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SHORT COMMUNICATION

A unique synthesis of *N*-(*Z*)-5-bromo-6-hydroxyhexahydro isobenzofuran-1(3*H*)-ylidene)methanaminium bromide

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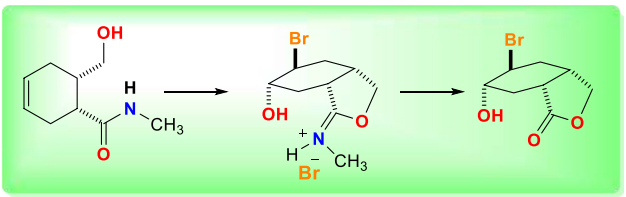
Abstract

Substituted cyclohexane derivatives are used as key compounds in the synthesis of different natural or synthetic compounds. In this context, we synthesized a new 1,6-disubstituted cyclohexene derivative and studied its bromination reaction. First, we obtained carboxamide **11** containing three functional groups by reduction of tetrahydro-1*H*-isoindole-1,3(2*H*)-dione with $NaBH_4$. Bromination of carboxamide **11** gave the interesting rearrangement product hexa-hydroisobenzofuran-1(3*H*) iliden)methanaminium depending on the groups in the cyclohexene ring and its exact configuration was determined by X-ray analysis. Hydrolysis of the iminium salt gave 5-bromo-6-hydroxyhexyhexahydro isobenzofuran-1(3*H*)one. The reaction mechanism for the rearrangement product was proposed. As a result, two unexpected reactions occurred in the bromination reaction. The first is the incorporation of halohydrin into the molecule in anhydrous medium and the second is the facile formation of the five-membered lactone ring.

Graphical abstract



Keywords Carboxamide · Reduction reaction · Bromination reaction · Ylidenemethanaminium bromide · Bicyclic lactone

Introduction

The reduction of imides to the corresponding products has been studied with various metal hydrides. In these reactions, the formation of products varies depending on the strength of the reducing agent used. In addition, the amount of reducing agent used and the reaction times are an important factor in these reactions (Brown and Heim 1973; Garmaise and Ryan 1970; Horii et al. 1961; Strassert and Awruch 2006; Guangni et al. 2015).

Recently, we studied the reduction reaction of the dibromo-imide **1** with $LiAlH_4$. In this reaction, the carbonyl groups in the molecule were reduced to methylene (CH_2) with $LiAlH_4$ and surprisingly, dibromine elimination also took place in the molecule (Tan et al. 2011) (Scheme 1a). Also, we investigated the reduction reaction of the imide compound **3** with $NaBH_4$ to synthesize the 3-hydroxy lactam **4** from the imide compound. In this study, in addition to lactam **4** (aminocarbinol compound), in which the hydroxy group is in the exo-position, we obtained the carboxamide compound as a secondary product (Gündoğdu et al. 2022) (Scheme 1b).

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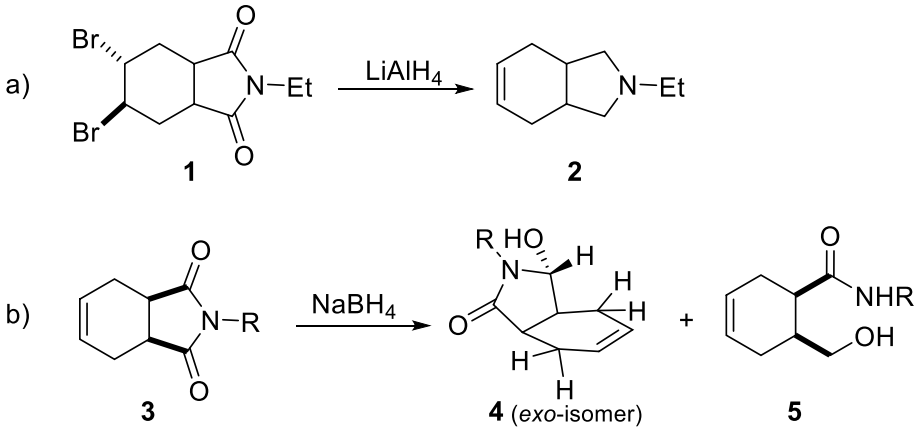


