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New Synthesis of Semisquaric Acid Derivatives via Chlorinated *N*-(Cyclobutylidene)amines

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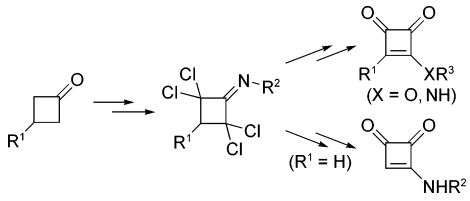

The synthesis and reactivity of new chlorinated *N*-(cyclobutylidene)amines leading to new synthetic pathways toward various substituted cyclobutenediones is described.

Cyclobutenediones have interested organic chemists for a long time because of their intriguing molecular skeleton, suggesting specific properties and reactivities such as a high ring tension and consequent enhanced electrophilicity. Indeed, since the first synthesis of 3-hydroxy-4-phenylcyclobutenedione **1**[1] via a cycloaddition of phenylacetylene with trifluorochloroethene and subsequent hydrolysis, numerous studies have been performed on this type of compounds.[2] Hydroxylated cyclobutenediones, e.g., **2** (squaric acid) and **3** (semisquaric acid) (Figure 1), have been synthesized via an acidic hydrolysis of polyhalogenated or polyalkoxylated cyclobutenes obtained by a thermal or photochemical [2 + 2]-cycloaddition of ketenes or ketene analogues to perhalogenated or alkoxylated alkenes and alkynes.[2−4] Often, difficult procedures or not readily available starting materials are used to get to these compounds. A 2,2,4,4-tetrabromination of cyclobutanone yielded semisquaric acid after dehydrobromination and successive aqueous hydrolysis.[5] Although the starting cyclobutanone is commercially available, the low overall yield (10%) makes this procedure of no preparative use. Other synthetic methods are based on the skeletal functionalization of (semi)squaric acid.[2,6,7]

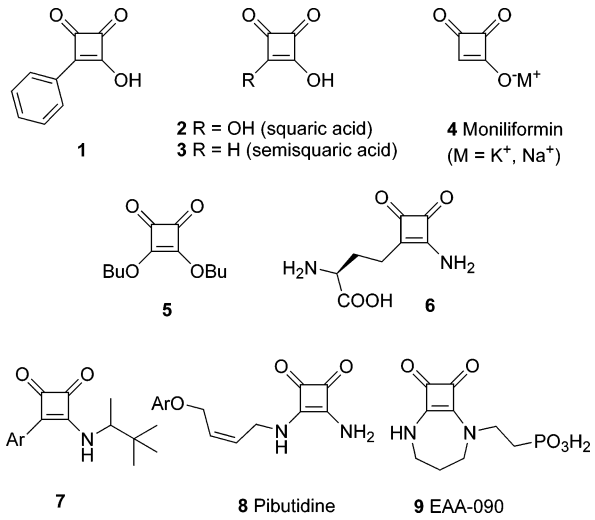

FIGURE 1. (Semi)squarates and related physiologically active cyclobutenediones

Semisquaric acid or 3-hydroxy-3-cyclobutene-1,2-dione **3** has been isolated from the maize molds *Fusarium moniliforme* and *Gibberella fujikuroi* as a sodium and potassium salt (pK_a = 0.88).[8] These salts were named moniliformin (**4**) and are toxic for mammals and possess plant growth regulating and phytotoxic effects.[9,10] Since the discovery of moniliformin, it served as a "lead" compound to synthesize numerous analogues which showed interesting physiological properties. Squaric acid derivatives were patented for their application in the treatment of chronic inflammatory diseases such as asthma, multiple sclerosis, and rheumatoid arthritis.[11] Dibutylsquarate **5** can be used as a therapy for alopecia areata, a kind of hair loss.[12,13] More general, positive results have been obtained in medicinal chemistry by the use of the squaryl group as a carboxylate isosteric group to enhance biological activity.[14] Squarates possess also a strong chelating ability to metal ions.[15]

More recently, significant research is focused on mono- and diamino-substituted cyclobutenediones, or (semi)-squaramides, which is reflected in the large number of

