HETEROCYCLES, Vol. 24, No. 5, 1986

ONE-FLASK SYNTHESIS OF 4-[BIS(METHYLTHIO)]METHYLENE-2-PHENYL-5-OXO-4,5-DIHYDRO-1,3-OXAZOLE AND ITS AMINOLYSES

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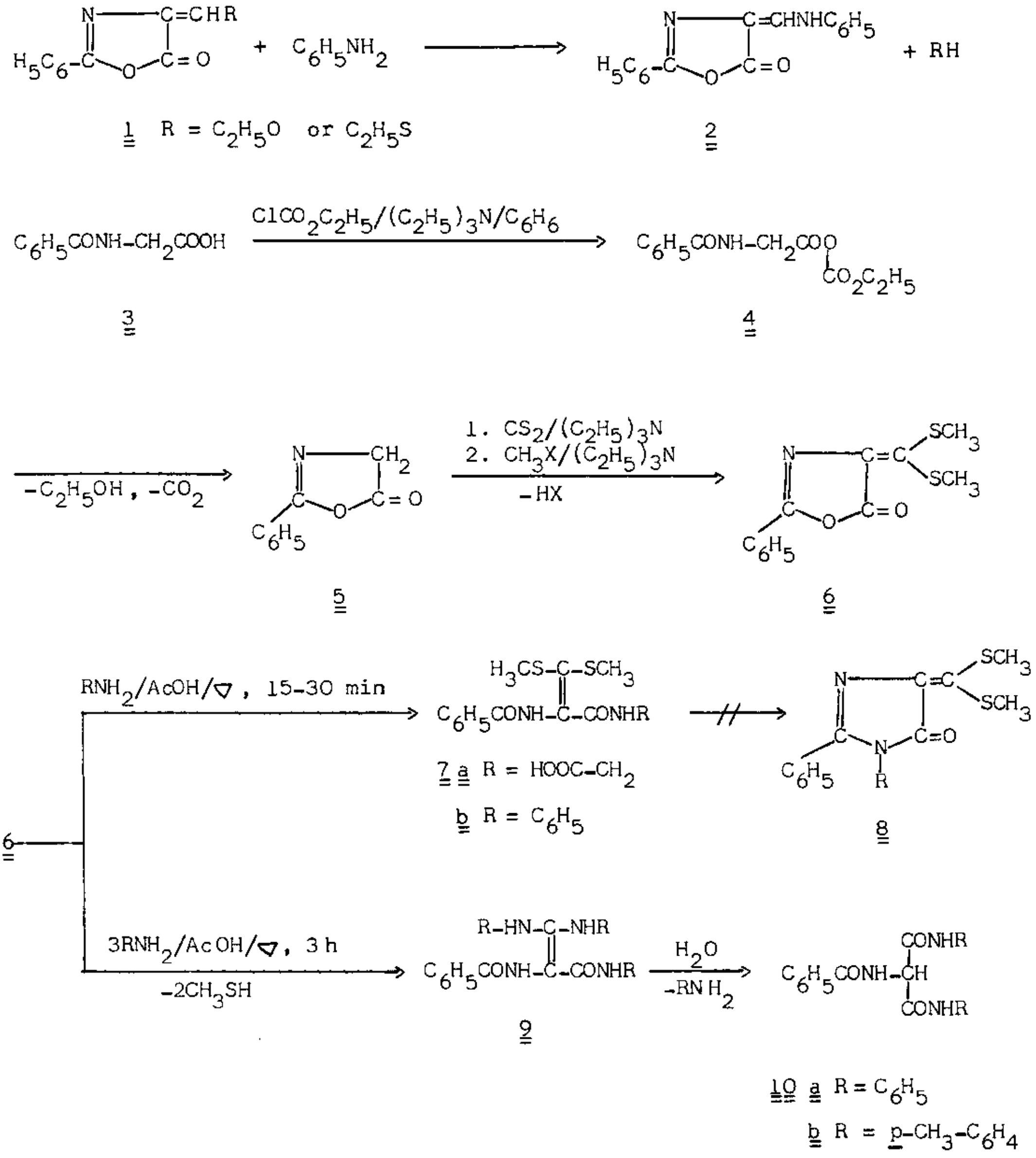
Abstract - Cyclisation of hippuric acid with ethyl chloroformate and triethylamine in benzene and subsequent triethylamine-mediated condensation with carbon disulphide and S-methylation afford the title compound which undergoes 1,5-bond cleavage on heating with molar proportion of a primary amine in the presence of glacial acetic acid, the ketenethioacetal moiety remaining intact. On increasing the proportion of the amine and heating the mixture for a longer period, the corresponding N,N'-disubstituted benzoylaminomalondiamides are obtained.

4-Alkoxy(alkylthio)methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazoles (**1**) react with primary amines, for example aniline, to afford **2**, the 1,5-bond of the ring remaining unaffected[1]. However, reactions with certain binucleophiles give heterocycles, the type of which depends on the nature of the reactants[1,2]. In this connection we examined aminolyses of 4-[bis(methylthio)]methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**6**). This compound is known in the literature[3], but the reported synthesis involves steps which are rather tedious. Also, its reactions do not seem to have been properly investigated. It should be mentioned that ketenedithioacetals have acquired importance in recent years[4,5], and the system **6** is specially interesting because of the reactive functionalities placed in juxtaposition to one another. Hippuric acid was cyclised with ethyl chloroformate and triethylamine in dry benzene, and to the resultant 2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**5**) were added in stages carbon disulphide and methyl bromide. On work-up and separation by chromatography, the pure product was obtained. The use of a large excess of the methyl halide gave a better result. The structure of **6** was confirmed by spectral data.

