Chemical Cleavage of Benzoyl Amino Acid Amides

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Recently we found that primary and secondary amide bonds could be cleaved by sodium hydride and carbon disulfide to give thioacids and isothiocyanate[1]. When we tried to utilize this reaction for the chemical cleavage of peptide bonds we were unable to obtain the expected reaction products. Even a simple derivative like methyl hippurate did not yield the expected products – thiobenzoic acid and methyl isothiocyanoacetate – although one could observe that a reaction indeed took place.

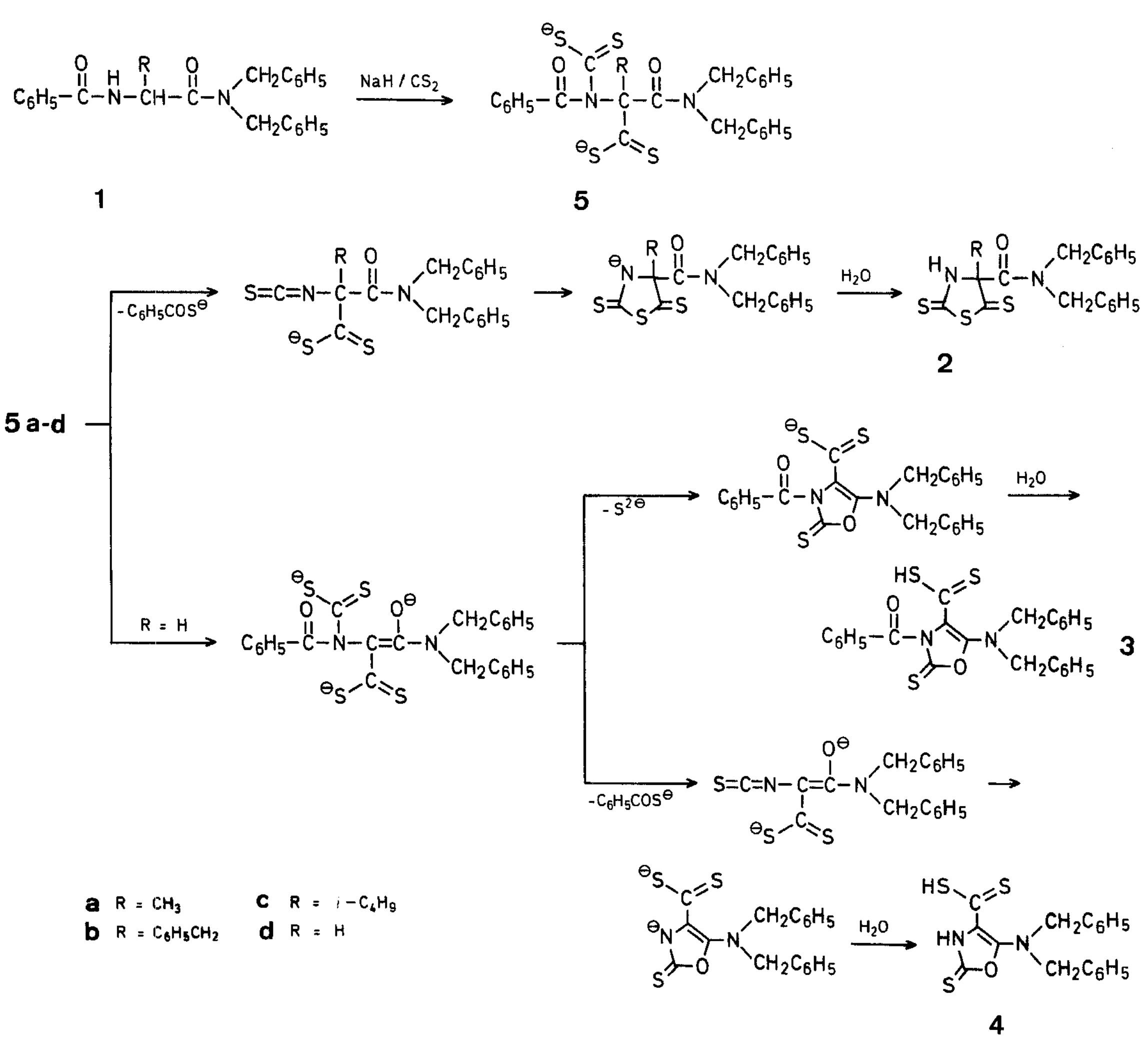
In order to isolate the reaction products we have chosen benzoyl dibenzylamides of various amino acids (**1**) as model compounds for the cleavage reaction. The reaction of **1** with sodium hydride and carbon disulfide in benzene/*N*,*N*-dimethylacetamide mixture always gave thiobenzoic acid due to the cleavage of the benzoyl group. In all cases (**1a**, **b**, **c**) except glycine the corresponding thioanhydride **2** was obtained in 40–60% yield. In the case of glycine (**1d**) the thioanhydride was obtained in 8–10% yield. The structure of the thioanhydrides are in accord with the elemental analysis, mass spectra, ^{1}H-N.M.R. and I.R. data of the products. The oxazolinethiones **3** and **4** were isolated in 75% and 10% yield respectively from the reaction of the glycine derivative (**1d**). Their structures are in accord with elemental analysis, mass spectra, ^{1}H-N.M.R. and I.R. data.

