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Phosphonium tosylates as solvents for the Diels–Alder reaction

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Abstract—Phosphonium tosylates have been investigated as solvents for the Diels–Alder reactions of isoprene with methyl acrylate, but-3-en-2-one and acrylonitrile. The reactions with oxygen-containing dienophiles showed high regioselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

The Diels–Alder reaction is one of the most useful carbon–carbon bond-forming reactions in organic synthesis. It is a common method for forming cyclic structures and is widely used in the synthesis of natural products.

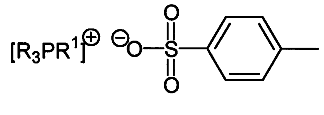
Some of the most thoroughly investigated Diels–Alder reactions are the reactions of isoprene **1** with dienophiles such as methyl acrylate **2a**, but-3-en-2-one **2b** and acrylonitrile **2c**. These reactions lead to a product mixture of two regioisomers, the 1,4-(**3a**–**c**) and the 1,3-disubstituted cyclohexenes (**4a**–**c**) as first reported by Petrov and Sapoznikova[1] and Alder and Vogt.[2]

In order to improve the selectivity and rate of these Diels–Alder reactions, Lewis acids such as $AlCl_3$[3] and $SnCl_4$[4] have been used. Among other methods are the use of supercritical carbon dioxide[5] as solvent, catalysts such as a cationic palladium(II) complex[6] and lithium perchlorate–diethyl ether mixtures.[7] One of the most recent developments for Diels–Alder reactions has been the use of room-temperature ionic liquids as solvents.[8–10] In all of those cases the ionic liquids investigated were based on imidazolium salts.

We have investigated the application of phosphonium tosylates **A**–**F** (Fig. 1) as ionic solvents for Diels–Alder reactions. This class of ionic solvent has been used very successfully in catalytic hydroformylation reactions[11] and transfer hydrogen reactions.[12] Some of the advantages of phosphonium tosylates as solvents are high thermal stability, tolerance towards air and moisture and low vapour pressures. They are non-corrosive and solid at room temperature, making them easy to handle and to separate from the products.

In a typical reaction, the diene (2.5 mmol) and the dienophile (3.75 mmol) where added to the ionic solvent (1 g). The mixture was sealed in a tube, heated and stirred. After the reaction was finished the reaction mixture was either treated with diethyl ether or petroleum ether (bp 40–60°C) and the phosphonium salt was removed by filtration or the product was distilled from the reaction mixture. The solvents were removed in vacuo and the resulting crude products were analysed by ^1H NMR (270 MHz, in $CDCl_3$). In some cases the product had to be purified by vacuum distillation. The pure ionic solvents were dried and may be reused. Selected results are presented in Table 1.

The reaction of isoprene **1** with methyl acrylate **2a** (entries 1–6) was carried out in solvents **A**–**E**. The regioselectivity was very high in all cases, and only the 1,4-isomer **3a** could be detected when solvents **A**–**C** were used. The selectivity was slightly lower for the reactions in phosphonium tosylates **D** and **E**, which



	A	**B**	**C**	**D**	**E**	**F**
R	Oct	*n*-Bu	Ph	Ph	*n*-Bu	Ph
R^1	Et	Et	Et	Oct	*n*-Bu	*n*-Bu

Figure 1.

Keywords: Diels–Alder reactions; ionic liquids; phosphonium salts; regioselectivity.

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gave some of the 1,3-isomer **4a**. Additionally $ZnCl_2$ was used as a catalyst together with ethyltriphenylphosphonium tosylate **C**. Although the reaction already proved to be virtually regiospecific (entry 3) the use of the catalyst improved the yield from 71 to 89% (entry 4).

The reaction of isoprene **1** with but-3-en-2-one **2b** was studied in solvents **D**–**F**. The results are very similar to those for the previous reaction, yielding the 1,4-isomer **3b** almost exclusively (entries 7–12).

The reaction of isoprene **1** with acrylonitrile **2c** proved to be less selective (entries 13–17). In all cases a significant amount of the 1,3-isomer **4c** was formed and the yields were low. The reaction of **1** and **2c** in solvent **F** gave the best yield.

The outstanding regioselectivity of the reactions of isoprene **1** with methyl acrylate **2a** and with but-3-en-2-one **2b** can be explained by formation of an adduct between the phosphorus atom of the phosphonium tosylates and the carbonyl oxygen, which results in a large increase in steric bulk causing the isoprene to approach with the methyl group as far away as possible from the coordinated carbonyl group.

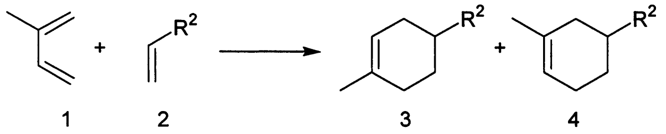
There seems to be some correlation between the structure of the phosphonium salts and the selectivity they induce. When comparing entries 3, 5 and 6 it becomes evident that the reaction carried out in the phosphonium tosylate with the smallest groups, ethyltriphenylphosphonium tosylate **C**, is virtually regiospecific, while the reaction carried out in tetrabutylphosphonium tosylate yields ~10% of the 1,3-isomer. Because the reaction conditions are otherwise identical, the only explanation can be that the bulky butyl groups shield the phosphorus atom to some degree, thus lowering the selectivity of the reaction.

The lower affinity of phosphorus towards nitrogen explains the low regioselectivity of the reactions with acrylonitrile.

