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Thermal 1,3-proton shift reaction and its application for operationally convenient and improved synthesis of α-(trifluoromethyl)benzylamine

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Abstract

This paper describes a synthesis of α-(trifluoromethyl)benzylamine via a novel base-free biomimetic reductive amination of α,α,α-trifluoroacetophenone with benzylamine. When the corresponding imine, derived from α,α,α-trifluoroacetophenone and benzylamine was heated at 200 °C under N_2 for 1 day, the thermal 1,3-proton shift reaction took place giving rise to the *N*-(benzylidene)-α-(trifluoromethyl)benzylamine in quantitative yield. This thermal 1,3-proton shift reaction was used a key step in the development of new and substantially simplified, practical and operationally convenient procedure for preparation of the target α-(trifluoromethyl)benzylamine on large scale.

Keywords: Thermal 1,3-proton shift reaction; Fluorine compounds; Imines; Operationally convenient conditions; Biomimetic reductive methodology

1. Introduction

In the recent years, the interest of the synthesis of organfluorine compounds has been ever increasing due to their unique physical properties and/or biological activities. In particular, α-trifluoromethyl-containing amines are currently indispensable building blocks in the design and synthesis of various fluorinated pharmaceuticals and agrochemicals [1,2]. For the last decade our group has been actively involved in the development of practical and general methodology for preparation of trifluoromethyl-containing amines [3], α-amino [4] and β-amino acids [5]. In particular, we developed a biomimetic approach for reductive amination of fluorinated carbonyl compounds to the corresponding amines and amino acids (Scheme 1) [6]. Our biomimetic approach is conceptually different from the conventional reducing methods requiring application of external reducing reagents. The biomimetic approach makes use of the intramolecular reduction/oxidation process via a base-catalyzed transposition of the imine functionality. One of the most attractive features of this reaction is that it is truly organocatalytic, metal-free and scaleable process which can be conducted under operationally convenient conditions [7].

The mechanism of this biomimetic 1,3-proton shift has never been studied in detail [8], however, it is widely believed that it might be very similar to that more general case of azomethine–azomethine isomerization, well-studied on biological [9] and synthetic [10] models. It is generally accepted that this isomerization occurs via a base-catalyzed 1,3-proton transfer across the corresponding azaallylic anionic intermediate equilibrium of which to the covalent state adequately correlated by the Hammett equation ($\rho = 0.94$) [11]. Thus, the abstraction of the azaallylic proton by base and formation of the corresponding close or solvent-separated ionic pair [10] is experimentally proven as a crucial and imperative first step for the general case of azomethine–azomethine isomerization.

Here we describe an unprecedented case of base-free, thermal 1,3-proton shift reaction and its synthetic application for substantially improved preparation of α-(trifluoromethyl)-benzylamine (**1**) (Scheme 2) via biomimetic reductive amination of α,α,α-trifluoroacetophenone with benzylamine.

2. Results and discussion

The literature [6a] procedure for preparation of amine **1** includes: (1) condensation of acetophenone **2** with benzylamine **3** under the Dean-Stark conditions; (2) chromatographic

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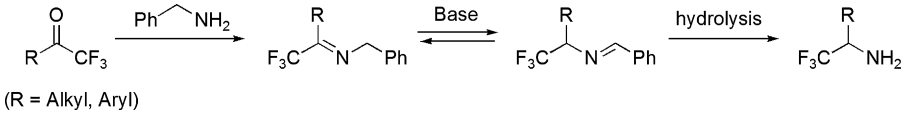
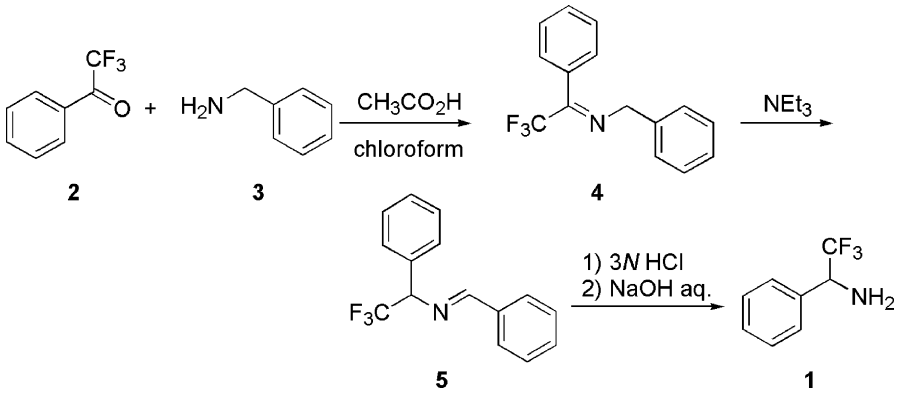


