NOVEL REARRANGEMENT OF 3-ACYL-5-ACYLAMINO-2,3-DIHYDRO-1,3,4-THIADIAZOLE 1-OXIDES INTO 1,3,4-OXADIAZOLES

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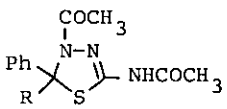
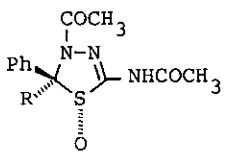
Abstract — Thermally, or in the presence of p-toluenesulfonic acid, 3-acyl-5-acylamino-2,3-dihydro-1,3,4-thiadiazole 1-oxides are transformed into 1,3,4-oxadiazoles, carbonyl compounds and sulfur.

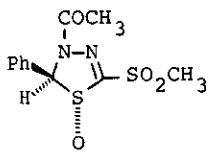
In the previous communication,[1] we reported that the oxidation of 3-acetyl-5-acetamido-2-phenyl-2,3-dihydro-1,3,4-thiadiazole (**1**) and the 2-methyl-2-phenyl derivative (**2**) with m-chloroperbenzoic acid (m-CPBA) gave single isomers of the S-oxides (**3**) and (**4**), respectively. We now report a novel rearrangement of these S-oxides into 1,3,4-oxadiazoles. Previously, we reported that 3-acetyl-5-methylsulfonyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**5**) was converted into 2-methylsulfonyl-5-phenyl-1,3,4-thiadiazole (**6**) in ethanol in the presence of base at room temperature or by heating in dimethylsulfoxide (DMSO) at 100°C.[2]



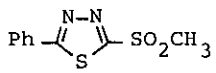
1 R = H
2 R = CH_3



3 R = H
4 R = CH_3



5



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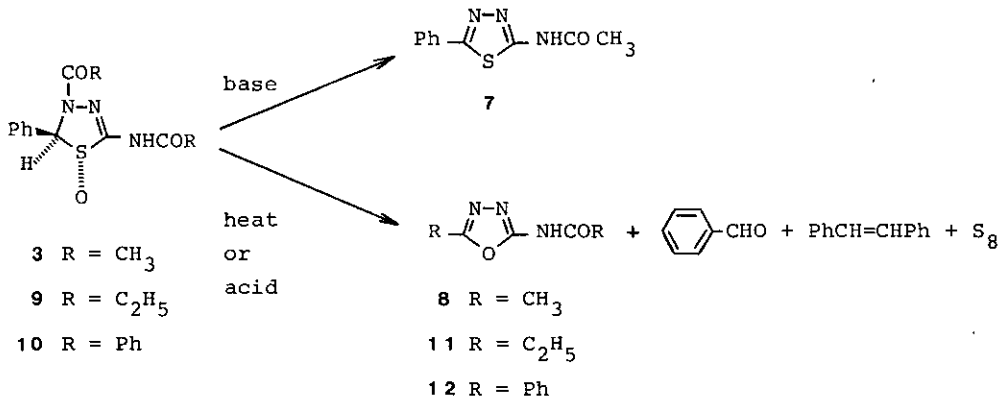
We examined a similar reaction of 3-acetyl-5-acetamido-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**3**). Treatment of compound (**3**) with a base in ethanol gave 2-acetamido-5-phenyl-1,3,4-thiadiazole (**7**)[3] in a 70 % yield (with pyridine) or in a 90 % yield (with triethylamine). However, heating compound (**3**) in DMSO

at 100°C for 3 h gave 2-acetamido-5-methyl-1,3,4-oxadiazole (**8**), mp 179-180°C (lit.[4], mp 180-181°C), in 74 % yield along with benzaldehyde, trans-stilbene and sulfur.

This novel rearrangement was also observed when compound (**3**) was heated in dimethylformamide at 100°C for 3 h (77 % yield). Similarly, 5-propionamido-3-propionyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**9**)[5] and 5-benzamido-3-benzoyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**10**),[6] which were obtained by oxidation of the corresponding 3-acyl-5-acylamino-2-phenyl-2,3-dihydro-1,3,4-thiadiazoles[3] with m-CPBA, were also transformed into 2-ethyl-5-propionamido-1,3,4-oxadiazole (**11**)[7] in 60 % yield and 5-benzamido-2-phenyl-1,3,4-oxadiazole (**12**), mp 198-200°C (lit.[4], 201-202°C), in 78 % yield, respectively, when heated in DMSO at 100°C for 3 h.



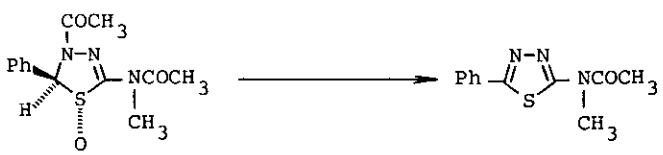
3 R = CH_3
9 R = C_2H_5
10 R = Ph

7

8 R = CH_3
11 R = C_2H_5
12 R = Ph

Refluxing compound (**3**) in dioxane for 20 h or in toluene for 1 h in the presence of a catalytic amount of p-toluenesulfonic acid gave the 1,3,4-oxadiazole (**8**) in 49 % or in 54 % yield, respectively, along with benzaldehyde and sulfur. Heating 3-acetyl-5-acetamido-2-methyl-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**4**)[1] in DMSO at 100°C gave many decomposition products, and the expected oxadiazole derivative was not detected. However, refluxing compound (**4**) in dioxane for 20 h or in toluene for 1 h in the presence of catalytic amount of p-toluenesulfonic acid gave the oxadiazole (**8**) in 49 % or in 35 % yield, along with acetophenone and sulfur.

