Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8433–8435

Preparation and structural characterization of a new class of stable thioketones: *ortho*-hydroxythioacetophenones

Trung Thanh Nguyen,[a,†] Thach Ngoc Le,[b] Poul Erik Hansen[a] and Fritz Duus[a,*]

[a]*Department of Life Sciences and Chemistry, Roskilde University, PO Box 260, DK-4000 Roskilde, Denmark*
[b]*Department of Organic Chemistry, University of Natural Sciences, National University of Hochiminh City, 227 Nguyen Van Cu St., Dist. 5, Hochiminh City, Viet Nam*

Received 28 June 2006; revised 25 August 2006; accepted 7 September 2006
Available online 5 October 2006

Abstract—*ortho*-Hydroxythioacetophenone and four structurally related *ortho*-hydroxyaryl methyl thioketones have been prepared from the corresponding ketones by reaction with gaseous H_2S and HCl in ethanol under strictly controlled reaction conditions. The remarkable stability of the new monomeric thioketones seems to be due to a strong intramolecular O–H···S=C hydrogen bonding.

1. Introduction

Since Woodward et al.[1] reported in 1960 the existence of the first stable thioaldehyde and, not least, also its importance as a precursor in the total synthesis of chlorophyll *a*, thiocarbonyl compounds have attracted increasing attention as auxiliaries in organic synthesis.[2,3] However, the sulfur analogue of acetophenone, thioacetophenone, as well as substituted analogues thereof, have not been studied as much, doubtless because of their instability as monomeric species.[2] As far back as 1895, Baumann and Fromm proclaimed that thioacetophenone cannot exist in a monomeric form, a cyclic trimeric form referred to as 'trithioacetophenone', that is, 2,4,6-trimethyl-2,4,6-triphenyl-1,3,5-trithiane, being found to represent the most well-defined form of thioacetophenone.[4] This finding was later corroborated by Campaigne and his co-workers,[5,6] who reported that monomeric thioacetophenone could be obtained as a reactive, but short-lived species, from its trimeric form, by heating above its melting point. A useful synthetic procedure to prepare trimeric thioacetophenone (in a 80% yield) from acetophenone by reaction with gaseous H_2S and gaseous HCl in ethanolic solution was published by Douglass and Hydro in 1951.[7]

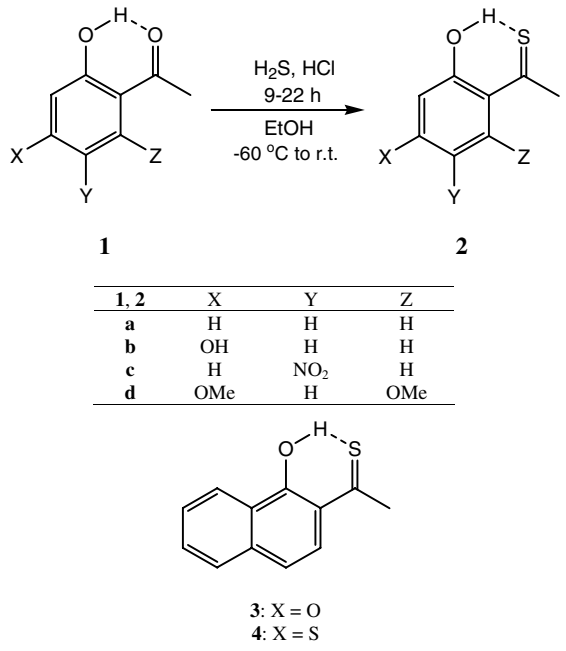
In connection with our studies on intramolecular hydrogen bonding in tautomeric β-thioxocarbonyl molecules,[8–10] *ortho*-hydroxythioacetophenones appeared as attractive new target molecules. An extensive search confirmed that such compounds have hitherto not been synthesised in the laboratory, although they have attracted attention at the theoretical level.[11] On the other hand, *ortho*-hydroxythiobenzophenone has been known since 1957, when Westheimer and his co-workers[12] reported its preparation from *ortho*-hydroxybenzophenone by reaction with gaseous H_2S and HCl in ethanolic solution, and on its successful isolation by preparative chromatography. 5-Methyl-2-hydroxythiobenzophenone was prepared by the same method in 1979.[13] Encouraged by these reports we ventured to synthesise a representative selection of *ortho*-hydroxythioacetophenones, believing that the presence of the *ortho*-hydroxy group would stabilise the thiocarbonyl group by enforcing a strong intramolecular hydrogen bonding.[8]

