Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2016, **26**, 511–512
Mendeleev Communications

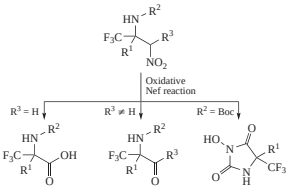
Oxidative Nef reaction of trifluoromethylated 2-nitroalkanamines

Irina V. Kutovaya,[a] Olga I. Shmatova,[a] Viktor M. Tkachuk,[b] Vladimir A. Sukach,[b] Mikhail V. Vovk*[b] and Valentine G. Nenajdenko*[a]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: nenajdenko@org.chem.msu.ru*
[b] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02660 Kiev, Ukraine. E-mail: mvovk@ioch.kiev.ua*

DOI: 10.1016/j.mencom.2016.11.017

Oxidative Nef reaction of 2-nitroalkanamines or *N*-(2-nitroalkyl)carboxamides bearing trifluoromethyl group affords amino acids, amino ketones or hydroxyhydantoins depending on structure of the starting compounds.

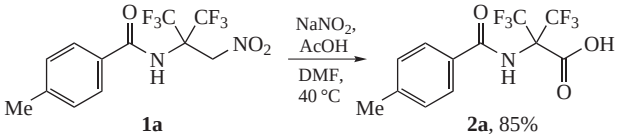


The value of organofluorine compounds for modern pharmaceuticals and materials science can not be overemphasized. About a quarter of all manufactured nowadays drugs and third part of all agrochemicals contain in their structure at least one fluorine atom.[1] Introduction of a fluorine atom or a perfluoroalkyl group (trifluoromethyl as usual) into biologically active compounds can significantly modify the physico-chemical properties and improve the metabolic stability of obtained substances. The significant effect of fluorine on the conformational properties of the compounds finds wide application in drug design.[2] Compounds with the isotope ^{18}F are especially valuable in positron emission tomography (PET) (rapidly developing diagnostic and research method in nuclear medicine).[3] Building block approach is commonly used for the synthesis of organofluorine compounds.[4] This article is devoted to the synthesis of trifluoromethyl-substituted derivatives by oxidation of 2-nitroalkanamines and the corresponding amides (oxidative Nef reaction).[5]

Recently we elaborated a convenient synthesis of trifluoromethyl-substituted 2-nitroalkanamines and relative amides based on aza-Henry reaction with fluorinated imines.[6] One of promising ways of application of such nitro compounds is their transformation into fluorinated α-amino acids and α-amino ketones. We investigated the possibility to perform the Nef reaction[7] under oxidative conditions with such nitro amines and amides.

We started our study from the reaction with trifluoromethylated compound **1a** containing the acyl group at the amino nitrogen (Scheme 1). Its heating in DMF in the presence of sodium nitrite and AcOH afforded the corresponding *N*-acyl amino acid **2a** in 85% yield.† However, the reaction with similar *N*-aryl-substituted nitro amines gave complex mixture of products. Most probably, nitrosation of amino group and other side reactions took place.

In contrast, homologous substrates **3a**–**c** were converted smoothly to the corresponding ketones **4a**–**c** (Scheme 2).‡ The

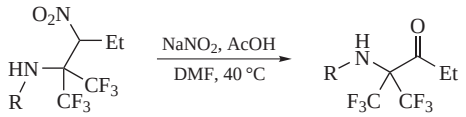


1a **2a**, 85%

Scheme 1

nitro amide **3c** containing strong electron-withdrawing group at the nitrogen gave ketone **4c** in higher yield than nitro amines **3a**,**b**.[8]

The oxidative Nef reaction of trifluoroacetophenone-derived nitro amides **5a**–**c** bearing Boc-group at amine nitrogen unexpectedly



