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Synthesis of a new 1,2,3,4,5-pentasubstituted cyclohexanol and determining its stereochemistry by NMR spectroscopy and quantum-chemical calculations

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The presence of substituents in cyclohexane can influence to the ratio of conformers; for some cases, the boat form is preferable. The new six-membered cyclohexanol derivative 2 has been obtained by the synthesis of (*E*)-1-(bromophenyl)-3-phenylpropen-2-one (1). The NMR and quantum-chemical conformational analysis for the 2 have carried out, and its possible mechanism of formation was given. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: chalcone; cyclohexanol; conformation; NMR

Introduction

The chemistry of chalcones is of great scientific interest and has been generated intensive studies in the organic chemistry. Chalcones are efficient synthones in building novel heterocycles and cyclohexane derivatives with good pharmaceutical properties, such as antimicrobial, antibacterial, antifungal, anticancer, antitubercular, antiviral, anti-inflammatory, antihyperglycemic, and other activities.[1–13]

The NMR is a very important analytical method for identifying the structure of organic molecules and studies of dynamic processes in different solutions.[14–27] We have applied NMR and quantum-chemical calculations methods to the cyclohexane derivative of the chalcone **1** to obtain insight into the three-dimensional structure of this system.

Experimental section

NMR spectra

The NMR experiments have been performed on a Bruker FT NMR spectrometer AVANCE 300 (Bruker, Karlsruhe, Germany) (300 MHz for ^{1}H and 75 MHz for ^{13}C) with a BVT 3200 variable temperature unit in 5-mm sample tubes using Bruker standard software (TopSpin 3.1). The ^{1}H and ^{13}C chemical shifts were referenced to internal tetramethylsilane; the experimental parameters for ^{1}H are as follows: digital resolution = 0.23 Hz, SWH = 7530 Hz, TD = 32 K, SI = 16 K, 90^{0} pulse-length = 10 μs, PL1 = 3 dB, ns = 1, ds = 0, and d1 = 1 s and for ^{13}C as follows: digital resolution = 0.27 Hz, SWH = 17985 Hz, TD = 64 K, SI = 32 K, 90^{0} pulse-length = 9 μs, PL1 = 1.5 dB, ns = 100, ds = 2, and d1 = 3 s.

COSY: pulse program = *cosygpqf*, digital resolution = 1.97 Hz, SWH = 2610, TD = 1 K, SI = 512, 90^{0} pulse-length = 10 μs, PL1 = 3 dB, ns = 4, ds = 16, and d1 = 1 s.

NOESY: pulse program = *noesyph*, digital resolution = 1.97 Hz, SWH = 2610 Hz, TD = 1 K, SI = 512 K, 90^{0} pulse-length = 10 μs, PL1 = 3 dB, ns = 16, ds = 8, d1 = 1.5 s, and d8 = 0.3 s.

ROESY: pulse program = *roesyph*, digital resolution = 1.49 Hz, SWH = 3063 Hz, TD = 2 K, SI = 512 K, 90^{0} pulse-length = 10 μs, PL1 = 3 dB, ns = 16, ds = 4, and d1 = 2 s.

HSQC: pulse program = *hsqcetgp*, digital resolution = 2.95 Hz, SWH = 3019 Hz, TD = 1 K, SI = 512 K, 90^{0} pulse-length = 10 and 9 μs, PL1 = 3 dB, PL2 = 1.5 dB, ns = 2, ds = 16, and d1 = 1.5 s.

HMBC: pulse program = *hmbcgppndqf*, digital resolution = 0.97 Hz, SWH = 4006 Hz, TD = 4 K, SI = 512 K, 90^{0} pulse-length = 10 and 9 μs, PL1 = 3 dB, PL2 = 1.5 dB, ns = 16, ds = 2, and d1 = 1.5 s.

The NMR-grade DMSO-d_6 (99.7%, containing 0.3% H_2O), acetone-d_6 (99.7%), and CCl_4 (100%, several drops of D_2O were added for the lock signal as external standard) were used for the solutions of **1** and **2**.

Quantum-chemical calculation has been carried out by the DFT B3LYP/6-31G and B3LYP/6-31G (d,p) methods.

Mass spectra were recorded on an Esquire 6000 (Bruker) using positive electrospray ionization.

