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CONDENSATION REACTIONS OF A NITRODIENAMINE WITH ORGANOCOPPER AND ALKYLLITHIUM REAGENTS PREPARED FROM PYRROLE DERIVATIVES

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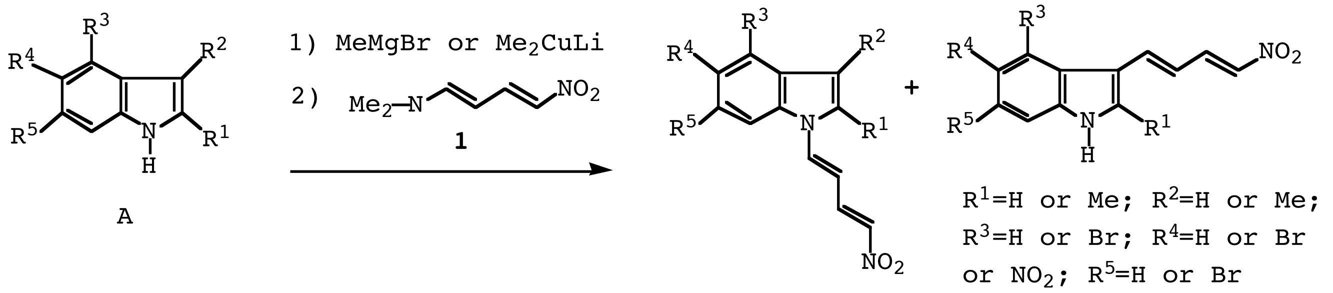
Abstract - Condensation reactions of a nitrodienamine (**1**) with Grignard, organocopper and alkyllithium reagents prepared from pyrrole derivatives were investigated.

Enamine chemistry has been considerably important to the progress of organic chemistry.[1] The nitrodienamines have the electronic "push-pull" character such as aminodienyl esters and aminoacrylates, which can lead to interesting cycloaddition reactions.[1-4] In our previous study,[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 Grignard and organocopper reagents prepared from indole derivatives (**A**) using methylmagnesium bromide and dimethylcopperlithium, respectively, as shown in Scheme 1. We studied the condensation reactions of **1** with Grignard, organocopper and lithium reagents prepared from pyrrole derivatives. The pyrrole derivatives having a 1,3-butadiene group would be interesting compounds in pyrrole organic chemistry.[3a] Although the condensation reaction of a nitrodienamine (**1**) with pyrrole (**2a**) under CF_3CO_2H or CH_3CO_2H condition was unsuccessful, the reaction of **1** with pyrrole (**2a**) using methylmagnesium iodide in ether-benzene afforded 2-(4-nitro-1,3-butadienyl)pyrrole (**3a**) in 12.2% yield as shown in Table 1. The structure of **3a** was confirmed by the following spectral data. The IR spectrum of **3a** shows absorption bands at 3380 and 1530 cm^{-1} due to an amino group and a nitro group, respectively. The ^{1}H-NMR spectrum of **3a** depicts the presence of four protons at the 1-, 3-, 4- and 5- positions of the pyrrole ring. On the other hand, reactions of **1** with pyrroles (**2b**) and (**2c**) under the same conditions were unsuccessful (Entries 2 and 3).



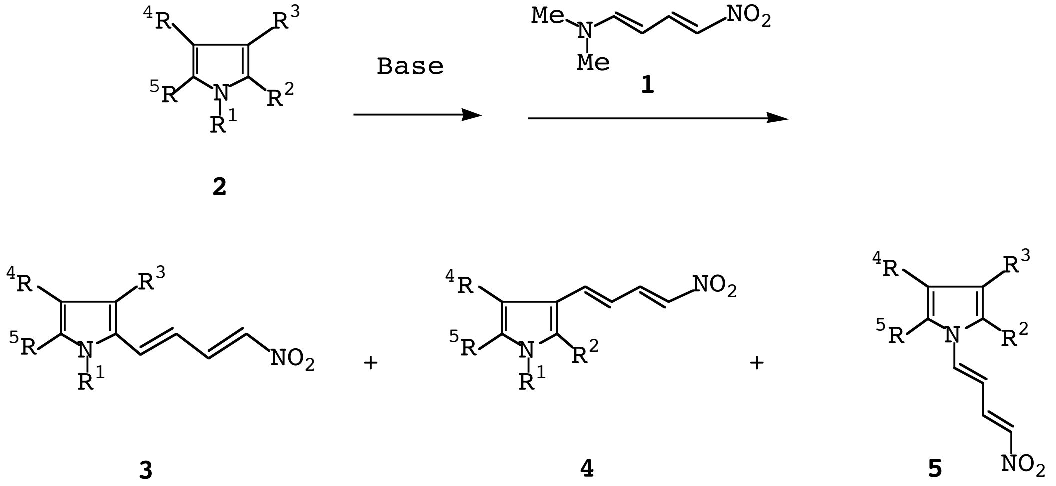
R^1=H or Me; R^2=H or Me; R^3=H or Br; R^4=H or Br or NO_2; R^5=H or Br

