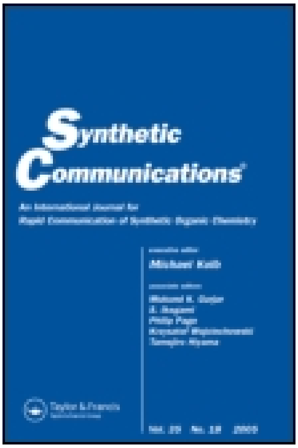

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Microwave-Assisted Methylation of Carboxylic Acids and Phenolic Compounds with Dimethyl-Carbonate Under Solvent-Free Condition

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Microwave-Assisted Methylation of Carboxylic Acids and Phenolic Compounds with Dimethyl-Carbonate Under Solvent-Free Condition

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ABSTRACT

Phenolic compounds and carboxylic acids are methylated with dimethyl carbonate in the presence of a catalytic amount of $BF_3 \cdot OEt_2$, DBU, or KOH, in good to excellent yields under microwave irradiation and solvent-free conditions.

Key Words: Carboxylic acid; Dimethyl carbonate; Methylation; Microwave irradiation; Phenolic compounds.

Methylation of carboxylic acids and phenolic compounds are industrially important process in chemistry.[1] Although many effective and reliable protocols for the synthesis of methyl esters and methyl aryl ethers have

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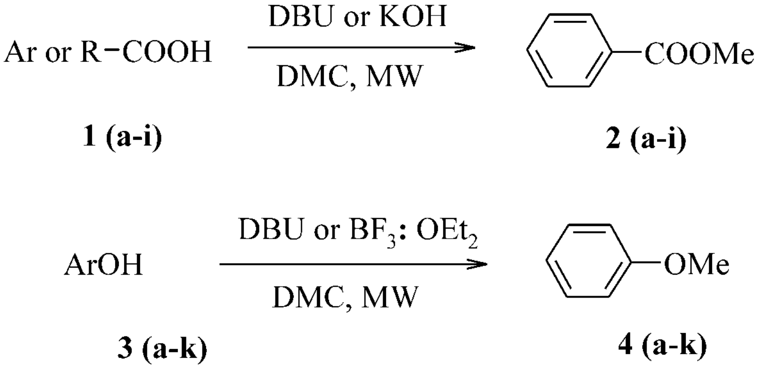
been reported in the literature, the common approaches to the synthesis of these compounds are methylating with hazardous reagents such as methyl iodide, dimethyl sulfate, orthoesters, and diazomethane, or methylating with nontoxic reagents under harsh condition, using a solvent such as DMF.[2] Furthermore, the development of an environmentally friendly process for synthesis of these compounds has also attracted extensive attention.[3]

More recently, methylation of phenols and *NH*-containing heteroaromatic compounds have been reported with dimethyl carbonate using a tertiary amine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or DABCO under conventional thermal heating with long reaction time. The rate enhancement was accomplished by applying microwave irradiation using CH_3CN or DMF as solvent. The same microwave reaction further accelerated by charging one equiv. of expensive phase-transfer catalyst such as tetrabutylammonium iodide (TBAI) to the reaction mixture.[4]

Solvent-free media under microwave irradiation are gaining more widespread use in organic chemistry. The published examples clearly show that microwave energy significantly reduces reaction time for a diverse selection of chemical processes traditionally performed under external heating.[5] In continuation of our work on solvent-free and microwave-assisted organic reactions,[6] we now report a very simple, fast, and general method for the *O*-methylation of carboxylic acids and phenolic compounds without using a first solvent with dimethyl carbonate (DMC) in the presence of $BF_3 \cdot OEt_2$ as a catalyst, under microwave irradiation with excellent yields. DMC is a green reagent and generates methanol and CO_2 as by-products after reaction. The methylating activity of DMC has been widely studied in recent years.[7,8]

