Mendeleev Communications

Mendeleev Commun., 2025, **35**, 639–641

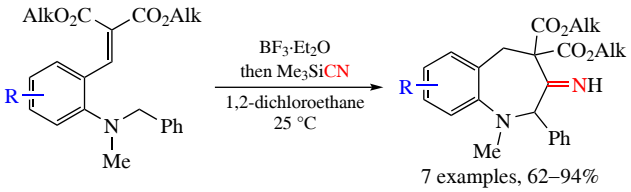
Synthesis of 3-imino-1-benzazepines by the cyanide-incorporating heterocyclization of (2-benzylaminobenzylidene)malonates

Dmitrii S. Ivanov,*[a] Marina V. Molchanova,[a] Aleksander Yu. Smirnov,[a,b] Andrey A. Mikhaylov,[a,b] Pavel N. Solyev[c] and Mikhail S. Baranov[a,b]

[a] *M. M. Shemyakin–Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 117997 Moscow, Russian Federation. E-mail: d-ivanov.dmitry@yandex.ru*
[b] *N. I. Pirogov Russian National Research Medical University, 117997 Moscow, Russian Federation*
[c] *V. A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.71267/mencom.7805

A method for the synthesis of 1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylates from 2-[2-(*N*-benzyl-*N*-methylamino)benzylidene]malonates and trimethylsilyl cyanide is proposed. The transformation can be considered as the 1,5-hydride shift–cyclization cascade sequence involving the formation of intermediate stable boronate complex.



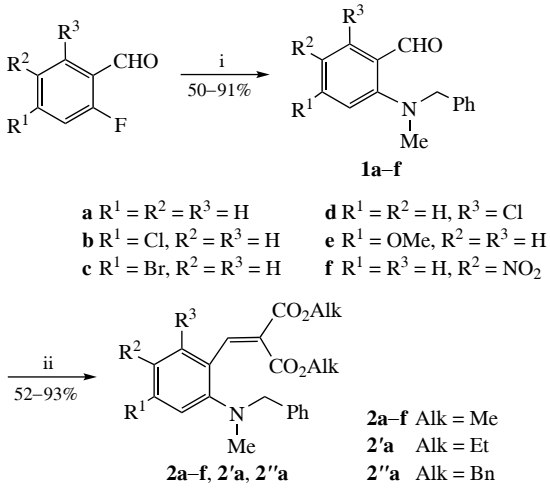
Keywords: 1-benzazepines, 1,5-hydride shift, cyanide ion, *tert*-amino effect, (benzylidene)malonates, heterocyclization.

1-Benzazepines are extensively utilized in medicinal chemistry.[1] Modern pharmacological studies are focused on their anti-inflammatory,[2] anxiolytic,[3] and antitumor[4] activity. These compounds can act as vasopressin receptor antagonists,[5,6] calcium channel blockers,[7] PLK1 protein inhibitors,[8] and analgesics.[9] Commercial drugs based on 1-benzazepines include mozavaptan, tolvaptan, benazepril (for the structures, see Online Supplementary Materials, Figure S1). The 1-benzazepine scaffold is also commonly found in natural compounds.[10–13]