3a–**c**

4a R = 4-ClC_6H_4, 47%
4b R = Ph, 54%
4c R = 4-MeC_6H_4CO, 61%

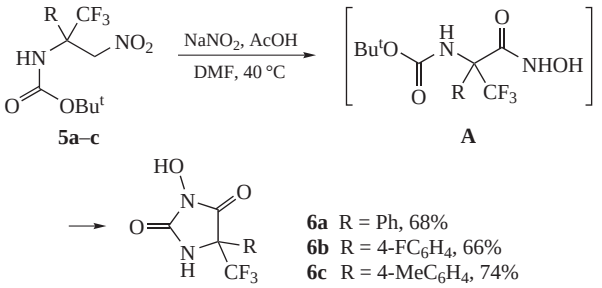
Scheme 2

† The starting compounds **1a**, **3a**–**c** and **5a**–**c** were prepared according to the literature.[6]

General procedure for the Nef reaction. To the solution of nitro amine or nitro amide **1a**, **3a**–**c**, **5a**–**c** (0.17 mmol) in mixture of DMF and water (7:1, 4 ml), sodium nitrite (0.8 mmol, 56 mg) and AcOH (0.3 ml) were added. The mixture was heated at 40 °C for 20 h (TLC control) and evaporated. In the case of substance **2a** after evaporation of DMF the residue was added to a solution of KOH (20 ml) and the resulting solution was washed with diethyl ether (3×15 ml). The aqueous layer was acidified to pH ~ 2 with diluted HCl and washed with ethyl acetate (3×15 ml). The aqueous phase was evaporated, washed with CH_2Cl_2 (3×15 ml) and evaporated to dryness. The residue was recrystallized from acetonitrile to give pure compound **2a**. Compounds **4a**–**c** were purified by column chromatography using CH_2Cl_2–MeOH (20:1) as an eluent. In the case of substances **5a**–**c** after heating, organic layer was extracted with CH_2Cl_2 (3×10 ml), dried (Na_2SO_4) and evaporated. Water (5 ml) was added to the residue, the precipitate was filtered off, washed with water (3 ml) and dried in air to give pure compounds **6a**–**c**.

*3,3,3-Trifluoro-*N*-(4-methylbenzoyl)-2-(trifluoromethyl)alanine* **2a**: yellowish oil (85%). ^1H NMR (400 MHz, DMSO-d_6) δ: 2.46 (s, 3H, Me), 3.54 (br. s, 1H, NH), 7.33–7.35 (m, 2H, Ar), 8.03–8.08 (m, 2H, Ar), 8.41 (br. s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.4 (Me), 120.0 (Ar), 120.5 (q, CF_3, $^1J_{CF}$ 283.5 Hz), 129.2 (Ar), 145.5 (C_q, Ar), 146.0 (C_q, Ar), 168.0 (C=O). Due to broadening of resonance signals, COOH group and $C(CF_3)_2$ carbon atom are not observed in the spectum. ^{19}F NMR (280 MHz, DMSO-d_6) δ: –74.61 (CF_3). IR (KBr, ν/cm^{-1}): 3400 (br., NH, OH), 1740 (C=O), 1680 (C=O), 1230 (CF). ESI-MS, *m*/*z*: 286.0669 $[M + H]^+$ [calc. for $C_{12}H_9F_6NNaO_3$ (–COOH), *m*/*z*: 286.0661].

brought about *N*-hydroxy hydantoins **6a**–**c** in good (66–74%) yields (Scheme 3).§ Most probably, the initially formed hydroxamic acids **A** would undergo cyclization by losing Boc-moiety. Similar to **A** intermediate can be formed in case of compound **1a**, which, however, being unable to cyclize undergoes further oxidation. *N*-Hydroxy hydantoins **6a**–**c** are the first representatives of trifluoromethylated *N*-hydroxy hydantoins.[9] Recently such compounds attracted attention due to their biological activity, for example, inhibition of serinehydrolase.[10]



Scheme 3

In concusion, oxidative Nef reaction of fluorinated nitro amines depending on their structure and especially protective group at the amino nitrogen atom provides an access to amino acids, amino ketones and hydroxyhydantoins in good yields.