When phenolic compounds were reacted with DMC in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ (ca. 0.2 equiv.) under microwave irradiation and solvent-free conditions, the corresponding *O*-methylated compounds were obtained in good yields (Scheme 1, Table 1). The same results were obtained when carboxylic acids or phenolic compounds were reacted with DMC in the presence of 0.1 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under microwave irradiation in about 1 min (Tables 1 and 2). We also studied methylation of carboxylic acids in the presence of potassium hydroxide as a base under solvent-free conditions and microwave irradiation. Although KOH is very cheap reagent and methylation reaction was carried out under solvent-free conditions, comparison of the yields and the reaction times in Table 1 clearly shows that by using DBU, better yields of methylating products were obtained with shorter reaction times. It should be pointed out that the methylation of carboxylic acids did not proceed without using DBU or KOH as a base. Thus, methylation reaction of 2-hydroxy benzoic acid (salicylic acid) with DMC in the presence of 0.1 equiv. of DBU in DMF



Scheme 1.

(Table 2, entry 7) gave methyl 2-methoxybenzoate in high yield. All products were known and identified by comparison with the literature known NMR data.

In conclusion, the results obtained in this study reveal that a clean, fast, efficient, environmentally benign and solvent-free *O*-methylation of phenolic compounds can be carried out with dimethyl carbonate (DMC) as a methylating agent in the presence of catalytic amounts of $BF_3 \cdot OEt_2$ under microwave irradiation with good to excellent yields. Methylation of carboxylic acids was carried out in the presence of catalytic amounts of DBU or KOH. Although, by using KOH, lower yields of methylating products were obtained with longer reaction time compared with DBU, no solvent was used in this method.

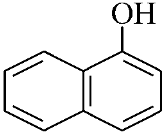
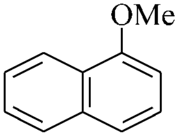
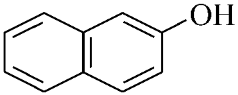
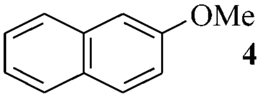
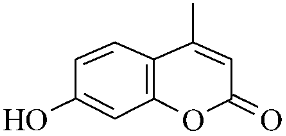
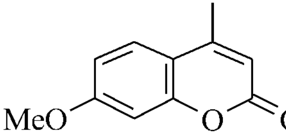
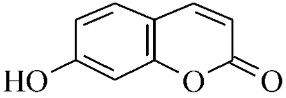
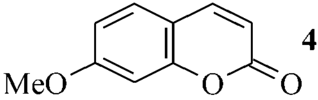
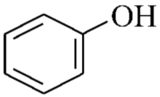
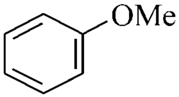
EXPERIMENTAL

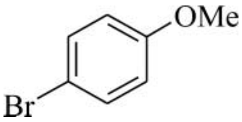
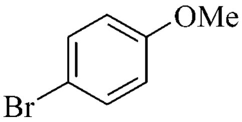
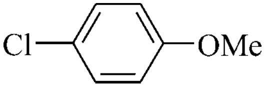
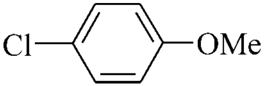
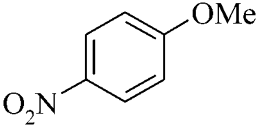
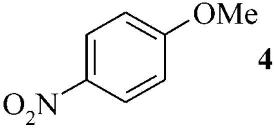
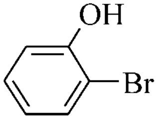
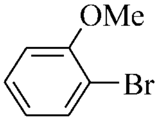
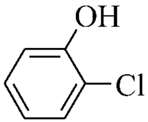
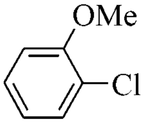
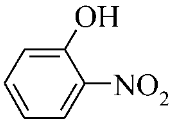
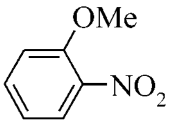
NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured with Perkin–Elmer 1600 FTIR and on Matt Son 1000 Unicam FTIR spectrophotometers.

General Procedure for *O*-Methylation of Phenolic Compounds with DMC Under Solvent-Free Condition.

