

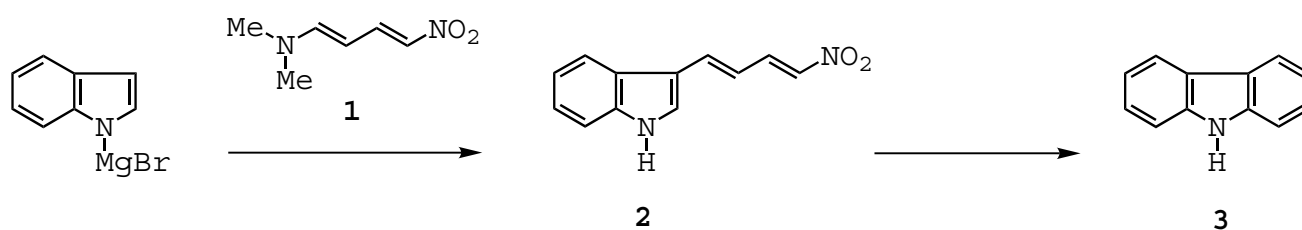
REACTIONS OF A NITRODIENAMINE WITH 1-PROTECTED INDOLYLLITHIUM

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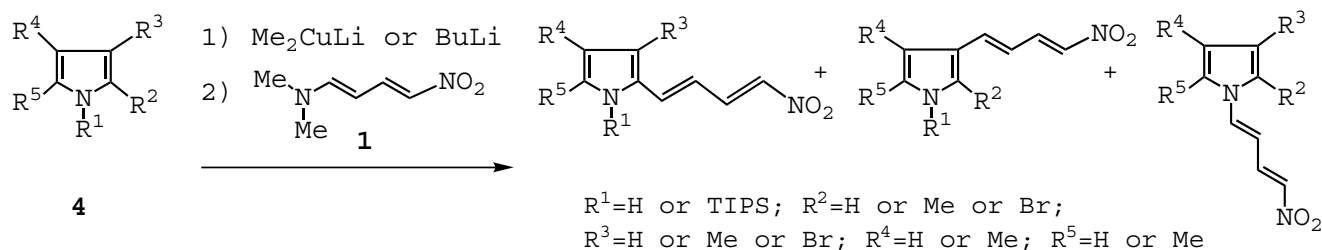
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Abstract - Reactions of a nitrodienamine (**1**) with indolyllithiums prepared from 1-protected indole derivatives were investigated.

The chemistry of enamine and nitroolefin has been considerably important to the progress of organic chemistry.¹ The nitrodienamines have an electronic “push-pull” character as observed in aminodienyl esters and aminoacrylates, which can lead to interesting cycloaddition reactions.¹⁻⁴ In our previous studies,⁵ we reported the synthesis of a nitrodienamine, 1-(*N,N*-dimethylamino)-4-nitro-1,3-butadiene (**1**), some cycloadditions of **1** with α,β -unsaturated carbonyl compounds and quinones, and condensation reactions of **1** with indolyl metal reagents (indolyl Grignard and organocopper reagents) which afforded two products of 1- and 3-(4-nitro-1,3-butadienyl)indole derivatives. Further, we found that the 1-(4-nitro-1,3-butadienyl)indole was not useful derivative of the cycloaddition reaction, but the 3-(4-nitro-1,3-butadienyl)indole (**2**) could yield the cyclization product, carbazole (**3**) as shown in Scheme 1. Therefore, we investigated the synthesis of 3-substituted indoles (**6**) from 1-protected indoles (**5**). We also studied



Scheme 1



Scheme 2

the condensation reactions of **1** with lithium reagents prepared from 1-protected pyrrole derivatives as shown in Scheme 2.

In this paper, we report reactions of **1** with 1-protected indoles (**5a-c**) using alkyllithium as shown in Scheme 3. The conditions of **1** with 3-bromo-1-*tert*-butyldimethylsilylindole (**5a**)⁶ using alkyllithium in THF were shown in Entries 1-7 in Table 1. Typical example is the reaction of **1** with compound (**5a**) using *tert*-butyllithium⁷ in THF affording three products, namely, 1-*tert*-butyldimethylsilyl-3-(4-nitro-1,3-butadienyl)indole (**6a**) (17.7%), the desilylated product, 3-(4-nitro-1,3-butadienyl)indole (**2**) (52.2%), and the debrominated product, 1-*tert*-butyldimethylsilylindole (**8a**) (21.8%) (Entry 6).