Scheme 1.



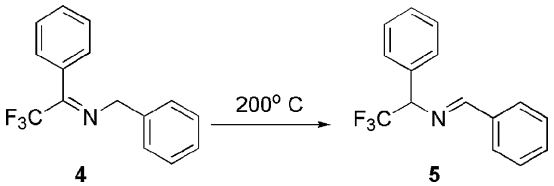
Scheme 2.

purification of imine **4**; (3) its TEA-catalyzed isomerization to Schiff base **5**; (4) chromatographic purification of **5**; (5) its hydrolysis to target amine **1**. Since one of the projects in our laboratories required relatively large amount of amine **1**, we decided to improve on this procedure and purify the intermediate imine **4** via distillation to avoid the expensive chromatographic purification. Imine **4** was prepared from **2** and **3** using acetic acid as a catalyst in chloroform as we reported previously [12]. The crude imine **4** was distilled under reduced pressure (10 mmHg) at the temperature of oil bath around 200 °C. First we were quite surprised to found that the distillate crystallized at room temperature into nice colorless crystals (mp 46.5 °C). However we were even more surprised to find out (NMR) that the product was not the expected imine **4** but isomerized Schiff base **5**. We reasoned that some small amounts of the starting benzylamine under high temperature can catalyzed the isomerization; however, based on our extensive knowledge of this reaction, this scenario was quite unlikely [13]. Therefore, we suspected a possibility of a thermal 1,3-proton shift reaction of imine **4**.

To explore a possibility of thermal isomerization, we prepared extremely pure imine **4**. Thus, to remove any possibility of the isomerization with trace amounts of benzylamine, imine **4** was subject to a short silica gel column chromatography, and then, distilled. In this case, due to substantially higher vacuum (4 mmHg) and lower boiling point (103 °C) the isomerization did not occur. Thus prepared chemically pure imine **4** was heated at 200 °C in inert (N_2) atmosphere. Monitoring of the reaction by ^{19}F NMR revealed that the thermal isomerization took place relatively fast being completed in 24 h. However, since we took several samples from the reaction mixture, some atmospheric moisture caused partial (∼5%) hydrolysis of the starting imine **4** generating acetophenone **2** and benzylamine **3**. Therefore, the result of this experiment was compromised by the presence of benzylamine **3**, a possible catalyst of the isomerization. To prevent this undesirable hydrolysis of the starting imine **4**, we placed it in an ampule under N_2 and sealed the vessel. After heating at 200 °C for 24 h the ampule was opened and the sample was analyzed by ^1H and ^{19}F NMR to show that only the isomerized product imine **5** was obtained in quantitative yield without any traces of acetophenone **2** or benzylamine **3** or any other impurities. Based on the result of this experiment, we concluded that this reaction is the first example of a base-free, thermal 1,3-proton shift reaction (Scheme 3).

