Transacylation

DOI: 10.1002/ange.200906055

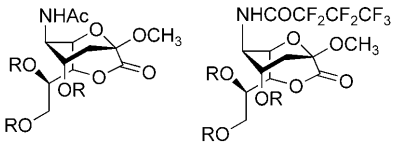
General and Chemoselective N-Transacylation of Secondary Amides by Means of Perfluorinated Anhydrides**

Paola Rota, Pietro Allevi, Raffaele Colombo, Maria L. Costa, and Mario Anastasia*

Examples of direct N-transacylations of amides are very rare and lacking in general applicability. For instance, earlier attempts at N-transacylation were performed under harsh conditions.[1] Other procedures required prolonged treatment with an equimolar mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA; 100 °C, 48 h),[2,3] or even running the reaction in TFAA followed by the addition of a strong base, reported as necessary to abstract the hydrogen atom in the alpha position to the eliminated acyl group.[4] Finally, some acetanilides were treated with chloroacetyl chloride under acid catalysis of zeolites or $AlCl_3$ at 83 °C for 16 h,[5] or in refluxing pyridine containing dimethylaminopyridine for 5 h.[6]

Thus, N-transacylations are usually accomplished by hydrolysis of the acylamides and successive re-acylation of the formed amines,[7] a procedure that does not allow the simultaneous presence, in the amide molecule, of functional groups labile to the basic or acidic conditions of the hydrolysis.[7d,8] Herein, we report the first direct, general, and chemoselective procedure for the N-transacylation of secondary acylamides to their perfluorinated analogues, in high yields, with perfluorinated anhydrides. Remarkably, the perfluorinated amide formed could then be directly converted to a different amide by simple treatment with the desired acyl chloride, followed by a very mild aqueous process of the reaction mixture.

Our work originated while studying sialic acid 1,7-lactone **1a**.[9] Surprisingly, on reacting the lactone **1a** with heptafluorobutyric anhydride (HFBAA) to volatilize it (135 °C for 5 min, in CH_3CN),[10] we did not obtain the expected derivative **1b** but the lactone **2b**, which could be quantitatively transformed into lactone **2a** by treatment of the reaction mixture with methanol at room temperature.



1a: R = H
1b: R = $CF_3(CF_2)_2CO$
2a: R = H
2b: R = $CF_3(CF_2)_2CO$

Prompted by these initial results, we explored the scope of this new reaction (Table 1). Because of the particular utility of the reaction in carbohydrate chemistry,[7a] we started with some sialic acid and amido sugar derivatives of interest in organic synthesis and in biological studies.[11] In particular, we were interested in testing molecules containing groups labile to the commonly used conditions of amide hydrolysis and re-acylation. In effect, our reaction conditions allowed the successful N-transacylation of several compounds containing a great variety of functional groups (often within the same molecule), such as hydroxy groups, lactones, benzyloxycarbonyls (OCbz), methyl esters, acetates, *tert*-butyldimethylsilyl (TBDMS) groups, and acyclic and cyclic acetals as their 2-methoxyethoxymethyl (MEM), methyl, and benzylidene derivatives (Table 1, entries 1–18). Moreover, to test possible anomerizations resulting from the perfluorinated acid liberated in the reaction, we tested α- and β-glycosidic compounds as well as a β-disaccharide. Finally, we selected carbohydrates with an equatorial or an axial acetamido group, to test the possible influence of the amide geometry.

The study was first performed with HFBAA,[10a] then the reaction was repeated on some representative samples with TFAA, which gave comparable results (Table 1, entries 3, 13, 14, and 17). In all cases, except for entry 7, the reaction occurred in good yields, chemoselectively, and involving exclusively the amido group independently of its equatorial or axial geometry. Other functional groups present in the treated compounds were conserved, with the exception of free hydroxy, alcoholic, or acetalic groups, which, as expected, were perfluoroacylated (mass spectrometry (MS) and NMR evidence) under the reaction conditions employed. However, they could be easily regenerated by simple, short treatment of the crude reaction mixture with a solution of aqueous TFA in THF.

