

# Comparative Study of the Effects of Aqueous Micellar Media Formed by Amphiphilic Ionic Liquids and Conventional Surfactants on Reactions of Synthetic Interest <sup>†</sup>

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**Abstract:** For polar Diels–Alder (DA) reactions, one of the most relevant aspects is its dependence on the reaction media; thus, in this work, the objective is to analyze the effect of aqueous micellar systems on the synthesis of compounds of biological interest. Based on the system formed by isoprene and 2-nitrofurane, the experiments were carried out in micellar media formed by amphiphilic ionic liquid (*N,N*-dodecylmethylimidazolium bromide) and by conventional surfactants (SDS and CTAB). In this sense, there are few studies that involve DA reactions in micro-heterogeneous systems. The challenge is to have the knowledge about the behavior of ILs in order to take advantage of all their potentialities in order to replace a toxic molecular solvent with ILs, which allows the development of a methodology framed within the concepts of Green Chemistry.

**Keywords:** ionic liquids; amphiphilic; micelles; Diels–Alder



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## 1. Introduction

The development of high-efficiency synthetic methodologies that can be used in the construction of carbogenic and heterogenic skeletons corresponding to compounds with high pharmacological and/or biological applicability represents a unique attraction of organic chemistry. In this direction, it can be thought that the incorporation into synthesis schemes of a series of cycloaddition reactions makes it possible to achieve a broad development and great potential, especially for its “economy in stages” [1].

Due to the synthetic applicability of cycloaddition reactions, there is a continuing interest in their exploration and in the study of simple strategies for the synthesis of very diverse molecules.

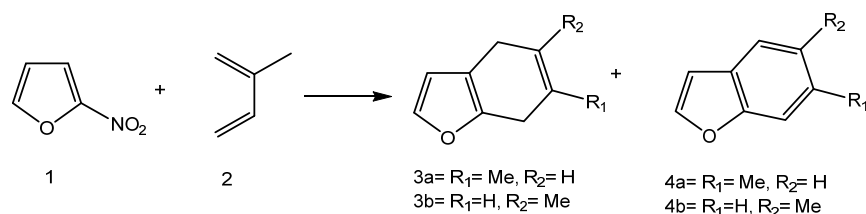
The exploration of new, more environmentally friendly reaction conditions such as the use of non-conventional solvents will, among others, reduce or eliminate the use of organic solvents and optimize the consumption of all reagents used in reactions.

Given our experience in Diels–Alder (DA) reactions, we have extended our studies developed in molecular solvents to ionic liquids (ILs) [2]. The DA reaction is of great value in organic synthesis and is a key step in the construction of compounds containing six-membered rings. Studies have appeared reporting beneficial effects of micellar systems on the yield of DA reactions [3]. Solubilization of the DA reaction partners in the micelles could offer a solution for improving the otherwise limited solubility of diene and dienophile in water. In this sense, we have started studies of these reactions in ILs with amphiphilic character of the type  $C_n\text{mim}$ . For the maleic anhydride/isoprene reactive pair in these micellar systems good yields at room temperature and 24/48 h were obtained [4]. Due to these results, it is of interest to expand these reaction media to other systems such

as 2-nitrofuran and isoprene. In this direction, there are few works involving DA cycloaddition reactions in micro-heterogeneous systems. In this regard and for comparative purposes, the objective is to analyze the effect of aqueous micellar systems formed by *N,N*-dodecylmethylimidazolium bromide [Domim] [Br] in a polar DA reaction taken as a reference, as well as in aqueous micellar systems formed by conventional surfactants such as sodium dodecyl sulphate (SDS) and hexadecyltrimethylammonium bromide (CTAB).

