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Catalyst-free three-component synthesis of hydroxyalkyltriazolylmethylidene barbiturates

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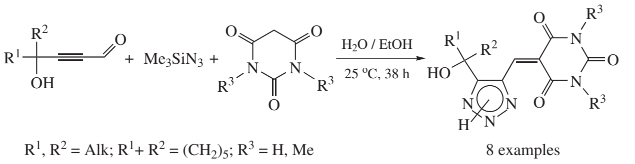
5-[(5-Hydroxyalkyl-1*H*-1,2,3-triazol-4-yl)methylidene]barbiturates were eco-friendly synthesized in up to 89% yields by one-pot three-component processing (no catalyst, H_2O–EtOH, room temperature, 38 h) of 4-hydroxyalkynals, trimethylsilyl azide and barbituric acids.



R^1, R^2 = Alk; R^1+ R^2 = $(CH_2)_5$; R^3 = H, Me

8 examples

One of the most important challenges for chemists is a search for efficient, economical and eco-friendly processes in organic synthesis. Multicomponent reactions allow one to synthesize the target compounds in a single operation from three or more reactants.[1] This rational strategy combines both the economic and environmental aspects of organic chemistry for practical applications. Considerable efforts have been directed to the development of multi-component procedures for the construction of various heterocycles due to their significant therapeutic potential.[2] Additionally, the molecular hybridization based on the combination of two bioactive parts may afford new compounds which can be more efficient, economical and safe as compared to the parent ones.[3]

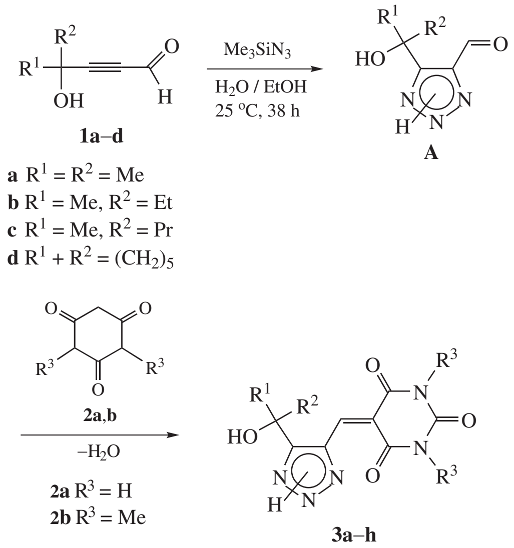
Among N-heterocycles, barbituric acid derivatives occupy an important place in pharmacology as quick-acting agents for urgent anesthesia, relieving seizures and preventing epileptic seizures,[4] and possessing antimicrobial,[5] antioxidant,[6] selective cell adhesion inhibitory[7] and DNA cleavage activities.[8] Some of them exhibit nonlinear optical properties[9] and are employed as ligands in coordination chemistry.[10] The important barbituric acid derivatives are the 5-ylidene ones.

In parallel, 1,2,3-triazoles are of great interest as pharmaceuticals,[11] agrochemicals,[12] corrosion inhibitors,[13] dyes[14] and photostabilizers.[15] The most important access to them is the ‘click’-synthesis based on 1,3-dipolar cycloaddition of alkynes and azides.[16]

The integration of 1,2,3-triazole and barbiturate heterocyclic rings in the same molecule may lead to new hybrid compounds with potential biological activities.

Early, we showed that available 4-hydroxyalkynals **1**[17] bearing sterically unhindered aldehyde group and the activated triple bond can be efficiently used in the metal-free synthesis of N-unsubstituted 1,2,3-triazolecarbaldehydes.[18] Also, 1*H*-1,2,3-triazolylmethylidenepyrimidines and -1,3-dioxanes were prepared from element-substituted propynals, trimethylsilyl azide and heterocyclic CH-acids.[19]

In continuation of our search for new polyfunctional N-unsubstituted 1,2,3-triazoles, we report herein on the results of three-component reaction of 4-hydroxyalkynals **1**, trimethylsilyl azide and barbituric acids **2** in aqueous medium with a goal to synthesize hydroxyalkyl-containing 5-(1*H*-1,2,3-triazol-4-ylmethylidene)-barbiturates. Our experiments revealed that the reaction proceeded under mild conditions (without catalyst, H_2O–EtOH, 20–25 °C, 38 h) to assemble new functionalized heterocyclic hybrids **3a–h** in 72–89% yields (Scheme 1).[†] It is important that all the products



