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Cascade transformation of 4-hydroxymethyl-2-carene into novel cage methanopyrano[4,3-*b*]thieno[3,2-*g*]benzofuran derivative

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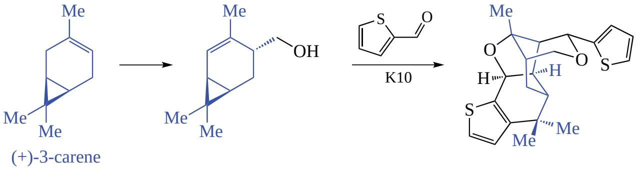
Reaction of *trans*-4-hydroxymethyl-2-carene with thiophene-2-carbaldehyde under heterogeneous catalysis by K10 clay affords substituted methanopyrano[4,3-*b*]thieno[3,2-*g*]-benzofuran, a complex 5-membered chiral cage heterocyclic compound containing two thiophene moieties. Its structure was determined by 1D and 2D NMR experiments (HSQC, HMBC, COSY, NOESY) and HRMS.



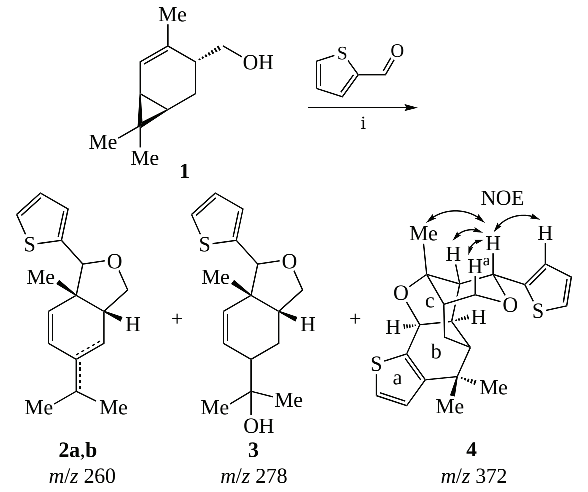
Keywords: terpenoids, carene, thiophene-2-carbaldehyde, pyrano[4,3-*b*]thieno[3,2-*g*]benzofuran, thieno[3,2-*g*]benzofuran, clays, montmorillonite K10, halloysite, heterogeneous catalysis.

This work is a part of our ongoing research on application of heterogeneous catalysts in the synthesis of pharmacologically valuable molecules based on monoterpenoids.[1,2] Monoterpenes and monoterpenoids are widely studied due to their broad spectrum of biological activity.[3–12] The availability and low cost of (+)-3-carene which is one of the main components of gum turpentine favored its use as a chiral matrix in targeted synthesis.[13,14] The important feature of this monoterpene is that it can be obtained from natural sources with high enantiomeric purity, which makes it attractive for enantioselective synthesis.[15–21]

