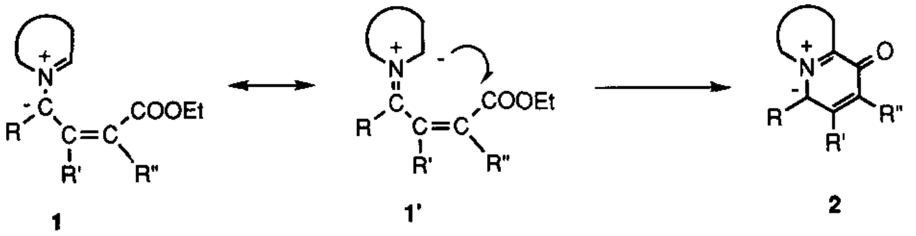
REACTION OF 4-AMINO-1,2,4-TRIAZOLIUM SALTS WITH POLARIZED OLEFINS

Yoshiro Matsuda,* Yasusige Chiyomaru, Kazuki Furuno, and Takanobu Nishiyori

School of Pharmaceutical Sciences, Nagasaki University,
1-14 Bunkyo-machi Nagasaki 852, Japan

Abstract - The reaction of 4-amino-1,2,4-triazolium salts (**5a,b**) with polarized olefins (**3a,b,4a**) in the presence of K_2CO_3 in EtOH or DMSO directly yielded the back-donated 1,6-cyclization products, mesomeric betaines (**6a-c,7a,b**) *via N*-vinylimino ylides, while the reaction of the salts (**5a,b**) with polarized olefins (**4b,c**) gave the 1,5-dipolar cyclization products, pyrazoles (**10a,b**) and [1,2,4]-triazolo[4,3-*b*]pyrazole (**11**).

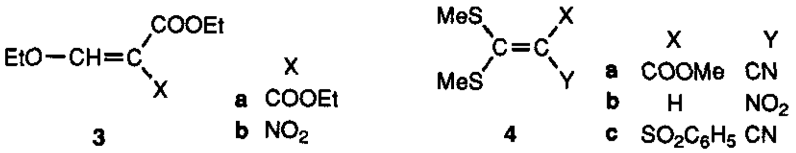
It is well known that heterocyclic salts react with polarized olefins to produce heterocyclic *N*-allylides (**1**) and these *N*-allylides (**1**) , acting as extended dipole are of interest in heterocyclic chemistry.[1] Recently we reported a synthesis of mesomeric betaine (**2**) due to the resonance structure (**1'**) and we proposed a mechanism which involves a back-donated 1,6-cyclization for this transformation[2] (Scheme 1).



Scheme 1

The purpose of the present investigation is to extend this back-donated 1,6-cyclization to the synthesis of [1,2,4]triazolo[4,3-*b*]pyridaziniumides (**6**,**7**) which were prepared by the reaction of 4-amino-1,2,4-

triazolium salt (**5**) with polarized olefins (**3a**,**b**,**4a**). The olefins (**3**,**4**)[3] used in the present work are shown in Scheme 2. The starting materials, 4-amino-1,2,4-triazolium salts (**5a**,**b**) were prepared by Becker's method.[1b]