Scheme 1 **a** Reduction reaction of imide **1** with $LiAlH_4$; **b** Reduction reaction of imide **3** with $NaBH_4$

In both studies, it was observed that different products were formed depending on the type of reducing reagent. On the other hand, it is known in the literature that secondary products are formed depending on the amount of reagent used and the reaction time. In this context, as part of our current studies on the development synthesis of isoindole derivatives from readily available building blocks, herein we report our results involving the reduction of bicyclic imide **3** to the corresponding cyclohex-3-en-1-carboxamide **5** using $NaBH_4$ and the bromination reaction of carboxamide are formed depending on the amount of reagent used and the reaction time.

Here we report the unique products formed from the bromination. We performed spectroscopic studies for structure determination and absolute configuration. Also, we discussed the for-mation mechanism of the products formed in the bromination reaction.

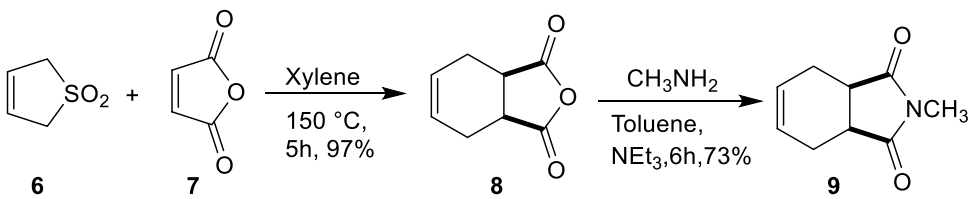
Result and discussion

Our starting material was **9**, 4,7,7a-tetrahydroisobenzofuran-1,3-dione (**8**) which has been obtained from Diels–Alder reaction of 3-sulfolene (**6**) with maleic anhydride (**7**). Condensation of primer amine with cyclic anhydride **8** in the presence of a 3:1 mixture of toluene and triethylamine gave the bicyclic imide **9** (Tan et al. 2014) (Scheme 2).

Generally, in the reduction reactions of cyclic imides; the reaction time, the type and amount of the reducing agent used in the reaction significantly affect the product formation (Hubert et al. 1975; Ilkei et al. 2014).). In our previous studies, we performed the conversion of the imide compound to 3-hydroxy lactam and cyclohex-3-en-1-carboxamide **5** derivative by reduction with $NaBH_4$ depending on the reaction conditions (Gündoğdu et al. 2022). It was observed that the amount of 3-hydroxy lactam **10** decreased and the amount of the carboxamide **11** increased when the reaction time was prolonged. This result showed that cyclohex-3-ene-1-carboxamide **11** is the secondary product of 3-hydroxy-isoindol-1-one **10**.

Reduction of bicyclic imide **9** with sodium borohydride in any solvents results in the formation of cyclohex-3-ene-1-carboxamide **11**, or a mixture of 3-hydroxyisoindol-1-one **10** and **11** depending on the amount of reducing agent present. In addition, the amount of product formation also depends on the solvent used. When the reduction products are compared according to the solvent used, it is seen that the yield in MeOH is better than THF itself. However, an excellent yield is obtained when a mixed solvent (THF/H_2O) is used. For instance, when two molar equivalents of sodium borohydride was employed, the product was the cyclohex-3-ene-1-carboxamide **8** (Table 1 entry 4). The reduction reaction was carried out under the conditions given in Scheme 3 to obtain cyclohex-3-ene-1-carboxamide **11** as a single product. Thus, the cyclohexene derivative containing 1,6-disubstituted groups was easily synthesized by this methodology.

