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RING OPENING REACTIONS 1. THE TRIAZINONE RING OPENING OF 2H-3,4-DIHYDRO-as-TRIAZINO [3,4-b] BENZOTHIAZOL-3-ONE

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Summary

The triazinone ring opening of the title compound 3 in the presence of aromatic aldehydes or ketones in hydrochloric acid or methanolic hydrochloric acid is described. The ir and nmr spectra of the resulting asymmetric azines 4 are given.

Key words: 2H-3,4-Dihydro-as-triazino [3,4-b] benzothiazol-3-one, 2-(4′-subst.-phenylidene) hydrazone-3-carb(ometh)oxymethylbenzothiazolines.

Introduction

As a part of a programme directed towards derivatives of 2-amino-benzothiazole with potential pharmacological activities, we studied the triazinone ring opening of 2H-3,4-dihydro-as-triazino [3,4-b] benzothiazol-3-one (3). Allen and Van Allan[1], in an attempt to synthesize 3-carbethoxymethyl-benzothiazoline-2-hydrazone (2a), treated 3-carbethoxymethyl-2-nitrosimino-benzothiazoline (1) with zinc in acetic acid, but the thiazinone 3 was formed instead of the desired hydrazone-ester 2a.

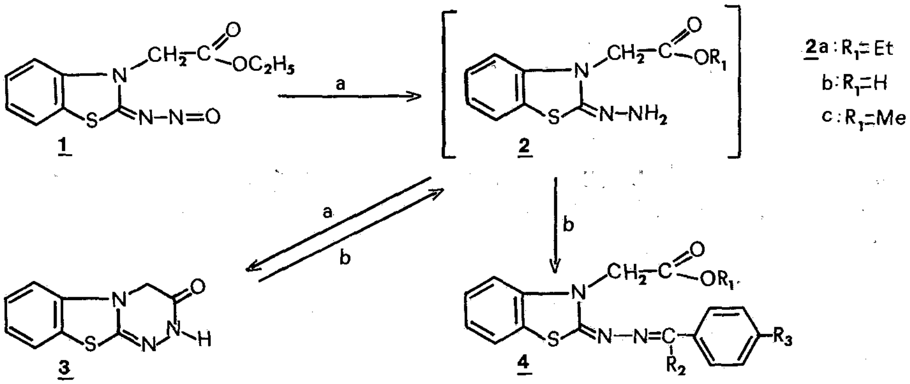
Hydrogenation of the nitrosiminoester 1 using palladium-charcoal catalyst afforded a mixture 2a and 3, which on heating in benzene or ethanol as well as in dillute hydrochloric acid gave exclusively 3[2] (Scheme 1, route a).

In this paper we report that the triazinone ring of 3 can be easily opened, affording the asymmetric azines 4, by treatment with hydrochloric acid or methanolic hydrochloric acid in the presence of aromatic aldehydes or ketones.

Results and Discussion

The required 2H-3,4-dihydro-as-triazino [3,4-b] benzothiazol-3-one (3) was synthesized according to a method described elsewhere[2], by heating under reflux 2-amino-3-carbethoxymethyl-benzothiazolium bromide[3] and hydrazine in ethanol.

Compound 3 was recovered unchanged after prolonged reflux with conc. hydrochloric acid or methanolic hydrochloric acid (see Experimental).



The triazinone ring opening of 3 was achived when refluxed with 4-subst.-benzaldehydes or -acetophenones in conc. hydrocloric acid (Scheme 1, route b), to give 2-(4' subst. -phenylidene) hydrazono-3-carboxymethylbenzothiazolines (Table I, 4a-h, R_1:H). When the reaction was carried out in methanolic hydrochloric acid the corresponding methyl esters, i.e. the 2-(4'-subst.-phenylidene) hydrazono-3-carbomethoxymethylbenzothiazolines where obtained. (Table I, 4i-p, R_1:CH_3)

The formation of the asymmetric azines 4 may be attributed to the postulated intermediates 2b and 2c, which in the absence of the carbonyl compounds recyclize to 3.

The structure of the azines 4 was confirmed by elemental analysis (Table I), ir and ^{1}H-nmr spectroscopy[4] (Table II).