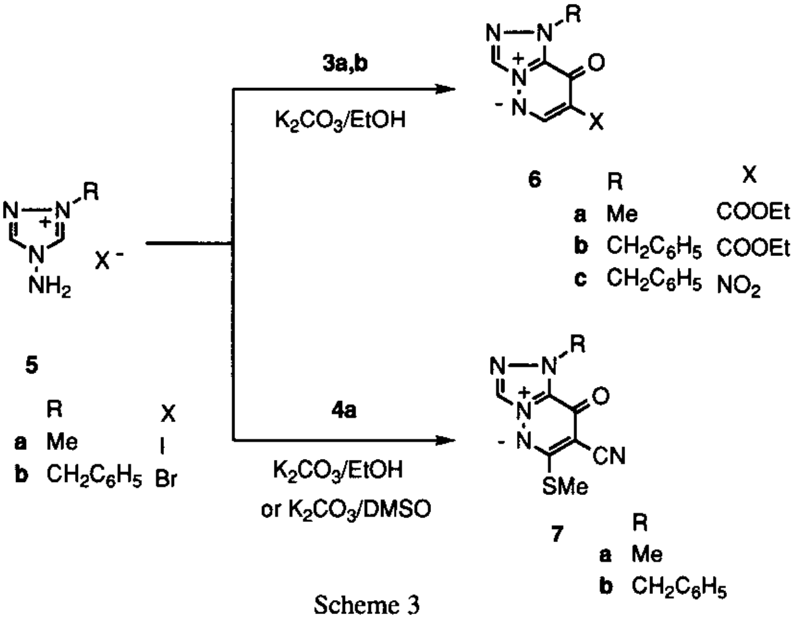
Scheme 2

Treatment of the salts (**5a**,**b**) and polarized olefins (**3a**,**b**) with K_2CO_3 in EtOH at room temperature for a week did not give *N*-vinylimino ylides, but directly afforded the betaines, [1,2,4]triazolo[4,3-*b*]-pyridaziniumides (**6a-c**). In addition, the salt (**5b**) and the olefin (**4a**) were treated with K_2CO_3 in EtOH to give the mesomeric betaine (**7b**). On the other hand, the reaction of **5a** with **4a** in EtOH did not proceed. In our previous paper we reported the synthesis of the mesomeric betaine, imidazo[1,2-*b*]pyridaziniumide by the reaction of aminoimidazolium salt with the olefin (**4a**) in the presence of K_2CO_3 in dimethyl sulfoxide (DMSO) at room temperature for a week.[2a,d] Therefore we treated **5a**,**b** with **4a** in DMSO to give the mesomeric betaines (**7a**,**b**) (Scheme 3).

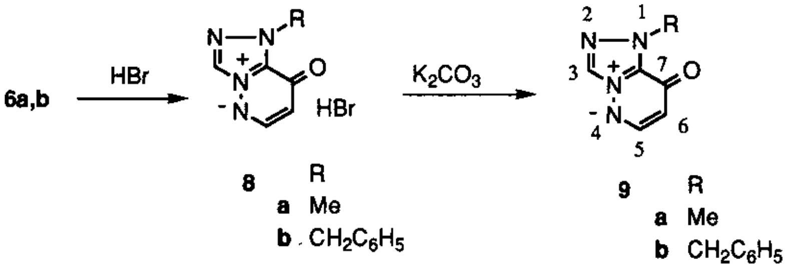
In order to obtain the parent base of the [1,2,4]triazolo[4,3-*b*]pyridaziniumide derivatives (**6**,**7**), we examined various conditions for removal of the ethoxycarbonyl or cyano groups, and succeeded in isolation of [1,2,4]triazolo[4,3-*b*]pyridaziniumides (**9a**,**b**). The ethoxycarbonyl group of **6a**,**b** could be easily removed upon treatment with 47% hydrobromic acid under reflux to give the hydrobromides (**8a**,**b**), which were converted to the free bases (**9a**,**b**) by the use of K_2CO_3 (Scheme 4).

The mesomeric betaines (**6**-**9**) can be described to a first approximation by the resonance structures A and B as shown in Scheme 5. The 7-carbonyl absorption maxima for the mesomeric betaines (**6a-c**) in the ir spectrum show at 1610-1640 cm^{-1}, while those for the other mesomeric betaines (**7-9**) show at 1560-1600 cm^{-1}. This fact indicates that the formers (**6a-c**) have the dipole form A due to the resonance structure (**6a'**,**b'** and **6c'**) and the latters (**7-9**) have the dipole form B.

