



## CARD (Computer-Aided Reaction Design) program as a heuristic tool to propose new reactions. Application to the de Mayo reaction

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### ABSTRACT

We present the CARD program which is a new approach in the field of Computer-Aided Reaction Design. The objective of CARD is to generate new reactions from the combination of two other reactions.

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## 1. Introduction

If the field of computer-aided organic synthesis has been widely studied,<sup>1</sup> less has been realized for finding new reactions. Nevertheless, the general description of reactions developed for the SYNGEN,<sup>2</sup> EROS,<sup>3</sup> and SOS<sup>4</sup> programs may allow the discovering of new reactions, but to our knowledge only three programs have been specifically developed for the design of new reactions: IGOR (Interactive Generation of Organic Reactions)<sup>5</sup> and SYMBEQ (Symbolic EQUation)<sup>6</sup> which generate all basic reactions from a general scheme and RENE (REaction geNERator)<sup>7</sup> which constructs all the possible combinations from a given set of atoms. With CARD (Computer-Aided Reaction Design) we are developing a third approach. The idea of this program derives from the observation of the de Mayo reaction (Scheme 1).<sup>8</sup>

This reaction is the combination of two elementary reactions: first, a [2+2] cycloaddition, followed by a retro-aldol reaction. The interesting feature of this reaction is that it allows to enlarge a ring by two atoms to build medium-sized rings (Scheme 2).<sup>8</sup>

Our idea was to develop a program which tries to generate a new reaction by combining two other reactions such as for the de Mayo one. This program will not generate directly new reactions, but only partial substructures (see Scheme 1), so it needs the active participation of the chemist to check if the generated substructures could lead to interesting reactions.

## 2. Program

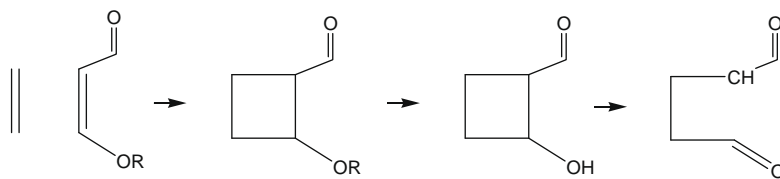
To develop CARD let us consider the two reactions involved in the de Mayo one (Scheme 3).

In these schemes the bold bonds are the ones which are in common in substructures **2** and **3**. So in a first approach if we consider two reactions  $A \rightarrow B$  and  $C \rightarrow D$ , CARD has to search for a common bond in the substructures B and C, then it has to build the environment of these bonds to generate the new reaction.

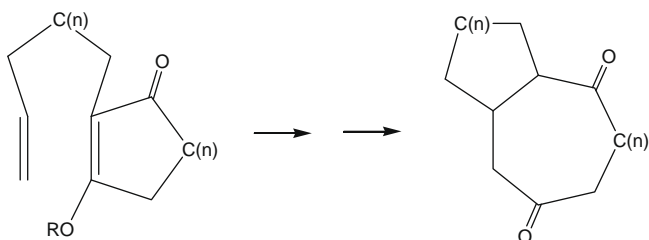
For testing CARD we used these two reactions ([2+2] and retro-aldol). Since the program works with two reactions, it generates solutions where the intermediate reaction ( $C-OR \rightarrow C-OH$ ) is not present, so, for the sake of clarity this step has been added in Scheme 4 which depicts the four solutions found by CARD.

The de Mayo reaction was found (reaction **5**) and three other variants were generated. Reactions **6** and **7** are similar and do not seem to be interesting since the four-membered ring is still present, but reaction **8** gives an interesting variation of the reaction since the  $C=O$  and the OR groups are not in the same substructure. The first step of this sequence has been described in several intramolecular reactions (Ref. 9 lists some recent articles). In the first step of reactions **7** and **8** two isomers can be formed. In this first version, CARD generates only the solution leading to the desired reaction. The chemist has to verify the validity of the proposed schemes. At first glance reaction **8** does not provide anything new since it generates the same final substructure as the original de Mayo reaction. The work of CARD was done; the one of the chemist starts here as indicated in the introduction of this Letter.

