Pergamon

Tetrahedron Letters 43 (2002) 5449–5452

TETRAHEDRON LETTERS

Biomimetic reductive amination of perfluoroalkylcarboxylic acids to α,α-dihydroperfluoroalkylamines

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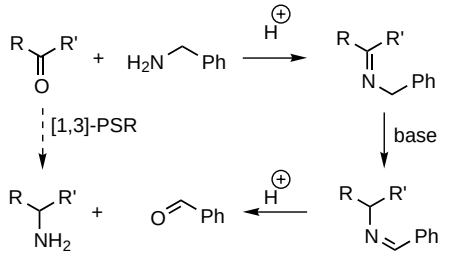
Received 20 March 2002; revised 5 June 2002; accepted 6 June 2002

Abstract—The first general method for the reducing reagent-free, biomimetic transformation of perfluorocarboxylic acids to the α,α-dihydroperfluoroalkyl amines is reported. High chemical yields and simplicity of the experimental procedure render this method immediately useful and synthetically superior to the conventional approaches relying on application of reducing reagents.

An amino group is one of a few truly fundamental functionalites of organic molecules and is critically involved in basic biological processes. Therefore, the development of novel and practical methodologies to prepare amino-compounds continues to be a topic of paramount importance in organic chemistry. One of the traditional approaches to create an amino group is a reductive amination of the corresponding carbonyl-compounds with application of external reducing reagents.[1] For quite some time, we have been interested in a conceptually different approach to reductive amination of carbonyl-compounds, based on an intramolecular reduction–oxidation process via a base-catalyzed [1,3]-proton shift in the azaallylic system of azomethines (imines) (Scheme 1). This approach, mimicking the biological transamination,[2] i.e. the enzyme-catalyzed interconversion of α-amino and α-keto carboxylic acids,[3] represents the most ideal solution to the reductive amination of carbonyl compounds (Scheme 1) and cannot be rivaled for the synthetic efficiency by the purely chemical methods using reducing reagents.[1] We were first to discover the synthetic potential of this reducing reagent-free biomimetic transamination process, referred to as a base-catalyzed [1,3]-proton shift reaction (PSR), for efficient preparation of fluorine-containing amino compounds of a wide range of potential synthetic, and biological applications.[4] Previously we reported practical approaches for biomimetic transamination, via PSR, of fluorine-containing aldehydes and ketones,[5] α- and β-keto carboxylic acids[6] to the corresponding fluorinated amines and amino acids. As an extension of our PSR methodology,[7] we report here our successful preliminary results on a reducing reagent-free, biomimetic reductive amination of perfluoroalkylcarboxylic acids to α,α-dihydroperfluoroalkylamines.



Scheme 1.

The major difference between the transamination of a single carbonyl function, which is the case in the reported[5–7] transamination of aldehydes, ketones or keto-acids, and a carboxylic group, is a necessity to conduct two consecutive PSRs via formation of the corresponding intermediate aldehyde **4** or its derivative **3** (Scheme 2). Moreover, the carboxylic group should be transformed to a derivative of type **1**, **2** to mimic the single carbonyl function, since the presence of acidic NH or OH groups might interfere with a successful outcome of PSR.[5–7] To avoid an undesirable isolation (and purification) of the intermediate aldehyde **4**, one

Keywords: biomimetic reactions; reduction; amination; fluorine and compounds; amines.

