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(E)-2-benzylidenecyclanones: part xv. stereochemistry of reaction of 2-arylidenecyclopentanones with dithiocarbamic acid

Abstract

The reaction of (E)-2-arylidenecyclopentanones (1a-c) with dithiocarbamic acid in acidic medium has been investigated. In the reactions taking place under mild acid conditions 4-aryl-7a-hydroxy-4,4a,5,6,7,7a-hexahydrocyclopenta[d][1–3] thiazine-2(1H)-thiones (2a-c) were formed. It was found that the compounds (2a-c) belonged to the same isomer series: the cyclopentane and the 1,3-thiazine rings are cis-fused and the 4-aryl group is in trans position to the annelated H-4a atom. ^{1}H NMR investigations proved the N-inside conformation of the compounds in solution where the 4-aryl group takes a pseudoequatorial position.

Keywords: enones, dithiocarbamic acid, michael addition, 1,3-thiazine-2(1h)-thione, conformational analysis, n-inside conformation

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Abbreviations: NMR, nuclear magnetic resonance; TLC, thin layer chromatography; MP, melting point

Introduction

The reaction of α,β-unsaturated carbonyl compounds with carbonic acid derivatives is a method frequently used for the synthesis of pyrimidines and 1,3-thiazines.[1–7] Although these methods have been mentioned in the literature for a long time, there are only a few examples of investigation on the mechanism and the stereochemistry of reactions. Based on earlier examinations[5–7] reaction of α,β-unsaturated carbonyl compounds with dithiocarbamic acid (Michael-recation) is a suitable synthetic pathway for studying the reaction leading to the formation of 1,3-thiazines.

In one of our earlier works, reaction of para-substituted chalcones and dithiocarbamic acid was studied. It was found that the reaction results in formation either open-chain or cyclic adducts depending on the substitution pattern of the aromatic rings of the chalcones.[6] Later, we have reported on stereochemical analysis of reactions with dithiocarbamic acid of (E)-2-benzylidenecyclohexanones[8,9] and some (E)-2-benzylidene-1-benzocylanones.[10] Reactions of the investigated compounds led to formation of cyclic[8,9] or open chain[10] adducts. Stereochemistry of the formed adducts were found to be determined by both the structure of the α,β-unsaturated carbonyls and the reaction conditions.

Addition reaction with dithiocarbamic acid of (E)-2-benzyldenecylohexanones resulted in formation of isomeric cyclic adducts.[8,9] In such a case three new chiral centers are formed allowing formation of four diastereomeric pairs. In the reactions formation of three of the possible diastereomers could be detected and characterized. Stereochemistry of cyclization of the primary (Michael-type) adducts was determined by the preferred conformation of the forming bicyclic saturated heterocycles.[8,9] The aim of the present work is to investigate the structure and stereochemistry of the dithiocarbamic acid adducts of the five-membered analogue (E)-2-arylidenecyclopentanones (1a-c).

Experimental

M.p.'s were determined With a Boetius hot plate apparatus, and are uncorrected. IR spectra were measured with a SPECORD 75 IR instrument. 60MHz ^{1}H NMR spectra were obtained with a Perkin-Elmer R-12 spectrometer, and 200MHz spectra with a Bruker WP 200 SY spectrometer for DMSO-d_6 solutions operating at 35°C and 25°C, respectively. Chemical shifts are reported as δ values in ppm. downfield from internal tetramethylsilane, and coupling constants in Hz. The starting 2-arylidenecyclopentanones (1a-c) were prepared by aldol condensation. All the compounds have (E) configuration.[11]

The progress of the reactions as well as the purity of the isolated compounds was checked by TLC performed on Kieselgel GF 254 plates (Merck) using benzene: ethanol 4:1 (v/v) as eluent. The isomeric composition of the crude products was determined by ^{1}H NMR spectroscopy (60MHz) based on investigation of the well-separated H-4a signals. Elemental analyses were performed at the Department of Organic Chemistry, Eötvös Loránd University, Budapest (Hungary).