Only acyclic acetals appeared to be labile under the reaction conditions, as observed for the MEM group (Table 1, entry 7). Remarkably, analysis of the ^{1}H NMR spectra of compounds **4**, **6**, **8**, **10**, **12**, **14**, and **16** clearly showed in all cases that the reaction does not modify the configuration of the anomeric centers (see the Supporting Information). The anomeric geometry for the sialic acid derivative **8a**, which lacks the anomeric proton, was established on the basis of the values of the heteronuclear vicinal coupling constant ($^3J_{C1,H3ax}$ and $^2J_{C2,H3ax}$).[12,13]

To further study the general applicability of the reaction, we tested it on other non-carbohydrate compounds, including

[*] Dr. P. Rota, Prof. Dr. P. Allevi, Dr. R. Colombo, Dr. M. L. Costa, Prof. Dr. M. Anastasia
Department of Medical Chemistry, Biochemistry, and Biotechnology
University of Milan
via Saldini 50, 20133 Milano (Italy)
Fax: (+39) 02-5031-6040
E-mail: paola.rota@unimi.it

[**] This work was financially supported by the Italian Ministero dell'Università e della Ricerca (MiUR).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200906055.

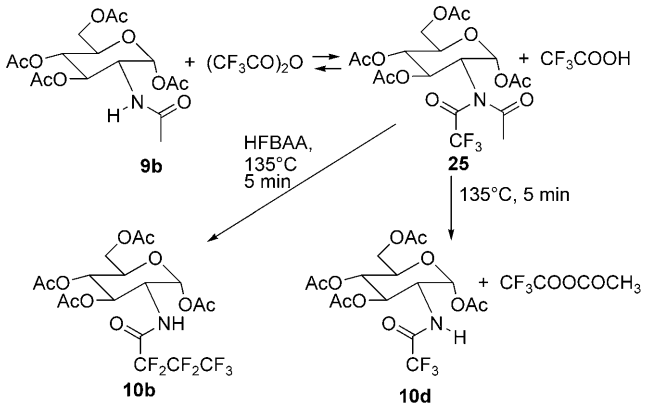
Table 1: N-Transacylation of secondary amides by the action of perfluorinated anhydrides.[a]

Entry	Substrate	Product	*t* [min]	Yield [%][b]
1	**3a**: $R^1 = H$	**4a**: $R^1 = H; n = 2$[c]	5	79
2	**3b**: $R^1 = Ac$	**4b**: $R^1 = Ac; n = 2$	5	82
3	**3b**	**4c**: $R^1 = Ac; n = 0$	5	80
4	**5a**: $R^1 = R^2 = H$	**6a**: $R^1 = R^2 = H$[c]	5	89
5	**5b**: $R^1 = R^2 = Ac$	**6b**: $R^1 = R^2 = Ac$	5	84
6	**5c**: $R^1 = Ac; R^2 = TBDMS$	**6c**: $R^1 = Ac; R^2 = TBDMS$	5	78
7	**5d**: $R^1 = Ac; R^2 = MEM$	mixture of compounds	5	–
8	**7a**: $R^1 = OMe$[e]	**8a**: $R^1 = OMe$[e]	5	53
9	**7b**: $R^1 = H$	**8b**: $R^1 = H$	5	82
10	**9a**: $R^1 = R^2 = H; R^3 = OH$[d]	**10a**: $R^1 = R^2 = H; R^3 = OH; n = 2$[c,d]	5	83
11	**9b**: $R^1 = Ac; R^2 = H; R^3 = OAc$[e]	**10b**: $R^1 = Ac; R^2 = H; R^3 = OAc; n = 2$[e]	5	87
12	**9c**: $R^1 = Ac; R^2 = OAc; R^3 = H$[e]	**10c**: $R^1 = Ac; R^2 = OAc; R^3 = H; n = 2$[e]	5	92
13	**9b**[e]	**10d**: $R^1 = Ac; R^2 = H; R^3 = OAc; n = 0$[e]	5	85
14	**9a**[d]	**10e**: $R^1 = R^2 = H; R^3 = OH; n = 0$[c,d]	5	86
15	**11**[e]	**12**[e]	5	63
16	**13**[f]	**14a**: $n = 2$[f]	5	81
17	**13**[f]	**14b**: $n = 0$[f]	5	79
18	**15**[e]	**16**[e]	5	90
19	**17a**: R = Ac	**18a**: R = Ac	15	88
20	**17b**: R = *t*BuCO	**18b**: R = *t*BuCO	15	84
21	**17c**: R = Bn	**18c**: R = Bn	15	56
22	**19a**: R = Ac	**20a**: R = Ac	15	91
23	**19b**: R = *t*BuCO	**20b**: R = *t*BuCO	15	84
24	**19c**: R = *i*PrCO	**20c**: R = *i*PrCO	15	88
25	**21**	**22a**: $n = 2$	90	92
26	**21**	**22b**: $n = 0$	90	89
27	**23**	**24**	30	87

