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Nucleophilic ring opening of imidazolone activated donor–acceptor cyclopropanes with alcohols

Viktoria A. Ikonnikova,[a,b] Ekaterina A. Zhigileva,[a,c] Andrei V. Kuleshov,[a,c] Vasilissa V. Shirokova,[a,b] Mikhail S. Baranov[a] and Andrey A. Mikhaylov*[a]

[a] *M. M. Shemyakin–Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 117997 Moscow, Russian Federation. E-mail: mikhaylov_andrey@yahoo.com*
[b] *Higher Chemical College of the Russian Academy of Sciences, D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*
[c] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation*

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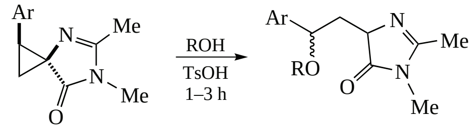
Imidazolone-activated donor–acceptor cyclopropanes undergo alcohol-assisted ring opening under the co-action of *p*-toluenesulfonic acid. Under the optimized conditions, cyclopropanes and alcohols are coupled in 1,3-fashion with the retention of heterocyclic fragment. Substrates with aromatic donor groups provide the addition products in 75–99% yields as mixtures of two diastereomers.

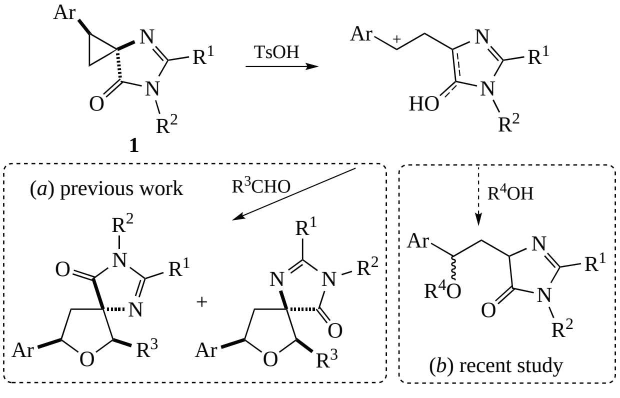


11 examples
75–99%, *dr* 1 : 1

Keywords: donor–acceptor cyclopropanes, spirocyclic compounds, imidazolones, alcohols, nucleophilic ring opening.

In the recent years, chemistry of donor–acceptor cyclopropanes (DACs) has witnessed a significant progress.[1–3] Such compounds are characterized by the ease of cleavage of one of the bonds leading to zwitter-ionic intermediates or their equivalents which could readily react with nucleophiles or undergo various cycloaddition reactions. Recent achievements in this field are associated with the development of catalytic asymmetric methods,[4,5] new types of nucleophiles[6–8] and cycloaddition partners,[9–11] as well as with new concepts for their activation and utilization in synthesis.[12–16]

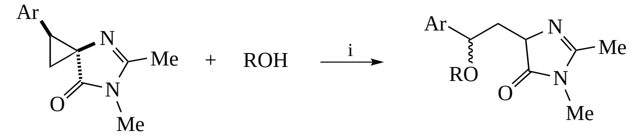
The present study is the continuing investigation of a new family of imidazolone-activated DACs of type **1** bearing spirocyclic structures (Scheme 1, pathway *a*).[17,18] Recently we have shown[17] that such reactants could be activated by *p*-toluenesulfonic acid (TsOH) and undergo cycloaddition with aldehydes to form tetrahydrofuran cycle. The reaction is likely to proceed *via* carbocation which was demonstrated when the enantiomerically pure substrate was used.[18] Herein we would like to describe the possibilities for nucleophilic ring opening of the imidazolone activated DACs on the example of the reaction with alcohols.



Scheme 1

It is noteworthy that the nucleophilic ring opening in the related cyclopropanes containing oxazolone fragment was a matter of intence previous studies.[19–24] During the studies on the cyclopropane amino acid synthesis, different conditions for saponification of the heterocyclic moiety were tested, and it was occasionally found that under acidic conditions the cyclopropane ring would also participate in the reaction. When that reaction was carried out in the presence of methanethiol, a product of nucleophilic ring opening corresponding to DAC reactivity was isolated.[20] However, none of the studies succeeded in isolation of the intermediates containing oxazoline cycle. Due to this matter the main objective of this work was the development of the method which would allow for isolation of primary nucleophilic addition products of DACs of type **1** with alcohols **2** (see Scheme 1, pathway *b*).

