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UNEXPECTED FORMATION OF THIINO[3',4':4,5]OXAZOLO[1,3-*b*]-[1,3]OXAZEPINE DERIVATIVES[1]

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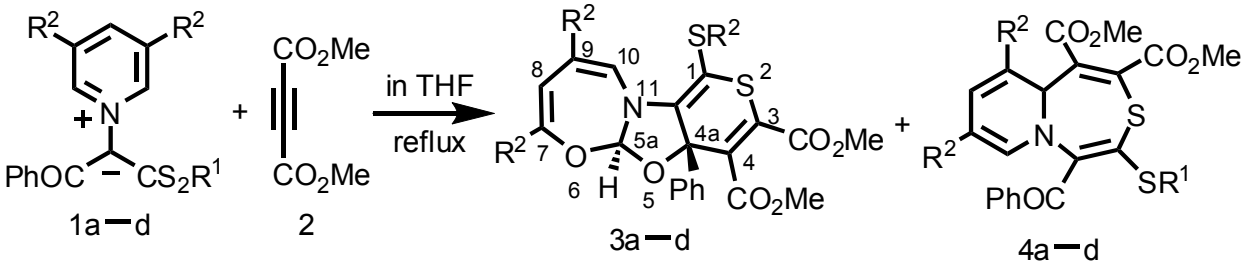
Abstract – The reactions of pyridinium 2-alkylthio-1-benzoyl-2-thioxoethylides with dimethyl acetylenedicarboxyate in THF at the reflux temperature afforded the unexpected products, dimethyl 2-alkylthio-4a-phenyl-4a*H*,5a*H*-thiino-[3',4':4,5]oxazolo[1,3-*b*][1,3]oxazepine-3,4-dicarboxylates, together with dimethyl 10a*H*-4-alkylthio-5-benzoylpyrido[1,2-*d*][1,4]thiazepine-1,2-dicarboxylates.

We previously reported that the reactions of various pyridinium 2-alkylthio-2-thioxoethylides and dimethyl acetylenedicarboxyate (DMAD) afforded the corresponding dimethyl 4-alkylthio-10a*H*-pyrido-[1,2-*d*][1,4]thiazepine-1.2-dicarboxylates and/or their intramolecular Diels-Alder adducts[2-4] and similar treatment of pyridinium (thiobenzoyl)aminides provided dimethyl 4-aryl-5-thia-2,3-diazatricyclo-[4.3.2.0^{2,7}]undeca-3,8,10-triene-6,11-dicarboxylates formed via the rearrangement of the initially generated dimethyl 2-aryl-5a*H*-pyrido[1,2-*d*][1,3,4]thiadiazepine-4,5-dicarboxylates.[5,6] We were very interested in the latter rearrangement and tried the extension to several pyridinium 2-thioxoethylides in anticipation of similar rearrangement, but our effort was fruitless. We recently found the unexpected formation of some dimethyl 2-[2-acylthieno[2',3':2,3][1,4]thiazino[4,5-*a*]pyrrol-8-ylidene]succinates in the one-pot synthesis for 5-acylthieno[3,2-*d*]thiazole derivatives from the reactions of 5-acyl-3-(1-pyridinio)thiophene-2-thiolates with DMAD in refluxing xylene.[7] This finding encouraged us to explore further this type of reaction, because the ring contraction from the pyridine ring to the pyrrole one in the structure of these products was distinctly confirmed. So, we reexamined the reaction of various pyridinium 2-thioxoethylides with DMAD by changing the reaction conditions and found the

formation of the unexpected products, dimethyl 2-alkylthio-4a-phenyl-4a*H*,5a*H*-thiino[3',4':4,5]-oxazolo[1,3-*b*][1,3]oxazepine-3,4-dicarboxylates, in the reactions of pyridinium 2-alkylthio-1-benzoyl-2-thioxoethylides with DMAD in nonstabilized tetrahydrofuran (THF).[8]

