

Strategies for Chemical Reaction Searching in SciFinder

Damon D. Ridley[†]

School of Chemistry, University of Sydney, Sydney, NSW 2006 Australia

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The bibliographic, chemical structure, and chemical reaction databases produced by Chemical Abstracts Service allow a number of possibilities for chemical reaction searching. While these same databases may be searched through the STN network, many end-users find the intuitive software interface SciFinder simpler, but there still are issues to address. Searching may be performed through keywords, chemical structures, or chemical reactions, and the answers may vary with respect to precision and comprehension. Often combinations of search options may be needed to best solve the problem. Retrosynthetic analyses are easily performed in the chemical reaction database and can give unique insights into synthetic alternatives.

INTRODUCTION

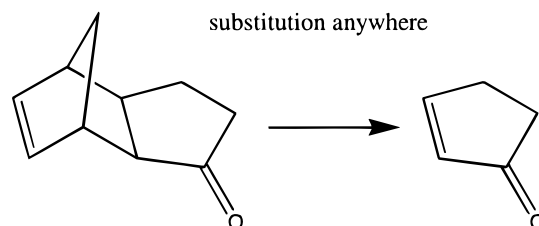
Particularly in the second half of the past century, so many advances were made in synthesis that chemists now have tools to effectively solve nearly all problems. However the vast array of methods available cannot easily be recalled, and commonly chemists need many resources to help solve specific problems. Many electronic databases have been built to assist with retrieval of chemical reaction information, and several publications report on general issues and comparisons of databases,^{1–10} on the Beilstein reaction database,^{11–14} and on the CAS database.^{15–18}

A comprehensive source of chemical reaction information is contained within the CAS bibliographic, structure, and reaction databases.¹⁹ While some problems may conveniently be solved only through the full command language functionality on the STN Network, many scientists are turning to the front-end interface SciFinder²⁰ and its academic version, SciFinder Scholar,²¹ for solution of everyday problems. The fundamental intent of SciFinder is that scientists can obtain good answers with limited knowledge of search mechanics, and through its “point and click” mode of operation it certainly achieves this goal. However, the bibliographic, chemical structure, and chemical reaction databases searched within SciFinder are very different, and it is essential that searchers understand a little about the databases being searched.

The search options relevant to retrieval of chemical reaction information are summarized in Table 1, and the first thing to understand is the time period and the coverage of the database involved. For example, if the searcher is looking for a reaction likely to be described before 1985, then there is little point in searching for it in the CAS reaction database.

Once the implications of the time period and coverage are understood, it is necessary to understand how to search for reaction information in the different databases, and in this paper we work through a few basic problems to illustrate some issues of chemical reaction searching. The first problem relates to the masking of the double bond in cyclopentenones

through Diels–Alder/retro-Diels–Alder chemistry. In particular we are interested in reactions of the following type:



CHEMICAL REACTION DATABASE

While reactions from over 100 serials are covered, since 1991 only structurally representative examples are entered, and the selection is based on author emphasis and yield. Because of this, it is better to search for broader reaction types rather than specific reactions—for example those where all substitution is blocked.

