Journal of Fluorine Chemistry 129 (2008) 785–787

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

First example of continuous-flow reaction conditions for biomimetic reductive amination of fluorine-containing carbonyl compounds

Vadim A. Soloshonok [a,b,*], Taizo Ono [a]

[a] National Institute of Advanced Industrial Science and Technology (AIST), 2266 Anagahora, Shimoshidami, Moriyama-ku, Nagoya, Aichi 463-8560, Japan
[b] Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, United States

ARTICLE INFO

Article history:
Received 2 May 2008
Received in revised form 24 May 2008
Accepted 29 May 2008
Available online 5 June 2008

Keywords:
1,3-Proton shift reaction
On-column reactions
Continuous-flow reactions biomimetic reductive amination
Fluorinated amino compounds

ABSTRACT

This study presents the first example of continuous-flow reaction conditions for biomimetic reductive amination of fluorinated carbonyl compounds using silica-adsorbed DBU as catalyst for on-column process. This new on-column process features operationally convenient conditions, higher chemical yields and purity of products as compared with traditional in-flask reactions. Furthermore the removal of base-catalyst is not an issue in this process at all, as the catalyst (DBU) remains on the column in the "reaction zone", the feature which makes the overall process substantially more efficient and inexpensive, in particular, for large-scale synthesis of the target α-perfluoroalkyl amines.

Biological transamination [1] (BTA) is among the most fundamental biological processes, providing a unique chemical solution to the reduction–oxidation processes that all living forms have adopted through the process of evolution. In particular, one of the most important biological transformations using BTA is the interconversion of α-keto and α-amino acids, catalyzed by pyridoxamine/pyridoxal-dependent enzymes [2]. Numerous investigations of the native [3] BTA and its various chemical models [4] have contributed to a reasonably detailed understanding of the corresponding mechanism including a rationale for the observed stereochemistry. Thus, in a simplified form, the mechanism of BTA involves a base-catalyzed 1,3-proton shift across the azaallyllic system of imine **3** resulting in a transposition of the imine-functionality and a formation of the isomeric imine **4** (Scheme 1).

As one can envision, this biological reduction–oxidation process *via* a base-catalyzed 1,3-proton shift could find a synthetic application for biomimetic oxidative deamination/reductive amination reactions, starting, in general, with amine **1** and ketone/aldehyde **2**, and ketone/aldehyde **5** and amine **6**, respectively.

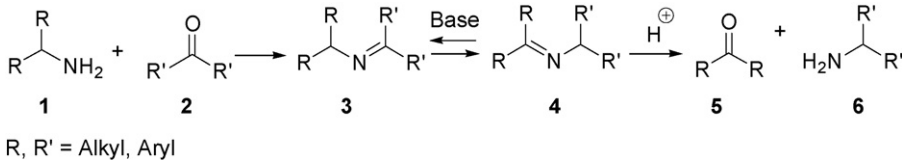
The first synthetic application of this biomimetic approach was reported by Corey's group who used the base-catalyzed imine–imine isomerization to achieve oxidative deamination, a key reaction step in several total syntheses of natural products [5a]. Other groups [5b–i] have developed even more efficient reagents and conditions for generalized transformations of amines to the corresponding carbonyl compounds.

On the other hand, the opposite transformation, reductive amination of carbonyl compounds, was found to be more difficult to realize, producing only a limited number of successful examples [6]. In sharp contrast to the not-so-successful application of the biomimetic approach for reductive amination of conventional carbonyl compounds, it was found that imines **9** (Scheme 2), derived from α-trifluoromethyl-containing carbonyl compounds **8** (aldehydes [7], ketones [7], including α-keto acids [8] and β-keto acids [9]) and benzylamine (**7**) readily undergo virtually irreversible isomerization to imines **10** under the action of regular organic bases (TEA, DBU, DBN, and guanidine). Easy hydrolysis (acid-catalyzed) of compounds **10** afforded various fluorinated amines **12** and benzaldehyde (**11**). This biomimetic method is general, affordable and truly practical for large-scale preparations of various fluorinated amines [10], α- and β-amino acids. An asymmetric version of this process, using chiral derivatives of benzylamine, has also been developed [11].