General procedures for addition reactions

A solution of 0.075mole ammonium dithiocarbamate[12] in 150ml 50% methanol was acidified by adding 25ml of 6,5N (0.165mole) hydrochloric acid. Both solutions were precooled to -5°C and the temperature was maintained at -5°C through the addition 5 minutes which was carried out with starring. To this solution of dithiocarbamic

acid a cooled methanolic solution of 0.03mole unsaturated ketone (1a-c) was added under continuous cooling and stirring, and the reaction mixture was stirred at -5°C for additional 4-5 hours. After completing the reaction (TLC), the reaction mixture was diluted with water, the forming precipitate was filtered off, washed with water, and dried in vacuum exiccator. The crude products were purified by crystallization from methanol to give colorless crystals (2a-c).

4-Phenyl-7a-hydroxy-4,4a,5,6,7,7a-hexahydrocyclopenta[d][1,3]thiazine-2(1H)-thione(2a): This was formed in 72% yield, m.p. 158-161°C. (Found: C, 58.59; H, 5.41; S, 24.31. $C_{13}H_{15}NOS_2$ requires C, 58.83; H, 5.70; S, 24.16%); ν_{max} (KBr pellet) 3500-3175 (OH+NH), 3130 (NH), 2960 (aliphatic), and 1500 (aromatic); δ_H (200MHz), 10.65 (1H, s, NH), 7.48-7.25 (5H, m, Ph), 6.65 (1H, s, OH), 4.96 (1H, d, $^3J_{4,4a}$ 3.3Hz, 4-H), 2.38 (1H, ddd, $^3J_{4a}$,5, 8Hz, $^3J_{4a}$,5', 11Hz, 4a-H), 2.38 (1H, ddd, $^3J_7$', 13.3Hz, $^3J_7$',6' 8.4 Hz, $^3J_7$',6, 2.3Hz, 7'-H), and 1.89-1.36 (5H, m, aliphatic).

4-(4'-Methylphenyl)-7a-hydroxy-4,4a,5,6,7,7a-hexahydrocyclopenta[d][1,3]thiazine-2(1H)-thione (2b): This was formed in 79% yield, m.p. 165-167°C. (Found: C, 59.92; H, 6.07; S, 23.19. $C_{14}H_{17}NOS_2$ requires C, 60,18; H, 6.13; S, 22,95%); ν_{max} (KBr pellet) 3550-3220 (OH+NH), 3160 (NH), 2975 (aliphatic), and 1510 (aromatic).

4-(4'-Methoxyphenyl)-7a-hydroxy-4,4a,5,6,7,7a-hexahydrocyclopenta[d][1,3]thiazine-2(1H)-thione (2c): This was formed in 81% yield, m.p. 160-163°C. (Found: C, 59.14; H, 5.96; S, 21.64. $C_{14}H_{17}NO_2S_2$ requires C, 56.92; H. 5, 80; S, 21, 71%); ν_{max} (KBr pellet) 3500-3200 (OH+NH), 3145 (NH), 2950 (aliphatic), and 1510 (aromatic).

Results and discussion

Reaction of (E)-2-arylidenecyclopentanones (1a-c) with dithiocarbamic acid was carried out in a hydrochloric methanol solution at -5°C. In the reactions taking place under acid conditions[8,9] formation of compounds (2a-c) were obtained (Figure 2).

In order to investigate the stereo chemical outcome of the reactions the crude products were analyzed by ^{1}H NMR (60MHz) spectroscopy. The analyses showed formation only one diastereoisomer in each case. Examination of the IR and the ^{1}H NMR spectra of the isolated compounds (2a-c) showed the adducts to exist in cyclic form both in the solid state and in solution. Thus three asymmetric centers are formed in the course of the reaction, which makes formation of four pairs of diastereoisomers possible. ^{1}H NMR data indicated the compounds to be stereohomogenous products having the same stereochemistry (Table 1).