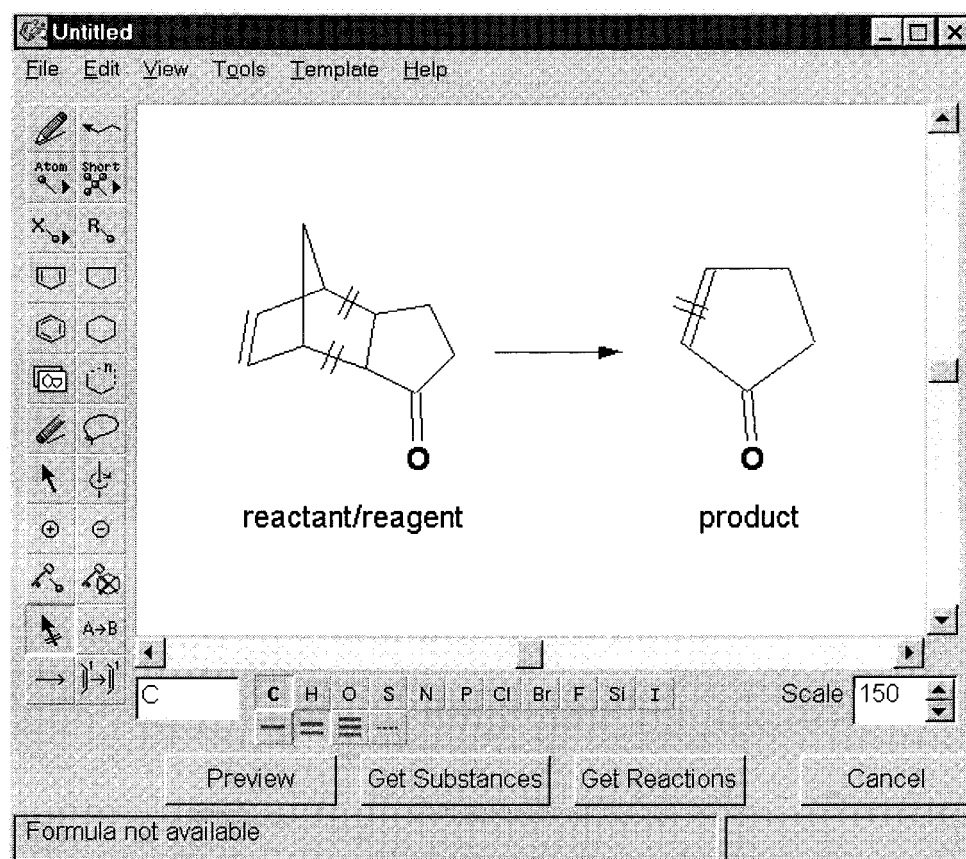
The key to the reaction database is precision since only in this database can the specific role(s) of the substance(s) be related exactly, with atom and bond mapping capabilities enabling further precision in answer sets. Chemists would quickly determine that the reaction to be searched is as shown in Figure 1.²² However, when **Get Reactions**²³ is chosen, the system comes up with a message that SciFinder cannot complete the search, and SciFinder suggests an “autofix” [The searches were originally performed in January 2000. At proof stage (July 2000) the search process had been modified and “autofix” was no longer necessary. Forty-five relevant reactions were now retrieved.]. The point here is that the search algorithm first proceeds through a screening process, and if too many potential reactions pass the screen test, the full search will not complete.²⁴

If the autofix is chosen, the rings will be isolated and all chain atoms/bonds will be specified chain values only.²⁵ This means that the answers will be restricted to isolated cyclopentenones only, but, presuming this is satisfactory at least in the first instance, the search can proceed. Twenty-eight records result, and one is shown in Figure 2. From here **Get References** takes the searcher into the CAS bibliographic

[†] Telephone: +61 2 9351 2180. E-mail: d.ridley@chem.usyd.edu.au.

Table 1. CAS Databases Searchable for Reaction Information in SciFinder

search option through SciFinder	database searched	time period	articles covered
Explore by Research Topic or Refine by Research Topic	CAS bibliographic database (CAPLUS)	1967–	Over 8000 serials and patent documents from over 30 countries
Explore by Chemical Substance (Chemical Structure), then Get Substances	CAS substance database (REGISTRY)	1967–	Note: once substances have been found, reactions are searched in the CAS bibliographic database
Explore by Chemical Substance (Chemical Structure), then Get Reactions	CAS reaction database (CASREACT)	1985– (serials) 1991– (patents)	over 100 of the key synthetic serials (but not reactions involving inorganic or coordination compounds, or polymers)

**Figure 1.** Reaction query for retro Diels–Alder reaction (bonds broken/formed in reaction specified).

database, from which either the CAS bibliographic record (Figure 3) can be displayed or else readily apparent and quick links to the original article in electronic format can be pursued, provided the searcher has access via an appropriate licensing agreement.

The original reaction search was actually performed in the CAS reaction database in which all structures are coded, and in which all participating bonds are tagged. With the possible exception of the autofix issue, every aspect of this search proceeds entirely as the searcher would expect. Indeed, in searching the CAS reaction database on SciFinder, there really is little need for training on how to proceed; it just takes a little thought on how to ask the right question in the first instance.