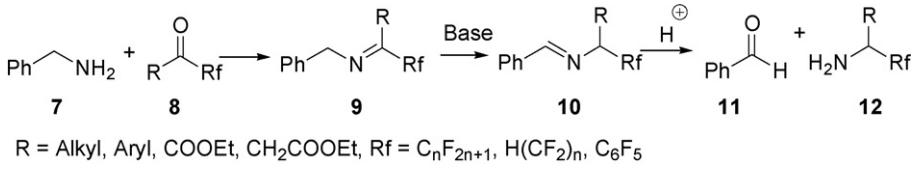
However, in spite of the high synthetic value of this biomimetic reductive amination for the preparation of fluorinated amines and amino acids, its application with major advantages over the

* Corresponding author at: National Institute of Advanced Industrial Science and Technology (AIST), 2266 Anagahora, Shimoshidami, Moriyama-ku, Nagoya, Aichi 463-8560, Japan.
E-mail address: vadim@ou.edu (V.A. Soloshonok).

0022-1139/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2008.05.019



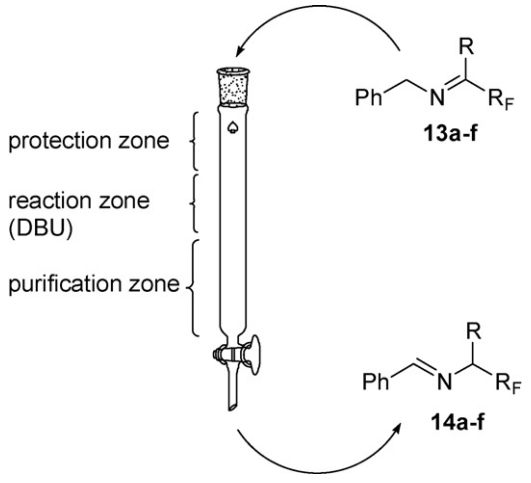
Scheme 1. General mechanism for biomimetic oxidative deamination/reductive animation.



Scheme 2. Biomimetic transamination of fluorinated carbonyl compounds.

conventional reduction amination methods, the intramolecular reduction–oxidation processes, has never been evaluated. Thus, we have envisioned that since this biomimetic process do not require the use of external reducing reagents, a conceptually new continuous-flow reductive amination process can be developed. Here we report the first example of continuous-flow reaction conditions for biomimetic reductive amination of fluorinated carbonyl compounds using silica-adsorbed DBU as catalyst for on-column process.

To demonstrate the proof of principle for the continuous-flow reaction using the principle of biomimetic transamination, we designed an extremely simple apparatus shown in Scheme 3. Thus, the usual glass column was filled about 1/2 with a regular silica gel (hexanes). Next, a calculated amount of DBU [12,13] (0.25 wt% of the whole amount of silica gel) in a solution of dichloromethane was charged carefully onto the top and allowed to percolate down to the surface. Then an additional amount (1/4 of the whole amount) of silica gel was charged carefully onto the column. According to our experimental data, the DBU penetrates into the silica gel to occupy about 1/4 of the whole silica gel column volume. Thus prepared column consists of three functional parts: protection zone (to prevent the direct contact of the starting materials with DBU) (about 1/4 of the volume), reaction zone (1/4) and purification zone (1/2). Fluorine-containing imines **13a–f**, prepared by standard procedures [7k] were charged onto the column using a mixture of hexanes/acetonitrile (4/1) as a solvent. As one can expect, the rate of the isomerization of starting imines



Scheme 3.

13a–f to products **14a–f** was found to depend heavily on concentration of **13a–f**, amount of DBU and rate of the elution. Preliminary optimization of these parameters indicated that for a given amount of the catalyst (see above) the imine concentration of 10 mol% and the elution rate about 1 drop/s from the column tip provide for complete isomerization of starting imines **13a–f** to products **14a–f**. The structure and purity of the products **14a–f**, conveniently collected from the column's tip, were determined by NMR.