Table 1 ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) of compounds (2a-c)[a]

Compound	NH[b] (s)	Aromatic (m)	Oh[b] (s)	H-4 (d)	Me or MeO (s)	Aliphatic	H-4a[c]	^{3}J4,4a[d]
(2a)	10.65	7.50-7.25	6.55	4.95	-	2.60-1.30	2.35	3.5
(2b)	10.65	7.45-7.20	6.65	4.95	2.4	2.55-1.30	2.35	3.5
(2c)	10.6	7.50-6.90	6.59	5	3.85	2.55-1.28	2.4	3.5

[a]Determined at 60MHz

[b]Signal disappears on the addition of D_2O

[c]Determined by double-resonance experiment

[d]In Hz

Since the exact determination of the configuration of asymmetric centers could not be unequivocally solved only on the basis of the ^{1}H NMR data, the steric structure of (2a) was established by X-ray diffraction. X-ray analysis of the compound showed the cyclopentane and the 1,3-thiazine rings being cis-fused and the 4-phenyl group in trans position to the annelated H-4a atom.[13] These results can be explained by trans-addition of dithiocarbamic acid onto the polarized carbon-carbon double bound followed by a conformation-driven cyclization of the open-chain adduct.[9] The stereochemistry of the isolated adduct is the same as that of obtained in similar reaction of (E)-2-benzylidenecyclohexanone under less acidic conditions.[8,9] On the other hand, the stereochemistry of the obtained adducts is opposite to that observed in the similar reaction of (E)-2-benzylidene-1-indanone-the benzocondensed analogue of (E)-2-benzylidenecyclopentanone (1a) -with dithiocarbamic acid.[14]

With full knowledge of configuration of (2a), the two possible conformations (N-inside and N-outside) of the obtained compounds are shown in Figure 1. Taking these conformations into account the chemical shift and multiplicity of the 4-H and the H-4a protons and that of the OH signal are determinative spectroscopic parameters.[15]

As it is shown in Table 1, the ^{1}H NMR data of the corresponding protons are almost the same in the three products. Although the ^{1}H NMR data suggest that the compounds have monoconformational behavior, these results are not enough for distinguishing the conformers. Namely, the only valuable fact considering these conformations is the splitting of the H-4 and the H-4a protons. This fact, however, does not allow distinguishing the conformers since the dihedral angle of the H-4 and the H-4a protons (based on the Dreiding models) is about 45° in both the N-inside and the N-outside conformers (Figure 1).

The conformational relations were determined by examination of (2a) carried out at 200MHz. In the spectrum recorded at 200MHz the H-4a signal appears separately (δ2.38). The coupling constants measured for the H-4a signal render it possible to investigate the conformations. The molecular model shows that the dihedral angles between the H-4a and the C-5 methylene protons in the N-outside conformer are ~30° and ~90°, respectively. The measured coupling constants of 8Hz and 11Hz rule out this conformer, but they fit in well with the angles of ~30°and ~180° in the N-inside conformer (Figure 1).

With the purpose of further examinations of the conformational relations ^{1}H-^{1}H N.O.E. investigations were carried out, the result of which are summarized in Table 2. The most remarkable experimental result is the NOE effect measurable well between the H-4 and OH protons, which support their spatial closeness. These ^{1}H NMR investigations also proves the dominant N-inside conformation in solution where the 4-aryl group takes a pseudoequatorial position.

Similar observations-predominance of this type conformation for bicyclic saturated heterocycles with unsubstituted N-1 atom -were made with cyclopentane- and cyclohexane-fused 1,3-oxazines and 1,3-thiazines with related structures.[16]

Addition of sulfur nucleophiles onto unsaturated carbonyl compounds has not only synthetic but bioorganic importance as well. Reduced glutathione (GSH) is the most abundant cytosolic thiol playing important role in protection of cells against electrophiles-initiated damages.[17] Earlier we have demonstrated that chalcones (open-chain α,β-unsaturated carbonyls)[18] and cyclic chalcone analogues[19,20] possess intrinsic reactivity towards GSH resulting in formation of the expected adducts. Accordingly, thiol reactivity of α,β-unsaturated carbonyl compounds is a basis of one of the biotransformation pathways of this kind of xenobiotics.