Still the following need to be remembered:

- (a) The database contains records from 1985 onward.
- (b) Single and multistep reactions are searched automatically.
- (c) In this case locking the rings and chains may have deleted answers of the general type of interest.

(d) The bonds in the query were specified as either single or double.²⁶

(e) All ring atoms were carbon atoms, although inclusion of variable atoms could have been made if required.

BIBLIOGRAPHIC DATABASE

While the reaction database in this case probably gave enough relevant information on which to proceed, in other cases (possibly because of the time period, or journals covered, or system limits for structure based queries, or indexing issues²⁷) the searcher will need to explore alternative options. Because of its much larger coverage, the CAS bibliographic database may be searched but the greater comprehensiveness may come at the cost of precision.

Additionally, many aspects of the content of the bibliographic database and of the mechanics of the search performed by SciFinder need to be understood. Content can be appreciated by looking at a few relevant articles, while the mechanics may be appreciated by looking very closely at the list of candidates that SciFinder produces following an initial **Explore by Research Topic**.

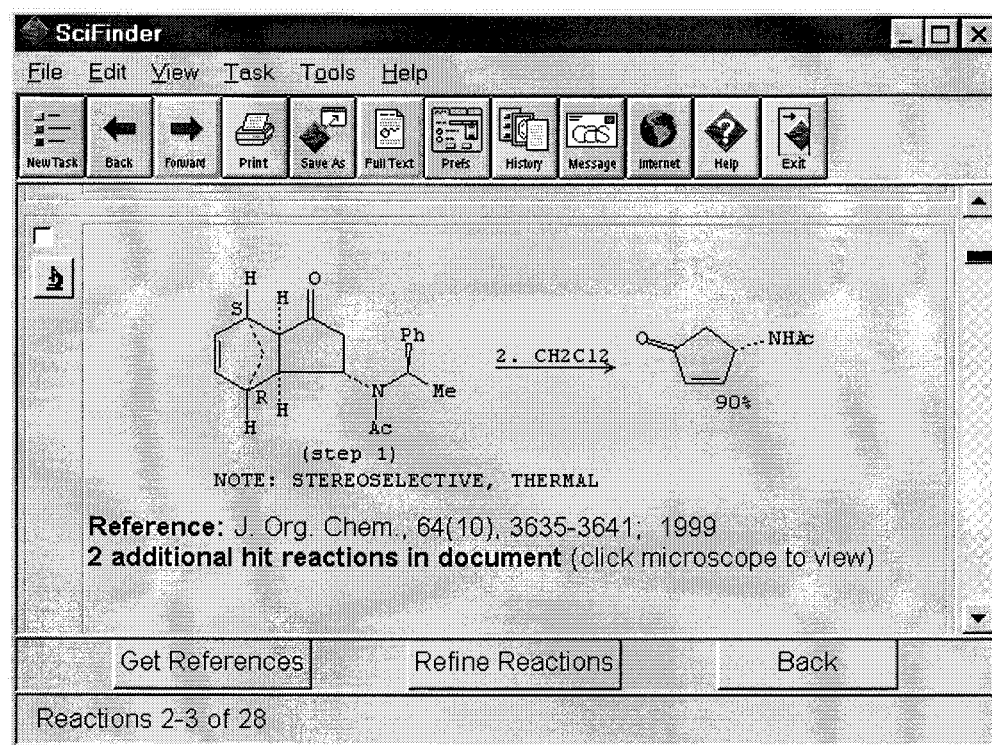


Figure 2. Sample answer for retro-Diels–Alder search from SciFinder.

Table 2. Search Options in the Bibliographic Database Searched in SciFinder

section of record	origin of entry	how searched in SciFinder
words in titles and abstracts; text modifying phrases	author ^a	through Research Topics either under Explore by Research Topic or Refine by Research Topic
CAS Chemical Reaction Index Headings	indexer	Through Analyze option then Index Entries
Supplementary Terms	indexer	Through Analyze option then Supplementary Terms
CAS Registry Numbers	indexer	Preferably through Explore by Chemical Substance
CAS Roles	indexer	Through Explore by Chemical Substance and then the list of roles which appears at Get References

^a Titles and abstracts may be modified by the indexer for patents, and text modifying phrases based on author terminology are entered by the indexer.

