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*Mendeleev Commun.*, 2020, **30**, 612–614

Mendeleev Communications

# Pathways of Pd-catalyzed cyclopropanation of tetrahydroindene with diazomethane

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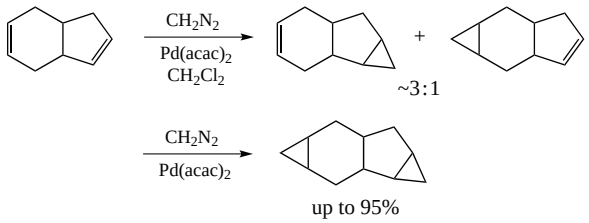
DOI: 10.1016/j.mencom.2020.09.020

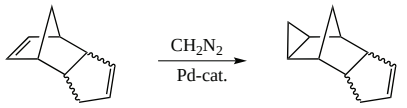
**The Pd-catalyzed cyclopropanation of 3a,4,7,7a-tetrahydro-1*H*-indene with diazomethane unexpectedly affords mono- and dicyclopropanation products in good yields, the cyclopentene double bond being approximately three times more reactive than the cyclohexene one. In contrast, similar independent competitive cyclopropanation of a cyclopentene–cyclohexene mixture has shown that cyclohexene exhibits an abnormally low reactivity differing by about two orders of magnitude.**




*Keywords*: 3a,4,7,7a-tetrahydro-1*H*-indene, diazomethane, *N*-methyl-*N*-nitrosourea, cyclopropanation, palladium catalysis.

Cyclopropane moiety is met in numerous natural and biologically active compounds, including polycyclic ones.[1–4] Cyclopropane compounds are widely used as intermediates in organic synthesis.[5–7] One of the general methods for building the cyclopropane moiety involves the catalytic cyclopropanation of double bonds with diazomethane in rather a wide range of unsaturated compounds. In this case, palladium compounds being the most efficient catalysts[8–12] generally depriving of side processes and formation of by-products. This reaction proceeds without formation of carbene intermediates. Its mechanism includes the initial formation of a complex of low-valence palladium with an olefin, which then would react with a diazo compound leading through a palladacyclobutane intermediate to a cyclopropane product.[7,8] Hence, palladium compounds effectively catalyze the cyclopropanation of only those olefins which are well coordinated with palladium. For example, terminal double bonds are cyclopropanated most easily in alkenes, whereas alkyl substituents at a double bond abruptly decrease its cyclopropanation capability or totally preclude this reaction.[8] In some cases, even partial cyclopropanation of a trisubstituted double bond requires 10- or even 100-fold excess of diazomethane.[13–15]

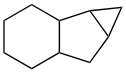
Similar regularities are observed in the cycloalkene series: on transition from cyclooctene to cyclohexene, the reactivity decreases significantly with decreasing ring size. In fact, the reactions of cyclooctene, cycloheptene and cyclohexene with an equimolar amount of diazomethane in the presence of various palladium-based catalysts [$Pd(OAc)_2$, $(PhCN)_2PdCl_2$, *etc.*] result in bicyclo[*n*.1.0]alkanes in yields of 90–93% (*n* = 6), 80–82% (*n* = 5), and no higher than 15% (*n* = 4).[8,16] The very low reactivity of cyclohexene in comparison with other unsaturated compounds was also confirmed by the method of competitive reactions:[17] approximately a thousand times lower than that of norbornene and two hundred times lower than that of styrene. The catalytic cyclopropanation of the next member of the cycloalkene series, cyclopentene, with diazomethane was not reported. It was known that the cyclopropanation of dicyclopentadiene **1** (both *endo* and *exo* isomers) with diazomethane in the presence of $Pd(OAc)_2$ or $(PhCN)_2PdCl_2$ occurred exclusively at the norbornene double bond to give a monocyclopropanation product, *viz.*, compound **2** (Scheme 1).[10,18–21] The cyclopentene moiety was not affected under these conditions. Based on these facts, it was believed until now that cyclopentene moiety was nearly inactive in the Pd-catalyzed cyclopropanation with diazomethane.




*endo*- or *exo*-**1** *endo*- or *exo*-**2**

**Scheme 1**

On the other hand, cycloalkenes annulated with other rings or incorporated into a polycyclic system can possess different reactivity and would not be unable to undergo catalytic diazomethane cyclopropanation.[8] Of such polycyclic hydrocarbons, compounds of polyhydro cyclopropa[*a*]indene family **3** in which the cyclopentane ring is fused with the cyclohexane one are of particular interest since they are not uncommon among natural and other practically valuable compounds (terpenes, steroids, *etc.*).