1a–d

a $R^1 = R^2$ = Me
b R^1 = Me, R^2 = Et
c R^1 = Me, R^2 = Pr
d $R^1 + R^2 = (CH_2)_5$

A

2a,**b**

2a R^3 = H
2b R^3 = Me

3a–h

a $R^1 = R^2$ = Me, R^3 = H (82%)
b R^1 = Me, R^2 = Et, R^3 = H (84%)
c R^1 = Me, R^2 = Pr, R^3 = H (87%)
d $R^1 + R^2 = (CH_2)_5$, R^3 = H (73%)
e $R^1 = R^2 = R^3$ = Me (89%)
f $R^1 = R^3$ = Me, R^2 = Et (83%)
g $R^1 = R^3$ = Me, R^2 = Pr (86%)
h $R^1 + R^2 = (CH_2)_5$, R^3 = Me (72%)

Scheme 1

[†] 4-Hydroxyalkynals **1** were prepared according to published methods.[17,21]

General procedure for the synthesis of compounds **3a–h**. A 10 ml round bottom flask was charged with water (2 ml) and 4-hydroxyalkynal **1** (1 mmol), trimethylsilyl azide (0.138 g, 1.2 mmol) was then added, and the are easily isolated by sequential washing the crude precipitate with ethyl acetate and methanol. The isolated yields of the products are not quantitative due to probable losses during purification and the insignificant polymerization of hydroxy alkynals **1**. The steric hindrance slightly affects the yields of products. Products **3d**,**h** bearing hydroxycyclohexyl substituent were isolated in 72–73% yield. Compounds **3a–h** turned to be poorly soluble in most organic solvents.

The structures of the hydroxyalkylated 5-(1*H*-1,2,3-triazol-4-ylmethylidene)barbiturates **3a–h** have been proven by ^{1}H, ^{13}C NMR and IR spectra. In the ^{1}H NMR spectra, alkyl protons of alcohol moieties, NMe groups (for **3e–h**) resonate at 3.18–3.16 ppm, and olefinic proton =CH resonates at 9.94–9.05 ppm. In the ^{13}C NMR spectra, the carbonyl carbons resonate in the region of 170.1–165.0, 164.1–158.6 and 152.4–149.7 ppm, the signals of the =CH and triazole carbons appear at 162.9–158.1 ppm, 160.3–150.0 and 137.1–134.4 ppm, respectively.

Apparently, the first step of three-component reaction involves 1,3-dipolar cycloaddition of hydroxyalkynals **1** and trimethylsilyl azide to create intermediate 5-(hydroxyalkyl)triazolecarbaldehyde **A** (see Scheme 1) as previously described.[18(*a*)] The next step is a Knoevenagel condensation between aldehyde **A** and barbituric acids **2**.

The transformation is best processed with the sequential loading of the reactants because their simultaneous administration makes the reaction non-selective. The Knoevenagel reaction between 4-hydroxyalkynals and barbituric acids proceeds at a higher rate resulting in adducts having a weakly polarized triple bond, which would interfere with the cycloaddition of trimethylsilyl azide.

The effect of aqueous medium on reaction is the spontaneous non-catalyzed reversible hydration of the aldehyde group with the *in situ* formation of intermediate *gem*-diols (quantitative determination of the aldehyde/*gem*-diol forms in water by ^{1}H NMR was performed[20]), which increases the solubility and reduces the polymerization of initial 4-hydroxyalkynals **1**.

In summary, eco-friendly one-pot synthesis of hydroxyalkyl-containing 5-(1*H*-1,2,3-triazol-4-ylmethylidene)barbiturates has been accomplished in good yields by catalyst-free three-component reaction of hydroxyalkynals, trimethylsilyl azide and barbuturic acids in aqueous medium. A simple route involves the 1,3-dipolar cycloaddition and subsequent Knovenegel condensation as the key steps. The synthesized hybrid molecules containing two important pharmacophores can be of interest as potential bioactive compounds and synthons in organic synthesis to produce new drugs, polydentate ligands for metal complexes, and fluorophores to create new materials.