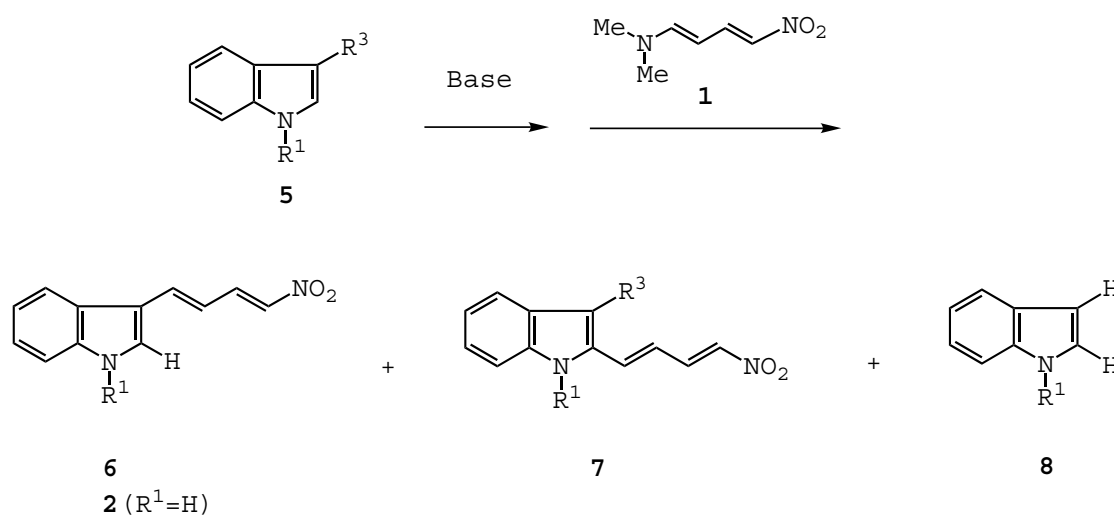
The structures of **6a** and **2** were identified by the following spectral data. The IR spectrum of **6a** shows an absorption band at 1515 cm^{-1} due to a nitro group. The $^1\text{H-NMR}$ spectrum indicates the presence of four olefinic protons at δ 6.88 (1H, dd, $J = 15.6, 12.2$ Hz), 7.23 (1H, d, $J = 12.2$ Hz), 7.36 (1H, d, $J = 15.6$ Hz), 7.84 (1H, t, $J = 12.2$ Hz) due to 4-nitro-1,3-butadienyl group at the 3-position and exhibits a singlet at δ 7.89 due to a proton at the 2-position of the indole ring. The compound (**2**) contains amino (3300 cm^{-1}) and nitro (1512 cm^{-1}) IR absorption bands, respectively. The $^1\text{H-NMR}$ spectrum reveals that **2** has a singlet ascribed to the 2-position [δ 7.86], and a broad singlet ascribed to the N-1 position [δ 10.95]. These facts depict that the nitrodienamine (**1**) reacts with 3-lithio intermediates generated by bromine-lithium interchange with the alkyllithium reagent. The desilylation of **6a** with tetrabutylammonium fluoride in THF furnished **2** in 74.9% yield (Entry 8).

Similarly, the reaction of **1** with 3-bromo-1-triisopropylsilylindole (**5b**)⁸ using *tert*-butyllithium in THF gave the condensation product, 1-triisopropylsilyl-3-(4-nitro-1,3-butadienyl)indole (**6b**) (95.0%) and the

debrominated product, 1-triisopropylsilylindole (**8b**)⁹ (3.2%) (Entry 10).

On the other hand, the 1-*p*-toluenesulfonylindole (**5c**)¹⁰ was prepared to investigate the reaction of a nitrodienamine (**1**). The reaction of **1** with compound (**5c**) using lithium diisopropylamide (LDA)¹¹ in