As it is known, compounds containing substituted cyclohexane ring are used as precursor compounds in the synthesis of different natural or synthetic compounds, in



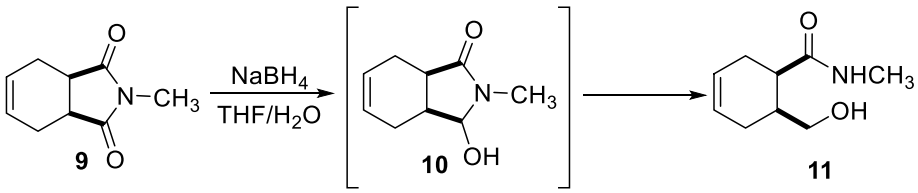
Scheme 2 Synthesis of bicyclic imide derivative **9**

Table 1 Reduction products of the bicyclic imide **9** with $NaBH_4$

Entry	Bicyclic imide 6 (equiv.)	$NaBH_4$ (equiv.)	Solvent	Time (h)	The ratio of compounds in reaction mixture according to the ^1H NMR spectrum (%)		
					9	10	11
1	1	1	THF	6	12	50	38
2	1	2	THF	6	10	50	40
3	1	1	THF/H_2O	6	–	65	35
4	**1**	**2**	**THF/H_2O**	**6**	**–**	**–**	**100**
5	1	1	MeOH	6		65	35
6	1	2	MeOH	6	–	35	65

The best yield was obtained under the conditions in entry 4 (in bold)

Scheme 3 Reagent and conditions; 2 equiv. $NaBH_4$, 0 °C to rt, 6 h, THF/H_2O (1:1)



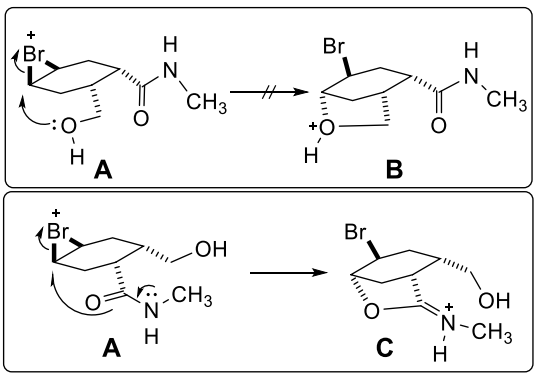
addition to their existing biological activities (Thebtaranonth and Thebtaranonth 1986; Marca-Contelles et al. 2004).

We specifically targeted these studies in terms of the secondary product carboxamide **11** because carboxamide **11** containing 1,6-disubstituted groups has the potential to be used as a key compound in the synthesis of polysubstituted cyclohexane derivatives (Scheme 3).

Due to its remarkable combination of functionality, the carboxamide **11** with three different functional groups (double bond, hydroxymethyl and amide functionality) has a very high potential for use as starting materials for the preparation of various cyclitol or related molecules (especially polysubstituted cyclohexanes).

We decided to use carboxamide **11** as the precursor compound for the synthesis of tetrasubstituted cyclohexane derivatives. For this purpose, we primarily focused on the bromination reactions of the carboxamide **11** to synthesize dibromocyclohexane derivatives. On the other hand, it has been reported the formation of interesting compounds in the bromination reaction of cyclic systems. In the reaction, unexpected compounds are formed depending on functional groups (Daştan et al. 1996; Altundaş et al. 2000; Kishalı et al. 2003, 2006).

In particular, groups such as hydroxy methyl and amide at the 1,6-position of carboxamide **11** are expected to be decisive in the formation of the product in the addition reactions of this compound and the formation of rearrangement products can occur in these reactions. Therefore, we



Scheme 4 Intermediate products **B** and **C** that can be formed by the the back side attack of the oxygen atom on the bromonium ion

performed the bromination of **11** to obtain a tetrasubstituted cyclohexane derivative.

The bromination of cyclohexane-1-carboxamide **11** in CH_2Cl_2 gave a very interesting sole product. ^1H and ^{13}C NMR spectroscopic data confirmed the addition of bromine to the double bond. In fact, we supposed that the bromine would add to double bond to give a dibromide. But, ^1H NMR spectra did interestingly show only one CH–Br proton and one CH–O protons in molecule. In addition, two different carbon signals which adjacent to oxygen appeared at ^{13}C-NMR.