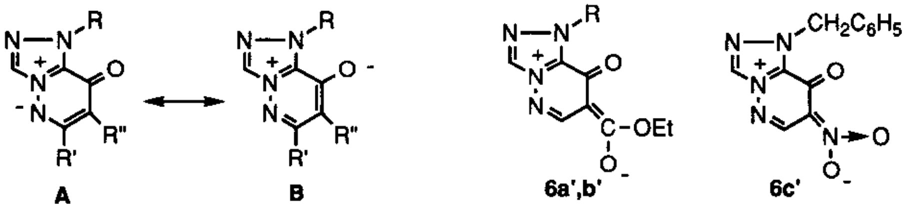
The reaction of **5a**,**b** with 2,2-bis(methylthio)-1-nitroethylene (**4b**) in the presence of K_2CO_3 in EtOH gave the 1,5-dipolar cyclization products, pyrazoles (**10a**,**b**). Similar treatment of **5a** with **4c** afforded the [1,2,4]triazolo[4,3-*b*]pyrazole derivatives (**11**) (Scheme 6).



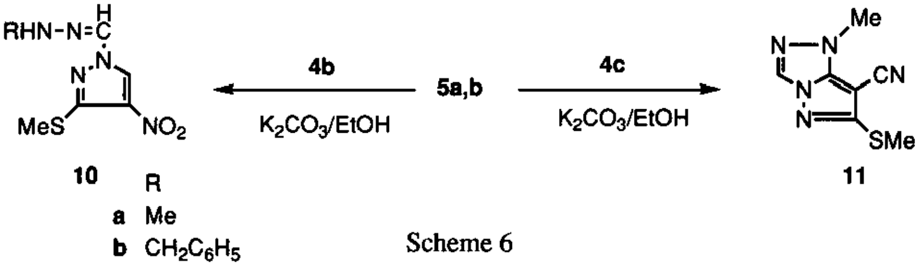
Scheme 3



Scheme 4

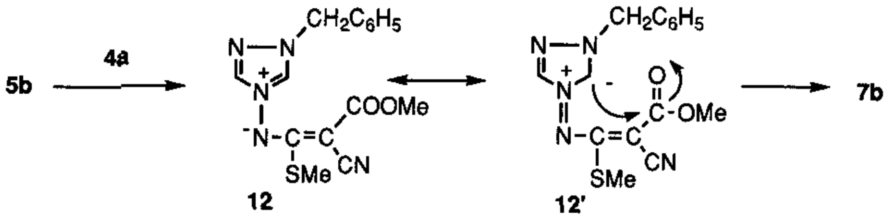


Scheme 5

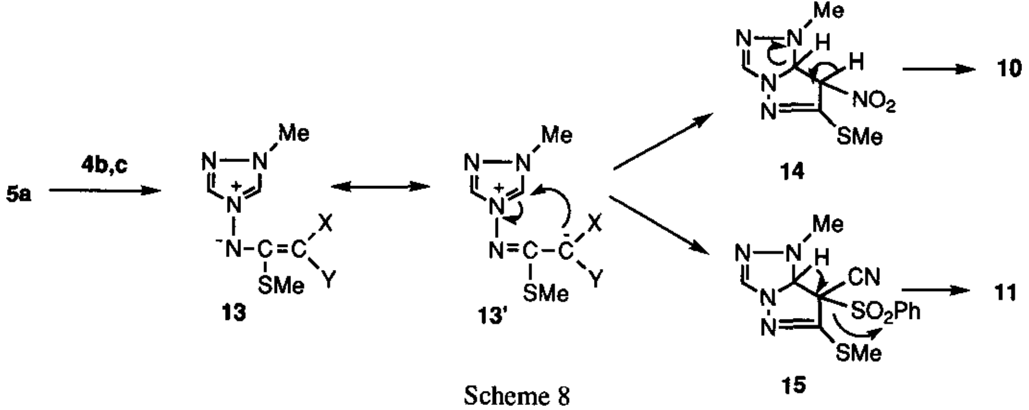


Scheme 6

The formation of **7b** may be rationalized by the outline in Scheme 7. As pointed out in our previous paper,[2] the mechanism for formation of **7b** may proceed *via* intermediate, *N*-vinylimino ylide (**12**). Thus, the intermediate (**12**) may undergo back-donated 1,6-cyclization due to the resonance structure (**12'**) to give the mesomeric betaine (**7b**). On the other hand, as pointed out by Meth-Cohn[1e] and Acheson,[1k] the formation of **10a** and **11** may be rationalized as outlined in Scheme 8.