## 2. Results and Discussion

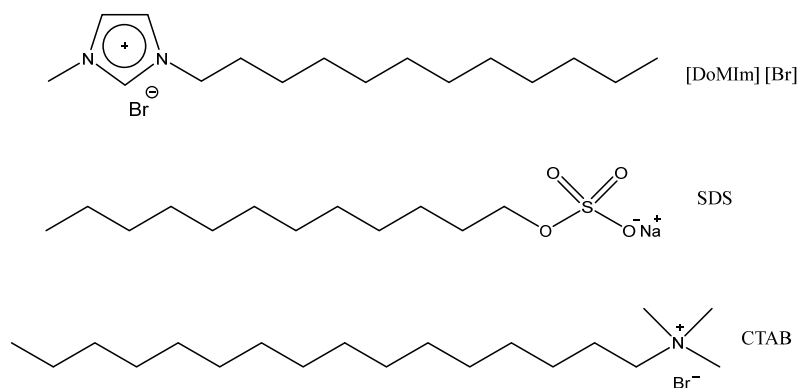
ILs are ‘more than an ionic solvent’, and their role within a physico-chemical system is far from passive, leaving behind the traditional thinking of ‘dissolving solutes’ or ‘homogenizing’ a reaction medium. That is why our working group has long been committed to developing experiences with aqueous reaction media in which micelles are generated from ILs with an amphiphilic character. The reaction under study is a polar Diels–Alder cycloaddition, which is taken as a reactive model for its synthetic relevance. The reactive pair consists of isoprene 1 and 2-nitrofuran 2 (Scheme 1). These reactions are proceeded by addition of the diene selectively to the nitro-substituted double bond of the furan to give a mixture of dihydrobenzofurans **3a**, **3b** and benzofurans **4a**, **4b**, respectively. These reactions proceeded by addition of the diene selectively to the nitro-substituted double bond of the furan. All addition products showed extrusion of the nitro group as nitrous acid.



**Scheme 1.** Diels–Alder reaction in micellar solution.

These reactions could be considered a domino process that is initialized by a polar DA reaction; the latter concerted elimination of nitrous acid from the [2 + 4] cycloadduct yields the corresponding observed reaction products. The irreversible character of the extrusion of nitrous acid makes the domino reaction thermodynamically feasible [5–7].

This system was put to react in different micellar aqueous media generated with ILs amphiphilic *N,N*-dodecylmethylimidazolium bromide ([DoMIm] [Br]) and conventional surfactants as sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) for comparative purposes (Figure 1).



**Figure 1.** Micelle forming surfactants used.

For [Domim] [Br] it was possible to determine the value of the CMC in the specially formed systems when the counterion is  $\text{Br}^-$  concluding that the organization in micelles

depends not only on the length of the alkyl chain but also on the contrail, and therefore, an appropriate combination between the two variables is required [8].

General procedure for the Diels–Alder reactions.

The temperature, the length of the reaction, and the diene/dienophile ratio are indicated in Table 1. The micellar medium concentration employed were: SDS and CTAB (Critical Micellar Concentration CMC), and [Domim] [Br] values slightly higher than CMC were used. The DA reactions were carried out in a glass reactor with magnetic stirring. After the reaction time was completed, the cycloadducts were extracted with ethyl acetate and purified using classical column chromatography using alumina as stationary phase and hexane-ethyl acetate mixtures as eluent [9]. The reaction products were analyzed by spectroscopic methods.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were recorded on a Bruker 300 MHz instrument with deuterated solvent and tetramethylsilane (TMS) as an internal reference. FTIR spectra were taken on neat samples by using a Shimadzu IR Affinity-1 (ATR-FTIR) spectrometer.

**Table 1.** Comparison of DA reaction in different aqueous micellar media.

| Reaction Media                             | Diene/Dienophile Ratio | Conditions  | Products   | Yield % |
|--------------------------------------------|------------------------|-------------|------------|---------|
| [DoMIm] [Br]/H <sub>2</sub> O <sup>a</sup> | 4:1                    | 120 °C/48 h | 3a,b; 4a,b | 32%     |
| [DoMIm] [Br]/H <sub>2</sub> O <sup>a</sup> | 4:1                    | 90 °C/48 h  | 3a,b; 4a,b | 15%     |
| [DoMIm] [Br]/H <sub>2</sub> O <sup>a</sup> | 6:1                    | 90 °C/72 h  | 3a,b; 4a,b | 20%     |
| SDS/H <sub>2</sub> O <sup>b</sup>          | 4:1                    | 120 °C/48 h | 3a,b; 4a,b | 20%     |
| SDS/H <sub>2</sub> O <sup>b</sup>          | 4:1                    | 90 °C/48 h  | 3a,b; 4a,b | 15%     |
| SDS/H <sub>2</sub> O <sup>b</sup>          | 6:1                    | 90 °C/72 h  | 3a,b; 4a,b | 33%     |
| CTAB/H <sub>2</sub> O <sup>b</sup>         | 4:1                    | 120 °C/48 h | 3a,b; 4a,b | 20%     |
| CTAB/H <sub>2</sub> O <sup>b</sup>         | 4:1                    | 120 °C/72 h | 3a,b; 4a,b | 22%     |
| CTAB/H <sub>2</sub> O <sup>b</sup>         | 6:1                    | 90 °C/48 h  | 3a,b; 4a,b | 12%     |

<sup>a</sup> values slightly higher than CMC (Critical Micellar Concentration); <sup>b</sup> CMC.