Careful examination of the information in Figure 3 will reveal much about the content of the database. The title and abstract, which are written by the author, contain considerable technical information but these sections are not written by authors with any specific or standardized policies in mind. On the other hand, the indexing is written subject to specific policies, and it is noted in this case that there is at least one index heading (Diels–Alder reaction) which relates to chemical reaction information. Indeed CAS applies many hundreds of index headings relating to chemical reactions, and these can be particularly useful in the retrieval of reaction information. The trick is to identify the relevant headings (see below).

The data in Figure 3 indicate two other important indexing issues, namely, the use of CAS Registry Numbers for substances and the association of the CAS Roles with these CAS Registry Numbers. The roles RCT and PREP are of special significance in reaction searching.

The words in parentheses after the index headings or CAS Registry Numbers are termed “text modifying phrases”. These are often author-related terms to highlight the specific aspect of the article related to the index heading, and we like to think of them as “author-related terms which enhance

the index heading”. Some of the text modifying entries, for example “retro” associated with the heading Diels–Alder reaction, are in fact index subheadings which should also be noted for search purposes. Finally, the Supplementary Terms are usually very specific entries which the indexer has selected as especially important to the article, and we like to think of them as “index-related terms which enhance the title”.

Accordingly chemical reaction information may be found in the CAS bibliographic database through a number of parts of the record. If the searcher needs to use these entries, then SciFinder has specific sections through which they may be entered, and Table 2 gives the relevant parts and how specifically they can be searched.

When searching for reaction information under **Explore by Research Topic**, a simple search should first be tried. Provided that the basic rules for setting up Research Topic queries are followed,²⁸ a series of candidates will be listed in which the topics are “closely associated” or “anywhere in the record”. Simple topic searches should definitely be considered as a first option for finding information on general processes, for which reaction diagrams may be difficult to construct, and usually excellent answers are retrieved.

Bibliographic Information

Enantioselective Synthesis of 4-Acetylamino-cyclopent-2-en-1-ols from Tricyclo[5.2.1.0^{2,6}]decenyl Enaminones. Precursors for 5'-Norcarbocyclic Nucleosides and Related Antiviral Compounds. Ramesh, Namakkal G.; Klunder, Antonius J. H.; Zwanenburg, Binne. Department of Organic Chemistry NSR Center for Molecular Structure Design and Synthesis, University of Nijmegen, Nijmegen, Neth. *J. Org. Chem.* (1999), 64(10), 3635-3641. CODEN: JOCEAH ISSN: 0022-3263. Journal written in English. CAN 131:58605 AN 1999:268702 CAPLUS

Abstract

An efficient synthesis of both (1S,4R) and (1R,4S)-4-N-acetylamino-1-benzoylcyclopent-2-enes was accomplished starting from enantiopure 5-(1'-phenylethylamino)-endo-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-ones. N-Acetylation of the above intermediates followed by single electron-transfer redn. using lithium in liq. ammonia afforded diastereomeric mixts. of β -amino ketones and the resp. enantiomers in high yields and with high diastereoselectivity. In this redn. process, the enaminone double bond is reduced with the concomitant removal of the α -methylbenzyl group as the chiral auxiliary. Thermolysis of the resp. diastereomeric mixts. of β -amino ketones in the gas phase (FVT) or in soln. afforded 4-(acetylamino)-2-cyclopenten-1-ones in high optical and chem. yields. Acidic hydrolysis of the latter gave (R)-(+)-4-aminocyclopentenone as its hydrochloride. Stereoselective redn. of 4-(acetylamino)-2-cyclopenten-1-ones using sodium borohydride and cerium chloride heptahydrate furnished an amido alc., which was isolated and characterized as its benzoyl deriv.

