CONDENSATION REACTIONS OF A NITRODIENAMINE WITH GRIGNARD REAGENTS PREPARED FROM PHENYL BROMIDE, BROMOTOLUENE, INDOLES, AND CARBAZOLE

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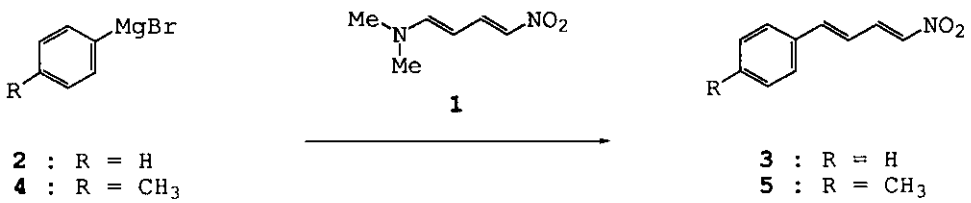
Abstract-Condensation reactions of a nitrodienamine (**1**) with Grignard reagents prepared from phenyl bromide, 4-bromotoluene, indole (**6a**), 3-methylindole (**6b**), 2,3-dimethylindole (**6c**), 3-cyanomethylindole (**6d**), and carbazole (**6e**) were investigated.

We are interested in the reactivities of nitrodienamines and aminodienyl esters having enaminic and diene moieties and an electronic "push-pull" character that can lead to interesting cycloaddition reactions.[1-5] In a previous study,[6] we reported a synthesis of nitrodienamine, 1-(*N,N*-dimethylamino)-4-nitro-1,3-butadiene (**1**), some cycloadditions of **1** with α, β-unsaturated carbonyl compounds and quinones, and condensations with nucleophiles. In this paper we describe the condensation reactions of **1** with Grignard reagents to afford the corresponding products (**3**), (**5**) and/or (**9**), (**10**). The Grignard reagents were prepared from phenyl bromide, 4-bromotoluene, indole (**6a**), 3-methylindole (**6b**), 2,3-dimethylindole (**6c**),

3-cyanomethylindole (**6d**), and carbazole (**6e**).

Treatment of nitrodienamine (**1**) with Grignard reagents phenylmagnesium bromide (**2**) and *p*-tolylmagnesium bromide (**4**) afforded the condensation products **3** (77.1% yield) and **5** (33.3% yield), respectively, as shown in Scheme 1. However, attempts to induce condensation reactions of nitrodienamine (**1**) with ethylmagnesium bromide, benzylmagnesium chloride, and phenyllithium were unsuccessful. The IR spectra of **3** and **5** show an absorption band at 1520 and 1515 cm^{-1} due to a nitro group, respectively. The ^{1}H-NMR spectra of **3** and **5** show the presence of four olefinic protons due to the 4-nitro-1,3-butadienyl group.



