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A new reagent for the methylation of carboxyl groups

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Abstract—A new reagent for the preparation of methyl esters of carboxylic acids is described. The reaction involves treatment of acids with methanesulfonyl chloride in pyridine at 0°C. © 2001 Published by Elsevier Science Ltd.

Methanesulfonyl chloride finds a general applicability in organic synthesis. It is used to prepare mesylates of alcohols in the presence of pyridine.[1] In 1976 Japanese chemists reported examples of an abnormal conversion of allylic alcohols into chlorides with inversion of configuration by treatment with methanesulfonyl chloride in pyridine.[2] For Beckmann fragmentations of oximes[3] and fragmentation of oxoalkane nitriles,[4] methanesulfonyl chloride is used in refluxing pyridine. In the present paper we report the methylation of carboxylic acids with mesyl chloride in pyridine at 0°C. Prior to this, the general applicability of this reagent for methylation has not been reported and in only one publication,[5] formation of methyl esters of carboxylic acid was noted during the synthesis of hindered α-diazoketones via acyl mesylates. The reaction was done in triethylamine. In an attempt to prepare 3-*O*-mesyl derivative of ursolic acid, we obtained its carbomethoxy derivative in addition to the required *O*-mesyl derivative.

$$\mathrm{RCOOH + MsCl} \xrightarrow{\text{Py, } 0^\circ\mathrm{C}} \mathrm{RCOOMe}$$

On further elaboration of the reaction to various classes of carboxylic acids (entries 2–8, Table 1), the general applicability of the reaction was observed. In each case a solution of the acid (1 mmol) in anhydrous pyridine (1.2 mmol) was treated with methanesulfonyl chloride (1.2–2.5 mmol) at 0°C (except entry 7). The reaction time required for completion of the reaction was variable.

Although methyl esters, which are the most simple esters can be prepared by numerous methods and a great variety of methods for their preparation is well documented,[6] our procedure offers the use of new and inexpensive reagent, mildness and simplicity. The scope of reagent can be gauged from the wide range of substrates entered in Table 1. In all cases mild conditions have been used.

The methylation of the carboxy group of ursolic acid **1** is representative. A solution of the acid (100 mg, 0.219 mmol) in anhydrous pyridine (2 ml, 0.3 mmol) was treated with methanesulfonyl chloride (0.041 ml, 0.54 mmol) at 0°C and the reaction was monitored by TLC. Evolution of SO_2 gas was observed and confirmed by collecting the gas through a delivery tube in a test tube containing H_2O. The sulfurous acid thereby formed turned blue litmus paper red. The gas also decolorized a dilute solution of $KMnO_4$. After 60 min, **1** was almost completely consumed and the reaction mixture was partitioned between ethyl acetate and H_2O. The organic phase was washed, dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the reaction mixture by column chromatography using hexane–EtOAc (7.5:2.5) as eluent, afforded a mixture of 3β-mesyloxyursolic acid **1A** and methyl 3β-mesyloxyursolate **1B** in a 40:60 ratio and an 83% overall yield (99.7 mg). Their ratio was determined by ^{1}H NMR spectroscopy and they were separated into **1A** and **1B** through thick layer chromatography (silica gel, hexane–EtOAc, 7.5:2.5)

Further studies on this new procedure are in progress and will be reported shortly.

Keywords: methylation; carboxylic acid; methanesulfonyl chloride.

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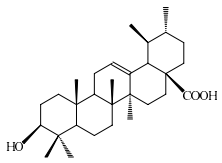
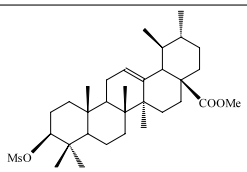
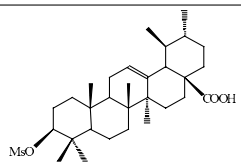
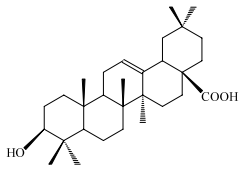
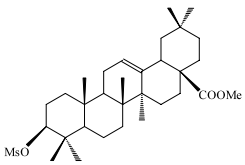
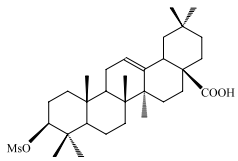
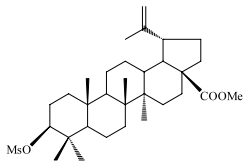
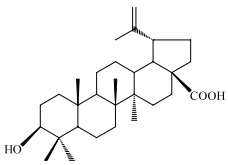
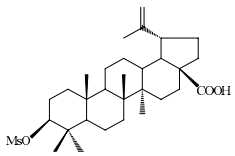
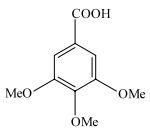
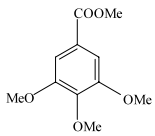
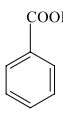
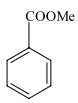
Table 1. Carboxyl group methylation by mesyl chloride

Entry	Substrate	Product A	Product B	Ratio* **A**:**B**	Reaction Time (min)	Overall yield (%)
1	 **1**	 **1A**	 **1B**	40:60	60	83
2				40:60	Over-night	80
3				20:80	Over-night	82
4	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	$CH_3(CH_2)_7CH{=}CH(CH_2)_7COMe$	-	-	45	66
5			-	-	20	70
6			-	-	40	71
7	$CH_3(CH_2)_{16}COOH$	$CH_3(CH_2)_{16}COOMe$	-	-	25	68
8			-	-	30	65

*Ratios have been determined through ^{1}H-NMR integrations

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