The experimental data collected in Table 1 on the isomerization of series of aldimines **13a–e** and ketimine **13f** to the target products **14a–f** clearly demonstrate for the superior efficiency of the continuous-flow reaction conditions (on-column) as compared with the conventional (in-flask) procedure. Thus in all cases studied the products **14a–f** were obtained in higher chemical yields and purity [7k] allowing for their further synthetic transformations (hydrolysis) without any purification. The durability of the catalyst used in this continuous-flow reaction procedure is currently under investigation. However, we can report at least a successful preparation 2Kg+ of product **14a** using only 10 g of the on-column catalyst.

Generalization of this novel continuous-flow reaction procedure for various different types of starting compounds and catalysts, large-scale preparations and its application for asymmetric transformations are currently under investigation.

In summary, the first example of a conceptually new continuous-flow reaction procedure for biomimetic transamination of fluorinated carbonyl compounds has been developed. As follows from the results obtained, the new procedure might be substantially more efficient, practical and operationally convenient as compared with the currently used conventional methods. We believe that this new dimension in the biomimetic transamination will further increase its synthetic efficiency leading to the development of ultimately practical, environmentally benign and metal-free reductive amination for the preparation of fluorinated amino compounds.

Table 1
Continuous-flow base-catalyzed isomerization of **13a–f** to **14a–f**

13	R	R_F	Yield of 14 (%) [7k]
a	H	CF_3	>98 (87)
b	H	C_3F_7	95 (86)
c	H	C_4F_9	96 (89)
d	H	$H(CF_2)_4$	92 (89)
e	H	$H(CF_2)_6$	95 (90)
f	Ph	CF_3	>98 (93)

References

[1] A.E. Braunshtein, M.G. Kritsman, Biokhimiya (Moscow) 2 (1937) 859–874.

[2] (a) A.E. Martell, Acc. Chem. Res. 22 (1989) 115–124;
(b) M.E. Tanner, Acc. Chem. Res. 35 (2002) 237–246;
(c) G. Wachtershauser, Microbiol. Rev. 52 (1988) 452–484.

[3] (a) L. Liu, W. Zhou, J. Chruma, R. Breslow, J. Am. Chem. Soc. 126 (2004) 8136–8137;
(b) L. Liu, R. Breslow, J. Am. Chem. Soc. 125 (2003) 12110–12111;
(c) R.F. Zabinski, M.D. Toney, J. Am. Chem. Soc. 123 (2001) 193–198;
(d) S. Ogo, K. Uehara, T. Abura, S. Fukuzumi, J. Am. Chem. Soc. 126 (2004) 3020–3021;
(e) J.B. Longenecker, E.E. Snell, J. Am. Chem. Soc. 79 (1957) 142–145;
(f) L. Casella, M. Gullotti, J. Am. Chem. Soc. 105 (1983) 803–809;
(g) L. Liu, M. Rozenman, R. Breslow, J. Am. Chem. Soc. 124 (2002) 12660–12661;
(h) L. Liu, R. Breslow, J. Am. Chem. Soc. 124 (2002) 4978–4979;
(i) R. Breslow, J.W. Canary, M. Varney, S.T. Waddell, D. Yang, J. Am. Chem. Soc. 112 (1990) 5212–5219.

[4] (a) D.A. Jaeger, M.D. Broadhurst, D.J. Cram, J. Am. Chem. Soc. 101 (1979) 717–732;
(b) For review see: R.W. Layer, Chem. Rev. 63 (1963) 489–510;
(c) P.A.S. Smith, C. Van Dang, J. Org. Chem. 41 (1976) 2013–2015;
(d) H. Brandenberger, P.P. Cohen, Helv. Chim. Acta 36 (1953) 549–554.