This work was supported by the Russian Science Foundation (grant no. 16-13-00114) (I. Kutovaya and V. Nenajdenko, synthesis of starting compounds and discussion) and the Russian Foundation for Basic Research and Moscow city Government according to the research project 15-33-70009 'mol_a_mos' (O. Shmatova, Nef reaction and discussion).

References

1 M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye and B. Koksch, *Chem. Soc. Rev.*, 2012, **41**, 2135.
2 P. Maienfisch and R.-G. Hall, *Chimia*, 2004, **58**, 93.
3 (*a*) J. P. Bégué and D. Bonnet-Delpon, in *Bioorganic and Medicinal Chemistry of Fluorine*, eds. A. Tressaud and G. Haufe, Elsevier, Amsterdam, 2008, pp. 553–778; (*b*) *Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals*, eds. A. Tressaud and G. Haufe, Elsevier, Amsterdam, 2008; (*c*) *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*, ed. V. A. Petrov, Wiley, Hoboken, 2009; (*d*) *Fluorine in Heterocyclic Chemistry*, ed. V. G. Nenajdenko, Springer, Berlin, 2014; (*e*) V. P. Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, 2015; (*f*) V. G. Nenajdenko, V. M. Muzalevskiy and A. V. Shastin, *Chem. Rev.*, 2015, **115**, 973; (*g*) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, UK, 2004; (*h*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, 2004.
4 (*a*) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler and V. G. Nenajdenko, *Mendeleev Commun.*, 2013, **23**, 92; (*b*) A. R. Romanov, A. Yu. Rulev, I. A. Ushakov, V. M. Muzalevskiy and V. G. Nenajdenko, *Mendeleev Commun.*, 2014, **24**, 269; (*c*) O. I. Shmatova, N. E. Shevchenko, E. S. Balenkova, G.-V. Röschenthaler and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2013, 3049; (*d*) O. I. Shmatova and V. G. Nenajdenko, *J. Org. Chem.*, 2013, **78**, 9214.
5 C. Matt, A. Wagner and Ch. Mioskowski, *J. Org. Chem.*, 1997, **62**, 234.
6 (*a*) V. N. Fetyukhin, A. S. Koretskii, V. I. Gorbatenko and L. I. Samarai, *Zh. Org. Khim.*, 1977, **13**, 271 (in Russian); (*b*) N. V. Mel'nichenko and M. V. Vovk, *Russ. J. Org. Chem.*, 2008, **44**, 149 (*Zh. Org. Khim.*, 2008, **44**, 150); (*c*) V. M. Tkachuk, N. V. Mel'nichenko, K. V. Koval'chuk, V. A. Sukach, M. V. Vovk and V. G. Nenajdenko, *J. Org. Pharm. Chem.*, 2014, **12**, 71; (*d*) I. V. Kutovaya, O. I. Shmatova, V. M. Tkachuk, N. V. Melnichenko, M. V. Vovk and V. G. Nenajdenko, *Eur. J. Org. Chem.*, 2015, 6749.
7 R. Ballini and M. Petrini, *Adv. Synth. Catal.*, 2015, **357**, 2371.
8 M. J. Garcia-Mucoz, H. K. Dema, F. Foubelo and M. Yus, *Tetrahedron: Asymmetry*, 2014, **25**, 362.
9 (*a*) V. G. Shtamburg, A. A. Anishchenko, V. V. Shtamburg, O. V. Shishkin, R. I. Zubatyuk, A. V. Mazepa, I. M. Rakipov and R. G. Kostyanovsky, *Mendeleev Commun.*, 2008, **18**, 102; (*b*) J. Paz, C. Pérez-Balado, B. Iglesias and L. Muñoz, *J. Org. Chem.*, 2010, **75**, 8039; (*c*) V. G. Shtamburg, V. V. Shtamburg, A. A. Anishchenko, R. I. Zubatyuk, A. V. Mazepa, E. A. Klotz, S. V. Kravchenko and R. G. Kostyanovsky, *Chem. Heterocycl. Compd.*, 2015, **51**, 553 (*Khim. Geterotsikl. Soedin.*, 2015, **51**, 553); (*d*) T. Kurtz, D. Gettken and K. Widyan, *Tetrahedron*, 2004, **60**, 2409.
10 A. B. Cognetta III, M. J. Niphakis, H.-C. Lee, M. L. Martini, J. J. Hulce and B. F. Cravatt, *Chem. Biol.*, 2015, **22**, 928.

