ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 6, pp. 906–908. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © D.V. Osipov, M.R. Demidov, V.A. Osyanin, M.Yu. Skomorokhov, Yu.N. Klimochkin, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 6, pp. 911–913.

SHORT COMMUNICATIONS

Adamantylation of Hydantoin

D. V. Osipov, M. R. Demidov, V. A. Osyanin,* M. Yu. Skomorokhov, and Yu. N. Klimochkin

Samara State Technical University, ul. Molodogvardeiskaya 244, Samara, 443100 Russia
**e-mail: vosyanin@mail.ru*

Received April 19, 2016

DOI: 10.1134/S1070428016060257

Cage compounds, in particular adamantane derivatives, exhibit a broad spectrum of biological activity [1–9]. Many adamantane derivatives are used as medicines with various therapeutic effects. Saxagliptin has recently been marketed under the trade name Onglyza as highly selective and efficient dipeptidyl peptidase-4 (DDP-4) inhibitor [10] for the treatment of type II diabetes. The key intermediate products in the synthesis of saxagliptin are (*S*)-(+)-(adamantan-1-yl)-glycin and its derivatives. Most known procedures for their preparation require the use of expensive and/or highly toxic reagents (such as oxalyl chloride, thionyl chloride, rhodium and palladium compounds, etc.) and are multistep and experimentally difficult [11–15].

Herein, we propose a convenient method for the synthesis of racemic 2-(adamantan-1-yl)-2-aminoacetic acid (**1**) from accessible adamantane or adamantan-1-ol and hydantoin. In continuation of our studies on adamantylation of nitrogen-containing substrates [16–23], we tried to introduce an adamantyl substituent into hydantoin molecule. Hydantoin derivatives are precursors to α-amino acids, and they also possess various biological activities [24].

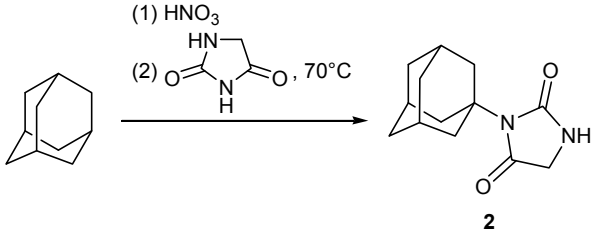
Hydantoin was subjected to adamantylation in two ways. The first of these involved oxidation of adamantane with fuming nitric acid, followed by addition of hydantoin (Scheme 1). In this way, 3-(adamantan-1-yl)imidazolidine-2,4-dione (**2**) was obtained in 71% yield [23]. The reaction required a large amount of hydantoin (5 equiv) because its considerable part underwent nitrosation and thorough control of the reaction conditions due to gas evolution in the course of decomposition of hydantoin in nitric acid.

N-Adamantylation of acetamide, oxamide, and carbamates was accomplished under analogous conditions [17, 18]; however, cyclic amides (such as ε-caprolactam) failed to react. The reaction of adamantan-1-ol with hydantoin on heating in 90% H_2SO_4 gave 39% of **2**, the main by-product being adamantane resulting from intermolecular hydride transfer [25–27].

The formation of just 3-(adamantan-1-yl)imidazolidine-2,4-dione (**2**) rather than isomeric 1-(adamantan-1-yl)imidazolidine-2,4-dione follows from the absence of a cross peak corresponding to coupling of C^1 of the adamantane fragment with methylene protons of hydantoin in the two-dimensional heteronuclear $^1H–^{13}C$ HMBC spectrum. The alkylation of hydantoin at the less basic nitrogen atom (N^3) may be rationalized assuming electrophilic addition of adamantyl cation to more stable lactim tautomer of hydantoin (**A**) (Scheme 2). This reaction is likely to be the first example of *N*-alkylation of hydantoin in acid medium.

