

ACTIVATED LACTAMS. RING-EXPANDING REACTION OF KETENE-S,N-ACETALS WITH DIMETHYL ACETYLENEDICARBOXYLATE¹

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Abstract— Reaction of ketene-S,N-acetals (1a,b,c) with DMAD gave ring-expanded products (3a,b,c) in good yields. In a similar manner, the reaction of ketene-S,N-acetal derivatives (4a,b,c) also afforded the corresponding ring-enlarged compounds (5a,b,c).

We have hitherto reported an interesting annulation of lactim ethers and lactim thioethers with β -aminoesters.² Although the reaction of cyclic iminoethers as activated lactams has extensively been investigated in heterocyclic syntheses,³ that of ketene-S,N-acetals (1) derived from N-methyl thiolactams remain to be investigated.⁴ They are expected to react as heterocyclic enamines. By the way, several reactions of enamines with dimethyl acetylenedicarboxylate (DMAD)⁵ have been reported.⁶ In general, [2+2] mode of addition leads to cyclobutene intermediates, which undergo ring opening to yield dienamines. In this communication, we now report the synthesis of 7-9 membered cyclic dienamines based upon the ring-expanding reaction of ketene-S,N-acetals with DMAD.

Reaction of 1a,b,c^{4a} with DMAD followed by chromatography on alumina (eluant: ether/n-hexane, 10:1) gave the ring-expanded products, azepine (3a), azocine (3b), and azonine (3c), in good yields, but cyclobutene adducts (2a,b,c) could not be isolated. The results are summarized in Table I. The use of acetonitrile as a solvent provided good yields of the products.

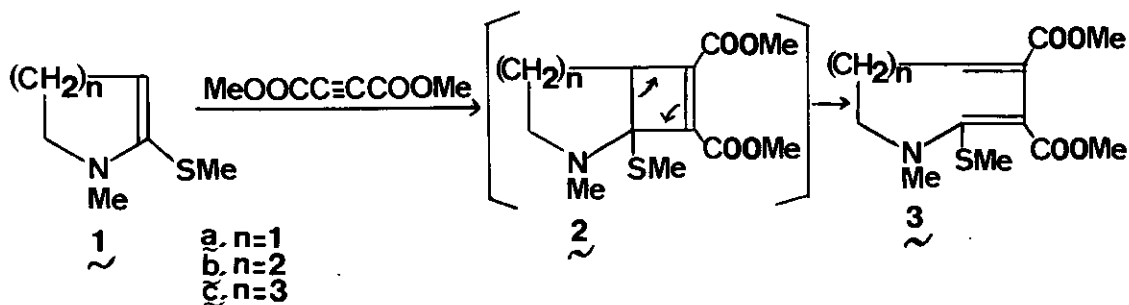


Table I. Reaction of 1a,b,c with DMAD.

| Product ^{a)} | Reaction conditions | | Yield (%) | I.R. (Neat) | N.M.R. (CCl ₄) |
|-------------------------|---------------------|--------------------------|-------------------------------------|---------------------------|-------------------------------------|
| | Solvent | temp./time | | ν (cm ⁻¹) | δ (ppm) |
| <u>3a</u> ^{b)} | Et ₂ O | r.t./overnight | --- | 1720, 1680 | 2.45 (3H,s,SMe), 3.25 (3H,s,NMe), |
| | CH ₃ CN | r.t./overnight | --- | | 3.67 (3H,s,OMe), 3.70 (3H,s,OMe), |
| | CH ₃ CN | reflux/3 h ^{c)} | 52 ^{d)} (72) ^{e)} | | 6.40 (1H,t,J=4Hz,C ₅ -H) |
| <u>3b</u> | Et ₂ O | r.t./overnight | 31 | 1720 (br) | 2.25 (3H,s,SMe), 2.53 (3H,s,NMe), |
| | CH ₃ CN | r.t./overnight | 22 | | 3.63 (3H,s,OMe), 3.70 (3H,s,OMe), |
| | CH ₃ CN | reflux/3 h | 75 | | 6.67 (1H,t,J=8Hz,C ₅ -H) |
| <u>3c</u> | Et ₂ O | r.t./overnight | 60 | 1720, 1690 | 2.33 (3H,s,SMe), 2.67 (3H,s,NMe), |
| | CH ₃ CN | r.t./overnight | 39 | | 3.63 (3H,s,OMe), 3.70 (3H,s,OMe), |
| | CH ₃ CN | reflux/3 h | 89 | | 7.00 (1H,t,J=9Hz,C ₅ -H) |

a) All products are pale yellow oils, practically pure, and exhibited satisfactory analytical data without distillation.

b) Product 3a was obtained in 14% yield (dioxane, 80°/30 min.) by Oishi. ref. 4b.

c) DMAD was added at -50°C.

d) 2,3-Dihydro-1-methyl-4,5,6,7-tetramethoxycarbonylindole (mp 184-6°) was obtained in 5% yield.

e) DMAD used was 2eq. mol.