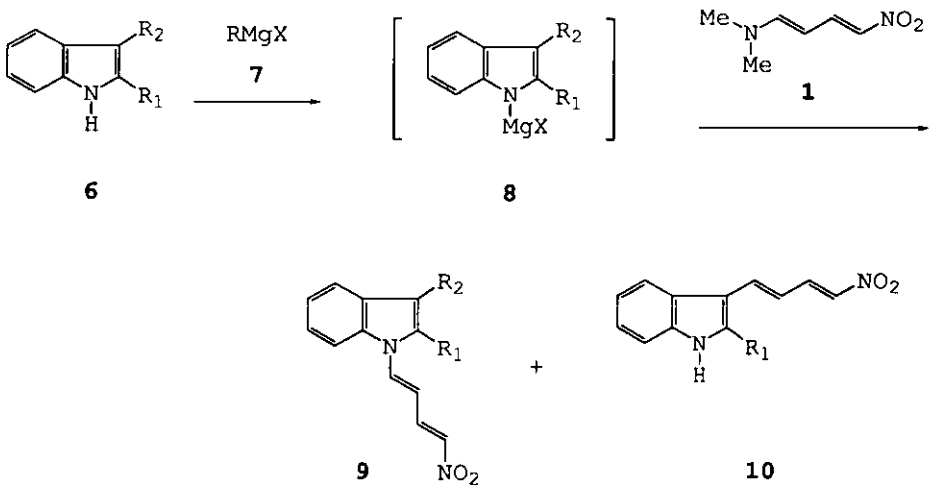
2 : R = H
4 : R = CH_3

3 : R = H
5 : R = CH_3

Scheme 1

Previously, we reported the reaction of nitrodienamine (**1**) with indoles in trifluoroacetic acid, which yielded the dimeric indole compounds, spiro[indole-indolo[1,2-*b*]isoquinoline] derivatives.[6] In this reaction the condensation with **1** occurred at the indole N-1 and indole C-3 positions of dimeric indoles. Therefore, we planned to study the condensation reaction of nitrodienamine (**1**) with indoles under basic conditions. First, we investigated reactivities of nitrodienamine (**1**) toward Grignard reagents, indolylmagnesium, and 3-methylindolylmagnesium bromides, as shown in Scheme 2. Treatment of indole (**6a**) with phenylmagnesium bromide (PhMgBr) in THF, followed by reaction with **1** afforded two condensation products, **9a** (4.5%

yield) and **10a** (2.8% yield). The structures of **9a** and **10a** were confirmed by the following spectral data. The IR spectrum of **10a** shows absorption bands at 3335 and 1512 cm^{-1} due to an amino group and a nitro group, respectively. The ^{1}H-NMR spectrum of **10a** reveals a singlet at δ 7.86 ppm due to a proton at the 2-position of the indole ring. The IR spectrum of **9a** shows no absorption due to an NH group, and the ^{1}H-NMR spectrum of **9a** reveals the presence of two protons at 2- and 3-positions of the indole ring.

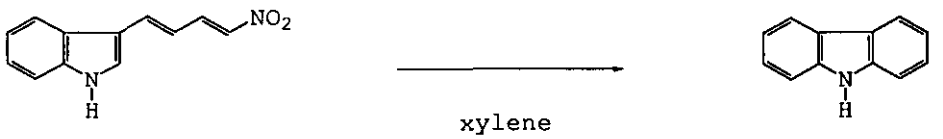


Entry	Initial compound	RMgX		R_1	R_2	Yield (%)	
		R	X			**9**	**10**
1	**6a**	Ph	Br	H	H	**9a** (4.5)	**10a** (2.8)
2	**6b**	Ph	Br	H	Me	**9b** (11.1)	
3	**6c**	*p*-Tol	Br	Me	Me	**9c** (26.4)	
4	**6c**	Bn	Cl	Me	Me	**9c** (19.8)	
5	**6c**	Et	Br	Me	Me	**9c** (46.3)	
6	**6d**	Et	Br	H	CH_2CN	**9d** (17.8)	
7	**6e**	Et	Br	$-(CH=CH)_2-$		**9e** (89.0)	

Scheme 2

Similarly, 3-methylindolylmagnesium bromide (**8b**) reacted with **1** to give 1-[1-(3-methylindolyl)]-4-nitro-1,3-butadiene (**9b**) (11.1% yield). When 2,3-dimethylindole (**6c**) was treated with *p*-tolylmagnesium bromide (**4**) followed by reaction with **1**, the yield of the condensation product (**9c**) was low. This result indicated that the lower reactivity of Grignard reagent (**4**) was caused by steric hindrance and weak basicity. The subsequent use of ethylmagnesium bromide improved the yield of **9c** (46.3% yield). Next, we investigated the reactivities of nitrodienamine (**1**) with Grignard reagents prepared from 3-cyanomethylindole (**6d**) and carbazole (**6e**). Treatment of 3-cyanomethylindole (**6d**) and carbazole (**6e**) with ethylmagnesium bromide followed by reaction with **1** afforded 1-[1-(3-cyanomethylindolyl)]-4-nitro-1,3-butadiene (**9d**) (17.8% yield) and 1-(1-carbazolyl)-4-nitro-1,3-butadiene (**9e**) (89.0% yield), respectively.

Further, we studied the cyclization of condensation products. Although the intramolecular cyclization of 1-phenyl-4-nitro-1,3-butadiene (**3**) and the cycloaddition reaction of 1-[1-(2,3-dimethylindolyl)]-4-nitro-1,3-butadiene (**9c**) with dimethyl 2-butynedionate were unsuccessful, the reaction of 4-nitro-1,3-butadienyl group and indole ring of **10a** by refluxing in xylene for 5 days afforded the intramolecular cyclization product, carbazole (**6e**)[7] (45.7% yield), as shown in Scheme 3.



