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Large scale microwave-accelerated esterification of carboxylic acids with dimethyl carbonate

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Abstract—An environmentally friendly process for the esterification of carboxylic acids with dimethyl carbonate can be accelerated by employing a combined strategy: using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as the catalyst (chemical means) and microwave as the energy source (physical means). This approach provides synthetic advantages, niches, and upscalability.

The transformation of carboxylic acids into the corresponding methyl esters is a popular and fundamental process in organic synthesis and has been thoroughly documented in the literature.[1] Protection of amino acids as their methyl esters is also an important strategy for peptide synthesis because of its simple deprotection conditions.[2] The reported procedures for the synthesis of methyl esters require the use of strong acids (e.g. sulfuric acid, hydrochloric acid), toxic chemicals (methyl iodide or dimethyl sulfate) or unsafe reagents (diazomethane). Esterification of sterically-hindered acids is also difficult, due to increased steric hindrance in their transition states. Considering the impacts of toxic and hazardous reagents on ecology and human beings, as well as the need for a more efficient method for the formation of sterically-hindered methyl esters, exploration of alternative syntheses to overcome these issues is a compelling task. Several advanced methodologies with improved process efficiency have been introduced recently.[3,4] However, the consequences of toxic reagents and wastes are not properly addressed by these new processes. Recently, we discovered that esterification of carboxylic acids with dimethyl carbonate (DMC), an environmentally friendly process that generates methanol and CO_2 as by-products, can be promoted by DBU under mild conditions.[5] We found that DBU functions as a nucleophilic catalyst and reacts with DMC to form a more activated alkylating reagent, which enables the esterification to proceed at a lower temperature (90°C)[5] without the use of autoclaves (175°C).[6]

In recent years, microwave-assisted transformations have become popular in promoting organic reactions.[7–13] A microwave-induced esterification for acetic acid is reported by Kabza.[14] However, most of these applications utilize domestic microwave ovens that lack scale-up capability. This constraint restricts the use of this valuable technology for large-scale synthesis. We report herein a microwave-accelerated esterification of carboxylic acids using a commercial continuous-flow reactor that is capable of processing large quantities (hundred grams) of substrates.[15]

This microwave reactor has an in-line thermal sensor, which is able to monitor the temperature profile of the reaction mixture. The reactor also has an in-line pressure control valve, which enables volatile DMC be processed safely at temperatures above its boiling point (90°C). In a typical procedure, a solution containing a carboxylic acid (5 g), DBU (1 equiv.), DMC (50 mL) and CH_3CN (50 mL) is circulated by a pump through the microwave reactor pre-heated to 160°C at 20 bar by microwave irradiation. Under these conditions, the esterification rate can be accelerated from hours to minutes, which represents a rate increase of approximately 80 folds (Table 1). Since quantitative conversions are achieved in many cases, clean products can be isolated after performing aqueous acid and base washes and evaporating solvents.

Employing the microwave protocol, benzoic acid was converted to its methyl ester in 12 min. For substituted

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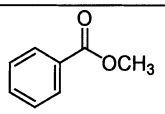
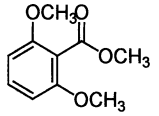
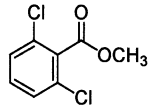
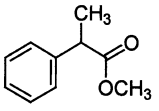
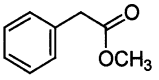
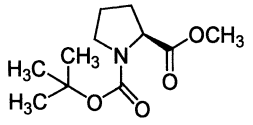
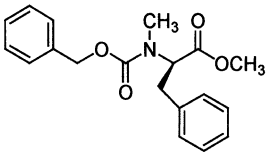
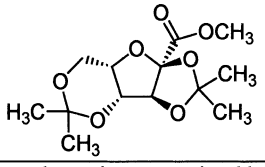
Table 1. Esterification of carboxylic acids with DMC and DBU

Entry	Ester		Thermal[a] time, HPLC yield[b]	Microwave[c] time, HPLC yield[b]	Approximate relative rate (fold)
1		**1**	4 h, 99%	12 min, 99%	20
2		**2**	4 h, 99%[5]	12 min, 98%	20
3		**3**	24 h, 99%[5]	24 min, 98%	60
4		**4**	5 h, 98%[5]	12 min, 99%	25
5		**5**	6 h, 98%[5]	12 min, 99%	30
6		**6**	16 h, 99%[5]	12 min, 99%	80
7		**7**	16 h, 90%	12 min, 97% 2 min, 99%[d]	80 480
8		**8**	16 h, 99%[5]	24 min, 95%	40

[a] General procedure using conventional heat: 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 reaction products were analyzed by HPLC. [b] The identity of the esters was confirmed by ^{1}H and ^{13}C-NMR and MS. [c] General procedure using microwave heat: A solution of substrate (5 g), DBU (1 equiv), DMC (50 mL) and CH_3CN (50 mL) was passed through a Milestone ETHOS-CFR continuous-flow reactor preheated by microwave irradiation to 160 °C at 20 bar. The reaction products were analyzed by HPLC after each pass (6 min). [d] Same as procedure c, except 1 equiv of tetrabutylammonium iodide was charged to the reaction mixture before passing through the microwave reactor, which was preheated to 190 °C.

