

# Arylation of Heterocyclic Ketene Aminals with 2,4-Dinitrohalobenzenes by a Radical Nucleophilic Substitution Mechanism

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The anions of heterocyclic ketene aminals reacted with 2,4-dinitrohalobenzenes to give arylated products by a radical nucleophilic substitution mechanism. The  $S_{RN}1$  mechanism was confirmed by EPR spectroscopy, EPR spin trapping, and by depression of the reaction rate by the addition of an inhibitor.

Since the radical nucleophilic substitution mechanism ( $S_{RN}1$ ) was first reported in 1966,<sup>1</sup> much work has been carried out in this field.<sup>2</sup> It is well recognized that the nitroaromatic radical anion  $[ArNO_2]^{•-}$  is quite stable<sup>3</sup> and may participate as an intermediate in numerous organic processes.<sup>4</sup> Nitroaromatic radical anions are readily formed by the reaction of a wide variety of anions with nitroaromatics,<sup>5</sup> or by photolysis of nitroaromatics in basic organic solvents.<sup>6</sup>

Heterocyclic ketene aminals are versatile starting materials for the synthesis of a wide variety of heterocyclic and fused heterocyclic compounds. Recently, the reaction of heterocyclic ketene aminals with  $\alpha,\beta$ -unsaturated esters to give fused heterocycles through addition and cyclocondensation sequences has been reported.<sup>7-13</sup> We have also reported on the alkylation of heterocyclic ketene aminals with benzyl chloride and ethyl bromoacetate.<sup>14</sup> However, the analogous arylation reaction with 2,4-dinitrohalobenzenes under similar conditions did not occur. Here, we report the results of the arylation of the anion of heterocyclic ketene aminals with 2,4-dinitrohalobenzenes by the  $S_{RN}1$  mechanism.

## Results and Discussion

The anion of the heterocyclic ketene aminals **1** and **2**, prepared from **1** or **2** with sodium hydride in dimethyl formamide (DMF), reacted with 2,4-dinitrohalobenzenes (**3**) to afford the arylated products **4** and **5** (Scheme 1). The starting materials (**1** or **2**) were prepared by reaction of the corresponding ketene mercaptans with 1,2-ethanediamine or 1,3-propanediamine.<sup>15</sup>

The compositions of **4** and **5** were determined by MS and elemental analysis. The absence of vinylic or methine proton signals in the <sup>1</sup>H NMR spectra excludes either the *N*-arylated product **A** or the tautomer of the amidine form, **B**. The other spectroscopic data are also consistent with the structures **4** and **5**.

The yields of **4** or **5** from reaction of the anion of **1** or **2** with **3** (with varying halogen substituents) are listed in Table 1. The yields of **4b** from the reaction of the anion of **1b** with **3** (with

Table 1 Reaction of **1** or **2** with **3**<sup>a</sup>

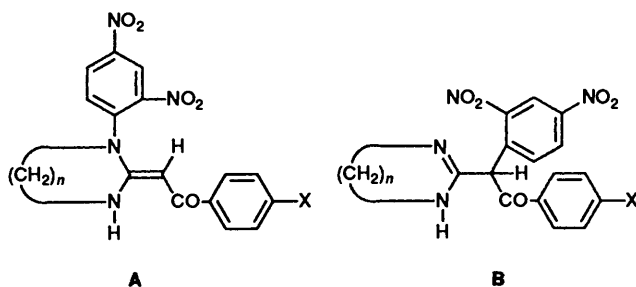
3	Yield (%)						
	4a	4b	4c	4d	5a	5b	5c
3a	73	92	95	64	97	100	100
3b	50	52	60	43	53	57	61
3c	36	44	46	31	41	48	51
3d	25	28	32	22	30	33	36

<sup>a</sup> Molar ratio **1** or **2**:**3** = 1:1, room temperature, 24 h; yield determined by scanning TLC.

