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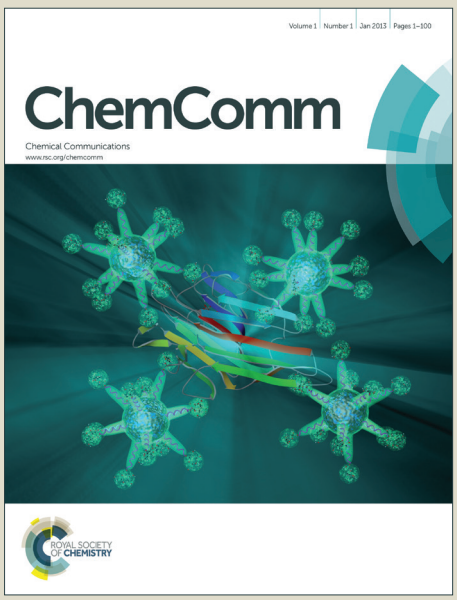

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ARTICLE TYPE

Facile Synthesis of 1-Trifluoromethylalkenes via the Decarboxylation of α-Trifluoromethyl-β-lactones

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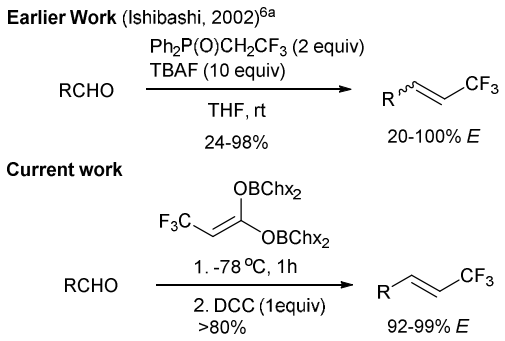
DCC-mediated cyclodehydration of α-trifluoromethyl-β-hydroxy acids provides α-trifluoromethylated β-lactone intermediates, without loss of stereoselectivity. These lactones undergo facile decarboxylation providing a simple route to both alkyl and aryl trifluoromethylated alkenes in excellent yields and stereoselectivity.

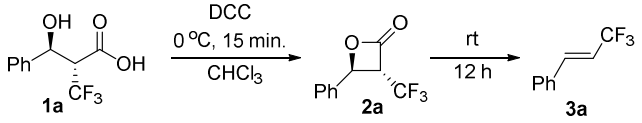
The extreme rarity of fluorine in natural products[1] makes the synthesis of fluoro-organic molecules inevitable for their examination in medicinal and materials chemistry.[2] Accordingly, development of novel methodologies for the preparation of fluorinated building blocks has since long attracted synthetic chemists.[3] Conversion of fluorinated substrates to useful synthons is a preferred alternative to cumbersome and often non-selective late-stage fluorination techniques. As part of our program on fluoroorganic synthesis via boranes,[4] we had recently reported the preparation of α-trifluoromethyl-β-hydroxy acids (**1**) in high stereoselectivity via the enolization-aldolization of 3,3,3-trifluoropropanoic acids.[5] This development opened the door for the preparation of hitherto unknown α-trifluoromethyl-β-lactones and a ready synthesis of 1-trifluoromethylalkenes (Scheme 1).



Scheme 1. Preparation of trifluoromethyl olefins from aldehydes

The chemistry of β-lactones has been reviewed several times in the literature.[7] They have been converted to several classes of functional derivatives, including olefins.[8,9] Yet, surprisingly, α-trifluoromethyl-β-lactones have not been reported thus far.[10] Considering the importance of trifluoromethylated alkenes in a variety of fields,[6,11] their ready synthesis from these lactones should be beneficial. Accordingly, we undertook such a project and the results are reported herein.