In this case, we assume that the oxygen atom of the primary alcohol or the oxygen atom of the carbonyl group is

bonded to the ring. For instance, the oxygen atom of the alcohol or the oxygen atom of the carbonyl can attack the bromonium ion from the back side and form the intermediates in Scheme 4. Although the chemical shift values of the alcohol's CH_2 protons showed that the molecule had converted to an etheric structure, we could not be certain of the formation of intermediate product B. On the other hand, the carbonyl oxygen in the amide group is more nucleophilic due to the mesomeric effect. Therefore, the formation of the second intermediate product C is also possible. In addition, the shift of the chemical shift value of the amide carbonyl carbon to the lower area indicates that it has reacted in this group. It can be in additional different arrangements over both intermediate products that are likely to occur as a result. Although all NMR spectral data support a fused cyclic ring structure. Based on the spectral data, as we were not sure what kind of structure was formed, a single crystal analysis was performed (Fig. 1).

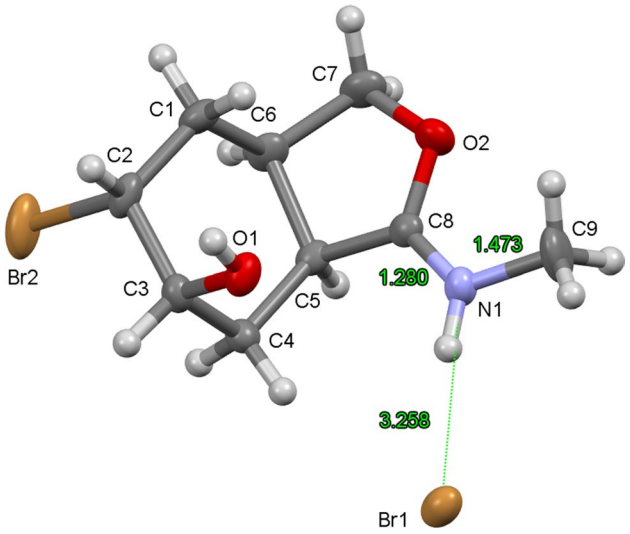
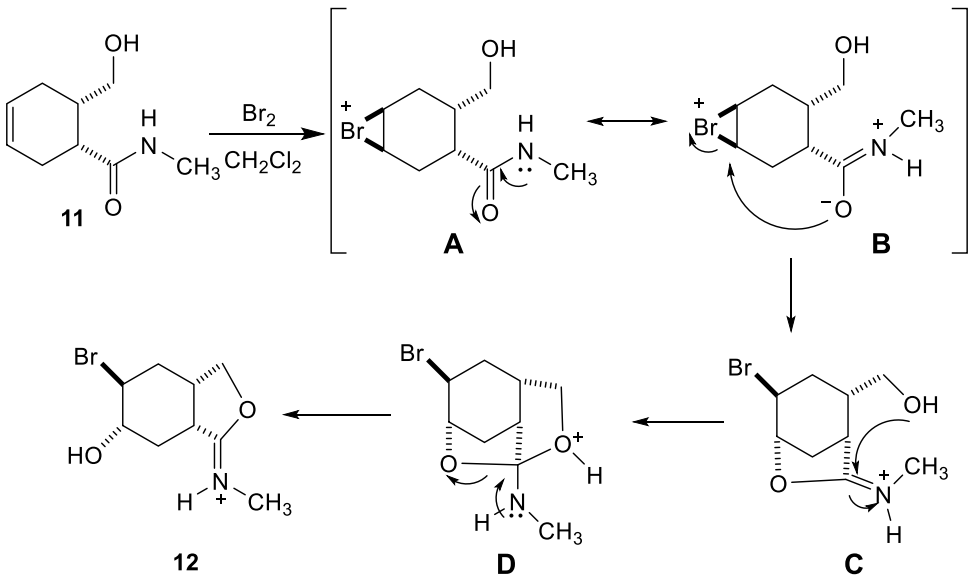
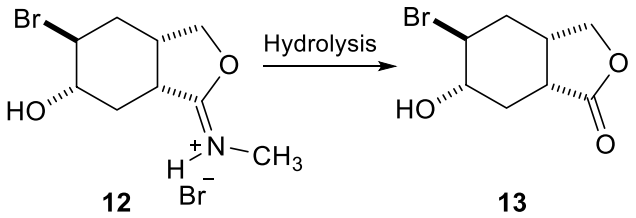


Fig. 1 X-ray structure of the molecule **12**. Thermal ellipsoids are drawn at the 40% probability level. Dashed green line indicates H-bonding interactions

