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Enhanced Diels–Alder reactions: on the role of mineral catalysts and microwave irradiation in ionic liquids as recyclable media

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Abstract—This manuscript explores in detail the combined effect of solid supports or microwave irradiation in ionic liquids on a series of Diels–Alder reactions involving 1,3-cyclopentadiene and numerous dienophiles.

1. Introduction

The Diels–Alder reaction has become the most venerable transformation in synthetic organic chemistry by virtue of its pluses, namely a facile construction of all-carbon or heterocyclic rings with a remarkable regio- and stereoselectivity.[1]

Devoted efforts have been applied to the investigation of ways of enhancing reaction rates and improving stereoselectivity by means of Lewis acid catalysts,[2] solid-support catalysis,[3] high-pressure conditions,[4] sonication[5] and microwave activation.[6] Several non-conventional reaction media have also been tested, with very good results. These include water,[7] lithium perchlorate–diethyl ether,[8] supercritical fluids[9] and ionic liquids.[10,11]

Our group has previously reported the enhancement of the Diels–Alder reaction encompassing the use of ionic liquids as solvents plus Lewis acid catalysts[11] and also the effect of the ultrasonic activation in this cycloaddition process[12] under similar conditions.

Almost all homogeneous Lewis acids have serious drawbacks, e.g., requirements of large amount of catalyst and laborious work-up procedures, problems of environmentally hazardous waste-streams and difficulty in their reuse.[13] Solids, such as silica, alumina or clays, are known to catalyse the Diels–Alder reaction with the advantage that, as inert inorganic solids, they are innocuous and easily removed during work-up of the heterogeneous reaction medium. K-10 montmorillonite lies in the group of cationic clays.[14] It is believed that clay minerals promote organic reactions via acid catalysis, though some controversy on this matter still exists.[15] In our lab, the use of K-10 montmorillonite and alumina under solvent-free conditions has been tested with promising results.[16]

On the other hand, microwave activation has now become a common methodology widely applied to organic synthesis.[17] It is energetically efficient, accelerates reactions manifold and allows fine control of reaction conditions, such as temperature and time.[1,17d] Microwave-assisted Diels–Alder reactions have been performed in solvents,[6a] in solventless conditions and in the presence of Lewis acids.[6b,c,16b,c] Sometimes some of these reaction conditions have been combined in the search of synergic effects.[1] In one case, ionic liquids have been used as solvent additives in Diels–Alder reactions under microwave irradiation.[18]

Ionic liquids interact very efficiently with microwaves through the ionic conduction mechanism and are rapidly heated at rates easily exceeding 10 °C/s without any significant pressure build-up.[17c,d]

As far as we know, the Diels–Alder reaction encompassing the use of ionic liquids as solvents plus solid supports or microwaves, has not been reported before. Our goal was to study how these conditions combine and to determine the best of these non-conventional combinations in promoting a series of typical [4+2] cycloadditions.

Keywords: Diels–Alder; Solid supports; Ionic liquids; Microwaves; Montmorillonite.
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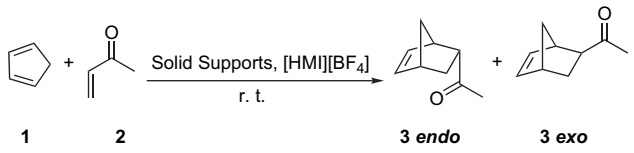
2. Results and discussion

Our initial experiments were aimed at establishing which solid support would yield the best results when used coupled with an ionic liquid and how this result would compare with the sole use of the molten salt as reaction medium. Alumina, silica gel and K-10 montmorillonite were chosen for testing the model reaction of cyclopentadiene with methyl vinyl ketone (MVK) (Scheme 1).



Scheme 1.

1-Hexyl-3-methylimidazolium tetrafluoroborate, [HMI][BF_4], was the solvent of choice for various reasons: (a) it can be synthesised in a straightforward manner, following a procedure previously reported,[11,19] (b) it is relatively cheap, (c) the reaction products can be easily extracted with diethyl ether,[11] (d) it is air- and moisture-stable and (e) due to its neutral and weakly coordinating nature, it does not interfere with the behaviour of Lewis acid catalysts.