During the first stage of the research, a screening of the conditions for the reaction with methanol **2a** (10-fold excess) on the model DAC **1a** with 4-methoxyphenyl substituent was carried out (Scheme 2). It was found out that at least one equivalent of the activating sulfonic acid was required to reach



1a–g	**2a–e**	**3aa–ae**,**ba–fa** (*dr* 1 : 1)	
a Ar = 4-MeOC$_6$H$_4$	**a** R = Me	**3aa**, 80%	**3ba**, 84%
b Ar = 2-MeOC$_6$H$_4$	**b** R = Et	**3ab**, 99%	**3ca**, 98%
c Ar = 2,4-(MeO)$_2$C$_6$H$_3$	**c** R = Pr^i	**3ac**, 94%	**3da**, 93%
d Ar = 2,5-(MeO)$_2$C$_6$H$_3$	**d** R = Pr	**3ad**, 75%	**3ea**, 76%
e Ar = 3,4-(MeO)$_2$C$_6$H$_3$	**e** R = allyl	**3ae**, 85%	**3fa**, 94%
f Ar = 2-thienyl			**3ga**, ~50%
g Ar = Ph			

Scheme 2 *Reagents and conditions*: i, ROH **2a–e** (5–10 equiv.), TsOH · H$_2$O (1.1 equiv.), 1,2-dichloroethane, room temperature, 1.5–3 h (for **3ga**, 1 week, side products were also formed).

full conversion (apparently, the acid proton would be trapped by the basic heterocyclic nitrogen atom). When using TsOH hydrate in dichloroethane, the target 1,3-adduct **3aa** containing imidazolone fragment was formed almost quantitatively within 1.5 h as two diastereomers (NMR data). The major problems did arise while attempting to purify the product. Column chromatography on different sorbents (30 and 60 Å silica, alumina of different grade) brought about the product contaminated with unidentified impurities. Ultimately, the chromatography was postponed, and the isolation was carried out by the extraction procedure (EtOAc/H_2O) after neutralization of the acid with *N*,*N*,*N*′,*N*′-tetramethylguanidine. This operation provided the isolation of the target **3aa** in 80% yield and satisfactory 95% purity.[†]

In this context, investigation of the reactivity was continued with low-boiling alcohols **2b–e** (see Scheme 2). In the case of two last reactants, it was possible to apply their just 5-fold excess. In all cases, products **3** were obtained in 75–99% yields as mixtures of diastereomers.

A scope of substituents in cyclopropanes **1** for the successful processing with methanol **2a** was studied next. Different donor aromatic substituents such as (poly)methoxyphenyl ones (compounds **1b–e**) as well as 2-thienyl (compound **1f**) facilitated the reaction (see Scheme 2). However, once the less-donating phenyl substituent in cyclopropane **1g** was introduced, a significant decrease in the reaction rate[24] was observed (full conversion occurred only after a week), which resulted in formation of much by-products, so product **3ga** was not isolated in a pure state.

In summary, we have demonstrated that imidazolone-activated DACs of type **1** could undergo nucleophilic ring opening with alcohols **2** under activation with TsOH. Products **3** of 1,3-addition are formed with the retention of heterocyclic fragment.

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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.2021.09.021.

