Cyclopropanation of Unactivated Alkenes

Biography

Aleksandar Stojanovic performed his undergraduate studies in chemistry at the University of Basel, Switzerland. After his diploma work with Prof. Bernd Giese, he moved to the University of Fribourg, Switzerland where he graduated under the supervision of Prof. Philippe Renaud. After a postdoctoral stay in Prof. Erick M. Carreira's lab at the California Institute of Technology, he worked for several years in different CRO's before starting his career in medicinal chemistry at Speedel Experimenta in Allschwil, Switzerland. He has been in his current position at Novartis since 2008.

Institution

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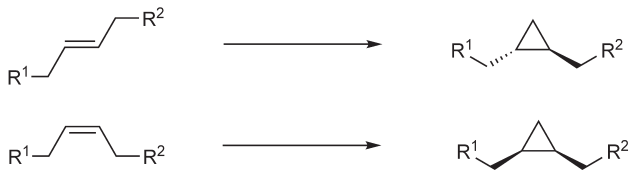
Abstract

The cyclopropanation of unactivated alkenes to prepare unsubstituted cyclopropane derivatives was investigated (Scheme 1).



Scheme 1 Preparation of Cyclopropane Derivatives from Unactivated Alkenes

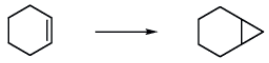
Discussion

Methods for the cyclopropanation of unactivated alkenes were researched. For this purpose two different approaches were used: (1) Full text search by keywords; (2) Reaction search by substructure.

Full Text Search

The following full text search was submitted: "cyclopropanation of unactivated alkenes". Only three hits were delivered, however, all of them were relevant to the topic. All three hits were well documented with recent and historic examples from the literature which was easily accessible by the hyperlink. I found the summary tables like the one shown in Figure 1 particularly useful:

Table 4 *Different Modifications of the Simmons–Smith Cyclopropanation of Cyclohexene To Yield Bicyclo[4.1.0]heptane* [181,203,204,211,212,214–216,221–223,228,232]



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Entry	Reagent	Conditions	Yield (%)	Ref
1	CH_2N_2, $PdCl_2(NCPh)_2$	CH_2Cl_2, −10°C, 1 h	60	[181]
2	Zn/Cu, CH_2I_2	Et_2O, 34°C, 16 h	57	[203,204]
3	Zn/CuCl, CH_2Br_2	AcCl, Et_2O, 34°C, 2 h	61	[216]
4	Et_2Zn, CH_2I_2	pentane, 20°C, 5 d	62	[232]
5	Zn/CuCl, CH_2I_2	$TiCl_4$, Et_2O, 34°C, 2 h	69	[215]
6	CH_2I_2	electrolysis, CH_2Cl_2/DMF, TBAB, 20°C	75	[223]
7	$Na_2S_2O_5$/$NaHCO_3$	*hν*, CH_2Cl_2, 20°C, 3 d	82	[222]
8	Zn	ultrasound, Et_2O, 34°C, 1 d	82	[211]
9	Et_2Zn, CH_2I_2, 2,4,6-$Cl_3C_6H_2OH$	CH_2Cl_2, −20 to 20°C, 12 h	90	[228]
10	In, CH_2I_2	MeCN, 25°C, 1.75 h	92	[221]
11	Zn/CuCl, CH_2I_2	Et_2O, 34°C, 1 d	92	[214]
12	Zn/Ag, CH_2I_2	Et_2O, 20–34°C, 3 h	95	[212]

Figure 1 Screenshot of Table Summarizing Alkene Cyclopropanation by Simmons–Smith Reaction

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Substructure search

When using the Science of Synthesis structure search functionality it is advisable to keep the search as general and as simple as possible (my first more advanced query provided no hits), e.g.:

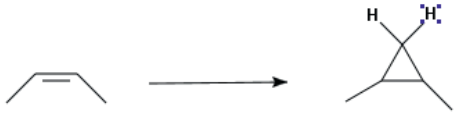

Figure 2 Example of Substructure Search for Cyclopropanation of Alkenes

This search returned a large number of hits (>10000 in my case). The hits could be easily filtered down with the refine tool on the left-hand side of the Results window (Reaction Substructure and Reaction Type Match). Some of these hits, but not all, were relevant to the search. For example some of the hits were with activated double bonds which were not relevant to my problem.

If one wants to perform a more precise substructure search, the ChemDraw plugin provided seems to be the better option for reaction drawing. My search returned for example all the hits from the text search but in addition to this, some examples which were not found by the text search were also delivered. Several of the hits were not relevant to the specific problem; however, these could be easily filtered out.

What I particularly liked about the substructure search in general is the Show Reaction hyperlink which allows you to check the relevance of each returned hit quickly.

Conclusion

Science of Synthesis Online is a very useful tool for every synthetic chemist and is complementary to other reaction databases. It also provides a short full text introduction with several relevant examples from the literature for a specific transformation. In some cases an experimental procedure is also included which can be very time-saving.

For more general searches the text search functionality is very useful giving for the most part very relevant hits for the search term. For the structure search, I found the integrated drawing program somewhat cumbersome and I personally preferred to use the ChemDraw plugin (one can also upload a molfile but this functionality was not tried out). When performing substructure searches it is advisable to do a simple, general search and refine the hit list with the filter tools afterwards.

The returned hits are listed in order of relevance and have hyperlinks to the table of contents and example reactions which can be very useful to triage the hits.