ORGANIC
LETTERS

2007
Vol. 9, No. 14
2685−2688

The First Cyclopropanation Reaction of Unmasked α,β-Unsaturated Carboxylic Acids: Direct and Complete Stereospecific Synthesis of Cyclopropanecarboxylic Acids Promoted by Sm/CHI_3[†]

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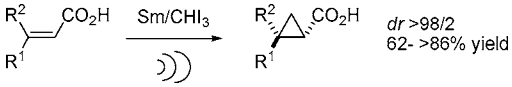
Received April 19, 2007

ABSTRACT



A samarium-promoted cyclopropanation of unmasked α,β-unsaturated acids is described. This reaction can be carried out on (*E*)- or (*Z*)-α,β-unsaturated carboxylic acids. In all cases the process is completely stereospecific and stereoselective. A mechanism has been proposed to explain the cyclopropanation reaction.

During the course of the synthesis of complex polyfunctionalized molecules, it is normally necessary to carry out a variety of protecting processes on one or multiple organic functional groups. An incorrect choice of protecting groups can result in failure of the synthesis since the precursor compounds or the target molecule can suffer undesirable side reactions during the protection/deprotection protocols. In addition, performance of the protection and deprotection steps increases the number of operations in the overall synthesis and decreases its overall yield. Among the different organic functional groups, the carboxylic acid moiety has proven to be unsuitable under a variety of reaction conditions (e.g., organometallic reagents and strong bases), thus it has to be masked (protected) through a synthetic sequence and deprotected in the final step to afford the corresponding carboxylic acid derivative.

Cyclopropanecarboxylic acids are important building blocks and have been used as starting materials to obtain different compounds such as pyrethrins, pyrethroids, and other industrially valuable compounds that are abundant in nature.[1]

To the best of our knowledge, no methods have been previously reported for the direct conversion of α,β-unsaturated carboxylic acids into cyclopropanecarboxylic acids. In the past, the reported syntheses of cyclopropanecarboxylic acids have been carried out in two steps: (a) the synthesis of the corresponding cyclopropanecarboxylic acid derivatives (generally esters or amides); and (b) the hydrolysis of the cyclopropyl esters or amides obtained to unmask the carboxylic acid function[1] in the second step. In some cases, this hydrolysis takes place under undesirable harsh reaction conditions that can produce enolization reactions.

[†] This paper is dedicated with best wishes to Professor Vincente Gotor on the occasion of his 60th birthday.

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10.1021/ol0709174 CCC: $37.00

Although the Simmons−Smith[2] is considered one of the most widely employed methods for cyclopropanation processes, the two most commonly utilized methodologies to access to cyclopropyl esters or amides with high stereoselectivity (such as precursors of cyclopropanecarboxylic acids) are the metal-catalyzed decomposition of diazo compounds,[3] and the cyclopropanation of a variety of Michael acceptors.[4] However, these methods can present some drawbacks: (a) the need to use explosive, flammable, and harmful reagents in the case of the transition-metal-catalyzed cyclopropanation of alkenes with diazo compounds; (b) the fact that total control of the stereoselectivity in the synthesis of cyclopropanes is not readily realized.[3b,c] In general, it can be considered that methods for the efficient synthesis of cyclopropanecarboxylic acids still remain unresolved. Consequently, the development of an efficient method to carry out a direct cyclopropanation reaction of unprotected α,*β*-unsaturated carboxylic acids that obviates the protection−deprotection steps would be of great interest.

Recently, as part of our interest in the development of new synthetic applications of samarium, we have reported the syntheses of 3-hydroxycarboxylic acids[5] and α,*β*-unsaturated acids[6] by the reaction of aldehydes with iodoacetic acid or dibromoacetic acid, respectively. In both cases, C−C bond formation took place using unmasked halogenated acetic acids. These transformations were the first examples of C−C bond formation reactions utilizing unprotected carboxylic acids promoted by samarium diiodide.

Previously, the employment of samarium(II) carbenoids was reported[7] in the stereospecific cyclopropanation of allylic or allenic alcohols[8] and α,*β*-unsaturated amides.[9] In this sense, (a) the structural analogy shown by α,*β*-unsaturated acids when compared with allylic alcohols or α,*β*-enamides (Figure 1), (b) the existence of the aforementioned methods for the cyclopropanation of unsaturated compounds using samarium carbenoids,[8−10] and (c) our own results regarding the compatibility of samarium species with the carboxylic acid function[5−6] prompted us to study the cyclopropanation process of unprotected α,*β*-unsaturated acids.