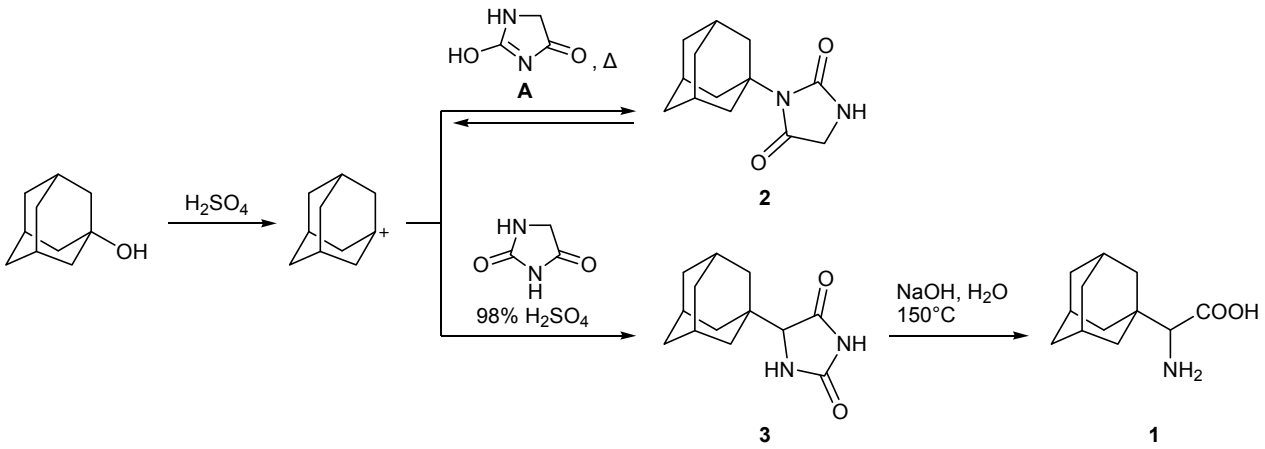
In order to suppress hydride transfer processes, more concentrated sulfuric acid was used. Under these conditions, 3-(adamantan-1-yl)imidazolidine-2,4-dione (**2**) underwent partial rearrangement into thermodynamically more stable 5-(adamantan-1-yl)imidazolidine-2,4-dione (**3**). Presumably, the reaction involves protonated form of hydantoin, which follows from a longer time required for the formation of **3** and complete isomerization of **2** in 98% sulfuric acid. Thus, compound **3** can be obtained from both hydantoin and directly from adamantan-1-ol and hydantoin without

Scheme 1.



2

Scheme 2.



isolation of **2**. Compound **3** can be used to obtain intermediate products for the synthesis of saxagliptin [28].

In the ^{1}H NMR spectrum of **2**, methylene protons on C^5 of the imidazole ring resonated at δ 3.96 ppm. In the ^{1}H NMR spectrum of **3**, the 5-H signal was observed in a stronger field (δ 3.49 ppm) due to shielding by the adamantane fragment. The C^5 signal of **2** was located at δ_C 48.7 ppm in the ^{13}C NMR spectrum, and the corresponding signal of **3** appeared at δ_C 66.7 ppm (in DMSO-d_6).

Hydrolysis of **3** with 6% aqueous sodium hydroxide at 150°C under pressure afforded 75% of α-adamantylglycine **1** (Scheme 2).

Thus, we have developed an efficient procedure for the synthesis of adamantylglycine via adamantylation of hydantoin.

3-(Adamantan-1-yl)imidazolidine-2,4-dione (2). *a*. A 100-mL three-necked flask equipped with a mechanical stirrer and thermometer was charged with 15 mL of fuming nitric acid, and 5 g (36.8 mmol) of adamantane was added in portions at a temperature not exceeding 30°C. After dissolution of adamantane, 12 g (0.12 mol) of hydantoin was added to the mixture on cooling with ice. The mixture was heated for 1 h at 70–80°C, cooled, and poured onto 100 g of ice, and the precipitate was filtered off, washed, and dried. Yield 6.5 g (71%), colorless crystals, mp >250°C (from DMF–*i*-PrOH). IR spectrum, ν cm^{-1}: 3167, 3048, 2909, 2851, 2766, 1771, 1690, 1443, 1227, 1130, 760, 741. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.58 br.s (6H), 1.99 br.s (9H), 3.96 s (2H), 10.54 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 29.4, 36.2, 39.8, 48.7, 54.2, 156.3, 172.3. Mass spectrum, *m*/*z* (I_{rel}, %): 234 (12) $[M]^+$, 177 (34), 107 (10), 106 (30), 91 (32), 79 (49), 77 (40), 55 (36). Found, %: C 66.70; H 7.76; N 11.92. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.64; H 7.74; N 11.96.

b. Hydantoin, 6.58 g (65.8 mmol), was added to 52 mL of 90% sulfuric acid, the mixture was heated to 70°C, and 10 g (65.8 mmol) of adamantan-1-ol was added under stirring. The product was isolated as described above in *a*. Yield 6 g (39%).