Next, the reaction of ketene-S,N-acetals (4a,b,c)⁷ derived from benzolactams with DMAD was carried out to afford the ring-opened products, benzazepine (5a), benzazocine (5b), and benzazonine (5c). The results are shown in Table II. Previously Acheson obtained the corresponding benzazepine from 1-methylindole lacking methylthio substituent and DMAD under the following conditions (reflux in acetonitrile, 7 days) in a low yield (15%).⁸ It was reported that the reaction of 1-methyl-1,4-dihydroquinoline with DMAD in acetonitrile gave the corresponding cyclobutene adduct.⁹ In conclusion, the enamine character of these ketene-S,N-acetals (1 and 4) seemed to be strengthened by the electron-donation of methylthio group at the 2-position. In addition, the replacement of the methylthio group of the above cyclicdienamines by nucleophiles is expected,¹⁰ and is now under investigation.

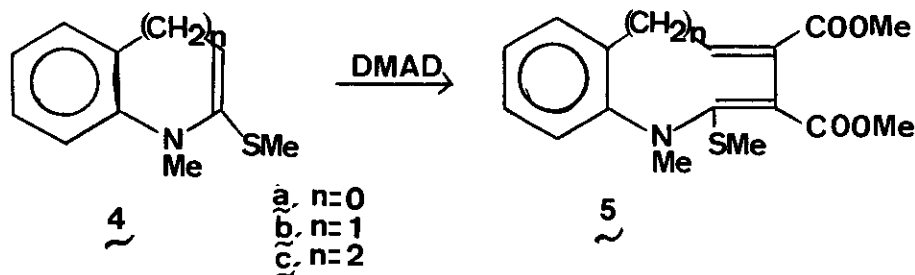


Table II. Reaction of 4a,b,c with DMAD.

| Product ^{a)} | Reaction conditions | | Yield m.p. ^{b)} | | I.R. (Nujol) N.M.R. (CDCl ₃) | |
|-----------------------|---------------------|-----------------------------|--------------------------|--------|--|--|
| | Solvent | temp./time | (%) | (°C) | ν (cm ⁻¹) | δ (ppm) |
| 5a | Et ₂ O | reflux/2 days | 10 | 99-100 | 1720, 1710 | 2.36 (3H, s, SMe), 3.35 (3H, s, NMe), |
| | Neat | 120°/overnight | 6 | | | 3.70 (3H, s, OMe), 3.80 (3H, s, OMe), |
| | CH ₃ CN | reflux/2 days | 40 | | | 7.74 (1H, s, C ₅ -H) |
| 5b | CH ₃ CN | reflux/3 h ^{c)} | 45 | 129-31 | 1720, 1680 | 2.26 (3H, s, SMe), 2.99 (3H, s, NMe), |
| | | | | | 3.40 (3H, s, OMe), 3.77 (3H, s, OMe), | |
| | | | | | 6.58 (1H, t, J=8Hz, C ₅ -H) | |
| 5c | Et ₂ O | reflux/2 days | --- | 144-5 | 1710, 1690 | 2.37 (3H, s, SMe), 3.30 (3H, s, OMe), |
| | Dioxane | 90°/5 h | --- | | | 3.53 (3H, s, OMe), 3.63 (3H, s, OMe), |
| | Neat | r.t./10 min | 25 | | | 6.50 (1H, dd, J ₁ =6Hz, J ₂ =5Hz, C ₅ -H) |
| | CH ₃ CN | reflux/45 min ^{c)} | 40 | | | |

a) All products exhibited satisfactory elemental analyses and molecular peaks (M⁺).

b) Recrystallized from CH₂Cl₂-isopropyl ether.

c) DMAD was added under ice cooling.

REFERENCES AND NOTES

- This work was presented at the 101 th Meeting of the Pharmaceutical Society of Japan, Kumamoto, April, 1981.
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