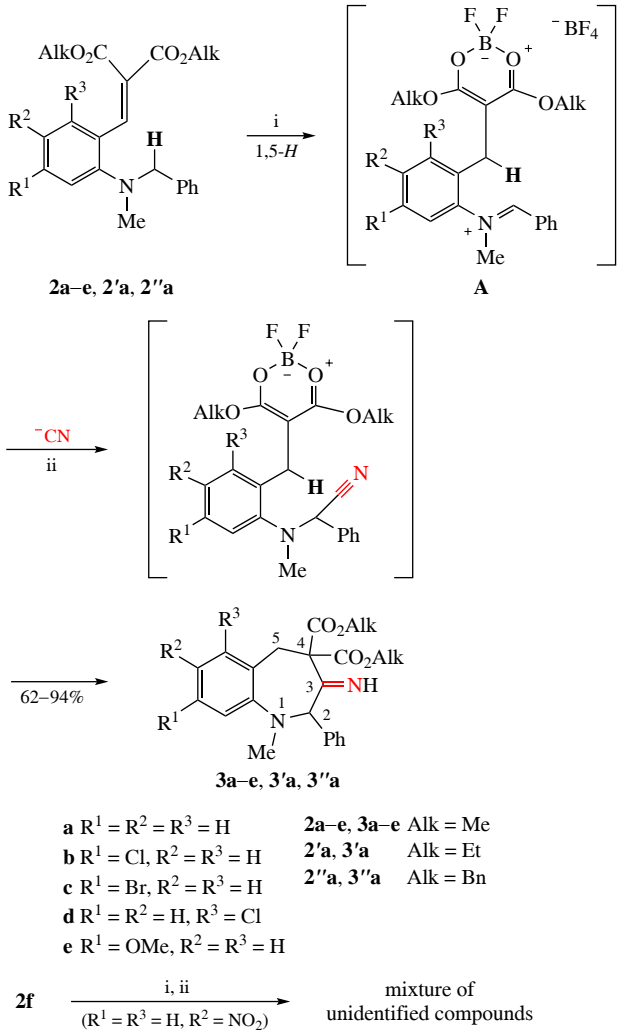
Several synthetic approaches for the synthesis of 1-benzazepines have been described in the literature.[1,14] Intramolecular 1,5-hydride shift reaction occupies a special place among these methods.[15] This process is atom-economical, redox-neutral, and usually does not require transition metal catalysts, aligning well with modern standards of 'green chemistry'.[16] 1,5-Hydride shift process (or so-called '*tert*-amino effect' reactions[17]) is most commonly employed in the synthesis of six-membered heterocycles.[18] Only three approaches have been reported[16] that extend this methodology to seven-membered 1-benzazepine derivatives: (a) ring expansion of cyclopropane-1,1-dicarboxylates;[19] (b) the Pictet–Spengler type cyclization of diarylmethanols;[20,21] (c) intermolecular Mannich reaction followed by expansion of the pyrrolidine moiety[22] (for the illustration, see Online Supplementary Materials, Scheme S1).

In this work, we propose an alternative and novel approach to 1-benzazepines from readily available *o*-aminobenzaldehyde derivatives **1** which were converted into key 2-[2-(*N*-benzyl-*N*-methylamino)benzylidene]malonates **2** (Scheme 1). The latter upon incorporation of trimethylsilyl cyanide gave novel tetrahydro-1-benzazepine derivatives **3** (Scheme 2). Previously, we showed that a 1,5-hydride shift–cyclization cascade could be interrupted at the first stage of the iminium intermediate by formation of a stable boronate complex.[23,24] Here, we demonstrate that such intermediates can react with cyanide resulting in the formation of a benzazepine system. Substrates **2a–f** for the proposed reaction were prepared in two steps using known methods[24] (see Scheme 1).

Initially, compounds **2a–f** were treated with $BF_3 \cdot Et_2O$ (1,2-dichloroethane, 25 °C, 12 h) under previously proposed conditions[24] which ensured stability of the corresponding intermediate boronate complex **A** (see Scheme 2). Next, Me_3SiCN was added as a cyanide ion source resulting in the rapid conversion of **A** into the target products **3**. The reaction scope was demonstrated on seven 1-benzazepines **3a–e**, **3′a**, **3″a** obtained in good yields (62–94%). The only exception was nitro-substituted derivative **2f** which gave a complex mixture of unidentified products. Apparently, destabilization of the cationic intermediate by the electron-withdrawing NO_2-group accelerated various undesired intramolecular reactions known for (2-dialkylaminobenzylidene)malonates.[24,25]



Scheme 1 *Reagents and conditions*: i, $PhCH_2N(Me)H$, K_2CO_3, DMF, 100 °C; ii, $CH_2(CO_2Alk)_2$, piperidine, AcOH, PhMe, reflux.

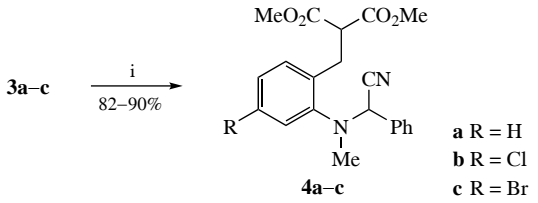


Scheme 2 *Reagents and conditions*: i, $BF_3 \cdot Et_2O$, 1,2-dichloroethane, 25 °C, ~ 12 h; ii, Me_3SiCN, 30 min.

