A NOVEL 1,6 CYCLIZATION OF IMIDAZOLIUM N-ALLYLIDES (1): FORMATION OF MESOMERIC BETAINES, 8-OXOIMIDAZO[1,2-a]-PYRIDINIUMIDES

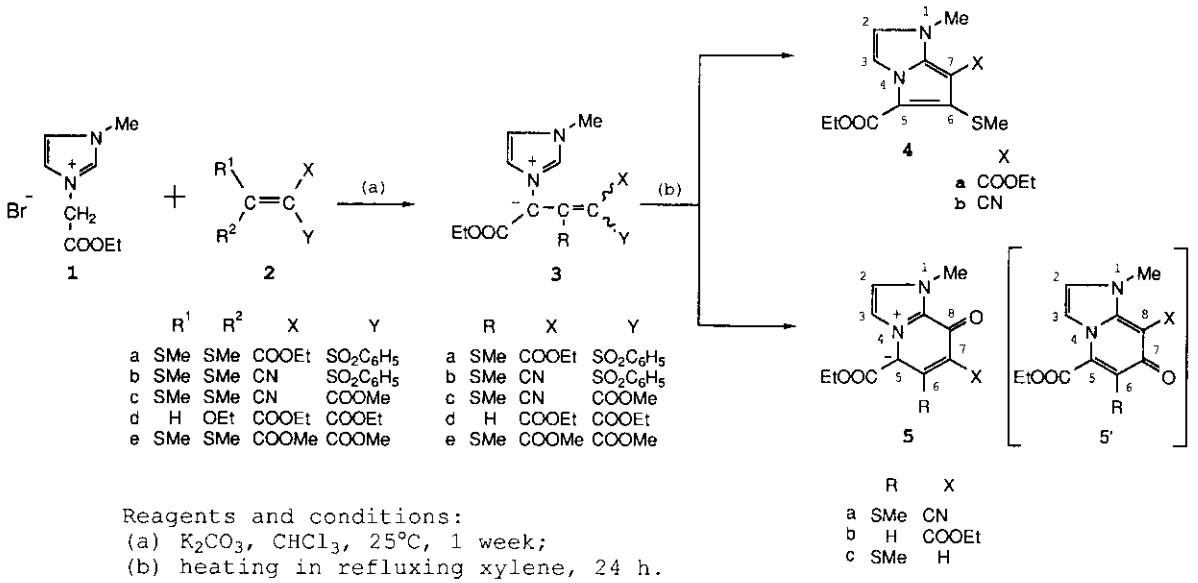
Yoshiro Matsuda*, Hiromi Gotou, Keisuke Katou, Hiroshi Matsumoto
Makoto Yamashita, Kimitoshi Takahashi, and Shizuki Ide

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

Abstract - Treatment of imidazolium N-allylides (3a,b) in refluxing xylene resulted in 1,5-dipolar cyclization to give pyrroloimidazoles (4a,b), whereas heating of N-allylides (3c,d,e) in refluxing xylene gave the mesomeric betaines, 8-oxoimidazo[1,2-a]pyridiniumides (5a,b,c), with 1,6 cyclization. Furthermore, treatment of the N-aminoimidazolium salt (9) and ketene dithioacetal (2c) with potassium carbonate in dimethyl sulfoxide (DMSO) directly afforded the mesomeric betaine, imidazo[1,2-b]pyridaziniumide (11). The benzimidazolium salt (12) and diethyl ethoxymethylenemalonate (2d) were treated with potassium carbonate in $CHCl_3$ to also produce the mesomeric betaine, 4-oxobenz[b]imidazo-[1,2-a]pyridiniumide (14).

Pyridinium N-allylides and N-vinylimino ylides are well known to undergo thermal 1,5-dipolar cyclization and aromatization giving the corresponding indolizines and azaindolizines.[1] These results prompted us to examine the reaction of pyridinium N-ylides with ketene dithioacetals for which we have already reported several new results.[1h] With regard to N-vinylimino ylides, it is especially worth noting that 1,6 cyclization has been found in the thermolysis and photolysis of pyridinium N-vinylimino ylides by Kakehi et al.[1j,k] On the other hand, 1,5-dipolar cyclization was also observed for the reaction of imidazolium N-ylides with acetylenes, giving the corresponding pyrroloimidazoles via imidazolium N-allylides.[1d] Furthermore, Boekelheide described that 1-dicyanomethylimidazolium N-ylide reacted with dimethyl

