

# 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and Microwave-Accelerated Green Chemistry in Methylation of Phenols, Indoles, and Benzimidazoles with Dimethyl Carbonate

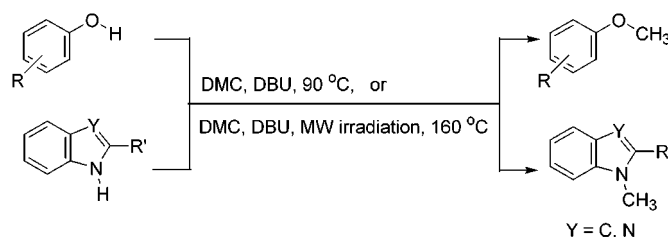
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## ABSTRACT



1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) is a novel and active catalyst in promoting the methylation reaction of phenols, indoles, and benzimidazoles with dimethyl carbonate under mild conditions. Additional rate enhancement is accomplished by applying microwave irradiation. By incorporating tetrabutylammonium iodide, the same microwave reactions can be further accelerated. By combining these acceleration strategies, very slow chemical transformations that take up to several days can be performed efficiently in high yield within minutes.

Methylation of phenols and *NH*-containing heteroaromatic compounds is an important transformation that regularly employs toxic and hazardous reagents such as methyl iodide<sup>1</sup> and dimethyl sulfate.<sup>2</sup> Dimethyl carbonate (DMC) as a methylating reagent for phenols,<sup>3–5</sup> *NH*-containing heteroaromatic compounds,<sup>3,6</sup> and anilines<sup>7,8</sup> is an attractive alternative. However, the use of this “green chemical” (DMC) as a

methylating reagent often requires high temperatures and long reaction times. As a result, autoclaves/sealed tubes<sup>4,5</sup> or the use of asymmetrical carbonates<sup>9</sup> with a higher boiling point than DMC have to be employed. The exploration for milder and more practical conditions to accelerate the rate of methylation using DMC is a worthy task. Herein, we describe a novel approach to enhance the methylation reaction of phenols, indoles, and benzimidazoles under milder conditions by employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the catalyst (chemical means). We will also demonstrate additional rate accelerations by utilizing microwave irradiations (physical means) and tetrabutylammonium iodide.

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


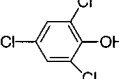

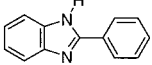
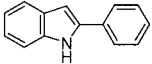
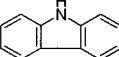
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Comparisons of reaction times for both *O*- and *N*-methylation reactions using DMC as the methylating reagent in the presence of different bases clearly exemplifies the rate enhancing ability of DBU. For example, methylation of 1-naphthol (**1**) with DMC using Na<sub>2</sub>CO<sub>3</sub> as the base requires 168 h at 120 °C for 91% completion.<sup>4</sup> We discovered that a more efficient conversion (99%) can be achieved in a shorter time (16 h) at a lower temperature (90 °C) when 1 equiv of DBU was used for the same transformation (Table 1, entry

**Table 1.** *O*- and *N*-Methylation with Dimethyl Carbonate and DBU

entry	substrate		thermal <sup>a</sup> time, HPLC yield <sup>d</sup>	microwave time, HPLC yield <sup>d</sup>
1		<b>1</b>	16 h, 99%	12 min, 99% <sup>b</sup>
2		<b>2</b>	16 h, 99%	24 min, 97% <sup>b</sup>
3		<b>3</b>	5 h, 99%	12 min, 97% <sup>b</sup>
4		<b>4</b>	192 h, 91%	54 min, 93% <sup>b</sup> 6 min, 98% <sup>c</sup>
5		<b>5</b>	2 h, 98%	6 min, 96% <sup>b</sup>
6		<b>6</b>	6 h, 98%	12 min, 97% <sup>b</sup>
7		<b>7</b>	28 h, 98%	48 min, 66% <sup>b</sup> 30 min, 91% <sup>c</sup>
8		<b>8</b>	7 h, 99%	36 min, 69% <sup>b</sup> 30 min, 97% <sup>c</sup>