We began the project by examining the lactonization of *anti*-3,3,3-trifluoro-2-(hydroxy(phenyl)methyl)propanoic acid (**1a**) via the most common method for this transformation.[12] Thus, **1a** was reacted with *p*-toluenesulfonyl chloride in the presence of pyridine and allowed to stand overnight in $CHCl_3$ at 0 °C. However, none of the expected β-lactone, 4-phenyl-3-(trifluoromethyl)oxetan-2-one (**2a**), was observed. Fortunately, after scanning a variety of reagents, we achieved the dehydration-cyclization, within 15 min, using dicyclohexylcarbodiimide (DCC)[13] in $CHCl_3$ at 0 °C (Scheme 2). Unfortunately, the separation of **2a** from the *N, N'*-dicyclohexylurea (DCU) byproduct was difficult. A modified workup was used, whereby the solvent was replaced with ethyl acetate and cooled to -78 °C, when the precipitated DCU could be filtered cold to yield 88% of **2a** as yellow oil (Scheme 2). Spectroscopic (PMR and FMR) analysis revealed that the *anti*-stereochemistry of **1a** is retained in **2a**.



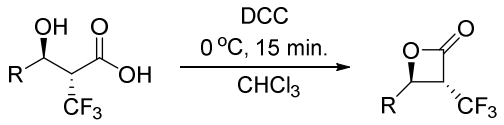
Scheme 2. Synthesis of β-lactone and trifluoromethyl styrene

The successful synthesis of **2a** led us to examine the effect of a trifluoromethyl group at the α-position on the preparation as well as the stability of such β-lactones (Table 1). Lactone **2a** was stable for a few minutes at room temperature (rt), after which the decarboxylation to the corresponding olefin, (*E*)-β-trifluoromethylstyrene (**3a**), initiated. The decarboxylation was complete within 12 h, at rt (Scheme 2). The stereochemistry of **3a** and all other olefins subsequently discussed was determined by comparing their ^{1}H NMR spectra with those reported.[14] The preparation of the olefins are summarized in Table 2.

The β-hydroxy acid bearing a β-tolyl group, (with the mildly electron-donating *p*-methyl group, (**1b**)), underwent lactonization under similar conditions (0 °C, 15 min.) to provide **2b**, which decarboxylated over 30 min. at rt (Table 2, entry 3). In comparison, a mildly electron-withdrawing β-4-

fluorophenyl substituent (**1c**) provided the corresponding lactone (**2c**), which was stable, at rt, for 3 d. A slow decarboxylation which sets in after 3 d takes 2-3 weeks for completion at rt (Table 2, entry 5). The β-lactone from the hydroxy acid bearing 4-anisyl group at the β-position (a stronger electron donating substituent (**1d**)) was not isolable and immediately decarboxylated to the corresponding olefin **3d** under the same reaction conditions (0 °C, 15 min.) (Table 2, entry 7). As expected, the hydroxyl acid with a stronger electron-withdrawing 4-nitrophenyl group at the β-position (**1e**) underwent cyclization only at rt and the isolated lactone **2e** was stable for several months. All of these observations are consistent with both theoretical and practical studies reported by various groups.[8,10,15,16] It has been reported that while π-donors at β-position destabilize β-lactones, π-acceptors stabilize them.[15] Hydroxy acids bearing 2-thiophenyl and cinnamyl groups (**1f** and **1g**) at the β-position underwent cyclization as soon as they were treated with DCC at 0 °C and the *anti*-lactones (**2f** and **2g**, respectively) underwent ready decarboxylation to the *E*-olefins (**3f** and **3g**, respectively, Table 2, entries 9 and 10) without any further delay. The lactones could not be isolated in these cases as well.

Table 1. Preparation of α-trifluoromethyl-β-lactones

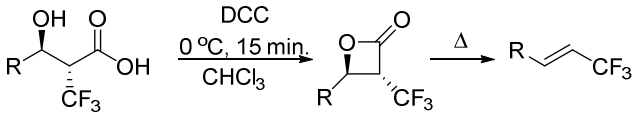


entry	aldol			β-lactone		
	1	R	Anti: Syn	**2**	yield (%)[a]	Anti: Syn[b]
1	**1a**	Ph	99:1	**2a**	88	99:1
2	**1b**	4-Me-C_6H_4	99:1	**2b**	85	99:1
3	**1c**	4-F- C_6H_4	99:1	**2c**	80	99:1
4	**1d**	4-MeO- C_6H_4	99:1	**2d**	-[c]	-[c]
5	**1e**	4-NO_2- C_6H_4	96:4	**2e**	80[d]	-
6	**1f**	2-Thioph	99:1	**2f**	-[c]	-[c]
7	**1g**	Ph-CH=CH	99:1	**2g**	-[c]	-[c]
8	**1h**	Chx	98:2	**2h**	97	98:2
9	**1i**	*i*-Pr	92:8	**2i**	97	92:8
10	1j	*t*-Bu	99:1	**2j**	98	99:1