2. Results and discussion

Thioketones are known to be strongly coloured compounds, non-aromatic representatives being shades of orange to red, and aromatic counterparts being shades of red, through purple, to blue.[2] Since ketones are usually colourless compounds, the conversion of these into the corresponding thioketones can be monitored by the change in the colour of the reaction mixture during the

Keywords: Thioketone synthesis; β-Hydroxythioketones; Intramolecular hydrogen bonding.
* Corresponding author. Tel.: +45 46742434; fax: +45 46743011; e-mail: fd@ruc.dk
† On leave from the University of Natural Sciences, National University of Hochiminh City, Viet Nam.

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.09.033



1, 2	X	Y	Z
a	H	H	H
b	OH	H	H
c	H	NO_2	H
d	OMe	H	OMe

Scheme 1.

course of the reaction. The *ortho*-hydroxythioacetophenones were prepared according to the same reaction principle as described for *ortho*-hydroxythiobenzophenone,[12] that is, by treating the *ortho*-hydroxyacetophenone in ethanolic solution with gaseous H_2S and HCl (Scheme 1). However, in order to avoid oligomerization or trimerization[4–6,14] of the products, as well as the formation of unwanted by-products such as *gem*-dithiols,[2,14–16] a careful control of the substrate concentration, reaction temperature, and of the intensity and duration of the supply of the reacting gases was required.

The preparation of *ortho*-hydroxythioacetophenone **2a** is described in detail below.[17] Somewhat surprised by the slowness of the thionation reaction, we decided to follow the same procedure for the preparation of the four related *ortho*-hydroxyaryl methyl ketones **2b–d**, and **4**, albeit using more dilute solutions of the starting materials. However, the duration of the second H_2S supply as well as deciding the final reaction temperature were determined on the basis of inspection of the colour of the reaction mixture (Table 1). In order to avoid unpleasant smells in the laboratory (in particular from excessive very toxic gaseous H_2S), the experimental equipment was fitted with an efficient outlet trap containing aqueous lead(II) acetate.

Table 2. Characteristic ^1H and ^{13}C NMR chemical shifts of new thioketones **2a–d** and **4**

Cpd	^1H NMR		^{13}C NMR	
	$\delta(OH)$	$\delta(CH_3)$	$\delta(C{=}S)/\delta(C{=}O)$	$\delta(CH_3)$
2a	13.35	3.12	234.93	39.73
1a	12.26	2.62	204.56	26.60
2b[b]	13.70	3.07	230.56	39.21
1b[b]	12.74	2.54	203.72	26.24
2c	13.87	3.23	234.84	40.37
1c	12.87	2.74	204.06	26.93
2d	14.21	3.15	231.76	44.73
1d	14.02	2.60	203.15	32.91
4	15.27	3.15	230.25	40.08
3	14.00	2.65	204.18	26.74

For comparison, the corresponding chemical shifts of the ketones **1a–d** and **3** have also been included[a].

[a] ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Varian Mercury 300 NMR spectrometer. Unless stated otherwise, the spectra were recorded on ca. 0.1 M solutions in $CDCl_3$.

[b] Solvent: acetone-d_6.

The five new thioketones were analysed and characterised structurally by ^1H and ^{13}C NMR spectroscopy (Table 2). They all appeared to be true thioketones, there being no evidence for the existence of a tautomeric enol–enethiol equilibrium system as observed for the related tautomeric β-thioxoketones.[8–10,16,18,19] This conclusion can be drawn unambiguously on the basis of the observed ^{13}C NMR chemical shifts $\delta(C{=}S)$ and $\delta(CH_3)$, which are characteristically shifted by 26–31 ppm and 11.8–13.3 ppm, respectively, relative to the related chemical shifts of the corresponding ketones (Table 2).[20,21] The observed ^1H NMR chemical shifts of the thioacetyl protons are 0.49–0.55 ppm higher than those of the acetyl protons of the corresponding ketones, which is consistent with the ca. 0.55 ppm reported for aliphatic methyl thioketones.[22] However, the most interesting observation is that the ^1H NMR chemical shift of the *ortho*-hydroxy proton for all the thioketones is higher than the same chemical shift of the corresponding ketones, the difference being ca. 1 ppm for compounds **2a/1a**, **2b/1b**, **2c/1c**, and **4/3**, and ca. 0.2 ppm for **2d/1d**. This observation allows the conclusion that the intramolecular O–H···S=C hydrogen bonding in the thioketones is even stronger than the corresponding hydrogen bonding in the parent