The main results were obtained using the equipment of Baikal analytical center of collective using SB RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.11.017.

References

1 (*a*) M. C. Pirrung and K. D. Sarma, *J. Am. Chem. Soc.*, 2004, **126**, 444; (*b*) A. Domling, *Chem. Rev.*, 2006, **106**, 17; (*c*) H. Ohno, Y. Ohta, S. Oishi and N. Fujii, *Angew. Chem., Int. Ed.*, 2007, **46**, 2295; (*d*) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156; (*e*) I. Monfardini, J. W. Huang, B. Beck, J. F. Cellitti, M. Pellecchia and A. Domling, *J. Med. Chem.*, 2011, **54**, 890; (*f*) A. Domling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083; (*g*) X. Guo and W. Hu, *Acc. Chem. Res.*, 2013, **46**, 2427; (*h*) R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958; (*i*) P. Singh and K. N. Singh, *Org. Biomol. Chem.*, 2018, **16**, 9084.

2 (*a*) J. Sunderhaus and S. Martin, *Chem. Eur. J.*, 2009, **15**, 1300; (*b*) B. Jiang, T. Rajale, W. Wever, S. Tu and G. Li, *Chem. Asian J.*, 2010, **5**, 2318; (*c*) R. P. Gore and A. P. Rajput, *Drug Invent. Today*, 2013, **5**, 148; (*d*) G. M. Ziarani, F. Aleali and N. Lashgari, *RSC Adv.*, 2016, **6**, 50895.

3 (*a*) C. Viegas-Jr, A. Danuello, V. da Silva Bolzani, E. J. Barreiro and C. A. Fraga, *Curr. Med. Chem.*, 2007, **14**, 1829; (*b*) S. B. Tsogoeva, *Mini-Rev. Med. Chem.*, 2010, **10**, 773; (*c*) K. Nepali, S. Sharma, M. Sharma, P. M. S. Bedi and K. L. Dhar, *Eur. J. Med. Chem.*, 2014, **77**, 422.

4 (*a*) P. S. García, M. K. Whalin and P. S. Sebel, in *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*, 2nd edn., eds. H. C. Hemmings and T. D. Egan, Elsevier, Philadelphia, 2019, ch. 9, pp. 137–158; (*b*) M. C. Smith and B. J. Riskin, *Drugs*, 1991, **42**, 365; (*c*) F. López-Muñoz, R. Ucha-Udabe and C. Alamo, *Neuropsychiatr. Dis. Treat.*, 2005, **1**, 329; (*d*) N. Siddiqui and W. Ahsan, *Arch. Pharm. Chem. Life Sci.*, 2009, **342**, 462.

5 (*a*) V. Padmavathi, G. D. Reddy, B. C. Venkatesh and A. Padmaja, *Arch. Pharm. Chem. Life Sci.*, 2011, **11**, 165; (*b*) M. M. Ibrahim, S. Al-Juaid, M. A. Mohamed and M. H. Yassin, *J. Coord. Chem.*, 2012, **65**, 2957; (*c*) A. M. Qureshi, M. Qadir, A. Rauf, M. Idrees, S. Mumtaz, M. Najamul-Haq, M. Ismail, M. Athar, R. Khushal, S. Riaz and H. Bokhari, *Lett. Drug Des. Discovery*, 2011, **8**, 980; (*d*) Q. Yan, R. Cao, W. Yi, Z. Chen, H. Wen, L. Ma and H. Song, *Eur. J. Med. Chem.*, 2009, **44**, 4235.

6 (*a*) H. B. Demopoulos, E. S. Flamm and M. L. Seligman, *Acta Neurol. Scand.*, 1977, **56**, 152; (*b*) K. M. Khan, M. Ali, A. Ajaz, S. Perveen, M. I. Choudhary and A. U. Rahman, *Lett. Drug Des. Discovery*, 2008, **5**, 286; (*c*) B. B. Sokmen, S. Ugras, H. Y. Sarikaya, H. I. Ugras and R. Yanardag, *Appl. Biochem. Biotechnol.*, 2013, **171**, 2030; (*d*) R. Almaas, O. D. Saugstad, D. Pleasure and T. Rootwelt, *Anesthesiology*, 2000, **92**, 764; (*e*) K. M. Moon, B. Lee, J. W. Jeong, D. H. Kim, Y. J. Park, H. R. Kim, J. Y. Park, M. J. Kim, H. J. An, E. K. Lee, Y. M. Ha, E. Im, P. Chun, J. Y. Ma, W.-K. Cho, H. R. Moon and H. Y. Chung, *Oncotarget*, 2017, **8**, 91662.

