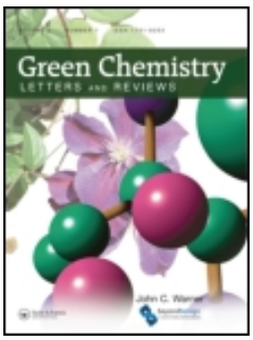

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RESEARCH LETTER

Methyl esterification of carboxylic acids with dimethyl carbonate promoted by K_2CO_3/tetrabutylammonium chloride

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A facile and green process in which K_2CO_3 in combination with the phase transfer catalyst tetrabutylammonium chloride was explored to promote the esterification of carboxylic acids with dimethyl carbonate has been developed. High yield and purity were observed for most of the investigated methyl esters.

Keywords: dimethyl carbonate; phase transfer catalyst; K_2CO_3; esterification; tetrabutylammonium chloride

Introduction

Methyl esters of carboxylic acids are widely used in many branches of industry, such as fine chemicals, pharmaceutical products, cosmetics, and food preservatives (*1*). The conversion of carboxylic acids into corresponding methyl esters is also an effective method for the protection of carboxyl group (*2*). The traditional Fisher esterification in which carboxylic acids are directly condensed with methanol under acid catalysis, however, is undesirable due to its reversibility and harmful effects to environment (*3*). In order to overcome the above limitations, the exploration of alternative methylating reagents, such as methyl iodide (*4*), dimethyl sulfate (*5,6*), and diazomethane (*7*), has been reported. Some less common reagents have also been investigated (e.g. *O*-methylcaprolactam, trimethylsulfonium hydroxide, trimethyl orthoacetate, and methyl trichloroacetate) (*8–11*). However, these procedures are less convenient for large scale synthesis owing to the expensiveness of the reagents.

Thus, the search for a new methylating reagent which is both highly economical and friendly to environment has great significance. Dimethyl carbonate (DMC) satisfies the above requirements and has already been used frequently to methylate various functional groups in organic chemistry: phenols (*12–17*), alcohols (*18,19*), amines (*20–22*), carboxylic acids (*23–33*), and activated methylenes (*34–37*).

The use of DMC as a reagent for methyl esterification has been reported increasingly in recent years. The conversion can be promoted by organic bases, such as 4-dimethylaminopyridine (*23*), 1,8-diazabicyclo[5.4.0]undec-7-ene (*24–26*), 1,4-diazabicyclo[2.2.2]-octane (*24*), and 1,2-dimethylimidazole (*27*). However, there are some unavoidable limitations: toxic chemicals, large consumption of catalysts (1 equiv.), harsh reaction conditions (high pressure and temperature in an autoclave), and requirement of a co-solvent (dimethylformamide, DMF). Some acidic solid catalysts have been also used: anion-modified metal oxides (*28*), mesoporous sulfated zirconia (*29*), zeolite (*30,31*), and mesoporous aluminosilicate (*32*). Although they can be recycled and gave the high yield of methyl esters, the esterification still proceeded under high pressure in a stainless steel autoclave due to the need of high temperature for the methylation. Strong inorganic base or acid, such as KOH (*26*) or H_2SO_4 (*33*), was also able to catalyze the esterification with DMC. However, they are corrosive chemicals and give the moderate yield of methyl esters.

Selva and Tundo explored the reaction of DMC with mercaptobenzoic acids and carboxylic acids bearing OH substituents in the presence of a cheap and nontoxic catalyst K_2CO_3 (*22*). In spite of the high conversion, there are several shortcomings: low selectivity, requirement of an autoclave. We reported herein the use of K_2CO_3/tetrabutylammonium chloride (TBACl) as a green catalyst that promoted the esterification under milder conditions (reflux heating under atmospheric pressure and lower consumption of K_2CO_3). Indeed, the phase transfer catalyst (PTC)

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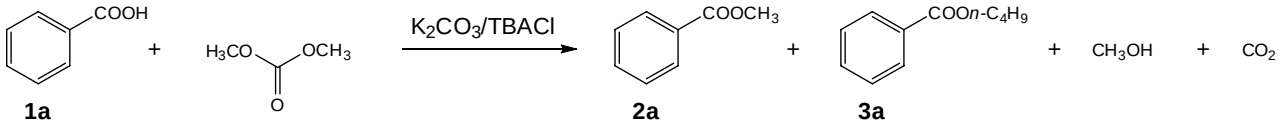
TBACl not only increases the interaction between K_2CO_3 and organic compounds, but also functions as reaction medium to keep the reaction mixture in high temperature so that the methylation with DMC can occur. This catalytic system was applied for the methylation of phenols with DMC (*17*), but this is the first time it is used to methylate carboxylic acids.