Scheme


1 R = C2H5O or C2H5S
2
+ C6H5NH2
+ RH
3
4
ClCO2C2H5/(C2H5)3N/C6H6
-C2H5OH, -CO2
5
1. CS2/(C2H5)3N
2. CH3X/(C2H5)3N
-HX
6
RNH2/AcOH/▽, 15-30 min
7 a R = HOOC-CH2
b R = C6H5
8
3RNH2/AcOH/▽, 3 h
-2CH3SH
9
H2O
-RNH2
10 a R = C6H5
b R = p-CH3-C6H4

Aminolyses of 6 were carried out with glycine, aniline and p-toluidine under different conditions. It has been found that on heating with one mole of aniline in benzene, 6 remains intact. However, in the presence of glacial acetic acid rapid cleavage of the 1,5-bond takes place affording 7b in good yield. Similarly, on heating 6 and glycine in glacial acetic acid alone, the dehydropeptide (7a) was obtained. The aminolysis is rapid and quite selective, the ketenedithioacetal moiety remaining unaffected, under the reaction conditions mentioned.

When the anilide (7b) was heated under reflux in glacial acetic acid for about 2 h with fused sodium acetate as a catalyst, a mixture was obtained from which 6 was separated by TLC (silica gel/benzene) in about 30% yield and it was confirmed by comparison with authentic sample. The other components of the mixture could not be properly characterised since these were always contaminated.

When 6 and aniline or p-toluidine, taken in the molar ratio of 1:3, were heated in boiling glacial acetic acid containing catalytic amount of fused sodium acetate for about 3 h and worked up, a sulphur free compound was obtained to which the structure 10 has been assigned on the basis of ir spectrum and mass M^+. Since these compounds are insufficiently soluble, their nmr spectra could not be recorded. Isolation of 10 can be accounted for only by assuming the formation of an unstable intermediate 9 which would undergo hydrolysis during the work-up, as shown in the scheme.

The present investigation reveals that 4-[bis(methylthio)]methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (6) is amenable to selective aminolysis. Also, it can afford acylaminomalondiamides (10). In view of the easy availability of the starting material, speed and certain amount of selectivity of the reaction, the present work seems to be potentially useful.

EXPERIMENTAL

All melting points are uncorrected. The ir and nmr spectra were recorded on Perkin-Elmer 720 and/or 257, and JEOL FX-90Q spectrophotometers, respectively.

4-[Bis(methylthio)]methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (6). To a mixture of hippuric acid (3.58 g; 0.02 mol) and triethylamine (3.8 ml; 0.02 mol) in dry benzene (80 ml) was added ethyl chloroformate (2.2 ml; 0.022 mol) with stirring, and after 15 min triethylamine (5.6 ml; 0.04 mol) and carbon disulphide (3.6 ml; 0.06 mol) were added drop-wise. The mixture was cooled in an ice bath and to it methyl bromide was passed for 15-20 min, when intense colour developed. The precipitate was filtered off, washed with benzene (3 x 5 ml). The filtrate and washings were combined and concentrated to dryness under reduced pressure. The crude product was purified over column (neutral alumina or silica gel/benzene); yield, 2.2 g (41%, based on hippuric acid); mp 118-120° (lit[3]. mp 119-120°). ν(KBr): 1800, 1765, 1750, 1650, 1610 cm^{-1}. nmr ($CDCl_3$/TMS)δ: 2.61 (s, 3H, CH_3); 2.85 (s, 3H, CH_3); 7.4 (m, 3H, arom); 7.96 (m, 2H, arom) ppm. M^+: 265 ($C_{12}H_{11}NO_2S_2$).

N-Substituted 2-Benzoylamino-3-[bis(methylthio)]acrylamides (7); General Procedure : Aniline or glycine and 6, taken in equimolar ratio, were heated under reflux in glacial acetic acid (20 ml/g of 6) for 15-30 min and concentrated to dryness over a steam bath. The residue was triturated with aqueous ethanol. 7a was isolated with saturated $NaHCO_3$ soln and precipitated with conc. HCl. The crude products were recrystallised from aqueous ethanol or benzene. The relevant data are given in the Table.

N,N'-Disubstituted Benzoylaminomalondiamides (10); General Procedure : Aniline or p-toluidine and 6, taken in the molar ratio of 3:1, and freshly fused sodium acetate (50 mg/g of 6) were heated under reflux in glacial acetic acid (20 ml/g of 6) for about 3 h, concentrated to dryness over a steam bath and triturated with aqueous ethanol. The crude products were recrystallised from ethanol. For the relevant data see the Table.

ACKNOWLEDGEMENT

We thank the C.S.I.R., New Delhi, for the award of a senior fellowship (to R.A.) and a position in the pool (to J.R.).

Table. Aminolyses of 4-[Bis(methylthio)]methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**6**).

Product	Yield [%]	mp [°C]	ir (Nujol) ν[cm^{-1}]	Molecular Formula	Combustion Analysis C	H	N
					Calculated (Found)	Calculated (Found)	Calculated (Found)
7a	82	188-189°	3350, 3300, 1740, 1660, 1620	$C_{14}H_{16}N_2O_4S_2$	49.41 (49.15)	4.70 (4.84)	8.23 (8.12)
7b	89	173-175°	3270, 1660, 1640	$C_{18}H_{18}N_2O_2S_2$	60.33 (60.34)	5.02 (5.14)	7.54 (7.67)
10a	80	222-224°	3270, 1680, 1640	$C_{22}H_{19}N_3O_3$[a]	70.76 (70.50)	5.13 (5.60)	11.25 (11.26)
10b	78	233-235°	3270, 1680, 1640	$C_{24}H_{23}N_3O_3$[b]	71.82 (72.28)	5.77 (5.55)	10.47 (10.31)

[a] M^+ : 373

[b] M^+ : 401.

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Received, 12th December, 1985