A mixture of phenol (5 mmol), dimethyl carbonate (10 mmol) and $BF_3 \cdot OEt_2$ (1 mmol) was placed in a sealed teflon container (screw cap type, 50 mL) and subjected to microwave irradiation in a conventional microwave

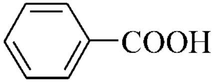
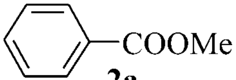
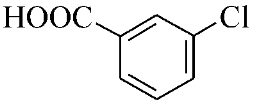
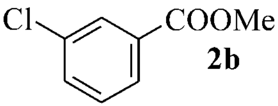
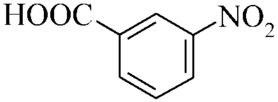
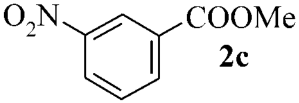
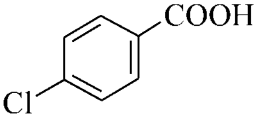
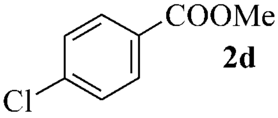
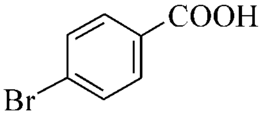
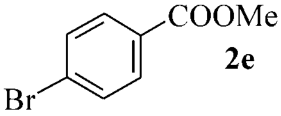
Table 1. Methylation of phenolic compounds with DMC in the presence of $BF_3 \cdot OEt_2$ and DBU.

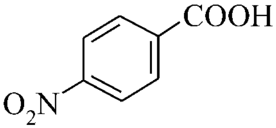
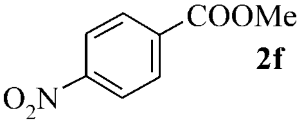
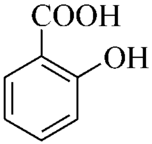
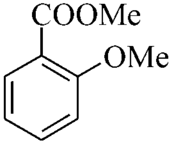
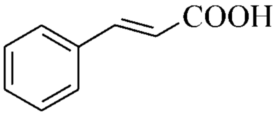
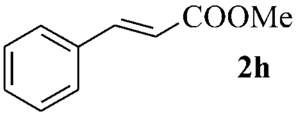
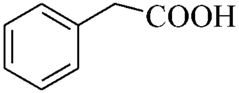
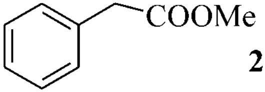
Entry	Substrate	Product	DBU yields (min)[a]	$BF_3 \cdot OEt_2$ yields (min)[a]
1		 **4a**	88 (1.5)	80 (3.0)
2		 **4b**	92 (1.0)	85 (2.5)
3		 **4c**	94 (1.2)	82 (2.5)
4		 **4d**	95 (1.5)	80 (2.5)
5		 **4e**	90 (2.0)	81 (3.5)

6		 **4f**	91 (2.5)	78 (4.0)
7		 **4g**	92 (2.5)	76 (4.5)
8		 **4h**	90 (2.5)	72 (4.5)
9		 **4i**	84 (3.5)	68 (5.0)
10		 **4j**	85 (3.5)	65 (5.0)
11		 **4k**	81 (4.0)	60 (5.5)

[a]Isolated yields.

Table 2. Methylation of carboxylic acids with DMC under microwave irradiation in the presence of DBU and KOH.

Entry	Substrate	Product	DBU, time (sec) (yield, %)[a]	KOH, time (min) (yields, %)[a]
1		 **2a**	45 (97)	3.0 (72)
2		 **2b**	50 (95)	3.1 (69)
3		 **2c**	60 (94)	3.5 (65)
4		 **2d**	45 (94)	3.6 (60)
5		 **2e**	55 (96)	3.5 (62)

6		 **2f**	65 (90)	4.0 (58)
7		 **2g**	75 (92)	4.2 (66)
8		 **2h**	75 (89)	3.8 (63)
9		 **2i**	70 (92)	3.2 (70)

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[a] Isolated yields.

oven with high power for 1–5 min (Table 2). After cooling, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with 5% solution of sodium hydroxide (2 × 20 mL) and then with water (2 × 20 mL), dried over MgSO4, and evaporated to give the pure products. Further purification was carried out by column chromatography on basic alumina eluting with ethyl acetate/hexane, if needed. All compounds were characterized on the basis of spectroscopic data (IR, NMR, and MS) and by comparison with those reported in the literature.