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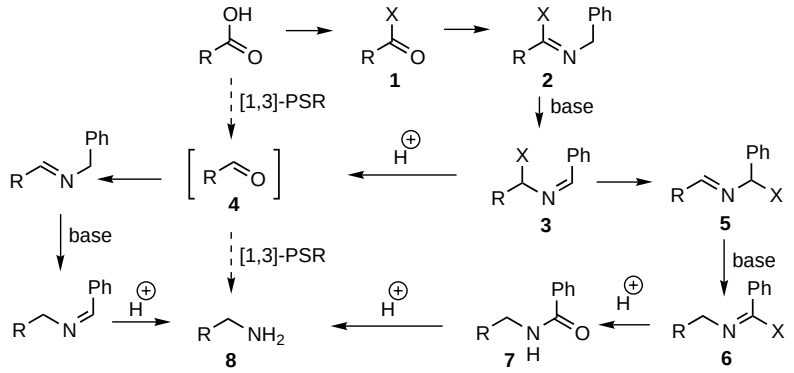
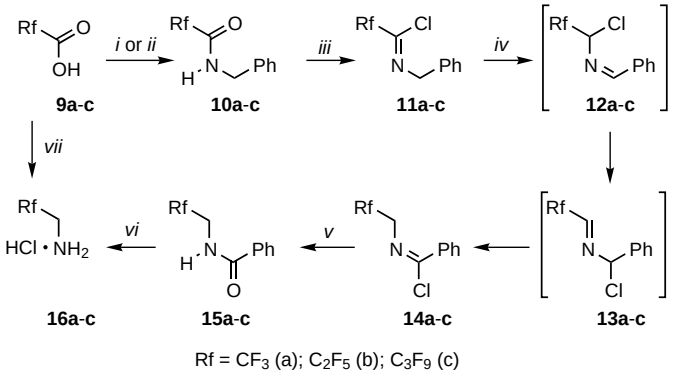
PII: S0040-4039(02)01104-8



Scheme 2.

could envision transformation of the derivative **3** to Schiff base **5**. This process, occurring without any change in the carbon atoms' oxidation state, would afford the product **5** capable of undergoing the PSR giving rise to the derivative **6** subsequent hydrolysis (two steps) of which could lead to the target amino-compound **8** (Scheme 2). Analysis of the relevant literature has revealed that the desired type of transformation, the isomerization of **3** to **5**, could be observed when the substituent X is chlorine,[8] phosphorus- [-P(O)(OAlk)$_2$; -PPh$_2$; -P(O)Ph$_2$][9] or sulfur-containing [-S-Aryl; -SP(S)(OEt)$_2$; -SP(S)Ph$_2$][10] groups. This transformation was shown to take place at high temperatures (usually >100°C), giving rise to a mixture of products of type **3** and **5** as a function of their thermodynamic stability. In particular, Tanaka and co-workers[8e–f] reported that the isomerization of *N*-benzyl-2,2,2-trifluoroacetimidoyl chloride (**11a**) (Scheme 3) to *N*-(2,2,2-trifluoroethyl)benzimidoyl chloride (**14a**) could be achieved with low-to-moderate chemical yields (49–78%) by heating (reflux) of the former in toluene solution. While this type of transformation, as believed to proceed through the corresponding nitrile ylides, has found some limited (low chemical yields and stereoselectivity) synthetic applications for preparing various heterocyclic compounds via [3+2]-cycloadditions,[8a,8e–f] it was never recognized and realized, whatsoever, as an important step in the direct preparation, designed by us, of the amino compounds **16** starting from the carboxylic acids **9** (Scheme 3). The synthetic problems, usually associated with preparation of the derivatives of type **3** and their transformation to compounds **5** (Scheme 2) are: (a) reversibility and therefore incomplete transformation of **3** to **5**; (b) harsh reaction conditions (high temperature: usually >100°C), and (c) unsatisfactory chemical yields (up to 80%).[8–10] These discouraging literature data, in particular, the unsatisfactory chemical yields, seemed to plague our goal of developing a synthetically practical and efficient method for direct transformation of fluorinated carboxylic acids **9** to the corresponding amines **16**. However, we reasoned that studying in detail each of the seven reactions, according to Scheme 3, would put us in position to face up to the challenge. First, we prepared *N*-benzylamide **10a** and, using the literature procedures[8e–f,11] converted it, in a moderate yield (up to 75%), to the imidoyl chloride **11a**. Treatment of compound **11a** with triethylamine (TEA) at room temperature brought about smooth and complete [1,3]-proton shift transfer giving rise to the Schiff base **12a**.[12] According to the literature data,[8e–f] further transformation of **12a** to **13a** and **14a** requires relatively harsh reaction conditions, as for instance prolonged heating of **12a** in a boiling toluene, thus suggesting that the chlorine transfer might be a rate-limiting step in our design.[13] Therefore, we concentrated our efforts on finding a way to facilitate this critical transformation. Drawing inspiration from the results reported by Onus'ko and co-workers on [1,3]-phosphorotropic shifts,[9] we found that addition of catalytic amounts of PPh$_3$/TEA to a solution of **11a** in chloroform substantially accelerates its transformation to the imidoyl chloride **14a**, through the intermediate products **12a** and **13a**. Thus, in the presence of PPh$_3$/TEA the desired isomerization of **11a** to the imidoyl chloride **14a** was observed even at room temperature albeit with low reaction rate, requiring about 3 days for the completion. At elevated temperature (boiling chloroform) the PPh$_3$/TEA-catalyzed isomerization was found to proceed with substantially higher rate (less than 1 h), affording clean and quantitative transformation of **11a**