7 G. C. Harriman, M. Brewer, R. Bennett, C. Kuhnb, M. Bazin, G. Larosa, P. Skerker, N. Cochran, D. Gallant, D. Baxter, D. Picarella, B. Jaffee, J. R. Luly and M. J. Briskin, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2509.

8 J. S. Biradar, B. S. Sasidhar and R. Parveen, *Eur. J. Med. Chem.*, 2010, **45**, 4074.

9 (*a*) B. B. Ivanova and M. Spiteller, *Cryst. Growth Des.*, 2010, **10**, 2470; (*b*) K. Kondo, S. Ochiai and K. Takemoto, *Appl. Phys. Lett.*, 1990, **57**, 101.

10 (*a*) E. Fırıncı, E. Giziroglu, D. B. Celepci, H. C. Söyleyici and M. Aygün, *J. Mol. Struct.*, 2017, **1137**, 113; (*b*) K. T. Mahmudov, M. N. Kopylovich, A. M. Maharramov, M. M. Kurbanova, A. V. Gurbanov and A. J. L. Pombeiro, *Coord. Chem. Rev.*, 2014, **265**, 1.

11 (*a*) S. G. Agalave, S. R. Maujan and V. S. Pore, *Chem. Asian J.*, 2011, **6**, 2696; (*b*) S. Haider, M. S. Alam and H. Hamid, *Inflammation Cell Signaling*, 2014, 1; (*c*) D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, 2017, **71**, 30; (*d*) F. C. da Silva, M. F. C. Cardoso, P. G. Ferreira and V. F. Ferreira, *Top. Heterocycl. Chem.*, 2014, **40**, 117.

12 (*a*) M. J. O'Mahony, R. J. Willis, *US Patent 5064844*, 1991; (*b*) X.-B. Chen, D.-Q. Shi and X.-F. Zhu, *Chin. J. Chem.*, 2007, **25**, 1854; (*c*) Z.-C. Dai, Y.-F. Chen, M. Zhang, S.-K. Li, T.-T. Yang, L. Shen, J.-X. Wang, S.-S. Qian, H.-L. Zhu and Y.-H. Ye, *Org. Biomol. Chem.*, 2015, **13**, 477; (*d*) A. V. Costa, M. V. L. Oliveira, R. T. Pinto, L. C. Moreira, E. M. C. Gomes, T. A. Alves, P. F. Pinheiro, V. T. Queiroz, L. F. A. Vieira, R. R. Teixeira and W. C. J. Júnior, *Molecules*, 2017, **22**, 1666.

13 (*a*) M. A. Quraishi and R. Sardar, *Corrosion*, 2002, **58**, 748; (*b*) M. A. Quraishi, Sudheer, K. R. Ansari and E. E. Ebenso, *Int. J. Electrochem. Sci.*, 2012, **7**, 7476; (*c*) P. S. Desai and N. S. Indorwala, *Int. J. Curr. Microbiol. Appl. Sci.*, 2015, **4**, 928; (*d*) S. U. Ofoegbu, T. L. P. Galvão, J. R. B. Gomes, J. Tedim, H. I. S. Nogueira, M. G. S. Ferreira

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mixture was stirred at room temperature for 18 h. Then a solution of barbituric acid **2** (1 mmol) in ethanol (4 ml) was added, and the mixture was stirred at room temperature for 20 h. The precipitate formed was collected on a filter, washed with water and cold methanol and dried at reduced pressure.