When the reactions of pyridinium 1-benzoyl-2-methylthio-2-thioxoethylides (**1a**, 1 mmol) with DMAD (**2**, 1.1 mmol) were heated in THF (20 mL) at the reflux temperature, a new type of product **3a**, yellow prisms, mp 167–171 °C, ν (KBr) 1734 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$): 2.40 (3H, s, SMe), 3.81 and 3.91 (each 3H, s, CO_2Me), 5.11 (1H, br t, *J* = 8.2, 7.1 Hz, 8-H), 5.17 (1H, br t, *J* = 8.2, 8.1 Hz, 9-H), 6.02 (1H, s, 5a-H), 6.31 (1H, d, *J* = 7.1 Hz, 7-H), 7.30–7.35 (3H, m, Ph-H), 7.42 (1H, d, *J* = 8.1 Hz, 10-H), 7.57–7.63 (2H, m, Ph-H), ^{13}C-NMR ($CDCl_3$): 20.49, 53.04, 53.20, 88,66, 93.85, 104.26, 105.58, 110.24, 124.21, 126.88, 128.13, 129.15, 130.39, 133.48, 134.32, 136.23, 142.17, 162.19, 164.68, was obtained in 13% yield, together with dimethyl 5-benzoyl-4-methylthio-5a*H*-pyrido[1,2-*d*][1,4]thiazepine-1,2-dicarboxylates (**4a**, 13%). Similar treatment of pyridinium 2-methylthio- and 2-ethylthio-1-benzoyl-2-thioxoethylides (**1b**–**d**) with **2** provided **3b** (6%)[9] and **4b** (9%), **3c** (25%, mp 179–180 °C, ν (KBr) 1732 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$): 1.82 (6H, s, 7-Me and 9-Me), 2.38 (3H, s, SMe), 3.81 and 3.90 (each 3H, s, CO_2Me), 4.81 (1H, br s, 8-H), 6.06 (1H, s, 5a-H), 6.98 (1H, br s, 10-H), 7.28–7.35 (3H, m, Ph-H), 7.57–7.64 (2H, m, Ph-H), ^{13}C-NMR ($CDCl_3$): 20.75, 21.84, 21.90, 52.99, 53.13, 88.83, 91.74, 104.35, 109.85, 116.22, 119.15, 127.11, 127.99, 129.00, 130.75, 133.51, 135.10, 136.42, 150.21, 162.31, 164.78), and **3d** (7%)[9] and **4d** (28%), respectively. These results are shown in Scheme 1.



1	R^1	R^2
a	Me	H
b	Et	H
c	Me	Me
d	Et	Me

Reactants	Reaction Time	Products (%)	R^1	R^2
1a + 2	2h	3a (13) + 4a (13)	Me	H
1b + 2	1h	3b (6) + 4b (9)	Et	H
1c + 2	2h	3c (25) + 4c (0)	Me	Me
1d + 2	13h	3d (7) + 4d (28)	Et	Me

Scheme 1

The structures of 5a*H*-pyrido[1,2-*d*][1,4]thiazepines **4a**–**d** were readily determined by spectral comparison with those of authentic samples prepared earlier by us.[3] However, the structures of **3a**–**d**

were beyond our imagination for these reactions because the analyses of the chemical shifts and signal patterns in these ^{1}H-NMR spectra precluded all of the structures which can be deduced from the reactions of **1a**–**d** and **2**. On the other hand, the elementary analyses and the high resolution mass spectra (HRMS)[10] of **3a**–**d** disclosed an interesting fact: that is, **3a**–**d** did not have the composition of the 1 : 1 adduct between methylide **1** and DMAD **2** and the increase of another oxygen atom on them was suggested. Eventually, the structures, dimethyl 1-methylthio- or 1-ethylthio-4a-phenyl-4a*H*,5a*H*-thiino[3',4':4,5]oxazolo[1,3-*b*][1,3]oxazepine-3,4-dicarboxylates, for **3a**–**d** were determined by the X-ray analysis (see Figure 1) of one compound **3a**.[11] As seen from this figure, products **3a**–**d** had a 1,3-oxazepine skeleton to suggest the oxidative ring enlargement of the pyridine ring.

To explore the origin of the additional oxygen we examined the reactions of methylides **1a**,**c** and **2** in stabilized and freshly purified THF at the reflux temperature and the reaction mixtures were analyzed by their ^{1}H-NMR spectra. The reactions of **1a**,**c** with **2** in THF stabilized by an antioxidant gave only pyridothiazepines **4a** (20%) and **4c** (36%). On the other hand, the reactions of **3a**,**c** and **2** in THF purified by glass contour solvent systems provided **4a** (37%) and **3c** (7%) + **4c** (40%) respectively. Interestingly, a small amount of oxazepine **3a** was detected in the reactions of **1a** with **2** in commercially available diethyl ether at the reflux temperature for 6h, but the similar reactions in $CHCl_3$ and benzene did not afford any **3a** at all.[4] From these findings and the fact that THF or diethyl ether easily form the peroxide, the origin of the additional oxygen in products **3a**–**d** can be considered to be peroxide. However, we have no idea for the formation mechanisms of **3a**–**d** at present, since a reaction like this has no precedent, though the formation of 1,3-oxazepine derivatives in the photolyses of 2,6-disubstituted pyridine *N*-oxides is well known.[12,13] Further investigation for the scope and the mechanism of this reaction is now in progress.