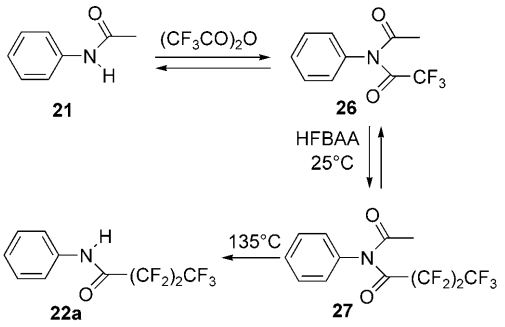
[a] Reaction conditions: acylamide (0.2 mmol) in MeCN (600 μL) was reacted with the perfluorinated anhydride (0.6–1.4 mmol) at 135 °C in a sealed tube. [b] Yield of isolated compound. [c] Isolated, by hydrolysis after 1 h of treatment of the final reaction mixture with TFA in H_2O/THF at 60 °C. [d] Anomeric mixture, α/β 85:15. [e] α Anomer. [f] Anomeric mixture, α/β 18:82.

their protective groups and also the benzyl (Bn) group (Table 1, entries 19–27). Some of these compounds allowed validation that the reaction is not limited to acetyl amides, but could be successfully performed on hindered acylamides and with amides lacking an α-hydrogen atom (Table 1, entries 20, 23, and 24). Other examples were chosen to verify that the reaction was not limited to compounds bearing a substituent (acetoxy or hydroxy group) at the α position of the amidic nitrogen atom (Table 1, entries 25 and 26). Interestingly, the reaction also worked with protected amino acids such as the acetyl phenylalanine methyl ester **23** (Table 1, entry 27), which is transformed into its heptafluorobutyrate analogue **24** in satisfactory yields and without any racemization, as demonstrated by its gas–liquid chromatography (GLC) analysis on a chiral column (see the Supporting Information). This latter result shows that the new reaction, besides being crucial for amino acid analysis, may represent a tool to selectively regenerate the amino group of acetylated amino esters.[2,14]

Finally, we performed some additional experiments to rationalize the reaction course and suggest a possible mechanism. For this purpose, we chose the 1,3,4,6-tetra-*O*-acetyl-2-acetamido-2-deoxy-α-D-glucopyranoside (**9b**) (Scheme 1) as a model compound, and reacted it with TFAA in CD_3CN at room temperature. By monitoring the reaction course with ^1H NMR spectroscopy, we observed from some diagnostic changes in the ^1H NMR spectrum of the reaction mixture that the starting amide **9b** was almost



Scheme 1. N-transperfluoroacylation of *N*-acetylglucosamine.



Scheme 2. N-transperfluoroacylation of acetanilide.