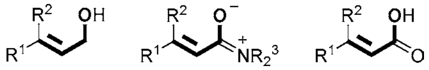

Figure 1. Structural analogy of allylic alcohols, α,*β*-unsaturated amides and acids.

Our first attempts were directed toward the cyclopropanation reaction of α,*β*-unsaturated acids **1** using similar conditions to those previously reported in the synthesis of cyclopropanecarboxamides[9] employing cinnamic acid **1a** as a model substrate. However, when we employed a mixture of 3.5 equiv of Sm and 3.5 equiv of CH_2I_2 (for the generation of samarium carbenoids) a 1/1 mixture of the desired cyclopropanoic acid **2a** and the product derived from the reduction of **1a** to 3-phenylpropionic acid (as a consequence of the acidic medium and the SmI_2 generated from the Sm/CH_2I_2 mixture)[11] was obtained. Similar results were obtained when 6 equiv of samarium and CH_2I_2 mixture were utilized. To avoid the 1,2-reduction of the conjugated carboxylic acid **1a** we employed the sodium or lithium salts of the cinnamic acid as starting compounds. However, we obtained a 1/1 mixture of product **2a** and the unreacted starting material **1a**.

Taking into account our previous results concerning the generation of SmI_2 from a mixture of Sm/CHI_3 in the presence of sonic waves,[12] we decided to attempt the cyclopropanation process using Sm, CHI_3, and sonic waves. Thus, after studying several reaction conditions, the best results were obtained after treatment of α,*β*-unsaturated acids with 6 equiv of samarium metal and 5 equiv of iodoform in THF for 1 h and in the presence of sonic waves (Table 1). When the process was performed on substrate **1a** in the absence of sonic waves, product **2a** was obtained in lower yield (15%) after a longer reaction time (8 h).

The results summarized in Table 1 show that this cyclopropanation reaction took place with complete stereoselectivity (determined by GC-MS and 300 MHz ^{1}H NMR analysis of the crude products **2**) and in moderate to high yields.

The cyclopropanation only took place with C−C double bonds which are activated by conjugation with an aryl group (entries 1−12) or with another C═C bond (entry 13). When

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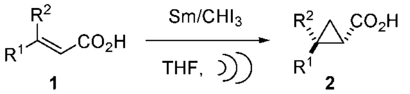
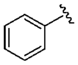
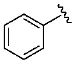
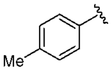
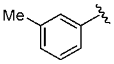
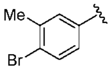
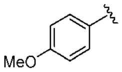
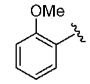
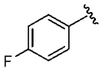
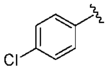
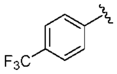
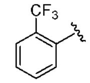
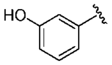
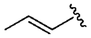
Table 1. Synthesis of Cyclopropanecarboxylic Acids **2**



entry	**2**	R^1	R^2	*dr*[a]	yield (%)[b]
1	**2a**		H	>98/2	80
2	**2b**	H		>98/2	77
3	**2c**		H	>98/2	62
4	**2d**		H	>98/2	35
5	**2e**[c]		H	>98/2	86
6	**2f**		H	>98/2	65
7	**2g**		H	>98/2	63
8	**2h**		H	>98/2	85
9	**2i**		H	>98/2	84
10	**2j**		H	>98/2	82
11	**2k**		H	>98/2	71
12	**2l**		H	>98/2	82
13	**2m**		H	>98/2	61

[a] Diastereoisomeric ratio (dr) was determined by GC−MS and 300 MHz ^{1}H NMR analysis of the crude products **2**. [b] Isolated yield after column chromatography purification based on compound **1**. [c] In compound **1e** R^1 is the same as that for compound **1d**; therefore, **2e** proceeds from the bromination of **2d**.

aliphatic α,*β*-unsaturated carboxylic acids, were utilized as starting materials, no reaction was observed, affording the unaltered unsaturated acids. In the case of maleic or fumaric acids no cyclopropanation took place either, probably because of the low solubility of the starting materials in THF.

Thus, the cyclopropanation of aromatic α,*β*-unsaturated carboxylic acids seems to be general and can be carried out using a range of cinnamic acid derivatives (with electron-donating or -withdrawing substituents) and with a variety of substitution patterns (Table 1, entries 3−4, 6−7, and 10−11).