The structures of all compounds were confirmed by ^1H, ^{13}C NMR and HRMS data. Additionally, compound **3a** was characterized by two-dimensional NMR spectroscopy (C–H HSQC, C–H HMBC). The C–H HMBC experiment for **3a** revealed the correlation peak between C^3(=NH) carbon atom and 5-positioned protons (see Online Supplementary Materials, page S11).

Surprisingly, the obtained 1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylates **3** were not sufficiently stable. We found that they underwent isomerization associated with ring opening and formation of nitriles **4** in solutions which could be traced by the NMR analysis. For compounds **3a–c**, we showed that this process could be selectively induced by their treatment with hydrochloric acid (Scheme 3).

To conclude, we developed a new approach to 1,2,3,5-tetrahydro-4*H*-1-benzazepine-4,4-dicarboxylates *via* the 1,5-hydride shift and cyanide ion addition starting from available



Scheme 3 *Reagents and conditions*: i, HCl, THF, H_2O, 25 °C.

2-[2-(*N*-benzyl-*N*-methylamino)benzylidene]malonates. This method continues our studies on hydride shift[26] and extends the synthetic potential of this powerful tool for C–H activation.

The study was carried out with financial support from the Russian Science Foundation (grant no. 20-73-10195).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7805.

References

1 I. Yu. Danyliuk, R. I. Vas'kevich, A. I. Vas'kevich and M. V. Vovk, *Chem. Heterocycl. Compd.*, 2019, **55**, 802; https://link.springer.com/article/10.1007/s10593-019-02540-3.
2 A. Tiwari, A. Bendi and A. S. Bhathiwal, in *Heterocyclic Anti-Inflammatory Agents: A Guide for Medicinal Chemists*, eds. A. Bendi, M. P. Kaushik and N. Raghav, Bentham Science, 2024, pp. 144–163; https://doi.org/10.2174/9789815223460124010010.
3 O. Reamtong, S. Lapmanee, J. Tummatorn, N. Palavong, C. Thongsornkleeb and S. Ruchirawat, *ACS Med. Chem. Lett.*, 2021, **12**, 1449; https://doi.org/10.1021/acsmedchemlett.1c00275.
4 I. Kuznetcova, M. Ostojić, N. Gligorijević, S. Aranđelović and V. B. Arion, *Inorg. Chem.*, 2022, **61**, 20445; https://doi.org/10.1021/acs.inorgchem.2c03134.
5 É. Bozó, F. Baska, K. Lövei, G. Szántó, K. Domány-Kovács, D. Kurkó, K. Szondiné Kordás, T. Szokoli and I. Bata, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127417; https://doi.org/10.1016/j.bmcl.2020.127417.
6 Z. Szeleczky, Z. Szakács, É. Bozó, F. Baska, K. Vukics, S. Lévai, K. Temesvári, E. Vass, Z. Béni, B. Krámos, I. Magdó, C. Szántay, J. Kóti, K. Domány-Kovács, I. Greiner and I. Bata, *J. Med. Chem.*, 2021, **64**, 10445; https://doi.org/10.1021/acs.jmedchem.1c00863.
7 D. M. Floyd, S. D. Kimball, J. Krapcho, J. Das, C. F. Turk, R. V. Moquin, M. W. Lago, K. J. Duff, V. G. Lee, R. E. White, R. E. Ridgewell, S. Moreland, R. J. Brittain, D. E. Normandin, S. A. Hedberg and G. G. Cucinotta, *J. Med. Chem.*, 1992, **35**, 756; https://doi.org/10.1021/jm00082a018.
8 M. O. Duffey, T. J. Vos, R. Adams, J. Alley, J. Anthony, C. Barrett, I. Bharathan, D. Bowman, N. J. Bump, R. Chau, C. Cullis, D. L. Driscoll, A. Elder, N. Forsyth, J. Frazer, J. Guo, L. Guo, M. L. Hyer, D. Janowick, B. Kulkarni, S. J. Lai, K. Lasky, G. Li, J. Li, D. Liao, J. Little, B. Peng, M. G. Qian, D. J. Reynolds, M. Rezaei, M. P. Scott, T. B. Sells, V. Shinde, Q. J. Shi, M. D. Sintchak, F. Soucy, K. T. Sprott, S. G. Stroud, M. Nestor, I. Visiers, G. Weatherhead, Y. Ye and N. D'Amore, *J. Med. Chem.*, 2012, **55**, 197; https://doi.org/10.1021/jm2011172.
9 S. B. Hoyt, C. London and M. Park, *Tetrahedron Lett.*, 2009, **50**, 1911; https://doi.org/10.1016/j.tetlet.2009.02.022.
10 L. Chen, J.-W. Tang, Y. Y. Liu and Y. Matsuda, *Org. Lett.*, 2022, **24**, 4816; https://doi.org/10.1021/acs.orglett.2c01918.
11 H. Li, C. L. M. Gilchrist, C.-S. Phan, H. J. Lacey, D. Vuong, S. A. Moggach, E. Lacey, A. M. Piggott and Y.-H. Chooi, *J. Am. Chem. Soc.*, 2020, **142**, 7145; https://doi.org/10.1021/jacs.0c01605.
12 L. K. Caesar, M. T. Robey, M. Swyers, R. Ye, P. P. Vagadia, G. E. Schiltz, P. M. Thomas, C. C. Wu, N. L. Kelleher, N. P. Keller and J. W. Bok, *mBio*, 2020, **11**, 1; https://doi.org/10.1128/mbio.01691-20.
13 X.-L. Hu, X.-Q. Bian, X. Wu, J.-Y. Li, H.-M. Hua, Y.-H. Pei, A.-H. Han and J. Bai, *Tetrahedron Lett.*, 2014, **55**, 3864; https://doi.org/10.1016/j.tetlet.2014.05.104.
14 W. Mazumdar and T. G. Driver, *Synthesis*, 2021, **53**, 1734; https://doi.org/10.1055/s-0040-1705995.
15 J. Nagaki, T. Kawasaki-Takasuka and K. Mori, *Synlett*, 2024, **35**, 2143; https://doi.org/10.1055/a-2287-9391.
16 X.-D. An and J. Xiao, *Org. Chem. Front.*, 2021, **8**, 1364; https://doi.org/10.1039/D0QO01502D.
17 A. Yu. Platonova, T. V. Glukhareva, O. A. Zimovets and Yu. Yu. Morzherin, *Chem. Heterocycl. Compd.*, 2013, **49**, 357; https://doi.org/10.1007/s10593-013-1257-6.
18 H. Liu, Y. Quan, L. Xie, X. Li and X. Xie, *Front. Chem.*, 2022, **10**, 840934; https://doi.org/10.3389/fchem.2022.840934.
19 C. W. Suh, S. J. Kwon and D. Y. Kim, *Org. Lett.*, 2017, **19**, 1334; https://doi.org/10.1021/acs.orglett.7b00184.
20 S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu and J. Xiao, *Org. Lett.*, 2018, **20**, 138; https://doi.org/10.1021/acs.orglett.7b03492.
21 S. Liu, J. Qu and B. Wang, *Chem. Commun.*, 2018, **54**, 7928; https://doi.org/10.1039/C8CC03804J.