Scheme 1

Next, based on the consideration of reactivity and stability of nitrodienamine (**1**), we investigated the condensation reactions of **1** with pyrrolyl organocopper reagents prepared from pyrrole derivatives using dimethylcopperlithium. Pyrrolyl copperlithium reagents are considerably less basic and less nucleophilic than the corresponding alkyllithiums. The condensation reaction of **1** with pyrrole (**2a**) using dimethylcopperlithium in ether-benzene gave two condensation products, **3a** (11.0% yield) and 1-(4-nitro-1,3-butadienyl)pyrrole (**5a**) (29.9% yield, Entry 4). The IR spectrum of **5a** does not have absorption band by an NH group, and shows an absorption band at 1530 cm^{-1} due to a nitro group. The ^{1}H-NMR spectrum of **5a** indicates the presence of four protons and the absence of a proton on nitrogen in the pyrrole ring. Grignard and organocopper reagents have divergent behavior toward 1,3-butadiene group, depending on the reaction conditions.

Similarly, we studied the reactivity of **1** with pyrrolyl organocopper reagents prepared from 2,5-dimethylpyrrole (**2b**) and 3,4-dimethylpyrrole (**2c**).[6] Lithium 2,5-dimethylpyrrolylcuprate (I) reacted with **1** to give 2,5-dimethyl-3-(4-nitro-1,3-butadienyl)pyrrole (**4b**) (36.9% yield, Entry 5). The compound (**4b**) contains amino (3328 cm^{-1}) and nitro (1530 cm^{-1}) IR absorption bands, respectively. The ^{1}H-NMR spectrum reveals that **4b** has a singlet resonance at the 4-position [δ 6.06], and a broad singlet resonance at the N-1 position [δ 10.00]. The treatment of **1** with an organocopper reagent prepared from 3,4-dimethylpyrrole (**2c**) using Me_2CuLi provided 3,4-dimethyl-2-(4-nitro-1,3-butadienyl)pyrrole (**3c**) (3.5% yield) and 3,4-dimethyl-1-(4-nitro-1,3-butadienyl)pyrrole (**5c**) (4.5% yield, Entry 6). The condensation conditions of **1** with compound (**2d**) using alkyllithium in THF were shown in Entries 7-9. The condensation reaction of **1** with 3-bromo-1-(triisopropylsilyl)pyrrole (**2d**)[7] using *tert*-butyllithium in THF afforded 1-triisopropylsilyl-3-(4-nitro-1,3-butadienyl)pyrrole (**4d**) (74.8% yield) and a debrominated product, 1-triisopropylsilylpyrrole (**2g**) (8.3% yield, Entry 9). The IR spectrum of **4d** shows an

Table 1. Equivalences, bases, and yields of **2-5**



Scheme 2

Entry	Starting material	R^1	R^2	R^3	R^4	R^5	**1** / equiv	Base	Yield (%)
1	**2a**	H	H	H	H	H	1.2	MeMgI	**3a** (12.2)
2	**2b**	H	Me	H	H	Me	1.2	MeMgI	Complex mixture
3	**2c**	H	H	Me	Me	H	1.2	MeMgI	Complex mixture
4	**2a**	H	H	H	H	H	2.0	Me$_2$CuLi	**3a** (11.0) **5a** (29.9)
5	**2b**	H	Me	H	H	Me	10.0	Me$_2$CuLi	**4b** (36.9)
6	**2c**	H	H	Me	Me	H	2.0	Me$_2$CuLi	**3c** (3.5) **5c** (4.5)
7	**2d**	TIPS	H	Br	H	H	2.5	n-BuLi	**4d** (13.4) **2g** (R^3=H,78.2)
8	**2d**	TIPS	H	Br	H	H	2.0	*tert*-BuLi	**4d** (69.8) **2g** (R^3=H,15.4)
9	**2d**	TIPS	H	Br	H	H	4.0	*tert*-BuLi	**4d** (74.8) **2g** (R^3=H,8.3)
10	**4d**	TIPS	H	-	H	H	-	Bu$_4$N$^+$F$^-$	**4a** (R^1=H,78.0)
11	**2e**	TIPS	Br	H	H	H	2.0	AlkylLi[a)]	**2g** (R^2=H,73.4)
12	**2f**	Ts	Br	H	H	H	2.0	AlkylLi	**2h** (R^2=H,60.0)