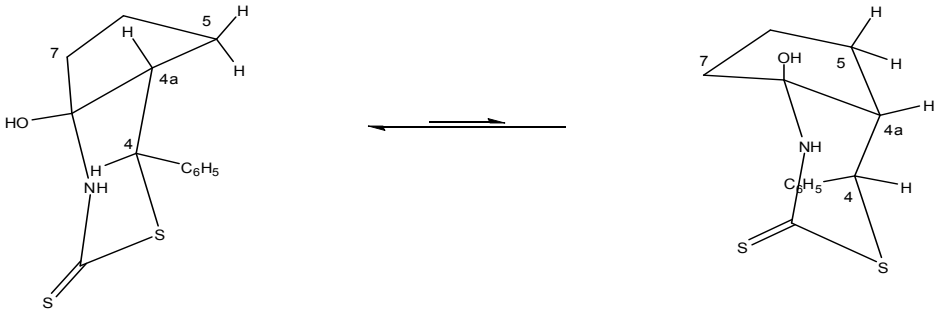

Figure 1 N-inside and N-outside conformations of 2a.

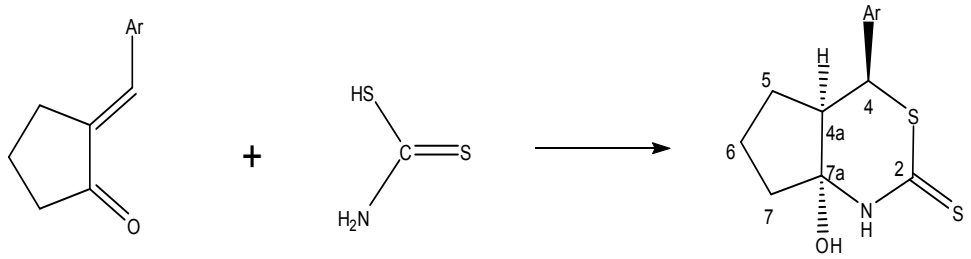

Figure 2 Reaction of (E)-2-arylidinecyclopentanones with dithiocarbamic acid.

Ar: (**a**) C_6H_5, (**b**) 4-CH_3-C_6H_4, (**c**) 4-CH_3O-C_6H_4

Table 2 NOE data for compound (2a)[a]

Hydrogen atom irradiated (δ)	Observed enhancement (%)
H-4 (4.95)	OH (+10), H-4a (+12)
OH (6.55)	H-4 (+10)
NH (10.65)	OH (+6), H-7' (+6)

[a]Determined at 200MHz in DMSO-d_6 solution.

Conclusion

Stereochemical analysis of reaction products of (E)-2-arylidenecyclopentanones (1a-c) and dithiocarbamic acid showed the reactions to yield stereohomogeneous 4aryl-7a-hydroxy-4,4a,5,6,7,7a- hexahydrocyclopenta[d][1,3]thiazine-2(1H)-thiones (2a-c). Combined X-ray and ^{1}H NMR analyses proved that the 1,3-thiazine rings are cis-fused and the 4-aryl group is in trans position to the annelated H-4a atom. The compounds adopt the energetically more preferred N-inside conformation where the 4-aryl group takes a pseudoequatorial position. The results indicate importance of ring size of (E)-2-benzylidenecyclanones in stereochemistry of Michael-type addition of dithiocarbamic acid. Stereochemistry of cyclization was found to be determined by the preferred N-inside conformation of the cis-anellated bicyclic products.

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Conflict of interest

The author declares no conflict of interest.

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