5-(Adamantan-1-yl)imidazolidine-2,4-dione (3). Hydantoin, 22.2 g (0.222 mol), was added under stirring to 250 mL of 98% sulfuric acid. The mixture was heated to 70°C until it became homogeneous, and 33.74 g (0.222 mol) of adamantan-1-ol was added in portions under stirring at that temperature. The mixture was stirred for 3 h at 70°C, and the brown homogeneous solution was cooled to room temperature and poured with stirring onto 1 kg of ice. The precipitate was filtered off, washed with water until neutral washings, and dried in air. Yield 37.4 g (72%). An analytical sample was obtained by recrystallization from DMF. Colorless crystals, mp >250°C (sublimes). IR spectrum, ν, cm^{-1}: 3356, 3163, 3055, 2905, 2851, 1763, 1701, 1420, 1288, 1196, 733, 640. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.40–1.68 m (12H), 1.90 s (3H), 3.49 s (1H), 7.85 s (1H), 10.49 s (1H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.9, 36.3, 36.8, 37.6, 66.7, 158.2, 174.8. Mass spectrum, *m*/*z* (I_{rel}, %): 234 (1) $[M]^+$, 135 (100) $[Ad]^+$, 107 (10), 93 (22), 79 (34). Found, %: C 66.72; H 7.75; N 11.91. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.64; H 7.74; N 11.96.

2-(Adamantan-1-yl)-2-aminoacetic acid (1). A 1-L high-pressure reactor was charged with 40 g (0.171 mol) of compound **3** and 700 mL of 6% aqueous sodium hydroxide. The mixture was stirred for 6 h at 150°C, the resulting solution was neutralized, and the precipitate was filtered off, washed with water, and dried. Yield 26.8 g (75%), colorless crystals,

mp >250°C. ^{1}H NMR spectrum (CD_3OD containing a drop of DCl/D_2O), δ, ppm: 1.61–1.82 m (12H), 2.02 br.s (3H), 3.52 s (1H). ^{13}C NMR spectrum (CD_3OD containing a drop of DCl/D_2O), δ_C, ppm: 28.2, 34.4, 36.0, 37.9, 62.2, 169.1. Found, %: C 68.90; H 9.17; N 6.68. $C_{12}H_{19}NO_2$. Calculated, %: C 68.87; H 9.15; N 6.69.

The IR spectra were recorded in KBr on a Shimadzu IR Affinity-1 spectrometer. The ^{1}H and ^{13}C NMR spectra, including DEPT spectra, were measured on a JEOL JNM-ECX400 spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard. The elemental analyses were obtained on a Euro Vector EA-3000 automated CHNS analyzer. The melting points were determined in capillaries on an SRS OptiMelt MPA100 melting point apparatus.

This study was performed under financial support by the Russian Science Foundation (project no. 15-13-0084).