Scheme 3. (i) $(CF_3CO)_2$ (instead of **9a**), $BnNH_2$, $CHCl_3$, 0°C; (ii) Ph_3P (1.6 equiv.)/CCl_4 (1.07 equiv.), $BnNH_2$ (2 equiv.), $CHCl_3$, reflux, 40 min; (iii) Ph_3P (1.6 equiv.)/CCl_4 (1.07 equiv.), $CHCl_3$ reflux, 40 min; (iv) Ph_3P/TEA (cat.), $CHCl_3$, reflux, 40 min; (v) TEA (3 equiv.)/H_2O (2 equiv.), $CHCl_3$ reflux, overnight; (vi) MeOH/HCl (conc.) 2/1 v, reflux, 24 h; (vii) $BnNH_2$ (1 equiv.), Ph_3P (4 equiv.)/CCl_4 (4 equiv.), TEA (1.5 equiv.), $CHCl_3$ reflux, 40 min, then (v) and (vi).

to **14a**. The catalytic role of PPh_3/TEA could be rationalized assuming that TEA facilitates the [1,3]-proton shifts (from **11a** to **12a** and from **13a** to **14a**), while PPh_3 might accelerate the chlorine transfer (from **12a** to **13a**) through intermediate formation of the corresponding phosphonium salt.[9] The imidoyl chloride **14a** was subjected first to TEA-catalyzed hydrolysis to furnish amid **15a** which then was hydrolyzed using MeOH/HCl to afford the target hydrochloride **16a**.

Having thus developed the stepwise procedure, we next concentrated our efforts on a preparatively useful one-pot protocol. Since PPh_3/TEA was found to accelerate the most crucial step, the chlorine transfer from **12a** to **13a**, we decided to use PPh_3/CCl_4 as a reagent which was demonstrated to be useful for preparation of carboxamides from carboxylic acids and primary amines[14] and for preparation of the corresponding imidoyl chlorides from *N*-mono-substituted carboxamides.[11] Moreover, one of us has previously reported successful application of PPh_3/CCl_4 for the direct transformation of perfluoroalkylcarboxylic acids to the corresponding *N*-(alkyl)-, -(aryl)imidoyl chlorides.[15] However, critical examination of the reported chemical yields of the products using these methods suggested incomplete transformation (on average 85% or less) of the starting compounds or formation of some byproducts. Therefore we assumed that while the original procedures[11,14,15] are highly synthetically valuable for one- or two-reaction transformations, the direct application of these methods for the one-pot seven-reactions process designed by us (Scheme 3) would not be successful. Thus, we decided to study each of the chlorination steps (**9a** to **10a** and **10a** to **11a**) in every detail to find the conditions allowing for quantitative preparation of compounds **10a** and **11a**. After the series of experiments varying the ratios of the starting compounds we finally determined that the reagent PPh_3/CCl_4 must be used in a ratio 1.30/1.07, respectively, to achieve complete transformation of the acid **9a** and benzylamine to the amid **10a**. The same excess of PPh_3/CCl_4 (1.30/1.07) was found to be effective for quantitative preparation of **11a** from **10a**, followed PPh_3/TEA-catalyzed isomerization of **11a** to **14a**. With these results in hand we conducted direct preparation of amine **16a** starting with trifluoroacetic acid (**9a**). One-pot preparation of **14a** from **9a**, followed by two hydrolyses afforded the target amine **16a** in 94% isolated yield.[16] Taking into account that the whole procedure involves seven reactions, the obtained yield of **16a** was truly remarkable. This procedure was successfully applied on 10 g scale demonstrating its preparative value and reliability. Inspired by these results we attempted to use this procedure for preparing fluorinated amines **16b**,**c** starting with perfluoropropionic (**9b**) and -buturic (**9c**) acids, respectively. Under the same one-pot conditions developed for transformation of **9a** to **16a**, the perfluorocarboxylic acids **9b**,**c** were smoothly converted to the target amines **16b**,**c**, albeit with noticeably lower chemical yields (up to 70%). Based on some preliminary data, we can assume that in sharp contrast to the transformation of **9a** to **16a**, preparation of **16b**,**c** from **9b**,**c**, under the standard reaction conditions is accompanied by partial dehydrofluorinaton of the perfluoroalkyl moieties, presumably on the stage of **12b**,**c** to **14b**,**c** isomerizations. These results demonstrated that while the reaction conditions for the perfluoroalkyl substrates are still in need of some improvement, the developed method could be generally applied for direct transformation of perfluorocarboxylic acids to the corresponding amines.