[5] Biomimetic oxidative deamination of amines:
(a) E.J. Corey, K. Achiwa, J. Am. Chem. Soc. 91 (1969) 1429–1432;
(b) V. Calo, L. Lopez, P.E. Todesco, J. Perkin Trans. 1 (1972) 1652–1653;
(c) S. Ohta, M. Okamoto, Synthesis (1982) 756–758;
(d) J.H. Babler, B.J. Invergo, J. Org. Chem. 46 (1981) 1937–1938;
(e) T.F. Buckley, H. Rapoport, J. Am. Chem. Soc. 104 (1982) 4446–4450;
(f) F.G. Baddar, Z. Iskander, Nature 167 (1951) 1069–1070;
(g) F.G. Baddar, J. Chem. Soc. (1950) 136–139;
(h) F.G. Baddar, Z. Iskander, J. Chem. Soc. (1954) 203–209;
(i) F.G. Baddar, Z. Iskander, J. Chem. Soc. (1954) 209–213.

[6] Biomimetic reductive amination of carbonyl compounds:
(a) G. Cainelli, D. Giacomini, A. Trere, P.P. Boyl, J. Org. Chem. 61 (1996) 5134–5139;
(b) M. Ando, H. Kuzuhara, Bull. Chem. Soc. Jpn. 63 (1990) 1925–1928, references therein on previous publications;
(c) J.G.H. Willems, J.G. de Vries, R.J.M. Nolte, B. Zwanenburg, Tetrahedron Lett. 36 (1995) 3917–3920;
(d) A. Hjelmencrantz, U. Berg, J. Org. Chem. 67 (2002) 3585–3594;
(e) S. Bachmann, K.R. Knudsen, K.A. Jørgensen, Org. Biomol. Chem. 2 (2004) 2044–2049;
(f) S. Zimmerman, R. Breslow, J. Am. Chem. Soc. 106 (1984) 1490–1491;
(g) Y. Wu, P. Ahlberg, J. Org. Chem. 57 (1992) 6324–6327;
(h) Y. Wu, P. Ahlberg, Acta Chem. Scand. 46 (1992) 60–72;
(i) K. Bernauer, R. Deschenaux, T. Taura, Helv. Chim. Acta 66 (1983) 2049–2058;
(j) R. Deschenaux, K. Bernauer, Helv. Chim. Acta 67 (1984) 373–377.

[7] Biomimetic transamination of fluorinated aldehydes and ketones:
(a) V.A. Soloshonok, I.L. Gerus, Y.I. Yagupolskii, V.P. Kukhar, Zh. Org. Khim. 23 (1987) 2308–2313, Chem. Abstr. 109, 55185;
(b) V.A. Soloshonok, I.L. Gerus, Y.I. Yagupolskii, V.P. Kukhar, Zh. Org. Khim. 24 (1988) 993–997, Chem. Abstr. 110, 134824v;
(c) V.A. Soloshonok, Y.I. Yagupolskii, V.P. Kukhar, Zh. Org. Khim. 24 (1988) 1638–1644, Chem. Abstr. 110, 154827b;
(d) A.B. Khotkevich, V.A. Soloshonok, Y.I. Yagupolskii, Zh. Obshch. Khim. 60 (1990) 1005–1008, Chem. Abstr. 113, 171274y;
(e) V.A. Soloshonok, A.G. Kirilenko, V.P. Kukhar, G. Resnati, Tetrahedron Lett. 35 (1994) 3119–3122;
(f) V.A. Soloshonok, T. Ono, Synlett (1996) 919–921;
(g) V.A. Soloshonok, T. Ono, Tetrahedron 52 (1996) 14701–14712;
(h) H. Ohkura, D.O. Berbasov, V.A. Soloshonok, Tetrahedron Lett. 44 (2003) 2417–2420;
(i) H. Ohkura, D.O. Berbasov, V.A. Soloshonok, Tetrahedron 59 (2003) 1647–1656;
(j) D.O. Berbasov, I.D. Ojemaye, V.A. Soloshonok, J. Fluor. Chem. 125 (2004) 603–607;
(k) T. Ono, V.P. Kukhar, V.A. Soloshonok, J. Org. Chem. 61 (1996) 6563–6569;
(l) V.A. Soloshonok, H. Ohkura, M. Yasumoto, Mendeleev Commun. (2006) 165–167;
(m) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluor. Chem. 127 (2006) 708–711;
(n) V.A. Soloshonok, M. Yasumoto, J. Fluor. Chem. 127 (2006) 889–893;
(o) V.A. Soloshonok, D.O. Berbasov, J. Fluor. Chem. 125 (2004) 1757–1763;
(p) M. Yasumoto, H. Ueki, V.A. Soloshonok, J. Fluor. Chem. 128 (2007) 736–739.

