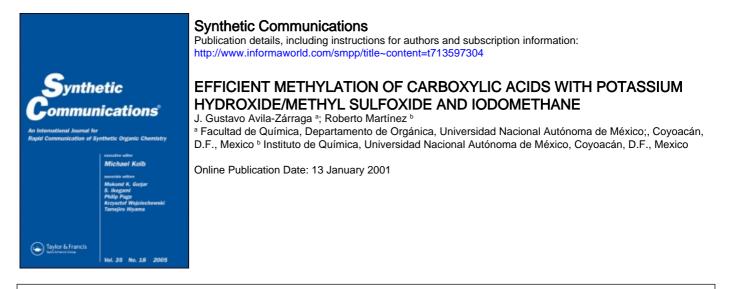
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EFFICIENT METHYLATION OF CARBOXYLIC ACIDS WITH POTASSIUM HYDROXIDE/METHYL SULFOXIDE AND IODOMETHANE

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ABSTRACT

Methylation of several carboxylic acids was promoted by potassium hydroxide in methyl sulfoxide and iodomethane to produce corresponding methyl esters in good yield. This method has advantage over other described methods because it uses inexpensive reagents and the reaction is carried out under mild and favorable conditions.

The development of methodology for the methylation of carboxylic acids has been a challenging goal for organic chemists. Numerous reagents and procedures have been recommended for this purpose. Many methods have been reported using methanol on: sulfuric acid,² hydrochloric acid,³

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amberlyst-15,⁴ sulfuric acid plus methyl sulfate,⁵ thionyl chloride,⁶ phosphorus oxychloride,⁷ boron trifluoride,⁸ phosphorus pentoxide,⁹ chlorotrimethylsilane,¹⁰ sulfonic acid,¹¹ triphenylphosphine and potassium hydroxide,¹² manganese(IV) oxide,¹³ iron(III) perchlorate,¹⁴ nickel(II) chloride,¹⁵ indium(II) iodide,¹⁶ iron(III) sulfate,¹⁷ dimethylthin dichloride,¹⁸ copper(II) chloride,¹⁹ DCC,²⁰ DMTMM,²¹ TCE.²² Another important route is the methylation with diazomethane reagent. However, in this case generation of diazomethane is hazardous and tedious.²³ A recently proposed approach uses cesium carbonate in hot methanol/water followed by iodomethane in DMF.²⁴ Unfortunately many of the methods mentioned still suffered from some disadvantage, as they require severe conditions, needing excess of the reagents, use dangerous reagents or employ tedious work up procedures. To explore further applications of methyl sulfoxide in organic synthesis,²⁵ herein we report an efficient unprecedented methylation of carboxylic acids using a slurry of potassium hydroxide in methyl sulfoxide and iodomethane.

 $\underset{1a-1}{\text{RCOOH} + \text{MeI}} \xrightarrow{\text{DMSO}} \underset{2a-1}{\text{RCOOMe}}$

In a typical experiment, treatment of acid (1 mmol) 1a with iodomethane (1.48 mmol) in the presence of a mixture of potassium hydroxide in DMSO at room temperature by 2 hours gave the methyl ester 2a in 94% yield. Under identical reaction conditions, the aromatic carboxylic acids (1b-h) afforded the corresponding methyl ester (2b-h) in good yields. Similar results were also obtained for aliphatic carboxylic acids **1i–I**. The ratio of carboxylic acid/iodomethane (1.0:1.48) proved to be the optimal system efficient for prepared the representative set of compounds listed in Table 1. When we used a lesser relation than this ratio the yields and rates of conversion to methyl esters was poor. This behavior is in accord with the results previously reported for a SN_2 type reaction. This method also was successfully applied for 1-10 g scale and gave identical yields. This result is very important because methylation of carboxylic acids constitutes a challenging goal for organic chemist due to the broad use of methyl esters as reaction intermediates, biologically active compounds, derivatives more easily separated than natural carboxylic acids, etc.

The formation of (2a–l) from (1a–l) with iodomethane in the presence of potassium hydroxide in methyl sulfoxide can be rationalized as shown below:

$$MeS(O)Me + KOH \rightleftharpoons KCH_2S(O)Me$$
(1)

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Compound No.	R	Reaction time (h)	Yield (%)	$IR (cm^{-1})$	Ref.
a	3,4,5-triMeOC ₆ H ₂	2	94	1714	3i
b	$4-BrC_6H_4$	2	92	1720	13/23a
c	$4 - FC_6H_4$	2	88	1725	23i/23a
d	$4-NH_2C_6H_4$	2	91	1706	23a
e	C_6H_5	1	95	1722	13
f	$3-NO_2C_6H_4$	2	98	1730	13
g	$4-ClC_6H_4$	2	76	1720	23a
ĥ	Pyridinyl	0.5	85	1732	23a
i	C ₆ H ₅ CH=CH	2	81	1716	2d
j	$C_{6}H_{11}$	2	94	1737	2g
k	C_5H_{11}	2	96	1742	2a
1	MeO ₂ CCH ₂	2	54	1735	3c

Table 1. Yields and Physical Data for Methyl Esters (2a-I)

$$RCOOH + KCH_2S(O)Me \rightleftharpoons RCOO^{-}K^{+}$$
(2)

$$RCOO^{-}K^{+} + MeI \longrightarrow RCOOMe$$
(3)

The superbasicity of the KOH/DMSO system, Eq. (1), as a first approximation is due to the separation of the base ion-pair²⁶ and the formation of a highly basic and poorly solvated dimsyl anion.²⁷ This anion could undergo a base-acid reaction with the corresponding carboxylic acid, Eq. (2). The nucleophilic attack of carboxylate anion on iodomethane produces the final products (2a–I).

