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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.

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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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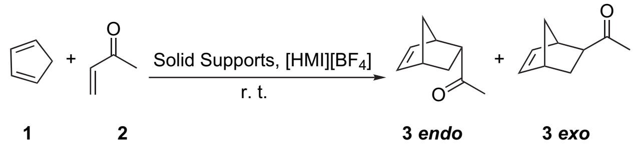
2. Results and discussion

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.

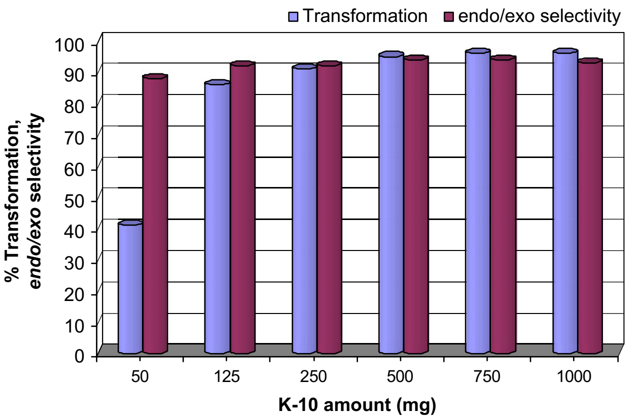


Chart 1. K-10 montmorillonite load study: transformation for CPD and MVK reaction in [HMI][BF_4] after 5 min.

in the ionic liquid without K-10 montmorillonite. Results are collected in Table 4.

This methodology gives excellent yields for some of the dienophiles explored and with very good *endo*:*exo* ratios. The addition of K-10 to the ionic liquid improves the outcome of the reaction taking it to completion in 5 min (entries 9–12). Acrolein and methyl vinyl ketone needed 30 min. It is most remarkable that some reactions that did not run well or at all in the ionic liquid (entries 1–7), now present notable activation in four cases (entries 1–4) and moderate activation in the cases of crotonaldehyde, acrylonitrile and dimethyl acetylenedicarboxylate (entries 5–7). Methyl acrylate still behaves as a poor dienophile (entry 8).

The other aim of this study was to assess the use of an ionic liquid as reaction medium irradiated with microwaves. It is expected that the high polarity of the ionic liquid makes it an efficient substrate for quick heating under microwave irradiation. Our key concern was whether the ionic liquid would be stable enough towards flash microwave heating. Leadbeater and Torenius explored the stability of mixtures of 1-methyl-3-propylimidazolium halides and organic solvents upon microwave irradiation, finding out that they remained stable up to at least 160 °C. Using neat ionic liquid, no significant pressure rise was noted in these conditions. Furthermore the BF_4^- based ionic liquids would be expected to be more thermally stable to decomposition than their halide counterparts.[18] For this reason, our experiments with microwave irradiation were controlled to keep temperature well below this limit. Results in Table 5 correspond to such cycloadditions carried out under microwave irradiation.

All the reactions proceeded smoothly. Interestingly, transformations were quantitative in 3 min for the two cyclic dienophiles with complete stereoselection (entries 5 and 6). Likewise, methyl vinyl ketone (entry 1) and acrolein (entry 2) are highly activated, although with less stereoselection. A dramatic acceleration effect is found for acrylonitrile and methyl acrylate (entries 3 and 4). At this particular point, it is worth stressing the good results obtained for the two acetylenes tested (entries 7 and 8), because both react easily under microwave activation whereas no conversion had been observed for these dienophiles under other conditions checked during this work.

Table 5. Microwave-assisted cycloadditions in [HMI][BF_4][a]

Entry	Dienophile	Yield[b] (%)	*endo*:*exo*[c]
1	Methyl vinyl ketone	97	77:23
2	Acrolein	96	76:24
3	Acrylonitrile	85	60:40
4	Methyl acrylate	79	71:29
5	*N*-Phenylmaleimide	97	100:0
6	Maleic anhydride	99	100:0
7	Dimethyl acetylenedicarboxylate	99	[d]
8	Methyl propiolate	70	[d]
9	Crotonaldehyde	24	71:29
10	Methacrolein	58	62:38
11	Methyl vinyl ketone[e]	53	78:22

[a] CPD (2.2 mmol)+dienophile (2.0 mmol)+[HMI][BF_4] (2 mL) under 3-min MW irradiation (maximum temperature attained 95 °C).
[b] Isolated yield.
[c] Determined by ^{1}H NMR (400 MHz) on the crude product.
[d] Not applicable.
[e] Reaction heated at 95 °C in oil bath for 3 min.

