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Study of the reaction of chalcone analogs of dehydroacetic acid and *o*-aminothiophenol: synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines

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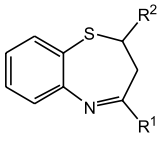
Abstract—Treatment of α,β-unsaturated carbonyl compounds, obtained by the reaction of DHA and aromatic (or heteroaromatic) aldehydes, with *o*-aminothiophenol results in the formation of 1,5-benzothiazepines and/or 1,4-benzothiazines depending upon the reaction conditions and structure of the aldehydes. The products were characterized by the combined use of multinuclear 1D and 2D NMR and GIAO/DFT calculations of ^{1}H, ^{13}C and ^{15}N chemical shifts. The tautomerism of these compounds in solution was determined, they have an exocyclic CC double bond.

1. Introduction

Both 1,5-benzothiazepine and 1,4-benzothiazine ring systems have derivatives of biological importance. Amongst those of the first group are diltiazem, clentiazem and thiazesim and amongst those of the second group are the trichosiderin pigments.[1] In this paper we would describe how in the case that single crystals cannot be grown, the combined used of multinuclear NMR and DFT calculations allows to identify pairs of isomers belonging to reduced derivatives **1** and **2** of these two classes.



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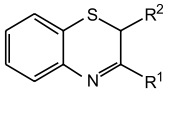

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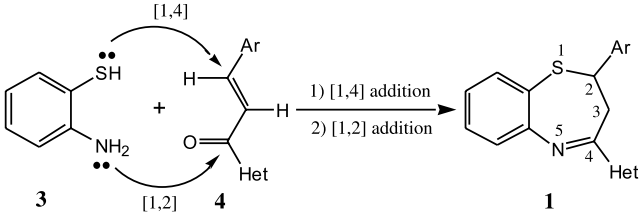
One of the most widely methods employed for the preparation of 1,5-benzothiazepines involves the reaction of *o*-aminothiophenol (*o*-ATP, **3**) with α,β-unsaturated esters,[2] α,β-unsaturated ketones (**4**),[3] or chalcones,[4] both under acidic and basic conditions. Although in all reactions between a dinucleophile (hydrazines, hydroxylamine, *o*-phenylenediamine, etc.) with a dielectrophile of the type above mentioned, two compounds can be formed,[5] since only benzothiazepines were isolated it was assumed that the reaction starts by the 1,4-Michael addition of the SH on the CC double bond followed by the condensation of the NH_2 on the carbonyl group (Fig. 1).



3 **4** **1**

Figure 1.

One of the most common synthesis of dihydro-1,4-benzothiazines involves also *o*-ATP, **3**, but alkynes or α-bromocarbonyl compounds (Fig. 2) instead of β-difunctional compounds.[1]

Although there is no precedent that in the reaction between

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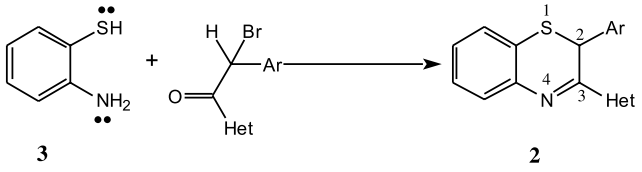

Figure 2.

3 and **4** other heterocycles than benzothiazepines **1** could be formed, nevertheless there is another possibility (Fig. 3). According to Baldwin's rules both 7-*endo-trig* and 6-*exo-trig* processes are favored.[6] The first one leading to the benzothiazepine **1** while the second one affords a dihydro-1,4-benzothiazine **5**. Compounds **1** and **5** are isomers and, as we will show, not easily differentiated.

In a first step, α,β-unsaturated ketones **7** are prepared from dehydroacetic acid (**6**). In a second step, compounds **7** reacted with *o*-aminothiophenol (*o*-ATP, **3**, Fig. 4) to afford dihydro-1,5-benzothia-zepines **1** and/or dihydro-1,4-benzothiazines **5**. This is the first time that the formation of **5** is reported.

