Tetrahedron Vol. 38, No. 9, pp. 1163 to 1168, 1982
Printed in Great Britain.

0040-4020/82/091163-06$03.00/0
Pergamon Press Ltd.

THE $\geq C=S \longrightarrow \geq C=O$ TRANSFORMATION USING THE SOFT $NO^{\oplus}$-SPECIES

K.A.JØRGENSEN,* A.-B.A.G.GHATTAS§ and S.-O.LAWESSON

Department of Organic Chemistry, Chemical Institute,
University of Aarhus, 8000 Aarhus C, Denmark

(*Received in UK 28 February 1982*)

Abstract - The reaction of $NaNO_2$ in acidic solution with thiocarbonyl compounds has been studied. Secondary- and tertiary thioamides, 1-benzyl-hexahydro-2H-azepine-2-thione, 5-ethyl-5-phenyl thiobarbituric acid, certain thiourea derivatives, 2H-1-benzopyran-2-thione, O,O-diphenyl-thiocarbonic ester, O,S-diphenyl-dithiocarbonic ester, N,N-dimethyl-S-phenyl-dithiocarbamatic ester, N-ethyl-N-phenyl-O-ethyl-thiocarbamatic ester are all converted into the corresponding carbonyl-analogues. 4,4'-Bis(dimethylamino)-thiobenzophenone (Michler's thioketone) gives 3-nitro-4,4'-bis(dimethylamino)-benzophenone at room temperature. At (-10 °C)-(-5 °C) the expected oxo compound is obtained as the main product together with 4-(N-nitroso-methylamino)-4'-(dimethylamino)-benzophenone.

The formation of carbonyl compounds from the corresponding thio-analogues can be achieved by a variety of methods, using nitric acid,[1] alkyl nitrites,[2] benzenselenic anhydride,[3] selenium dioxide,[4] diaryl selenoxide,[5] dimethyl selenoxide,[6] diaryltelluroxide,[7] I_2-DMSO,[8] alkoxides and hydroxide[9] with different degrees of success.

A recent note[10] about the formation of N,N'-disubstituted urea from the corresponding thiourea prompts us to publish these results at this stage of the investigation.

This paper reports on the reaction of $NO^{\oplus}$ in water (from $NaNO_2$ and HCl) with thiocarbonyl compounds to give the corresponding oxo-analogues, and mechanistic considerations are elaborated according to the Hard and Soft Acids and Bases (HSAB) principle. Included is also a method for the preparation of thiocarbamates from the corresponding carbamates using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (LR) as thiation reagent.

STARTING MATERIAL

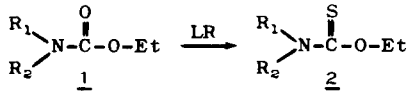
The thio compounds are easily prepared according to known methods or are commercially available.

The thiocarbamates are synthesized from the corresponding carbamates using 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (LR) as thiation reagent. As LR is known to be a very efficient thiation reagent for ketones,[11] carboxamides,[12-16] esters and S-substituted thioesters,[17,18] lactones,[19] lactames and amides,[20] and enaminones,[21] the

*Presented at the 7th International Meeting on N-Nitroso Compounds, Tokyo, Sep.28-Oct.1,1981.

§On leave from Faculty of Science, Assiut University, Sohag, Egypt.

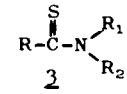
reaction of LR with carbamates has been studied and found to give reasonable yields of thiocarbamates (1 → 2).



1,2 a: $R_1 = R_2 = H$
b: $R_1 = C_2H_5$; R_2 = Ph
c: R_1 = H; $R_2 = C_2H_5$

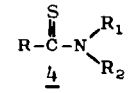
RESULTS AND DISCUSSION

When excess of $NaNO_2$ is added to thiocarbonyl compounds in 4 M HCl, the corresponding carbonyl compounds are isolated in high yields after a short reaction time (Table 1). The nitrosation of primary thioamides gives 1,2,4-thiadiazole derivatives.[22] Besides the carbonyl compounds elemental sulfur in equivalent amounts is isolated. The tertiary thioamides (3, 4) are all smoothly transformed into the corresponding amides.



