Tetrahedron Letters 56 (2015) 3019–3022

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereoselective synthesis of *anti*-3-hydroxy-2-trifluoromethyl carboxylic acids

P. Veeraraghavan Ramachandran *, Barnabas Otoo, Prem B. Chanda

Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084, United States

ARTICLE INFO

Article history:
Received 24 September 2014
Revised 8 December 2014
Accepted 9 December 2014
Available online 15 December 2014

Keywords:
Aldol reaction
Diastereoselective
Trifluoromethyl
3,3,3-Trifluoropropanoic acid
B-Chlorodicyclohexylborane

ABSTRACT

Unlike the hydrocarbon analogs, this first report of enolboration–aldolization of 3,3,3-trifluoropropanoic acid provides essentially pure *anti*-diastereomers of α-trifluoromethyl-β-hydroxy carboxylic acids in 77–90% yields.

Diverse classes of carbonyls have been subjected to enolization–aldolization, an extremely versatile, century-old, carbon–carbon bond forming reaction.[1] For over three decades, the boron-mediated version of this reaction[2] has been a favorite protocol of synthetic organic chemists. Carboxylic acids, a prominent carbonyl class, have not been subjected to the aldol reaction to the same extent as, for example, ketones.[3] This is surprising, given the fact that the β-hydroxy acid products can serve as useful synthons for the preparation of a variety of molecules including the versatile β-lactones,[4] and several natural and unnatural bio-active molecules, such as pheromones and polyketide natural products.[5] For example, the common structural feature of the intermediates of the β3-adrenergic receptor agonist (**A**),[6] the opioid receptor ligand (**B**),[7] and the antibacterial (**C**)[8] is the β-hydroxy carboxylic acid moiety (Fig. 1).

We recently reported a simple and general protocol for the enolboration–aldolization of propanoic acid using *B*-bromodicyclohexylborane/triethylamine mixture.[9] The use of haloboranes has positive advantages over boron triflates during the bicarbonate workup and purification of the aldol, in that triflic acid contamination can be circumvented. The reaction afforded *anti*-hydroxy acids selectively in very high yields. However, higher diastereoselectivity was dependent on the aldehyde sterics and electronics. We envisaged that the sterics and electronics of the carboxylic acids might also influence the diastereoselectivity providing pure diastereomers. Accordingly, the scope of the reaction was expanded to include 3,3,3-trifluoropropanoic acid (**1**). Our long-standing interest in fluoroorganic chemistry[10] and the unique opportunity to obtain the hitherto unknown α-trifluoromethylated β-hydroxy acids provided the necessary impetus. Fluorination of bio-active molecules is often undertaken to enhance their potency and lipophilicity.[11] Newer methods for trifluoromethylation have been the focus of several recent publications.[12] Herein we describe an important addition to the repertoire of organic chemists; a process for the preparation of novel α-trifluoromethylated β-hydroxy acids. The development of the aldol reaction of **1** is also discussed.

3,3,3-Trifluoro-2-(hydroxy(phenyl)methyl)propanoic acid (**4a**), obtained by a simple aqueous $NaHCO_3$ extraction following the enolization of **1** with *B*-bromodicyclohexylborane (Chx_2BBr, **2**) (2.4 equiv) in diethyl ether (Et_2O), in the presence of Et_3N, at 0 °C, and aldolization with benzaldehyde (**3a**) at −78 °C to 0 °C (condition A) revealed a 1:4 mixture of *syn*- and *anti*-isomers. In contrast, the same protocol was instrumental in providing up to 97% *anti*-diastereoselectivity (ds) for the hydrocarbon analog.[9] A systematic investigation was begun in search of the conditions for exclusive *syn*- or *anti*-diastereoselection during the aldol reaction of **1**. The boron reagent, solvent, and reaction temperature were all targeted to achieve the goal (Table 1).

The effects of the halide leaving group of the reagent was probed first. Enolization and aldolization using *B*-chlorodicyclohexylborane (Chx_2BCl, **5**) under the same conditions (condition A) improved the yield of **4a** from 78% to 88%, while

* Corresponding author.
E-mail address: chandran@purdue.edu (P.V. Ramachandran).

http://dx.doi.org/10.1016/j.tetlet.2014.12.045
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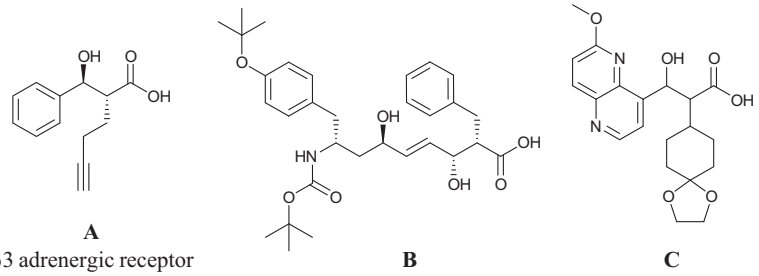


Figure 1. Bio-active molecules derived from α-substituted β-hydroxy acids.

the ds remained unchanged (*syn*:*anti*-1:4, entry 2). Due to the instability of *B*-iododicyclohexylborane (Chx_2BI, **6**) in Et_2O, the reaction with this reagent was carried out in pentane under similar conditions, when the ds improved to 97% *anti*-isomer at the cost of the product yield (59%, entry 3). Aiming to improve the ds with the more readily accessible reagent **5**, the effect of enolization and aldolization temperatures was examined.