Scheme 1



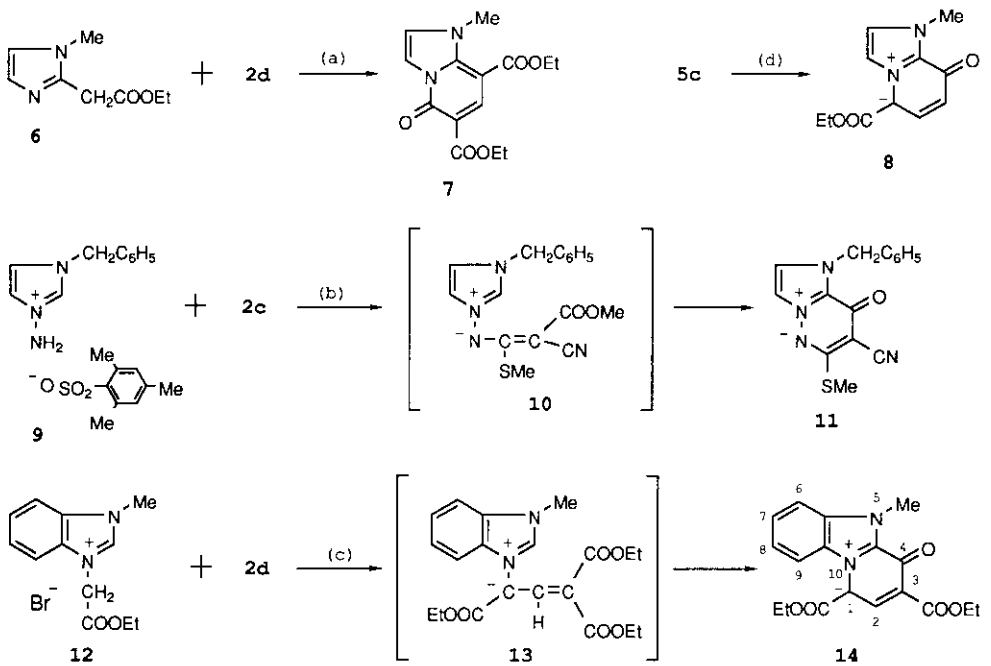
	R^1	R^2	X	Y
a	SMe	SMe	COOEt	$SO_2C_6H_5$
b	SMe	SMe	CN	$SO_2C_6H_5$
c	SMe	SMe	CN	COOMe
d	H	OEt	COOEt	COOEt
e	SMe	SMe	COOMe	COOMe

	R	X	Y
a	SMe	COOEt	$SO_2C_6H_5$
b	SMe	CN	$SO_2C_6H_5$
c	SMe	CN	COOMe
d	H	COOEt	COOEt
e	SMe	COOMe	COOMe

	R	X
a	SMe	CN
b	H	COOEt
c	SMe	H

Reagents and conditions:
(a) K_2CO_3, $CHCl_3$, 25°C, 1 week;
(b) heating in refluxing xylene, 24 h.

Scheme 2



Reagents and conditions:
(a) K_2CO_3, DMSO, 25°C, 1 week;
(b) K_2CO_3, DMSO, 25°C, 3 days;
(c) K_2CO_3, $CHCl_3$, 25°C, 1 week;
(d) Raney-Ni, heating in refluxing THF, 24 h.

acetylenedicarboxylate to give imidazopyridine.[2] However, there has been no report on the reaction of stable imidazolium N-allylides having two electron-attracting groups at the 3-position of the allyl group. In this communication we examine the thermal behavior of stable imidazolium N-allylides (3c,d,e) and show that these compounds (3c,d,e) undergo 1,6 cyclization to afford the mesomeric betaines, 8-oxoimidazo[1,2-a]pyridiniumides (5a,b,c) via intermediate (17).