The formation of **2**, **3**, and **4** instead of the expected isothiocyanate could be explained by the formation of the bis-[dithiocarboxy] dianion intermediate **5** from the dianion $[C_6H_5—CO—N—C(R)—N(CH_2C_6H_5)_2]^{2\ominus}$, which could react further according to the scheme.

The formation of the intermediate **5** in this case is very interesting as reaction of methyl iodide and sodium hydride with any acylamino acid ester or free acylamino acid results in the formation of the corresponding mono-*N*-methyl derivative[2,3]. This presumably shows that the carbanion formed in this case has only a limited reactivity and therefore reacts only with powerful acceptors like carbon disulfide.

4-(*N*,*N*-Dibenzylaminocarbonyl)-4-methyl-thiazolidine-2,5-dithione (2a):

To a solution of benzoylalanyl *N*,*N*-dibenzylamide (7.44g, 2 mmol) in a mixture of benzene (80 ml) and carbon disulfide (10 ml) sodium hydride (2.4g, 80% in mineral oil) was added. A reaction began upon the addition of dimethylacetamide (5 ml), after 5 min the reaction mixture was cooled in ice water and additional amount of dimethylacetamide was added (20 ml). After 2 hours excess of sodium hydride is decomposed by the addition of a small amount of cold water. Water (80 ml) and concentrated hydrochloric acid (25 ml) were added with cooling and the aqueous layer is extracted with benzene (50 ml). The combined organic layers are washed with water and extracted with 10% sodium hydroxide solution (2 × 50 ml). The combined basic layers were acidified with concentrated hydrochloric acid and extracted with benzene (2 × 50 ml). The benzene solution was dried and evaporated to give a residue which was crystallized from benzene/cyclohexane; yield: 4.6g (60%); m.p. 199°.



$C_{19}H_{18}N_2OS_3$	calc.	C 59.1	H 4.6	N 7.2	S 24.8
(386.5)	found	59.0	4.6	7.0	24.4

I.R. (Nujol): $\nu_{C=O} = 1680\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.6$ (s, 3H), 4.1 (s, 4H), 7.2 ppm (m, 10H).

Mass spectrum: $m/e = 386$ (M^+, 3%), 310 (7%), 295 (12%), 224 (42%), 219 (13%), 106 (21%), 91 (100%).

4-(*N*,*N*-Dibenzylaminocarbonyl)-4-benzyl-thiazolidine-2,5-dithione (2b):

The same procedure was followed starting with benzoylphenylalanyl *N*,*N*-dibenzylamide (9 g, 2 mmol). The residue was dissolved in hot cyclohexane and a crystalline product precipitated upon heating. The compound was crystallized from benzene/cyclohexane; yield: 4.2g (45%); m.p. 162°.