10a **6e**

Scheme 3

These results introduce a new condensation reaction using Grignard reagents

and indicate the potential utility of this method in the synthesis of indole alkaloids.

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, ^{1}H-NMR spectra with a JEOL EX-90, JEOL JNM-GX 270, JEOL JNM-α 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. Wakogel C-200 (silica gel) and Merck Kieselgel 60 F_{254} (silica gel) were used for column chromatography and TLC, respectively.

The Reaction of the Nitrodienamine (1) with Phenylmagnesium Bromide (2)

A solution of **1** (14.2 mg, 0.1 mmol) in dry THF (1.5 mL) was added dropwise to a solution of 2 M phenylmagnesium bromide (PhMgBr) in THF solution (0.1 mL, 0.2 mmol) in dry THF (1.5 mL) with stirring at rt under argon atmosphere. The whole was stirred at rt for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl and the whole was stirred at rt for 10 min, then extracted with ethyl acetate. The organic layer was washed with brine, then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel chromatography. The eluate with 8% ethyl acetate in hexane gave 13.5 mg (77.1%) of 1-phenyl-4-nitro-1,3-butadiene (**3**) as yellow plates (ether-hexane), mp 41~42 °C. IR (KBr) cm^{-1}: 1620, 1610, 1595, 1520, 1495. ^{1}H-NMR ($CDCl_3$) δ: 7.78 (1H, t, J = 13.1 Hz, olefinic H), 7.53~7.50 (2H, m, aromatic H), 7.43~7.38 (3H, m, aromatic H), 7.24 (1H, d, J = 13.1

Hz, olefinic H), 7.16 (1H, d, J = 15.3 Hz, olefinic H), 6.87 (1H, dd, J = 15.3, 11.6 Hz, olefinic H). High MS m/z: Calcd for $C_{10}H_9NO_2$ (M^+): 175.0633. Found: 175.0635. Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.48; H, 5.24; N, 8.14.

The Reaction of the Nitrodienamine (1) with *p*-Tolylmagnesium Bromide (4)

1 M *p*-TolylMgBr in ether solution: 1 mL, 1 mmol. Reaction time: 2 h. Solvent for chromatography: 10% ethyl acetate in hexane. Product: 6.3 mg (33.3%) of 1-(*p*-tolyl)-4-nitro-1,3-butadiene (**5**) as orange prisms (ether-hexane), mp 63~64 °C. IR ($CHCl_3$) cm^{-1}: 1620, 1605, 1515. ^{1}H-NMR ($CDCl_3$) δ: 7.77 (1H, t, J = 12.6 Hz, olefinic H), 7.41 (2H, d, J = 8.2 Hz, aromatic H), 7.23 (1H, t, J = 12.6 Hz, olefinic H), 7.21 (2H, d, J = 7.9 Hz, aromatic H), 7.12 (1H, d, J = 15.3 Hz, olefinic H), 6.82 (1H, dd, J = 15.6 and 11.6 Hz, olefinic H), 2.38 (3H, s, Me). High MS m/z: Calcd for $C_{11}H_{11}NO_2$ (M^+): 189.0787. Found: 189.0786. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.85; H, 5.99; N, 7.35.

General Procedure for Reactions of the Nitrodienamine (1) with Indoles and Carbazole Grignard Reagents

The RMgBr in THF solution (1 mmol) was added to a solution of substrate (**6**) (1 mmol) in dry THF (3 mL) with stirring at rt under argon atmosphere. The whole was stirred at rt for 2 h. A solution of **1** (0.25 or 0.1 mmol) in dry THF (2 mL) was added dropwise to the reaction mixture with stirring at rt. The whole was stirred for an appropriate period. The reaction mixture was poured into saturated aqueous NH_4Cl and the whole was stirred at rt for 10 min, then extracted with ethyl acetate. The organic layer was washed with

brine, then dried over $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel chromatography.