References

1 H. U. Reissig and R. Zimmer, *Chem. Rev*., 2003, **103**, 1151.
2 T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed*., 2014, **53**, 5504.
3 A. J. Craig and B. C. Hawkins, *Synthesis*, 2020, **52**, 27.
4 V. Pirenne, B. Muriel and J. Waser, *Chem. Rev*., 2021, **121**, 227.
5 Y. Xia, X. Liu and X. Feng, *Angew. Chem., Int. Ed*., 2021, **60**, 9192.
6 A. A. Akaev, M. Ya. Melnikov and E. M. Budynina, *Org. Lett*., 2019, **21**, 9795.
7 I. A. Borisova, D.-M. V. Ratova, K. V. Potapov, A. V. Tarasova, R. A. Novikov and Y. V. Tomilov, *J. Org. Chem*., 2021, **86**, 4567.
8 K. L. Ivanov, H. B. Tukhtaev, F. O. Tukhtaeva, S. I. Bezzubov, M. Ya. Melnikov and E. M. Budynina, *Synthesis*, 2020, **52**, 3356.
9 A. U. Augustin, J. L. Merz, P. G. Jones, G. Mlostoń and D. B.Werz, *Org. Lett*., 2019, **21**, 9405.
10 M. Petzold, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed*., 2019, **58**, 6225.
11 B.-Q. Li, Z.-W. Qiu, A.-J. Ma, J.-B. Peng, N. Feng, J.-Y. Du, H.-P. Pan, X.-Z. Zhang and X.-T. Xu, *Org. Lett*., 2020, **22**, 1903.
12 D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed*., 2020, **59**, 3385.
13 I. A. Andreev, N. K. Ratmanova, A. U. Augustin, O. A. Ivanova, I. I. Levina, V. N. Khrustalev, D. B. Werz and I. V. Trushkov, *Angew. Chem., Int. Ed*., 2021, **60**, 7927.
14 R. A. Novikov, D. A. Denisov, K. V. Potapov, Y. V. Tkachev, E. V. Shulishov and Y. V. Tomilov, *J. Am. Chem. Soc*., 2018, **140**, 14381.
15 A. A. Suleymanov, E. Le Du, Z. Dong, B. Muriel, R. Scopelliti, F. Fadaei-Tirani, J. Waser and K. Severin, *Org. Lett*., 2020, **22**, 4517.
16 D. B. Werz, S. Kolb, M. Petzold, F. Brandt, P. G. Jones and C. R. Jacob, *Angew. Chem., Int. Ed*., 2021, doi: 10.1002/anie.202101477.
17 A. A. Mikhaylov, A. V. Kuleshov, P. N. Solyev, A. A. Korlyukov, P. V. Dorovatovskii, K. S. Mineev and M. S. Baranov, *Org. Lett*., 2020, **22**, 2740.
18 A. A. Mikhaylov, P. N. Solyev, A. V. Kuleshov, V. S. Kublitskii, A. A. Korlyukov, V. A. Lushpa and M. S. Baranov, *Chem. Heterocycl. Compd*., 2020, **56**, 1092.
19 S. W. King, J. M. Riordan, E. M. Holt and C. H. Stammer, *J. Org. Chem*., 1982, **47**, 3270.
20 J. W. Hines, E. G. Breitholle, M. Sato and C. H. Stammer, *J. Org. Chem*., 1976, **41**, 1466.
21 I. Arenal, M. Bernabé, E. Fernández-Alvarez and S. Penadés, *Synthesis*, 1985, 773.
22 I. Arenal, M. Bernabé, E. Fernández-Alvarez, M. L. Izquierdo and S. Penadés, *J. Heterocycl. Chem*., 1983, **20**, 607.
23 C.-L. Zhu, L.-J. Yang, S. Li, Y. Zheng and J.-A. Ma, *Org. Lett*., 2015, **17**, 3442.
24 A. Kreft, A. Lücht, J. Grunenberg, P. G. Jones and D. B. Werz, *Angew. Chem., Int. Ed*., 2019, **58**, 1955.

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[†] *General procedure*. Alcohol **2** (7.5 mmol, 10 equiv. for **2a**–**c**; or 3.8 mmol, 5 equiv. for **2d**,**e**) and TsOH·H_2O (158 mg, 0.83 mmol, 1.1 equiv.) were added successively to a solution of cyclopropane **1** (0.75 mmol, 1 equiv.) in 1,2-dichloroethane (4 ml). The reaction mixture was stirred at room temperature for 1–3 h (7 days for **1g**) until the full conversion of cyclopropane **1** was reached (TLC control, EtOAc). The mixture was then neutralized with *N*,*N*,*N*′,*N*′-tetramethylguanidine (0.14 ml, 130 mg, 1.13 mmol, 1.5 equiv.). After stirring for additional 15 min, the mixture was poured into separatory funnel containing EtOAc (20 ml) and H_2O (40 ml), the flask was rinsed with EtOAc (20 ml). The combined organic phase was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to provide desired product **3** in 75–99% in >95% purity (except for **3ga**).