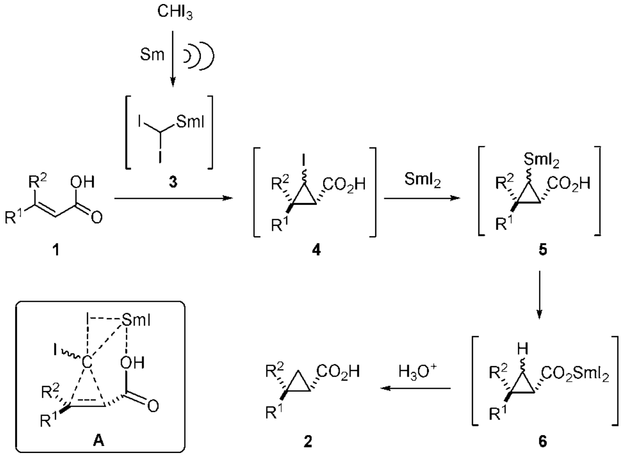
The relative *trans*- or *cis*- configuration of the cyclopropane ring was established by analysis of ^{1}H NMR coupling constants between the cyclopropane protons and by comparison with the coupling constants shown by other related cyclopropanecarboxamides previously reported.[9,13]

It is noteworthy that this process took place with complete stereospecificity since *trans*- and *cis*-cyclopropanecarboxylic acids were obtained from (*E*)- and (*Z*)-α,*β*-unsaturated carboxylic acids, respectively (Table 1, entries 1 and 2). It is also important to point out that this process takes place with total chemoselectivity. Hence, when the reaction was carried out using a dienic carboxylic acid (sorbic acid, Table 1, entry 13), only selective cyclopropanation of the 2,3-double bond was observed.

In the crude reaction products both the α,*β*-unsaturated carboxylic acids **1** and the cyclopropyl acids **2** were always observed. Therefore, to simplify the chromatographic separation of the obtained mixture of **1** and **2**, the addition of bromine in CCl_4 to the crude reaction mixture was performed to transform the unsaturated acid **1** into the corresponding 2,3-dibromo derivative.[14] In the case of compounds **2d** the bromination of the corresponding crude reaction mixture afforded the product derived from the regioselective bromination of the aryl group. Hence, **2e** (**2d**-brominated derivative) was isolated in 86% yield rather than product **2d** (Table 1, entry 5).

The synthesis of products **2** could be explained by assuming the generation of samarium(II) carbenoids,[7] which have been also proposed as intermediates in the cyclopropanation reaction of allylic alcohols,[8b,c] α,*β*-unsaturated amides,[9] or during the generation of SmI_2 solutions from samarium metal and a variety of iodo compounds such as diiodomethane, 1,2-diiodomethane, or iodoform.[12,15] Hence, during the sonication of the Sm/CHI_3 mixture in THF, an iodocarbenoid **3** could be generated. The reaction of this carbenoid **3** with the α,*β*-unsaturated acid could take place through a transition state (depicted as **A** in Scheme 1) similar to the model proposed by Houk for the addition of carbenoids to olefins,[16] and which was also utilized to explain other samarium promoted cyclopropanation processes.[8,9] This

Scheme 1. Proposed Mechanism



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transition-state model shows the coordination between the samarium and the oxygen atom from the carboxylic acid (owing to the oxophilic nature of samarium)[17] which could explain the conservation of the geometry of the C═C bond of the starting unsaturated acid **1** in the cyclopropanation reaction and, consequently, the stereospecificity. Therefore, cyclopropanation through the transition state **A** could provide the iodocyclopropyl carboxylic acid **4**. Indirect support for this mechanism could be the detection of small amounts (<5%) of the corresponding compounds **4** (determined by ^{1}H NMR) in the crude reaction mixture of **2j** and **2m**.

The iodocyclopropane **4** generated could be metalated *in situ* by SmI_2 to afford **5**, which could undergo an intramolecular hydrolysis to give the final cyclopropyl acid **2**.

In conclusion, the first method to cyclopropanate unprotected α,*β*-unsaturated carboxylic acids with complete stereospecificity has been described. Studies to fully delineate the factors involved in this transformation are currently under investigation within our laboratory.

Acknowledgment. We thank the Ministerio de Educación y Ciencia (CTQ2004-1191/BQU) for financial support. J.M.C. thanks Carmen Fernández-Flórez for her time. H.R.S. and C.S. thank the Ministerio de Educación y Ciencia for a Ramón y Cajal Contract (Fondo Social Europeo) and a predoctoral FPI fellowship, respectively. Our thanks to Euan C. Goddard for his revision of the English.

Supporting Information Available: General procedure, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) During the isolation of cyclopropyl acids bearing activated aromatic rings (compounds **2c**, **2d**, **2f**, **2g**, and **2l**), no bromination was carried out due to the generation of unidentified brominated materials other than those desired, as a consequence of an indiscriminate bromination of the aromatic ring. The only exception was product **2d** which afforded regioselectively **2e**.

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