Many of the reported rate enhancements under microwave irradiation can be rationalised by simple thermal/kinetic effects.[17c] In order to assure the nature of the activation observed in the experiments run under microwave irradiation, a control reaction was performed. On this way, cyclopentadiene and methyl vinyl ketone were added to the ionic liquid and the mixture was kept at 95 °C with an external bath. After 3 min, an aliquot was extracted and analysed by ^{1}H NMR, resulting in 53% conversion and an *endo*:*exo* ratio of 78:22 (Table 5, entry 11). The same reaction under microwave assistance gave 97% yield and a selectivity of 77:23 (Table 5, entry 1). Therefore, it seems clear that the reaction course is driven by the effect of efficient microwave dielectric heating of materials and not by the overall temperature of the medium during the process.[17c]

As we can observe from the results in Table 5, the remarkable rate enhancement achieved with microwave activation

Table 4. Cycloadditions in [HMI][BF_4] with or without K-10 montmorillonite[a]

Entry	Dienophile	Time (min)	[HMI][BF_4]		[HMI][BF_4]+K-10	
			Yield[b] (%)	*endo*:*exo*[c]	Yield[b] (%)	*endo*:*exo*[c]
1	Methyl vinyl ketone	30	51	78:22	99	94:6
2	Ethyl vinyl ketone	60	61	71:29	99	93:7
3	Acrolein	30	45	75:25	99	86:14
4	Methacrolein	60	0	—	95	84:16
5	Crotonaldehyde	60	0	—	45	83:17
6	Acrylonitrile	60	15[d]	66:34[d]	25[d]	60:40[d]
7	Dimethyl acetylenedicarboxylate	30	58	[f]	68	[f]
8	Methyl acrylate	60	12[d]	79:21[d]	13[d]	80:20[d]
9	*N*-Phenylmaleimide	5	96	100:0	99	100:0
10	Maleic anhydride	5	97	100:0	99	100:0
11	1,4-Benzoquinone	5	91	96:4[e]	98	96:4[e]
12	1,4-Naphthoquinone	5	67	100:0	96	100:0

[a] CPD (2.2 mmol)+dienophile (2.0 mmol)+K-10 (0.75 g or nil)+[HMI][BF_4] (2 mL) at rt.
[b] Isolated yield.
[c] Determined by ^{1}H NMR (400 MHz) on the crude product.
[d] Not isolated. Estimated by ^{1}H NMR (400 MHz).
[e] Monoadduct:bisadduct ratio evaluated by ^{1}H NMR (400 MHz).
[f] Not applicable.

comes at the cost of a somewhat poorer stereoselection. In one of our previous works a very good *endo*:*exo* selectivity for the cycloaddition reaction of cyclopentadiene and methyl vinyl ketone carried out in [HMI][BF_4] in the presence of some Lewis acid catalysts was reported.[11] Consequently, it was interesting to check whether the use of these catalysts combined with microwave activation in the ionic liquid could exert an improvement on selectivities. Again, the reaction between cyclopentadiene and methyl vinyl ketone was chosen as a model. The results of these experiments are displayed in Table 6.

A careful inspection of these results evidence, however, that microwave irradiation is the driving force for the transformations and *endo*:*exo* selectivities attained. Reactions were controlled over 3 min. It appears that none of the catalysts added exerted any noticeable influence on the stereoselection of the cyclodditions run under microwave irradiation.

At this point, having tested one ionic liquid, we turned our attention to the study of the influence that different ionic liquids could have on this Diels–Alder reaction. For that purpose three 1-hexyl-3-methylimidazolium based ionic liquids other than the tetrafluoroborate were chosen.

The trifluoromethanesulfonate (OTf^-) and the bis(trifluoromethylsulfonyl)imide (NTf_2^-) constitute air- and moisture-stable, weakly coordinating, widely used anions in ionic liquids. The third ionic liquid chosen was the chloride one, which is more economic than the other three, but is also air sensitive and highly hygroscopic. Furthermore, the chloride anion, unlike the other three anions, is capable of strong coordination and H-bonding. The reaction between cyclopentadiene and methyl vinyl ketone was carried out in each of these ionic liquids following the same procedures as those described for the tetrafluoroborate analogue. Results are summarised in Table 7.

As it can be observed, [HMI][Cl] yields the poorest results both in terms of conversion and stereoselection for reactions in ionic liquid-solution at room temperature (entry 1, Table 7).