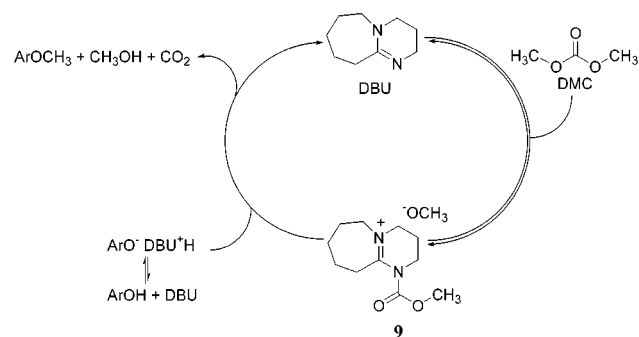
<sup>a</sup> General procedure using conventional thermal heating: A reaction flask was charged with substrate (1 g), DBU (1 equiv), and DMC (10 mL). The mixture was heated to 90 °C and the products were analyzed by HPLC.

<sup>b</sup> General procedure using microwave heating: A solution of substrate (5 g), DBU (1 equiv), DMC (50 mL), and solvent (CH<sub>3</sub>CN or DMF, 50 mL) was passed through a Milestone ETHOS-CFR continuous-flow reactor preheated to 160 °C at 20 bar. The reaction products were analyzed by HPLC after each pass (6 min). <sup>c</sup> Same as procedure *b*, except 1 equiv of TBAI was charged to the reaction mixture before passing through the reactor. <sup>d</sup> The identity of the methylated products was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR and MS.

1). Rate acceleration assisted by DBU is also evident for an *NH*-containing heteroaromatic compound. For *N*-methylation of benzimidazole (**5**), the protocol produced the desired *N*-methyl derivative in 2 h at 90 °C in excellent yield (98%) (entry 5). This rate is at least 4 times faster than a literature-reported procedure (K<sub>2</sub>CO<sub>3</sub> 18-crown-6, 100 °C, 8 h, 81% yield).<sup>3</sup> The reaction conditions are quite simple. In a typical experiment, a mixture of substrate, DBU (1 equiv), and DMC is heated to reflux. In most of the cases we examined, this protocol afforded excellent yields. It worked well for

unactivated *p*-chlorophenol (16 h, 99%, entry 2), as well as the congested phenol 2,6-dimethoxyphenol (5 h, 99%, entry 3). The methylation rate of an unactivated and a congested phenol, 2,4,6-trichlorophenol, is slow and 91% conversion is observed after 192 h (entry 4). Efficient methylation of *NH*-containing heteroaromatic compounds, 2-phenylbenzimidazole (**6**) and carbazole (**8**), are accomplished within 7 h (98%, entry 6; 99%, entry 8). In comparison, a literature-reported methylation of 2-phenylbenzimidazole (**6**) with DMC and 18-crown-6 is accomplished in 10 h with only 70% yield.<sup>6</sup> For substituted indole **7**, the methylation is slower and takes 28 h for completion (98%, entry 7). When aniline was subjected to the same reaction conditions, a mixture of *N*-methyl- (24%) and *N*-methoxycarbonylaniline (76%) was obtained. Therefore, this protocol is not efficient for the methylation of primary aromatic amines.

We believe that DBU functions as a catalyst in our methylation protocol. This hypothesis is supported by the fact that when 0.5 equiv of DBU was used, quantitative conversions (99%) of 1-naphthol (**1**) or benzimidazole (**5**) to their methyl derivatives can be achieved in 120 and 5 h, respectively, at 90 °C as indicated by HPLC analyses. The kinetic difference of these two substrates can be explained in terms of their physicochemical properties. In the former case, 1-naphthol (p*K*<sub>a</sub> = 9.34)<sup>10a</sup> could consume some DBU (p*K*<sub>a</sub> = 12),<sup>8b</sup> which functions as an acid scavenger toward phenolic protons. This interaction lowers the concentration of free DBU that performs as a catalyst and contributes to a slower methylation rate for 1-naphthol than that of benzimidazole. In the absence of DBU, methylation of 1-naphthol affords no product at 90 °C over a period of 24 h. Methylation of benzimidazole, which contains the same amidine substructure as DBU, is extremely slow without DBU and affords a minimal amount (6%) of product after 24 h. We chose to use 1 equiv of DBU in our methylation protocol so that both atom economy and process efficiency (rate) are balanced. A plausible mechanism for phenol methylation is proposed in Figure 1, in which DBU performs