a) AlkylLi: n-BuLi and/or *tert*-BuLi

absorption band ascribable to a nitro function at 1520 cm^{-1}. The ^{1}H-NMR spectrum of **4d** exhibits the presence of four olefinic protons due to the 4-nitro-1,3-butadienyl group at the 3-position. These facts show that the nitrodienamine (**1**) reacts with 3-lithio intermediates by bromine-lithium interchange with the alkyllithium reagent. The desilylation of **4d** with tetrabutylammonium fluoride in THF afforded the 3-(4-nitro-1,3-butadienyl)pyrrole (**4a**) in 78.0% yield (Entry 10). On the other hand, the reaction of **1** with 2-bromo-1-(triisopropylsilyl)pyrrole (**2e**) using alkyllithium in THF only afforded the 1-triisopropylsilylpyrrole (**2g**) in 73.4% yield (Entry 11). It seemed that the condensation reaction was unsuccessful because the lithium intermediate was unstable.
Similarly, the 2-bromo-1-(*p*-toluenesulfonyl)pyrrole (**2f**) and 1-(*p*-toluenesulfonyl)pyrrole (**2h**)[8] were prepared to investigate the condensation reaction with **1**. However, the reaction of **1** with **2f** using alkyllithium in THF only afforded the debrominated product (**2h**) (Entry 12), while **2h** did not afford an identifiable product.

These results illustrate a condensation reaction of **1** with organocopper and alkyllithium reagents prepared from pyrrole derivatives.

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. Silica gel 60 (Cica-MERCK) and Merck Kieselgel 60 F_{254} (silica gel) were used for column chromatography and TLC, respectively.

The Reaction of the Nitrodienamine (1) with Pyrrole (2a) Using Methylmagnesium Iodide: 2-(4-Nitro-1,3-butadienyl)pyrrole (3a)

The 0.98 M MeMgI in ether solution (0.6 mL) was added to a solution of pyrrole (**2a**) (33.5 mg, 0.50 mmol) in dry benzene (2 mL) with stirring at 0 °C under an argon atmosphere. The whole was stirred at 0

°C for 10 min. A solution of **1** (85 mg, 0.60 mmol) in dry benzene (4 mL) was added to the reaction mixture and the whole was stirred at 0 °C for 30 min. The reaction mixture was poured into 10% NH_4Cl, and 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 10% ethyl acetate in chloroform gave 10.0 mg (12.2%) of **3a** as dark red prisms (ether-hexane), mp 126-128 °C. IR (KBr) cm^{-1}: 3380, 1620, 1600, 1530, 1478. ^{1}H-NMR (acetone-d_6) δ: 6.25 (1H, m, aromatic H), 6.60 (1H, m, aromatic H), 6.76 (1H, dd, J = 14.4, 13.7 Hz, olefinic H), 7.07 (1H, m, aromatic H), 7.27 (1H, d, J = 13.7 Hz, olefinic H), 7.31 (1H, d, J = 13.1 Hz, olefinic H), 7.83 (1H, dd, J = 14.4, 13.1 Hz, olefinic H), 10.85 (1H, br s, NH). High resolution MS m/z: Calcd for $C_8H_8N_2O_2$ (M^+): 164.0586. Found: 164.0617.