All products 4 showed the characteristic vC=0 ir bands, the acid derivatives (R_1:H) at 1710 cm^{-1} – 1730 cm^{-1}, the esters (R_1:Me) at 1735 cm^{-1} – 1750 cm^{-1}.

In the ^{1}H-nmr spectra compounds 4 a, c, e, g, i, k, m, o, (R_2:H) showed a peak at δ= 8.27 - 8.50 ppm characteristic of the –N = C (H) –Ar formyl proton[5], while compounds 4b, d, f, h, j, l, n, p, (R_2:CH_3) showed a peak at δ= 2,38 - 2,46 ppm for the –N = C (CH_3) -Ar methyl group protons. In the case of compound 4h (R_1, R_2, R_3: CH_3) the protons of R_2, R_3 methyl groups gave one singlet at δ= 2.38 ppm. The peak of the ester methyl group protons of compounds 4 i-p (R_1:CH_3) appeared at δ= 3.72 - 3.78 ppm, while the peak of the ether methyl group of compounds 4g, h, o, p (R_3: OCH_3) appeared at δ= 3.84 - 3.85 ppm (Table II).

Experimental

I *Treatment of 2H-3,4-dihydro-as-triazino [3,4-b] benzothiazol-3-one (3) with a: conc. hydrochloric acid, b: methanolic hydrochloric acid.* An amount of 1.02 gr (5 mmol) of 3 in 50 ml conc. hydrochloric acid was heated under reflux for 24 hours. The resulting reaction mixture was cooled at r.t. and the precipitate filtered to give 0.95 gr of starting material, m.p. 260-262° C (Lit.[2]

TABLE I. *Compounds of general formula 4.*

	R_1	R_2	R_3	Yield %	Recryst. solvents	M.p.(°C)[6]	Molecular formula	Calculated/Found		
								%C	%H	%N
a	H	H	H	65	THF–n-Hex	207-09	$C_{16}H_{13}N_3O_2S$	61.7 61.8	4.2 3.9	13.5 13.4
b	H	CH_3	H	95	THF–n-Hex.	192-98	$C_{17}H_{15}N_3O_2S$	62.8 62.5	4.7 4.8	12.9 12.7
c	H	H	NO_2	90	EtOH	196-98	$C_{16}H_{12}N_4O_4S$	53.9 54.0	3.4 3.4	15.7 15.7
d	H	CH_3	NO_2	95	EtOH	166-68	$C_{17}H_{14}N_4O_4S$	55.1 54.8	3.8 3.8	15.1 14.8
e	H	H	CH_3	95	THF–n-Pent.	220-21	$C_{17}H_{15}N_3O_2S$	62.7 62.5	4.6 4.6	12.9 13.1
f	H	CH_3	CH_3	75	THF–n-Pent.	184-86	$C_{18}H_{17}N_3O_2S$	63.7 63.6	5.0 5.2	12.4 12.2
g	H	H	OCH_3	80	THF–n-Pent.	210-11	$C_{17}H_{15}N_3O_3S$	59.8 59.7	4.4 4.5	12.3 12.2
h	H	CH_3	OCH_3	70	THF–n-Pent.	170-71	$C_{18}H_{17}N_3O_3S$	60.8 60.5	4.8 4.7	11.8 11.6
i	CH_3	H	H	80	C_6H_6	153-54	$C_{17}H_{15}N_3O_2S$	62.7 62.7	4.6 4.6	12.9 13.2
j	CH_3	CH_3	H	70	C_6H_6–n-Pent.	105-07	$C_{18}H_{17}N_3O_2S$	63.7 63.5	5.0 5.0	12.4 12.3
k	CH_3	H	NO_2	90	THF–n-Pent.	216-18	$C_{17}H_{14}N_4O_4S$	55.1 54.8	3.8 3.9	15.1 15.3
l	CH_3	CH_3	NO_2	90	THF–n-Pent.	187-88	$C_{18}H_{16}N_4O_4S$	56.2 55.9	4.2 4.3	14.6 14.7
m	CH_3	H	CH_3	95	C_6H_6–n-Pent.	136-38	$C_{18}H_{17}N_3O_2S$	63.7 63.9	5.0 5.1	12.4 12.3
n	CH_3	CH_3	CH_3	75	C_6H_6–n-Pent.	138-40	$C_{19}H_{19}N_3O_2S$	64.6 64.3	5.4 5.3	11.9 12.0
o	CH_3	H	OCH_3	95	THF–Et_2O	146-48	$C_{18}H_{17}N_3O_3S$	60.8 60.5	4.8 4.8	11.8 11.9
p	CH_3	CH_3	OCH_3	75	THF–Et_2O	143-45	$C_{19}H_{19}N_3O_3S$	61.8 61.8	5.2 5.2	11.4 11.2