Table 1. Bases and yields of **2, 6-8**



Entry	Starting material	R ¹	R ³	1 (equiv)	Base (equiv)	Yield (%)		
1	5a	TBDMS	Br	1.1	<i>n</i> -BuLi (1.1)	6a (24.2)	2 (10.8)	8a (58.3)
2	5a	TBDMS	Br	2.5	<i>n</i> -BuLi (2.2)	6a (43.1)	2 (20.5)	8a (28.1)
3	5a	TBDMS	Br	6.0	<i>n</i> -BuLi (2.0)	6a (37.8)	2 (28.1)	8a (32.9)
4	5a	TBDMS	Br	6.0	<i>n</i> -BuLi (5.0)	6a (48.2)	2 (16.8)	8a (30.1)
5	5a	TBDMS	Br	10.0	<i>n</i> -BuLi (9.0)	6a (20.8)	2 (20.3)	8a (56.3)
6	5a	TBDMS	Br	4.0	<i>tert</i> -BuLi (1.0)	6a (17.7)	2 (52.2)	8a (21.8)
7	5a	TBDMS	Br	6.0	<i>tert</i> -BuLi (5.0)	6a (3.0)	2 (9.4)	8a (81.5)
8	6a	TBDMS	-	-	Bu ₄ N ⁺ F ⁻ (0.3)	2 (74.9)		
9	5b	TIPS	Br	2.5	<i>n</i> -BuLi (2.2)	6b (44.6)	8b (40.9)	
10	5b	TIPS	Br	4.0	<i>tert</i> -BuLi (2.1)	6b (95.0)	8b (3.2)	
11	6b	TIPS	-	-	Bu ₄ N ⁺ F ⁻ (0.3)	2 (68.8)		
12	5c	Ts	H	4.0	LDA (1.1)	7c (7.4)	5c (66.0)	

THF provided the condensation product at the 2-position, 2-(4-nitro-1,3-butadienyl)-1-*p*-toluenesulfonylindole (**7c**) in 7.4% yield (Entry 12).⁷

In this time, the reactions of **1** with 1-protected indolyl lithium reagents prepared from 1-silylated 3-bromoindoles (**5**) using alkyl lithiums afforded 3-substituted indoles (**2** and **6**) without giving *N*-substituted product, followed by 1-deprotection of the silyl group in **6** could provide 3-substituted indole (**2**).

These results illustrate that alkyl lithium reagents have divergent behavior toward 1,3-butadiene group, depending on the reaction conditions.

EXPERIMENTAL

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT/IR-8000, JASCO FT/IR-200 spectrophotometer, ¹H-NMR spectra with a JEOL EX-90, JEOL JNM-GX 270, JEOL JNM- 500 spectrometer with tetramethylsilane as an internal standard, MS with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed with a Yanaco CHN-corder MT-3. Silica gel 60 (Cica-MERCK) and Merck Kieselgel 60 F₂₅₄ (silica gel) were used for column chromatography and TLC, respectively.

The Reaction of the Nitrodienamine (1) with 1-Protected Indoles (5a-c) Using Alkyl lithium:

1-*tert*-Butyldimethylsilyl-3-(4-nitro-1,3-butadienyl)indole (6a) and 3-(4-Nitro-1,3-butadienyl)indole (2) and 1-*tert*-Butyldimethylsilylindole (8a)

The 1.7 M *tert*-BuLi in hexane solution (75.9 μ L, 0.13 mmol) was added to a solution of 3-bromo-1-*tert*-butyldimethylsilylindole (**5a**)⁶ (40 mg, 0.13 mmol) in dry THF (3 mL) with stirring at -78 °C under a nitrogen atmosphere and the whole was stirred at -78 °C for 15 min. To resultant solution, a solution of **1** (73.3 mg, 0.52 mmol) in dry THF (4 mL) was added at -78 °C and then the whole was stirred for 1 h under the same conditions. The reaction temperature was gradually raised to rt and the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over MgSO₄ and concentrated. The residue was subjected to silica gel chromatography. The first eluate