Received: 30th June 2016; Com. 16/4975

‡ *2-(4-Chlorophenylamino)-1,1,1-trifluoro-2-(trifluoromethyl)pentan-3-one* **4a**: yellow oil (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, 3H, *Me*CH_2, $^3J_{HH}$ 7.5 Hz), 2.41–2.47 (m, 2H, MeCH_2), 4.35 (br.s, 1H, NH), 6.68–6.70 (m, 2H, Ar), 7.16–7.18 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.9 (*Me*CH_2), 20.1 (Me*C*H_2), 69.3 (sept., *C*CF_3, $^2J_{CF}$ 27.4 Hz), 118.0 (Ar), 125.1 (q, CF_3, $^1J_{CF}$ 227.1 Hz), 128.7 (Ar), 135.4 (C_q, Ar), 140.0 (C_q, Ar). Due to broadening of resonance signal, carbonyl carbon atom is not observed in the spectrum. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –69.81 (CF_3). IR (KBr, ν/cm^{-1}): 3420 (br., NH), 1720 (C=O), 1670 (C=O), 1230 (CF). Found (%): C, 40.46; H, 3.51; N, 4.08. Calc. for $2C_{12}H_{10}ClF_6N{\cdot}H_2O$ (%): C, 40.47; H, 3.54; N, 3.93.

2-Phenylamino-1,1,1-trifluoro-2-(trifluoromethyl)pentan-3-one **4b**: brown oil (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (t, 3H, *Me*CH_2, $^3J_{HH}$ 7.5 Hz), 2.45–2.47 (m, 2H, MeCH_2), 4.37 (br.s, 1H, NH), 6.73–6.78 (m, 2H, Ar), 6.90–6.93 (m, 1H, Ar), 7.18–7.23 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.0 (*Me*CH_2), 20.1 (Me*C*H_2), 69.3 (sept., *C*CF_3, $^2J_{CF}$ 27.7 Hz), 116.6 (Ar), 120.8 (Ar), 128.7 (Ar), 141.5 (C_q, Ar). Due to broadening of resonance signals, CF_3 group and carbonyl carbon atom are not observed in the spectum. ^{19}F NMR (376.5 MHz, $CDCl_3$) δ: –69.65 (CF_3). IR (KBr, ν/cm^{-1}): 3410 (br., NH), 1700 (C=O), 1225 (CF). Found (%): C, 48.50; H, 3.51; N, 4.74. Calc. for $C_{12}H_{11}F_6NO$ (%): C, 48.17; H, 3.71; N, 4.68.

4-Methyl-N-*[2-oxo-1,1-bis(trifluoromethyl)butyl]benzamide* **4c**: brown oil (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21–1.34 (m, 3H, *Me*CH_2), 2.46 (s, 3H, Me), 2.46–2.52 (m, 2H, MeCH_2), 6.62 (br.s, 1H, NH), 7.28–7.30 (m, 2H, Ar), 7.68–7.70 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.0 (*Me*CH_2), 21.1 (Me*C*H_2), 29.3 (Me), 67.9 (sept., *C*CF_3, $^2J_{CF}$ 27.8 Hz), 126.8 (Ar), 127.2 (C_q, Ar), 128.2 (C_q, Ar), 129.2 (Ar), 152.0 (C=O). Due to broadening of resonance signals, CF_3 group and carbonyl carbon atom are not observed in the spectum. ^{19}F NMR (280 MHz, $CDCl_3$) δ: –69.81 (CF_3). IR (KBr, ν/cm^{-1}): 3420 (br., NH), 1780 (C=O), 1670 (C=O), 1230 (CF). ESI-MS, *m*/*z*: 357.01033 $[M + Na]^+$ (calc. for $C_{14}H_{15}F_6N_2NaO_2$, *m*/*z*: 357.1032).

