## Mechanochemical Diels–Alder Cycloaddition Reactions for Straightforward Synthesis of *endo*-Norbornene Derivatives

Ze Zhang,\* Zhi-Wei Peng, Ming-Feng Hao, Jian-Gang Gao

School of Biochemical Engineering, Anhui Polytechnic University, Wuhu, Anhui 241000, P. R. of China Fax +86(553)2871254; E-mail: zzhang@ahpu.edu.cn *Received 16 August 2010* 

**Abstract:** Under mechanochemical milling conditions, Diels– Alder cycloaddition of cyclopentadiene with maleic anhydride and maleimide derivatives proceeded very smoothly, affording *endo*norbornenes exclusively in quantitative yield. All the transformations were accomplished at room temperature without using any catalyst or organic solvent, thus the workup and purification procedure is very simple. Control experiments on traditional and other tentative conditions were also investigated.

**Key words:** norbornenes, mechanochemical milling, solvent-free, cyclopentadiene, Diels–Alder reaction

Norbornene and its derivatives, which carry a double bond inducing significant ring strain and thus significant reactivity, can be utilized to make pharmaceutical intermediates, pesticide compounds, specialty fragrances, and in organic synthesis.<sup>1</sup> They are also employed as important monomers in ring-opening metathesis polymerizations (ROMP) for the synthesis of various polynorbornenes with high glass-transition temperatures, high light harvesting and liquid crystal properties, high optical clarity, and so on.<sup>2,3</sup> Norbornene moiety is normally constructed via Diels-Alder cycloaddition reaction, which represents the favorite protocol to synthesize sixmembered carbo- or heterocycles.<sup>4-6</sup> In fact, different solvents, catalysts, and reaction conditions have proved to be robust for this kind of transformation.4-7 However, current methods often involve the use of toxic solvents, relatively expensive or harmful catalysts, long reaction time or tedious purification workup procedures. To circumvent these problems, one of the best methods is to carry out this kind of reaction under solvent-free or uncatalyzed conditions, which has the advantages of reduced pollution, low cost, and simplicity in process and handling.<sup>8,9</sup> Other than traditional solvent-free conditions, mechanical ball-milling technique has recently contributed significantly to promote various organic transformations.<sup>10,11</sup>

In light of the great successes of mechanochemistry in organic synthesis and with a view to the above reasons for the synthesis of norbornene derivatives, we are inspired to perform Diels–Alder cycloaddition reactions of cyclopentadiene with maleic anhydride and maleimide derivatives promoted by mechanical milling technique. Herein, we wish to report the results of this transformation under neat





conditions without using any catalyst or solvent (Scheme 1).

In a typical procedure, cyclopentadiene 1 (5.2 mmol, 0.44 mL, freshly distilled maintaining the head temperature below 45 °C) and maleic anhydride or maleimide derivatives 2 (5.0 mmol), together with a stainless ball of 7.0 mm in diameter, were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (Retsch MM400 mixer mill, Retsch GmbH, Haan, Germany), and were vibrated vigorously at a rate of 1800 rpm (30 Hz) at room temperature for 30 minutes. TLC analysis on the resulting mixtures demonstrated that reactions in all cases proceeded completely and only the desired products 3 were generated, which were obtained just by washing with about 5 mL hexane to remove the slightly excessive cyclopentadiene. The results are summarized in Table 1.

As shown in Table 1, the cycloaddition reactions gave products 3 in remarkably high yields, which are almost quantitative. Generally, the efficiency would not be affected by various substituents at the X position, including O, aliphatically and aromatically substituted N. This means that a large variety of norbornene derivatives could be synthesized by this method. Furthermore, this protocol does not require the use of any organic solvent during the reaction process and only an excess of 4% molar equivalent of cyclopentadiene is enough to promote the reaction. In fact, the resulted crude products in most cases can even be directly used for normal IR and <sup>1</sup>H NMR analysis. As anticipated, all cycloadducts were formed exclusively in endo conformation according to <sup>1</sup>H NMR analysis. We have attempted to further decrease the usage amount of cyclopentadiene even up to 1.0 equivalent, but the product turned out to be contaminated by a trace amount of unreacted **2** as indicated by <sup>1</sup>H NMR analysis on these cases.