1-(1-Indolyl)-4-nitro-1,3-butadiene (9a) and 1-(3-Indolyl)-4-nitro-1,3-butadiene (10a)

RMgBr: 2 M PhMgBr. **1**: 35.5 mg, 0.25 mmol. Reaction time: 14 h. Solvent for chromatography: chloroform. First eluate product: 2.5 mg of **9a** (4.5%) as yellow plates (ethyl acetate-hexane), mp 131-133 °C. IR (KBr) cm^{-1}: 1630, 1604, 1581, 1523. ^{1}H-NMR (acetone-d_6) δ: 6.84 (1H, dd, J = 13.7, 11.9 Hz, olefinic H), 6.85 (1H, d, J = 3.7 Hz, aromatic H), 7.23 (1H, dt, J = 7.3, 0.9 Hz, aromatic H), 7.35 (1H, dt, J = 7.3, 0.9 Hz, aromatic H), 7.41 (1H, d, J = 12.8 Hz, olefinic H), 7.65 (1H, d, J = 3.7 Hz, aromatic H), 7.83 (1H, d, J = 3.7 Hz, aromatic H), 7.84 (1H, d, J = 7.3 Hz, aromatic H), 8.04 (1H, dd, J = 12.8, 11.9 Hz, olefinic H), 8.37 (1H, d, J = 13.7 Hz, olefinic H). High MS m/z: Calcd for $C_{12}H_{10}N_2O_2$ (M^+) : 214.0740. Found: 214.0738. Second eluate product: 1.5 mg of **10a** (2.8%) as dark red prisms, (ethyl acetate-hexane), mp 175.5-177.5 °C. IR (KBr) cm^{-1}: 3335, 1599, 1574, 1512. ^{1}H-NMR (acetone-d_6) δ: 7.15 (1H, dd, J = 15.6, 11.6 Hz, olefinic H), 7.21 (1H, dt, J = 7.0, 1.2 Hz, aromatic H), 7.27 (1H, dt, J = 7.0, 1.2 Hz, aromatic H), 7.48 (1H, d, J = 10.7 Hz, olefinic H), 7.53 (1H, dd, J = 7.0, 1.2 Hz, aromatic H), 7.63 (1H, d, J = 15.6 Hz, olefinic H), 7.86 (1H, s, aromatic H), 7.91 (1H, dd, J = 11.6, 10.7 Hz, olefinic H), 8.02 (1H, dd, J = 7.0, 1.2 Hz, aromatic H), 10.95 (1H, s (br.), N-H). High MS m/z: Calcd for $C_{12}H_{10}N_2O_2$ (M^+): 214.0740. Found: 214.0738. Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.05; H, 4.80; N, 12.73.

1-[1-(3-Methylindolyl)]-4-nitro-1,3-butadiene (9b)

RMgBr: 2 M PhMgBr. **1**: 14.2 mg, 0.1 mmol. Reaction time: 20 min. Solvent for chromatography: benzene. Product: 2.5 mg of **9b** (11.1%) as yellow brown prisms (ethyl acetate), mp 204-206 °C. IR (KBr) cm^{-1}: 1622, 1586, 1485. ^{1}H-NMR (acetone-d_6) δ: 2.33 (3H, s, -Me), 6.71 (1H, dd, J = 13.7, 11.9 Hz, olefinic H), 7.25 (1H, dt, J = 7.3, 0.9 Hz, aromatic H), 7.35 (1H, dt, J = 7.3, 0.9 Hz, aromatic H), 7.37 (1H, d, J = 12.5 Hz, olefinic H), 7.59 (1H, dd, J = 7.3, 0.9 Hz, aromatic H), 7.60 (1H, s, aromatic H), 7.78 (1H, d, J = 7.9 Hz, aromatic H), 8.04 (1H, dd, J = 12.5, 11.9 Hz, olefinic H), 8.30 (1H, d, J = 13.7 Hz, olefinic H). High MS m/z: Calcd for $C_{13}H_{12}N_2O_2$ (M^+): 228.0899. Found: 228.0927. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.46; H, 5.18; N, 12.26.