Table 1. Preparation of thioketones **2** and **4** from corresponding ketones **1** and **3** (Scheme 1)[a]

Starting material	Concentration (Solvent: EtOH) (M)	Second supply of H_2S (duration (h), final reaction temp.)	Product	Yield (GC/MS) (%)	Method of purification[b]
1a	0.6	7 (−30 °C)	**2a**	41	CC
1b	0.07	22 (−10 °C)	**2b**	63	PLC
1c	0.03	16 (−20 °C)	**2c**	10	CC
1d	0.05	22 (rt)	**2d**	7–10	CC
3	0.05	22 (−10 °C)	**4**	77	CC

[a] The first H_2S supply, in all cases: 1 h (at −60 °C). The following supply of gaseous HCl, in all cases: 1 h (at −60 °C to −40 °C).

[b] CC: Column chromatography.[17] PLC: Preparative layer chromatography (silica gel; eluent: $CHCl_3$/MeOH, 4:1).

ketones.[8,9,18] This finding also offers an explanation for the existence of the thioketones as monomeric species: a thiocarbonyl group engaged in strong intramolecular hydrogen bonding apparently is better protected and hence more resistant towards cyclic trimerization. Furthermore, the comparatively stronger intramolecular hydrogen bonding in the thioketones also nicely explains the fact that the thioketones are always eluted first in column chromatography.[17] Full NMR spectroscopic data for all new thioketones are given below.[23]

Acknowledgement

We thank DANIDA for financial support via the ENRECA programme.

