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Synthesis of Methyl-1-(*tert*-butoxycarbonylamino)-2-vinylcyclopropanecarboxylate via a Hofmann Rearrangement Utilizing Trichloroisocyanuric Acid as an Oxidant

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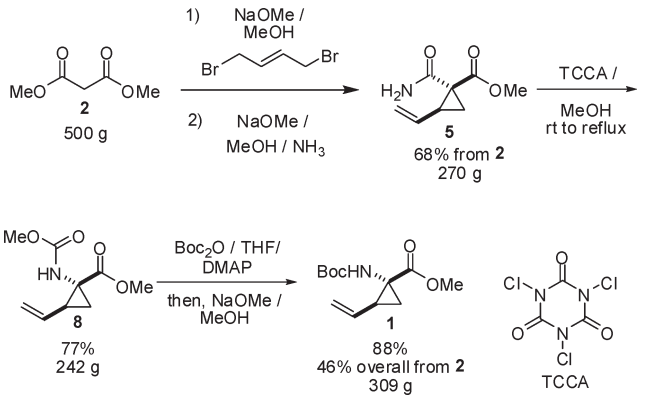

A trichloroisocyanuric acid (TCCA) mediated Hofmann rearrangement was utilized to synthesize methyl-1-(*tert*-butoxycarbonylamino)-2-vinylcyclopropanecarboxylate. A variety of functional groups are tolerated in this reaction including vinyl, cyclopropyl, pyridyl, aryl, benzyl, and nitro groups.

A number of naturally occurring and biologically active compounds contain cyclopropane amino acids (Figure 1).[1] More recently, cyclopropane moieties have found application in peptomimetics, presumably due to conformational rigidity.[1c] The synthesis of this class of unnatural amino acids has been described in the literature, with preparations on the kilogram scale.[2−4]

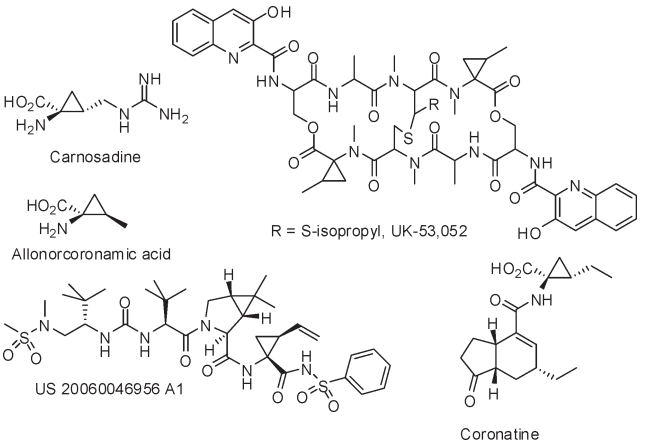

FIGURE 1. Examples of naturally occurring and biologically active molecules containing cyclopropane amino acids.

We wished to develop a novel approach to compound **1** (Scheme 1) that would be efficient and amenable to kilogram scale. The racemic synthesis outlined in Scheme 1 accomplishes this goal and produces **1** in high yield from stable, crystalline intermediates and inexpensive starting materials.

Further, the lipase-catalyzed kinetic resolution of **1** is known,[4] and proceeds with high efficiency, thereby providing convenient access to nonracemic material.

The synthesis begins with the known[3a] alkylation of dimethyl malonate with *trans*-1,4-dibromobutene to provide vinylcyclopropane **3** along with small amounts (~8%) of cyclopentene **4**. This reaction was not subjected to workup, and was instead directly treated with a methanolic solution of ammonia[5] (9 equiv) and sodium methoxide (0.8 equiv) to provide **5** as a crystalline solid that was isolated in 68% yield. Under these conditions, malonamide **6** is formed from cyclopentene **4**, as is a small amount of malonamide **7**. Both of these compounds are water-soluble and are removed during the workup by an aqueous wash. This procedure provides **5** exclusively with the stereochemistry depicted in Scheme 1 to the limits of NMR detection.[6] This is likely due to steric effects rendering the less hindered carbonyl of the malonate more prone to substitution. Further, it is likely that any of the minor isomer of **5** that is produced will be consumed by undergoing substitution to malonamide **7** under the reaction conditions.