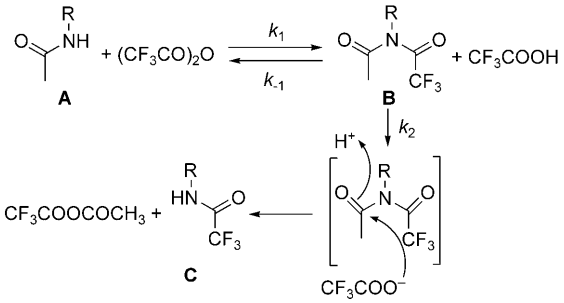
instantly transformed into the mixed imide **25** (90% yield, accompanied by 10% of the starting amide **9b**). Interestingly, the mixed imide **25** was stable in the reaction mixture but completely reverted to the starting amide **9b** when the more volatile TFAA and TFA were removed from the reaction mixture by a direct stream of nitrogen. This suggested that the amide **9b** and the imide **25** were in a rapid equilibrium and that the removal of TFAA, which is more volatile than its acid, drives the reaction back to the starting acetyl amide **9b**.

On the contrary, when the reaction mixture containing the imide **25** was heated at 135°C for 5 min, or kept at room temperature for 6 days, the trifluoroacetamide **10d** was quantitatively obtained (Scheme 1). Moreover, while monitoring the reaction course by ^{1}H NMR spectroscopy at 25°C, we observed a slow increase of the final amide **10d** which was accompanied by a parallel progressive decrease of the imide **25** and of the starting amide **9b**, although they maintained a constant reciprocal ratio during the entire reaction course. Furthermore, we also observed that the final fluorinated acylamide **10d** was practically irreversibly formed. In fact, it could not be converted into the imide **25** or into the non-fluorinated analogue **9b** by treatment with acetic anhydride or other non-fluorinated anhydrides, or with the mixed anhydride $CF_3COOCOCH_3$ under various conditions. In addition, the trifluoroacetylated amide **10d** did not react with TFAA or HFBAA.

The existence of a rapid equilibrium between the amide **9b** and the imide **25** was also confirmed by a different experiment, in which we first formed the imide **25** (^{1}H NMR, in CD_3CN) and then added a strong excess of HFBAA (40 molar equiv) to the reaction mixture and heated it for 5 min at 135°C. Under these conditions, we obtained the heptafluorobutyrate amide **10b** as the main product, together with trace amounts of the trifluoroacetate analogue **10d**.

A parallel result was reached upon studying the reaction of the acetanilide **21**, which formed the trifluoroacetylated imide **26** that was stable and isolable by distillation (Scheme 2).[1e] In this case, we prepared the pure imide **26** and subjected it to a short treatment (5 min) with a strong excess of HFBAA (40 molar equiv) at room temperature. Under these conditions the trifluoroacetate imide was quantitatively transformed into the homologous heptafluorobutyrate imide **27**. In fact, in the final reaction mixture, the imide **27** was only accompanied by minor amounts of the starting imide **26** (ca. 3%) and by trace amounts (0.6%) of the acetanilide **21** (GLC analysis). Moreover, when the reaction mixture was heated at 135°C for 5 min, it afforded the transacylated amide **22a** as expected.

All this evidence describes the observed N-transacylation as a consecutive reaction, with a fast pre-equilibrium between the starting amide **A** and the intermediary mixed imide **B**, which is more slowly transformed into the perfluorinated amide **C** (Scheme 3).



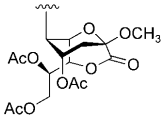
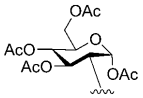
Scheme 3. Suggested mechanism of the N-transacylation of amides, with $k_2 < k_1$ and k_{-1}.

This rationalization of the reaction mechanism suggested the possibility of reverting the N-transacylation and transforming the fluorinated amide **C** into the starting non-fluorinated (normal) amide **A**, or into a different acylamide. This remarkable and unprecedented goal could be achieved as long as appropriate acylation reagents were found to attack the poorly reactive perfluorinated amide **C**. In fact, at the beginning of our work we observed that by the action of water, imides such as **B** lose the perfluorinated acyl group affording the parent amide **A**. In effect, after some unsuccessful attempts, we reached a positive result by reacting, in separate experiments, the trifluoroacetylanilide **22b** with acetyl, propionyl, and pivaloyl chlorides in the presence of triethylamine (Table 2, entries 1–3).