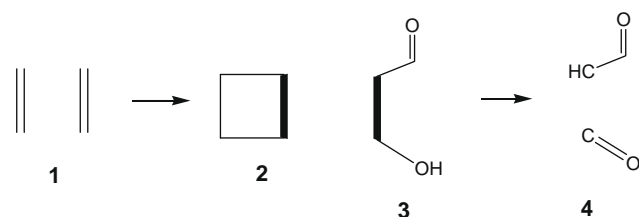
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E-mail address: [rene.barone@univ-cezanne.fr](mailto:rene.barone@univ-cezanne.fr) (R. Barone).



Scheme 1.



Scheme 2.



Scheme 3.

### 3. Discussion

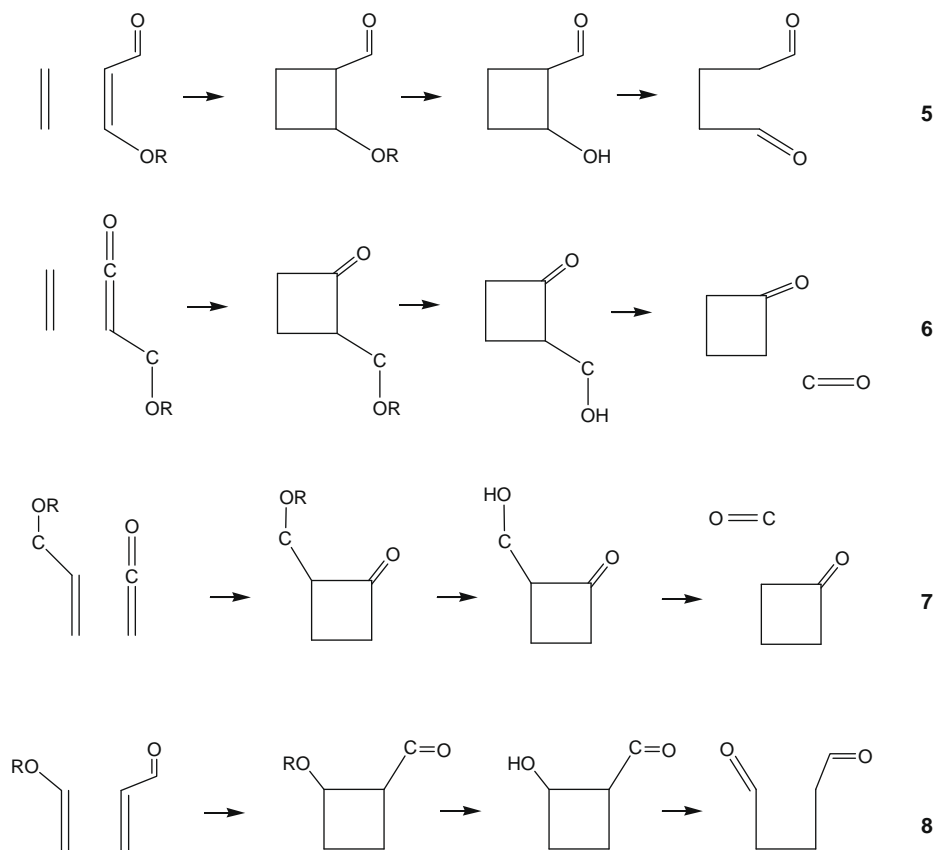
With this reaction in mind, we ask ourselves: what kind of structures is it possible to build from reaction **8**? The first idea which arises is to generate a ring (Scheme 5).

This solution seems new by the position of the OR group but it yields to structures similar to the 'classical' de Mayo reaction.

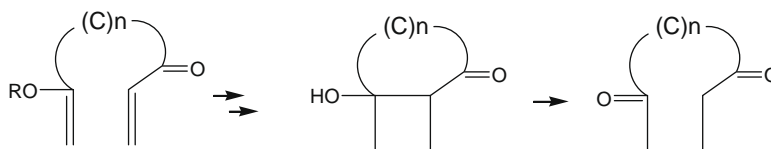
Then, after a discussion in our group, we had a new idea: why not to combine this scheme with the 'standard' de Mayo one? Scheme 6 shows the result of this combination.