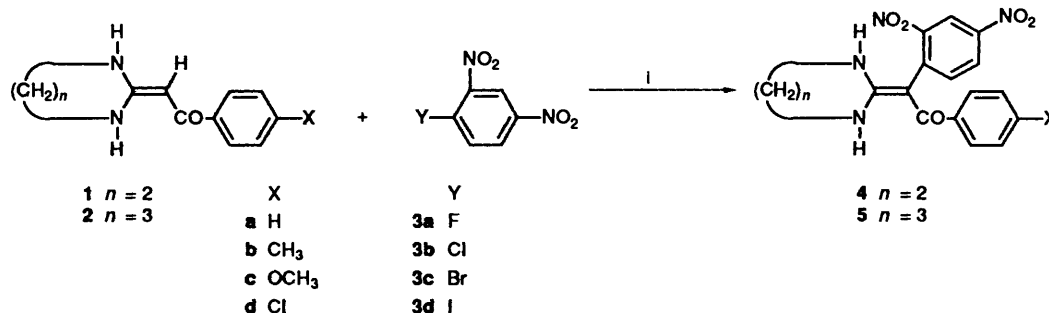
Table 2 Reaction of **1b** with **3** to give **4b**<sup>a</sup>

3	%Yield (t/min)			
3a	79 (30)	80 (60)	92 (138)	
3b	22 (30)	35 (60)	38 (120)	42 (172)
3c	15 (30)	18 (60)	25 (120)	38 (450)
3d	10 (30)	16 (60)	28 (275)	44 (1320)

<sup>a</sup> Molar ratio **1b**:**3** = 1:1, room temperature; yield determined by scanning TLC.



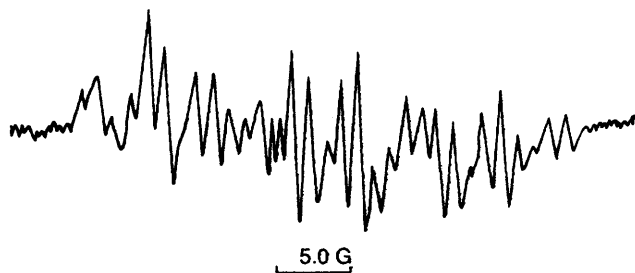
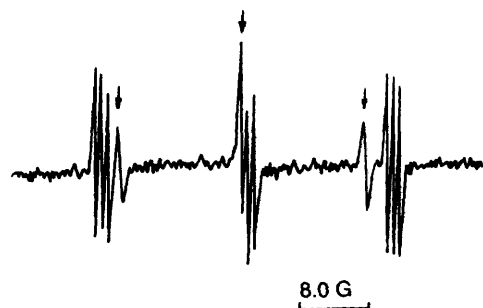
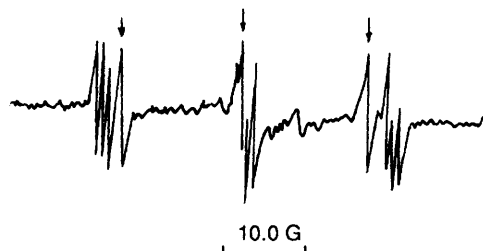
varying halogen substituents) at different times are listed in Table 2. From Tables 1 and 2, it is obvious that the reaction rates of **1** or **2** with **3**, and the yields of **4** or **5**, are dependent on



Scheme 1 Reagents and conditions: i, NaH/DMF, room temperature

**Table 3** Oxidation and reduction potentials

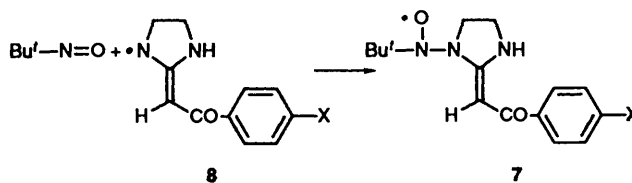
	1	1 <sup>-</sup>	3a	3b	3c	3d
$E_{\text{oxid}}^{\circ}/\text{V}$	1.22	-1.50				
$E_{\text{red}}^{\circ}/\text{V}$			-0.59	-0.43	-0.41	-0.39

**Fig. 1** The EPR spectrum of the radical anion of **3c** recorded during the reaction of the anion of **1b** with **3c** in DMF**Fig. 2** The EPR spectrum of aminoxyl radical **7b** recorded during the reaction of the anion of **1b** with **3b** in the presence of NTB in DMF**Fig. 3** The EPR spectrum of aminoxyl radical **7c** recorded during the reaction of the anion of **1c** with **3b** in the presence of NTB in DMF

different halogen substituents in **3**, and decrease in the order:  $F > Cl > Br > I$ . The yields are also dependent upon the structure of **1** or **2**. In general, an electron-donating group substituted in the benzoyl moiety of **1** or **2** favours the reaction. Also, ketene aminals (**2**) with a six-membered heterocyclic ring give better yields than the ketene aminals (**1**) with a five-membered heterocyclic ring.