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(6) Compound **5** is directly converted to compound **8** via Hofmann rearrangement. The stereochemistry of compound **5** was determined by NOE analysis on compound **8** and is consistent with the relative stereochemistry depicted in Schemes 1 and 2. Details are provided in the Supporting Information.

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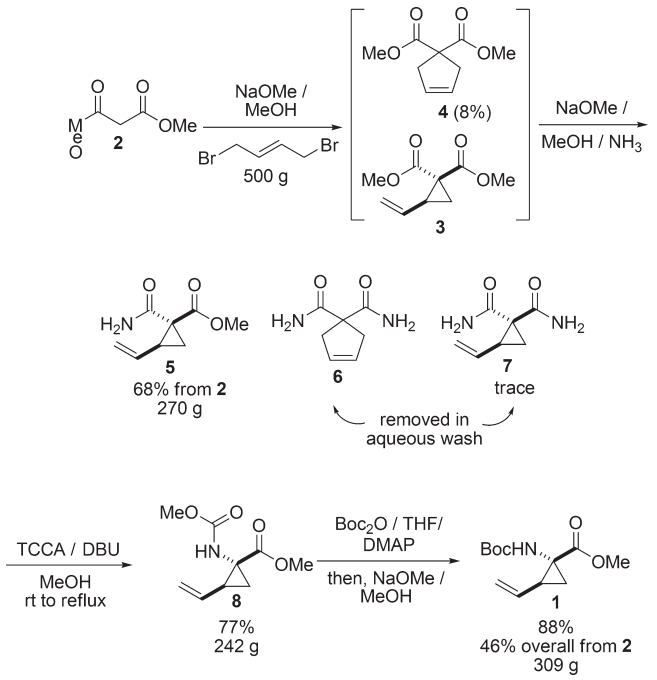
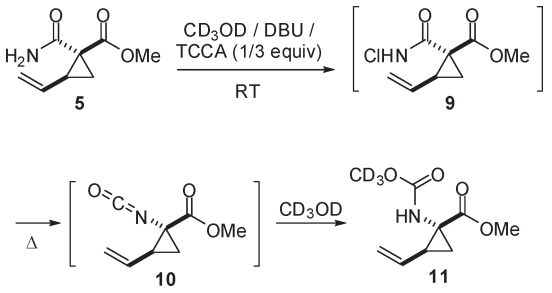
SCHEME 1. Synthesis of 1 via the Hofmann Rearrangement



Amide **5** was then converted to methylcarbamate **8** in high yield by a trichloroisocyanuric acid (TCCA)-mediated Hofmann rearrangement. The Hofmann rearrangement converts a primary amide to either an amine or a carbamate, depending on the conditions, with the loss of a carbon atom.[7] The reaction is an oxidation and can be performed with

SCHEME 2. Hofmann Rearrangement NMR Experiment



a variety of oxidants including bromite,[8] *N*-bromosuccinimide (NBS),[9] $Pb(OAc)_4$,[10] and hypervalent organoiodine compounds,[11] among others. The rearrangement proceeds via an isocyanate and is mechanistically related to the Curtius,[12] Lossen,[13] and Schmidt[14] reactions. It has been used in the synthesis of natural products[15] and demonstrated in large scale manufacturing processes.[16]

The challenge in the application of this transformation to substrate **3** is to effect oxidation and rearrangement of the amide without disturbing the alkene or the cyclopropane in the molecule. We studied the traditional reagents and procedures used in the Hofmann rearrangement with limited success. The succinimide reagents, NBS and *N*-chlorosuccinimide (NCS), were found to effect the desired transformation in methanol. Unfortunately, using the typical procedures for NBS (refluxing the amide and NBS in methanol in the presence of base), only partial conversion was observed. It is known that NBS undergoes decomposition in the presence of base at higher temperature,[17] and as such, excess NBS can be used to force the reaction to completion.[9a] However, using excess NBS resulted in bromination of the product. The use of NCS was deemed inferior due to the decomposition of the reagent via a nucleophilic ring-opening and subsequent Hofmann rearrangement of the ring-opened product as suggested by the presence of impurities in the NMR spectrum of the crude reaction mixture. The use of NaOCl in aqueous solution produced a complex mixture of products. The hypervalent iodine reagent [*I*,*I*-bis(trifluoroacetoxy)iodo]benzene (PIFA) was studied but is known to be sensitive to halogen and solvent impurities[18] and was found to be capricious. TCCA and sodium methoxide in refluxing methanol[19] gave the desired methylcarbamate with some overoxidation of the product to the *N*-chloro species. This reaction was deemed promising and chosen for further study.