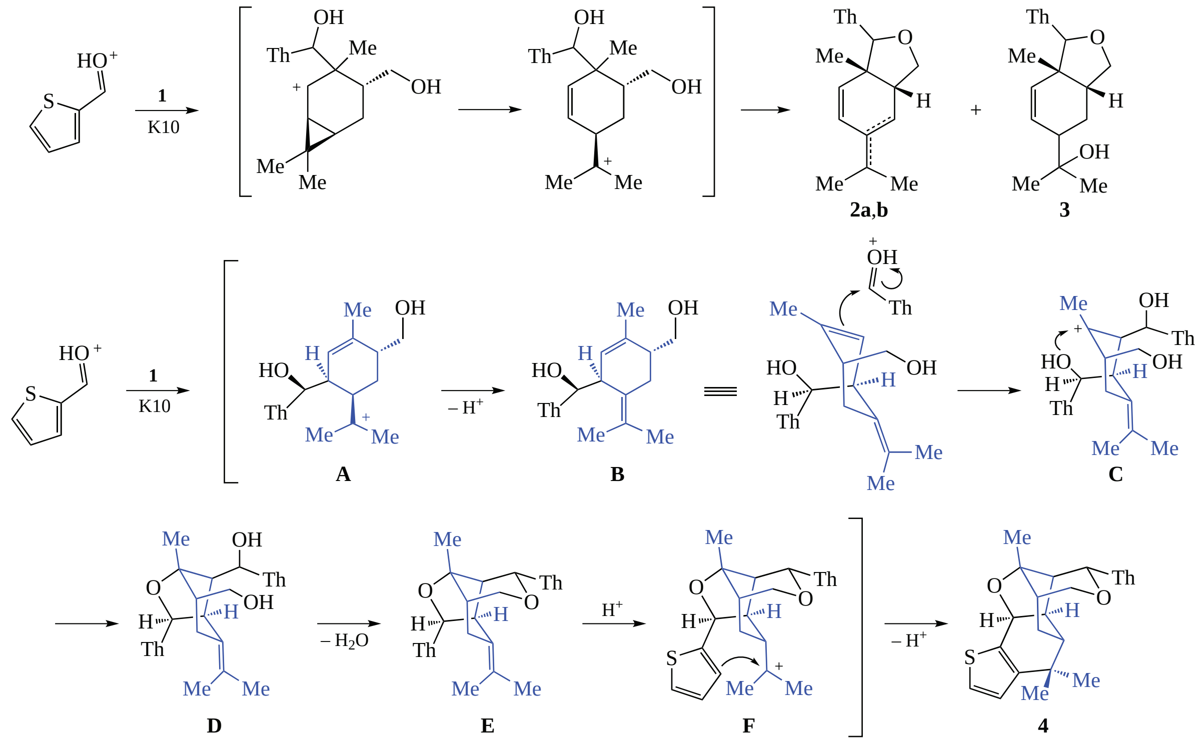
In present study, we used *trans*-4-hydroxymethyl-2-carene **1** readily accessible from (+)-3-carene by its reaction with paraformaldehyde in acetic acid.[22,23] Compound **1** has a very interesting but poorly studied reactivity. It is known that clay-catalyzed reaction of *trans*-4-hydroxymethyl-2-carene **1** with various aldehydes gives mixture of isobenzofurans, however, in addition to them, various polycyclic compounds are stereoselectively formed depending on the type of aldehyde[24] (see Online Supplementary Materials, Scheme S1). In the case of acrolein, the formation of complex four-membered polycyclic product (**S2**) was observed,[25] while the reaction with benzaldehyde led exclusively to isobenzofurans. On the other hand, the reaction with isovanillin affords polycyclic compounds (**S3)** with the tetrahydrofuran moiety *via* the Prins–Friedel–Crafts reaction, this product induced apoptosis in lymphoblastoid cancer cell lines and its activity is comparable with that of the reference drug Doxorubicin.[26] Also, in case of salicylic aldehyde containing nucleophilic OH group the reaction with *trans*-4-hydroxymethyl-2-carene **1** resulted in selective formation of furanochromene derivative (**S4**).[15]

Herein, we report on the reaction of *trans*-4-hydroxymethyl-2-carene **1** with heteroaromatic aldehyde, namely, thiophene-2-carbaldehyde in the presence of clays as heterogeneous catalysts. At first, the reaction was performed in the presence of montmorillonite K10 clay without solvent. Based on GC-MS data, the reaction mixture contained four products with *m/z* value 260, and products with 278 which corresponded to isobenzofurans **2a**,**b** and **3** (Scheme 1). Moreover, product **4** with *m/z* value 372 was detected (the product content in the reaction mixture was 10% for **2a**,**b**, 65% for **3** and 8% for **4**). Molecular mass of the compound **4** corresponds to the attachment of two aldehyde molecules, as in compound **S2** (see Online Supplementary Materials, Scheme S1).[16]

We carried out series of experiments to study the dependence of the selectivity to product **4** on the type of catalyst and reaction conditions. Two clays (commercial montmorillonite K10 and acid-treated halloysite nanotubes HNT[27]) were used in this reaction based on the previous results.[23] The best selectivity to **4** (25%) was observed over commercial montmorillonite K10 in CH_2Cl_2 medium. Using both of catalysts K10 and HNT without



Scheme 1 *Reagents and conditions*: i, K10 clay, solvent-free, room temperature, 3 h.



Scheme 2

solvent showed less selectivity (up to 12.5%), also increasing in the excess of aldehyde (from 1.5-fold to 10-fold) did not improve the selectivity. To obtain an analytically pure sample, it was necessary to carry out several successive purifications using column chromatography. The main difficulty was the separation from remainder thiophene-2-carbaldehyde. After purification, compound **4** was obtained in 5% yield.