$C_{25}H_{22}N_2OS_3$	calc.	C 64.9	H 4.8	N 6.1	S 20.8
(462.6)	found	64.8	4.8	6.1	20.6

I.R. (Nujol): $\nu_{C=O} = 1680\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.6$ (s, 2H), 4.3 (s, 4H), 7.2 ppm (m, 15H).

Mass spectrum: $m/e = 462$ (M^+, 4%), 461 (20%), 386 (5%), 385 (9%), 372 (5%), 371 (13%), 295 (4%), 224 (7%), 105 (98%), 91 (100%).

4-(*N*,*N*-Dibenzylaminocarbonyl)-4-isobutyl-thiazolidine-2,5-dithione (2c):

The same procedure was followed starting with benzoylleucyl *N*,*N*-dibenzylamide (8.3g, 2 mmol). The product was obtained as an oil (3.5g, 40%).

$C_{22}H_{24}N_2OS_3$	calc.	C 61.5	H 5.6	N 6.5	S 22.4
(428.6)	found	61.6	5.5	6.7	22.0

I.R. (Nujol): $\nu_{C=O} = 1680\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.0$ (m, 7H), 1.8 (d, 2H, $J = 5$ Hz), 4.3 (s, 4H), 7.2 ppm (m, 10H).

Mass spectrum: $m/e = 428$ (M^+, 4%), 427 (4%), 352 (16%), 337 (5%), 261 (30%), 224 (55%), 105 (98%), 91 (100%).

4-(*N*,*N*-Dibenzylaminocarbonyl)-thiazolidine-2,5-dithione (2d):

The same procedure was followed starting from benzoylglycyl *N*,*N*-dibenzylamide (7.16g, 2 mmol). The product was obtained as an oil; yield: 0.6g (8%).

$C_{18}H_{16}N_2OS_3$	calc.	S 25.8	N 7.5
(372.5)	found	25.5	6.9

I.R. (Nujol): $\nu_{C=O} = 1680\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 4.1$ (s. 4H), 7.2 ppm (m. 10H).

Mass spectrum: $m/e = 372$ (M^+, 3%), 296 (10%), 281 (13%), 224 (59%), 195 (25%), 106 (15%), 91 (100%).

3-Benzoyl-5-dibenzylamino-4-dithiocarboxyoxazoline-2-thione (3):

Upon the decomposition of the reaction mixture of **2d** with water and acid, a yellow solid separated, which was filtered and extracted with boiling ethanol (60 ml). The fraction which was not soluble in ethanol was crystallized from dimethylformamide/methanol; yield: 7.5g (75%): m.p. 175°.

$C_{25}H_{20}N_2O_2S_3$	calc.	C 63.0	H 4.2	N 5.9	S 20.2
(476.6)	found	62.8	4.3	5.8	19.8

I.R. (Nujol): $\nu_{C=O} = 1695\ cm^{-1}$, $\nu_{C=C} = 1610\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.8$ (s, 1H), 4.3 (s, 4H), 7.2 (m, 13H), 7.8 ppm (m, 2H).

Mass spectrum: $m/e = 376$ (M^+, 3%), 340 (10%), 307 (4%), 249 (20%), 196 (16%), 144 (13%), 105 (100%), 91 (100%).

5-Dibenzylamino-4-dithiocarboxyoxazoline-2-thione (4):

The ethanol solution from the above procedure (compound **3**) was evaporated and the residue was crystallized from aqueous methanol; yield: 0.7g (10%); m.p. 157°.

$C_{18}H_{16}N_2OS_3$	calc.	C 58.0	H 4.3	N 7.5	S 25.8
(372.4)	found	58.1	4.3	7.5	25.8

I.R. (Nujol): $\nu_{C=C} = 1605\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.3$ (s, 1H), 4.2 (s, 4H), 7.2 ppm (m, 10H).

Mass spectrum: $m/e = 372$ (M^+, 5%), 281 ($M^+ - 91$, 4%), 196 (7%), 112 (13%), 105 (17%), 91 (100%).

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