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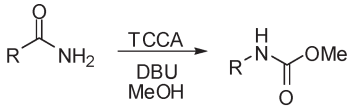
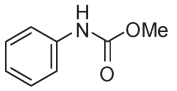
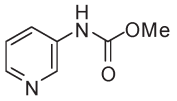
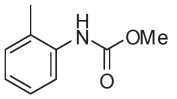
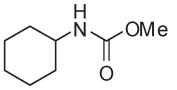
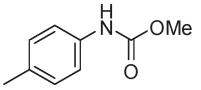
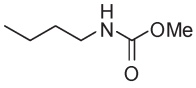
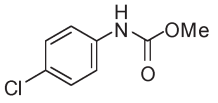
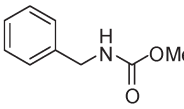
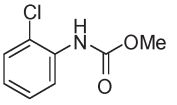
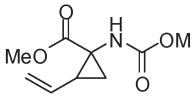
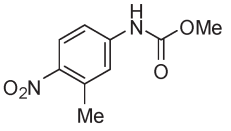
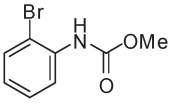
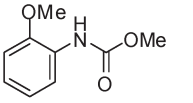
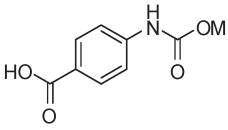
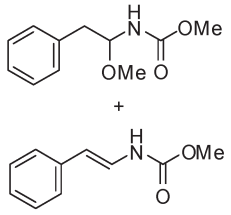
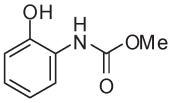
TABLE 1. Scope of the TCCA Hofmann Rearrangement



entry	product		yield	entry	product		yield
1		**12**	92%	9		**21**	84%
2		**13**	83%	10		**22**	80%
3		**14**	96%	11		**23**	65%
4		**15**	75%	12		**24**	84%
5		**16**	67%	13		**8**	77%
6		**17**	90%	14		**25**	Multiple products
7		**18**	71%	15		**26**	decomposition
8		**19** **20**	79% (19:20 = 60/40)	16		**27**	decomposition

We first studied reducing the amount of active chlorine to 1 equiv in order to prevent over-oxidation of the product. TLC evidence suggested that the chlorination of the amide was rapid with TCCA in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), but the rearrangement was slower. Therefore, the progress of the reaction was studied by NMR in CD_3OD (Scheme 2). At room temperature and in the presence of stoichiometric amounts of DBU, TCCA cleanly and quantitatively converts amide **5** to chloroamide **9**. Both the oxidant and chloroamide **9** are stable under these conditions, thereby allowing for the use of stoichiometric amounts of active chlorine (i.e., 1/3 equiv of TCCA) for the full conversion of the amide to the chloroamide. Heating this intermediate to reflux in methanol for 2.5 h then induces the rearrangement and provides the desired carbamate cleanly with no over-oxidation. This two-stage procedure wherein chlorination is allowed to proceed to completion under mild conditions prior to heating and rearrangement was found to be a significant process improvement as compared to procedures in which the oxidant is added at high temperature.[9a] The fact that TCCA is inexpensive and easily handled on scale[20] further adds to the appeal of this method.