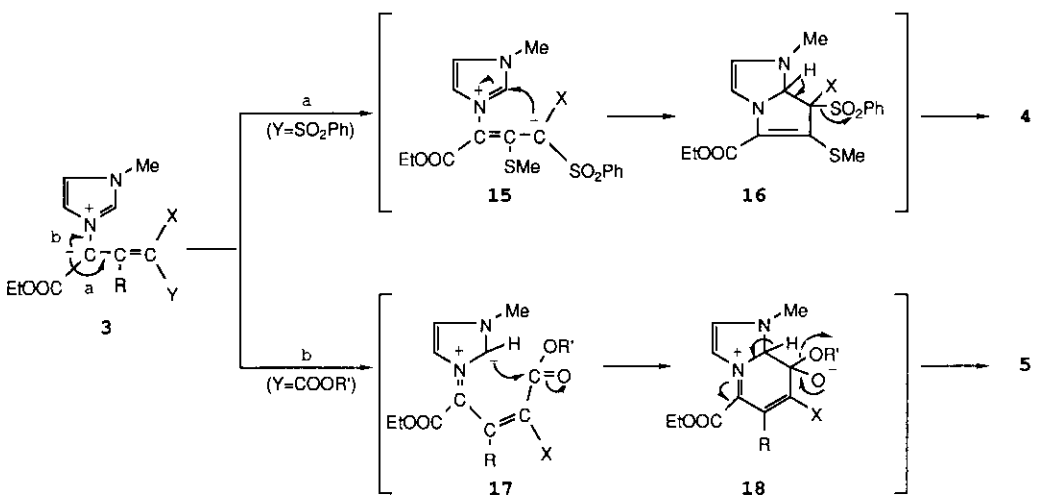
The starting imidazolium N-allylides (3a-e) used in the present work were prepared by the reaction of 1-ethoxycarbonylmethyl-3-methylimidazolium bromide (1) with ketene dithioacetals (2a,b,c,e) or the ethoxymethylene compound (2d) in the presence of potassium carbonate. A solution of 3a,b in xylene was refluxed to give pyrroloimidazoles (4a,b)[3] with 1,5-dipolar cyclization in 60-63% yields, respectively. It should be noted that heating of 3c,d in refluxing xylene resulted in 1,6 cyclization giving rise to the mesomeric betaines, 8-oxoimidazo[1,2-a]pyridiniumides (5a,b)[4a,b], in 48-67% yield. Moreover, compound (3e) was heated in refluxing xylene to give 5c[4c] with decarboxylation. From the molecular formula of 5b, 5b might have been a possible structure (7). However, the spectral data of 5b were not in accord with those of 7 which was synthesized by the reaction of ethyl 1-methylimidazolylacetate (6) with 2d. For example, the proton nuclear magnetic resonance (^{1}H-nmr) spectrum of 5b showed a singlet signal due to C_6-H at 8.60 ppm, whereas that of 7 showed a singlet signal assignable to C_7-H at 8.90 ppm. The doublet signal due to C_3-H in 5b appeared at lower field (8.96 ppm) than that for 7 (8.00 ppm), probably because of the shielding effect of the 5-ethoxycarbonyl group in 5b. In addition, 5 might have been an alternate possible structure (5'), but the structure of 5 was further confirmed by the synthesis of compound (8)[6] via desulfurization of 5c. The ^{1}H-nmr spectrum of 8 showed two doublet signals assignable to C_7-H and C_6-H at 6.44 and 7.91 ppm (J=9Hz), respectively. In contrast to the case of 1, treatment of the N-aminoimidazolium salt (9) and 2c with potassium carbonate in DMSO did not give N-(vinylimino)imidazolium ylide (10), but directly afforded the mesomeric betaine, 8-oxoimidazo[1,2-b]pyridaziniumide derivative (11)[7] in 55% yield. The benzimidazolium salt (12) and 2d were treated with potassium carbonate in $CHCl_3$ to also produce the mesomeric betaine, 4-oxobenz[b]imidazo[1,2-a]pyridiniumide derivative (14)[8] in 13% yield.

The formation of compounds (4 and 5) may be rationalized as outlined in Scheme 3. In the case of 3a,b, the initial step may be 1,5 cyclization to give 16. This step is then followed by elimination of the phenylsulfonyl group (Y) that leads to 4. Previously, Kakehi[1k] described that the mechanism for the formation of mesoionic[9] pyri-

dotriazines was confirmed to proceed via isocyanate intermediates (π6s cyclization). However, we alternatively presume that, in the case of 3c,d, and e, the intermediate (17) may cyclize to give 5 via intermediate (18). As for the contribution of 17, Okamoto [1e,m] pointed out that the nitration at the 4-position of pyridine N-(trinitrophenyl)imine might reflect the high electron density on that position by a back-donating effect of the negative charge. For the reaction of pyridine 1-oxide, the same paradox of activation of both electrophilic and nucleophilic substitutions in the same structure was described by Ochiai.[1n]

The synthesis of mesoionic pyridopyridazines,[1j] pyridotriazines,[1k] and triazolopyridazines[1l] from N-vinylimino ylides has been reported. However, the present result provides the first example of the 1,6 cyclization of N-allylides giving the mesomeric betaines, 8-oxoimidazo[1,2-a]pyridiniumides.