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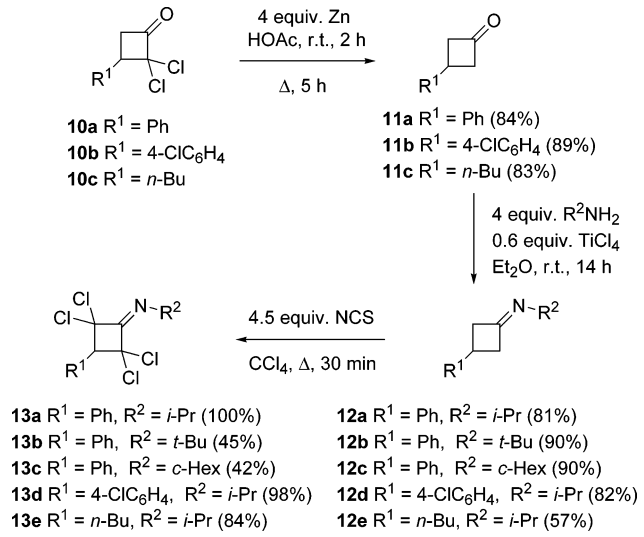
patents concerning this topic. For instance, semisquaramide **6** and derivatives showed potent paralytic activities (Figure 1).[16] Other semisquaramides display smooth muscle relaxation (**7**)[17] and antimigraine activities.[18]

In addition, diaminocyclobutenediones have been the subject of considerable research and resulted in pharmacologically interesting compounds, such as pibutidine **8**, a histamine H2 receptor antagonist[19] and EAA-090 **9**, a neuroprotectant with potential as a treatment for brain damage resulting from stroke.[20] Besides the abovementioned physiological properties of cyclobutenediones, these compounds also proved to be powerful synthetic building blocks for the synthesis of a variety of carbo- and heterocycles, such as quinones, furanones, xanthones, cyclopentenediones, phenols, and 2-pyridones.[21]

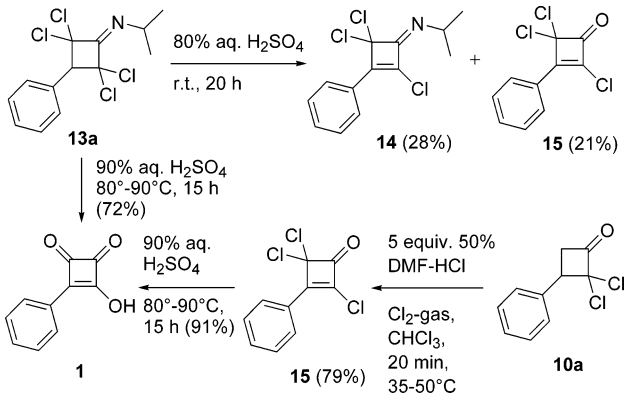
The present report describes the application of *N*-(cyclobutylidene)amines in the synthesis of different semisquarates and semisquaramides. It is surprising that no monocyclic *N*-(3-arylcyclobutylidene)alkylamines have been described so far, which makes the study of these compounds worthwhile. In addition, halogenated *N*-(cyclobutylidene)amines in general have barely been studied. Besides theoretical calculations,[22] only one paper was found concerning halogenated *N*-(cyclobutylidene)-amines. This paper deals with the synthesis of the *N*-*tert*-butylimine of a benzo-annelated 2,2-dichlorocyclobutanone.[23] Other publications deal with the synthesis and reactivity of enamines[24] or oximes[25] which are a completely different classes of compounds.

Readily available 3-substituted 2,2-dichlorocyclobutanones **10**[26] were dehalogenated with zinc in acetic acid prior to the conversion to imines **12** because a direct imination of dichlorinated cyclobutanones **10** was not successful and resulted in complex reaction mixtures. In contrast, dehalogenated cyclobutanones **11**[27] were easily

SCHEME 1



SCHEME 2



iminated using titanium(IV) chloride as an activating and dehydrating agent, resulting in new imines **12** (Scheme 1). The reaction of these new compounds with 4.5 equiv of NCS in refluxing CCl_4 for 30 min resulted in a 2,2,4,4-tetrachlorination toward novel imines **13** in high yields. To verify whether these tetrachlorinated imines could be used as precursors for 3-hydroxy-4-phenylcyclobutenedione **1**,[28] *N*-(2,2,4,4-tetrachloro-3-phenylcyclobutylidene)-isopropylamine was treated with aqueous oxalic acid, HCl, or H_2SO_4.