Scheme 7



Scheme 8

EXPERIMENTAL

Melting points were determined with a Mitamura Mel-Temp and are uncorrected. Ir spectra were recorded in KBr pellets on a JASCO IRA-2 spectrophotometer. Uv spectra were recorded on a Hitachi 323 spectrophotometer. ^{1}H-Nmr and ^{13}C-nmr spectra were obtained on JNM-FX-90Q and JNM-GX400 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ). Elemental analyses (C,H,N) of all compounds described here were performed on a Yanagimoto MT-2 CHN recorder.

The preparation of the salt (5b)

By Becker's method,[1b] a mixture of 4-amino-1,2,4-triazole (Aldrich) (16.8 g, 0.2 mol) and benzyl bromide (34.2 g, 0.2 mol) in acetone (200 ml) was stirred at room temperature for a week and the precipitate was collected by filtration, washed with acetone, dried and recrystallized from EtOH to give **5b**.

5b: mp 141-143 °C (28.1 g, 55%). Ir (KBr) 3270, 3230 cm^{-1}; ^{1}H-nmr (DMSO-d_6) 5.58 (2H, s, CH_2Ar), 6.92 (1H, s, C_3-H), 7.42 (5H, s, Ar-H), 9.19 (1H, s, C_5-H). *Anal.* Calcd for $C_9H_{11}N_4Br$: C, 42.37; H, 4.35; N, 21.96. Found: C, 42.15; H, 4.49; N, 21.88.

General Procedure for the Preparation of 6, 7, 10, and 11

Method A: A mixture of 4-amino-1,2,4-triazole (0.17 g, 2 mmol) and iodomethane (0.29 g, 2 mmol) in acetone (20 ml) was stirred at room temperature for a week and the mixture was then evaporated under reduced pressure to give the salt (**5a**). A mixture of the crude salt (**5a**), a olefin (**3a,4b,c**) (2 mmol) and K_2CO_3 (0.61 g, 4 mmol) in EtOH (40 ml) was stirred at room temperature for a week and the mixture was poured into ice-cold water (100 ml). The mixture was extracted with $CHCl_3$ (4x30 ml) and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was submitted to column chromatography on silica gel. From a benzene-$CHCl_3$ (10:1) fraction, the product (**6a,10a,11**) was obtained.

Method B: A mixture of the salt (**5b**) (0.51 g, 2 mmol), a olefin (**3a,b,4a,c**) (2 mmol), and K_2CO_3 (0.61 g, 4 mmol) in EtOH (40 ml) was stirred at room temperature for a week. The resulting mixture was treated as described for method A. From a benzene-$CHCl_3$ (10:1) fraction, the product (**6b,c,7b,10b**) was obtained.

Method C: A mixture of the salt (**5a,b**) (2 mmol) , a olefin (**4a**) (0.41 g, 2 mmol), and K_2CO_3 (0.61 g, 4 mmol) in DMSO (30 ml) was stirred at room temperature for a week and the mixture was then poured into ice-cold water (100 ml). The precipitate was filtered, washed with water, dried and recrystallized from $CHCl_3$-EtOH to give product (**7a,b**).

