Pergamon

Tetrahedron Letters 40 (1999) 6253–6256

TETRAHEDRON
LETTERS

An Unexpected Sequel of an Alcohol Oxidation Study: Stereoselective Cyclisation of an Unsaturated Keto-Sulfide

T. Zoller, P. Breuilles and D. Uguen*

Laboratoire de Synthèse Organique, associé au CNRS
Ecole Européenne de Chimie, Polymères et Matériaux, Université Louis Pasteur
25, rue Becquerel; 67087 Strasbourg (France)

A. De Cian and J. Fischer

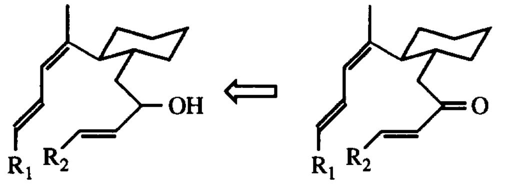
Laboratoire de Cristallochimie, associé au CNRS
Université Louis Pasteur; 67070 Strasbourg (France)

Received 19 May 1999; accepted 1 July 1999

Abstract: Whereas the ketones **1** were obtained in high yield by reacting the allylic alcools **2** with the IBX reagent, treatment of the phenylthio-substituted alcohol **2d** with $BaMnO_4$ afforded, besides the expected ketone **1d**, the keto-aldehyde **3**, presumably formed from **1d** by a free-radical chain process.

As explained in the preceding letter, we needed to prepare unsaturated ketones with structure **1** in order to study their intramolecular Diels-Alder reaction. A conceivable way for obtaining these compounds was, as represented, to oxidise the corresponding allylic alcohols **2** and indeed both **2a** and its *E* isomer *E*-**2a** could be efficiently converted into the ketones **2a and** *E*-**2a**, respectively, by using either freshly-prepared manganese dioxide or $BaMnO_4$ in methylene chloride.[1a]

These oxidation conditions appeared not general however. Hence, attempt to obtain the keto sulfone **1b** by reacting the hydroxy sulfone **2b** with these reagents proved not really useful, the desired oxidation product **1b** being then formed in low yield, with extensive degradation of the starting material. Other reagents (*i.a.* Swern, nickel peroxide) gave also poor results but we succeeded finally by using the Dess-Martin periodinane (DMP), a very high yield in ketone **1b** being then achieved.[1b]



2a-e (R_1, R_2 as in **1**)

1a, $R_1=R_2=H$
1b, $R_1=H$; $R_2=SO_2Ph$
1c, $R_1=H$; $R_2=CO_2Me$
1d, $R_1=SPh$; $R_2=H$
1e, $R_1=SPh$; $R_2=Tosyl$

The use of the DMP reagent for preparing similarly the phenylthio-substituted derivatives **1d** and **1e** appeared more problematic since a possible oxidation of the thioether functionality of these compounds, with formation of the corresponding sulfoxide (or sulfone), could compete with the desired oxidation process. Indeed, reacting **2d** with this reagent afforded the ketone **1d** in poor yield (44%), besides various overoxidation products.

0040-4039/99/$ - see front matter © 1999 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)01298-8

Examination of the relevant literature suggested that either the IBX reagent,[2a] which is an intermediate in the current preparation of the DMP reagent,[2b] or manganese dioxide[2c] might oxidise selectively the allylic alcohol of **1d** (or **1e**) without affecting the dienylsulfide. Indeed, stirring **2d** with the former reagent in DMSO afforded the target ketone **1d** in high yield, with an efficiency that proved to be general (Table).[3]

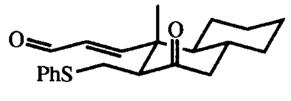
Table: Oxidation of the alcohols **2** by the IBX reagents

Substrate	Product	Yield
2a	**1a**	100 %
***E*-2a**	***E*-1a**	100 %
2b	**1b**	94 %
2c	**1c**	97 %
2d	**1d**	86 %
2e	**1e**	91 %

Notwithstanding this success, the oxidation of **2d** by BaMnO4 was also tried since the preparation of this reagent, whose reactivity parallels that of manganese dioxide, is really straightforward.

Though the expected oxidation took place effectively, formation of a side product was noticed by TLC and after a few hours at room temperature, a column chromatography on silica gel of the crude reaction mixture permitted to isolate, besides the desired ketone **1d** and unreacted **2d** (25%), a less polar, unique (^{13}C NMR, GLC), compound, whose NMR (^{1}H, ^{13}C) analysis indicated the presence of both a saturated ketone and an α-β-unsaturated aldehyde.[4] Further high-field NMR experiments (COSY, NOESY, ^{1}H-^{13}C correlation, HMBC) strongly suggested the structure **3** for this new product, which was confirmed by its reaction with excess 2,4-dinitrophenylhydrazine. Recrystallisation from hot dioxane of the bis-DNPH derivative which then formed furnished a single crystal suitable for X-ray analysis.