Taking into account previously reported yields for the DA reaction of 2-nitrofuran and isoprene (diene:dienophile ratio 12:1/benzene/150 and 200 °C/72 h), the yields obtained by employing aqueous micellar media of amphiphilic ionic liquid and traditional surfactants with lower temperature –90 and 120 °C and diene:dienophile ratio of 6:1 and 4:1, were similar. In general, the higher temperature generated better yields in almost all the aqueous media tested.

### 3. Conclusions

The results obtained so far indicate that the micellar system of [DoMIm] [Br] produces approximately the same yields as those obtained through the use of micellar systems of traditional surfactants. These conditions are far softer than traditional thermals [5,9].

Decision making to replace traditional solvents with others is a critical point of control. The challenge is to have the finished knowledge about the behavior of an LI to be able to take advantage of all its potentialities in order to replace a toxic molecular solvent with an LI that allows us to develop a methodology framed within the concepts of Green Chemistry.

**Author Contributions:** J.B.S.: Doctoral student responsible for the synthesis of dienophiles and to carrying out the Diels–Alder reactions using different experimental conditions. C.G.A.: Researcher responsible for the synthesis of ionic liquids, design of experiences and evaluation of results. C.D.R.: Researcher responsible for the design of cycloaddition reactions in aqueous media, synthesis of dienophiles and evaluation of results. All authors have read and agreed to the published version of the manuscript.

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## References

1. Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, NY, USA, 1998; p. 30.
2. Della Rosa, C.; Ormachea, C.; Kneeteman, M.N.; Adam, C.; Mancini, P.M.E. Diels-Alder reactions of N-tosylpyrroles developed in protic ionic liquids. Theoretical studies using DFT methods. *Tetrahedron Lett.* **2011**, *52*, 6754–6757. [CrossRef]
3. Otto, S.; Engberts, J.B.F.N. Diels-Alder Reactions in Micellar Media. In *Reactions and Synthesis in Micellar Media*; Texter, J., Ed.; Marcel Dekker: New York, NY, USA, 2001; Chapter 9; pp. 247–263.
4. Soffietti, J.B.; Adam, C.G.; Della Rosa, C.D. Aqueous Micellar Systems Formed by Surfactant Ionic Liquids. Application in Diels-Alder Reactions. *Proceedings* **2019**, *41*, 72. [CrossRef]
5. Della Rosa, C.; Kneeteman, M.N.; Mancini, P.M.E. 2-Nitrofurans as dienophiles in Diels-Alder reactions. *Tetrahedron Lett.* **2005**, *46*, 8711–8714. [CrossRef]
6. Arroyo, P.; Picher, M.T.; Domingo, L.R. The domino reaction between 4,6-dinitrobenzofuroxan and cyclopentadiene. Insights on the nature of the molecular mechanism. *J. Mol. Struct. (Theochem)* **2004**, *709*, 45. [CrossRef]
7. Arroyo, P.; Picher, M.T.; Domingo, L.R.; Terrier, F. A DFT study of the polar Diels-Alder reaction between 4-aza-6-nitrobenzofuroxan and cyclopentadiene. *Tetrahedron* **2005**, *61*, 7359–7365. [CrossRef]
8. Adam, C.G.; Bravo, M.V.; Granados, A. Anion Influence on Aggregation Behavior of Imidazolium-Based Ionic Liquid in Aqueous Solutions: Effect on Diverse Chemical Processes. *Ind. Eng. Chem. Res.* **2017**, *56*, 1214–1222. [CrossRef]
9. Della Rosa, C. *Doctoral thesis in Organic Chemistry. Facultad de Ingeniería Química*; Universidad Nacional del Litoral: Santa Fe, Argentina, 2006. Available online: <https://www.fiq.unl.edu.ar/institucional/biblioteca/> (accessed on 15 July 2022).