Journal of Fluorine Chemistry 152 (2013) 38–45

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

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

Construction of chiral trifluoromethylated materials by combination of stereochemically predictable S_N2' reaction and Ireland-Claisen rearrangement

Tomoaki Ichikawa [a], Tomoko Kawasaki-Takasuka [a], Shigeyuki Yamada [a], Takashi Yamazaki [a,*], Toshio Kubota [b]

[a] Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei 184-8588, Japan
[b] Department of Biomolecular Functional Engineering, Ibaraki University, Nakanarusawa 4-12-1, Hitachi 316-851, Japan

ARTICLE INFO

Article history:
Received 11 September 2012
Received in revised form 23 October 2012
Accepted 28 October 2012
Available online 6 November 2012

Keywords:
S_N2' reaction
Ireland-Claisen rearrangement
Stereodivergent synthesis
2-Bromo-3,3,3-trifluoropropene
Trifluoromethyl group

ABSTRACT

We have succeeded in establishment of a novel route for the construction of optically active CF_3-containing carboxylic acids in a stereochemically predictable manner starting from easily available mandelic acid by convenient combination of the copper-mediated *anti*-S_N2' type substitution and Ireland-Claisen rearrangement.

1. Introduction

Incorporation of a trifluoromethyl (CF_3) group to organic molecules has been drawing significant attention of chemists because its strong electrostatic feature endows unique properties, which cannot be realized by any other elements or groups [1]. Because of wide utilization in the field of fine chemistry [2], preparation of such substances is highly desirable as optically active forms from readily available reagents and by way of simple methods. Among them, especially difficult is the construction of *structure A* in Fig. 1 where the carbon atom with a CF_3 moiety does not possess any other heteroatoms connected directly [3,4]. This is due to the following characteristics of this group: its powerful electron-withdrawing property plays a pivotal role in strengthening the proximate F_3C–*C*–*O* bond and, at the same instance, restricts the access of nucleophiles from the backside of this C–O bond during substitution reactions due to steric as well as electronically repulsive interactions [5,6]. Thus, in spite of facile syntheses of molecules with the F_3C–C–OH partial structure by, for example, the reaction of appropriate aldehydes or ketones with Ruppert–Prakash reagent [7] or the nucleophilic attack of organometallic species to CF_3CHO or its precursors [8], because cleavage of the resultant C–O bond is not the easy task even with the aid of adequate leaving groups [9], these methods are not the one to be chosen. As a solution to such problems, we have focused our attention to S_N2' reactions of cuprates to easily accessible allylic alcohols with a CF_3 group at the γ-position [4g,10] which enables the construction of the desired new carbon–carbon bond from the direction *anti* to the cleaving C–O bond [11].

In this article is described our recent success on the preparation of the chiral target molecules with the above specific structure by the combination of stereochemically predictable Cu-mediated S_N2' reactions and Ireland-Claisen rearrangement from the readily available chiral starting material, mandelic acid, in diastereoselective as well as stereodivergent fashions.

2. Results and discussion

The substrates required for the S_N2' process were synthesized as follows (Scheme 1). Thus, MOM-protected mandelaldehyde [12] was treated with the 3,3,3-trifluoropropynyl anion generated by our previously established technique [13,14] to afford the CF_3-containing propargylic alcohol **1** in 70% yield in a ratio of 77:23 in a *syn* preferential manner. This alcohol **1** was quantitatively converted to the (*Z*)-allylic alcohol **2** by the Lindlar-catalyzed hydrogenation [13] under atmospheric pressure of H_2 with retention of the original diastereomeric ratio. To our delight, the stereoisomeric pairs obtained were found to be separable by silica gel column chromatography and the major product, **syn-2**, was able to be obtained almost as a sole isomer. On the other hand, in

* Corresponding author. Tel.: +81 42 388 7038; fax: +81 42 388 7038.
E-mail address: tyamazak@cc.tuat.ac.jp (T. Yamazaki).

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.10.013

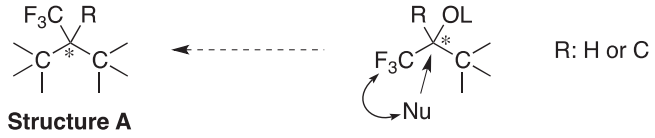
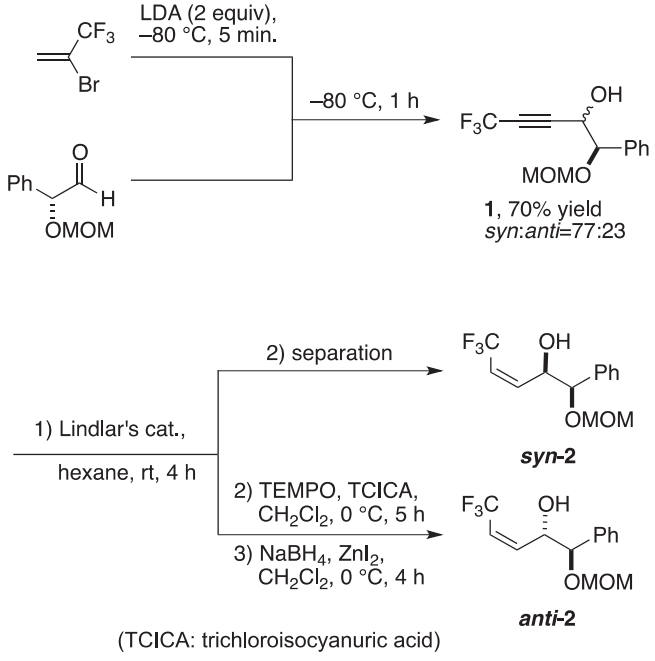


Fig. 1.