General Procedure for Reactions of the Nitrodienamine (1) with Pyrroles (2a-c) Using Dimethylcopperlithium:

The 1.06 M MeLi (0.7-1.5 mL) in ether solution was added to a suspension of CuI (75-380 mg, 0.4-2.0 mmol) in anhydrous ether (4 mL) with stirring at 0°C under an argon atmosphere. A solution of pyrrole (**2a-c**) (0.2 mmol) in dry benzene (2 mL) was added to the mixture and the whole was stirred at 0 °C for 10 min under the same conditions. To the resultant solution, a solution of **1**(56-284 mg, 0.4-2.0 mmol) in dry benzene (26 mL) was added at 0 °C and then the reaction mixture was stirred at rt for 3 h. The reaction mixture was poured into 10% NH_4Cl and 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 with appropriate solvents. The isolated yields of **3**, **4** and **5** were based on the corresponding starting pyrroles.

2-(4-Nitro-1,3-butadienyl)pyrrole (3a) and 1-(4-Nitro-1,3-butadienyl)pyrrole (5a)

Substrate: pyrrole (**2a**), 13.4 mg, 0.2 mmol. 1.06 M MeLi in ether solution: 1.5 mL. CuI: 152 mg, 0.8 mmol. **1**: 56.8 mg, 0.4 mmol. Solvent for chromatography: chloroform. First eluate product: 9.8 mg (29.9%) of **5a** as yellow needles (ether-hexane), mp 125-127 °C. IR (KBr) cm^{-1}: 1638, 1613, 1530, 1510, 1480. ^{1}H-NMR (acetone-d_6) δ: 6.19 (2H, t, J = 2.2 Hz, aromatic H), 6.58 (1H, dd, J = 14.0, 11.0 Hz, olefinic H), 7.07 (2H, t, J = 2.2 Hz, aromatic H), 7.24 (1H, d, J = 13.1 Hz, olefinic H), 7.70 (1H, d, J =

14.0 Hz, olefinic H), 7.75 (1H, dd, *J* = 13.1, 11.0 Hz, olefinic H). High resolution MS *m/z*: Calcd for $C_8H_8N_2O_2$ (M^+): 164.0586. Found: 164.0584. Second eluate product: 1.8 mg (11.0%) of the **3a** as dark red prisms (ether-hexane), mp 126-128 °C. This compound was identical with **3a** previously obtained.

2,5-Dimethyl-3-(4-nitro-1,3-butadienyl)pyrrole (4b)

Substrate: 2,5-dimethylpyrrole (**2b**)[6], 19.0 mg, 0.2 mmol. 1.06 M MeLi in ether solution: 3.8 mL. CuI: 380 mg, 2.0 mmol. **1**: 284 mg, 2.0 mmol. Solvent for chromatography: chloroform. Product: 14.2 mg (36.9%) of **4b** as dark red prisms (ether-hexane), mp 187-188 °C. IR (KBr) cm^{-1}: 3328, 1593, 1530, 1480. ^{1}H-NMR (acetone-d_6) δ: 2.17 (3H, s, -Me), 2.31 (3H, s, -Me), 6.06 (1H, s, aromatic H), 6.52 (1H, dd, *J* = 14.9, 11.7 Hz, olefinic H), 7.26 (1H, d, *J* = 13.0 Hz, olefinic H), 7.34 (1H, d, *J* = 14.9 Hz, olefinic H), 7.86 (1H, dd, *J* = 13.0, 11.7 Hz, olefinic H), 10.00 (1H, br s, NH). High resolution MS *m/z*: Calcd for $C_{10}H_{12}N_2O_2$ (M^+): 192.0899. Found: 192.0925.

3,4-Dimethyl-2-(4-nitro-1,3-butadienyl)pyrrole (3c) and 3,4-Dimethyl-1-(4-nitro-1,3-butadienyl)pyrrole (5c)