Table 2 shows some of our results for the Diels–Alder reaction of isoprene **1** and methylacrylate **2a** in comparison with literature data. The reaction carried out in ethyltriphenylphosphonium tosylate **C** has a yield (71%) similar to the standard reaction in toluene[5] (78%), yet is far superior because of its excellent selectivity. The reaction has also been examined in supercritical carbon dioxide ($scCO_2$),[5] but this method gives neither a good yield nor is there any improvement in terms of selectivity. A selectivity similar to that in phosphonium tosylates was obtained by using the catalyst $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$ but the yield was lower (55%).[6]

When comparing the Diels–Alder reaction of isoprene **1** and but-3-en-2-one **2b** in butyltriphenylphosphonium tosylate **F** with the literature data (Table 3), the selec-

Table 1. Diels–Alder reactions of isoprene **1** with methyl acrylate **2a**, but-3-en-2-one **2b** and acrylonitrile **2c** in tetraaryl/alkyl phosphonium tosylates as solvents



	R^2
a	CO_2CH_3
b	$COCH_3$
c	CN

Entry	Dienophile	Isoprene/dienophile	Solvent	Time/h	Temp./°C	Yield (%) (**3**+**4**)[b]	Ratio **3**:**4**
1	**2a**	1:1.5	**A**	24	70–80	34[c]	>99:1
2	**2a**	1:1.5	**B**	24	70–80	68	>99:1
3	**2a**	1:1.5	**C**	24	110–120	71[c]	>99:1
4[a]	**2a**	1:1.5	**C**	24	110–120	89[c]	>99:1
5	**2a**	1:1.5	**D**	24	110–120	72	93:7
6	**2a**	1:1.5	**E**	24	110–120	87	91:9
7	**2b**	1:1	**D**	24	60	48[c]	>99:1
8	**2b**	1.5:1	**D**	24	80	78[c]	>99:1
9	**2b**	1:1.5	**E**	17	80	22	>99:1
10	**2b**	1:1	**F**	24	40	27	>99:1
11	**2b**	1:1.5	**F**	1.5	80	57	>99:1
12	**2b**	1:1.5	**F**	24	80	87[c]	>99:1
13	**2c**	1:1.5	**B**	24	80	18[c]	70:30
14	**2c**	1:1.5	**C**	24	80	13	72:28
15	**2c**	1:1.5	**D**	24	80	32	72:28
16	**2c**	1:1.5	**E**	24	80	18	76:24
17	**2c**	1:1.5	**F**	24	80	38[c]	69:31

[a] 5 mol% $ZnCl_2$ added.

[b] Yield and ratio of 1,4-:1,3-isomer determined by ^1H NMR.

[c] Isolated yield.

Table 2. Reaction of isoprene **1** with methylacrylate **2a** in various solvents

Conditions	**1a**:**2a** (mmol)	Yield (%)	Ratio (**3a**:**4a**)
$Ph_3PEt^+OTs^-$, 110–120°C, 24 h	2.5:3.75	71[a]	>99:1[b]
$Ph_3PEt^+OTs^-$, 110–120°C, 24 h, $ZnCl_2$	2.5:3.75	89[a]	>99:1[b]
$PhCH_3$, 145°C, 15 h[c]		78[d]	71:29[b]
$scCO_2$, 49.5 bar, 50°C, 4 days[c]	29.2:14.6	11[d]	69:31[b]
CH_2Cl_2, rt 20 h, $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$[e]	5.5:5	55	98:2[f]

[a] Isolated yield.
[b] Ratio of isomers determined by ^1H NMR.
[c] Ref. 5.
[d] Yield determined by ^1H NMR.
[e] Ref. 6.
[f] Ratio of isomers determined by GC.

Table 3. Reaction of isoprene **1** with but-3-ene-2-on **2b** in various solvents

Conditions	**1**:**2b** (mmol)	Yield (%)	Ratio (**3b**:**4b**)
$Ph_3PBu^+OTs^-$, 80°C, 1.5 h	2.5:3.75	57[a]	>99:1[c]
$Ph_3PBu^+OTs^-$, 80°C, 17 h	2.5:3.75	87[b]	86:14[c]
$PhCH_3$, 120°C, 15 h[d]		71	71:29[e]
CH_2Cl_2, rt 20 h, $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$[f]	5.5:5	0	–
$[bmim][PF_6]$, 20°C, 18 h[g]	1.5:1[h]	11	80:20[e]
$[bmim][PF_6]$, 20°C, 18 h, ZnI_2[g]	1.5:1[h]	98	95:5[e]

[a] Yield determined by ^1H NMR.
[b] Isolated yield.
[c] Ratio of isomers determined by ^1H NMR.
[d] Ref. 3.
[e] Ratio of isomers determined by GC.
[f] Ref. 6.
[g] Ref. 8.
[h] Molar ratio, no amount given.

tivity (**3a**:**4a** >99:1) of the uncatalysed reaction is superior to the reaction in toluene,[3] but the yield is slightly lower. The method using the palladium catalyst $[Pd(PPh_3)_2(CH_3CN)_2](BF_4)_2$ does not give any of the desired product. The reaction of **1** and **2b** has also been studied in the more commonly known ionic solvent, 1-butyl-3-methylimidazolium tetrafluoroborate [bmim]-[BF_4]. The uncatalysed reaction gives low yields (11%) and only a small improvement in selectivity (**3a**: **4a** = 80:20)[6] compared with the reaction in toluene, but gives a good selectivity when Lewis acid ZnI_2 is added as a catalyst.

We have shown that phosphonium tosylates are very good solvents for the Diels–Alder reaction of isoprene with oxygen-containing dienophiles. The reaction proceeds with high regioselectivity, even without the use of Lewis acids as catalysts and is often virtually regiospecific. The reaction temperatures are moderate and the solvents can be reused.

Further studies are now being carried out on other reactions with a wider range of phosphonium salts as solvents.

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