1-[1-(2,3-Dimethylindolyl)]-4-nitro-1,3-butadiene (9c)

RMgBr: 0.92 M EtMgBr. **1**: 14.2 mg, 0.1 mmol. Reaction time: 25 min. Solvent for chromatography: benzene. Product: 11.2 mg of **9c** (46.3%) as orange plates (ethyl acetate), mp 187-188 °C. IR ($CHCl_3$) cm^{-1}: 1640, 1610, 1520. ^{1}H-NMR (acetone-d_6) δ: 8.09 (1H, d, J = 14.0 Hz, olefinic H), 8.04 (1H, t, J = 11.9 Hz, olefinic H), 7.87 (1H, d, J = 7.9 Hz, aromatic H), 7.51 (1H, d, J = 7.6 Hz, aromatic H), 7.51 (1H, d, J = 12.5 Hz, olefinic H), 7.27 (1H, td, J = 7.0 and 1.2 Hz, aromatic H), 7.23 (1H, td, J = 7.3 and 1.2 Hz, aromatic H), 6.96 (1H, d, J = 11.6 Hz, olefinic H), 2.51 (3H, s, Me), 2.24 (3H, s, Me). High MS m/z: Calcd for $C_{14}H_{14}N_2O_2$ (M^+): 242.1055. Found: 242.1068. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.51; H, 5.94; N, 11.45.

1-[1-(3-Cyanomethylindolyl)]-4-nitro-1,3-butadiene (9d)

RMgBr: 0.92 M EtMgBr. **1**: 14.2 mg, 0.1 mmol. Reaction time: 3 h. Solvent for chromatography: 30% ethyl acetate in hexane. Product: 4.5 mg (17.8%)

of **9d** as orange prisms (ethyl acetate), mp 195-196 °C. IR ($CHCl_3$) cm^{-1}: 2310, 1630, 1520, 1510. ^{1}H-NMR (acetone-d_6) δ: 4.12 (2H, d, J = 1.22 Hz, methylene H), 6.89 (1H, dd, J = 13.4, 11.9 Hz, olefinic H), 7.32 (1H, t, J = 7.9 Hz, aromatic H), 7.43 (1H, t, J = 7.0 Hz, aromatic H), 7.44 (1H, d, J = 12.8 Hz, olefinic H), 7.73 (1H, d, J = 7.0 Hz, aromatic H), 7.86 (1H, d, J = 8.6 Hz, aromatic H), 7.88 (1H, s, aromatic H), 8.02 (1H, t, J = 11.0 Hz, olefinic H), 8.35 (1H, d, J = 13.7 Hz, olefinic H). High MS m/z: Calcd for $C_{14}H_{11}N_3O_2$ (M^+): 253.0849. Found: 253.0848. Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.40; H, 4.43; N, 16.46.

1-(1-Carbazolyl)-4-nitro-1,3-butadiene (9e)

RMgBr: 0.92 M EtMgBr. **1**: 14.2 mg, 0.1 mmol. Reaction time: 3 h. Solvent for chromatography: 30% benzene in hexane. Product: 23.5 mg (89.0%) of **9e** as orange plates (ethyl acetate), mp 228-229 °C. IR ($CHCl_3$) cm^{-1}: 1640, 1620, 1520. ^{1}H-NMR (acetone-d_6) δ: 7.22 (1H, dd, J = 14.0, 11.6 Hz, olefinic H), 7.43 (2H, t, J = 7.9 Hz, aromatic H), 7.59 (2H, t, J = 8.2 Hz, aromatic H), 7.59 (1H, d, J = 12.8 Hz, olefinic H), 8.06 (2H, d, J = 8.2 Hz, aromatic H), 8.15 (1H, t, J = 11.9 Hz, olefinic H), 8.21 (2H, d, J = 7.6 Hz, aromatic H), 8.54 (1H, d, J = 14.0 Hz, olefinic H). High MS m/z: Calcd for $C_{16}H_{12}N_2O_2$ (M^+): 264.0899. Found: 264.0911. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.91; H, 4.84; N, 10.45.

Carbazole (6e)

A solution of **10a** (20.0 mg) in xylene (2 mL) was refluxed for 5 days. The reaction mixture was concentrated under a vacuum and the residue was subjected to silica gel chromatography. The benzene eluate gave 7.1 mg (45.7%) of carbazole (**6e**) as a colorless plates (ether-hexane), mp 245 °C

(lit.,[7] mp 245 °C). This compound (**6e**) was identical with authentic sample by mixed mp and IR, ^{1}H-NMR comparisons.

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7. This product was identified by comparison with an authentic sample obtained from a commercial supplier.

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