Scheme 3



ACKNOWLEDGMENT

The authors thank Prof. A. Kakehi for useful discussions on this work.

REFERENCES AND NOTES

1. a) K. Matsumoto, J. Syn. Org. Chem. Japan, 1974, 32, 731. b) T. Uchida and K. Matsumoto, Synthesis, 1976, 209. c) F. J. Swinbourne, J. H. Hunt, and G. Klinkert, "Advances in Heterocyclic Chemistry" ed. by A. R. Katrizky and A. J. Boulton, Academic Press, New York, 1978, Vol. 23, p. 103. d) R. M. Acheson and N. F. Flmore, ibid., 1978, Vol. 23, p. 263. e) Y. Tamura and M. Ikeda, ibid., 1981,

Vol. 29, p. 71. f) E. C. Taylor and I. J. Turchi, Chem. Rev., 1979, 79, 181. g) Y. Tamura, Y. Sumida, S. Haruki, and M. Ikeda, J. Chem. Soc., Perkin Trans. 1, 1975, 575. h) Y. Tominaga and Y. Matsuda, J. Syn. Org. Chem. Japan, 1985, 43, 669. i) H. Sashida, M. Katou, and T. Tsuchiya, Chem. Pharm. Bull., 1988, 36, 3826. j) A. Kakehi, S. Ito, T. Funahashi, and Y. Ota, J. Org. Chem., 1976, 41, 1570. k) A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, ibid., 1977, 42, 443. l) H.-J. Timpe, H. G. O. Becker, and R. Radeglia, J. Prakt. Chem., 1977, 319, 945. m) T. Okamoto, S. Hayashi, H. Horikiri, and H. Hirobe, Yakugaku Zasshi, 1971, 91, 261. n) E. Ochiai, "Aromatic Amine Oxide", Elsvier Publishing Company, New York, 1967, p. 14.

2. V. Boekelheide and N. A. Fedoruk, J. Am. Chem. Soc., 1968, 90, 3830.

3. a) For 4a, mp 63 °C(60%); ^{1}H-nmr($CDCl_3$) δ 1.41(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 1.42(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 2.51(3H, s, SCH_3), 3.97(3H, s, NCH_3), 4.32(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 4.40(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 6.74(1H, d, J=2Hz, C_2-H), 7.67(1H, d, J=2Hz, C_3-H); ir(KBr) 1690(CO), 1670(CO) cm^{-1}; uv(EtOH) λmax(log ε) 258(4.24), 267(4.17), 328(4.38) nm. Anal. Calcd for $C_{14}H_{18}N_2O_4S$: C, 54.18; H, 5.85; N, 9.03. Found C, 54.13; H, 5.85; N, 8.81.

b) For 4b, mp 140 °C(63%); ^{1}H-nmr($CDCl_3$) δ 1.41(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 2.67(3H, s, SCH_3), 3.85(3H, s, NCH_3), 4.38(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 6.80(1H, d, J=2Hz, C_2-H), 7.62(1H, d, J=2Hz, C_3-H); ir(KBr) 2200(CN), 1680(CO) cm^{-1}; uv(EtOH) λmax(log ε) 243(4.30), 317(4.36) nm. Anal. Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found C, 54.91; H, 5.03; N, 15.90.

4. a) For 5a, mp 182 °C(48%); ^{1}H-nmr($CDCl_3$) δ 1.45(3H, t, J=7Hz, $CH_2\underline{CH_3}$), 2.59(3H, s, SCH_3), 4.46(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 4.46(3H, s, NCH_3), 7.35(1H, d, J=2Hz, C_2-H), 8.27(1H, d, J=2Hz, C_3-H); ir(KBr) 2200(CN), 1695(CO), 1660(CO) cm^{-1}; uv(EtOH) λmax(log ε) 238(4.13), 244(4.14), 258(4.09), 265(4.10), 345(4.21). 360(4.15) nm. Anal. Calcd for $C_{13}H_{13}N_3O_3S$: C, 53.59; H, 4.50; N, 14.42. Found C, 53.55; H, 4.44; N, 14.27.