with 5% ethyl acetate in hexane gave 6.5 mg (21.8%) of **8a** as colorless needles (ether-hexane), mp 39-40 °C (lit.,⁷ mp 38-39 °C). This compound was identical with **8a** previously reported on the basis of IR, MS and NMR spectral comparisons.⁷ Second eluate gave 7.5 mg (17.7%) of **6a** as orange plates (hexane-chloroform), mp 136-137 °C. IR (KBr) cm^{-1} : 1620, 1515, 1490. ¹H-NMR (CDCl_3) : 0.64 (6H, s, Me), 0.95 (9H, s, Me), 6.88 (1H, dd, $J = 15.6, 12.2$ Hz, olefinic H), 7.23 (1H, d, $J = 12.2$ Hz, olefinic H), 7.26-7.29 (2H, m, aromatic H), 7.36 (1H, d, $J = 15.6$ Hz, olefinic H), 7.46 (1H, m, aromatic H), 7.51-7.55 (1H, m, aromatic H), 7.84 (1H, t, $J = 12.2$ Hz, olefinic H), 7.89 (1H, s, aromatic H). ¹³C-NMR (CDCl_3) : 3.97 (SiMe₂), 19.26 (SiCMe₃), 26.22 (SiCMe₃), 114.73 (C7), 116.74 (C2'), 116.95 (C3), 120.21 (C5), 121.70 (C6), 123.12 (C4), 128.18 (C3a), 135.55 (C4'), 136.17 (C2), 140.35 (C1'), 141.76 (C3'), 142.48 (C7a). High resolution MS m/z : Calcd for C₁₈H₂₄N₂O₂Si (M⁺): 328.1606. Found: 328.1636. Anal. Calcd for C₁₈H₂₄N₂O₂Si: C, 64.52; H, 7.65; N, 8.85. Found: C, 64.82; H, 7.32; N, 8.55. Third eluate gave 14.4 mg (52.2%) of **2** as dark red prisms (ethyl acetate-hexane), mp 166-167 °C (lit.,^{5c} mp 175.5-177.5 °C). IR (KBr) cm^{-1} : 3300, 1599, 1574, 1512. ¹H-NMR (acetone-*d*₆) : 6.98-8.07 (9H, m, aromatic and olefinic H), 7.89 (1H, br s, NH). High resolution MS m/z : Calcd for C₁₂H₁₀N₂O₂ (M⁺): 214.0740. Found: 214.0738. Anal. Calcd for C₁₂H₁₀N₂O₂: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.05; H, 4.80; N, 12.73.

3-(4-Nitro-1,3-butadienyl)indole (**2**) from **6a**

The 1.0 M tetrabutylammonium fluoride in THF solution (27.9 μL , 0.03 mmol) was added to a solution of **6a** (30.5 mg, 0.09 mmol) in dry THF (2 mL) with stirring at -10 °C under an argon atmosphere and the whole was stirred at -10 °C for 10 min. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over MgSO₄ and concentrated. The residue was subjected to silica gel chromatography. The eluate with 50% ethyl acetate in hexane gave 14.9 mg (74.9%) of **2** as dark red prisms (ethyl acetate-hexane), mp 165-167 °C (lit.,^{5c} mp 175.5-177.5 °C). This compound was identical with **2** previously obtained.

3-Bromo-1-triisopropylsilylindole (**5b**)

The *N*-bromosuccinimide (NBS) (1.4 g, 7.87 mmol) was added to a solution of 1-triisopropylsilylindole (**8b**)⁹ (2.11 g, 7.73 mmol) in dry THF (40 mL) with stirring at -10 °C under an argon atmosphere and the

whole was gradually raised to rt and was stirred at the rt for 30 min. Pyridine (0.25 mL) and hexane (25 mL) was added to the reaction mixture, then the whole was filtered by Celite. The filtrate was evaporated. The residue was subjected to Al₂O₃ chromatography. The eluate with hexane gave 1.74 g (63.9%) of **5b** as colorless prisms (ethyl acetate-hexane), mp 63-64 °C (lit.,⁸ mp 62-64 °C). This compound was identical with **5b** previously reported on the basis of IR, MS and NMR spectral comparisons.⁸

1-Triisopropylsilyl-3-(4-nitro-1,3-butadienyl)indole (6b) and 1-Triisopropylsilylindole (8b)

The 1.7 M *tert*-BuLi in pentane solution (72.8 μL, 0.12 mmol) was added to a solution of **5b** (20.5 mg, 0.06 mmol) in dry THF (1 mL) with stirring at -78 °C under a nitrogen atmosphere and the whole was stirred at -78 °C for 20 min. To resultant solution, a solution of **1** (33.1 mg, 0.23 mmol) in dry THF (2 mL) was added at -78 °C and then the whole was gradually raised to rt. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over MgSO₄ and concentrated. The residue was subjected to silica gel chromatography. The first eluate with 30% hexane in chloroform gave 0.5 mg (3.2%) of **8b** as colorless oil. This compound was identical with **8b** previously reported on the basis of IR, MS and NMR spectral comparisons.⁹ Second eluate gave 20.4 mg (95.0%) of **6b** as dark red oil. IR (neat) cm⁻¹: 1615, 1520. ¹H-NMR (CDCl₃) δ: 1.16 (18H, d, *J* = 7.3 Hz, Me), 1.72 (3H, sept, *J* = 7.3 Hz, methine H), 6.89 (1H, dd, *J* = 15.4, 12.0 Hz, olefinic H), 7.24 (1H, d, *J* = 12.0 Hz, olefinic H), 7.27-7.28 (2H, m, aromatic H), 7.38 (1H, d, *J* = 15.4 Hz, olefinic H), 7.53 (1H, s, aromatic H), 7.54-7.55 (1H, m, aromatic H), 7.86 (1H, t, *J* = 12.0 Hz, olefinic H), 7.88-7.90 (1H, m, aromatic H). ¹³C-NMR (CDCl₃) δ: 12.71 (SiCHMe₂), 18.01 (SiCHMe₂), 114.64 (C7), 116.53 (C2'), 116.95 (C3), 120.19 (C6), 121.73 (C5), 123.15 (C3a), 128.18 (C4), 135.43 (C4'), 136.52 (C2), 140.54 (C1'), 141.85 (C3'), 142.32 (C7a). High resolution MS *m/z*: Calcd for C₂₁H₃₀N₂O₂Si (M⁺): 370.2076. Found: 370.2075.