Under these conditions, after a short reaction time (20 min), we observed the disappearance of the starting amide **22b** and the appearance of the intermediary mixed imides (GLC–MS evidence) which, by simple aqueous workup of the reaction mixtures, afforded the non-fluorinated

Table 2: N-Transacylation of perfluorinated amides by the action of acyl chlorides.

R^1–NH–$COCF_3$ $\xrightarrow{R^2CO-Cl}$ R^1–NH–COR^2

Entry	Substrate	R^1	R^2	Product	Yield [%][a]
1	**22b**	Ph	Me	**21**	65[b]
2	**22b**	Ph	Et	**28**	60[b]
3	**22b**	Ph	Me_3C	**29**	64[b]
4	**4c**		Me	**3b**	71[c]
5	**10d**		Me	**9b**	70[c]

[a] Yield of isolated compound. [b] Reaction conditions: the acyl chloride (0.6 mmol) was added at 0 °C to a solution of trifluoroacetyl anilide (**22b**, 0.2 mmol) and triethylamine (0.64 mmol) in CH_2Cl_2 (500 μL). [c] Reaction conditions: the acetyl chloride (0.6 mmol) was added at 0 °C to a solution of trifluoroacetamide (**4c** or **10d**, 0.1 mmol) and diisopropylethylamine (2.0 mmol) in CH_2Cl_2 (500 μL).

amides (**21**, **28**, or **29**). The applicability of the reaction to more complex molecules was then satisfactorily proved by operating on *N*-trifluoroacetyl lactone **4c** (Table 2, entry 4) and *N*-trifluoroacetylglucosamine **10d** (Table 2, entry 5), and performing the reaction with acetyl chloride in the presence of excess diisopropylethylamine.

All these results permit the conclusion that our N-transacylation reaction is general in scope and of high utility in organic chemistry. Moreover, the two-step replacement of an acyl group of a secondary amide with a different one through the formation of a trifluorinated intermediate allows one to prepare in a simple way the acyl analogues of a variety of molecules having synthetic or pharmaceutical applications.[15] Not less importantly, the disclosure of this reaction is of high utility in analytical protocols where the overlooking of this N-transacylation may be a pitfall affording puzzling results. Work is ongoing in our laboratory to apply the new knowledge to synthetic and analytical protocols.

Experimental Section

General procedure: The acylamide (0.2 mmol) dissolved in CH_3CN (600 μL) was reacted with the perfluorinated anhydride (0.6–1.4 mmol) at 135 °C for the time reported in Table 1. Then the reaction mixture was ice-cooled, methanol (200 μL) was added, and the solvent was removed under vacuum to afford the crude N-transacylated amidic compound, which was purified by column chromatography. More specific workup is reported in the Supporting Information. Comparable results were obtained at room temperature but with longer reaction times (1 week).

Received: October 28, 2009
Revised: December 1, 2009
Published online: February 9, 2010

Keywords: amides · chemoselectivity · perfluorinated anhydrides · synthetic methods · transacylation