22 S. Wang, X.-D. An, S.-S. Li, X. Liu, Q. Liu and J. Xiao, *Chem. Commun.*, 2018, **54**, 13833; https://doi.org/10.1039/C8CC08238C.
23 E. R. Zaitseva, A. Yu. Smirnov, V. I. Timashev, V. I. Malyshev, E. A. Zhigileva, A. A. Mikhaylov, M. G. Medvedev, N. S. Baleeva and M. S. Baranov, *Eur. J. Org. Chem*., 2022, e202200547; https://doi.org/10.1002/ejoc.202200547.
24 E. R. Zaitseva, D. S. Ivanov, A. Yu. Smirnov, A. A. Mikhaylov, N. S. Baleeva and M. S. Baranov, *Molecules*, 2022, **27**, 5270; https://doi.org/10.3390/molecules27165270.
25 S. Murarka, C. Zhang, M. D. Konieczynska and D. Seidel, *Org. Lett*., 2009, **11**, 129; https://doi.org/10.1021/ol802519r.
26 A. M. Al Mufti, V. A. Ikonnikova, A. Yu. Smirnov, V. A. Lushpa, P. N. Solyev, M. N. Azmi, M. S. Baranov and A. A. Mikhaylov, *Mendeleev Commun*., 2025, **35**, 18; https://doi.org/10.71267/mencom.7550.

Received: 18th April 2025; Com. 25/7805