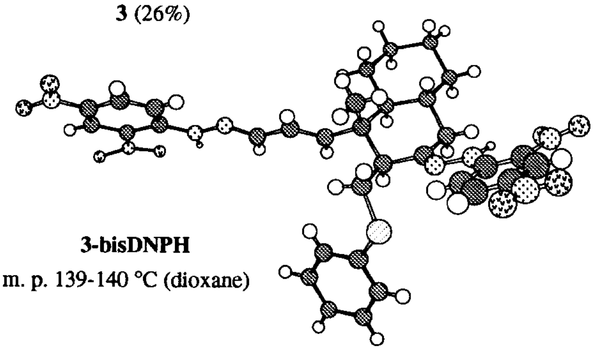
2d $\xrightarrow{1}$ **1d** (27 %) +



$\xrightarrow{2}$ **3-bisDNPH**

3 (26%)

Reagents and conditions: 1- see ref. 4; 2- 2,4-dinitrophenylhydrazine (5.6 eq.), 1% solution of HCl (25%, aqueous) in MeOH; 45 °C, 10 min (67%, after recristallisation from hot dioxane).

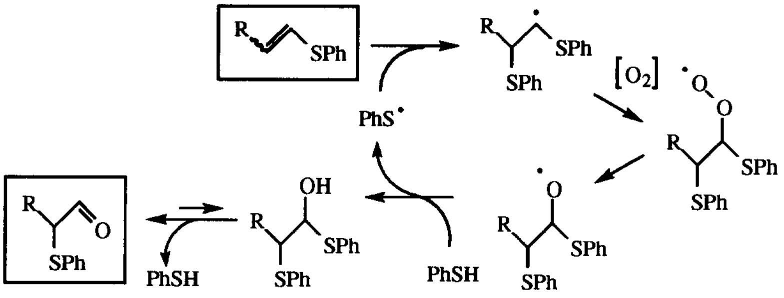


3-bisDNPH

m. p. 139-140 °C (dioxane)

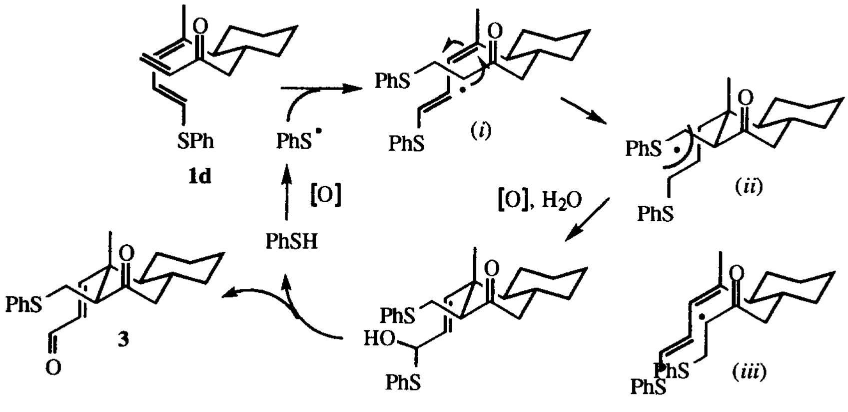
The Chem3D® structure shown, generated from crystal data,[5] confirms clearly the structure **3**, deduced from the preceding high-field NMR experiments.

In quest for a rationale for this unexpected cyclisation process, we found in literature that vinyl phenylsulfides had previously been shown to afford α-phenylthio aldehydes under oxidative (anodic) conditions,[6a] a conversion that was later demonstrated to occur by the indicated free-radical chain-transfer pathway.[6b]



(from ref. 6b)

Accordingly, a possible explanation for the formation of 3 is that the normal, leading to **1d**, oxidation process was accompanied by partial oxidation of the phenylthiobutadiene residue of **2d** (or **1d**) with formation of thiophenol. In the event, a possible, kinetically-favoured on an electronic ground, process could be, as represented below, addition of the thiyl radical formed by oxidation of PhSH to the enone moiety of **1d** to give the α-keto free radical (*i*), which would then cyclised to afford the α-phenylthio-substituted allylic radical (*ii*). Due to the development of a severe steric interaction between the phenylthiovinyl and the phenylthioethyl residue in the alternate conformer *(iii)*, this intramolecular free-radical addition should proceed with the indicated stereoselectivity via (*i*), where no such interaction develops when the phenylthio substituent occupies a pseudo-equatorial position. Oxidation of the radical (*ii*) into the corresponding cation, followed by hydration and decomposition of the resulting hemi-thioacetal would then produced the keto aldehyde 3, effectively observed, and thiophenol.



Hypothetical pathway for the 1d-3 conversion

In order to test the validity of this hypothetical chain pathway, a CH_2Cl_2 solution of the vinylic ketone **1d** and of traces of thiophenol was stirred in the air with the hope that the phenythio radical, which should then form, will induce the formation of 3. Though the resulting crude reaction product was not as clean as that formed by treatment of **2d** with $BaMnO_4$, formation of the aldehyde 3 could be proved by NMR after fractionation by column chromatography.