The structure of product **4** was determined by 1D and 2D NMR experiments (HSQC, HMBC, COSY, NOESY). The thiophene substituent at pyran ring occupies an equatorial position that was confirmed by an intensive NOESY correlation between three protons of pyran ring, one proton of thiophene ring and protons of methyl group (see Scheme 1). *cis*-Fusion of rings c and b was proved by measurement of spin–spin coupling constant ($J = 3.6$ Hz) and NOESY correlations.

Possible mechanism of formation of compound **4** includes cyclopropane ring opening by protonated aldehyde to give carbocation **A** followed by dehydrogenation to form **B** (Scheme 2). It is of interest to note that reaction of protonated aldehyde with *trans*-4-hydroxymethyl-2-carene **1** gives an intermediate **A** with isopropyl and thiophenyl moieties in *cis*-configuration as we observed earlier in the reaction of (+)-2-carene with 4-methoxybenzaldehyde on K10.[28] Attachment of the second aldehyde molecule leads to intermediate **C** which undergoes two consecutive heterocyclization to yield compound **E**. At the last stage alkylation of thiophene ring occurs to give target compound **4**. The formation of products **2a**,**b** and **3** (see Scheme 2) agrees with the initial attack of the protonated aldehyde on the double bond of substrate **1**.

It should be noted that the reaction of *trans*-4-hydroxymethyl-2-carene **1** with heteroaromatic thiophene-2-carbaldehyde is more similar to the case of using aliphatic aldehydes than aromatic ones in terms of the formation of polycyclic products. Reactions with thiophene-2-carbaldehyde and acrolein lead to derivatives containing two molecules of aldehyde, while reactions with substituted benzaldehydes afford polycyclic compounds **S3** and **S4** (see Scheme S1).

In summary, the reaction of (+)-3-carene-derived *trans*-4-hydroxymethyl-2-carene with thiophen-2-carbaldehyde in the presence of clay K10 led to previously unknown five-membered polycyclic chiral product **4** incorporating two thiophene moieties. The reaction proceeds with very high stereoselectivity, and four new stereocenters are formed. Despite the low yield of (5*R*,5a*R*,5b*R*,6*R*,9*S*,9a*S*,10a*S*)-4,4,9a-trimethyl-6-(thiophen-2-yl)-4,5,5a,5b,8,9,9a,10a-octahydro-6*H*-5,9-methanopyrano[4,3-*b*]thieno[3,2-*g*]benzofuran **4**, its unusual structure seems promising since to the best of our knowledge compounds with such a cage have not been described.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.005.

References

1 A. Yu. Sidorenko, Yu. M. Kurban, I. V. Il'ina, N. S. Li-Zhulanov, D. V. Korchagina, O. V. Ardashov, J. Wärnå, K. P. Volcho, N. F. Salakhutdinov, D. Yu. Murzin and V. E. Agabekov, *Appl. Catal.*, 2021, **618**, 118144.

2 A. Yu. Sidorenko, A. V. Kravtsova, P. Maki-Arvela, A. Aho, T. Sandberg, I. V. Il'ina, N. S. Li-Zhulanov, D. V. Korchagina, K. P. Volcho, N. F. Salakhutdinov, D. Yu. Murzin and V. E. Agabekov, *Mol. Catal.*, 2020, **490**, 110974.

3 N. F. Salakhutdinov, K. P. Volcho and O. I. Yarovaya, *Pure Appl. Chem.*, 2017, **89**, 1105.

4 O. I. Yarovaya and N. F. Salakhutdinov, *Russ. Chem. Rev.*, 2021, **90**, 488.

5 J. F. R. de Alvarenga, B. Genaro, B. L. Costa, E. Purgatto, C. Manach and J. Fiamoncini, *Crit. Rev. Food Sci. Nutr.*, 2021, doi.org/10.1080/10408398.2021.1963945.

6 T. M. Le and Z. Szakonyi, *Chem. Rec.*, 2022, **22**, e202100194.

7 A. Kozioł, A. Stryjewska, T. Librowski, K. Sałat, M. Gaweł, A. Moniczewski and S. Lochynski, *Med. Chem.*, 2014, **14**, 1156.

8 R. S. S. Barreto, R. L. C. Albuquerque-Júnior, A. A. S. Araújo, J. R. G. S. Almeida, M. R. V. Santos, A. S. Barreto, J. M. DeSantana, P. S. Siqueira-Lima, J. S. S. Quintans and L. J. Quintans-Júnior, *Molecules*, 2014, **19**, 846.