6a: mp 161-163°C (Method A: 50%). Ir (KBr) 1680, 1610 cm^{-1}; uv (EtOH) λmax (log ε) 208 (4.21), 280 (3.94), 317 (4.11) nm; ^{1}H-nmr ($CDCl_3$) 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H_3}$), 4.20 (2H, q, J=7 Hz, $C\underline{H_2}CH_3$), 4.38 (3H, s, NCH_3), 8.50 (1H, s, C_5-H), 9.63 (1H, s, C_3-H); ^{13}C-nmr (DMSO-d_6) 14.3, 59.3, 106.7, 137.7, 141.1, 152.0, 159.0, 164.4. *Anal.* Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.77; H, 4.49; N, 25.11.

6b: mp 185-187°C (Method B: 50%). Ir (KBr) 1690, 1620 cm^{-1}; uv (EtOH) λmax (log ε) 205 (4.42), 283 (3.96), 321 (4.22) nm; ^{1}H-nmr (DMSO-d_6) 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H_3}$), 4.22 (2H, d, J=7 Hz, $C\underline{H_2}CH_3$), 6.06 (2H, s, CH_2Ph), 7.34-7.43 (5H, m, Ar-H), 8.56 (1H, s, C_5-H), 9.69 (1H, s, C_3-H); ^{13}C-nmr (DMSO-d_6) 14.2, 54.3, 59.4, 107.2, 128.2, 128.3, 128.6, 134.7, 138.6, 141.0, 152.0, 158.9, 164.4. *Anal.* Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.38; H, 5.02; N, 18.83.

6c: mp 223-225°C (Method B: 65%). Ir (KBr) 1640 cm^{-1}; uv (EtOH) λmax (log ε) 277 (3.92), 355 (4.11) nm; ^{1}H-nmr ($CDCl_3$) 6.05 (2H, s, CH_2Ph), 7.36-7.48 (5H, m, Ar-H), 9.02 (1H, s, C_5-H), 9.84 (1H, s, C_3-H). *Anal.* Calcd for $C_{18}H_{14}N_4O$: C, 53.14; H, 3.34; N, 25.82. Found: C, 52.99; H, 3.46, N, 25.60.

7a: mp 262-264°C (Method C: 62%). Ir (KBr) 2200, 1600 cm^{-1}; uv (EtOH) λmax 225, 248, 317 nm; ^{1}H-nmr ($CDCl_3$) 2.45 (3H, s, SCH_3), 4.31 (3H, s, NCH_3), 9.68 (1H, s, C_3-H). *Anal.* Calcd for $C_8H_7N_5OS$: C, 43.43; H, 3.19; N, 31.65. Found: C, 43.13; H, 3.18; N, 31.31.

7b: mp 200-203°C (Method B: 65%. Method C: 80%). Ir (KBr) 2200, 1600 cm^{-1}; uv (EtOH) λmax 225, 249, 320 nm; ^{1}H-nmr ($CDCl_3$) 2.52 (3H, s, SCH_3), 6.03 (2H, s, CH_2Ph), 7.31-7.60 (5H, m, Ar-H), 8.59 (1H, s, C_3-H). *Anal.* Calcd for $C_{14}H_{11}N_5OS$: C, 56.55; H, 3.73; N, 23.55. Found: C, 56.18; H, 3.67; N, 23.33.

10a: mp 132-135°C (Method A: 53%). Ir (KBr) 3420, 3350 cm^{-1}; uv (EtOH) λmax (log ε) 275 (3.96), 370 (3.57) nm; ^{1}H-nmr ($CDCl_3$) 2.56 (3H, s, SCH_3), 2.96 (3H, NCH_3), 7.76 (1H, s, C_5-H), 8.66 (1H, s, C_5-H). *Anal.* Calcd for $C_6H_9N_5O_2S$: C, 33.48; H, 4.21; N, 32.54. Found: C, 33.85, H, 4.12; N, 32.48.