*5-{[4-(1-Hydroxy-1-methylethyl)-1*H*-1,2,3-triazol-5-yl]methylidene}-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* **3a**. Yield 220 mg (82%). Colourless powder, mp > 260 °C (decomp.). ^{1}H NMR (400.13 MHz, DMSO-d_6) δ: 15.57 (br. s, 1H, NH), 11.67 [br. s, 1H, NH(C=O)], 11.50 [br. s, 1H, NH(C=O)], 9.11 (s, 1H, HC=), 5.62 (br. s, 1H, OH), 1.58 (s, 6H, 2Me). ^{13}C NMR (101.62 MHz, DMSO-d_6) δ: 169.9 (C^{8}), 163.8 (C^{12}), 162.5 (CH=), 159.6 (C^{4}), 149.7 (C^{10}), 136.8 (C^{5}), 116.3 (C^{7}), 69.7 (C–OH), 31.6 (Me). IR (KBr, ν/cm^{-1}): 3476, 3415, 3196, 3086, 2983, 2850, 2789, 1742, 1674, 1598, 1517, 1410, 1379, 1315, 1223, 1172, 1122, 1092, 1069, 994, 959, 857, 798, 753, 681, 649, 612, 564, 513, 481, 421. Found (%): C, 45.39; H, 4.03; N, 26.34. Calc. for $C_{10}H_{11}N_5O_4$ (%): C, 45.29; H, 4.18; N, 26.41.

and M. L. Zheludkevich, *Phys. Chem. Chem. Phys.*, 2017, **19**, 6113; (*e*) G. O. Resende, S. F. Teixeira, I. F. Figueiredo, A. A. Godoy, D. J. F. Lougon, B. A. Cotrim and F. C. de Souza, *Int. J. Electrochem.*, 2019, Article ID 6759478.

14 (*a*) T. Duan, K. Fan, Y. Fu, C. Zhong, X. Chen, T. Peng and J. Qin, *Dyes Pigm.*, 2012, **94**, 28; (*b*) H. Khanmohammadi, M. Erfantalab, A. Bayat, A. Babaei and M. Sohrabi, *Spectrochim. Acta, Part A*, 2012, **97**, 876; (*c*) S.-Y. Zhu, H.-Y. Guo, F.-F. Yang and Z.-S. Wang, *Chin. Chem. Lett.*, 2015, **26**, 1091.

15 R. J. Willis and I. D. Marlow, *Eur. Pat. Appl. 400842*, 1990 (*Chem. Abstr.*, 1991, **114**, 164247b).

16 (*a*) S. Chandrasekaran, *Click Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2016; (*b*) M. M. Heravi, M. Tamimi, H. Yahyavi and T. Hosseinnejad, *Curr. Org. Chem.*, 2016, **20**, 1591; (*c*) S. Lin and A. Sharma, *Chem. Heterocycl. Compd.*, 2018, **54**, 314 (*Khim. Geterotsikl. Soedin.*, 2018, **54**, 314); (*d*) V. M. Muzalevskiy, M. N. Mamedzade, V. A. Chertkov, V. A. Bakulev and V. G. Nenajdenko, *Mendeleev Commun.*, 2018, **28**, 17; (*e*) I. V. Karsakova, A. Yu. Smirnov and M. S. Baranov, *Chem. Heterocycl. Compd.*, 2018, **54**, 755 (*Khim. Geterotsikl. Soedin.*, 2018, **54**, 755).

17 I. A. Novokshonova, V. V. Novokshonov and A. S. Medvedeva, *Synthesis*, 2008, 3797.

18 (*a*) A. S. Medvedeva, M. M. Demina, T. L. H. Nguyen, T. D. Vu, D. A. Bulanov and V. V. Novokshonov, *Russ. J. Org. Chem.*, 2013, **49**, 1221 (*Zh. Org. Khim.*, 2013, **49**, 1236); (*b*) A. S. Medvedeva, M. M. Demina, T. D. Vu, M. V. Andreev, N. S. Shaglaeva and L. I. Larina, *Mendeleev Commun.*, 2016, **26**, 326.

19 M. M. Demina, A. S. Medvedeva, T. L. H. Nguyen, T. D. Vu and L. I. Larina, *Russ. Chem. Bull., Int. Ed.*, 2017, **66**, 2253 (*Izv. Akad. Nauk, Ser. Khim.*, 2017, 2253).

20 A. S. Medvedeva, I. V. Mitroshina, A. V. Afonin, D. A. Bulanov and A. V. Mareev, *Russ. J. Org. Chem.*, 2013, **49**, 828 (*Zh. Org. Khim.*, 2013, **49**, 845).

21 A. S. Medvedeva, L. P. Safronova and G. G. Chichkareva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1976, **25**, 107 (*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1976, 121).

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