3

a: R = Ph; $R_1, R_2 = -(CH_2)_2-O-(CH_2)_2-$
b: R = CH_3; $R_1, R_2 = -(CH_2)_2-O-(CH_2)_2-$
c: R = CH_3; $R_1, R_2 = -(CH_2)_4-$



4

a: R = Ph; $R_1 = R_2 = CH_3$
b: R = H; R_1 = Ph; $R_2 = CH_3$

The highest yield is obtained with N-phenylthioacetamide, 4b, (97%) and the lowest with N-thiobenzoyl-morpholine, 3a, (88%).

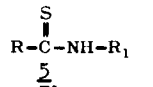
The yields of secondary amides from the corresponding thioamides, 5, are slightly lower than found for tertiary amides. Thus the yields vary from 60%, 5e, to 97% for N-benzyl-propanthioamide, 5d.

Under these conditions the corresponding N-nitrosamides are never isolated. The formation of 2-pyridine-

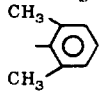
TABLE 1. Experiment data for the >S → >O transformation

Compound	Reaction time (hrs)	Reaction temperature (°C)	Yields (%)	Reaction procedure
3a	½	20	88[35]	B
3b	¼	20	93[36]	B
3c	¾	20	92[31]	B
4a	½	20	94[38]	B
4b	½	20	97[39]	B
5a	4	20	65[40]	B
5b	3	20	71[41]	B
5c	½	20	80[42]	B
5d	¼	20	87[43]	B
5e	40	45	60[23]	B
6	¼	20	81[44]	A
7	1½	45	64[40]	A
8a	¼	20	38[40]	A
8b	¼	20	60[40]	A
8c	¼	20	98[45]	A
9	22	45	64[39]	A
12	20	45	15[46]*	A
13	25	45	86[47]*	A
14	4	45	40[44]*	A
2c	20	45	38[49]	A

*Based on GLC and structure identity, yields calculated by GLC

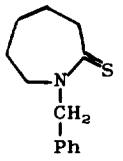


5

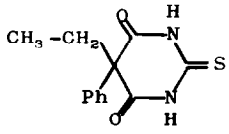
a: R = R_1 = Ph
b: R = Ph; R_1 = Ph-CH_2
c: R = R_1 = Ph-CH_2
d: R = CH_3-CH_2; R_1 = Ph-CH_2-
e: R =  ; R_1 = 

carboxamide-N-(2,6-dimethylphenyl)[23] might be of pharmaceutical interest because it is shown to have local anaesthetic effect.

The thiolactam, 1-benzylhexahydro-2H-azepine-2-thione, 6, gives the corresponding oxo compound in 81% yield, and 5-ethyl-5-phenyl-thio-barbituric acid, 7, yields the corresponding oxo compound in 64% yield.

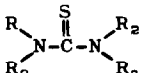


6



7

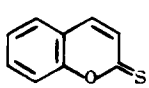
The treatment of the thiourea derivatives, 8, with $NaNO_2$ in 4 M HCℓ and $CH_2Cℓ_2$ gives a smooth reaction and the urea derivatives are isolated in different yields, the highest being 98% (N,N'-dihexyl-thiourea, 8c) and the lowest 38% (N,N,N',N'-tetramethylthiourea, 8a). Mono-substituted thioureas produce intractable mixtures of products.



8

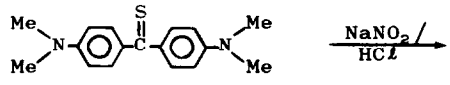
a: R = R_1 = R_2 = R_3 = CH_3
b: R = R_1 = R_2 = CH_3; R_3 = H
c: R = R_2 = C_6H_{11}; R_1 = R_3 = H

The thiolactone 2H-1-benzopyran-2-thione, 9, reacts similary and gives 2H-1-benzopyran-2-one in 64% yield.

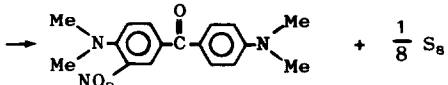


9

When 4,4'-bis(dimethylamino)-thiobenzophenone (Michler's thioketone), 10, is reacted with $NaNO_2$ in 4 M HCℓ and $CH_2Cℓ_2$, 3-nitro-4,4'-bis(dimethylamino)-benzophenone,[24,25] 11, is obtained (98%), the structure of which is proved by MS, ^{1}H NMR, and microanalyses. The microanalyses and mass spectrum (M^+ = 313) correspond to the composition $C_{17}H_{19}N_3O_3$. Other observed peaks in the mass spectra are, M^+-NO, M^+-NO_2 which are characteristic for nitro compounds.[26] The ^{1}H NMR spectra show 7 aromatic hydrogens (δ 6.5-8.2) and 12 aliphatic ones (δ 3.0).