References and notes

1. Woodward, R. B.; Ayers, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Gloss, G. L.; Dutter, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemann, A.; LeGoff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Voltz, H. *J. Am. Chem. Soc.* **1960**, *82*, 3800–3802.
2. Duus, F. *Thiocarbonyl Compounds*, in *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Vol. 3; Jones, D. N., Vol. Ed; Pergamon Press: Oxford, 1979; Chapter 11.22, 373–487, and references cited therein.
3. Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Academic Press: Bodmin, 1994; pp 30–50, and references cited therein.
4. Baumann, E.; Fromm, E. *Ber.* **1895**, *28*, 895–907.
5. Cline, J. K.; Campaigne, E.; Spies, J. W. *J. Am. Chem. Soc.* **1944**, *66*, 1136–1137.
6. Campaigne, E.; Rutan, P. V. *J. Am. Chem. Soc.* **1947**, *69*, 1211.
7. Douglass, I. B.; Hydro, W. R. *J. Am. Chem. Soc.* **1951**, *73*, 3507.
8. Duus, F. *J. Am. Chem. Soc.* **1986**, *108*, 630–638.
9. Andresen, B.; Duus, F.; Bolvig, S.; Hansen, P. E. *J. Mol. Struct.* **2000**, *552*, 45–62.
10. Posokhov, Y.; Gorski, A.; Spanget-Larsen, J.; Duus, F.; Hansen, P. E.; Waluk, J. *Chem. Phys. Chem.* **2004**, *5*, 495–502.
11. Korth, H.-G.; de Heer, M. I.; Mulder, P. *J. Phys. Chem. A* **2002**, *106*, 8779–8789.
12. Abeles, R. H.; Hutton, R. F.; Westheimer, F. H. *J. Am. Chem. Soc.* **1957**, *79*, 712–716.
13. Uhlemann, E.; Bukowsky, H. *Z. Chem.* **1979**, *19*, 226–227.
14. Duus, F.; Lawesson, S.-O. *Arkiv Kemi* **1968**, *29*, 127–138.
15. Duus, F. *Tetrahedron* **1972**, *28*, 5923–5947.
16. Duus, F.; Anthonsen, J. W. *Acta Chem. Scand.* **1977**, *B31*, 40–46.
17. Preparation of *ortho*-hydroxythioacetophenone **2a**: Fifty millilitres of a 0.6 M solution of *ortho*-hydroxyacetophenone **1a** was cooled to −60 °C and saturated with gaseous H_2S for 1 h. Subsequently, gaseous HCl was supplied also for 1 h, during which time the temperature was allowed to rise to −40 °C, and the initially colourless reaction mixture changed through yellow to orange. Then more gaseous H_2S was supplied gently for 7 h, the colour of the reaction mixture becoming deep red, whilst the reaction temperature was kept at −30 °C. Since no further enhancement of the intensity of the colour could be observed, the reaction was stopped. The reaction mixture was poured cautiously into an efficiently stirred mixture of 300 mL of ice water and 200 mL of diethyl ether (attention: liberation of dissolved gases!). The red ethereal layer was separated from the colourless aqueous layer, dried (Na_2SO_4), and evaporated to leave a dark red oil, which was found by GC/MS to contain a mixture of the desired product **2a** (41%) and the starting material (59%). The product was subsequently isolated quantitatively as the first fraction by column chromatography (silica gel; eluent: chloroform (carcinogenic to humans!)/ethyl acetate, 9:1). ^1H and ^{13}C NMR spectra, as well as GC/MS analyses[24] confirmed the identity and analytical purity of the product.
18. Berg, U.; Sandström, J.; Carlsen, L.; Duus, F. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1321–1325.
19. Nørskov-Lauritsen, L.; Carlsen, L.; Duus, F. *J. Chem. Soc., Chem. Commun.* **1983**, 496–498.
20. Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley and Sons: Chippenham, 1991; p 191 and pp 209–211.
21. Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223–228.
22. Paquer, D.; Vialle, J. *Bull. Soc. chim. Fr.* **1969**, 3595–3601.
23. Full NMR spectroscopic data (cf. Table 2) of the new thioketones. *ortho*-Hydroxythioacetophenone, **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 13.35 (d, $J = 0.4$ Hz, 1H), 7.88 (dd, $J = 8.3$, 1.5 Hz; 1H), 7.46 (dddd, $J = 8.5$, 7.2, 1.5, 0.4 Hz; 1H), 7.07 (dd, $J = 8.5$, 1.5 Hz; 1H), 6.89 (ddd, $J = 8.3$, 7.2, 1.5 Hz; 1H), 3.12 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 234.93, 162.79, 136.74, 127.66, 127.11, 120.27, 118.65, 39.73. 2,4-Dihydroxythioacetophenone, **2b**: ^1H NMR (300 MHz, acetone-d_6) δ 13.70 (s, 1H), 9.88 (s, 1H), 7.97 (d, $J = 9.6$ Hz, 1H), 6.49 (dd, $J = 9.6$, 2.7 Hz; 1H), 6.43 (d, $J = 2.7$ Hz, 1H), 3.07 (s, 3H). ^{13}C NMR (75 MHz, acetone-d_6) 230.56, 167.29, 166.48, 132.22, 123.69, 109.65, 104.57, 39.21. 2-Hydroxy-5-nitrothioacetophenone, **2c**: ^1H NMR (300 MHz, $CDCl_3$) δ 13.87 (s, 1H), 8.91 (d, $J = 2.7$ Hz, 1H), 8.33 (dd, $J = 9.3$, 2.7 Hz; 1H), 7.20 (d, $J = 9.3$ Hz, 1H), 3.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 234.84, 166.84, 138.36, 130.52, 124.47, 124.05, 121.42, 40.37. 2-Hydroxy-4,6-dimethoxy-thioacetophenone, **2d**: ^1H NMR (300 MHz, $CDCl_3$) δ 14.21 (s, 1H), 6.15 (d, $J = 2.5$ Hz, 1H), 5.94 (d, $J = 2.5$ Hz, 1H), 3.85 (s, 6H), 3.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 231.76, 166.74, 165.67, 161.62, 117.62, 94.40, 91.50, 55.69 (2C), 44.73. 1-Hydroxy-2-thioacetonaphthone, **4**: ^1H NMR (300 MHz, $CDCl_3$) δ 15.27 (s, 1H), 8.56 (dm, $J = 8.3$ Hz, 1H), 7.75 (d, $J = 9.3$ Hz, 1H), 7.70 (dd, $J = 8.0$, 1.5 Hz; 1H), 7.63 (ddd, $J = 8.0$, 6.8, 1.3 Hz; 1H), 7.51 (ddd, $J = 8.3$, 6.8, 1.5 Hz; 1H), 7.19 (d, $J = 9.3$ Hz, 1H), 3.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 230.25, 163.65, 137.28, 130.76, 127.40, 126.40, 126.26, 125.63, 123.15, 122.00, 118.05, 40.08.
24. The GC/MS analyses were performed on a Hewlett Packard 5890 GC-5971A MS apparatus equipped with a J&W DB-5MS capillary column (30 m, 0.25 mm i.d., 0.25 μm film thickness) and a Hewlett Packard 7673A autosampler.