We have searched the Beilstein<sup>®10</sup> and CAS-SciFinder<sup>®11</sup> databases and we were delighted that this scheme had not been described! This approach, which combines a [2+2] and two retroaldol reactions, could be a new way for the construction of medium-sized rings.

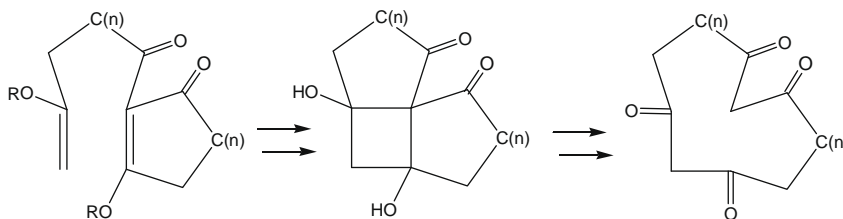
The aim of this program was to combine two reactions for generating a new one. In the example of the de Mayo reaction described here, this goal has been accomplished. It should be clear that this principle could be applied to other reactions to get an extended use of CARD.



Scheme 4.



Scheme 5.



Scheme 6.

#### 4. Conclusion

This first version of CARD is encouraging since at its first attempt a new approach has been suggested from the de Mayo reaction. In this version, CARD searches for only one common bond inside substructures **2** and **3** (Scheme 3). New developments are planned such as searching for two or more common bonds; we also plan to develop automatic and interactive options.

CARD is written in Visual Basic for PCs. Input of reactions and results are done through a full graphic interface. The exe file is about 900 Ko. It is available upon request.

#### References and notes

1. Barone, R.; Chanon, M. Computer Assisted Synthesis Design. In *Chemoinformatics. From Data to Knowledge*; Gasteiger, J., Ed.; J. Wiley, 2003; Vol. 4, pp 1428–1456.
2. Hendrickson, J. B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 323–334.
3. Ihlenfeldt, W. D.; Gasteiger, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2613–2633.
4. (a) Barone, R.; Chanon, M.; Metzger, J. *Tetrahedron Lett.* **1974**, *32*, 2761–2764; (b) Azario, P.; Barone, M.; Chanon, M. *J. Org. Chem.* **1988**, *53*, 720–724.
5. (a) Bauer, J.; Herges, R.; Fontain, E.; Ugi, I. *Chimia* **1985**, *39*, 43–58; (b) Herges, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 255–276.
6. (a) Zefirov, N. S.; Trachtch, S. S. *Anal. Chim. Acta* **1990**, *235*, 115–134; (b) Zefirov, N. S.; Baskin, I. I.; Palyulin, V. A. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 994–999.
7. Barone, R.; Arbelot, A.; Baldy, A.; Chanon, M.; Gallo, R. *Rev. Roum. Chim.* **1993**, *36*, 994–999.
8. (a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41–48; (b) Meier, H.. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller, E., Ed.; Georg Thieme: Stuttgart, 1975; Vol. 4/5b, p 924; (c) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135–141; (d) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473; (e) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003–2029; (f) <http://rawalgroup.uchicago.edu/litmeetings/demayo.htm> by J. MacKay.
9. (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668–3669; (b) Boxer, M.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 3127–3129; (c) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Perez-Fernandez, M. *Org. Lett.* **2005**, *7*, 3597–3600; (d) Takasu, K.; Nagao, S.; Ueno, M.; Ihara, M. *Tetrahedron* **2004**, *60*, 2071–2078.
10. (a) <http://www.beilstein.com>; (b) *The Beilstein Online Database. Implementation, Content and Retrieval*; Heller, S. R., Ed. ACS Symposium Series, 436; Am. Chem. Soc.: Washington, DC, 1990.
11. <http://www.cas.org/products/scifindr/index.html>.