The purity and the structure of the synthesized compounds were confirmed by layer chromatography (Silufol UV-254, 0.1-mm silica gel plates, iodine vapor as visualizing agent, and eluent 5 : 2 hexane/ethyl acetate), 1D/2D NMR spectra (Figs. S1–S9). The ^{1}H and ^{13}C NMR data of compound **2** were given in Table 1.

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Table 1. The ^{1}H and ^{13}C NMR data of compound **2** in acetone-d_6 (δ in ppm, J in Hz)

Position												
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
—	1.91 and 3.43 (d-d and t, $^2J = 12.4$, $^3J = 4.3$, $^3J = 7.6$, CH$_2$)	4.19 (m, CH)	4.53 (t, $^3J = 4.6$, CH)	4.31 (d-d, $^3J = 12.5$, $^3J = 7.6$)	5.13 (d, $^3J = 12.5$, CH)	4.91 (d, OH)	—	7.21–7.39 (m, CH)	7.21–7.39 (m, CH)	—	7.21–7.39 (m, CH)	7.21–7.39 (m, CH)
76.9	38.7	40.8	44.9	51.3	52.1	—	143.2	126.0–132.0	126.0–132.0	120.0	126.0–132.0	126.0–132.0
14	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
—	6.85–7.40 (m, CH)	6.85–7.40 (m, CH)	6.85–7.40 (m, CH)	6.85–7.40 (m, CH)	6.85–7.40 (m, CH)	—	—	7.42–7.54 (m, CH)	7.42–7.54 (m, CH)	—	6.85–7.54 (m, CH)	7.42–7.54 (m, CH)
142.8	126.0–132.0	126.0–132.0	126.0–132.0	126.0–132.0	126.0–132.0	200.1	137.1	126.0–132.0	126.0–132.0	126.9	126.0–132.0	126.0–132.0
27	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**
—	7.1–7.2 (m, CH)	7.1–7.2 (m, CH)	7.1–7.2 (m, CH)	7.1–7.2 (m, CH)	7.1–7.2 (m, CH)	—	—	7.52–7.71 (m, CH)	7.52–7.71 (m, CH)	—	7.52–7.71 (m, CH)	7.52–7.71 (m, CH)
137.3	126.0–132.0	126.0–132.0	126.0–132.0	126.0–132.0	126.0–132.0	204.6	147.7	126.0–132.0	126.0–132.0	128.9	126.0–132.0	126.0–132.0

Synthesis

A mixture of 4-bromoacetophenone (1.99 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in 20 ml ethanol and 0.5 and 5 ml of 10–60% sodium (or potassium) hydroxide solution was added and stirred at room temperature for 3 h. The precipitate formed was collected by filtration and recrystallized in ethanol.

In the presence of 0.5 and 5 ml of 10–40% sodium or potassium hydroxide solution, a white compound **1** is obtained, which is known in the literature[28]; in the presence of 5 ml of 50% and 60% sodium or potassium hydroxide solution, a new pale pink compound **2** is obtained. Both compounds were obtained as powders; the yield of the chalcone **1** is 67–90% (Scheme 1, Table 2). the new product **2** is 26–37%, M.p. 180–183 °C (Table 2), electrospray ionization–MS: m/z [M + H]$^+$ 773, 697, 555, 502, 413, 360, 307.

Results and discussion

The synthesis of the chalcone **1** and its halogenated cyclohexane derivative **2** are given in Scheme 1 and in the experimental section.

In 1896, Kostanecki and Rossbach prepared two compounds (Kostanecki's triketone) for the first time by the reaction of benzaldehyde and acetophenone in a 2 : 3 molar ratio in concentrated alcoholic NaOH with melting points of 198 °C and 256 °C, respectively.[29] In 1990, Vasilyev's research group confirmed the three-dimensional molecular structure of 1,2,3,4,5-pentasubstituted cyclohexanol by a single-crystal X-ray diffraction analysis.[30]

Later on, Kessler, Gareth, and Colin's group investigated the stereochemistry of pyridinyl-containing analog of Kostanecki's triketone by X-ray, 2D NMR spectroscopy.[31,32] In 2006, Z. Shan reported on synthesis, X-ray, NMR studies, and formation mechanism of polysubstituted cyclohexanols in the presence of solid NaOH and K$_2$CO$_3$.[33]