To take a synthetic advantage of this new, thermal 1,3-proton shift reaction, our attention was turned to practical and convenient synthesis of amine **1**. As discussed above, the literature method [6a] for the synthesis of α-(trifluoromethyl)-benzylamine **1**, requires several chromatographic purifications and TEA-catalyzed 1,3-proton shift. First step, to synthesize imine **4**, was conducted in benzene as a solvent with Dean-Stark trap. High conversion was obtained in this condensation (>93%), but small amount of isomerization to imine **5** and partial hydrolysis of the imine **5** was also observed. After evaporation of the solvent, the crude mixture was subjected to the thermal 1,3-proton shift reaction conditions: without adding any solvents or bases, by heating at 200 °C. After 24 h, the isomerization was completed, and the product imine **5** was obtained by distillation (130 °C/5 mmHg). Then, the imine **5** was hydrolyzed by 3N HCl, and neutralized by aq. NaOH to furnish α-(trifluoromethyl)-benzylamine **1** in 78% overall yield based on ketone **2**.

Compared to the previous method [6a], this procedure is much more operationally convenient with the respect to (1)



Scheme 3.

simple work-up after the condensation reaction (only evaporation of the solvent without any further purification) and (2) a base-free 1,3-proton shift reaction.

In conclusion, we found the unprecedented example of a base-free 1,3-proton shift reaction. This finding allows us to prepare the amine **1** in high chemical yield and purity via biomimetic transamination of α,α,α-trifluoroacetophenone **2** with benzylamine under operationally convenient conditions. The detail mechanistic studies of the thermal 1,3-proton shift reaction are in progress now.

3. Experimental

3.1. General methods

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under regular atmosphere without any special caution to exclude air. Unless indicated, ^{1}H, ^{19}F NMR spectra were taken in $CDCl_3$ solutions at 299.95 and 282.24 MHz, respectively on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS (^{1}H NMR) and fluorotrichloromethane (^{19}F NMR) as the internal standards. Yields refer to isolated yields of products with greater than 95% purity as estimated by ^{1}H NMR spectrometry. Melting points (mp) are uncorrected and were obtained in open capillaries.

3.2. Procedure for preparation of α-(trifluoromethyl)benzylamine (*1*) from α,α,α-trifluoroacetophenone (*2*)

To the solution of α,α,α-trifluoroacetophenone **2** (5.00 g, 28.7 mmol) and acetic acid (1.90 g, 31.6 mmol) in benzene (20 mL), a benzene (9 mL) solution of benzylamine **3** (3.38 g, 31.5 mmol) was added at r.t. The solution was refluxed with azeotropic removal of water for 1 day using a Dean-Stark trap. Then, benzene was removed under reduced pressure. The mixture was heated at 200 °C for 24 h. Upon the completion of isomerization (monitored by ^{19}F NMR), the product imine **5** (6.20 g) was obtained by distillation (130 °C/5 mmHg). Imine **5** was stirred with 3N HCl (50 mL) and diethyl ether (10 mL) for 1 day at r.t. After separation, aqueous layer was washed with diethyl ether (20 mL). Water was removed under reduced pressure to provide hydrochloride salt of amine **1**. The salt was dissolved with ethyl acetate, 3N NaOH aq. was added until the aqueous layer became pH 14. After extraction of the aqueous layer, the ethyl acetate was removed under reduced pressure to give α-(trifluoromethyl)benzylamine **1** (3.90 g, 78% yield from acetophenone **2**) (>95% purity by ^{1}H, ^{19}F NMR).

3.3. N-Benzylidene-1-phenyl-2,2,2-trifluoroethylamine *5* [6a]

^{1}H NMR δ 4.80 (q, 1 H, J = 7.6 Hz), 7.38–7.46 (m, 6 H), 7.55–7.57 (m, 2 H), 7.83–7.85 (m, 2 H), 8.39 (s, 1 H); mp 46.5 °C.

Acknowledgements

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References

[1] For the most recent collections of research articles, see:;
(a) V.A. Soloshonok, V.A. Petrov (Guest Editors), J. Fluor. Chem. 125 (4) (2004) 487–645 (Special Issue).;
(b) D.P. Curran, K. Mikami, V.A. Soloshonok (Guest Editors), J. Fluor. Chem. 127 (4–5) (2006) 456–656 (Special Issue).

[2] For the most recent collection of review articles, see:
V.A. Soloshonok (Ed.), Fluorine-containing Synthons, ACS Symposium Series #911, Oxford University Press, 2005.