spite of separation of the other diastereomer **anti-2**, exclusive construction of this compound was planned by the oxidation of an isomeric mixture of **2** and then reduction again under the chelation controlled condition. First of all, the well-known Swern oxidation protocol was utilized to furnish more than 90% yield of the crude α,β-unsaturated ketone, but *ca.* 10% was isomerized to the thermodynamically more stable *E* isomer which, as mentioned in our previous report [4g,10], is not the appropriate substrate for the S_N2' reaction from the standpoint of stereoselectivity. Then, we turned our attention to the recently reported technique using trichloroisocyanuric acid (TCICA) [15] in the presence of a catalytic amount of TEMPO because this process did not require any additional nucleophilic species which was considered to be susceptible for promotion of the undesired *in situ E,Z* interconversion. While a larger amount (20 mol%) of TEMPO was required than the one in the original method, as our expectation, *Z* stereochemistry of the product was almost preserved during the oxidation process (*E*:*Z* = 1:99). In the case of the diastereoselective reduction of this intermediary ketone, combination of $NaBH_4$ and ZnI_2 [16] was found to be quite effective, and a high degree of *anti* selectivity was attained as a result of the chelation control at 0 °C for 5 h in CH_2Cl_2. These successive two step procedures furnished **anti-2** [17] in 51% total yield (*syn*:*anti* = 6:94).

With these key intermediates **syn-** and **anti-2** in hand, our interest was next focused on the S_N2' type substitution reactions. First of all, ability of the leaving acyl moiety at the hydroxy group of **2** was investigated by using a diastereomer mixture of **2** (*syn*:*anti* = 75:25) under the reaction with EtMgBr in the presence of substoichiometric amounts of CuCN and TMSCl [10], whose results were summarized in Table 1. From the viewpoint of chemical yields, acetate **3a** seemed to be the best substrate among esters with other acyl groups (entries 1 and 2), but the highest



Scheme 1. Distereoselevtive prepration of **2**.

chirality transmission (CT) was recorded by the corresponding pivalate **3c** with a small drop of yields (entries 5 and 6). A *p*-nitrobenzoyl group with the more potent leaving ability was proved to be irrelevant because of lower yield as well as CT (entry 8), which would be explained by partial contamination of the S_N1 route. On the basis of this brief examination, we have introduced *n*-Bu and *i*-Pr moieties as R′ instead of the Et group following to the conditions in entry 6, and excellent results were obtained for both instances (entries 9 and 10), while Me and Ph Grignard reagents furnished only 16% yield and a complex mixture, respectively. In spite of these results with acceptable chemical yields and CT values (entries 6, 9, and 10), alternative routes should be considered because of difficulty of clean removal of the methoxymethyl (MOM) protective group from **4** with production of the corresponding diene [18] to some extent.

Switch of the MOM group was at first considered while, as described in Scheme 2, our basic synthetic route was eventually unchanged because we have found out a method for the selective MOM removal from **3c** in the presence of the pivaloyl moiety by the action of Me_2S with $BF_3{\cdot}OEt_2$ [19] to furnish the homoallylic alcohols **5**. On the other hand, some byproducts including the undesired diol were noticed when **3c** was exposed under usual acidic deprotection conditions. Requirement of **8** as the substrates for the Ireland-Claisen rearrangement led to two possible pathways to access these compounds. Path A would be suffered from the "double S_N2' reaction" because the first S_N2' process should produce the new allylic ester structure, while this route would be convenient as long as such a problem was overcome by control of the amount of reagents. Our study proved that 2 equiv of RMgX was necessary for complete conversion of **6** to preferentially afford the "double S_N2' reaction" product, and reduction of the amount to 1 equiv effectively suppressed this byproduct with conversion up to only 60%. Although path B requested inevitable consumption of 1 equiv of Grignard reagents by the free hydroxy group, this difficulty in path A rendered us to eventually select path B.

As described in Scheme 3, the CF_3-containing allylic alcohols **syn-** and **anti-2** with *Z* configuration were independently treated with pivaloyl chloride in the presence of Et_3N and a catalytic amount of DMAP under reflux for 4 h to afford the esters **syn-** and **anti-3c** in excellent yields, respectively. Then, selective MOM deprotection was performed by the Me_2S-$BF_3{\cdot}OEt_2$ system to conveniently synthesize the corresponding homoallylic alcohols **syn-** and **anti-5**. The resultant **5** were further subjected to a mixture of EtMgBr, CuCN, and TMSCl in Et_2O at 0 °C for 1 h for affecting the *anti*-S_N2' substitution reaction and allylic alcohols **syn-** and **anti-7** were obtained in good chemical yields as well as high diastereoselectivity. Propionylation of **syn-** and **anti-7** readily and successfully prepared the substrates **syn-** and **anti-8** for the next step.

For performance of Ireland-Claisen rearrangement, three protocols were attempted as described in the footnote (a) of Table 2. As long as LDA was employed, methods A and B were found to be inadequate with causing such undesired transformations as deacylation, intermolecular Claisen type condensation, and so on (entries 1 and 2). On the other hand, a weaker base LHMDS worked better from the standpoint of chemical yields, but the reaction proceeded with almost no stereoselectivity (entries 3 and 4). Among three methods tried, method C (addition of LDA to a premixed **8** and TMSCl, *in situ* or internal quench method [20]) turned out to be the most acceptable which attained excellent diastereoselectivity in spite of slightly decreased yields than the case of LHMDS (entries 5 *vs* 7). Strongly coordinating HMPA is known to effectively switch the stereoselectivity of ketene silyl acetals from *E* to *Z* by decomposition of the six-membered transition state [21], while in our instance, this familiar additive seemed to promote deprotonation not from the carbonyl α