To contrast with traditional methods, we also prepared these norbornene derivatives by carrying out the cycload-

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dition reactions in THF-hexane as the following: to a stirring mixture containing maleic anhydride or maleimide derivatives 2 (50 mmol), THF (30 mL), and hexane (70 mL) was added a solution of cyclopentadiene 1 (15 mL, 180 mmol) and hexane (50 mL) under nitrogen, and the resulting reaction mixture was kept stirring at room temperature overnight. After removal of most solvent, the residue was diluted with hexane, and the white precipitate was collected by filtration to afford the crude product, which was further purified via crystallization from ethyl acetate-hexane (v/v = 1:1). The isolated yields from this condition were also summarized in Table 1, from which we could see that these compounds were also practically synthesized in moderate to good yield (ca. 80-90%), and <sup>1</sup>H NMR analysis also suggested exclusive *endo* selectivity. In fact, TLC analysis on reactant 2 showed that these reactions also proceeded completely, but this method involves the use of largely excessive cyclopentadiene (3.6 equiv), anhydrous organic solvents, relatively long reaction time, and tedious work up procedure. Whereas the present mechanochemical (MM400) conditions exhibits the main advantages of milder conditions, higher yield (90–98%), shorter reaction time (30 min), only 4% excess of cyclopentadiene, and fairly easy operation. We also employed the same usage amount of cyclopentadiene (1.04 equiv) as that under MM400 neat conditions. But in most cases, the reactant 2 was not completely reacted, which contaminated the crude product and made column chromatography necessary for effective purification. The corresponding isolated yield is moderate (65-78%) as shown in Table 1. The reasons for the high efficiency of the current mechanochemical solvent-free conditions may be due to an enhanced second-order reaction rate resulting from ultimately high concentrations of reactants in the absence of solvent. Furthermore, the high mechanical energy caused by local high pressure, friction, shear strain, etc. could also greatly enforce the reaction to a great extent.<sup>19</sup>

To further investigate the effect of reaction conditions (solvent, vibration frequency, reaction temperature, and time) on the chemoselectivity, we performed some control experiments on cycloaddition of *N*-4-tosylmaleimide (**2g**, 5.0 mmol) with cyclopentadiene (**1**, 5.2 mmol) under various conditions (Scheme 2). The results are summarized in Table 2.

From Table 2 it can be seen that this kind of cycloaddition reactions took place readily. Both solvent-added and neat conditions could promote this transformation to a certain extent just in 30 minutes at room temperature (entry 1, 7,



Scheme 2

 Table 1
 Results of Cycloaddition of Cyclopentadiene with Maleic Anhydride and Maleimide Derivatives under MM400 Neat Conditions and in THF–Hexane (1:4 v/v)

Compound <b>2</b> <sup>a</sup>			Product <b>3</b> <sup>b</sup>	Yield (%) <sup>c</sup>	Yield (%) <sup>d</sup>	Yield (%) <sup>e</sup>	Mp (°C)
	Х						
2a	0	_	3a	94	89	77	163–165 (lit. <sup>14</sup> 164–165)
2b	Ν	Н	3b	98	87	74	186–187 (lit. <sup>15</sup> 187)
2c	Ν	c-Hex	3c	90	78	65	156–157 (lit. <sup>16</sup> 157–158)
2d	Ν	Ph	3d	92	89	76	142–143 (lit. <sup>17</sup> 144)
2e	Ν	$4-BrC_6H_4$	3e	94	90	78	156–157 (lit. <sup>18</sup> 153–155)
2f	Ν	$4-F_3CC_6H_4$	3f	95	79	68	191–192
2g	Ν	$4-MeC_6H_4$	3g	93	84	76	157-158 (lit. <sup>17</sup> 157)
2h	Ν	4-MeOC <sub>6</sub> H <sub>4</sub>	3h	96	88	73	170–172 (lit. <sup>18</sup> 172–173)
2i	Ν	4-EtOOCC <sub>6</sub> H <sub>4</sub>	3i	92	85	75	133–134

<sup>a</sup> Compounds **2c–i** were prepared according to reported method.<sup>12,</sup>

<sup>b</sup> Characterized by mp, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS analysis.<sup>13,</sup>

<sup>c</sup> Isolated yield combined from two parallel runs via MM400 ball miller.

<sup>d</sup> Isolated yield from reactions carried out in THF-hexane (1:4 v/v) overnight at r.t. (1/2 = 3.6:1).

<sup>e</sup> Isolated yield from reactions carried out in THF-hexane (1:4 v/v) overnight at r.t. (1/2 = 1.04:1).