Indexing -- Section 24-4 (Alicyclic Compounds)**Thermal decomposition**

(one electron-transfer; stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

Diels-Alder reaction

(retro; stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

Stereochemistry**Stereoselective reduction****Stereoselective synthesis**

(stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

227941-44-8P

Role: SPN (Synthetic preparation); PREP (Preparation)

(prepn. of)

185542-09-0, 204275-02-5

Role: RCT (Reactant)

(stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

204274-99-7P, 204275-05-8P, 204275-11-6P, 204275-13-8P, 205675-76-9P, (1R-cis)-N-(4-Hydroxy-2-cyclopenten-1-yl)acetamide, 227941-40-4P, 227941-41-5P, 227941-42-6P, 227941-43-7P, 227941-45-9P, 227941-48-2P

Role: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

227941-46-0P, 227941-47-1P, 227941-49-3P, 227941-50-6P

Role: SPN (Synthetic preparation); PREP (Preparation)

(stereoselective prepn. of (acetylamino)cyclopentenols from tricyclo[5.2.1.0^{2,6}]decenyl enaminones)

Supplementary Terms

cyclopentenol acetylamino stereoselective synthesis; hydroxycyclopentenyl acetamide prepn stereochem

Figure 3. Example of record from the CAS bibliographic database.

Table 3. Typical Answer Sets from Research Topic Search for Chemical Reactions in SciFinder

Query "I am interested in ..."	no. of hits where concepts are "closely associated"
catalysts for asymmetric Heck	56
synthesis (preparation) of dihydropyridines by Hantzsch	91
metal removal (demetalation) of porphyrins	93
reaction of propiolates with triethylamine (trimethylamine)	5
synthesis (preparation) of bromo tropolones	12
reviews on preparation (synthesis) of transition metal carbonyls	34
combinatorial libraries (combinatorial synthesis) of thiazoles	18

For example, Table 3 gives some representative answer sets when **Explore by Research Topic** is used. The word "reaction" or "preparation" may be entered in the question—although the list of candidates should be reviewed since candidates without these words may be very relevant. The point is that quick topic searches such as this almost invariably provide answers that provide an excellent introduction to the literature.

While the examples in Table 3 give relatively precise and comprehensive coverage, and manageable answer sets are immediately obtained, in other cases large answer sets result and refinement tools are needed. For example some initial options for the problem of masking cyclopentenones discussed above may be as follows:

(a) "I am interested in retro Diels–Alder with cyclopentenones".

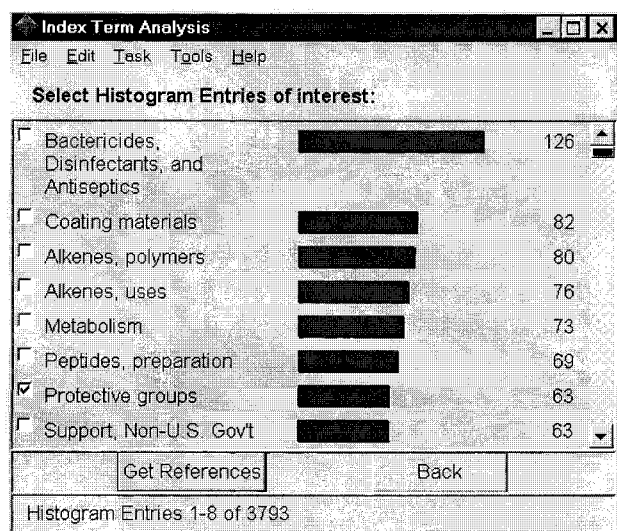


Figure 4. Option under Analyze. This allows Index Terms to be listed, and from here refinement of answers by Index Term Headings is possible.

- (b) "I am interested in protection by Diels–Alder".
 (c) "I am interested in protection of double bonds (alkenes)".

In all cases, many answers are retrieved and refinements with further topics, which may be author- or index-based, need to be conducted. For example, the third topic above gives over 2000 hits where the terms are "closely associated". To take advantage of index headings in the refinement, it is

necessary first to identify relevant terms. Accordingly once the bibliographic answers have been obtained through **Get References**, the button **Analyze** is chosen followed by **Index Term** and the result is a histogram of Index Terms (Figure 4).

The term "protective groups" seems particularly relevant, and when **Get References** for these is selected, the 63 records are retrieved. Some of these are the same as those in the chemical reaction search obtained earlier, but others, because of the time period involved or the serial coverage, are new, and Figure 5 gives an example.