9 S. Dragomanova, L. Tancheva and M. Georgieva, *Scr. Sci. Pharm.*, 2018, **5**, 22.

10 A. Marchese, I. E. Orhan, M. Daglia, R. Barbieri, A. Di Lorenzo, S. F. Nabavi, O. Gortzi, M. Izadi and S. M. Nabavi, *Food Chem.*, 2016, **210**, 402.

11 J. D. Dheer, D. Singh, G. Kumar, M. Karnatak, S. Chandra, V. P. Verma and R. Shankar, *Curr. Bioact. Compd.*, 2019, **15**, 454.

12 K. A. Wojtunik-Kulesza, K. Kasprzak, T. Oniszczuk and A. Oniszczuk, *Chem. Biodiversity*, 2019, **16**, e1900434.

13 P. Yuan, C. K. G. Gerlinger, J. Herberger and T. Gaich, *J. Am. Chem. Soc.*, 2021, **143**, 11934.

14 R. K. Jackson III and J. L. Wood, *Org. Lett.*, 2021, **23**, 1243.

15 L. E. Nikitina, V. A. Startseva, N. P. Artemova, L. Yu. Dorofeeva, I. V. Kuznetsov, S. A. Lisovskaya, N. P. Glushko and M. P. Kutyreva, *Pharm. Chem. J.*, 2012, **45**, 664 [*Khim.-Farm. Zh.*, 2011, **45** (11), 16].

16 L. E. Nikitina, V. A. Startseva, L. Yu. Dorofeeva, N. P. Artemova, I. V. Kuznetsov, S. A. Lisovskaya and N. P. Glushko, *Chem. Nat. Compd.*, 2010, **46**, 28 (*Khim. Prir. Soedin.*, 2010, 27).

17 O. A. Banina, D. V. Sudarikov, P. A. Slepukhin, L. L. Frolova and A. V. Kuchin, *Chem. Nat. Compd.*, 2016, **52**, 240 (*Khim. Prir. Soedin.*, 2016, 211).

18 M. P. Yakovleva, K. S. Denisova, G. R. Mingaleeva, Yu. V. Myasoedova, L. R. Garifullina, N. M. Ishmuratova and G. Yu. Ishmuratov, *Chem. Nat. Compd.*, 2020, **56**, 487 (*Khim. Prir. Soedin.*, 2020, 419).

19 Yu. V. Myasoedova, E. R. Nurieva, L. R. Garifullina and G. Yu. Ishmuratov, *Russ. J. Org. Chem.*, 2020, **56**, 1673 (*Zh. Org. Khim.*, 2020, **56**, 1471).

20 F. Z. Macaev and A. V. Malkov, *Tetrahedron*, 2006, **62**, 9.

21 S. N. Curlat, A. N. Barba, V. V. Boldescu, K. Panekok and F. Z. Macaev, *Chem. Nat. Compd.*, 2019, **55**, 269 (*Khim. Prir. Soedin.*, 2019, 232).

22 G. Ohloff, H. Farnow and W. Philipp, *Justus Liebigs Ann. Chem.*, 1958, **613**, 43.

23 A. Yu. Sidorenko, Yu. M. Kurban, A. V. Kravtsova, I. V. Il’ina, N. S. Li-Zhulanov, D. V. Korchagina, J. E. Sánchez-Velandia, A. Aho, K. P. Volcho, N. F. Salakhutdinov, D. Yu. Murzin and V. E. Agabekov, *Appl. Catal.*, 2022, **629**, 118395.

24 O. S. Patrusheva, K. P. Volcho and N. F. Salakhutdinov, *Russ. Chem. Rev.*, 2018, **87**, 771.

25 N. F. Salakhutdinov, K. P. Volcho, D. V. Korchagina, L. E. Tatarova and V. A. Barkhash, *Tetrahedron*, 1998, **54**, 15619.

26 S. Yu. Kurbakova, I. V. Il’ina, O. S. Mikhalchenko, M. A. Pokrovsky, D. V. Korchagina, K. P. Volcho, A. G. Pokrovsky and N. F. Salakhutdinov, *Bioorg. Med. Chem.*, 2015, **23**, 1472.

27 P. Komadel, *Appl. Clay Sci.*, 2016, **131**, 84.

28 I. V. Il’ina, K. P. Volcho, D. V. Korchagina, V. A. Barkhash and N. F. Salakhutdinov, *Helv. Chim. Acta*, 2010, **93**, 2135.

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