[8] Biomimetic transamination of fluorinated α-keto acids:
V.A. Soloshonok, V.P. Kukhar', Tetrahedron 53 (1997) 8307–8314.

[9] Biomimetic transamination of fluorinated β-keto acids:
(a) V.A. Soloshonok, A.G. Kirilenko, V.P. Kukhar, G. Resnati, Tetrahedron Lett. 34 (1993) 3621–3624;
(b) V.A. Soloshonok, A.G. Kirilenko, N.A. Fokina, I.P. Shishkina, S.V. Galushko, V.P. Kukhar, V.K. Svedas, E.V. Kozlova, Tetrahedron: Asymmetry 5 (1994) 1119–1126;
(c) V.A. Soloshonok, A.G. Kirilenko, N.A. Fokina, S.V. Galushko, V.P. Kukhar, V.K. Svedas, G. Resnati, Tetrahedron: Asymmetry 5 (1994) 1225–1228;
(d) V.A. Soloshonok, V.P. Kukhar, Tetrahedron 52 (1996) 6953–6964.

[10] "Double" biomimetic transamination of fluorinated acids to amines has been reported: V.A. Soloshonok, H. Ohkura, K. Uneyama, Tetrahedron Lett. 43 (2002) 5449–5452.

[11] Asymmetric version of the biomimetic transamination:
(a) V.P. Kukhar, V.A. Soloshonok, S.V. Galushko, A.B. Rozhenko, Dokl. Akad. Nauk SSSR 310 (1990) 886–889, Chem. Abstr. 113, 78920w;
(b) V.A. Soloshonok, T. Ono, J. Org. Chem. 62 (1997) 3030–3031;
(c) V.A. Soloshonok, T. Ono, I.V. Soloshonok, J. Org. Chem. 62 (1997) 7538–7539;
(d) V.A. Soloshonok, A.G. Kirilenko, S.V. Galushko, V.P. Kukhar, Tetrahedron Lett. 35 (1994) 5063–5064;
(e) V.A. Soloshonok, I.V. Soloshonok, V.P. Kukhar, V.K. Svedas, J. Org. Chem. 63 (1998) 1878–1884;
(f) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluor. Chem. 127 (2006) 924–929;
(g) V.A. Soloshonok, H. Ohkura, M. Yasumoto, J. Fluor. Chem. 127 (2006) 930–935;
(h) V.A. Soloshonok, Angew. Chem. Int. Ed. Engl. 45 (2006) 766–769;
(i) V.A. Soloshonok, D.O. Berbasov, J. Fluor. Chem. 127 (2006) 597–603;
(j) V.A. Soloshonok, M. Yasumoto, J. Fluor. Chem. 128 (2007) 170–173.

[12] In typical experiment, a glass column (3 × 80 cm) was charged with 200 g of silica gel (hexanes). While leaving about 1 cm of the solvent on top of silica gel, a suspension of 100 g of silica gel in dichloromethane containing 1 g of DBU was charged onto the top and allowed to percolate down to the surface of silica gel. Finally, additional 100 g of silica gel (hexanes) was added on the top of the column allowing the solvent to percolate down to the surface of silica gel completely. Using thus prepared column, a solution [10 mol % in hexanes/acetonitrile (4/1)] of fluorinated imine 13**a**–**f** was eluted through the column at the rate of 1 drop per second. UV-active fractions (detection by TLC) were collected and evaporated to afford products 14**a**–**f** (for yields, see Table 1).

[13] The choice of DBU as a catalyst was based on our recent mechanistic studies: P. Nagy, H. Ueki, D.O. Berbasov, V.A. Soloshonok, J. Fluor. Chem. 129 (2008) 409–415.