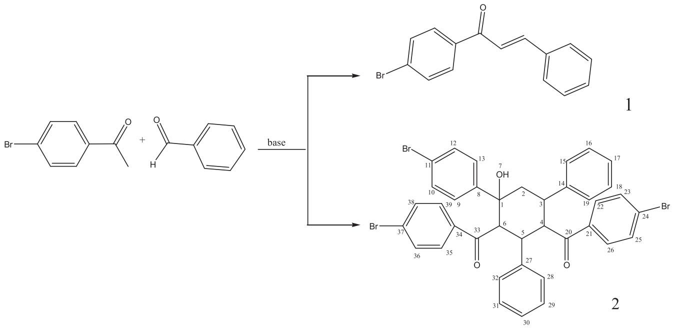
In the previously mentioned work[29,33], benzaldehyde (or its substituted derivatives) and acetophenone were used as a starting materials. In the present work, we decided to take 4-bromoacetophenone, benzaldehyde, and different concentration (10–60%) of alcoholic NaOH and KOH solutions.

However, our studies confirmed that types of substrate (in our case 4-bromoacetophenone) do not influence to the reaction product (influence to the yield), and new six-membered Kostanecki triketone derivative **2** was obtained at high concentrations of bases (Table 2). As seen from the obtained data, the yield of triketone was reduced significantly (26–37%), but in previously indicated works[29,33] for some triketone derivatives, yield was made up higher than 90%.

A new product **2** was synthesized by the presence of 5 ml, 50% and 60% base catalyst. Possible formation mechanism of **2** in the presence of a base catalyst is given in Scheme 2. As can be seen from the Scheme 2, after formation of compound **1**, interaction of obtained chalcone with the carbanion **A** occurs in the second step. In the third step, a second molecule of chalcone **1** reacts with the newly formed carbanion **B**, and the carbanion **C** is obtained as a result of cyclization. In the last step, migration of hydrogen from the medium occurs, and the six-membered cycle is formed.

For the investigation of the stereochemistry of compound **2**, we have applied NMR and quantum-chemical methods (Figs. 1 and 2, Figs. S6 and S7). Calculated relative energies of conformers are given in Table 3.

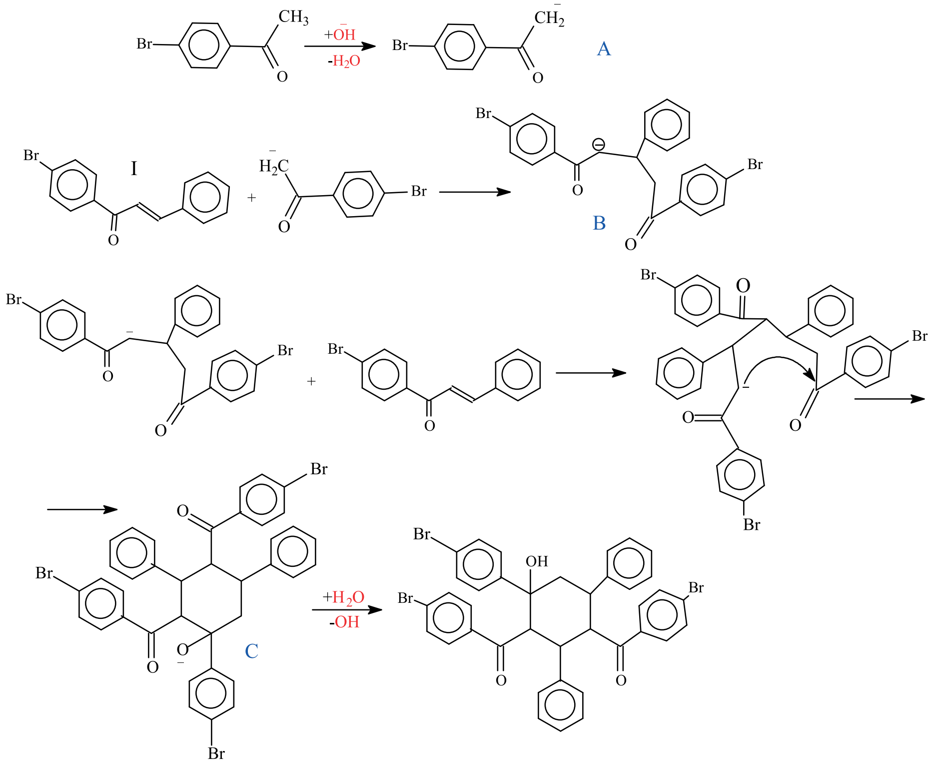
As seen from the 2D NOESY and ROESY (Fig. S6 and S7), spectra spatial interactions between the 2A-2B, 2A-3, 2B-4, 2B-6, 2B-Ar, 3-5, 3-OH, 3-Ar, 5-OH, 5-Ar, 4-6, 4-Ar, OH-Ar, 6-Ar protons have been observed inside the molecule.