In order to explore the  $S_{RN}1$  mechanism of this reaction, the course of the reaction was investigated by EPR spectroscopy, EPR spin trapping, and the effect of radical reaction inhibitors on the product yield. The EPR spectroscopic results indicate that the reaction solution was EPR active, and the EPR spectrum of the radical anion of 2,4-dinitrobenzene was recorded during the course of the reaction between the anion of **1b** and **3c** in DMF (Fig. 1). The hyperfine coupling constants of the radical anion of **6** are:  $a_N = 9.22$  and  $1.06$  G;  $a_H = 3.73$  G (3-, 5-H) and  $1.86$  G (6-H).

The spin trapping technique provides the possibility of detection and identification of short-lived free radicals, and nitroso compounds or nitrones are usually used as spin trapping agents. Figs. 2 and 3 show the EPR spectra of the reaction solution of **1b** or **1c** with **3b** in the presence of nitroso-*tert*-

**Scheme 2**

butane (NTB). The signals indicated by arrows were assigned to the aminoxyl  $Bu'-NO^{\cdot}-Bu'$  with  $a_N = 15.53$  G ( $a_N = 16.0$  G in methanol).<sup>16</sup> The other three triplets with hyperfine coupling constants  $a_N = 18.63$  G and  $a_{\beta N} = 0.93$  G, indicate a nitrogen radical trapped by NTB, and were assigned to the aminoxyl radical **7**, which was formed by the radical addition reaction of radical **8** with the trapping agent. In the literature, values of nitrogen hyperfine coupling constants for some aminoxyl radicals with NTB are:  $a_N = 16.77$  G or  $15.9$  G, and  $a_{\beta N} = 1.37$  G or  $1.75$  G,<sup>17,18</sup> respectively.

