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Facile synthesis of 1-trifluoromethylalkenes *via* the decarboxylation of α-trifluoromethyl-β-lactones†

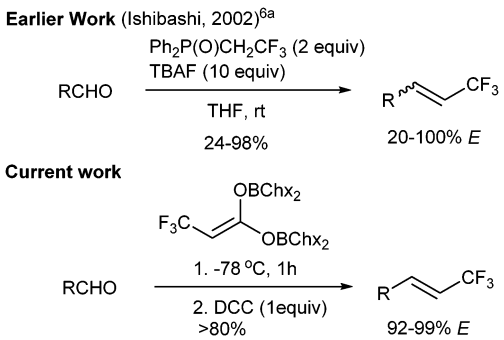
P. Veeraraghavan Ramachandran* and Barnabas Otoo

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 obtain 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 for 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).[6]

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 allowed to react 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 a yellow oil (Scheme 2).‡ Spectroscopic (PMR and FMR) analysis revealed that the *anti*-stereochemistry of **1a** is retained in **2a**.



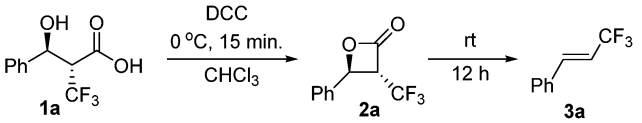
Scheme 1 Preparation of trifluoromethyl olefins from aldehydes.

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

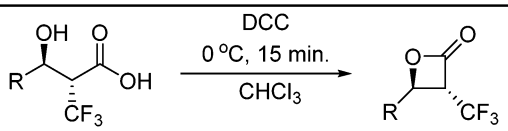
Herbert C. Brown Center for Borane Research, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, USA. E-mail: chandran@purdue.edu

† Electronic supplementary information (ESI) available: Further details on the synthesis and characterization data of the compounds and ^{1}H, ^{13}C, and ^{19}F NMR spectra. See DOI: 10.1039/c5cc03230j



Scheme 2 Synthesis of β-lactone and trifluoromethyl styrene.

Table 1 Preparation of α-trifluoromethyl-β-lactones



	Aldol			β-Lactone		
Entry	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

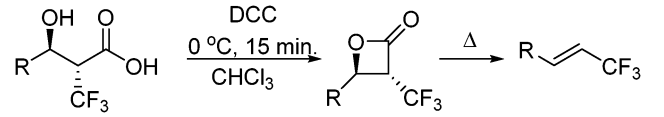
[a] Isolated yield. [b] *E*/*Z* ratio determined by ^{19}F NMR spectroscopy. [c] Unstable lactones convert to olefins immediately. [d] The stable lactone bearing the 4-nitrophenyl group (**2e**) was isolated in 80% yield as a mixture containing 20% unidentified impurities, which was carried to the olefination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

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 a 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 the 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.

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

Hydroxy acids bearing aliphatic groups, such as cyclohexyl, isopropyl, and *tert*-butyl substituents at the β-position (**1h**, **1i**, and **1j**,

Table 2 Preparation of 1-trifluoromethylalkenes



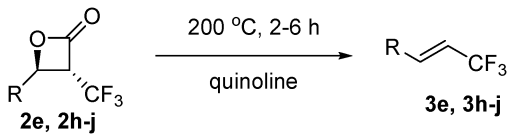
	Aldol/lactone	Alkene				
Entry	1	R	3	Method[a]	Yield[b] (%)	*E* : *Z*[c]
1	**1a**	C_6H_5	**3a**	A	98[d]	99 : 1
2	**2a**	C_6H_5	**3a**	B	94	99 : 1
3	**1b**	4-Me-C_6H_4	**3b**	A	98[e]	99 : 1
4	**2b**	4-Me-C_6H_4	**3b**	B	95	99 : 1
5	**1c**	4-F-C_6H_4	**3c**	A	97[f]	99 : 1
6	**2c**	4-F-C_6H_4	**3c**	B	93	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 2 h. [f] Decarboxylation takes place within 4–14 days. [g] ^{19}F NMR yields with $PhCOCF_3$ as an internal standard.

respectively), were converted to the lactones in 15 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 maintained at 140 °C for 3 d. Quinoline as the 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).

In all of the cases, we obtained (*E*)-olefins with 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.

In conclusion, the first synthesis of *anti*-α-trifluoromethyl-β-lactone intermediates *via* a DCC-mediated cyclodehydration of



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

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

‡ *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 (precooled 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 12 h. (Other hydroxyacids may require longer times. See text for details.) The solvent was removed on a rotovap and 10% ethyl acetate/hexane solution (50 mL) was added to the slurry, filtered through a silica pad and concentrated 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 was dissolved in Et_2O, washed with aq. 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.†

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