Facile Deacylation of *N*-Acyl-2,3-dihydrobenzo-1,4-thiazine 1-Oxide and 1,1 Dioxide

*Saverio Florio**

Istituto di Chimica Organica, Università, via Amendola 173, 70126 Bari, Italy

John L. Leng

ICI Blackley Manchester, United Kingdom

Charles J. M. Stirling

University College of North Wales, Bangor, United Kingdom

Received February 4, 1981

The title amides react easily with methanolic sodium methoxide at room temperature affording 2,3-dihydrobenzo-1,4-thiazine 1-oxide and 1,1-dioxide and methylacetate. An unusual mechanism of deacylation is proposed.

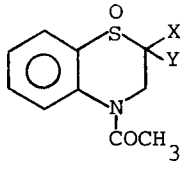
J. Heterocyclic Chem., **18**, 857 (1981).

It is well known that common amides are rather reluctant to undergo hydrolysis or solvolysis (1). The reaction, thoroughly examined because of its relevance to the behaviour of proteins and peptides, can be effected, however, with the assistance of either base and acid catalysts and prolonged heating.

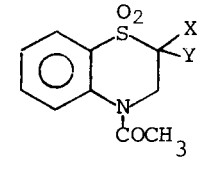
We have found that *N*-acetyl-2,3-dihydrobenzo-1,4-thiazine 1-oxide **1** and 1,1-dioxide **2**, obtained by oxidation of the corresponding *N*-acetylsulphides **3** with *m*-chloroperbenzoic acid in dichloromethane or hydrogen peroxide in water/methanol, undergo facile deacetylation simply by refluxing in dry methanol or, much more rapidly, on treatment with methanolic sodium methoxide at room temperature leading to 2,3-dihydrobenzo-1,4-thiazine 1-oxide **4** and 1,1-dioxide **5**, respectively, and methylacetate in quantitative yield. A few heterocyclic amides have been reported to exhibit a similar behaviour (2).

In contrast, *N*-acetylsulphides **3** could not be deacetylated except under rather severe conditions (reflux and long reaction time).

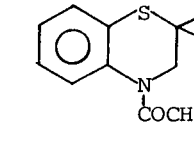
Then, the sulphoxide and sulphonyl groups probably play a determining role in the deacetylation. The reaction, followed titrimetrically, does not consume base, which therefore would have only a catalytic effect. The second order rate constants, measured spectrophotometrically (see Table), turned out to be fairly high and this could be probably due to the polar effect of the -SO- and SO_2-groups, which on one hand enhance the electrophilic character of the carbonyl group and on the other help to



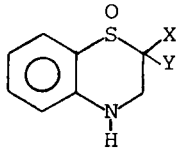
1 a): X=H; Y=Cl
b): X=Y=Cl



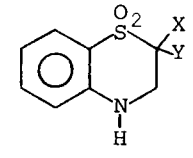
2 a): X=Y=H
b): X=H ; Y=Cl
c): X=Y=Cl



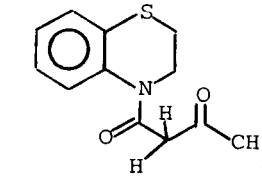
3 a): X=Y=H
b): X=H ; Y=Cl
c): X=Y=Cl



4 a): X=H ; Y=Cl
b): X=Y=Cl

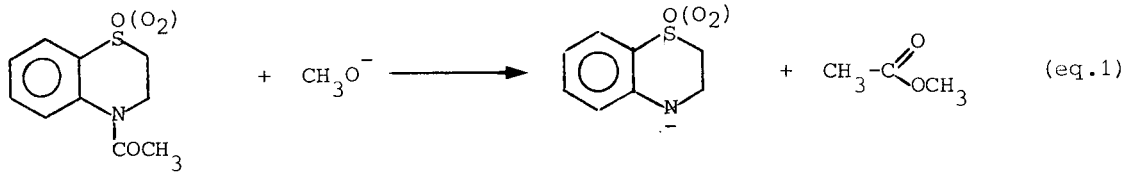


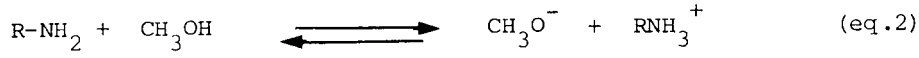
5 a): X=Y=H
b): X=H ; Y=Cl
c): X=Y=Cl



6

0022-152X/81/040857-03$02.25





stabilize the negative charge on the nitrogen atom, thus making the benzothiazinyl residue a good leaving group (equation 1). The deacetylation has been found to be further accelerated by electron-withdrawing substituents (halogens) in position 2 of the heterocyclic ring. As for the halogens in that position, we have observed that they are, as expected (3), not affected by the nucleophile (methoxide).