Much to our surprise, a considerable amount of dehydrochlorinated imine **14** was recovered after workup (Scheme 2). Even when **13a** was treated with an excess of 80% aq H_2SO_4 at room temperature, a dehydrohalogenation occurred toward *N*-(2,4,4-trichloro-3-phenyl-2-cyclobutenylidene)isopropylamine **14** which appeared to be quite stable and was only partially converted to the hydrolyzed cyclobutenone **15** after 20 h. Eventually, a complete hydrolysis of imine **13a** toward 3-hydroxy-4-phenylcyclobutenedione **1** was established under very harsh hydrolytic conditions, i.e., 90% aq H_2SO_4 at 80−90 °C for 15 h (yield 72%). To develop a most efficient pathway toward 4-phenylsemisquaric acid **1**, attempts were performed to chlorinate 2,2-dichloro-3-phenylcyclobutanone with the use of NCS or trichloroisocyanuric

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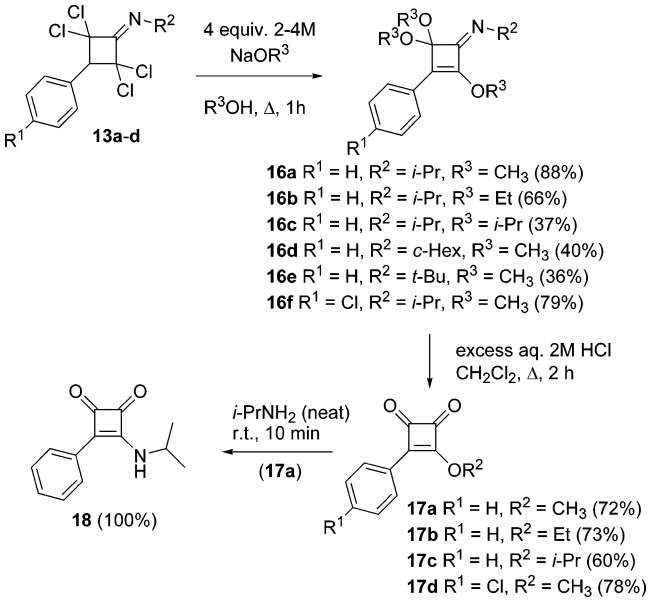
SCHEME 3



acid. Because both methods were unsuccessful, cyclobutanone **10a** (R^1 = Ph) was treated with chlorine gas in $CHCl_3$ in the presence of DMF−HCl. Under the reaction conditions used, no tetrachlorocyclobutanone was detected during the course of the reaction, but instead, trichlorocyclobutenone **15** was obtained in good yield. A final hydrolysis of the obtained cyclobutenone **15** indeed yielded 4-phenylsemisquaric acid **1** in good yield (Scheme 2). This new synthesis is more efficient and easier to perform as compared to other procedures reported in the present literature.[2]

In an approach to reach 4-substituted 3-alkoxycyclobutenediones, tetrachlorinated imines **13** were treated with 4 equiv of a 2−4 M solution of various sodium alkoxides in the respective alcohols (Scheme 3). The resulting trialkoxycyclobutenylimines **16** originated from an initial dehydrohalogenation toward imines **14** followed by a 3-fold substitution of the remaining chlorine atoms by the respective alkoxides. Unfortunately, the reaction of *N*-(3-butylcyclobutylidene)amine **13e** resulted in a tarry reaction mixture which could not be purified. In contrast, this reaction pathway proceeded very smoothly when using *N*-(3-arylcyclobutylidene)amines **13a**−**d**. The obtained new cyclobutenimines **16** were efficiently hydrolyzed in a biphasic CH_2Cl_2/aq 2 M HCl system toward 3-alkoxy-4-arylcyclobutenediones **17**[29] in high yields. This method provides alkyl 4-arylsemisquarates directly, without the need for a transformation of semisquaric acid to the vinylogous esters. Methyl 4-phenylsemisquarate was easily converted to the corresponding *N*-isopropylsemisquaramide **18** by reaction with isopropylamine at room temperature.

Encouraged by these results, efforts were made to apply this synthetic methodology to unsubstituted cyclobutanone **19**, which should lead to semisquarates in a very straightforward manner. Commercially available cyclobutanone was reacted with NCS, trichloroisocyanuric acid or chlorine gas, but unfortunately, in no cases could a clean reaction mixture be obtained. The reaction resulted in a mixture of compounds which could not be separated by distillation or column chromatography. In