Rates for reactions conducted in [HMI][BF_4] in the presence of solid catalysts are shown in Table 1. Yields from good to excellent were obtained for any of the solid supports tested. With alumina (entry 1) a good *endo*:*exo* selectivity is obtained along with a good yield in 3 h. Silica gel (entry 2) gave better selectivity and a higher reaction rate, although in the same order of magnitude. Remarkably, K-10 montmorillonite (entry 3) proved to be the most active support, and the cycloaddition came to completion in 30 min with excellent yield and an enhanced stereoselection. These results are even better than those previously reported under solventless conditions with the same inorganic solids.[16a]

When considering the design of sustainable processes in chemistry, recyclability of the reaction medium is of paramount importance. The system consisting of ionic liquid plus solid support was hence submitted for testing several cycles over. The reaction was set as it has been described above using 1.0 g of the clay, and after 15 min, the conversion was checked by ^{1}H NMR. The reaction medium was then washed and extracted with diethyl ether and dried under vacuum. It was subsequently used to perform the next cycle, and so forth. Results are presented in Table 2. This medium could be used as many as four times with only minor loss of activity after the second cycle, for reaction times of 15 min or longer.

Table 1. Solid support tests[a]

Entry	Support	Time	Yield[b] (%)	*endo*:*exo*[c]
1	Al_2O_3[d]	3 h	86	88:12
2	SiO_2[e]	3 h	95	90:10
3	K-10[f]	30 min	99	94:6
4	None	3 h	79	84:16

[a] CPD (2.2 mmol)+MVK (2.0 mmol)+solid support (1.0 g)+[HMI][BF_4] (2 mL).
[b] Isolated yield.
[c] Estimated by ^{1}H NMR spectroscopy (400 MHz) on the crude product.
[d] Activated, neutral, Brockmann I (150 mesh) aluminium oxide.
[e] Silica gel 60 (0.040–0.063 mm).
[f] K-10 montmorillonite.

Henceforward, we also performed a study on the K-10 load, in order to adjust the amount used to the optimal quantity-to-catalytic activity ratio in these cycloaddition processes. Table 3 collects those results obtained for the model reaction between cyclopentadiene and methyl vinyl ketone. As it can be observed, the maximum conversion is attained with 0.750 g of K-10 montmorillonite. Larger amounts of K-10 produce no significant improvement of the reaction outcome (Chart 1).

To further establish the scope of this methodology, the most active catalytic combination, i.e., the most active load of K-10 plus ionic liquid was tested with a variety of dienophiles. For comparative purposes, the reaction was also carried out

Table 2. Recyclability of the system [HMI][BF_4] and K-10 montmorillonite[a]

Entry	Cycle	*t* (min)	Yield[b] (%)	*endo*:*exo*[b]
1	1	15	99	93:7
2	2	15	99	93:7
3	3	15	86	92:8
4	4	15	85	92:8
5	5	15	76	90:10

[a] CPD (2.2 mmol)+MVK (2.0 mmol)+K-10 (1.0 g)+[HMI][BF_4] (2 mL) at rt.
[b] Determined by ^{1}H NMR (400 MHz) on the crude product.

Table 3. K-10 montmorillonite load study for the CPD and MVK reaction in [HMI][BF_4][a]

Entry	K-10 (g)	*t* (min)	Yield[b] (%)	*endo*:*exo*[c]
1	0.050	5	41	88:12
2	0.125	5	86	92:8
3	0.250	5	91	92:8
4	0.500	5	95	94:6
5	0.750	5	96	94:6
6	1.000	5	96	93:7

[a] CPD (2.2 mmol)+MVK (2.0 mmol)+K-10+[HMI][BF_4] (2 mL) at rt.
[b] Isolated yield.
[c] Determined by ^{1}H NMR (400 MHz) on the crude product.

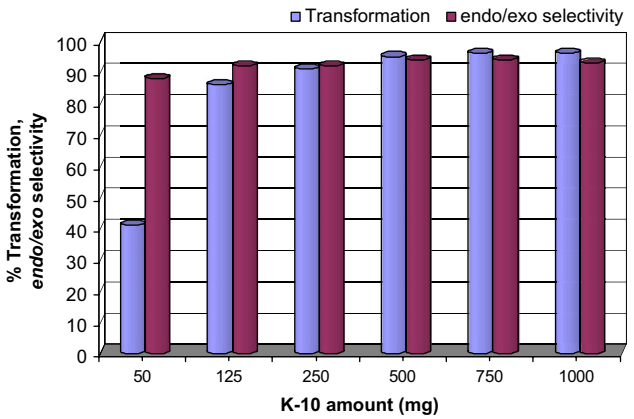


Chart 1. K-10 montmorillonite load study: transformation for CPD and MVK reaction in [HMI][BF_4] after 5 min.