General Procedure for *O*-Methylation Carboxylic Acids or *O*-Methylation of Phenolic Compounds with DMC in the Presence of DBU

A mixture of phenol or carboxylic acid (5 mmol), DMC (10 mmol), DBU (0.5 mmol), and DMF (5 mL) was placed in a sealed teflon container (screw cap type, 50 mL) and subjected to microwave irradiation in a conventional microwave oven with high power for 30 sec to 4.0 min. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL), washed with 5% solution of sodium hydroxide (2 × 20 mL), washed with 5% solution of HCl (2 × 20 mL), and with water (2 × 20 mL), dried over MgSO4, and evaporated to give the pure products. Further purification was carried out by column chromatography on basic alumina eluting with ethyl acetate/hexane, if needed. All compounds were characterized on the basis of spectroscopic data (IR, NMR, and MS) and by comparison with those reported in the literature.

General Procedure for *O*-Methylation Carboxylic Acids with DMC in the Presence of KOH

A mixture of phenol or carboxylic acid (5 mmol), DMC (10 mmol), and KOH (5 mmol) was placed in a sealed teflon container (screw cap type, 50 mL) and subjected to microwave irradiation in a conventional microwave oven with high power for 30 sec to 4.0 min. After cooling, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 × 20 mL), dried over $MgSO_4$, and evaporated to give the pure products. Further purification was carried out by column chromatography on basic alumina eluting with ethyl acetate/hexane, if needed. All compounds were characterized on the basis of spectroscopic data (IR, NMR, and MS) and by comparison with those reported in the literature.

Methoxy Naphthalene, 4b

Solid, mp, 69–72°C (lit., mp 70–73°C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.30–7.32 (m, 1H), 7.39–7.41 (m, 1H), 7.53–7.56 (m, 1H), 7.64–7.67 (m, 1H), 7.90–7.98 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.7 (CH_3), 106.4 (CH), 119.4 (CH), 124.1 (CH), 126.9 (CH), 127.8 (CH), 128.4 (CH), 129.6 (C), 130.1 (CH), 135.3 (C), 158.3 (C); IR: (KBr), υ, 3059.5, 3030.7, 3000.0, 2953.2, 1600.3, 1498.6, 247.6, 1040.4, 784.6, 690.1 cm^{-1}.

7-Methoxy 4-Methyl Coumarin, 4c

Solid, mp 159–161°C (lit., mp 161–162°C), ^{1}H NMR (500 MHz, $CDCl_3$), δ 2.36 (s, 3H), 3.87 (s, 3H), 6.11 (s, 1H), 6.78 (d, $J = 2.3$ Hz), 6.84 (m, 1H), 7.47 (d, $J = 8.7$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.0 (CH_3), 56.0 (CH3), 96.5 (CH), 101.2 (CH), 112.4 (C), 113.9 (CH), 152.6 (C), 155.7 (C), 161.3 (C), 163.0 (C); MS, 190 (M+), 162, 147 (base peak), 91, 77; IR: (KBr), υ, 3356.6, 3097.2, 2961.2, 1730.5, 1523.1, 1445.3, 1392.3, 1261.3, 1051.5 cm^{-1}.