§ *3-Hydroxy-5-phenyl-5-(trifluoromethyl)imidazolidine-2,4-dione* **6a**: white solid (68%), mp ~230 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.53 (br.s, 3H), 7.77 (br.s, 2H), 10.34 (br.s, 1H), 11.20 (br.s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 64.5 (q, *C*CF_3, $^2J_{CF}$ 28.2 Hz), 122.5 (q, CF_3, $^1J_{CF}$ 286.7 Hz), 126.6 (Ar), 129.0 (Ar), 129.6 (Ar), 130.2 (Ar), 152.8 (C=O), 162.6 (C=O). ^{19}F NMR (280 MHz, DMSO-d_6) δ: –74.9. IR (KBr, ν/cm^{-1}): 3415 (br., OH), 3290 (br., NH), 1745 (C=O), 1720 (C=O). Found (%): C, 45.97; H, 2.65; N, 10.87. Calc. for $C_{10}H_7F_3N_2O_3$ (%): C, 46.16; H, 2.71; N, 10.77.

5-(4-Fluorophenyl)-3-hydroxy-5-(trifluoromethyl)imidazolidine-2,4-dione **6b**: white solid (66%), mp ~235 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.41 (t, 2H, $^3J_{HF}$ 8.8 Hz), 7.83 (m, 2H), 10.42 (br.s, 1H), 11.26 (br.s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 64.0 (q, *C*CF_3, $^2J_{CF}$ 30.0 Hz), 116.1 (d, Ar, $^2J_{CF}$ 21.2 Hz), 122.4 (q, CF_3, $^1J_{CF}$ 283.7 Hz), 125.7 (d, Ar, $^4J_{CF}$ 2.5 Hz), 129.1 (d, Ar, $^3J_{CF}$ 8.75 Hz), 152.7 (Ar), 162.5 (Ar), 163.0 (d, Ar, $^1J_{CF}$ 246.2 Hz). ^{19}F NMR (280 MHz, DMSO-d_6) δ: –75.3 (CF_3), –111.3 (F). IR (KBr, ν/cm^{-1}): 3410 (br., OH), 3295 (br., NH), 1745 (C=O), 1720 (C=O). Found (%): C, 43.30; H, 2.13; N, 10.00. Calc. for $C_{10}H_6F_4N_2O_3$ (%): C, 43.18; H, 2.17; N, 10.07.

3-Hydroxy-5-(4-methylphenyl)-5-(trifluoromethyl)imidazolidine-2,4-dione **6c**: white solid (74%), mp ~230 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.32 (s, 3H, Me), 7.32 (br.s, 2H), 7.64 (br.s, 2H, Ar), 10.26 (br.s, 1H, Ar), 11.19 (br.s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 20.7 (Me), 64.4 (q, *C*CF_3, $^2J_{CF}$ 28.7 Hz), 122.6 (q, CF_3, $^1J_{C,F}$ 282.5 Hz), 126.6 (Ar), 126.7 (Ar), 129.6 (Ar), 140.0 (Ar), 152.9 (C=O), 162.8 (C=O). ^{19}F NMR (280 MHz, DMSO-d_6) δ: –75.4 (CF_3). Found (%): C, 48.32; H, 3.13; N, 10.15. Calc. for $C_{11}H_9F_3N_2O_3$ (%): C, 48.18; H, 3.31; N, 10.22.