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REARRANGEMENT OF N-ACYLSPIROCYCLOALKYLBENZOTHIAZOLINES. A NEW EXAMPLE OF NITROGEN→CARBON ACYL MIGRATION.

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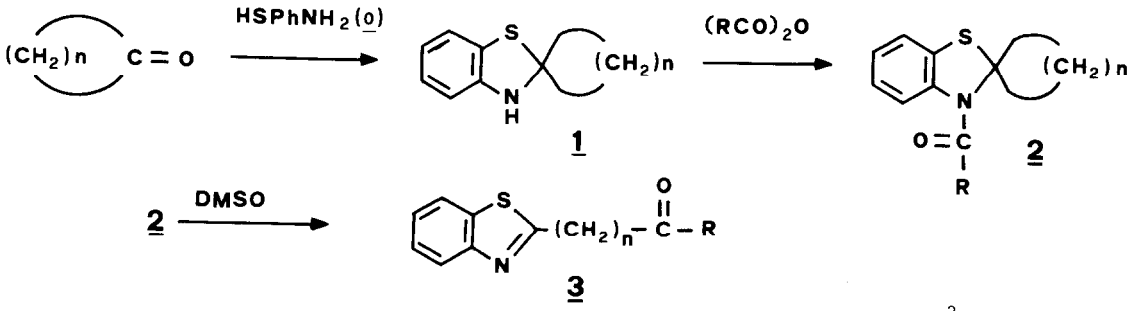
Abstract: In boiling dimethyl sulfoxide (DMSO) the title compounds 2 rearrange to ω(benzothiazolyl)alkyl,aryl(or alkyl)ketones 3.

Acyl migrations constitute an important class of reactions providing, inter alia, useful information in bioorganic studies. Up to date, only a few examples of N→C acyl migrations are known and these are both of inter-[1] and intramolecular[2] type.

We are now reporting a new example of an intramolecular N→C acyl migration in easily available N-acylspirocycloalkyl-2,3-dihydrobenzothiazoles 2 which rearrange to hitherto unknow and synthetically useful ω(benzothiazolyl)alkyl,aryl(or alkyl)ketones 3. The general synthetic scheme is as follows:



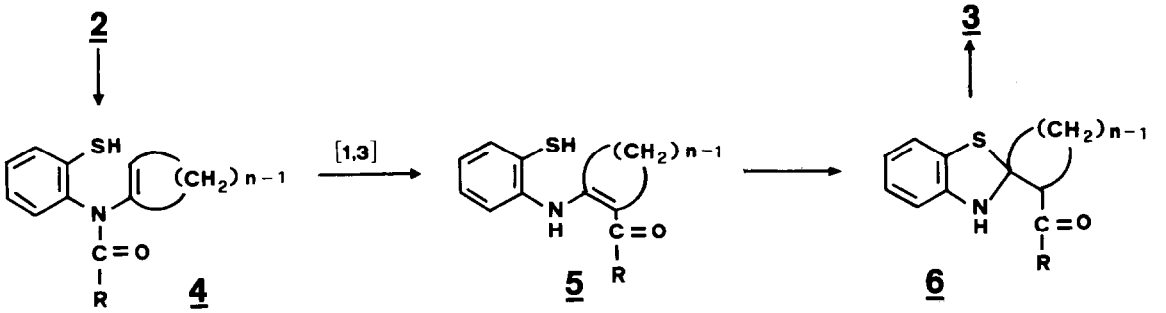
Compounds 2a-g (Table 1) are prepared by acylation of the benzothiazoline[3] of the appropriate ketone with carboxylic anhydride. The amides 2 in boiling DMSO, are easily converted to the corresponding ketones 3 from moderate to good yields[4] (Table 1).

The positive results obtained in the various cases examined in this study indicate that the reaction has a wide range of applicability. In particular, ease of rearrangement as a function of the ring size of cycloalkyl moiety rather than the nature of the acyl group is also evident. In fact, as the cycloalkyl group varies, yields decrease in the order 5 ≥ > 6 ≃ 7 > 8 while comparable yields are obtained in those cases were the R group was changed (2a-c). Furthermore, the rate of the rearrangement is highly dependent on the polarity of the solvent media since the 2a→3a conversion occurs to a considerable extent also in N,N-dimethyl-

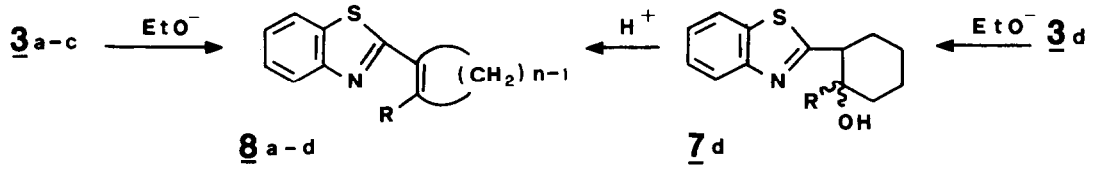
formamide (DMF) at 153° (95% in 20 hr) while only a 6% yield is obtained in tetrahydronaphtalene (THN) at 207° after 40 hr.

The 2→3 conversion process has been shown to be intramolecular by a crossed experiment between 2b and 2g since no scrambling of the acyl groups has occurred. In this case, the exclusive formation of the two corresponding isomerized compounds 3b and 3g, both in high yields (90% and 83% respectively), is obtained.