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REFERENCES

1. (a) Henk, L.; Aalten, H.L.; Koten, G.; Grove, D.; Kuilman, M.T.; Piekstra, O.G.; Lumbertus, A.; Hulshof, L.A.; Roger, A.; Sheldon, R.A. Tetrahedron **1989**, *45*, 5565; (b) Grinev, A.N.; Ryabova, S.Yu. Chem. Heterocycl. Compd., Engl. Transl. **1982**, *18*, 153; (c) Kotake, Y.; Okauchi, T.; Jijima, A.; Yoshimatsu, K.; Nomura, H. Chem. Pharm. Bull. **1995**, *43*, 829.
2. (a) Minisci, F.; Vismara, E.; Fontana, F. J. Org. Chem. **1989**, *54*, 5224; (b) Zabirov, N.G.; Shamsevaleev, F.M.; Cherkasov, R.A. J. Gen. Chem. USSR, Engl. Transl. **1990**, *60*, 464; (c) Mizrakh, L.I.; Polonskaya, L.Yu.; Gvozdetskii, A.N.; Ivanova, T.M.L.; Karpunina, B. Chem. Heterocycl. Compd., Engl. Transl. **1990**, *26*, 482; (d) Jursic, B.; Bregant, N. Synth. Commun. **1989**, *19*, 2087; (e) Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. J. Org. Chem. **2001**, *66*, 2246; (f) Sulko, J. J. Acta Pol. Pharm. **2000**, *57*, 79.

3. (a) Green, T.W.; Wuts, P.G.M. *Protective Groups In Organic Synthesis*, 2nd ed.; John Wiley & Sons, Inc.: New York, 1991; 224–276; (b) Lee, A.S.; Yang, H.; Su, F. Tetrahedron Lett. **2001**, *42*, 301.
4. Shieh, W.; Dell, S.; Bach, A.; Repic, O. Org. Lett. **2001**, *3*, 4279.
5. Shieh, W.; Dell, S.; Bach, A.; Repic, O. Tetrahedron Lett. **2002**, *43*, 5607.
6. (a) Saidi, M.R.; Bigdeli, K. J. Chem. Res. (S) **1998**, 800; (b) Sharifi, A.; Mojtahedi, M.M.; Saidi, M.R. Tetrahedron Lett. **1999**, *40*, 2661; (c) Mojtahedi, M.M.; Saidi, M.R.; Heravi, M.M.; Bolourtchian, M. Monash. Chem. **1999**, *130*, 1175; (d) Mojtahedi, M.M.; Saidi, M.R.; Bolourtchian, M.; Heravi, M.M. Phosphorus, Sulfur, and Silicon **2002**, *177*, 289; (e) Saidi, M.R. Indian J. Chem. **1982**, *21B*, 474; (f) Saidi, M.R.; Rajabi, F. Heterocycles **2001**, *55*, 1805.
7. (a) Katritzky, A.R.; Singh, S.K. J. Org. Chem. **2002**, *67*, 9077; (b) Pottorof, R.S.; Chadha, N.K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M.R. Tetrahedron Lett. **2003**, *44*, 175; (c) Ferret, R.R.; Hyde, M.J.; Lahti, K.A.; Friebe, T.L. Tetrahedron Lett. **2003**, *44*, 2573; (d) Villemin, D.; Caillot, F. Tetrahedron Lett. **2001**, *42*, 639; (e) Ouk, S.; Thiebaud, S.; Borredon, E.; Legars, P.; Lecomte, L. Tetrahedron Lett. **2002**, *43*, 2661; (f) He, H.; Wu, Y.-J. Tetrahedron Lett. **2003**, *44*, 3445.
8. (a) Shieh, W.; Dell, S.; Bach, A.; Repic, O. J. Org. Chem. **2002**, *67*, 2188; (b) Selva, M.; Tundo, P.; Pesora, A. J. Org. Chem. **2002**, *67*, 9238; (c) Perosa, A.; Selva, M.; Tundo, P.; Zordan, F. Synlett **2000**, 272; (d) Kirumakki, S.R.; Nagaraju, N.; Murthy, K.V.V.S.B.S.R.; Narayanan, S. Applied Catal. **2002**, *226*, 175; (e) Lee, Y.; Shimizu, I. Synlett. **1998**, 1063; (f) Bomben, A.; Marques, C.A.; Selva, M.; Tundo, P. Tetrahedron **1995**, *51*, 11573; (g) Bomben, A.; Selva, M.; Tundo, P. J. Chem. Res. (S) **1997**, 2688.

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