This process utilizes methanol as the solvent and therefore provides a methylcarbamate product that must then be converted to a Boc-carbamate in a subsequent step. The use of *tert*-butanol as solvent in place of methanol would save a synthetic step by directly producing the Boc-carbamate. Unfortunately, TCCA and other halogen-based oxidants (NBS and NCS) were incompatible with *tert*-butanol forming dark insoluble products under the reaction conditions. Fortunately, the transformation

(20) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384–393.

of methyl carbamate **8** to the Boc-carbamate could be accomplished in high yield (88%) by modification of the Burk[21] method wherein a Boc-group is first installed on the carbamate by treatment with $(Boc)_2O$ and DBU in refluxing THF followed by selective removal of the methyl carbamate by treatment with sodium methoxide. The route shown in Scheme 1, featuring the TCCA-mediated Hofmann rearrangement, provides racemic **1** in 46% overall yield on 270 g scale. An additional benefit to this approach is the potential for enzymatic resolution on intermediates **5** or **8** as well as ester **1** to provide a single enantiomer.

During the course of this research, Hiegel and Hogenauer reported the use of TCCA in the Hofmann rearrangement of amides to methyl carbamates.[22] However, their work was limited to simple aliphatic and aromatic substrates. To further define the scope of this transformation, a number of substrates bearing a variety of functional groups were examined (Table 1). We utilized the procedure developed in the synthesis of **1** wherein TCCA is added portion-wise to a mixture of the amide, methanol, and base, at room temperature. Following chloroamide formation, the mixture is then heated to reflux overnight, concentrated, and purified by flash chromatography.

In general, the reactions proceeded smoothly with a few exceptions as shown in Table 1. Both nonsubstituted (entry 1, Table 1) methyl-substituted (entries 2 and 3) and chloro-substituted (entries 4 and 5) aromatic amides provide high yields under these conditions. The reaction proceeds in the presence of both electron-withdrawing and electron-donating aromatic substituents (entries 6 and 7). Cinnamamide undergoes rearrangement to provide the corresponding enamide as a 60/40 mixture of the methoxy-substituted product **19** and the expected product **20** (entry 8). Nicotinamide provides the desired product without oxidation of the pyridyl amine (entry 9). Cyclic (entry 10) and straight chain (entry 11) aliphatic substrates, as well as phenylacetamide (entry 12), give good yields. Attempted application of this method to 2-bromo benzamide resulted in multiple products (entry 14). Benzoic acid and 2-hydroxybenzamide substrates (entries 15 and 16) decompose under these conditions. In the case of the 2-hydroxybenzamide, this may be attributed to TCCA's ability to chlorinate phenols and anilines under mild conditions without acid catalyst.[23]

In conclusion, an efficient, safe, and scalable TCCA-mediated Hofmann rearrangement has been employed in a novel synthesis of an unnatural amino acid moiety that is becoming a building block in many novel drug candidates. The scope of the TCCA-mediated Hofmann rearrangement has also been expanded to include a number of functional groups including olefins, esters, halogens, ethers, heteroaromatic, cyclopropyl, and nitro functionality.

Experimental Section

General Procedure for the TCCA-Mediated Hofmann Rearrangement (12). To a flask equipped with magnetic stirring, reflux condenser, and N_2 inlet was added benzamide (2.0 g, 16.51 mmol), MeOH (20 mL, 10 vol to amide), and 1,8-diazabicyclo-[5.4.0]undec-7-ene (5.6 g, 37.15 mmol). To the reaction was added trichloroisocyanuric acid (TCCA) (0.73 g, 3.14 mmol). The reaction was allowed to stir for 15 min at which time additional TCCA (0.73 g, 3.14 mmol) was added. The reaction temperature was increased to 65 °C and was stirred for 16 h. The reaction was judged complete by disappearance of the starting material using TLC. The reaction was concentrated on a rotary evaporator at 40 °C. The oil was dissolved in a minimal amount of EtOAc and the solvent was concentrated. Compound **12** was purified by chromatography to give 2.3 g (92%) of a white solid: mp 48−50 °C (lit.[1] mp 46−46.8 °C); ^{1}H NMR[2] (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.58 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 138.1, 129.2, 123.6, 118.9, 52.5; IR (cm^{-1}) 3355, 3297, 1702, 1600, 1541. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.61; H, 5.66; N, 9.27.

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Supporting Information Available: Experimental procedures for compounds **1**, **5**, and **8**, as well as full characterization of **12**−**18**, **21**−**24**, and compounds **1**, **5**, and **8**, and ^{1}H NMR of compounds **19** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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