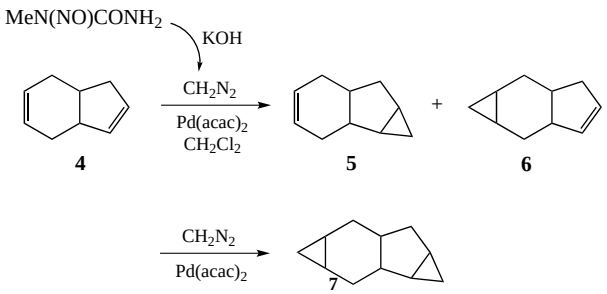


**3**

To create moiety **3**, multistage schemes are usually employed in the targeted syntheses of hydrocarbons, in particular, with preliminary incorporation of activating substituents at the double bond.[5] Development of methods for the direct cyclopropanation of bicyclo[4.3.0]nonene derivatives should allow one to simplify the synthesis of such compounds.

To identify the effect of annulation of a cyclopentene moiety with a six-membered ring, we studied the cyclopropanation of

3a,4,7,7a-tetrahydro-1*H*-indene **4** which, in contrast to cyclopentadiene dimers, contains no bridging methylene moiety that determines the specific properties of the norbornene double bond. The catalytic cyclopropanation of tetrahydroindene was carried out in the presence of $Pd(acac)_2$ under conditions of *in situ* diazomethane generation from *N*-methyl-*N*-nitrosourea (MNU). To our delight, we accomplished cyclopropanation of each double bond in the molecule and even both double bonds depending on the amount of diazomethane generated. In this way, both regioisomeric monocyclopropanation products **5**, **6** and diadduct **7** were accessed (Scheme 2). Importantly, to complete cyclopropanation of both double bonds, no more than 3 equiv. of $CH_2N_2$ were required, which corresponded to the application of about 4 equiv. of technical grade MNU (see Online Supplementary Materials).[22]




**Scheme 2**

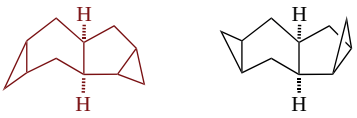
Since each of the monocyclopropane adducts **5**, **6** can be *anti*- and *syn*-configured and diadduct **7** structure can be conceived as four stereoisomers, it was necessary to find out their spatial configuration. It should be noted that preparative separation of monocyclopropanation adducts just like dicyclopropanation ones was not possible. At the same time, the use of various amounts of generated diazomethane allowed us to obtain a mixture of monoadducts **5**, **6** in one experiment and diadduct **7** (as stereoisomer mixture) in the separate synthesis (Table 1).

The conversion of tetrahydroindene **4** up to 70–75% gave monoadducts **5**, **6** as the main reaction products which were separated from other components by fractional distillation. GC/MS analysis revealed all the 4 isomers, of which only two in a ratio of (3.1–3.4) : 1.0 predominated, whereas the amount of other two was *ca.* 1–2%. Approximately the same ratio of the main isomeric monoadducts was observed in the $^1H$ and $^{13}C$ NMR spectra. Analysis of the spectra showed that the signals for the protons and C atoms at the double bond in the main component nearly coincided and corresponded to two $CH_2$ moieties. This was possible only if the cyclohexene moiety was preserved and, accordingly, the cyclopropanation of the cyclopentene double bond in the starting diene **4** took place. In the minor monoadduct, the signals for the olefinic H and C atoms diverge strongly and correlate with different fragments (with CH on one side, and with $CH_2$ on the other side), which evidenced for the cyclopropanation of the cyclohexene double bond. Thus, the catalytic cyclopropanation of tetrahydroindene with diazomethane at the first stage occurs at both double bonds, but mainly at the cyclopentene one. Unfortunately, we failed to identify unambiguously whether the resulting cyclopropane moiety had *anti* or *syn* orientation. However, based on the regularities of cyclopropanation of 1,3-cyclopentadiene and 1,5-cyclooctadiene moieties, it can be expected that the less sterically hindered *anti*-**5** and *anti*-**6** tricyclic hydrocarbons should be the main isomers.

**Table 1** The composition of the reaction mixture at different ratios of diene **4** and generated diazomethane.

| Entry | $CH_2N_2$ (equiv.) | Composition of the reaction mixture (%) | | | |
|---|---|---|---|---|---|
| | | **4** | **5** | **6** | **7** |
| 1 | 0.8 | 57 | 29 | 9 | 5 |
| 2 | 1.6 | 26 | 48 | 15 | 11 |
| 3 | 2.3 | 9 | 23 | 7 | 61 |
| 4 | 2.9 | 0.5 | 3.4 | 1.1 | 95 |

Product of double cyclopropanation **7**, according to NMR data, is a mixture of three isomers (of four possible) in approximately 8 : 1 : 1 ratio. The assignment of these isomers seems to be even more difficult due to overlapping of the majority of signals. However, if we take into account the predominant formation of *anti*-isomers in the case of monoadducts and the effect of steric factors in their further cyclopropanation, then the predominant formation of the *anti*,*anti*-isomer among diadducts **7** appears quite reasonable (see Online Supplementary Materials, Scheme S1). Most probably, *syn*,*syn*-**7** should be the missing isomer.