b) For 5b, mp 244 °C(67%); ^{1}H-nmr($CDCl_3$) δ 1.40(3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.42 (3H, t, J=7Hz, $CH_2\underline{CH_3}$), 4.43(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 4.36(2H, q, J=7Hz, $\underline{CH_2}CH_3$), 4.49(3H, s, NCH_3), 7.22(1H, d, J=2Hz, C_2-H), 8.60(1H, s, C_6-H), 8.96(1H, d, J=2Hz, C_3-H); ir(KBr) 1680-1710(CO) cm^{-1}; uv(EtOH) λmax(log ε) 236(4.14), 255 (4.23), 265(4.25), 328(4.29), 342(4.29) nm. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.22; H, 5.53; N, 9.44.

c) For 5c, mp 97°C(15%); ^{1}H-nmr($CDCl_3$) δ 1.45(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 2.43(3H, s, SCH_3), 4.43(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.45(3H, s, NCH_3), 6.43(1H, s, C_7-H), 7.11 (1H, d, J=2.2, C_2-H), 8.95(1H, d, J=2.2, C_3-H); ir(KBr) 1670(CO) cm^{-1}; uv(EtOH) λmax(log ε) 246(4.19), 262(4.10), 274(4.21), 284(4.36) 348(4.28), 360(4.32) nm. Anal. Calcd for $C_{12}H_{14}N_2O_3S\cdot 1/2H_2O$: C, 52.35; H, 5.49; N, 10.17. Found: C, 52.33; H, 5.26; N, 10.09. Ms z/e 275(M^+).

5. For 7, mp 138°C(62%); ^{1}H-nmr($CDCl_3$) δ 1.41(6H, t, J=7Hz, $CH_2\underline{CH}_3$x2), 4.06(3H, s, NCH_3), 4.35(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.37(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 6.99(1H, d, J= 2Hz, C_2-H), 8.00(1H, d, J=2Hz, C_3-H), 8.90(1H, s, C_7-H); ir(KBr) 1720-1700(CO), 1660(CO) cm^{-1}; uv(EtOH) λmax(log ε) 221(3.86), 295(3.98), 345(4.08) nm. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found C, 57.15; H, 5.50; N, 9.46.

6. For 8, mp 164-167 °C(90% hygroscopic); ^{1}H-nmr($CDCl_3$) δ 1.38(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 4.34(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.49(3H, s, NCH_3), 6.44(1H, d, J=9Hz, C_7-H), 7.16(1H, d, J=2.2Hz, C_2-H), 7.91(1H, d, J=9Hz, C_6-H), 9.00(1H, d, J=2.2Hz, C_3-H); ir(KBr) 1690(CO) cm^{-1}; uv(EtOH) λmax(log ε) 232(4.02), 244(4.00), 260(4.05), 307(3.75), 344(4.32), 355(4.38) nm. High-resolution ms: 220.0854(M^+, $C_{11}H_{12}N_2O_3$ requires 220.0848).

7. For 11, mp 227 °C(55%); ^{1}H-nmr($CDCl_3$) δ 2.53(3, s, SCH_3), 5.89(2H, s, CH_2), 7.36 (5H, s, Ar-H), 8.06(1H, d, J=2Hz, C_2-H or C_3-H); 8.16(1H, d, J=2Hz, C_2-H or C_3-H); ir(KBr) 2200(CN), 1590(CO) cm^{-1}; uv(EtOH) λmax(log ε) 246(4.51), 258 (4.23), 267(3.88), 314(4.19), 325(4.14) nm. Anal. Calcd for $C_{15}H_{12}N_4OS$: C, 60.80; H, 4.08; N, 18.91. Found C, 60.66; H, 4.13; N, 18.70.

8. For 14, mp 262 °C(13%); ^{1}H-nmr($CDCl_3$) δ 1.44(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 1.46(3H, t, J=7Hz, $CH_2\underline{CH}_3$), 4.44(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.45(2H, q, J=7Hz, $C\underline{H}_2CH_3$), 4.72(3H, s, NCH_3), 7.24-7.72, 8.42-8.53(4H, m, Ar-H), 8.56(1H, s, C_2-H); ir(KBr) 1680-1740(CO) cm^{-1}; uv(EtOH) λmax(log ε) 232(4.21), 250(4.12), 283(4.30), 289 (4.33), 318(3.86), 330(3.86), 362(3.86), 384(4.12), 403(4.14) nm. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found C, 62.82; H, 5.30; N, 8.19.

9. The term 'mesoionic' should be restricted to the five-membered heterocycles and the use of 'mesomeric betaine' is recommended for the six-membered compounds. W. D. Ollis and C. A. Ramsden, "Advances in Heterocyclic Chemistry", ed. by A. R. Katrizky and A. J. Boulton, Academic Press, New York, 1976, Vol. 19, p. 105.

Received, 1st March, 1990