0	5	0	0	0
3	ROH-MFA	NaH	109	1	0	0	75	0	0	0	0
4	ROH -DMF	Na	99	1.5	5	19	0	0	19	0	0
5	ROH -DMF	NaH	99	2.0	7	15	0	0	17	0	0
6	ROH -DMF	KH	98	2.0	12	18	0	0	12	0	0
7	ROH-HMPA	KH	88	0.5	39	27	0	0	6	0	0
8	R'OH-DMF	NaH	93	1.5	0	0	0	0	0	4	5

ROH =  ; R'OH =  ; MFA = *N*-methyl formamide ; DMF = *N,N*-dimethylformamide

and **5d** in 58 and 49% yields, respectively.

Based on the above results, we first attempted to prepare (±)-3a,8-diallyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**10a**) as a model compound of **10b**. As expected, the reaction of **4** with allyl alcohol/NaH in DMF at 86°C produced 2-allyloxy-3-(2-nitrovinyl)indole (**5e**) and (±)-3-allyl-3-(2-nitrovinyl)-2-oxindole (**6a**) in 65 and 6% yields, respectively. Claisen type rearrangement of **5e** proceeded by heating it at 144°C on celite resulting in the formation of **6a** in 95% yield. Reduction of **6a** with Zn(Hg)-HCl gave 3-allyl-3-(2-aminoethyl)-2-oxindole (**7a**) in 99% yield. After preparation of 3-allyl-3-[2-(methoxycarbonyl)aminoethyl]-2-oxindole (**8a**) in 88% yield by reacting **7a** with methyl *chloroformate, reduction of* **8a** *with* LiAlH$_4$ *produced* 3a-allyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (**9a**) in 62% yield. Subsequent treatment of **9a** with BuLi at -18°C and then with allyl bromide produced **10a** in 96% yield. Since the synthesis of **10a** was successful, we turned our attention to the synthesis of (±)-debromoflustramine B (**10b**). Unexpectedly, the reaction of **4** with bulky 2-methyl-3-buten-2-ol was troublesome step and required various examinations. Some typical results are shown in Table 1. As can be seen from the Table, product distributions have dramatically changed depending on the solvent and base. Although the optimum reaction conditions are still not made, we can now obtain the desired 3-(3,3-dimethylallyl)-3-(2-nitrovinyl)-2-oxindole (**6b**) in 39% yield (Entry 7). It should be *mentioned that the formation* of 3-(1,1-dimethylallyl)-3-(2-nitroethyl)-2-oxindole (**14**) was observed, though the yield was low, together with **13**[3d] in the reaction of **4** with 3-methyl-2-buten-1-ol (Entry 8).

With the desired **6b** in hand, we could prepare **10b** without any trouble by the same sequence of reactions as shown above. Thus, **6b** was transformed to **7b** in 76% yield. Then, **7b** was converted to **8b** in 77% yield. Reduction of **8b** with LiAlH$_4$ led to **9b** in 61% yield. Finally, the treatment of **9b** with BuLi at -18°C and then with prenyl bromide produced **10b** in 54% yield.

Optical resolution of (±)-**6a** was readily achieved by utilizing Chiralpak AS column (Daicel) chromatography. As shown in Chart 1, both enantiomers showed base line resolution to give pure (+)-**6a** and (-)-**6a**. Pure (+)-**6b** was resolved utilizing Chiralcel OC column (Daicel), yet (-)-**6b**[9] was obtained as 76% ee mixture. For the syntheses of chiral pyrrolo[2,3-*b*]indole derivatives, study to determine the absolute configulations of (+)-**6a** and (-)-**6a** is now in progress.

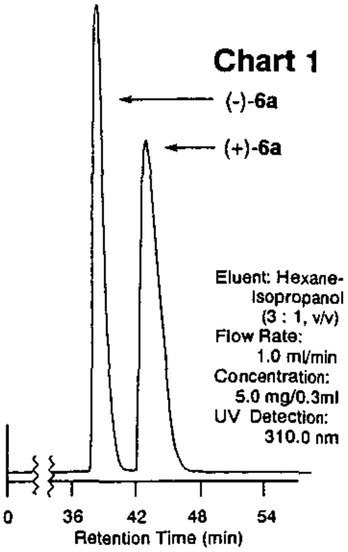


Chart 1

Eluent: Hexane-Isopropanol (3 : 1, v/v)
Flow Rate: 1.0 ml/min
Concentration: 5.0 mg/0.3ml
UV Detection: 310.0 nm

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(-)-**6a**) mp 144.0-150.5°C (decomp), $[\alpha]_D^{24}$ -41.68° (c = 0.300, $CHCl_3$); **6b**) mp 84.0-85.0°C; (+)-**6b**) mp 64.5-65.5°C, $[\alpha]_D^{25}$ +28.44° (c = 0.307, $CHCl_3$); (-)-**6b**) oil, $[\alpha]_D^{25}$ -21.68° (76% ee, c = 0.304, $CHCl_3$); **7a**) oil; **7b**) oil; **8a**) mp 125.0-126.0°C; **8b**) oil; **9a**) mp 103.5-105.0°C; **9b**) mp 57.0-59.0°C; **10a**) oil; **10b**) oil; **13**) mp 149.0-150.0°C; **14**) oil.

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Received, 4th September, 1997