REFERENCES

1. Wanka, L., Iqbal, K., and Shreiner, P.R., *Chem. Rev*., 2013, vol. 113, p. 3516.
2. Klimochkin, Yu.N., Shiryaev, V.A., and Leonova, M.V., *Russ. Chem. Bull., Int. Ed*., 2015, vol. 64, p. 1473.
3. Geldenhuys, W.J., Malan, S.F., Bloomquist, J.R., Marchand, A.P., and van der Schyf, C.J., *Med. Res. Rev*., 2005, vol. 25, p. 21.
4. Liu, J., Obando, D., Liao, V., Lifa, T., and Codd, R., *Eur. J. Med. Chem*., 2011, vol. 46, p. 1949.
5. Lamoureux, G. and Artavi, G., *Curr. Med. Chem*., 2010, vol. 17, p. 2967.
6. Joubert, J., Geldenhus, W.J., van der Schyf, C.J., Oliver, D.W., Kruger, H.G., Govender, T., and Malan, S.F., *Chem. Med. Chem*., 2012, vol. 7, p. 375.
7. Spasov, A.A., Khamidova, T.V., Bugaeva, L.I., and Morozov, I.S., *Pharm. Chem. J*., 2000, vol. 34, no. 1, p. 1.
8. Stockdale, T.P. and Williams, C.M., *Chem. Soc. Rev*., 2015, vol. 44, p. 7737.
9. Morozov, I.S., Petrov, V.I., and Sergeeva, S.A., *Farmakologiya adamantanov* (Pharmacology of Adamantanes), Volgograd: Volgograd. Med. Akad., 2001, p. 320.
10. Mohler, M.L., He, Y., Wu, Z., Hwang, D.J., and Miller, D.D., *Med. Res. Rev*., 2009, vol. 29, p. 125.
11. Wang, A., Deng, Y., Pan, X., Chen, Y., Tao, Z., Liang, D., and Hu, X., *Lett. Org. Chem*., 2014, vol. 11, p. 627.
12. Hanson, R.L., Goldberg, S.L., Brzozowski, D.B., Tully, T.P., Cazzulino, D., Parker, W.L., Lyngberg, O.K., Vu, T.C., Wong, M.K., and Patel, R.N., *Adv. Synth. Catal*., 2007, vol. 349, p. 1369.
13. Vu, T.C., Brzozowski, D.B., Fox, R., Godfrey, J.D., Hanson, R.L., Kolotuchin, S.V., Mazzullo, J.A., Patel, R.N., Wang, J.J., Wong, K., Yu, J., Zhu, L., Magnin, D.R., Augeri, D.J., and Hamann, L.G., Int. Patent Appl. no. WO 2004052850 A2; *Chem. Abstr*., 2004, vol. 141, no. 54618a.
14. Augeri, D.J., Robl, J.A., Betebenner, D.A., Magnin, D.R., Khanna, A., and Hamann, L.G., *J. Med. Chem*., 2005, vol. 48, p. 5025.
15. Benito-Garragori, D., Felzmann, W., Knepper, K., and Wilhelm, T., Int. Patent Appl. no. WO 2012028721 A; *Chem. Abstr*., 2012, vol. 156, no. 363248a.
16. Klimochkin, Yu.N. and Moiseev, I.K., *Zh. Org. Khim*., 1987, vol. 23, p. 2025.
17. Klimochkin, Yu.N., Bagrii, E.I., Dolgopolova, T.N., and Moiseev, I.K., *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1988, vol. 37, no. 4, p. 757.
18. Klimochkin, Yu.N., Moiseev, I.K., Vladyko, G.V., Korobchenko, L.V., and Boreko, E.I., *Pharm. Chem. J*., 1991, vol. 25, no. 7, p. 485.
19. Klimochkin, Yu.N. and Moiseev, I.K., *Zh. Org. Khim*., 1991, vol. 27, p. 1795.
20. Butov, G.M., Lysykh, B.A., Dalinger, I.L., Vatsadze, I.A., Shkineva, T.K., Klimochkin, Yu.N., and Osyanin, V.A., *Chem. Heterocycl. Compd*., 2014, vol. 50, p. 752.
21. Shadrikova, V.A., Golovin, E.V., and Klimochkin, Yu.N., *Chem. Heterocycl. Compd*., 2014, vol. 50, p. 1586.
22. Leonova, M.V., Skomorokhov, M.Yu., Moiseev, I.K., and Klimochkin, Yu.N., *Russ. J. Org. Chem*., 2015, vol. 51, p. 1703.
23. Klimochkin, Yu.N., *Doctoral (Chem.) Dissertation*, Samara, 1999.
24. Meusel, M. and Gütschow, M., *Org. Prep. Proced. Int*., 2004, vol. 36, p. 391.
25. Simonetti, D.A., Ahn, J.H., and Iglesia, E., *ChemCatChem*, 2011, p. 704.
26. Tobe, Y., Terashima, K., Sakai, Y., and Odaira, Y., *J. Am. Chem. Soc*., 1981, vol. 103, p. 2307.
27. Cuddy, B.D., Grant, D., Karim, A., McKervey, M.A., and Rea, E.J.F., *J. Chem. Soc., Perkin Trans. 1*, 1972, p. 2701.
28. Gouzu, R. and Miyata, T., Int. Patent Appl. no. WO 2013081100 A1; *Chem. Abstr*., 2013, vol. 159, no. 59200b.