10b: mp 94-96°C (Method B: 45%). Ir (KBr) 3420, 3350 cm^{-1}; uv (EtOH) λmax (log ε) 286 (4.41), 343 (4.48) nm; ^{1}H-nmr ($CDCl_3$) 2.54 (3H, s, SCH_3), 2.96 (2H, d, *J*=5 Hz, CH_2Ph), 5.65 (1H, brs, NH), 7.33-7.39 (5H, m, Ar-H) 7.86 (1H, s, C_5-H), 8.68 (1H, s, C_5-H). *Anal.* Calcd for $C_{12}H_{13}N_5O_2S$: C, 49.47; H, 4.50; N, 24.04. Found: C, 49.57; H, 4.47; N, 23.97.

11: mp 147-150°C (Method A: 26%). Ir (KBr) 2200 cm^{-1}; uv (EtOH) λmax (log ε) 218 (4.03), 255 (3.78) nm; ^{1}H-nmr ($CDCl_3$) 2.62(3H, s, SCH_3), 3.97(3H, s, NCH_3), 8.18(1H, s, C_3-H). *Anal.* Calcd for $C_7H_7N_5S$: C, 43.51; H, 3.65; N, 36.24. Found: C, 43.89; H, 3.66; N, 36.36.

1,7-Dihydro-7-oxo(1,2,4)triazolo[4,3-*b*]pyridazin-3a-ium-4-ide Hydrobromides (8a,b)

A solution of **6a,b** (4 mmol) in 47% HBr (20 ml) was refluxed for 1 h. The reaction mixture was evaporated under reduced pressure. The residue was recrystallized from EtOH to give **8a,b**.

8a: mp 281-283°C (80%). Ir (KBr) 1590 cm^{-1}; uv (EtOH) λmax (log ε) 306 (4.04) nm; ^{1}H-nmr (DMSO-d_6) 4.38 (3H, s, NCH_3), 6.80 (1H, d, *J*=6 Hz, C_6-H), 8.57 (1H, d, *J*=6 Hz, C_5-H), 9.99 (1H, s, C_3-

H); ^{13}C-nmr (DMSO-d_6) 107.0, 138.1, 138.6, 151.2, 153.8. *Anal.* Calcd for $C_6H_7N_4OBr$: C, 31.19; H, 3.05; N, 24.25. Found: C, 31.30; H, 3.01; N, 24.28.

8b: mp 229-232°C (86%). Ir (KBr) 1560 cm^{-1}; uv (EtOH) λmax (log ε) 308 (4.07) nm; ^{1}H-nmr (DMSO-d_6) 6.03 (2H, s, CH_2Ph), 6.54 (1H, d, *J*=6 Hz, C_6-H), 7.32-7.43 (5H, m, Ar-H), 8.40 (1H, d, *J*=6 Hz, C_5-H), 9.87 (1H, s, C_3-H); ^{13}C-nmr (DMSO-d_6) 54.2, 107.4, 128.3, 135.0, 138.4, 139.9, 150.9, 154.8. *Anal.* Calcd for $C_{12}H_{11}N_4OBr$: C, 46.92; H, 3.61; N, 18.24. Found: C, 46.95; H, 3.65; N, 18.12.

1,7-Dihydro-7-oxo(1,2,4)triazolo[4,3-b]pyridazin-3a-ium-4-ides (9a,b)

A solution of **8a,b** (2 mmol) in water (20 ml) was made basic to litmus with K_2CO_3 and immediately extracted with $CHCl_3$ (3x10 ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was recrystallized from EtOH to give **9a,b**.

9a: mp 214-216°C (78%). Ir (KBr) 1600 cm^{-1}; uv (EtOH) λmax (log ε) 203 (4.17), 305 (4.04) nm; ^{1}H-nmr (DMSO-d_6) 4.56 (3H, s, NCH_3), 6.28 (1H, d, *J*=6 Hz, C_6-H), 8.03 (1H, d, *J*=6 Hz, C_5-H), 8.68 (1H, s, C_3-H); ^{13}C-nmr (DMSO-d_6) 38.4, 106.4, 137.3, 141.1, 150.7, 159.8. *Anal.* Calcd for $C_{10}H_9N_4O_3$: C, 48.00; H, 4.05; N, 37.32. Found: C, 48.49; H, 4.15; N, 36.80.