3-(4-Nitro-1,3-butadienyl)indole (2) from 6b

The 1.0 M tetrabutylammonium fluoride in THF solution (39.4 μL, 0.04 mmol) was added to a solution of **6b** (48.6 mg, 0.15 mmol) in dry THF (1 mL) with stirring at -10 °C under an argon atmosphere and the whole was stirred at rt for 15 min. The reaction mixture was poured into water and extracted with ethyl

acetate. The organic layer was washed with brine, then dried over MgSO_4 and concentrated. The residue was subjected to silica gel chromatography. The eluate with 50% ethyl acetate in hexane gave 21.8 mg (68.8%) of **2** as dark red prisms (ethyl acetate-hexane), mp 165-167 °C. This compound was identical with **2** previously obtained.

2-(4-Nitro-1,3-butadienyl)-1-*p*-toluenesulfonylindole (7c)

The 1.5 M BuLi in hexane solution (82.5 μL , 0.12 mmol) was added to a solution of diisopropylamine (18.6 μL , 0.13 mmol) in dry THF (1 mL) with stirring at -78 °C under a nitrogen atmosphere and the whole was stirred at 0 °C for 30 min. To resultant solution, a solution of 1-*p*-toluenesulfonylindole (**5c**)¹⁰ (30.0 mg, 0.11 mmol) in dry THF (1 mL) was added at -78 °C and then the whole was stirred at -78 °C for 1 h and then at 0 °C for 1 h. A solution of **1** (62.9 mg, 0.44 mmol) in dry THF (1 mL) was added to the reaction mixture at -78 °C and the whole was stirred at -78 °C for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, then dried over MgSO_4 and concentrated. The residue was subjected to silica gel chromatography. The first eluate with 50% chloroform in hexane gave 19.8 mg (66.0%) of **5c** as colorless prisms (ether-hexane), mp 85 °C (lit.¹⁰ mp 85 °C). This compound was identical with **5c** previously reported on the basis of IR, MS and NMR spectral comparisons.¹⁰ Second eluate gave 3.0 mg (7.4%) of **7c** as dark red prisms (methanol), mp 205 °C (decomp). IR (KBr) cm^{-1} : 1610, 1500. ¹H-NMR (CDCl_3) δ : 2.32 (3H, s, Me), 6.82 (1H, dd, $J = 15.1$, 12.3 Hz, olefinic H), 7.03 (1H, s, aromatic H), 7.24 (1H, d, $J = 12.3$ Hz, olefinic H), 7.18 (2H, d, $J = 8.6$ Hz, aromatic H), 7.27 (1H, t, $J = 7.6$ Hz, aromatic H), 7.39 (1H, t, $J = 7.6$ Hz, aromatic H), 7.50 (1H, d, $J = 7.6$ Hz, aromatic H), 7.60 (2H, d, $J = 8.6$ Hz, aromatic H), 7.85 (1H, t, $J = 12.3$ Hz, olefinic H), 7.96 (1H, d, $J = 15.1$ Hz, olefinic H), 8.22 (1H, d, $J = 7.6$ Hz, aromatic H). ¹³C-NMR (CDCl_3) δ : 21.60 (-Me), 112.17 (C3), 115.37 (C2'), 121.52 (C3), 123.18 (C5), 124.52 (C6), 126.51 (C3",5"), 126.57 (C4), 129.37 (C3a), 129.89 (C2",6"), 134.53 (C4'), 135.10 (C4"), 137.05 (C2), 138.08 (C7a), 138.51 (C1'), 139.19 (C3'), 145.31 (C1"). High resolution MS m/z : Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$ (M^+): 368.0828. Found: 368.0802.

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