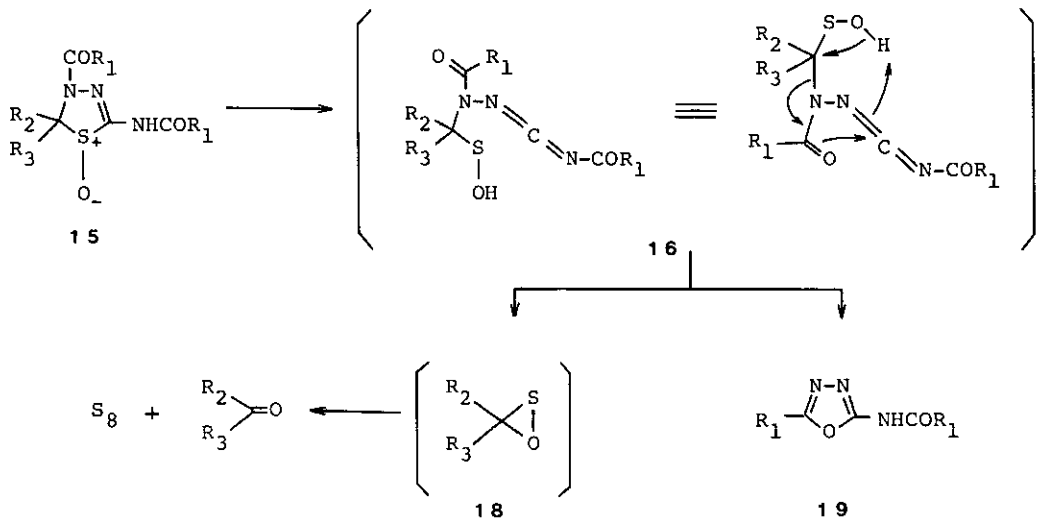
3-Acetyl-5-(N-methylacetamido)-2-phenyl-2,3-dihydro-1,3,4-thiadiazole 1-oxide (**13**)[8]



13 **14**

which was obtained from 3-acetyl-5-(N-methylacetamido)-2-phenyl-2,3-dihydro-1,3,4-thiadiazole[3] by oxidation with m-CPBA did not change at 100°C in DMSO, but was converted into 2-(N-methylacetamido)-5-phenyl-1,3,4-thiadiazole (**14**), mp 191-193°C (lit.[3], 191-192°C), in 40 % yield at 150°C in DMSO for 5 h.

This fact suggests that the presence of an NH proton in acylamino side chain is necessary for this rearrangement. A possible mechanism to explain the formation of the oxadiazole is shown in the following scheme.



The ring expansion reaction which occurs on heating heterocyclic sulfoxides containing β-hydrogen atoms is well documented,[9-13] and the initial step of these reaction is the thermal ring opening to a sulfenic acid intermediate. In the present reaction, the intermediate sulfenic acid (**16**) would be produced from the sulfoxide (**15**) by a prototropic rearrangement or by the initial protonation with p-toluenesulfonic acid. The subsequent intramolecular reaction of **16** affords the oxadiazole (**17**) and the thermally highly unstable oxathiirane (**18**)[14,15] which is converted into the corresponding carbonyl compounds and sulfur.

ACKNOWLEDGEMENT

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5. Compound **9** : yield 90 % ; mp 149.5-151.0 °C (decomp.). IR (KBr): 1705, 1685 (C=O), 1025 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.11 (3H, t, CH_2CH_3), 1.18 (3H, t, CH_2CH_3), 2.36 (2H, q, CH_2CH_3), 2.80 (2H, q, CH_2CH_3), 6.63 (1H, s, C_2-H), 7.05-7.46 (5H, m, C_6H_5), 9.35 (1H, br.s, NH). All new compounds in this paper gave satisfactory elemental analyses.

6. Compound **10** : yield 82 % ; mp 158.5-160.0 °C (decomp.). IR (KBr): 1690, 1660 (C=O), 1030 (SO) cm^{-1}. ^{1}H-NMR (Me_2SO-d_6): δ 7.06 (1H, s, C_2-H), 7.32-8.12 (15H, m, ArH), 12.40 (1H, br.s, NH).

7. Compound **11** : mp 127.5-129.0 °C. MS m/z: 169 (M^+). IR (KBr): 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.23 (3H, t, CH_2CH_3), 1.37 (3H, t, CH_2CH_3), 2.59 (2H, q, CH_2CH_3), 2.86 (2H, q, CH_2CH_3), 11.82 (1H, br.s, NH).

8. Compound **13** : yield 84 % from 3-acetyl-5-acetylmethylamino-2-phenyl-2,3-dihydro-1,3,4-thiadiazole. mp 144.0-145.0 °C (decomp.). MS m/z: 293 (M^+). IR (KBr): 1690, 1675 (C=O), 1065 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.33 (3H, s, $COCH_3$), 2.49 (3H, s, $COCH_3$), 3.51 (3H, s, N-CH_3), 6.62 (1H, s, C_2-H), 6.96-7.52 (5H, m, ArH).

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