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and 9). Under solvent-added or hand-grinding conditions, it was not easy to make the reaction proceed to completion unless prolonged reaction time was employed (entry 2, 3, and 8). However, it is well known that cyclopentadiene dimerizes easily and rapidly to dicyclopentadiene even at room temperature. Therefore, too long reaction time in these cases led to dimerization of unreacted cyclopentadiene into the corresponding dimer 4, thus high product yield was difficult to achieve. It appeared that elevating the reaction temperature may be an alternative to avoid this problem. As a result, higher reaction temperature (refluxing) was employed in order to induce rapid conversion of the reactant, but the reaction chemoselectivity was somewhat decreased (entry 4). In addition, <sup>1</sup>H NMR analysis on the resulting mixture under these conditions showed that the *endo* product **3g** was contaminated with minor thermally more stable exo side products 3g'. When neat hexane was used as the solvent, the transformation was very slow (entry 5). In the presence of THF as solvent, the reaction could be promoted to some extent (entry 6 vs. entry 1). This can be easily understood from the fact that the solubility of reactant 2g in hexane is very poor but higher in THF. Based on the results of these control experiments, we could deduce that the best way was to perform this reaction under neat conditions at room temperature within a short reaction time. We then carried out this reaction under different vibration frequencies for further investigations. It was found that the vibration frequency of the applied vibration mill had a significant effect on the reaction process and conversion (entries 9-11). Generally, higher vibration frequency accelerated the reaction process. It is easy to understand that the faster the mill vibrates the higher the mechanical energy, and therefore the higher local pressure applied to the reaction system. Furthermore, when a mill vibrates at higher speed, it may be advantageous for the diffusion process to promote homogenization and thus beneficial for the ongoing reaction.<sup>19</sup> Considering the very exothermic nature of the Diels–Alder reaction, a relatively low temperature ( $< 5 \,^{\circ}$ C, entry 12) was employed, giving almost the same result as that at 20 °C (entry 11). This means that the high efficiency of mechanical milling promoted reactions cannot be simply ascribed to the simultaneously generated heat energy.

In conclusion, we have developed a powerful method for the synthesis of various norbornene derivatives via the Diels–Alder reaction of cyclopentadiene with maleic anhydride and maleimide derivatives, in which a novel solvent-free technique – mechanical ball milling – was employed to promote this transformation efficiently at room temperature without using any solvent or catalyst. Under these mild conditions, the *endo*-norbornenes were exclusively formed in quantitative yields within 30 minutes, and the products could be obtained. The advantages of neat conditions, high chemoselectivity, and higher product yield, shorter reaction time together with a straightforward procedure make this protocol a very efficient alternative to traditional methods.

**Table 2** Results of Control Experiments on Cycloaddition of Cyclopentadiene with N-4-Tosylmaleimide under Different Conditions

Entry	Solvent	Temp (°C)	Time (h)	Products distribution (%) <sup>a</sup>
1	THF-hexane <sup>b</sup>	20	0.5	<b>3g</b> (48)
2	THF-hexane <sup>b</sup>	20	3	<b>3g</b> (62) + <b>4</b> (trace)
3	THF-hexane <sup>b</sup>	20	overnight	<b>3g</b> (88) + <b>4</b> (trace)
4	THF-hexane <sup>b</sup>	reflux	0.5	$3g(83) + 3g'(6)^d$
5	hexane	20	0.5	<b>3g</b> (14)
6	THF	20	0.5	<b>3g</b> (59)
7	–/hand grinding	20	0.5°	<b>3g</b> (54)
8	–/hand grinding	20	3°	<b>3g</b> (80) + <b>4</b> (7)
9	–/MM400 (10 Hz)	20	0.5	<b>3g</b> (62)
10	-/MM400 (20 Hz)	20	0.5	<b>3g</b> (78)
11	–/MM400 (30 Hz)	20	0.5	<b>3g</b> (>99) <sup>e</sup>
12	–/MM400 (30 Hz)	<5 <sup>f</sup>	0.5	<b>3g</b> (>99) <sup>e</sup>

<sup>a</sup> Based on HPLC analysis.

<sup>b</sup> THF–hexane (1:4 v/v; 25 mL).

<sup>c</sup> Including several standing intermission (about 5 min each).

<sup>d</sup> Based on <sup>1</sup>H NMR analysis on the resulted crude mixture.

<sup>e</sup> The excessive cyclopentadiene was subtracted.

<sup>f</sup>Keeping the mixer mill in a ice-cooling box  $[80 \text{ cm} \times 80 \text{ cm} \times 50 \text{ cm}]$ and the temperature was detected by a thermometer around 3–5 °C).

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