9b: mp 124-126°C (68%). Ir (KBr) 1590 cm^{-1}; uv (EtOH) λmax (log ε) 308 (4.08) nm; ^{1}H-nmr (DMSO-d_6) 6.09 (2H, s, CH_2Ph), 6.13 (1H, d, *J*=6 Hz, C_6-H), 7.32-7.46 (5H, m, Ar-H), 8.12 (1H, d, *J*=6 Hz, C_5-H), 9.64 (1H, s, C_3-H); ^{13}C-nmr (DMSO-d_6) 54.2, 107.2, 128.2, 128.4, 128.6, 135.3, 138.1, 140.8, 150.3, 159.6. *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.84; H, 4.59; N, 24.40.

REFERENCES

1. a) V. Boekelheide and N. A. Fedoruk, *J. Am. Chem. Soc.*, 1968, **90**, 3830. b) H. G. O. Becker, D. Nagel, and H. J. Timpe, *J. Prakt. Chem.*, 1973, **315**, 97. c) K. Matsumoto, *J. Syn. Org. Chem. Japan*, 1974, **32**, 731. d) Y. Tamura, Y. Sumida, S. Haruki, and M. Ikeda, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 575. e) O. Meth-Cohn, *Tetrahedron Lett.*, **1975**, 413. f) T. Uchida and K. Matsumoto, *Synthesis*, **1976**, 209. g) A. Kakehi, S. Ito, T. Funahashi, and Y. Ota, *J. Org. Chem.*, 1976, **41**, 1570. h) A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, *ibid.*, 1977, **42**, 443. i) H. J. Timpe, H. G. O. Becker, and R. Radeglia, *J. Prakt. Chem.*, 1977, **319**, 945. j) F. J. Swinbourene, J. H. Hunt, and G. Klinkert, *Adv. Heterocycl. Chem.*, 1978, **23**, 103. k) R. M. Acheson and N. F. Elmore, *ibid.*, 1978, **23**, 263. l) E. C. Taylor and I. J. Turchi, *Chem. Rev.*, 1979,

79, 181. m) Y. Tamura and M. Ikeda, *Adv. Heterocycl. Chem.*, 1981, **29**, 71. n) Y. Tominaga and Y. Matsuda, *J. Syn. Org. Chem. Japan*, 1985, **43**, 669.

2. a) Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, and S. Ide, *Heterocycles*, 1990, **31**, 977. b) Y. Matsuda, H. Gotou, K. Katou, H. Matsumoto, M. Yamashita, K. Takahashi, S. Ide, K. Furuno, and K. Torisu, *ibid.*, 1991, **32**, 2217. c) Y. Matsuda, M. Yamashita, K. Takahashi, S. Ide, K. Torisu, and K. Furuno, *ibid.*, 1992, **33**, 295. d) Y. Matsuda, M. Yamashita, K. Takahashi, S. Ide, T. Itou, C. Motokawa, and Y. Chiyomaru, *Chem. Pharm. Bull.*, 1994, **42**, 454. e) Y. Matsuda, Y. Chiyomaru, C. Motokawa, and T. Nishiyori, *Heterocycles*, 1995, **41**, 329.

3. a) E. G. de Bollemount, *Bull. Soc. Chim. Fr.*, 1902, **25**, 20. b) O. Diels, H. Gärtner, and R. Kaack, *Ber.*, 1922, **55**, 3439. c) R. Gompper and W. Töpfl, *Chem. Ber.*, 1962, **95**, 2861. d) M. Prystas and J. Gut, *Coll. Czech. Chem. Commun.*, 1963, **28**, 2501. e) B. S. Thyagarajan and P. V. Gopalakrishnan, *Tetrahedron*, 1964, **20**, 1051.

Received, 14th July, 1995