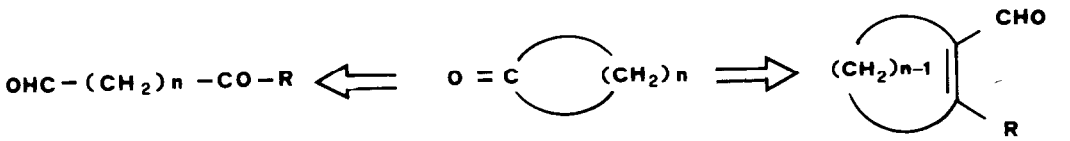
A possible pathway[5] accounting for the formation of 3 is shown in the following scheme involving a [1,3] N→C acyl shift[6] in the ring-opened species of 2[7], such as 4, to generate the enamino ketone 5 which in turn yields 3 via the spirocompound 6[8].



One example of synthetic usefulness of 3 is reported: compounds 3a-d were cyclized in very good yields (Table 2) to the corresponding vinyl benzothiazoles 8 which are known to be useful Michael acceptors[9], through intermediate alcohols 7[10].



These results in conjunction with the fact that the C-2 of the benzothiazole nucleus has recently been shown[11] to be a synthetic equivalent of the carbonyl group, enables the construction of the scheme illustrated below:



Further studies involving the 2→3 rearrangement and its applications to synthesis sre under way.

Table 1

Carbonyl Compound	% Yield of 2[a,b]	Conditions for 2→3 Conversion Solvent	time hr	% Yield of 3[b] (R'=Substituent on the benzothiazole's C-2)	
Cyclopentanone	2a[c] (R=CH_3) 87[d]	DMSO	2	3a (R'=$-(CH_2)_4COCH_3$)	98
		DMF	20	3a (R'=$-(CH_2)_4COCH_3$)	95
		THN	40	3a (R'=$-(CH_2)_4COCH_3$)	6
Cyclopentanone	2b (R=C_2H_5) 71[e]	DMSO	2	3b (R'=$-(CH_2)_4COC_2H_5$)	92
Cyclopentanone	2c (R=C_6H_5) 66[f]	DMSO	2	3c (R'=$-(CH_2)_4COC_6H_5$)	81
Cyclohexanone	2d[c] (R=CH_3) 85[d]	DMSO	2	3d (R'=$-(CH_2)_5COCH_3$)	42
Cycloheptanone	2e (R=CH_3) 68[d]	DMSO	2	3e (R'=$-(CH_2)_6COCH_3$)	40
Cyclooctanone	2f (R=CH_3) 52[d]	DMSO	5	3f (R'=$-(CH_2)_7COCH_3$)	26
1-Indanone	2g (R=CH_3) 82[g]	DMSO	2	3g (R'=o-$C_6H_4(CH_2)_2COCH_3$)	80

a) Yield based on starting ketone. b) Yield after column chrom. (SiO_2). c) Spectral and physical data are in agreement with those reported[12]. d) 1 (10 mmol) in acetic anhydride (40 ml) at reflux for 1 hr. e) 1b (1.7 mmol) in propionic anhydride (12 ml) at r.t. for 5 days. f) 1c (7.0 mmol), benzoic anhydride (7.0 mmol) in toluene (30 ml) at 60° for 18 hr. g) 1g (3.5 mmol) in acetic anhydride (10 ml) at r.t. for 3 days.

Table 2

Substrate	Reflux time hr for 3→8 or 7 Cyclization[a]	Product	% Yield of 8[b]
3a	15	8a	98
3b	15	8b	96
3c	24	8c	67
3d	20	7d[c]	80

a) All reactions were performed in C_2H_5OH (40 ml) on 2-4 mmol scales by using 15 mmol of C_2H_5ONa/mmol substrate. b) Yield after preparative tlc(SiO_2). c) 4:1 mixture of isomers. 7d yielded quantitatively 8d by standard acid-catalyzed dehydration (4 mg TsOH in 50 ml of toluene per mmol of substrate) with azeotropic removal of H_2O.

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3. a) In agreement with the general standard method for the synthesis of benzothiazolines[3b], compounds 1 were conveniently prepared by acid-catalyzed condensation of o-aminothiophenol and appropriate ketone (molar ratio 1:1) in toluene with azeotropic removal of water. b) A.I.Kiprianov and V.A.Portnjagina, Zhur.Obshch.Khim., 25, 2257 (1955); Chem. Abstr., 50 9378b (1956).

4. General procedure for 2→3 conversion: a DMSO (25 ml) solution of 2 (4 mmol) was refluxed for the time reported in Table 1. The solution, when cold, was poured in water and extracted with $CHCl_3$. The organic layer, washed with water, was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2).

5. According to our data other possible pathways may be formulated.

6. [1.5] N→C acyl shift in enamide compounds has been reported[1].

7. Ring-chain tautomeric equilibria between the benzothiazoline and the enaminothiol form 4 is known: F.J.Goetz, J.Heterocyclic Chem., 4,80 (1967).

8. By thermal rearrangement compounds 6 (R=O-alkyl)are quantitatively converted into 3(R=O-alkyl) P.Marchini, G.Trapani, G.Liso, V.Berardi, F.Liberatore, and F.Micheletti, Phosphorus and Sulfur, 2, 109 (1976).

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10. Structures of all compounds reported herein are confidently supported by pmr,ir,mass spectra (M^+) and elemental analysis.

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