Scheme 1. Synthesis of the chalcone **1** and its cyclohexanol derivative **2**.

Table 2. Yield of compounds (**1** and **2**) at the presence of KOH and NaOH

NaOH								KOH							
ml	%	yield		ml	%	yield		ml	%	yield		ml	%	yield	
		1	2			1	2			1	2			1	2
0.5	10	67	—	5	10	85	—	0.5	10	71	—	5	10	89	—
0.5	20	68	—	5	20	85	—	0.5	20	74	—	5	20	90	—
0.5	30	68	—	5	30	86	—	0.5	30	74	—	5	30	90	—
0.5	40	71	—	5	40	86	—	0.5	40	75	—	5	40	89	—
0.5	50	71	—	5	50	7	26	0.5	50	76	—	5	50	5	31
0.5	60	73	—	5	60	—	33	0.5	60	76	—	5	60	—	37



Scheme 2. Formation mechanism of the compound **2** at the presence of base catalyst.

As we can be seen in the Table 3, the most stable conformer is a chair (**A**) with zero relative energy. NMR investigations in acetone-d_6 and diluted CCl_4 solutions have confirmed the formation of intramolecular hydrogen bond between the OH and O = C groups (^{1}H hydroxyl proton signal in acetone-d_6 at $\delta = 4.92$ ppm and in diluted CCl_4 at the 4.9 ppm was observed). The stability of the chair conformation (**A**) may be connected with the formation of intramolecular hydrogen bond between the hydroxyl and

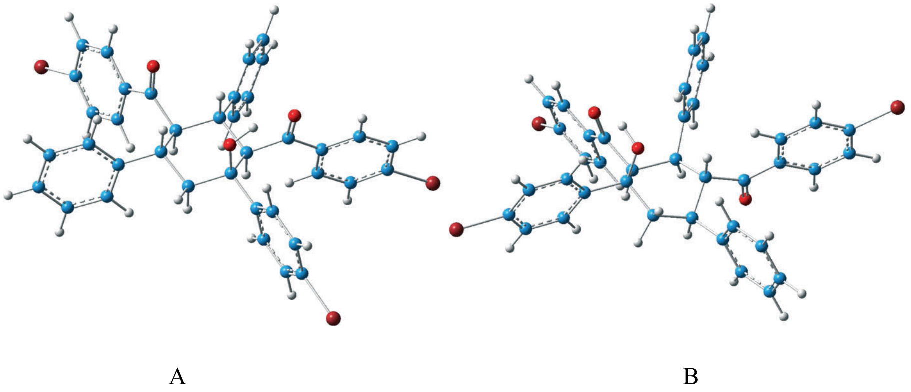


Figure 1. The chair A and boat B conformations for **2** calculated by the DFT B3LYP/6-31G and B3LYP/6-31G(d,p) methods.