Specifically in the case of **2a**, other bases have been used to carry out the deacetylation and it has been observed that only fairly strong anionic bases like alkoxides (sodium ethoxide, potassium *t*-butoxide) in the corresponding alcohols, lithium[2,2,6,6]tetramethylpiperidide and *n*-butylmagnesium bromide in dry tetrahydrofuran caused reaction, while neutral bases such as triethylamine, *n*-butylamine and 1,4-diazobicyclo[2,2,2]octane in tetrahydrofuran and sodium acetate, phenoxide and thiophenoxide (despite its well recognized nucleophilic properties) in dimethylsulphoxide did not bring about deacetylation. Also *n*-butylamine was capable of inducing deacetylation when treated with **2a** in methanol, but the product of the reaction was not the *n*-butylacetamide but the methylacetate. This could be due to the equilibrium which exists between the amine and the methanol (equation 2). The methoxide thus generated would then react with the sulphone leading to the methylacetate.

The sulphone **2a**, recovered after a short treatment with sodium methoxide in deuteromethanol and quenching with deuterohydrochloric acid, revealed deuterium hydrogen exchange at the methyl group of the acetyl function.

These findings seem to suggest that the abstraction of a proton is the crucial point of the reaction and that suitable bases must be used. Therefore, an EA mechanism of the kind depicted in the Scheme might be hypothesized. According to this mechanism, which is unusual for the deacylation of the amides (4), the base abstracts an α-proton giving, on release of the benzothiazine moiety (Het^- in the Scheme), the ketene as an intermediate, which then reacts with the conjugate acid BH affording the new acetylated product.

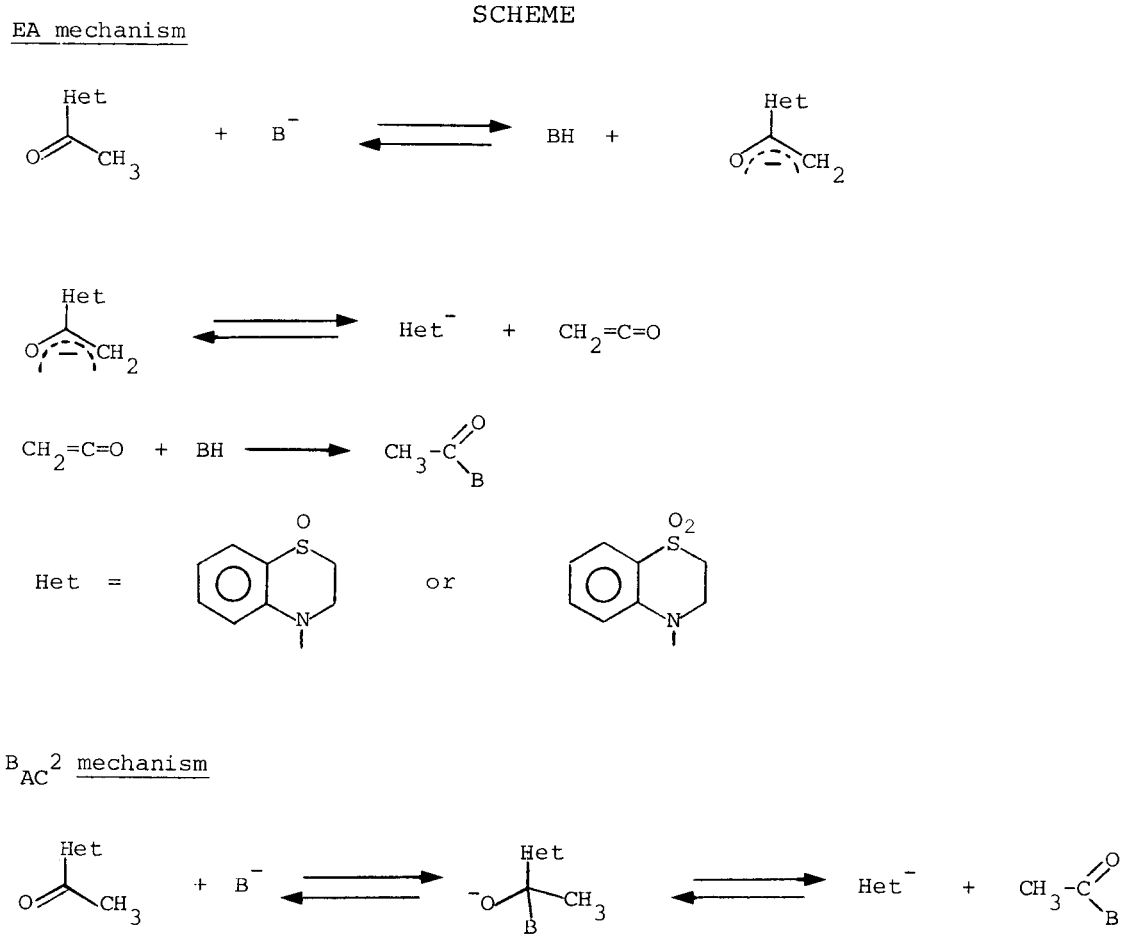
We also came to this conclusion by considering first the fact that sulphide **3a**, which had been found to be inert toward sodium methoxide, reacted rapidly with *n*-butyllithium or *n*-butylmagnesium bromide providing the compound **6** (5), whose formation has been accounted for by assuming a basic behaviour of the organometallic according to a Claisen-type condensation mechanism. This seems to indicate that either in the reaction of **2a** or **3a** with *n*-butylmagnesium bromide, the first step of the whole process is the abstraction of an α-proton. However, the corresponding enolates have a quite different fate, the