In a similar way, an initial **Explore by Research Topic** "I am interested in cyclopentenones" followed by analysis of the index terms reveals the heading Diels–Alder Reaction. The answer set of 75 is then refined with "retro", and one of the key answers, shown in Figure 6, dates from 1979. The point is that the **Analyze** option may be used to focus the search, and specific Index Headings are particularly useful.

CAS REGISTRY NUMBERS

CAS Registry Numbers and CAS Roles offer another chemical reaction approach (Table 2), and here the starting point is **Explore by Chemical Substance** followed by **Chemical Structure**. It should be remembered that CAS Registry Numbers may be refined either by preparation or reactant, and a decision must first be taken as to which option to choose. It turns out that while there are approximately equal numbers of records listing CAS roles Preparation or

Bibliographic Information

Protection of multiple C-C and single C-H bonds in organic synthesis. Svoboda, Jiri; Palecek, Jaroslav. Ustav Org. Chem., Vysoka Skola Chem-Technol., Prague, Czech Rep. Chem. Listy (1994), 88(2), 86-98. CODEN: CHLSAC ISSN: 0009-2770. Journal; General Review written in Czech. CAN 121:204491 AN 1994:604491 CAPLUS

Abstract
 A review with 78 refs. The protection and deprotection of the double and triple C-C bond (section 2) and single C-H bond (section 3) are surveyed. Used methods, agents, and reaction conditions are summarized. Attention is drawn to illustrative, preparatively applicable and verified procedures in the synthesis of compds. of various structures.

Indexing -- Section 21-0 (General Organic Chemistry)
 Protective groups
 (protection of multiple C-C and single C-H bonds in org. synthesis)
 Bond
 (carbon-carbon, protection of multiple C-C and single C-H bonds in org. synthesis)
 Bond
 (carbon-hydrogen, protection of multiple C-C and single C-H bonds in org. synthesis)
 Bond
 (multiple, carbon-carbon; protection of multiple C-C and single C-H bonds in org. synthesis)
 Synthesis
 (org., protection of multiple C-C and single C-H bonds in org. synthesis)
 7440-44-0
 Role: PRP (Properties)
 (bond, carbon-carbon, protection of multiple C-C and single C-H bonds in org. synthesis)
 7440-44-0
 Role: PRP (Properties)
 (bond, carbon-hydrogen, protection of multiple C-C and single C-H bonds in org. synthesis)
 7440-44-0
 Role: PRP (Properties)
 (bond, multiple, carbon-carbon; protection of multiple C-C and single C-H bonds in org. synthesis)

Supplementary Terms
 review protection multiple carbon org synthesis; single hydrogen carbon bond protection review

Figure 5. Sample answer from Research Topic search for protection of double bonds.

Detail of Reference 14

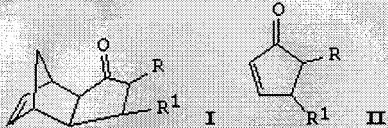
File Edit Help

Bibliographic Information

A short, convenient synthesis of cyclopentenones via derivatives of exo-dicyclopentadiene. Schore, N. E. Dep. Chem., Univ. California, Davis, Calif., USA. Synth. Commun. (1979), 9(1), 41-7. CODEN: SYNCAV ISSN: 0039-7911. Journal written in English. CAN 90:168114 AN 1979:168114 CAPLUS

Abstract

Dihydrodicyclopentadienones (R = Bu, Ph; R¹ = Me, Bu, CMe₃) were heated at 600° to give the resp. cyclopentenones II. The reaction of norbornadiene with RC≡CH (R = Bu, Ph) and Co₂(CO)₈ followed by treatment of the products with Li alkylcuprates yielded I.



I II

Indexing -- Section 24-4 (Alicyclic Compounds)

Diels-Alder reaction
(retro, of dihydrodicyclopentadienones, cyclopentenones from)

10210-68-1
Role: RCT (Reactant)
(cycloaddn. reaction of carbon monoxide from, with norbornadiene and 1-alkynes)

121-46-0
Role: RCT (Reactant)

Close

Figure 6. Sample answer from Research Topic search on retro-Diels–Alder reaction.