In summary, the first general method for the reducing reagent-free, biomimetic transformation of perfluorocarboxylic acids to the α,α-dihydroperfluoroalkyl amines is reported. High chemical yields and simplicity of the experimental procedure render this method immediately useful and synthetically superior to the conventional approaches relying on application of reducing reagents. Currently we are working on further improvement and generalization of the method to embrace partially fluorinated and fluoroaromatic compounds.

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12. The reaction was followed by ^{19}F NMR: disappearance of a singlet at −72.13 ppm (**12a**) and appearance of a doublet ($J=6.3$ Hz) at 77.04 ppm (**13a**).
13. As suggested by the referee, "the temporary loss of conjugation accompanying this 1,3-halide shift (from compound **12a** to **13a**) may be responsible for both unfavorable kinetics and thermodynamics" of this transformation. We fully agree with this suggestion.
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16. General procedure for preparing amines **16a–c** starting from acids **9a–c**. To a solution of triphenylphosphine (19.704 mmol) in $CHCl_3$ (4 mL) at 0°C and under air atmosphere TEA (7.389 mmol), fluoroalkylcarboxylic acid **9a–c** (4.926 mmol), benzylamine (4.926 mmol) and carbon tetrachloride (19.704 mmol) were added and the mixture was stirred for 10 min. After that, the mixture was stirred for 40 min at 80°C. The resultant mixture was evaporated and treated with AcOH (10 mL) and hexane (30 mL). The AcOH phase was separated and washed with hexane (30 mL×3). Combined hexane extracts were washed with $NaHCO_3$ and evaporated. The residue obtained was treated with TEA (6 mL) and H_2O (2 mL) and stirred at 80°C for 12 h. The resultant mixture was evaporated and treated with conc. hydrochloric acid (5 mL) and methanol (2.5 mL) and heated under reflux for 12 h. The resultant product was treated with AcOEt (20 mL) and H_2O (10 mL). The aqueous layer was separated and washed by AcOEt (20 mL×2). The aqueous layer was evaporated. The solid compound obtained was washed with $CHCl_3$ (2 mL) to afford white crystalline hydrochloric salt of the corresponding fluorinated amine. Yields of **16a–c** are discussed in the text. **14a**: ^1H NMR: 4.18 (q, 2H, $J=9.3$ Hz), 7.35–7.55 (m, 3H), 8.03–8.09 (m, 2H). ^{19}F NMR: −71.5 (t, $J=9.3$ Hz). ^{13}C NMR: 55.0 (q, $J=33.0$ Hz), 124.4 (q, $J=276.8$ Hz), 128.4, 128.5, 129.1, 129.15, 132.2, 134.7, 148.2.