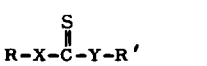
10



11

Nitrosation of 10 at (-10)-(-5) ℃ gives 4,4'-bis(dimethylamino)-benzophenone (Michler's ketone) as the main product (67%) and also 4-(N-nitroso-methylamino)-4'-(dimethylamino)-benzophenone,[27-30] The structure of the main product (Michler's ketone) is proved by m.p. and mixed m.p., while the second known product,[30] is characterized by physical data and MS, from which the following peaks are observed: M^+ (283, 44%), M^+-NO (253, 100%), M^+-NO-CO (225, 100%) (for mass spectra of nitroso compounds, see ref.31). The ^{1}H NMR spectra show the presence of 8 aromatic hydrogens (δ 6.60-8.32) and 9 aliphatic ones (δ 3-10).

The thiono compounds, 12-15, can also be transformed into the carbonyl analogues:

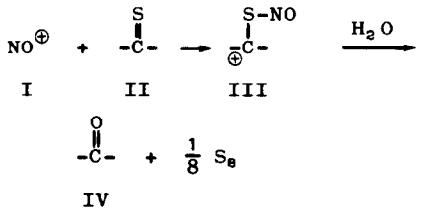


12: X = Y = O; R = R' = Ph
13: X = S; Y = O; R = R' = Ph
14: X = S; YR' = $N(CH_3)_2$; R = Ph
15: X = O; YR' = N(Ph)(C_2H_5); R = C_2H_5

Attempts to transform a protected thiodipeptide: Z-Glyt-Gly-OEt into the corresponding protected dipeptide yields

several products in low yields beside the protected dipeptide. The protected dipeptide is observed in TLC and MS.

The formation of oxo compounds from the corresponding thiono compounds can be accounted for by the HSAB principle.[32,33] The soft (borderline) acid $NO^{\oplus}$ (I) attacks the soft sulfur of the thiocarbonyl (II) under formation of a S-nitroso intermediate (III) which can be detected by UV spectrsocopy; the S-nitroso intermediate is known to show absorption at 340 nm.[34]



The S-nitroso intermediate is hydrolyzed by the solvent, and IV is formed together with elemental sulfur. A detailed kinetic and mechanistic study will be presented shortly in a separate paper.

EXPERIMENTAL

^{1}H NMR spectra are recorded at 60 MHz on a Varian EM 360 spectrometer. ^{13}C NMR spectra at 20 MHz on a Varian CFT 20 spectrometer. TMS is used as internal standard. IR spectra are recorded on a Bechman IR-18 spectrometer. Mass spectra are recorded at a Micromass 7070 F spectrometer operating at 70 eV using direct inlet. Microanalyses are carried out by Løvens Kemiske Fabrik, DK-2750 Ballerup (Microanalytical Laboratory).

General procedure for the formation of thionocarbamates

Starting compound (0.02 mol) and LR (0.015 mol) were heated in 50 ml anhydrous xylene until no more of the starting material could be detected (TLC). After cooling to room temperature, the excess of LR was filtered off. Then the reaction mixture was evaporated on silica gel under reduced pressure and applied to a silica gel column using ether-petroleum as eluent. The reaction conditions (temp./°C for a period of X h) and the physical data are given below.

Compound 2a[47] 140 °C, 22 h, yield 71%, m.p. 37 °C, MS [*m/e* (% rel.int.)] 105(100), 76(12).

Compound 2b[48] 140 °C, 24 h, yield 76%, liq. [*m/e* (% rel.int.)] 209(50), 180(7), 148(33), 120(100%).

Compound 2c[49] 140 °C, 2 h, yield 62%, liq. [*m/e* (% rel.int.)] 133(100), 104(21), 88(16), 72(44).

The $\geq S \rightarrow \geq O$ transformation

General procedures

A: Thiocarbonyl compound (0.01 mol) is mixed with 20-40 ml of HCl and CH_2Cl_2 under vigorous stirring. Then 0.015 mol of $NaNO_2$ in 10 ml H_2O is added. Reaction times and temperatures are given in Table 1. The phases are separated; the water phase is extracted with CH_2Cl_2 and the combined organic layers are washed with H_2O, filtered and dried ($MgSO_4$). Evaporation of the solvent gives the oxo compound which is checked by MS, ^{1}H NMR, IR m.p. (b.p.), and by comparison with authentic oxo compound.