Results and discussion

The increase in transformation is consistent with the utilized amount of TBACl (entry 1–6). No conversion is observed in the absence of TBACl. However, the more amount of TBACl is used, the more by-product butyl benzoate (**3a**) which is formed by the interaction between potassium carboxylate and TBACl, is achieved. By contrast, the conversion proceeds with a low yield even without K_2CO_3 (entry 7). High selectivity toward methyl benzoate achieves with any amount of K_2CO_3, but the transformation gets the maximum with 0.1 equiv. of K_2CO_3 and reduces when more K_2CO_3 is used. That the presence of too much K_2CO_3 blocks the heat transfer from the oil-bath to the reaction mixture can be a reason for the decrease in transformation. Exploration of too much DMC also makes the transformation lower. Indeed, using DMC as a solvent with an excess quantity makes the reaction mixture not reach the temperature in which the methylation can take place [the boiling point of DMC is only 90°C whereas the methylation occurs above 120°C (*38*). Herein, aside from catalyzing the esterification of carboxylic acids, PTC (TBACl) can also serve as a solvent to keep the reaction temperature high enough for the methylation to occur. Shortening reaction time (entry 16) leads to poor transformation, whereas expanding reaction time over 12 h did not give better transformation. Raising the temperature from 130 to 190°C can improve the transformation from 4 to 89% in Table 1.

We applied the most optimal condition for benzoic acid (entry 21) to other carboxylic acids, and got some results given in Table 2. The steric

Table 1. Esterification of benzoic acid with DMC under catalysis of K_2CO_3/TBACl.

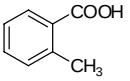
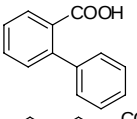
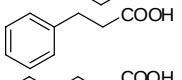
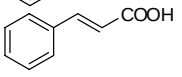
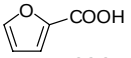
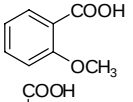
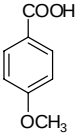
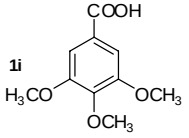
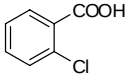
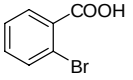
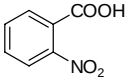


1a **2a** **3a**

Entry	**1a**:DMC:K_2CO_3:TBACl[a]	Temperature. (°C)[b]	Time (h)	Products (%, GC) **2a**	**3a**	Transformation (%)	Yield of **2a** (%)
1	1:2:1:0	150	12	–	–	No reaction	–
2	1:2:1:0.1	150	12	99	1	23	22
3	1:2:1:0.2	150	12	97	3	57	55
4	1:2:1:0.3	150	12	94	6	64	61
5	1:2:1:0.5	150	12	61	39	79	53
6	1:2:1:1	150	12	44	56	82	42
7	1:2:0:0.3	150	12	96	4	24	23
8	1:2:0.1:0.3	150	12	98	2	83	82
9	1:2:0.2:0.3	150	12	98	2	77	76
10	1:2:0.5:0.3	150	12	97	3	67	65
11	1:2:0.7:0.3	150	12	96	4	61	59
12	1:1:0.1:0.3	150	12	75	25	35	28
13	1:3:0.1:0.3	150	12	100	0	77	77
14	1:4:0.1:0.3	150	12	84	16	80	70
15	1:5:0.1:0.3	150	12	84	16	16	14
16	1:2:0.1:0.3	150	9	99	1	44	43
17	1:2:0.1:0.3	150	15	98	2	83	82
18	1:2:0.1:0.3	150	18	98	2	84	83
19	1:2:0.1:0.3	150	24	99	1	82	81
20	1:2:0.1:0.3	130	12	99	1	4	4
21	1:2:0.1:0.3	170	12	97	3	88	86
22	1:2:0.1:0.3	190	12	97	3	89	87

[a]Molar ratio.
[b]The temperature in the oil-bath.