Table 6. Microwave tests with catalysts in [HMI][BF_4][a]

Entry	Catalyst (0.2 mol %)	Yield[b] (%)	*endo*:*exo*[c]
1	$Sc(OTf)_3$	94	77:23
2	$Sc(NTf_2)_3$	96	75:25
3	$Y(OTf)_3$	91	73:27
4	HOTf	97	73:27
5	$HNTf_2$	90	69:31
6	ZnI_2	91	75:25
7	BF_3	88	71:29
8	$AlCl_3$	94	69:31
9	$LiNTf_2$	98	75:25
10	LiOTf	98	73:27
11	K-10[d]	91	83:17
12	SiO_2[e]	95	78:22
13	Al_2O_3[f]	97	67:33
14	None	97	77:23

[a] CPD (2.2 mmol)+MVK (2.0 mmol)+catalyst+[HMI][BF_4] (2 mL), 3 min.
[b] Isolated yield.
[c] Determined by ^1H NMR (400 MHz) on the crude product.
[d] K-10 montmorillonite (0.75 g).
[e] Silica gel (1.0 g).
[f] Aluminium oxide (1.0 g).

Table 7. Results for the Diels–Alder reaction in 1-hexyl-3-methylimidazoliums[a]

Entry	Anion	% Conversion and selectivity (*endo*:*exo*)[b]		
		rt [30 min]	K-10[c] [5 min]	MW[d] [3 min]
1	Cl^-	34 (83:17)	16 (73:27)	90 (50:50)
2	OTf^-	52 (87:13)	95 (94:6)	94 (73:27)
3	NTf_2^-	47 (87:13)	99 (94:6)	92 (67:33)
4	BF_4^-	51 (78:22)	96 (94:6)	97 (77:23)

[a] CPD (2.2 mmol)+MVK (2.0 mmol)+Ionic liquid (2 mL).
[b] Determined by ^1H NMR (400 MHz) on the crude product.
[c] K-10 montmorillonite (0.75 g).
[d] Highest temperature attained 95 °C.

A plausible explanation is that the chloride anion H-bonds with the imidazolium H-2; following the reasoning provided by Welton et al.,[20] this bond would prevent substantial catalytic effect by precluding the coordination with the dienophile. In these conditions (ionic liquid-solution at room temperature), all the other three ionic liquids studied performed similarly (entries 2–4). Likewise, no stark differences arise among OTf^-, NTf_2^- and BF_4^- ionic liquids when they are used in combination with K-10 montmorillonite. However, the combination of the clay with [HMI][Cl] produces a very low conversion value. Possibly this is, at least partially, due to its high viscosity that hampers mixing with the clay. When reactions were irradiated with microwave, excellent conversions but also loss of selectivity were obtained in all cases.

With this set of experiments, we can conclude that [HMI][BF_4], chosen as reaction medium for the experiments in this work, affords very good results, comparable with those obtained with [HMI][OTf] and [HMI][NTf_2]. Besides, it is cheaper, and easy to prepare and purify. There is a potential downside, though, when using BF_4^- based ionic liquids. This is that of hydrolytic decomposition leading to the release of, among others, hydrogen fluoride.[21]

To rule out this possibility, in every reaction condition where [HMI][BF_4] has been used in this work, checks for decomposition by-products have been performed by means of ^{19}F NMR. In all cases, including the harsh conditions imposed by microwave irradiation, ^{19}F NMR spectra revealed no presence of any fluorinated species other than tetrafluoroborate.

3. Conclusions

In summary, one inorganic solid support, namely K-10 montmorillonite, embedded in ionic liquids has been used for enhancing Diels–Alder reactions for the first time. One of these systems has been tested for recycling up to four cycles without significant loss of activity. We have shown that this protocol stands as an efficient methodology; both improved reaction rates, and high stereoselectivities are achieved. On the other hand, we have found that coupling the ionic liquid with microwave irradiation affords good rate enhancements, yet poor stereoselection, for the Diels–Alder reaction; completion occurs typically in a matter of few minutes. We can also conclude that essentially the same results are obtained changing the anion from tetrafluoroborate to trifluoromethanesulfonate or to bis(trifluoromethylsulfonyl)imide;

however, the chloride counterpart can be singled out as the poorest of these four solvents for this reaction, probably because of the strong coordinating ability of the halide. Under the conditions tested in this study, no decomposition of tetrafluoroborate was observed. These methodologies will be improved and applied in our lab to other important reactions in the near future.