B: Thiocarbonyl compound (0.01 mol) is mixed with 20-40 ml 4 M HCl and 0.015 mol $NaNO_2$ in 10 ml H_2O is added under vigorous stirring. Reaction times and temperatures are given in Table 1. The reaction mixture is neutralized with NaOH, extracted with CH_2Cl_2 and the combined organic layers are washed with H_2O and dried ($MgSO_4$). Evaporation of the solvent gives the oxo compound which is checked by MS, ^{1}H NMR, IR (m.p.(b.p.)) and by comparison with authentic oxo compound.

Nitrosation of 4,4'-bis(dimethylamino)-thiobenzophenone (Michler's thioketone). Michler's thioketone (2.84 g, 0.01 mol) is mixed with 25 ml 4 M HCl and 50 ml CH_2Cl_2 under vigorous stirring to which 0.04 mol of $NaNO_2$ in 20 ml H_2O is added. The reaction is complete after 15 min. The phases are separated; the water phase neutralized with $NaHCO_3$ and extracted with CH_2Cl_2.

The combined organic layers are collected and washed with H_2O and dried ($MgSO_4$). Evaporation of the solvent gives 3.06 g (98%) of 3-nitro-4,4'-bis-(dimethylamino)-benzophenone which is recrystallized from MeOH, m.p. 144 °C (lit.[38]/144 °C). MS: [*m/e* (rel.int.)]: 313 (M^+,100), 296(65), 283(18), 267 (36), 266(60), 255(9), 254(44), 251 (44), 225(36), 210(27). ^1H NMR, δ ($CDCl_3$): 6.50-8.20 (7H,m) aromatic, 3.00 (12H,s) aliphatic. (Anal. Found: C 64.49, H 6.15, N 13.53. Calc. for $C_{17}H_{18}N_3O_3$: C 65.17, H 6.07, N 13.42 %).

The same reaction as above is repeated at (-10)-(-5) °C for 0.5 h and then stirred for another 1.5 h at room temperature. The mixture of the two products is separated and purified by fractional crystallization (MeOH). 4,4'-Bis(dimethylamino)-benzophenone (Michler's ketone) is isolated in 67%, m.p. and mixed m.p. with an authentic sample gives no depression. 4-(N-nitrosomethylamino)-4'-dimethylaminobenzophenone is isolated in 22%, m.p. 183 °C (lit.[39] 183 °C). MS: [*m/e* (rel.int.)]: 283(M^+,44), 268(40), 255(55), 254(100), 253(100), 237(36), 225(100), 210(64). ^1H NMR, δ ($CDCl_3$): 6.60-8.32 (8H,m) aromatic, 3.10 (9H,s) aliphatic.