Table

Second Order Rate Constants ($mol^{-1}s^{-1}l$) for the Reaction of *N*-Acetyl-2,3-dihydrobenzo-1,4-thiazine 1-Oxide and -1,1-Dioxide with Sodium Methoxide in Methanol at 27°

Substrate	Sub/M x 10^4	CH_3O^-/M x 10^3	k_2 x 10^2	λ (nm)
1a	2.5	43	7.9	325
1b	2	86	51	320
2a	4	21.3	5.3	320
2b	2	53	15.4	318
2c	3	43	316	320

SCHEME



sulphone enolate only being able to lead to the ketone upon release of the supposed mobile benzothiazinyl residue. Secondly, in the deacetylation of **2a** promoted by *n*-butylmagnesium bromide or lithium[2,2,6,6]tetramethylpiperidide (stoichiometric amount), no substitution product, potentially deriving from the nucleophilic attack of the organometallic reagent on the carbonyl of the starting amide or on the ketene, could be detected. However the same reaction carried out in the presence of an excess of the organometallic allowed us to obtain 2-hexanone.

However, at the moment, we cannot exclude that the more usual $B_{AC}2$ mechanism, which has been proposed for the deacylation of the azolides (2), might operate at least competitively with the EA mechanism.

The easy deacetylation of the *N*-acylbenzothiazine derivatives might be, in principle, exploited to synthetize a variety of compounds such as esters, ketones, aldehydes, *etc.* On the other hand, the fact that alkoxides promote rapid deacylation of the above sulphoxides and sulphones whereas amines, acetate, phenoxide and thiophenoxide do not react at all, seems to open a useful way to a selective acylation of the alcoholic groups. Further experiments are in progress to this end.

REFERENCES AND NOTES

(1) B. C. Challis and J. A. Challis, in "The Chemistry of Amides", J. Zabicky, Ed., Interscience Publishers, New York, N.Y., 1970, pp. 731-857, and references cited therein; C. O'Connor, *Q. Rev., Chem. Soc.*, **24**, 553 (1970).

(2) H. A. Staab, *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962); H. A. Staab and Rohe, *Newer Methods Prep. Org. Chem.*, **5**, 61 (1968); K. H. Scholz, H. G. Heine and W. Hartmann, *Ann. Chem.*, 1319 (1976); Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao and E. Fujita, *Tetrahedron Letters*, **21**, 841 (1980).

(3) N. Kharasch, "Organic Sulfur Compounds", Vol. 1, Pergamon Press, New York, N.Y., 1961, p. 150.

(4) F. I. Luknitskii and B. A. Vovsi, *Russ. Chem. Rev.*, **38**, 487 (1969).

(5) F. Ciminale, L. Di Nunno and S. Florio, *Tetrahedron Letters*, **21**, 3001 (1980).

Acknowledgemnt.

We thank ICI (Manchester) for the grant and Dr. D. R. Marshall (Bangor) for valuable discussions.