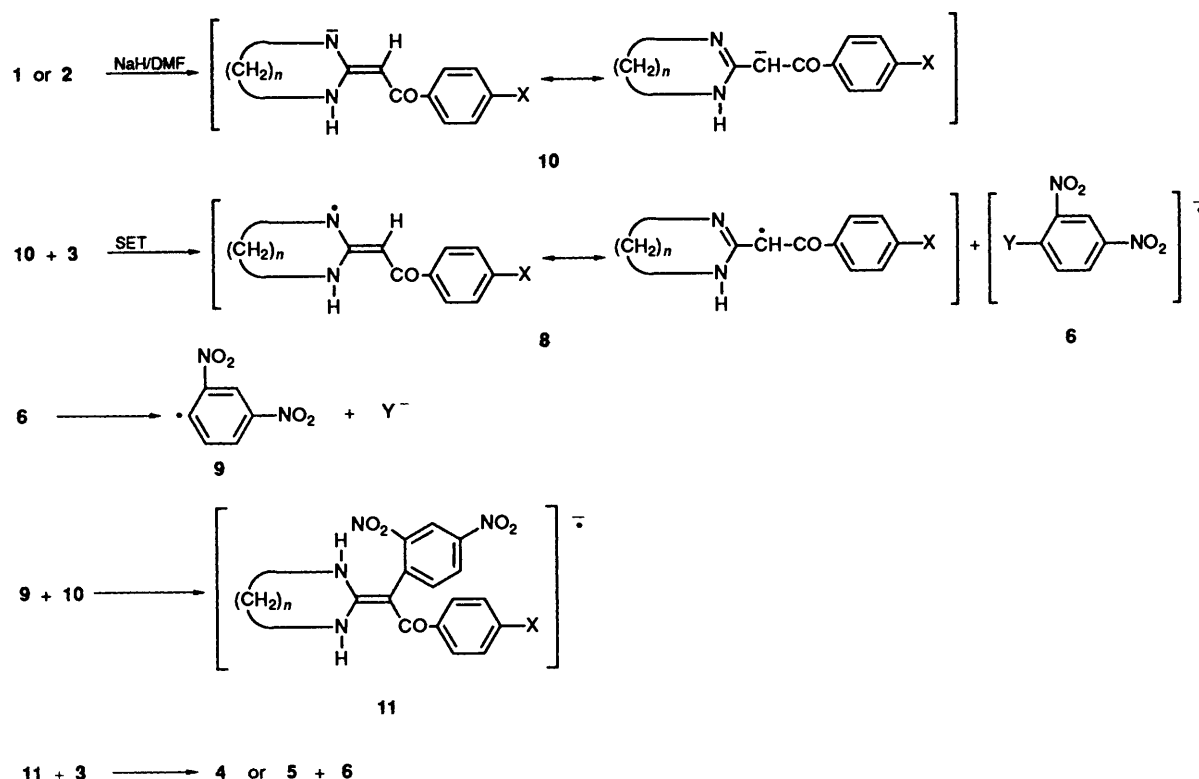
Two reactive intermediates, radical anion **6** and nitrogen radical **8**, have been identified by EPR spectroscopy and EPR spin trapping. These results suggest a single electron transfer occurring between the anion of **1** or **2**, and **3**. The radical anion **6** dissociates to form an aryl radical (**9**) and the anion of the nucleofugal group. However, the formation of products **4** or **5** could be *via* two pathways: the coupling reaction between the two radicals; or the  $S_{RN}1$  process. In order to differentiate these two pathways, an experiment involving the addition of inhibitor to the reaction mixture was carried out. The anion of **1b** was reacted with **3**: in the case of **3a** the addition of a 0.9 molar ratio of iron(III) chloride depressed the yield of **4b** to 46, 64 and 67% at 30, 60 and 212 min, respectively; in the case of **3b-d**, the reaction was totally inhibited. Similar results were obtained for the reaction of the anion of **1c** with **3**. This is a strong evidence for the radical character of the  $S_{RN}1$  mechanism for this reaction. However, it is not affected by bubbling oxygen gas through the reaction mixture. In order to explain this fact, the oxidation or reduction potentials of the reagents were measured by cyclic voltammetry as shown in Table 3. On comparison with the reduction potential of **3**, the couple  $O_2/O_2^{\cdot-}$  has a relatively negative reduction potential ( $-0.77$  V),<sup>19</sup> while the couple  $Fe^{3+}/Fe^{2+}$  has a more positive reduction potential ( $+0.771$  V). This explains the inhibition of the reaction by iron(III) chloride, and the lack of effect with oxygen.

Based on the experimental evidence, an  $S_{RN}1$  mechanism for the formation of **4** or **5** from the anion of **1** or **2** with **3** was proposed (Scheme 3).

## Experimental

M.p.s are uncorrected. Microanalyses were carried out by the Analytical Laboratory of the Institute. Mass spectra were obtained on a AEI MS-50 instrument. IR spectra (KBr disks) were recorded on a Perkin-Elmer 782 spectrometer. <sup>1</sup>H NMR spectra were recorded on a Varian EM-360L instrument. EPR spectra were measured on a Bruker ESR 300D spectrometer.

**2-[Benzoyl(2,4-dinitrophenyl)methylene]imidazolidine (4a).**—A mixture of **1a** (100 mg, 0.53 mmol) and sodium hydride (19 mg, 0.8 mmol) in 3 cm<sup>3</sup> of dimethylformamide (DMF) was allowed to react for 15 min at room temperature. Compound **3c** (130 mg, 0.53 mmol) in 2 cm<sup>3</sup> of DMF was then added. The reaction mixture was stirred at room temperature for 24 h. After the addition of 10 cm<sup>3</sup> water, the mixture was extracted with chloroform ( $3 \times 10$  cm<sup>3</sup>), and the extracts were washed with water ( $3 \times 10$  cm<sup>3</sup>) and dried (magnesium sulphate). Chloroform was removed and the crude product was purified by silica gel column chromatography using ethyl acetate–light



petroleum (60–90 °C) as the eluent. **4a** (56 mg, 30%) was obtained: m.p. 253–254 °C;  $\nu_{\max}/\text{cm}^{-1}$  3320, 3260 (NH), 1580 (C=O), 1520 and 1330 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$  8.45 (1 H, d), 8.18 (1 H, dd), 7.55 (1 H, d), 7.10 (5 H, s) and 3.71 (4 H, s);  $m/z$  354 (M<sup>+</sup>, 10%), 307 (3), 249 (100) and 233 (44) (Found: C, 57.55; H, 4.0; N, 15.6. C<sub>17</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub> requires C, 57.6; H, 4.0; N, 15.8%).