[a]Isolated yield. [b]*E*/*Z* ratio determined by ^{19}F NMR spectroscopy [c]Unstable lactones convert to olefins immediately. [d]The stable lactone bearing the 4-nitrophenyl group (**2e**) was isolated in 80% yield as a mixture containing 20% unidentified impurities, which was carried to the olefination step without purification.

Indeed, it is also possible to conveniently convert all of the aromatic hydroxy acids, except **1e**, directly to the olefins by allowing the reaction to proceed for longer periods at rt, without isolating the lactones (Method B, Table 2).

Table 2. Preparation of 1-Trifluoromethylalkenes

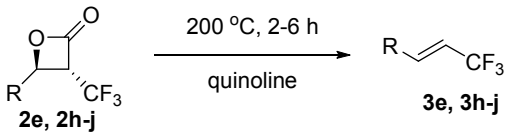


entry	Aldol/ lactone	Alkene				
	1	R	**3**	Method[a]	Yield (%)[b]	*E*: *Z*[c]
1	**1a**	C_6H_5	**3a**	A	98[d]	99:1
2	**2a**	C_6H_5	**3a**	B	94	99:1
3	**1b**	4-Me-C_6H_4	**3b**	A	98[e]	99:1
4	**2b**	4-Me-C_6H_4	**3b**	B	95	99:1
5	**1c**	4-F-C_6H_4	**3c**	A	97[f]	99:1
6	**2c**	4-F-C_6H_4	**3c**	B	93	99:1
7	**1d**	4-MeO-C_6H_4	**3d**	B	96	99:1
8	**2e**	4-NO_2-C_6H_4	**3e**	C	72	96:4
9	**1f**	2-Thioph	**3f**	B	98	99:1
10	**1g**	Ph-CH=CH	**3g**	B	79	99:1
11	**2h**	Chx	**3h**	C	52, (99)[g]	98:2
12	**2i**	*i*-Pr	**3i**	C	48, (99)[g]	92:8
13	**2j**	*t*-Bu	**3j**	C	58, (99)[g]	99:1

[a]A: Allow neat β-lactone to stand at rt for periods mentioned: see *d-f* below. B: Stir aldol with DCC in chloroform for 15 min at 0 °C, followed by warming to rt and stirring for 4-48 h. C: Heat β-lactone in quinoline at 200 °C for 2-6 h. [b]Isolated yields. [c]*E*/*Z* ratio determined by ^{19}F NMR spectroscopy. [d]Overnight decarboxylation. [e]Decarboxylation complete in 2h. [f]Decarboxylation takes place within 4-14 days. [g]^{19}F NMR yields with $PhCOCF_3$ as internal standard.

Hydroxy acids bearing aliphatic groups, such as cyclohexyl, isopropyl, and *tert*-butyl substituents at the β-position (**1h**, **1i**, and **1j**, respectively) were converted to the lactones in 30 min. at 0 °C and were very stable. They could be stored at rt for several weeks without any noticeable decomposition, similar to **2e**. The stable aromatic lactone **2e** and aliphatic lactones **2h-j** failed to decarboxylate at rt and formed amides with DCU upon heating. Refluxing **2h** in pyridine for 5 d resulted in partial decarboxylation to the olefin and olefinic acid, (*E*)-3-cyclohexyl-2-(trifluoromethyl)acrylic acid. Olefin (**3h**) was the sole product when the bath temperature was kept at 140 °C for 3 d. Quinoline as solvent allowed the decarboxylation to be conducted at 200 °C (Method C, Table 2) (entry 11) and the lower boiling olefin was isolated in 52% yield within 2 h

(Scheme 3). This process was then extended to **2e**, **2i** and **2j** (Table 2, entries 8, 12, and 13).