Table 2. Esterification of some carboxylic acids with DMC under catalysis of K_2CO_3/TBACl.

Entry	Substrate	Products (%, GC)		Transformation (%)	Yield of methyl ester (%)	References[b]
		Methyl ester[a]	Butyl ester			
23	**1b** 	98	2	92	90	(*38*)
24	**1c** 	94	6	95	90	(*39*)
25	**1d** 	98	2	90	89	(*40*)
26	**1e** 	96	4	94	90	(*40*)
27	**1f** 	97	3	74	72	(*41*)
28	**1g** 	94	6	79	75	(*41*)
29	**1h** 	98	2	90	88	(*41*)
30	**1i** 	96	4	89	86	(*38*)
31	**1j** 	98	2	75	74	(*38*)
32	**1k** 	98	2	85	84	(*42*)
33	**1l** 	98	2	8	8	(*41*)

[a]The purity and authenticity of methylated products were checked by GC–MS and ^{1}H NMR spectroscopy.
[b]The ^{1}H NMR spectral data of methyl esters are consistent with those reported in Section References.

hindrance caused by an ortho-positioned hydrocarbon substituent such as methyl (**1b**) or even phenyl group (**1c**) did not give any considerable differences in the transformation and the yield of methyl esters when compared with benzoic acid. No significant change in conversion is also observed when moving the carboxyl group far away the benzene ring (**1d** and **1e**). On the other hand, the electronic effects have evident influences on the esterification. This can be explained if carboxylate anion is accepted as an intermediate in the esterification with DMC. Under the basic activity of K_2CO_3, the carboxylic acid changes into the carboxylate anion which interacts to one of the methyl groups of DMC molecule. The efficiency of conversion thus depends on the density of negative charge on the corresponding carboxylate anions. Good conversion is obtained in the cases of **1b**, **1h**, and **1i** which possess electron-donating substituents – methyl or methoxy. However, for **1f** and **1g** in which the methoxy substituent is positioned closer to the carboxyl group, the lower conversion is observed as a result of the competition between the resonant electron-donating effect and the inductive electron-withdrawing effect. Therefore, the mere electron-withdrawing groups definitely reduce the conversion into corresponding esters. This trend is observed the most evidently in **1l** in which the ortho-positioned nitro group reduces the density of electrons on the carboxyl group via resonance as well as inductive electron-withdrawing effect. Bromo substituent (**1k**) gives higher transformation and yield (10%) than chloro substituent (**1j**) due to its less electronegativity.

Experimental

General

All chemicals were purchased from Sigma-Aldrich and employed without further purification. Solvents were high performance liquid chromatography (HPLC) grade from Labscan. The identity of methylated products was confirmed by ^{1}H NMR and mass spectra. The ^{1}H NMR spectra were recorded on Varian Mercury 300 MHz using $CDCl_3$ and tetramethylsilane (TMS) as solvent and internal standard, respectively. GC–MS analyses were performed on Agilent GC System 6890 Series, equipped with a mass selective detector Agilent 5973 and a capillary column DB-5MS (60 m $\times$ 0.25 mm $\times$ 0.3 μm).

Typical procedure for the esterification with DMC

A flask (10 mL volume) was filled with benzoic acid (366 mg, 3.0 mmol), DMC (540 mg, 6.0 mmol), K_2CO_3 (41 mg, 0.3 mmol), and TBACl (205 mg, 0.9 mmol). Then, it was connected to a condenser and placed in an oil-bath that was preheated at 170°C. Upon completion, the resulting mixture was cooled to room temperature and diluted with EtOAc. This mixture then was washed twice with 2 M HCl, twice with saturated aqueous $NaHCO_3$, and twice with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under vacuum to afford methyl benzoate as colorless liquid (86%).

Conclusion

We have presented an environmentally benign method to synthesize common methyl esters by using DMC under catalysis of K_2CO_3–TBACl. The conversion for most carboxylic acids obtained in good yield with very high selectivity toward corresponding methyl esters. The steric hindrance of substituents has negligible influences on the conversion while the inductive or resonance electron-withdrawing effect causes the decrease in conversion. The competition between inductive electron-withdrawing and resonance electron-donating effect caused by the same substituent lead to the moderate conversion into esters.

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