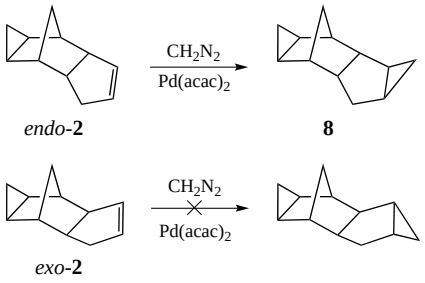



*anti*, *anti*-**7** *syn*, *syn*-**7**

When $(PhCN)_2PdCl_2$ is used as the catalyst, the conversion of the starting **4** with the same amount of diazomethane decreases by 15–20% compared to the case of $Pd(acac)_2$. However, the reaction products and their ratio remain almost the same.

Thus, the change in the geometric and, apparently, electronic parameters of the double bonds in tetrahydroindene **4** in comparison with dicyclopentadiene made it possible to efficiently perform its cyclopropanation. In order to estimate the reactivity of double bonds in cycloalkenes themselves, we studied the competitive cyclopropanation of an equimolar mixture of cyclopentene, cyclohexene, cycloheptene, cyclooctene and 3a,4,7,7a-tetrahydro-1*H*-indene **4** with diazomethane in the presence of $Pd(acac)_2$. The ratio of bicyclo[*n*.1.0]alkene derivatives $C_6H_{10}/C_7H_{12}/C_8H_{14}/C_9H_{16}$/**5**/**6** in the reaction with 0.8 equiv. $CH_2N_2$ was approximately 100 : 1 : 110 : 120 : 160 : 55. The fact that cycloheptene or cyclooctene rather well underwent cyclopropanation in the presence of $(PhCN)_2PdCl_2$ has been known previously.[17] However, the fact that cyclopentene is by two orders of magnitude more reactive than cyclohexene appears rather unexpected, especially in view of the comparison of the reactivity of the double bonds in tetrahydroindene **4**. Annulation of the cyclopentene and cyclohexene moieties leads to the activation of both double bonds, moreover, the reactivity of the cyclopentene double bond increases by about one and a half times, while the reactivity of the cyclohexene double bond increases by more than 50 times. Thus, in a series of simple cycloalkenes, the cyclopentene double bond has a high reactivity, whereas the reactivity of cyclohexene is abnormally low.

Taking the results obtained into account, we studied the cyclopropanation of dicyclopentadiene **1** (both *endo* and *exo* isomers) with excess diazomethane in the presence of $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$ more thoroughly. Cyclopropanation of the *endo*-isomer with a threefold excess of diazomethane afforded 1–3% of the pentacyclic bis-adduct **8** along with the main monoadduct *endo*-**2** (Scheme 3). In this case, after the cyclopropanation of the norbornene double bond in compound **1** is complete, the catalyst quickly decomposed to give a Pd-containing precipitate and the catalyst activity decreased sharply. In the case of $Pd(acac)_2$, which obviously gives a more stable




**Scheme 3**

catalytic form, and with a threefold excess of diazomethane, the yield of hydrocarbon **8** from *endo*-dicyclopentadiene **1** can be increased to ~25%, whereas in the case of *exo*-isomer **2**, the analogous bis-adduct is practically not formed (see Scheme 3).

The results obtained in this study show that the catalytic cyclopropanation of double bonds with diazomethane is very subtly affected by the nature of these bonds and their ability for coordination with the active form of the palladium catalyst. Even in the case of same-type double bonds in unsaturated hydrocarbons where no significant electronic effect of substituents is observed, their reactivity can differ by orders of magnitude. In this case, cyclopropanation of even low-activity double bonds can be achieved if the activity of the Pd catalyst itself is preserved, like, for example, in the case of $Pd(acac)_2$, and with a large excess of diazomethane, which in such cases mainly decomposes to give ethylene and cyclopropane. The discovered possibility of relatively facile cyclopropanation of tetrahydroindene **4**, mainly at the cyclopentene moiety, opens a way for the synthesis of a number of practically important compounds, in particular, lindenane sesquiterpenes that have a broad spectrum of biological activity.[23–25]

The authors are grateful to V. A. Korolev (N. D. Zelinsky Institute of Organic Chemistry) for GC-MS analyses, and to Yu. A. Strelenko (N. D. Zelinsky Institute of Organic Chemistry) for assistance in performing NMR analyses.

This study did not receive any grant from funding agencies in the public, commercial, or nonprofit sectors.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.09.020.

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*Received: 23rd April 2020; Com. 20/6204*