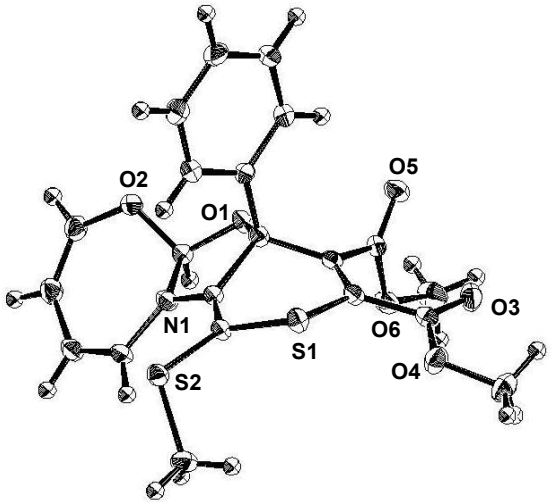


Figure 1. ORTEP drawing of **3a**

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8. THF stored at room temperature without antioxidant for several years was employed in these reactions. 20 mL of the solvent left about 0.15g of residue after the evaporation of THF. The ^{1}H-NMR spectrum of the residue showed complex signals and the presence and the quantity of THF peroxide could not be determined.
9. **3b**: yellow prisms, mp 138–140 °C, ν (KBr) 1730 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$): 1.24 (3H, t, J = 7.2 Hz, SCH_2CH_3), 2.75 and 2.89 (each 1H, m, SCH_2CH_3), 3.81 and 3.91 (each 3H, s, CO_2Me), 5.12 (1H, br t, J = 8.2, 7.1 Hz, 8-H), 5.16 (1H, br t, J = 8.2, 8.1 Hz, 9-H), 6.02 (1H, s, 5a-H), 6.31 (1H, d, J = 7.1 Hz, 7-H), 7.30–7.35 (3H, m, Ph-H), 7.55 (1H, d, J = 8.1 Hz, 10-H), 7.57–7.63 (2H, m, Ph-H). **3d**: mp 152–154 °C, ν (KBr) 1734 cm^{-1} (C=O), ^{1}H-NMR ($CDCl_3$): 1.22 (3H, t, J = 7.3 Hz, SCH_2CH_3), 1.82 (3H, s, 7-Me or 9-Me), 1.83 (3H, s, 9-Me or 7-Me), 2.72 and 2.86 (each 1H, m, SCH_2CH_3), 3.81 and 3.90 (each 3H, s, CO_2Me), 4.82 (1H, br s, 8-H), 6.06 (1H, s, 5a-H), 7.13 (1H, br s, 10-H), 7.28–7.35 (3H, m, Ph-H), 7.57–7.64 (2H, m, Ph-H).
10. The compounds **3a–d** gave satisfactory elementary analyses and the HRMS data are as follows: **3a**, $C_{21}H_{20}NO_6S_2$ $(M+H)^+$: Calcd; 446.0727 (Found; 446.0729). **3b**, $C_{22}H_{22}NO_6S_2$ $(M+H)^+$: Calcd; 460.0883 (Found; 460.0893). **3c**, $C_{23}H_{24}NO_6S_2$ $(M+H)^+$: Calcd; 474.1040 (Found; 474.1039). **3d**, $C_{24}H_{26}NO_6S_2$ $(M+H)^+$: Calcd; 488.1196 (Found; 488.1190).
11. A yellow crystal (0.20 x 0.14 x 0.10 mm) grown from $CHCl_3$-hexsane was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated CuKα radiation (λ = 1.54187 Å). Crystal data of this compound are as follows: **3a**: $C_{21}H_{20}N_2O_2S_2$; M = 445.50; triclinic, space group P-1 (#2), Z = 2 with a = 8.71314 (16) Å, b = 9.23899 (17) Å, c = 14.5356 (10) Å, α = 87.223 (6)°, β = 85.705 (6)°, γ = 62.075 (4)°; V = 1030.86 (8) Å^3, and $D_{calc.}$= 1.435 g/cm^3. The structure was solved by a direct method (SHELX97).[18] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final $R1$- and $_wR_2$-factors after full-matrix least-squares refinements were 0.0325 for (I>2.00σ(I)) and 0.0857 for all observed reflections (3699).
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