The critical importance of temperature on the ds during the aldol reaction of methyl phenylacetate[13] formed the basis of this approach. Accordingly, the enolization of **1** was conducted in Et_2O with **5** at −78 °C, followed by aldolization at the same temperature for 30 min and warming to 0 °C (condition B) when the yield dropped to 80% without any improvement in the stereoselectivity (entry 4). Another attempt was made; this time the aldolization temperature was maintained at −78 °C throughout the reaction (condition C). We were elated to achieve 87% yield of **4a** with near quantitative (99%) ds favoring the *anti*-isomer (entry 5) (Scheme 1).[14]

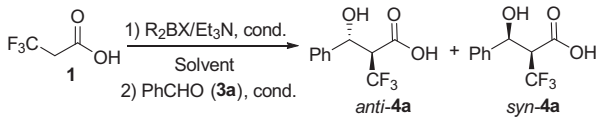
The *anti*-stereochemistry of **4a** was determined on the basis of the chemical shifts (δ −66.05 (d), J = 7.6 Hz for *anti*-isomer and −65.26 (d), J = 7.9 Hz for *syn*-isomer) from its ^{19}F NMR spectrum (Fig. 2)[15] and confirmed by comparing the ^1H NMR of the acetonide of the corresponding diol (Scheme 2) reported by Loh and co-workers.[16] Thus, **4a** was reduced with $LiAlH_4$ to obtain 1-phenyl-2-(trifluoromethyl)propane-1,3-diol (**7a**), which was refluxed with 2,2-dimethoxypropane in the presence of catalytic *p*-TsOH to form the acetonide, 2,2-dimethyl-4-phenyl-5-(trifluoromethyl)-1,3-dioxane (**8a**). The coupling constant (J = 10.20 Hz) of the axial H4–H5 protons in the ^1H NMR spectrum compared well with that reported in the literature (J = 10.11 Hz) for *anti*-**8a**.[16]

Chx_2BBr also gave similar results under the modified condition C (entry 6). However, the ease of synthesis and cost persuaded to employ **5** for further experiments. With the optimum conditions for the *anti*-selective enolboration–aldolization of **1** in hand (Scheme 1), the electronic and steric requirements of the aldehydes were varied to validate the protocol. Results are summarized in Table 2.

A bicyclic aromatic aldehyde, 1-naphthaldehyde (**3b**) followed the same trend as **3a** and provided 80% *anti*-aldol **4b** in 98% ds (entry 2). Benzaldehydes with electron-donating groups, such as 4-tolualdehyde (**3c**) and 4-anisaldehyde (**3d**), provided excellent ds (99% and 98% *anti*, respectively) in 85% and 79% yields, respectively (entries 3 and 4). Those with electron-withdrawing fluorine atom (4-fluorobenzaldehyde, **3e**) also showed 99% *anti*-diastereoselectivity (89% yield, entry 5).

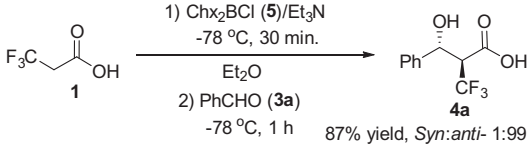
Heteroaromatic aldehydes, such as furan-2-carbaldehyde (**3f**) and thiophene-2-carbaldehyde (**3g**) also maintained near perfection in *anti*-selectivity with very high yield (95–99% *anti*, 83–86% yield, entries 6 and 7). The steric requirements of aliphatic aldehydes were then evaluated. The ds amplified with an increase in steric requirements. The straight chain aldehyde, butanal (**3h**), showed 91% *anti*-selectivity (77% yield, entry 8). However branched aldehydes, cyclohexanecarbaldehyde (**3i**) and isobutyraldehye (**3j**) provided the products in higher yields and higher

Table 1
Optimization of the reaction conditions for the enolization–aldolization of 3,3,3-trifluoropropanoic acid (**1**)



No.	Chx_2BX[a] X	#	Solvent	Concd[b]	Yield[c] (%)	*anti*:*syn*[d]
1	Br	**2**	Et_2O	A	78	4:1
2	Cl	**5**	Et_2O	A	88	4:1
3	I	**6**	Pentane	A	59	97:3
4	Cl	**5**	Et_2O	B	80	4:1
5	Cl	**5**	Et_2O	C	87	99:1
6	Br	**5**	Et_2O	C	89	99:1

[a] In all of the cases, 2.4 equiv of the reagent was used for enolization.
[b] Reaction conditions: A = enolization: 0 °C, 45 min.; aldolization: −78 °C, 30 min., 0 °C, 1 h; B = enolization: −78 °C, 45 min.; aldolization: −78 °C, 30 min., 0 °C, 1 h; C = enolization: −78 °C, 30 min.; aldolization: −78 °C, 1 h.
[c] Combined yields of *syn* and *anti*-isomers.
[d] *syn* and *anti* ratios were determined by ^{19}F NMR spectroscopy of the crude reaction mixture.



Scheme 1. Optimum conditions for aldol reaction of 3,3,3-trifluoropropanoic acid (**1**).

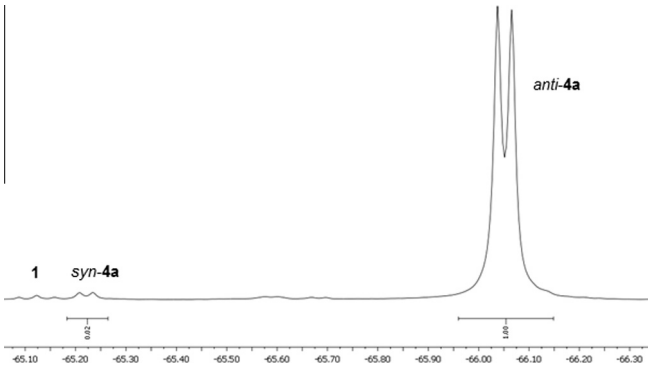


Figure 2. ^{19}F NMR of the crude reaction mixture in diethyl ether revealing the diastereoselectivity of **4a**.