4. Experimental

4.1. General methods

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures. All chemicals were used as purchased from Aldrich or Acros except cyclopentadiene that was cracked from dicyclopentadiene (Aldrich) and then freshly distilled before use. Activated, neutral, Brockmann I (150 mesh) aluminium oxide and K-10 montmorillonite were purchased from Aldrich, silica gel 60 (0.040–0.063 mm) for column chromatography from Merck. Solid supports were not activated before use. The preparation of [HMI][Cl], [HMI][BF_4][11] and [HMI][NTf_2][22] followed previously described procedures. [HMI][OTf] was purchased from Fluka. Melting points were determined on Gallenkamp and/or Electrothermal apparatus. Analytical TLC was performed on precoated Merck 60 GF_{254} silica gel plates with a fluorescent indicator, and detection by means of UV light at 254 and 360 nm. Flash chromatography was performed on Merck 60 silica gel (230–400 mesh).[23] IR spectra were recorded in the range 4000–600 cm^{-1} on an FT-IR MIDAC spectrophotometer; solid samples were recorded on KBr (Merck) pellets and, liquid samples as a film between NaCl plates (Spectra-Tech). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM400 instrument at 400 and 100 MHz, respectively, in $CDCl_3$. TMS was used as the internal standard (δ=0.00 ppm). ^{19}F NMR spectra were recorded on a Bruker Avance DPX300 instrument at 282.3 MHz in deuterated acetone and/or deuterated chloroform. Fluorobenzene was used as the internal standard (δ=−113.15 ppm). Ion-chromatographic analyses were recorded on an Ion Chromatograph Dionex, DX-120 with suppressor column ASRS-ULTRA (4 mm), equipped with an AS-HC anion analytical column (4 mm) and an AG-9-HC guard column (4 mm) and performed by CTAEX Laboratories, Badajoz (Spain) following a previously described procedure,[24] or at QUILL Research Centre using a Dionex DX-120 ion-chromatograph with anionic Ionpac AS16 analytical column (250×4 mm) used in combination with an Ionpac AG16 guard column (50×4 mm) with helium carrier gas.[25]

For all different experiments in this paper, results correspond to, at least, duplicate runs. Work-up consisted of the extraction of the products from the reaction media with diethyl ether and further purification by flash chromatography and/or crystallisation if necessary. Isolation of the final products, following this simple protocol, proved to be quantitative for both stereoisomers.

4.2. Analyses of the ionic liquids used

All the ionic liquids used in this study were systematically dried by heating at 70 °C under vacuum for five days. Their purity was checked by means of TLC, ^1H, ^{13}C and ^{19}F NMR, and further analyses as detailed below.

- [HMI][BF_4]: water content 1.80%; chloride content 217 ppm
- [HMI][OTf]: water content 0.66%; chloride content 0.097 ppm
- [HMI][NTf_2]: water content 0.19%; bromide content 0.693 ppm.

4.3. Typical procedure for cycloaddition reactions with and without solid supports

In a flat-bottomed vial of 25 mL capacity, 2.0 mmol of dienophile and 2.2 mmol of freshly distilled cyclopentadiene were added under stirring to a mixture of 2 mL of ionic liquid and the appropriate amount of the corresponding solid support, if any, at room temperature, as previously described in the text. All processes were monitored by ^1H NMR and/or TLC. After completion or selected time, whichever applicable, the crude was extracted with diethyl ether (5×4 mL) and subsequently decanted off. The ethereal solution was reduced to half volume under vacuum in a rotary evaporator and then filtered through a 3 cm silica gel bed, to get rid of any ionic liquid contamination. The final adducts were isolated by evaporation of the crude mixture and, if necessary, purified by chromatography and/or crystallisation.

4.4. Typical procedure for microwave irradiated cycloaddition reactions

In a flat-bottomed vial of 25 mL capacity, 2.0 mmol of dienophile and 2.2 mmol of freshly distilled cyclopentadiene were added to a mixture of the corresponding catalyst or solid support (exact amount stated in the main text), when applicable, in 2 mL of ionic liquid. Samples were irradiated in 1-min steps up to 3 min in a monomode microwave reactor (Synthewave 402, Prolabo: 2.45 GHz, 300 W), at 10% relative intensity, controlling temperature not to overpass 95 °C. Reactions were monitored by ^1H NMR (400 MHz). After selected time the crude was extracted using the previously described work-up.

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