260-261°C, 95% recovery). A mixture m.p. with 3 was undepressed. I.r. spectrum was identical with that of 3, v C=O 1665 cm^{-1}. The same behavior was observed when methanol was added in the reaction mixture.

II. *2-(4′-subst.-phenylidene) hydrazono-3-carbomethylbenzothiazolines.*

(4, R_1:H). A suspension of 3 (1.02 gr 5 mmol) and 5 mmol of the appropriate benzaldeyde or acetophenone in 15 ml conc. hydrochloric acid was refluxed for 3 hrs. After cooling to room temperature the product was filtered off, washed several times with water, dried over P_2O_5 and recrystallized.

III. *2-(4′subst.-phenylidene) hydrazono-3-carbomethoxymethylbenzothiazolines.*

(4, R$_1$:Me). These derivatives were prepared in a manner similar to the above reaction, except that 20 ml methanol were added into the reaction mixture.

The physical constants, yields and solvents of recrystallisation are listed in Table I.

TABLE II. *Ir and nmr spectral data of Compounds 4.*

Compound	ν C=O cm^{-1}	^{1}H -nmr δ (ppm)
4a	1715	4.94 (s, 2H, CH$_2$), 7.25-7.92 (m, 9H, ar), 8.42 (s,1H,R$_2$)
4b	1710	2.44 (s,3H,R$_2$), 4.96 (s, 2H,CH$_2$), 7.22-7.99 (m, 9H,ar.).
4c	1730	4.92 (s,2H,CH$_2$), 7.05-8.13 (m,8H,ar.), 8.50 (s,1H,R$_2$).
4d	1725	2.46 (s,3H,R$_2$), 5.04 (s,2H,CH$_2$), 6.94-8.19 (m,8H,ar.).
4e	1710	2.35 (s,3H,R$_3$), 4.81 (s,2H,CH$_2$), 6.99-7.65 (m,8H,ar), 8.27 (s,1H,R$_2$).
4f	1725	2.36 (s,3H,R$_3$), 2.39 (s,3H,R$_2$), 4.90 (s,2H,CH$_2$), 7.04-7.82 (m,8H,ar.).
4g	1710	3.84 (s,3H,R$_3$), 4.86 (s,2H,CH$_2$), 6.98-7.76 (m,8H,ar.), 8.32 (s,1H,R$_2$).
4h	1710	2.41 (s,3H,R$_2$), 3.85 (s,3H,R$_3$), 4.95 (s,2H,CH$_2$), 6.95-7.94 (m,8H,ar.).
4i	1750	3.72 (s,3H,R$_1$), 4.99 (s,1H,CH$_2$), 7.13-7.83 (m,9H,ar.) 8.37 (s,1H,R$_2$).
4j	1750	2.40 (s,3H,R$_2$), 3.75 (s,3H,R$_1$), 5.02 (s,2H,CH$_2$), 7.03-7.93 (m,9H,ar.).
4k	1750	3.78 (s,3H,R$_1$), 5.09 (s,2H,CH$_2$), 7.06-8.17 (m,8H,ar.), 8.48 (s,1H,R$_2$).
4l	1750	2.45(s,3H,R$_2$), 3.78 (s,3H,R$_1$), 5.09 (s,2H,CH$_2$), 6.95-8.20 (m,8H,ar.).
4m	1745	2.36(s,3H,R$_3$), 3.74(s,3H,R$_1$), 4.99(s,2H,CH$_2$), 7.03-8.71(m,8H,ar) 8.34(s,1H,R$_2$).
4n	1735	2.38(s,6H,R$_2$ and R$_3$), 3.75(s,3H,R$_1$), 4.91(s,2H,CH$_2$), 7.01-7.08(m,8H,ar)
4o	1745	3.77(s,3H,R$_1$), 3.85(s,3H,R$_3$), 5.00(s,2H,CH$_2$), 6.95-7.80(m,8H,ar), 8.33(s,1H,R$_2$)
4p	1745	2.38(s,3H,R$_2$), 3.77(s,3H,R$_1$), 3.85(s,3H,R$_3$), 5.02(s,2H,CH$_2$), 6.92-7.93(m,8H,ar).