Substrate: 3,4-dimethylpyrrole (**2c**)[6], 19.0 mg, 0.2 mmol. 1.06 M MeLi in ether solution: 0.7 mL. CuI: 75 mg, 0.4 mmol. **1**: 56.1 mg, 0.4 mmol. Solvent for chromatography: chloroform. First eluate product: 1.7 mg (4.5%) of **5c** as yellow needles (ether-hexane), mp 121-123 ℃. IR (KBr) cm^{-1}: 1636, 1607, 1585, 1535, 1483. ^{1}H-NMR (acetone-d_6) δ: 1.98 (6H, s, -Me), 6.19 (2H, s, aromatic H), 6.52 (1H, dd, *J* = 13.4, 11.9 Hz, olefinic H), 7.33 (1H, d, *J* = 12.8 Hz, olefinic H), 7.66 (1H, d, *J* = 13.4 Hz, olefinic H), 7.85 (1H, dd, *J* = 11.9, 12.8 Hz, olefinic H). High resolution MS *m/z*: Calcd for $C_{10}H_{12}N_2O_2$ (M^+): 192.0897. Found: 192.0892. Second eluate product: 1.3 mg (3.5%) of **3c** as dark red prisms (ethyl acetate-hexane), mp 119-121 ℃. IR (KBr) cm^{-1}: 3335, 1615, 1586, 1557, 1499. ^{1}H-NMR (acetone-d_6) δ: 1.98 (3H, s, -Me), 2.12 (3H, s, -Me), 6.63 (1H, dd, *J* = 15.3, 12.5 Hz, olefinic H), 6.88 (1H, s, aromatic H), 7.25 (1H, d, *J* = 12.5 Hz, olefinic H), 7.33 (1H, d, *J* = 15.3 Hz, olefinic H), 7.89 (1H, t, *J* = 12.5 Hz, olefinic H). High resolution MS *m/z*: Calcd for $C_{10}H_{12}N_2O_2$ (M^+): 192.0899. Found: 192.0909.

The Reaction of 1 with 1-Protected Pyrroles (2d-f) Using Alkyllithium:

1- Triisopropylsilylpyrrole (2g) and 1-Triisopropylsilyl-3-(4-nitro-1,3-butadienyl)pyrrole (4d)

The 1.7 M *tert*-BuLi in pentane solution (85.1 mL) was added to a solution of 3-bromo-1-triisopropylsilylpyrrole (**2d**)[7] (21.2 mg, 0.07 mmol) in dry THF (3 mL) with stirring at -78 °C under an argon atmosphere and the whole was stirred at -78 °C for 20 min. To resultant solution, a solution of **1** (39.9 mg, 0.28 mmol) in dry THF (3 mL) was added at -78 °C. 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 $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel chromatography. The first eluate with 5% chloroform in hexane gave 1.3 mg (8.3%) of **2g** as colorless oil. This compound was identical with **2g** previously reported on the basis of IR, MS and NMR spectral comparisons.[7] Second eluate gave 16.8 mg (74.8%) of **4d** as dark red oil. IR (neat) cm^{-1}: 1615, 1520, 1500, 1490. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (18H, d, *J* = 7.6 Hz, Me), 1.46 (3H, sept, *J* = 7.6 Hz, methine H), 6.53 (1H, dd, *J* = 15.2, 12.0 Hz, olefinic H), 6.55 (1H, dd, *J* = 2.7, 1.5 Hz, aromatic H), 6.78 (1H, t, *J* = 2.7 Hz, aromatic H), 7.00 (1H, t, *J* = 1.5 Hz, aromatic H), 7.14 (1H, d, *J* = 15.2 Hz, olefinic H), 7.15 (1H, d, *J* = 12.0 Hz, olefinic H), 7.78 (1H, t, *J* = 12.0 Hz, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 11.55, 17.69, 17.69, 108.32, 116.60, 124.48, 126.80, 128.44, 135.51, 141.32, 141.37. High resolution MS *m/z*: Calcd for $C_{17}H_{28}N_2O_2Si$ (M^+): 320.1920. Found: 320.1946.

3-(4-Nitro-1,3-butadienyl)pyrrole (4a)

The 1.0 M tetrabutylammonium fluoride in THF solution (56.7 mL) was added to a solution of **4d** (60.5 mg, 0.19 mmol) in dry THF (5 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 $MgSO_4$ and evaporated under reduced pressure. The residue was subjected to silica gel chromatography. The eluate with 25% ethyl acetate in hexane gave 24.2 mg (78.0%) of **4a** as orange prisms (methanol), mp 171-172 °C. IR (KBr) cm^{-1}: 3290, 1610, 1600, 1540, 1500. ^{1}H-NMR ($CDCl_3$) δ: 6.36 (1H, dd, *J* = 4.4, 2.2 Hz, aromatic H), 6.60 (1H, dd, *J* = 15.1, 12.2 Hz, olefinic H), 6.76 (1H, dd, *J* = 4.4, 2.2 Hz, aromatic H), 7.10 (1H, m, aromatic H), 7.20 (1H, d, *J* = 12.2 Hz, olefinic H), 7.21 (1H, d, *J* = 15.1 Hz, olefinic H), 7.69 (1H, t, *J* = 12.2 Hz, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 106.77, 116.91, 121.45, 123.05, 123.37, 136.27, 142.27, 142.96. High resolution MS *m/z*: Calcd for $C_8H_8N_2O_2$ (M^+): 164.0586. Found: 164.0606. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.48; H, 4.97; N, 17.48.