benzoic acids, such as sterically-hindered 2,6-dimethoxy and unactivated 2,6-dichlorobenzoic acid, transformation into the esters was achieved in 12 and 24 min, respectively (entries 2 and 3). A clean regioselectivity was observed for the preparation of methyl ester of phenylacetic acid (entry 5). Although ester **5** contains an activated methylene carbon, no α-methylated product **4** was generated under the microwave conditions.[16] For a Boc-protected amino acid, the esterification yield was excellent (entry 6). The isolated *N*-α-*t*-Boc-L-proline methyl ester (**6**) was essentially epimerization-free as determined by a chiral HPLC analysis. In comparison, when the thermal protocol (90°C, 16 h) was employed for the same esterification, partial epimerization (3.5%)[5] was detected in the isolated ester **6**. The microwave protocol (160°C, 20 bar) was also applied to the synthesis of an epimerization-sensitive amino ester, *N*-α-Cbz-*N*-methylphenylalanine methyl ester (**7**), and afforded the product in 12 min (97% yield, 58% ee) (entry 7). In comparison, when thermal conditions (90°C, 16 h) were utilized, a nearly total epimerization (2% ee) was observed for the isolated ester **7**. These results suggest that ester **7** is epimerization-sensitive in the presence of DBU (pK_a = 12).[17] The degree of epimerization presumably depends more on reaction time than on reaction temperature. Indeed, by increasing the reaction temperature to 190°C by microwave irradiation in the presence of a phase transfer catalyst, tetrabutylammonium iodide (TBAI), synthesis of **7** can be accomplished in 2 min (99%) with

higher optical purity (70% ee).[18] To expand the synthetic utility, an acid-sensitive carbohydrate ester **8** was prepared in excellent yield (95%) under microwave conditions (entry 8). Esterification of 2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (entry 8) and *N*-α-*t*-Boc-L-proline (entry 6) demonstrates another niche for this methodology. These esters, containing acid-sensitive functionalities, would not survive acid-catalyzed esterification conditions.[19]

Investigation of the reproducibility and scale-up feasibility of the microwave protocol was also conducted. To prove the concept, esterification of benzoic acid was chosen because of its economic advantage. We found that methyl benzoate could be synthesized at a 10 g scale with consistent yield and time. Similarly, benzoic acid at 50 and 100 g scales was regularly converted to its methyl ester in 20 min (microwave residency time).

In conclusion, the present microwave protocol provides an efficient method for the esterification of the following carboxylic acids: aromatic, sterically-hindered, amino, and carbohydrate. The notable advantages of this synthetic strategy are: (a) the use of a cheaper and 'green' methylating reagent (DMC), (b) the efficiency and applicability to sterically-hindered acids, (c) reproducibility and upscalability, (d) feasibility for acid-sensitive functionality, (e) compatibility with commonly used amino acid protecting groups, such as Boc and Cbz, (f) tolerance or minimization of epimerization, (g) rapid reaction rates (in minutes), and (h) high yields.

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References

1. Larock, R. C. *Comprehensive Organic Transformations*; VCH Publisher: New York, Weinheim and Cambridge, 1989; Chapter 9.
2. Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Krieger Publishing Company: Malabar, 1984; Vol. 2, Chapter 10.
3. Chakraborti, A. K.; Basak (née Nandi), A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014.
4. Bryson, T. A.; Dyke, C. A. *Tetrahedron Lett.* **2001**, *42*, 3959.
5. Shieh, W.; Dell, S.; Repic, O. *J. Org. Chem.* **2002**, *67*, 2188.
6. Thompson, R. B. U.S. Patent 4,513,146, **1985**.
7. Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.
8. Caddick, S. *Tetrahedron* **1995**, *51*, 10403.
9. Kingston, H. M.; Haswell, S. J. *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation, and Applications*; American Chemical Society: Washington, DC, 1997; Chapter 8.
10. Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18.
11. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213.
12. Varma, R. S. *Green Chem.* **1999**, 43.
13. Krstenansky, J. L.; Cotterill, I. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 454.
14. Kabza, K. G.; Chapados, B. R.; Gestwicki, J. E.; McGrath, J. L. *J. Org. Chem.* **2000**, *65*, 1210.
15. All our microwave operations were performed on a Milestone ETHOS-CFR continuous-flow reactor.
16. For examples of α-methylation with DMC for activated methylenes see: (a) Bomben, A.; Marques, C. A.; Selva, M.; Tundo, P. *Tetrahedron* **1995**, *51*, 11573; (b) Tundo, P. *Pure Appl. Chem.* **2000**, *72*, 1793; (c) Selva, M.; Marques, C.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1323; (d) Tundo, P.; Trotta, F.; Moraglio, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1070.
17. Granitza, D.; Beyermann, M.; Wenschuh, H.; Haber, H.; Carpino, L. A.; Truran, G. A.; Bienert, M. *J. Chem. Soc., Chem. Commun.* **1995**, 2223.
18. For an example of using phase transfer catalyst to accelerate a homogeneous reaction under classical thermal conditions see: Matsui, M.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2663.
19. For an example of acid-catalyzed esterification see: Nakao, R.; Oka, K.; Fukomoto, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1267.