[1] a) G. S. Kulikova, V. E. Kirichenko, K. I. Pashkevich, *Zh. Anal. Khim.* **1989**, *44*, 1148; b) S. Nagubandi, G. Fodor, *Heterocycles* **1981**, *15*, 165; c) M. Michman, D. Meidar, *J. Chem. Soc. Perkin Trans. 2* **1972**, 300; d) M. Michman, S. Patai, I. Shenfeld, *J. Chem. Soc. C* **1967**, 1337, and references therein; e) E. J. Bourne, S. H. Henry, C. E. M. Tatlow, J. C. Tatlow, *J. Chem. Soc.* **1952**, 4014.
[2] B. Nilsson, S. Svensson, *Carbohydr. Res.* **1978**, *62*, 377.
[3] Under these conditions some 2-acetamido-2-deoxy sugars are severely degraded, see: a) B. Nilsson, S. Svensson, *Carbohydr. Res.* **1978**, *65*, 169; b) B. Nilsson, S. Svensson, *Carbohydr. Res.* **1979**, *72*, 183.
[4] A. G. M. Barrett, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1629.
[5] a) H. R. Sonawane, A. V. Pol, P. P. Moghe, A. Sudalai, S. S. Biswas, *Tetrahedron Lett.* **1994**, *35*, 8877; b) H. R. Sonawane, A. V. Pol, B. S. Nanjundiah, A. Sudalai, *J. Chem. Res. Synop.* **1998**, 90.
[6] Y. Li, C. Li, P. Wang, S. Chu, H. Guan, B. Yu, *Tetrahedron Lett.* **2004**, *45*, 611.
[7] For some examples of multistep transacylations, see: a) C. De Meo, U. Priyadarshani, *Carbohydr. Res.* **2008**, *343*, 1540; b) I. Hemeon, A. J. Bennet, *Synthesis* **2007**, 1899; c) H. Myszka, D. Bednarczyk, M. Najder, W. Kaca, *Carbohydr. Res.* **2003**, *338*, 133; d) M. Oba, M. Tanaka, M. Kurihara, H. Suemune, *Helv. Chim. Acta* **2002**, *85*, 3197; e) K. Ikeda, K. Konishi, K. Sano, K. Tanaka, *Chem. Pharm. Bull.* **2000**, *48*, 163.
[8] See, for example: a) T. Q. Gregar, J. Gervay-Hague, *J. Org. Chem.* **2004**, *69*, 1001; b) H. Ando, Y. Koike, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6883; c) A. A. Sherman, O. N. Yudina, A. S. Shashkov, V. M. Menshov, N. E. Nifantiev, *Carbohydr. Res.* **2002**, *337*, 451; d) T. Axenrod, J. Sun, K. K. Das, P. R. Dave, F. Forohar, M. Kaselj, N. J. Trivedi, R. D. Gilardi, J. L. Flippen-Anderson, *J. Org. Chem.* **2000**, *65*, 1200.
[9] R. Colombo, M. Anastasia, P. Rota, P. Allevi, *Chem. Commun.* **2008**, 5517.
[10] a) D. Bratosin, C. Palii, A. D. Moicean, J. P. Zanetta, J. Montreuil, *Biochemie* **2007**, *89*, 355; b) J. P. Zanetta, V. Srinivasan, R. Shauer, *Biochemie* **2006**, *88*, 171, and references therein.
[11] For an interesting review on sialic acid chemistry, see: a) F. Kimio, *Trends Glycosci. Glycotechnol.* **2004**, *89*, 143.
[12] J. Haverkamp, T. Spoormaker, L. Dorland, J. F. G. Vliegenthart, R. Schauer, *J. Am. Chem. Soc.* **1979**, *101*, 4851.
[13] a) S. Prytulla, J. Lambert, J. Lauterwein, M. Klessinger, J. Thiem, *Magn. Reson. Chem.* **1990**, *28*, 888; b) S. Prytulla, J. Lauterwein, M. Klessinger, J. Thiem, *Carbohydr. Res.* **1991**, *215*, 345.
[14] D. J. Silva, H. Wang, N. M. Allanson, R. K. Jain, M. J. Sofia, *J. Org. Chem.* **1999**, *64*, 5926.
[15] a) J. C. Biffinger, H. W. Kim, S. G. DiMagno, *ChemBioChem* **2004**, *5*, 622; b) J. Jubert, S. Roussel, C. Christophe, T. Billard, B. R. Langlois, T. Vidal, *Angew. Chem.* **2003**, *115*, 3241; *Angew. Chem. Int. Ed.* **2003**, *42*, 3133.