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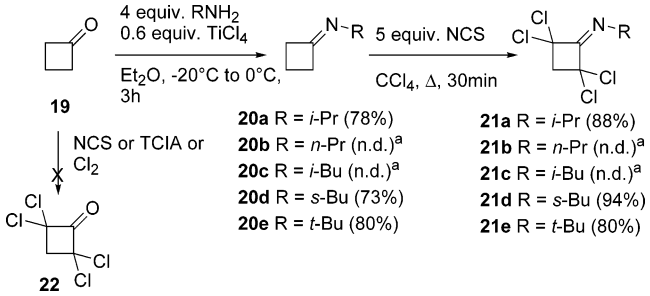
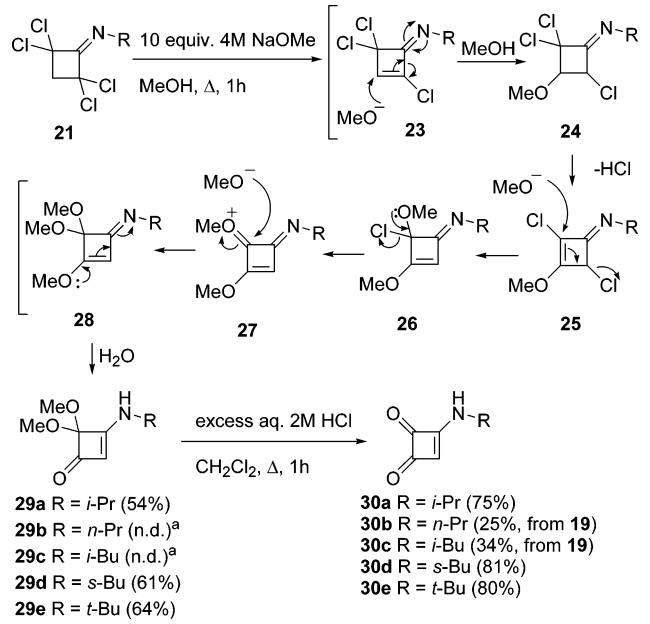


[a] n.d.: yield not determined (unstable compounds; the reaction mixture was used as such for further transformation).

SCHEME 5[a]



[a] n.d.: yield not determined (unstable compounds; the reaction mixture was used as such for further transformation).

contrast, the reaction of *N*-(cyclobutylidene)amines **20a**[30]−**e**, which were prepared from cyclobutanone, with 5 equiv of NCS in dry tetrachloromethane nicely resulted in *N*-(2,2,4,4-tetrachlorocyclobutylidene)amines **21** in good yields (Scheme 4). Attention must be drawn to the fact that *N*-(cyclobutylidene)amines **20** are low-boiling, heat- and moisture-sensitive compounds which have to be used for further transformation immediately after isolation. In particular, imines **20b** and **20c**, derived from less sterically hindered amines, could not be stored even at low temperature (−20 °C). Nevertheless, when used directly in the chlorination reaction, no special precautions had to be taken. Treatment of the chlorinated imines **21** with an excess of 4 M sodium methoxide in methanol did not yield the expected *N*-(2,4,4-trimethoxy-2-cyclobutenylidene)alkylamines, but gave compounds **29** (Scheme 5). The formation of these compounds can be rationalized by an initial Michael addition of methoxide to the intermediate *N*-(trichlorocyclobutenylidene)amine **23** and subsequent dehydrochlorination and substitution of the remaining chloro atoms by methoxide. The intermediates **24** and **25** and the resulting imines **28** could not be isolated even when using a nonaqueous workup.

Instead, cyclobutenones **29** resulting from the hydrolysis of imines **28** were obtained after aqueous workup. The structural assignment of these compounds was confirmed by an X-ray analysis of the isopropyl derivative **29a**, which was purified by recrystallization from $Et_2O/CCl_4/CH_2Cl_2$ 50:50:5.

After hydrolysis of the vinylogous amides **29** with aqueous HCl, crystalline semisquaramides **30a**−**e**[31] were isolated and purified by chromatography in good yields. Due to the low stability of *n*-propyl- and isobutylamino intermediates **20b**,**c**, **21b**,**c** and **29b**,**c**, a rapid synthesis of **30b** and **30c** was necessary, without purification of the intermediates. In that way, an overall yield of about 30% for squaramides **30b**,**c** and ca. 40−45% for derivatives **30a**,**d**,**e** could be accomplished starting from commercially available cyclobutanone.

In conclusion, it can be stated that an evaluation of the synthetic utility of chlorinated *N*-(cyclobutylidene)-amines, a virtually unknown class of compounds, emerged in new straightforward syntheses of various semisquarates and new semisquaramides. The latter compounds are of particular interest having in mind the renewed attention focused on these compounds which often display potent physiological activities. In addition, an efficient synthesis of 4-phenylsemisquaric acid was developed via initial chlorination of 2,2-dichloro-3-phenylcyclobutanone and subsequent hydrolysis.

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Supporting Information Available: General experimental conditions; ^{1}H NMR, ^{13}C NMR, IR, MS, and EI analytical data for compounds **12**−**18**, **20**, **21**, **29**, and **30**; X-ray crystallographic data for compound **29a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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