[3] V.A. Soloshonok, in: P.V. Ramachandran (Ed.), Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions, ACS Books, American Chemical Society, Washington, DC, 1999 , pp. 74–83 (Chapter 6).

[4] (a) V.P. Kukhar, G. Resnati, V.A. Soloshonok, in: V.P. Kukhar, V.A. Soloshonok (Eds.), Fluorine-containing Amino Acids. Synthesis and Properties, vol. 5, John Wiley & Sons Ltd., 1994, pp. 221–242 (Chapter 6);
(b) V.A. Soloshonok, in: I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, ACS Books, American Chemical Society, Washington, DC, 1996 , pp. 26–41 (Chapter 2);
(c) V.A. Soloshonok, in: V.A. Soloshonok (Ed.), Enantiocontrolled Synthesis of Fluoro-organic Compounds: Stereochemical Challenges and Biomedicinal Targets, John Wiley & Sons Ltd., 1999, pp. 229–262 (Chapter 7).

[5] (a) V.A. Soloshonok, in: E. Juaristi (Ed.), Enantioselective Synthesis of β-Amino Acids, VCH Publishers Inc., New York, 1997 , pp. 443–464 (Chapter 21);
(b) S. Fustero, J.F. Sanz-Cervera, V.A. Soloshonok, in: E.C. Juaristi, V.A. Soloshonok (Eds.), Enantioselective Synthesis of β-Amino Acids, 2nd ed., Wiley-VCH Ltd., 2005;
(c) V.A. Soloshonok, D.O. Berbasov, in: E.C. Juaristi, V.A. Soloshonok (Eds.), Enantioselective Synthesis of β-Amino Acids, 2nd ed., Wiley-VCH Ltd., 2005.

[6] For full papers on biomimetic transamination of fluorinated carbonyl compounds, see:
(a) T. Ono, V.P. Kukhar, V.A. Soloshonok, J. Org. Chem. 61 (1996) 6563;
(b) V.A. Soloshonok, T. Ono, Tetrahedron 52 (1996) 14701;
(c) V.A. Soloshonok, T. Ono, J. Org. Chem. 62 (1997) 3030;
(d) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 52 (1996) 6953;
(e) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 53 (1997) 8307;
(f) V.A. Soloshonok, I.V. Soloshonok, V.P. Kukhar, V.K. Svedas, J. Org. Chem. 63 (1998) 1878.

[7] Operationally Convenient Conditions is a significant issue in the development of contemporary organic synthetic methodology, see:
(a) S.M. Taylor, T. Yamada, H. Ueki, V.A. Soloshonok, Tetrahedron Lett. 45 (2004) 9159;
(b) V.A. Soloshonok, D.O. Berbasov, J. Fluor. Chem. 125 (2004) 1757.

[8] A.B. Khotkevich, V.A. Soloshonok, Y.L. Yagupolskii, Zh. Obshch. Khim. 60 (1990) 1005 (Chem. Abstr. 113: 171274y).

[9] For reviews, see:
(a) M.E. Tanner, Acc. Chem. Res. 35 (2002) 237;
(b) A.E. Martell, Acc. Chem. Res. 22 (1989) 115.

[10] D.A. Jaeger, M.D. Broadhurst, D.J. Cram, J. Am. Chem. Soc. 101 (1979) 717, and references therein on previous work reported by Cram's group..

[11] For review see:
(a) R.W. Layer, Chem. Rev. 63 (1963) 489;

(b) P.A.S. Smith, C.V. Dang, J. Org. Chem. 41 (1976) 2013;
(c) H. Brandenberger, P.P. Cohen, Helv. Chim. Acta 36 (1953) 549.
[12] D.O. Berbasov, I.D. Ojemaye, V.A. Soloshonok, J. Fluor. Chem. 125 (2004) 603.
[13] We have unpublished data suggestion that benzylamine is quite inefficient in catalyzing the isomerization of **4** to **5**. Catalytic role of benzylamine, even at high temperature, could account for partial but not complete isomerization.