Scheme 3. Preparation of aliphatic (*E*)-trifluoromethyl olefins

In all of the cases, we obtained (*E*)-olefins in very high diastereoselectivity from the *anti*-hydroxy acids/lactones. The enolboration-aldolization protocol has not been standardized for the preparation of pure *syn*-α-trifluoromethyl-β-hydroxy acids.[5] However, when such β-hydroxy acids with lower diastereoselectivities (*syn*:*anti*::7:3)[5] are decarboxylated under this protocol, the dr was transferred to the corresponding olefin (*Z*:*E*::7:3). Thus, the new protocol could be extended to prepare *syn*-α-trifluoromethyl-β-lactones and (*Z*)-trifluoromethyl olefins.

Conclusions

In conclusion, the first synthesis of *anti*-α-trifluoromethyl-β-lactone intermediates via a DCC-mediated cyclodehydration of *anti*-α-trifluoromethyl-β-hydroxy carboxylic acids has been described. β-Substituted α-trifluoromethyl lactones with β-aliphatic groups and β-π-acceptors are stable while those with β-π-donors are transient. A simple synthesis of trifluoromethylated (*E*)-olefins has also been developed. The preparation of pure *syn*-lactones and (*Z*)-olefins is in progress. Also, further transformations of the stable novel trifluoromethyl β-lactones are in progress.

Notes and references

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General procedure for the dehydration of β-hydroxyacids

Anti-3,3,3-trifluoro-2-(hydroxy(phenyl)methyl)propanoic acid,[5] (**1a**), (0.47 g, 2 mmol) was weighed into an oven dried 50 mL round-bottom flask and dissolved in 5 mL of chloroform (additional amounts of chloroform and longer periods of stirring may be required to completely dissolve some of the aldols). The solution was cooled to 0 °C and *N*, *N*'-dicyclohexylcarbodiimide (DCC) (0.412 g, 2 mmol) was added. The mixture was stirred for 15 min. at 0 °C, when the clear solution turned into a white suspension indicating the formation of *N*,*N*'-dicyclohexylurea (DCU). The solvent was removed on a rotovap at room temperature and 20 mL of ethyl acetate (pre-cooled to -78 °C) was added to the slurry. The suspension was filtered carefully while keeping it cold and concentrated at room temperature to obtain **2a** (0.39 g, 88%). For characterization data and NMR spectra, see ESI.

General procedure for the one-pot preparation of trifluoromethyl olefins from β-hydroxy acids.

Anti-3,3,3-trifluoro-2-(hydroxy(phenyl)methyl)propanoic acid (**1a**), (0.47 g, 2 mmol) was weighed into a 50 mL round-bottom flask and dissolved in 5 mL of chloroform (additional amounts of chloroform and longer periods of stirring may be required to fully dissolve some of the aldols). The solution was cooled to 0 °C and *N*, *N*'–dicyclohexylcarbodiimide (DCC) (0.412 g, 2 mmol) was added. The mixture was stirred for 15 min. at 0 °C, warmed to rt and stirred for 16-48 h. The solvent was removed on a rotovap and 10% ethyl acetate/hexanes solution (50 mL) was added to the slurry, filtered through a silica pad andconcentrated on a rotary evaporator to afford **3a** (0.33 g, 98%). For characterization data and NMR spectra, see ESI.

General Procedure for the decarboxylation of aliphatic β-lactones: Preparation of (*E*)-(3,3,3-trifluoroprop-1-en-1-yl)cyclohexane (**3h**) is representative.

Anti-4-cyclohexyl-3-(trifluoromethyl)oxetan-2-one (**2h**), (4.0 g, 10 mmol) was dissolved 15 mL of quinoline, contained in a 50 mL round-bottom flask fitted with a reflux condenser. The solution was maintained in an oil bath at 200 °C. The reaction, followed by ^{19}F nmr spectroscopy, was complete within 2 h. The cooled mixture dissolved in Et_2O, washed with aqu. 6 N HCl, water, and dried (Na_2SO_4). Removal of ether and distillation provided 0.85 g (52%) of **3h**. For characterization data and NMR spectra, see ESI.

† Electronic Supplementary Information (ESI) available: For further details on the synthesis and characterization data of the compounds and ^1H, ^{13}C, and ^{19}F NMR spectra, see DOI: 10.1039/b000000x/

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