REFERENCES

1. A.Husemann, Liebigs Ann.Chem. 126, 269 (1863).
2. K.A.Petrov and L.N.Andrew, Russ. Chem.Rev. 40, 505 (1971).
3. N.J.Cussans, S.V.Ley, and D.H.R. Barton, J.Chem.Soc. Perkin I 1650 (1980).
4. R.Boudet, Bull.Soc.Chim.France 846 (1951).
5. M.Mikolajczyk and J.Łuczak, J.Org. Chem. 43, 2132 (1978)
6. S.Tamagaki, I.Hatanaka, and S. Kozuka, Bull.Chem.Soc.Japan 50, 3421 (1977).
7. S.V.Ley, C.A.Meerholz, and D.H.R. Barton, Tetrahedron Vol.37, Supp. No.9, 213 (1981).
8. a. Y.Kinoshita, S.Kubota, S.Hasimoto, and H.Ishikawa, Agric. and Biol. Chem. Japan) 37, 701 (1973). b. M. Mikolajczyk and J.Łuczak, Synthesis, 491 (1974); 114 (1975).
9. H.Singh, P.Singh, and N.Malhotra, J.Chem.Soc. Perkin I 2647 (1981).
10. J.W.Lown and S.M.S.Chauhan, J.Chem. Soc., Chem.Commun. 675 (1981).
11. B.S.Pedersen, S.Scheibye, N.H.Nilsson, and S.-O.Lawesson, Bull.Soc. Chim.Belg. 87, 223 (1978).
12. H.Fritz, P.Hug, S.-O.Lawesson, E. Logeman, B.S.Pedersen, H.Sauter, S. Scheibye, and T.Winkler, ibid. 87, 525 (1978).
13. S.Scheibye, B.S.Pedersen, and S.-O.Lawesson, ibid. 87, 229 (1978).
14. S.Scheibye, B.S.Pedersen, and S.-O.Lawesson, ibid. 87, 299 (1978).
15. K.Clausen, B.S.Pedersen, S.Scheibye, S.-O.Lawesson, and J.H.Bowie, Org.Mass.Spectrom. 14, 101 (1979).
16. K.Clausen, B.S.Pedersen, S.Scheibye, S.-O.Lawesson, and J.H.Bowie, Int.J.Mass spectrom.Ion Phys. 29, 223 (1979).
17. B.S.Pedersen, S.Scheibye, K.Clausen, and S.-O.Lawesson, Bull.Soc. Chim.Belg. 87, 293 (1978).
18. B.S.Pedersen and S.-O.Lawesson, Tetrahedron 35, 2433 (1979).
19. S.Scheibye, J.Kristensen, and S.-O.Lawesson, ibid. 35, 1339 (1979).
20. R.Shabana, S.Scheibye, K.Clausen, S.O.Olesen, and S.-O.Lawesson, Nouv.J.Chim. 4, 47 (1980).
21. R.Shabana, J.B.Rasmussen, S.O.Olesen, and S.-O.Lawesson, Tetrahedron 3047 (1980).
22. M.W.Cronyn and T.W.Nakagawa, J. Amer.Chem.Soc. 74, 3693 (1952).
23. H.Rinderknecht, Helv.Chim.Acta 142, 1324 (1959).
24. M.Nathansohn and P.Müller, Chem. Ber. 22, 1875 (1889).
25. A.Kliegl, ibid. 39, 1266 (1906).
26. H.Buzikiewicz, C.Djerassi, and D. H.Williams, Interpretation of Mass Spectra of Organic Compounds, Holden-Day, Inc. San Francisco, 205 (1964).
27. E.Bischoff, Chem.Ber. 21, 2452 (1888).
28. Item, ibid. 22, 337 (1889).
29. W.Herzberg and M.Polonowsky, ibid. 24, 3197 (1891).
30. C.Donald and T.H.Reade, J.Chem. Soc. 53 (1935).
31. G.Schroll, R.G.Cooks, P.Klemmensen, and S.-O.Lawesson, Arkiv Kemi 28, 413 (1968).
32. T.-L.Ho, Hard and Soft Acids and Bases Principle in Organic Chemistry, Academy Press, 1977.
33. R.G.Pearson, Hard and Soft Acids and Bases, Dowden, Hutchinson and Ross, Inc., 1973, and references cited therein.
34. K.Al.-Mallah, P.Collings, and G. Stedman, J.Chem.Soc., Dalton, 2469 (1974).
35. L.Knorr, Liebigs Ann.Chem. 301, 1 (1898).
36. L.Médar, Bull.Soc.Chim.France 3, 1343 (1936).
37. S.Komori, M.Okahara, and E.Shinsugi, Technol.Rept.Osaka Univ. 8, 497 (1958).
38. H.Staudinger and N.Kon, Liebigs Ann.Chem. 384, 38 (1911).
39. O.Schmidt, Chem.Commun. 36, 2459 (1903).
40. Handbook of Chemistry and Physics, 59th Edition, 1976-77.
41. E.Beckmann, Chem.Ber. 23, 3331 (1890).
42. A.Weiss, Monatshefte für Chemie 40, 401 (1909).

43. C.A.Buehler and C.A.Mackenzie, J. Am.Chem.Soc. 59, 421 (1937).
44. J.Perregaard, S.Scheibye, H.J. Meyer, I.Thomsen, and S.-O.Lawesson, Bull.Soc.Chim.Belg. 86, 679 (1977).
45. K.V.Auwers and K.Schwegler, Chem. Ber. 53, 1211 (1920).
46. C.A.Bishoff and A.von Hedenström, ibid. 35, 3431 (1902).
47. E.Biilmann, Liebigs Ann.Chem. 348, 120 (1906).
48. O.Billeter and A.Strohl, Chem.Ber. 21, 102 (1888).
49. A.W.Hofmann, ibid. 2, 116 (1869).