In conclusion, this methylation method using an inexpensive, safe, and easily handled solvent, methyl sulfoxide, is a simple and efficient protocol that is applicable to a variety of carboxylic acids. The operation simplicity, rapid reaction rates, and formation of pure products in good yields at very moderate temperature make this method superior to existing one.

EXPERIMENTAL

All reactions were performed in oven-dried glassware at room pressure. Reaction mixtures were concentrated by using a rotary evaporator (*ca.* 20° C/20 Torr). Thin layer chromatography was carried out on Merck Kieselgel 60 PF₂₅₄. Commercial grade reagents were used without further



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purification except when indicated. All melting points are uncorrected. The IR spectra were recorded on a Nicolet FT-55X spectrophotometer. The ¹H-NMR spectra were determined on a Varian FT-200 instrument. All nmr spectra were obtained with the pulse sequence as part of the spectrometer's software and was determined in deuteriochloroform solution containing SiMe₄ as the internal standard with chemical shifts (δ) expressed downfield from SiMe₄. Mass spectra were recorded using Jeol SX-102 mass spectrometer using the direct inlet system with an ionization energy of 70 eV, an emission current of 100 µA and ion source temperature of 150°C.

The structures of compounds 2a-1 were supported by IR, ¹H-NMR and MS spectral data which are identical to those reported. The purity of compounds was checked by thin layer chromatography and ¹H-NMR.

Preparation of Methyl 3-Nitrobenzoate (2f)

Typical Procedure

0.25 g of powered potassium hydroxide 85% (1.26 mmol) and 5 mL of methyl sulfoxide was vigorously stirred for 30 minutes at room temperature. To this slurry was added a solution of 0.5 g of **1f** (2.99 mmol) in 5 mL of methyl sulfoxide and the resulting mixture was stirred for 15 minutes and then cooled with a ice-water bath. After the addition of iodomethane (0.63 g, 4.43 mmol) the mixture was stirred for a further 2 hours at room temperature and then added a mixture of ice-water. The resulting solution was extracted with ethyl acetate ($15 \text{ mL} \times 3$). The organic layer was washed with a sodium chloride saturated solution ($15 \text{ mL} \times 5$) and dried (sodium sulphate) and concentrated to give **2f** as an oil (0.53 g, 98%).

¹H-NMR: δ 8.28 (m, 5H), 3.99 (s, 3H); MS: m/z (%), M⁺:181 (58).

Methyl 3,4,5-trimethoxybenzoate (**2a**), ¹H-NMR: δ 7.30 (s, 2H), 3.91 (s, 12H); MS: m/z (%), M⁺: 226 (100%).

Methyl 4-Bromobenzoate (**2b**); ¹H-NMR: δ 7.24 (AA', BB'; 4H), 3.90 (s, 3H). MS: m/z (%), M⁺: 214, 216 (56%).

Methyl 4-fluorobenzoate (**2c**); ¹H-NMR: δ 8.05 (m, 2H), 7.10 (m, 2H), 3.91 (s, 3H); MS: m/z (%), M⁺: 154 (35).

Methyl 4-aminobenzoate (2d); ¹H-NMR: δ 7.26 (AA', BB'; 4H), 4.0(brs, 2H, exchange with D₂O), 3.88 (s, 3H): MS m/z (%), M⁺: 151 (42).

Methyl benzoate (**2e**); ¹H-NMR: δ 7.73 (m, 5H), 3.91 (s, 3H); MS: m/z (%), M⁺: 136 (85).

Methyl 4-chlorobenzoate (**2g**); ¹H-NMR: δ 7.96 (AA', BB': 4H), 3.91 (s, 3H); MS: m/z (%), M⁺+2; 172 (8), M⁺; 170 (25).



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Methyl isonicotinate (2h); ¹H-NMR: δ 8.48 (m, 2H), 7.85 (m, 2H), 3.96 (s, 3H); MS: m/z (%), M⁺: 137 (100).

Methyl *trans*-cinnamate (2i); ¹H-NMR: δ 7.70 (d, J=16 Hz, 1H), 7.45 (m, 5H), 6.44 (d, J = 16 Hz, 1H), 3.81 (s, 3H); MS: m/z (%), M⁺: 162 (89).

Methyl cyclohexanecarboxylate (2j); ¹H-NMR: δ 3.66 (s, 3H), 2.30 (m, 1H), 1.9–1.2(brs.,11H); MS: m/z (%), M⁺: 142 (30).

Methyl hexanoate (**2k**); ¹H-NMR: δ 3.66 (s, 3H), 2.30 (t, J = 8 Hz, 2H), 1.66 (m, 2H), 1.33 (m, 2H), 0.89 (m, 5H); MS: m/z (%), M⁺: 130 (20).

Dimethyl malonate (21); ¹H-NMR: δ 3.75(s, 6H), 3.40(s, 2H); MS: m/z (%), M⁺: 132 (34).

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