In summary, the IBX reagent proved to be very efficient for oxidising alcohols with structure **2** into the corresponding unsaturated ketones **1**, especially in cases where the starting alcohol was additionally substituted with the sensitive phenylthio residue (e.g. **2d**). Though of moderate interest with regards to our initial synthetic purpose, the use of $BaMnO_4$ for mediating the **2d**-**1d** conversion resulted in the formation of the keto aldehyde **3** probably by a cyclisation process induced by the addition of a phenylthio radical to the enone **1d**. Obviously, additional experiments will be necessary to clarify the precise nature of the involved oxidising species. It is clear, however, given the high stereoselectivity observed, that this process should be of value for synthesizing various polycyclic compounds. Results along these lines will be published in due course.

Acknowledgements: Thanks are due to the Région Alsace and the C.N.R.S. for a grant (to T. Z.) and to Dr. S. Sablé (Rhône-Poulenc Rorer Vitry-sur-Seine) for the high-field NMR experiments.

References and Notes

1- a) Zoller, T.; Uguen, D.; De Cian, A.; Fischer, J.; Sablé, S. *Tetrahedron Lett.* **1997**, *38*, 3409-3412, and references cited therein; b) Zoller, T.; Uguen, D. *Eur. J. Org. Chem.* **1999**, *4*, 1545-1550.

2- a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272-7276; b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287; c) Fatiadi, A. J. *Synthesis* **1976**, 65-104 and 133-167.

3- *Protocol for the oxidation of the alcohols **2a-d** with the IBX reagent*: According to ref. 2a, IBX (1.8 eq.) was added to a stirred solution of the alcohol **2** in DMSO (3 ml/mmol) under an argon atmosphere, with development of a yellow colour. After 30 min at room t., a white precipitate formed. The mixture was stirred for 30 min, then diluted with water (50 ml/mmol) and ether (50 ml/mmol), and filtered. The aqueous layer was further extracted with ether and the pooled organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The oily residue thus left was chromatographed over a column of silica gel (hexane/AcOEt mixtures) to afford the pure ketone **1**. Compounds **1a**, ***E*-1a** and **1b** have been previously described (see ref. 1). All new compounds have been fully characterised by NMR, mass, and IR spectroscopies, and by elemental analysis.

4- Finely-grounded $BaMnO_4$ (1.56 g; 6.08 mmol) was added all at once to a solution of the alcohol **2d** (200 mg; 0.61 mmol) in deaerated CH_2Cl_2 and the resulting mixture was stirred for two days at room t. under an argon atmosphere, then filtered on Celite®. The residue left by evaporation of the solvents was chromatographed on a column of silica gel (hexane/AcOEt mixtures) to afford successively: *i)* the ketone **1d** (53 mg; 27%); *ii)* unreacted **2d** (48 mg); *iii)* the keto-aldehyde **3** (55 mg; 26%); **3**: ^{13}C NMR ($CDCl_3$): 12, 25.6, 26.2, 27.1, 28.6, 35.1, 39.6, 49, 50.2, 50.6, 59, 126.7, 129, 130.5, 132.3, 135.9, 163.3, 193.3, 207.1.

5- Crystal data of **3-bisDNPH**: $C_{41}H_{50}N_8O_{12}S$ ($C_{33}H_{34}N_8O_8S{\bullet}2O_2C_4H_8$): $M = 878.97$, monoclinic, space group $P2_1/c$, $a = 15.792(1)$, $b = 10.779(1)$, $c = 25.066(3)$ Å, $\beta = 90.278(8)$ °, $V = 4266$ Å^3, $Z = 4$, $r_{calcd} = 1.37$ gcm^{-3}, μ(MoKα) = 0.140 mm^{-1}. Data were collected on a Nonius CAD4 diffractometer using MoKα graphite monochromated radiation ($\lambda = 0.71073$ Å) at -100°C. A yellow crystal of dimensions 0.25*0.25*0.20 mm^3 was used and a total of 9342 reflections was collected, $2.5° < \theta < 26.29°$. 3884 reflections having $I > 3\sigma(I)$ were used for structure determination and refinement. Absorption corrections from the psi scans of 7 reflections, transmission factors : 0.94/1.00. The structure was solved using direct methods and refined against $|F|$. Hydrogen atoms were introduced as fixed contributors with the exception of the two N and the eight protons of one solvent molecule. For all computations the Nonius OpenMoleN package (OpenMoleN, Interactive Structure Solution, Nonius B.V., Delft, The Nederlands (1997)) was used. Final results : $R(F) = 0.070$, $Rw(F) = 0.098$, $GOF = 1.86$, maximum residual electronic density = 0.93 eÅ^{-3}.

6- a) Matsumoto, A.; Suda, K.; Yijima, C. *J. Chem. Soc. Chem. Commun.* **1981**, 263; b) Yoshida, J.-I.; Nakatani, S.; Isoe, S. *J. Org. Chem.* **1993**, *58*, 4855-4865.