**Figure 1.** Plausible catalytic cycle for phenol methylation.

as a nucleophilic catalyst. In the catalytic cycle, DBU reacts with DMC to generate a more activated methylating agent, **9**, which presumably reduces the activation energy required for the methylation. A mechanistic study is in progress in

our lab to clarify the pathways for methylations employing DMC/DBU.

Microwave heating has been shown to promote a variety of chemical transformations.<sup>11–17</sup> For example, synthesis of aromatic ethers under microwave irradiation has been reported by several laboratories.<sup>18</sup> Therefore, microwave irradiation is another potential strategy, besides employing a suitable catalyst, to accelerate the rate of methylation. The substrates in Table 1 along with a mixture of DMC/DBU were subjected to microwave radiation in a continuous-flow reactor. This reactor has an in-line thermal sensor, which allows for the monitoring of the actual reaction temperature during the entire course of reaction. This reactor also has an in-line pressure control valve, which provides the capability to process volatile DMC safely at elevated temperatures above its boiling point (90 °C). In a typical procedure, a solution containing a substrate, DBU (1 equiv), DMC, and a solvent (either CH<sub>3</sub>CN or DMF) is circulated by a pump through the microwave reactor which is preheated to 160 °C at 20 bar by microwave irradiation. Under these conditions, the methylation rate for phenols is accelerated from hours to minutes, which represents a rate increase of up to 80-fold (Table 1, entries 1–3). Dramatic rate enhancement using microwave heating is observed for 2,4,6-trichlorophenol (**4**), an unactivated and congested phenol. Phenol **4** is methylated in only 54 min (93%), which is approximately 200 times faster than that using conventional thermal heating (192 h, 91%) (entry 4). Furthermore, by adding 1 equiv of phase-transfer catalyst (PTC) tetrabutylammonium iodide

(TBAI) to the reaction mixture, methylation of phenol **4** under the same microwave conditions can be further accelerated to 6 min (98% yield), which represents greater than a 1,900-fold rate increase! The reason for this striking rate enhancement by adding a PTC to a homogeneous reaction system<sup>19,20</sup> is not fully understood. For *NH*-containing heteroaromatic compounds, such as benzimidazole **5** and **6**, rate acceleration of a magnitude of up to a 30-fold is observed when microwave conditions are employed (entries 5–6). Under the same conditions, methylations of 2-phenylindole **7** (48 min, 66%, entry 7) and carbazole **8** (36 min, 69%, entry 8) are much slower with lower yields than imidazoles (entries 5 and 6). To optimize the methylation for indole **7** and carbazole **8**, TBAI (1 equiv) was added under microwave conditions. This addition shortens the reaction time and increases the methylation yield of **7** and **8** to 91% (30 min, entry 7) and 97% (30 min, entry 8), respectively.

In summary, methylation of phenols, indoles, and benzimidazoles with DMC can be achieved under conventional thermal conditions without using an autoclave by employing DBU as a highly effective catalyst (chemical acceleration). This protocol provides a practical, efficient, and environmentally friendly process for an important chemical transformation. Methylation rates can be further accelerated by utilizing microwave heating (physical acceleration). Dramatic rate enhancement greater than 1,900-fold is observed for an unactivated and congested phenol when the phase-transfer reagent TBAI is incorporated. By combining these acceleration strategies, a very slow methylation that takes up to several days can be performed efficiently in high yield within minutes.

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