The exact conformation of the 5-bromo-6-hydroxy-*N*-methylhexahydro-2-benzofuran-1(3*H*)-iminium bromide (**12**) was confirmed by X-ray diffraction analysis (Sheldrick 2008) (Fig. 1). Molecule **12** crystallizes in monoclinic space group P21/c with four molecules in the unit cell. Cyclohexane unit has the chair-shape with the lowest conformation energy and the C–C (cyclohexane) bond lengths are in the range of 1.512(3)–1.548(3) Å, all have the single bond character. C2–Br2 and N1-C8 bond distances are 1.972(3) and 1.280(3) Å, respectively. Racemic formations of **9** has four asymmetric carbon atoms and stereogenic centers are as follows; C2(RS), C3(RS), C5(SR) and C6(RS). In the solid state, the compound **9** is stabilized via effective in-termolecular N1–H•••Br1 [D•••A = 3.258(3) Å] and O1–H•••Br1 [D•••A = 3.269(3) Å] hydrogen bonds which lead to the formation of the polymeric structure. Considering the structure of the molecule formed, the OH group was added to the double bond in the reaction. Although there is no H_2O or free OH group in the reaction medium, halohydrin is formed in the bromination reaction. In this case, it can be explained by an intramolecular oxygen transfer. Based on the structure of the product, we propose the reaction mechanism shown in Scheme 5. First, a cyclic bromonium ion is formed as a result of bromine adding the double bond. After this bromonium ion is formed, the oxygen atom of the carbonyl group in the amide group attacks the bromonium ion from back side and the oxygen atom is attached to the ring. At the same time, while the carbonyl oxygen is attached to the cyclohexane ring, the oxygen of the primary alcohol is attached to the

Scheme 5 Mechanism for the formation of hexahydro-isobenzofuran-1(3*H*)-ylidenemethanaminium bromide (**12**)





Scheme 6 Synthesis of 5-bromo-6-hydroxyhexahydroisobenzofuran-1(3*H*)-one (**13**)

carbonyl carbon, forming the structure of tricyclic intermediate product **D**. As shown in Scheme 5, rearrangement of intermediate **D** in the final step produces hexahydroisobenzofuran-1(3*H*)ylidene)methanaminium bromide (**12**).

In particular, the attachment of the hydroxy group to the cyclohexane ring in this reaction carried out in anhydrous medium strongly supports the proposed mechanism. During the purification of the crude product by column chromatography, the lactone compound was obtained. It was suggested that this situation resulted from the partial hydrolysis of the iminium group in the silica gel column. To better understand this situation, the iminium salt was mixed with silica gel in methylene chloride for overnight and the hydrolysis product lactone was obtained (Scheme 6). The structure of **13** was assigned by ^{1}H and ^{13}C NMR spectra. On the other hand, bicyclic lactone **13** was synthesized different method by Olejniczak et al. (Olejniczak et al. 2011).

In conclusion, we studied the reduction reaction of isoindole-1,3-dione **9** with sodium borohydride. Cyclohex-3-ene-1-carboxamide **11** was synthesized from this reduction reaction in 95% yield. Depending on the amount of $NaBH_4$, and solvents, different product distribution was observed. On the other hand, we demonstrated a short and stereocontrolled synthesis of a new class of isobenzofuran yliden iminium structure starting from cyclohex-3-ene-1-carboxamide **11** The reaction mechanism for the formation of isobenzofuran yliden iminium salt is proposed. As a result, two unexpected reactions occurred in the bromination reaction of carboxamide. The first reaction is the addition of halohydrin to the molecule in anhydrous medium. The second reaction is the formation of a five-membered lactone ring very easily. Furthermore, the chemical conversion of carboximide **11** to related compounds is currently under the progress.

Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra are provided in the Supplementary Material.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11696-023-03141-3.

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Author contributions ÖG contributed to Investigation, Writing– original draft. EŞ contributed to Software, Formal analysis. YK contributed to Conceptualization, Methodology, Writing–original draft.

Data availability The author confirms that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Conflict of interest Declares that the authors have no financial interests or personal relationships.

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