2-[(2,4-Dinitrophenyl)(4-methylbenzoyl)methylene]-imidazolidine (**4b**).—According to the procedure for **4a**, **4b** (364 mg, 40%) was obtained from **1b** (500 mg, 2.47 mmol) and **3c** (610 mg, 2.47 mmol) **3c**: m.p. 270–271 °C;  $\nu_{\max}/\text{cm}^{-1}$  3220 (NH), 1580 (C=O), 1530 and 1335 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$  8.48 (1 H, d), 8.21 (1 H, dd), 7.55 (1 H, d), 7.01 (2 H, d), 6.88 (2 H, d), 3.72 (4 H, s) and 2.22 (3 H, s);  $m/z$  368 (M<sup>+</sup>, 8%), 249 (43), 233 (23) and 119 (100) (Found: C, 58.4; H, 4.3; N, 15.05. C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub> requires C, 58.7; H, 4.4; N, 15.2%).

2-[(2,4-Dinitrophenyl)(4-methoxybenzoyl)methylene]-imidazolidine (**4c**).—According to the procedure for **4a**, **4c** (310 mg, 44%) was obtained from **1c** (400 mg, 1.84 mmol) and **3c** (460 mg, 1.86 mmol): m.p. 139–140 °C;  $\nu_{\max}/\text{cm}^{-1}$  3210 (NH), 1582 (C=O), 1520 and 1332 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$  8.48 (1 H, d), 8.24 (1 H, dd), 7.58 (1 H, d), 7.06 (2 H, d), 6.62 (2 H, d) and 3.71 (7 H, s);  $m/z$  384 (M<sup>+</sup>, 6%), 249 (28), 233 (10), 135 (100) (Found: C, 56.45; H, 4.25; N, 14.4. C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>6</sub> requires C, 56.25; H, 4.2; N, 14.6%).

2-[(4-Chlorobenzoyl)(2,4-dinitrophenyl)methylene]-imidazolidine (**4d**).—According to the procedure for **4a**, **4d** (230 mg, 26%) was obtained from **1d** (500 mg, 2.25 mmol) and **3c** (556 mg, 2.25 mmol): m.p. 195–196 °C;  $\nu_{\max}/\text{cm}^{-1}$  3220 (NH), 1570 (C=O), 1525 and 1324 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{SOCD}_3)$  8.53 (1 H, d), 8.27 (1 H, dd), 7.50 (1 H, d), 7.20 (2 H, d), 7.05 (2 H, d) and 3.57 (4 H, s);  $m/z$  390 (2%), 388 (M<sup>+</sup>, 7), 249 (100), 233 (17) (Found: C, 52.9; H, 3.6; N, 14.3. C<sub>17</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>5</sub> requires C, 52.5; H, 3.4; N, 14.4%).

2-[Benzoyl(2,4-dinitrophenyl)methylene]hexahydropyrimidine (**5a**).—According to the procedure for **4a**, **5a** (291 mg, 32%) was obtained from **2a** (500 mg, 2.47 mmol) and **3c** (610 mg, 2.47 mmol): m.p. 225–227 °C;  $\nu_{\max}/\text{cm}^{-1}$  3350 (NH), 1575 (C=O), 1515 and 1335 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$  8.45 (1 H, d), 8.16 (1 H, dd), 7.50 (1 H, d), 7.05 (5 H, s), 3.39 (4 H, t) and 1.96 (2 H, quin.);  $m/z$  368 (M<sup>+</sup>, 15%), 322 (14), 263 (87), 105 (100) (Found: C, 58.6; H, 4.5; N, 14.9. C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub> requires C, 58.7; H, 4.4; N, 15.2%).