Reactant in the bibliographic database,²⁹ nevertheless many more substances are listed as preparations, and since in any case the substances prepared are often more complicated than the starting materials,³⁰ then more specific structures can be built and greater precision results. However in the case involving the retro-Diels–Alder reaction, the starting material is a more specific structure type and so the Reactant role is possibly preferred.

Once a structure has been built, one of the options under **Preview** is **Real-atom Attachments** which can be particularly useful when exploring possibilities with more general structures. Under this option various atom substituents are analyzed, and Figure 7 shows an example. That is, at the nonbridgehead carbon adjacent to the carbonyl group it is found that 33% of the substances have no substituent (that is a CH₂ group adjacent to the carbonyl group) and 59% have a carbon substituent. If the latter is of more specific interest, then the box next to the carbon in “Atom attachments” is checked, and a full search results in 402 substances.

Finally, **Get References** followed by selecting only answers of the following type: reactant gives 55 references, and this answer set can be easily scanned.

This procedure covers very extensive literature from 1967 onward but lacks in precision in terms of the specific bonds broken in the reaction. It also depends on two levels of indexing, namely, on the insertion of the CAS Registry Number and on the specific qualification of this Registry Number with the Reactant Role.

Note that the reaction discussed here is complicated because only relatively general structures can be built, and either large answer sets or system limit issues are met. However the problem was chosen because these issues will come up at times, and it is necessary to understand the consequences of various solutions. Nevertheless, in the majority of cases information on much more specific structures and reactions will be required, and the option of performing a substructure search through **Chemical Structure** and then getting references which have associated roles

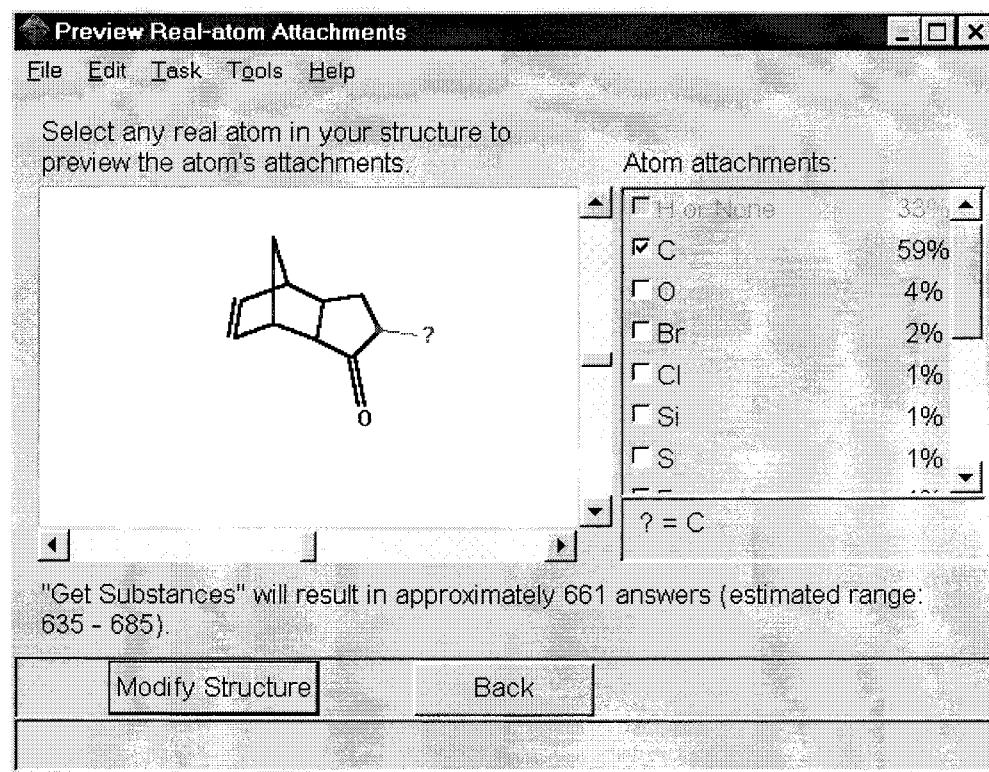


Figure 7. Result of Preview of Real-atom Attachments which provides information on substituent atoms on query structure.