Περίληψη

Ἀντιδράσεις ἀνοίγματος δακτυλίου 1. Ἄνοιγμα τοῦ τριαζινικοῦ δακτυλίου τῆς 2H-3,4-διϋδρο-as-τριαζινο [3,4-b] βενζοθειαζολ-3-όνης.

Ἀναγωγὴ τῆς 3-καρβαιθοξυμεθυλο-2-νιτροζιμινοθειαζολίνης (1) μὲ ψευδάργυρο σὲ ὀξικὸ ὀξὺ δὲν ὁδηγεῖ στὴν ἀντίστοιχη ὑδραζόνη 2α, ἀλλὰ στὴν 2H-3,4-διϋδρο-as-τριαζινο [3,4-b] βενζοθειαζολ-3-όνη (3). Καταλυτικὴ ὑδρογόνωση τοῦ νιτροζιμινο-εστέρος 1 μὲ παλλάδιο-ἄνθρακα παρέχει μῖγμα τῶν 2α καὶ 3, τὸ ὁποῖον ὅταν θερμανθεῖ σὲ βενζόλιο ἢ αἰθανόλη ἢ ἀραιὸ ὑδροχλωρικὸ ὀξὺ δίδει ἀποκλειστικὰ τὴν as-τριαζινόνη 3[2] (Σχῆμα 1, πορεία a).

Βρασμὸς τῆς 3 σὲ πυκνὸ ὑδροχλωρικὸ ὀξὺ ἢ μεθανολικὸ ὑδροχλωρικὸ ὀξὺ ἐπὶ 24 ὧρες δὲν ὁδήγησε στὸ ἄνοιγμα τοῦ δακτυλίου, ἀλλὰ στὴν ἐπαναπόκτηση τῆς 3. Παρουσία ὅμως ἀρωματικῶν ἀλδεϋδῶν ἢ κετονῶν ὁ δακτύλιος τῆς 3 ἀνοίγει (Σχῆμα 1, πορεία b) γιὰ νὰ δώσει τὶς ἀσύμμετρες ἀζίνες 4 (Πίνακας I).

῾Ο σχηματισμὸς τῶν ἀσυμμέτρων ἀζινῶν 4 μπορεῖ νὰ ἀποδοθεῖ στὰ ἐνδιάμεσα 2b καὶ 2c τὰ ὁποῖα, ἀπουσία τῆς καρβονυλικῆς ἑνώσεως, ἐπανακυκλώνουν πρὸς τὴν 3.

῾Η ἐπιβεβαίωση τῆς δομῆς τῶν 4 ἔγινε μὲ τὴν βοήθεια ir καί ^{1}H-nmr φασματοσκοπίας (Πίνακας II).

References and Notes

1. Allen, C.F.H. and VanAllen, J.A.: J. Org. Chem., 13, 603 (1948).
2. Paollini, J.P.: J. Org. Chem., 33, 888, (1968).
3. Parric, J. and Pearson, K.: Chem. and Ind., 1261 (1970).
4. Ir spectra were recorded on a Perkin Elmer Model 177 spectrophotometer using nujoll mulls. ^{1}H-nmr spectra were determined on a 60 MHz instrument in DMSO (D_6), using TMS as internal standard.
5. Jackman, L.H. and Sternhell, S.: Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, (2nd edition), p. 191, Pergamon, Oxford (1969).
6. Melting points were determined in a Büchi capillary melting point apparatus and are uncorrected.

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