2-Bromo-1-(*p*-toluenesulfonyl)pyrrole (2f)

N-Bromosuccinimide (2.9 g, 16.3 mmol) was added to a solution of pyrrole (**2a**) (1.0 g, 14.9 mmol) in dry THF (60 mL) with stirring at -78 °C under an argon atmosphere and the whole was allowed to stand at - 15 °C for 15 h. 60% NaH (1.26 g, 31.5 mmol) and dry DMF (18 mL) were added to a solution of the reaction mixture at -20 °C and the whole was stirred at the same conditions for 3 h. A solution of *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmol) in dry THF (15 mL) was added to the reaction mixture at -20 °C and the whole was stirred at the same conditions for 1 h. The reaction mixture was concentrated, and the residue was poured into water and 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 25% chloroform in hexane gave 2.3 g (51.4%) of **2f** as colorless needles (ethanol), mp 122-123 °C. IR (KBr) cm^{-1}: 1670, 1595, 1535, 1465. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s, Me), 6.24 (1H, t, *J* = 3.6 Hz, aromatic H), 6.27 (1H, dd, *J* = 3.6, 1.9 Hz, aromatic H), 7.32 (2H, d, *J* = 8.3 Hz, aromatic H), 7.46 (1H, dd, *J* = 3.6, 1.9 Hz, aromatic H), 7.81 (2H, d, *J* = 8.3 Hz, aromatic H). High resolution MS *m/z*: Calcd for $C_{11}H_{10}NO_2BrS$ (M^+ for ^{79}Br): 298.9613. Found: 298.9623.

REFERENCES

1. a) A. Gilbert Cook, " Enamines: Synthesis, Structure, and Reactions", Marcel Dekker, New York and London, 1969; b) S. Rajappa, *Tetrahedron*, 1981, **37**, 1453.
2. a) T. Severin and I. Ipack, *Chem. Ber*., 1976, **109**, 3541; b) *idem, ibid*., 1978, **111**, 692.
3. a) B. I. Rosen, and W.P.Weber, *Tetrahedron Lett*., **1977**, 151; b) G. S. Silverman, and P. E. Rakita, "Handbook of Grignard Reagent", Marcel Dekker, New York, 1996.
4. a) T. Koike, M. Tanabe, N. Takeuchi, and S. Tobinaga, *Chem. Pharm. Bull*., 1997, **45**, 27; b) *idem, ibid*., 1997, **45**, 243; c) *idem, ibid*., 1997, **45**, 1117; d) T. Koike, N. Takeuchi, and S.

Tobinaga, *ibid*., 1998, **46**, 1497; e) *idem, ibid*., 1999, **47**, 128; f) T. Koike, Y. Shinohara, M. Tanabe, N. Takeuchi, and S. Tobinaga, *ibid*., 1999, **47**, 1246; g) T. Koike, Y. Shinohara, N. Ishibashi, N. Takeuchi, and S. Tobinaga, *ibid*., 2000, **48**, 436.

5. a) N. Takeuchi, J. Ohki, and S. Tobinaga, *Chem. Pharm. Bull*., 1988, **36**, 481; b) N. Takeuchi, M. Tanabe, M. Hagiwara, K. Goto, T. Koike, and S. Tobinaga, *Heterocycles*, 1994, **38**, 613; c) T. Koike, M. Hagiwara, N. Takeuchi, and S. Tobinaga, *ibid*., 1997, **45**, 1271; d) T. Koike, N. Takeuchi, M. Hagiwara, K. Yamazaki, and S. Tobinaga, *ibid*., 1999, **51**, 2687.
6. K. Ichimura, S. Ichikawa, and K. Imamura, *Bull. Chem. Soc. Jpn*., 1976, **49**, 1157.
7. B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis, and J. M. Muchowski, *J. Org. Chem*., 1990, **55**, 6317.
8. R. Kitzing, R. Fuchs, M. Joyeux, and H. Prinzbach, *Helv. Chim. Acta*, 1968, **51**, 888.