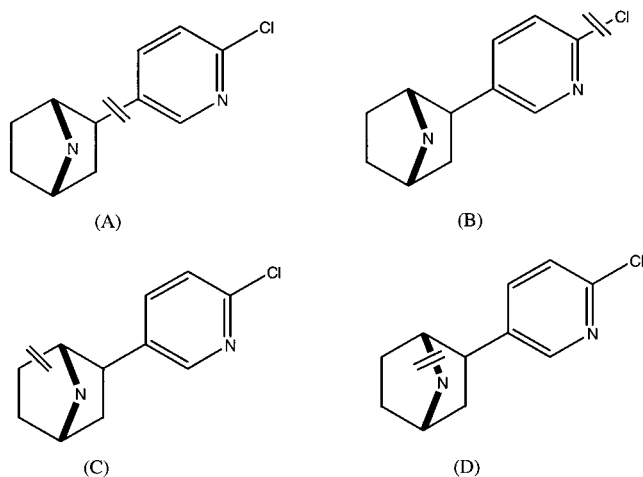


Figure 8. Examples of separate queries to explore retrosynthetic routes. For example, a search on query A would yield actual answers relating to the retrosynthetic disconnection between the two rings.

of preparation or reactant will cover a wide section of the literature back to 1967.

RETROSYNTHETIC ANALYSIS

Only two issues need to be addressed to set up excellent retrosynthetic analyses through the chemical reaction database. First, the structure needs to be drawn and the role Product selected from the **A→B** toolbox in the structure drawing program, and second the bond to be formed must be indicated. Answers for the different bond-breaking processes can be viewed in turn. For example, Figure 8 indicates four different structures which can be drawn to investigate four different routes, and currently 14, 4, 8, and 8 records are retrieved that described retrosynthetic processes A–D, respectively.

Retrosynthetic analyses starting with the bibliographic or chemical substance databases lack precision. The preferred choice is to search for preparations and then to work through answers.

CONCLUSION

The databases available through SciFinder offer a number of alternatives for searching for chemical reaction information. Specific queries may be set up through the chemical reaction database, or, for wider coverage, through the chemical substance database and restricting with the preparation or reaction roles. More general reactions are possibly better approached in the first instance through research topic queries where combinations of refinements with author- or index-based terms are possible.

ACKNOWLEDGMENT

All displays are Copyright by the American Chemical Society and are reprinted with permission. We thank Ken Ostrum and Fred Winer of the Chemical Abstracts Service for assistance.

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- (19) The databases are called CAPLUS, REGISTRY, and CASREACT, respectively, on the STN online network.
- (20) For general information see: <http://www.cas.org/SCIFINDER>.
- (21) For general information see <http://www.cas.org/SCIFINDER/SCHOLAR/index.html>.
- (22) This paper does not detail search mechanics, which in any case are intuitive in SciFinder. However, the structure is drawn through the **Chemical Structure** option, and the cross-lines indicate that the requirement is that these bonds be either formed or broken in the reaction.
- (23) SciFinder radio buttons are displayed in bold text in this article.
- (24) In this case, the structure drawn has essentially carbon–carbon and carbon–oxygen bonds in relatively common ring systems, and those few screens generated are common to many reactions.
- (25) The defaults are that ring atoms may be in isolated or fused ring systems and that chain atoms/bonds may be in chains or rings.
- (26) Any bonds could have been changed to unspecified if required, although in this example allowing for single or double bonds in the structures drawn would not have been sensible from a chemical point of view (for example, cyclopentadieneones or double bonds at bridgeheads are not realistic).
- (27) Chemical structure and reaction databases are wholly constructed by database producers and are subjected to indexing policies. Indexing policies for representations of structures in the CAS reaction database are entirely intuitive. However, only those reactions that are new and adjudged critical to the main emphasis of the original article (and not all the reactions) will be entered in the database.
- (28) Ridley, D. D. Teaching the Basics of SciFinder Scholar. *J. Chem. Educ.*, submitted for publication.
- (29) Just over 2.5 and 2.2 million records are listed with the role Preparation and Reactant, respectively.
- (30) This of course is true when new carbon–carbon bonds are formed, although is not necessarily true when simple functional group transformations are involved.

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