2. Results and discussion

In view of these observations and our ongoing interest in the chemistry of DHA and its derivatives[7–9] (for a review on DHA see Ref. 10), it was considered worthwhile to explore the reaction depicted in Figure 4. The experimental procedure consists in treating DHA derivatives with *o*-ATP in EtOH/AcOH, a method which has effectively been employed previously for the synthesis of several 1,5-benzothiazepines. In order to attempt the proposed method, chalcone analogs of DHA (**7**), available by the condensation of DHA (**6**) with benzaldehydes or their heterocyclic analogs in chloroform in the presence of piperidine,[11] were prepared. The chalcones **7** were transformed into **1** and/or **5** derivatives in 76–86% yields (Table 1).

Actually, although **1** is the expected compound according to literature results, there are further structural possibilities. We have assumed, like other authors, that the carbonyl group involved in the hydrogen bond is the C(4′)=O.[11] But at least three reasonable tautomeric forms (Fig. 5) can be written for the benzothiazepines **1** and three similar ones for the benzothiazines **5**.

2.1. Determination of the structure and tautomerism of compounds a–l

We have used a combination of NMR spectroscopies (^{1}H, ^{13}C and ^{15}N) and GIAO–DFT calculations. In two

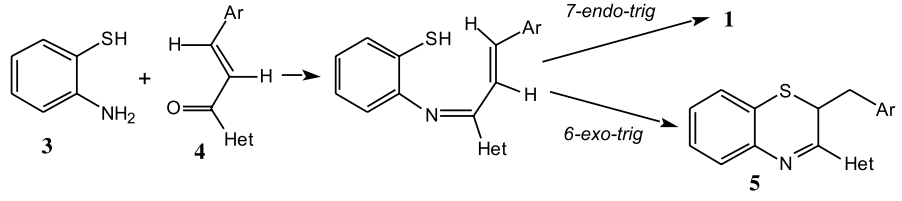

Figure 3.

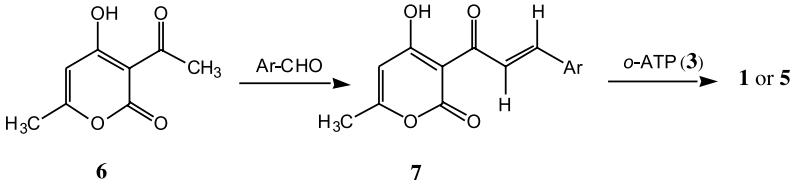

Figure 4.

Table 1. Heterocycles of the **a–l** series prepared according to Figure 4

Compounds **1** and **5**	Mp (°C)	Yield (%)	Method[a]	Molecular formula
1a, Ar=C_6H_5	228–229	85	A	$C_{21}H_{17}NO_3S$
1b, Ar=4-ClC_6H_4	218–219	83	A	$C_{21}H_{16}ClNO_3S$
1c, Ar=4-$CH_3C_6H_4$	230–231	84	A	$C_{22}H_{19}NO_3S$
1d, Ar=4-OHC_6H_4	255–256	79	A	$C_{21}H_{17}NO_4S$
1e, Ar=2-OHC_6H_4	244–246	82	A	$C_{21}H_{17}NO_4S$
1f, Ar=4-$OCH_3C_6H_4$	238–240	85	A	$C_{22}H_{19}NO_4S$
1g, Ar=4-$N(CH_3)_2C_6H_4$	234–235	86	A	$C_{23}H_{22}N_2O_3S$
1h, Ar=2-$NO_2C_6H_4$	200–202	76	A	$C_{21}H_{16}N_2O_5S$
5h, Ar=2-$NO_2C_6H_4$	230–232	83	B	$C_{21}H_{16}N_2O_5S$
1i, Ar=3-$NO_2C_6H_4$	210–212	75	A/B	$C_{21}H_{16}N_2O_5S$
1j, Ar=4-$NO_2C_6H_4$	232–233	78	A	$C_{21}H_{16}N_2O_5S$
5j, Ar=4-$NO_2C_6H_4$	190–191	81	B	$C_{21}H_{16}N_2O_5S$
1k, Ar=2-thienyl	180–182	81	A/B	$C_{19}H_{15}NO_3S_2$
5l, Ar=4-pyridyl	195–197	79	A/B	$C_{20}H_{16}N_2O_3S$

[a] Conditions: (A) *o*-aminothiophenol plus two drops of piperidine in EtOH, 15 min reflux; (B) *o*-aminothiophenol plus two drops piperidine in EtOH, 2 h reflux and then addition of AcOH and 2 h reflux.