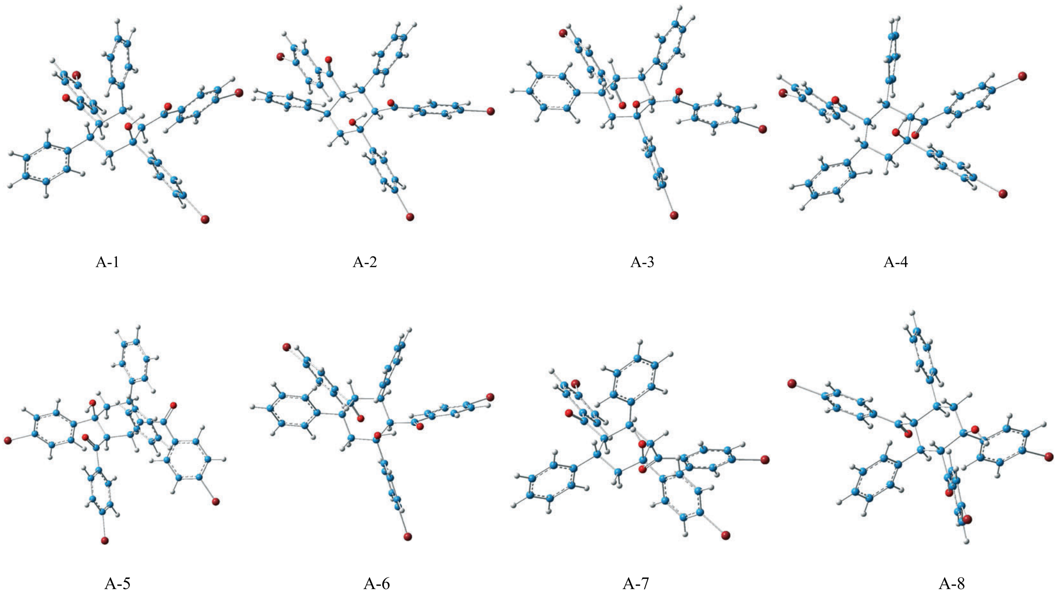


Figure 2. Different type of chair (A) conformation for the **2** calculated by the DFT B3LYP/6-31G and B3LYP/6-31G(d,p) methods.

Table 3. The calculated relative energies of conformers, (kcal/mol)

Different conformers	Calculation methods	
	B3LYP/6-31G	B3LYP/6-31G(d,p)
Chair (**A**)	0.000	0.000
Boat (**B**)	5.654	6.307
A-I	7.027	6.891
A-II	7.861	7.608
A-III	0.182	0.295
A-IV	7.009	6.883
A-V	23.397	21.642
A-VI	2.341	3.319
A-VII	9.829	10.330
A-VIII	7.072	7.568

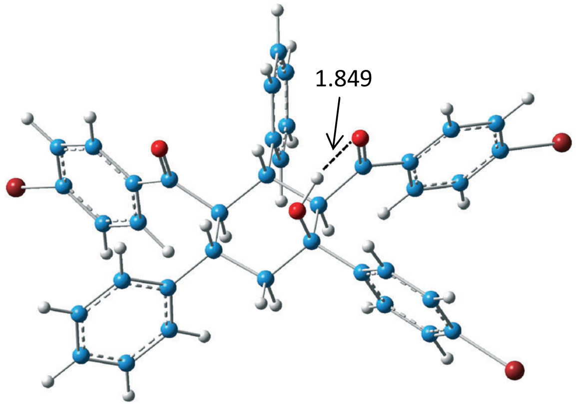


Figure 3. The calculated distance (Å) between the O-H···O by the DFT B3LYP/6-31G and B3LYP/6-31G(d,p) methods.

the carbonyl groups (Fig. 3). The O-H···O distances have been calculated by the DFT B3LYP/6-31G, B3LYP/6-31G(d,p) methods and equal 1.848 and 1.849 Å, respectively.

The preferred chair conformation for the six-membered ring [4-(4-bromophenyl)-4-hydroxy-2.6-diphenylcyclohexane-1.3-diyl) bis(4-bromophenyl)methanone, **2**] was confirmed by 2D NOESY, ROESY NMR (because of space interaction between the 2A-2B, 2A-3, 2B-4, 2B-6, 2B-Ar, 3-5, 3-OH, 3-Ar, 5-OH, 5-Ar, 4-6, 4-Ar, OH-Ar, 6-Ar, Figs. S6 and S7), and quantum-chemical calculations; the most stable conformer is chair (**A**) with zero relative energy, Table 3, Figs. 1 and 2) methods.

Conclusions

Concentration (%) and volume (ml) influences of the bases on the reaction products were studied. Formation of product **1** (alcoholic NaOH, KOH concentration – 10–40%, volume – 0.5 and 5 ml), product **2** (alcoholic NaOH, KOH concentration – 50 and 60%, volume – 5 ml), and polymer products (alcoholic NaOH, KOH concentration – 50 and 60%, volume – higher than 5 ml) at the presence of indicated bases were revealed. We could not obtain concentrations higher than 60%, because of the poor solubility of bases in water.

Our studies have confirmed that types of substrate (in our case 4-bromoacetophenone) and bases do not influence the reaction product, but influence to the yield and new six-membered Kostanecki triketone derivative **2** was detected.

The NMR investigations in different solvents and quantum-chemical calculations have confirmed the presence of six-membered chair conformation (**A**) in solutions. The substituents (including three bromine atoms) in cyclohexane do not influence the ratio of conformers; the chair conformation **A** is more preferable in solution of **2**.

The formation of an intramolecular hydrogen bond between OH and O = C groups in solutions were confirmed by the NMR and O-H···O distance calculated by the quantum-chemical methods (~1.85 Å).

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