2-[(2,4-Dinitrophenyl)(4-methylbenzoyl)methylene]hexahydropyrimidine (**5b**).—According to the procedure for **4a**, **5b** (245 mg, 39%) was obtained from **2b** (500 mg, 2.31 mmol) and **3c** (570 mg, 2.31 mmol): m.p. 218–219 °C;  $\nu_{\max}/\text{cm}^{-1}$  3330 (NH), 1585 (C=O), 1518 and 1330 cm<sup>-1</sup> (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CDCl}_3)$  8.46 (1 H, d), 8.07 (1 H, dd), 7.90 (1 H, dd), 7.23 (2 H, d), 6.80 (2 H, d), 3.37 (4 H, t), 2.20 (3 H, s) and 1.98 (2 H, quin.);  $m/z$  383 (M + 1, 15%), 307 (12), 263 (10), 246 (25), 154 (100) (Found: C, 60.1; H, 4.4; N, 14.2. C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub> requires C, 59.7; H, 4.7; N, 14.65%).

2-[(2,4-Dinitrophenyl)(4-methoxybenzoyl)methylene]hexahydropyrimidine (**5c**).—According to the procedure for **4a**, **5c** (281 mg, 40%) was obtained from **2c** (400 mg, 1.72 mmol) and **3c** (426 mg, 1.72 mmol): m.p. 192–193 °C;  $\nu_{\max}/\text{cm}^{-1}$  3200 (NH), 1585 (C=O), 1515 and 1338 (NO<sub>2</sub>);  $\delta_{\text{H}}(\text{CD}_3\text{COCD}_3)$  8.45 (1 H, d), 8.17 (1 H, dd), 7.48 (1 H, d), 6.93 (2 H, d), 6.58 (2 H, d), 3.69 (3 H, s), 3.36 (4 H, t) and 1.95 (2 H, quin.);  $m/z$  398 (M<sup>+</sup>, 2%), 350 (13), 135 (100) (Found: C, 57.3; H, 4.5; N, 14.0. C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>6</sub> requires C, 57.3; H, 4.55; N, 14.1%).

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**References**

- 1 (a) N. Kornblum, R. E. Michel and R. C. Kerber, *J. Am. Chem. Soc.*, 1966, **88**, 5662; (b) G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, 1966, **88**, 5663.
- 2 R. A. Rossi and R. H. Rossi, *Aromatic Substitution by the  $S_{RN}1$  Mechanism*, ACS Monograph 178, Washington, DC, 1983.
- 3 G. A. Russell and A. G. Bernis, *Inorg. Chem.*, 1967, **6**, 403.
- 4 G. A. Russell and E. G. Janzen, *J. Am. Chem. Soc.*, 1962, **84**, 4153.
- 5 G. A. Russell, E. G. Janzen and E. T. Strom, *J. Am. Chem. Soc.*, 1965, **87**, 1807.
- 6 G. A. Russell and E. J. Geels, *Tetrahedron Lett.*, 1963, 1333.
- 7 Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 1856.
- 8 Z.-T. Huang and H. Wamhoff, *Chem. Ber.*, 1984, **117**, 1926.
- 9 Z.-T. Huang and Z.-R. Liu, *Heterocycles*, 1986, **24**, 2247.
- 10 Z.-T. Huang and L.-H. Tzai, *Chem. Ber.*, 1986, **119**, 2208.
- 11 Z.-T. Huang and X.-J. Wang, *Tetrahedron Lett.*, 1987, **28**, 1527.
- 12 Z.-T. Huang and X.-J. Wang, *Chem. Ber.*, 1987, **120**, 1803.
- 13 Z.-T. Huang and Z.-R. Liu, *Synth. Commun.*, 1989, **19**, 1801.
- 14 Z.-T. Huang and Z.-R. Liu, *Chem. Ber.*, 1989, **122**, 95.
- 15 Z.-T. Huang and Z.-R. Liu, *Synth. Commun.*, 1989, **19**, 943.
- 16 V. E. Zubarev, V. N. Belevskii and L. T. Bugaenko, *Russ. Chem. Rev., Engl. Trans.*, 1979, **48**, 729.
- 17 S. Terabe and R. Konaka, *J. Am. Chem. Soc.*, 1969, **91**, 5655.
- 18 G. R. Chalfont and M. J. Perkins, *J. Chem. Soc. B*, 1970, 401.
- 19 R. G. Kyger, J. P. Lorano, N. P. Stevens and N. R. Herron, *J. Am. Chem. Soc.*, 1977, **99**, 7589.

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