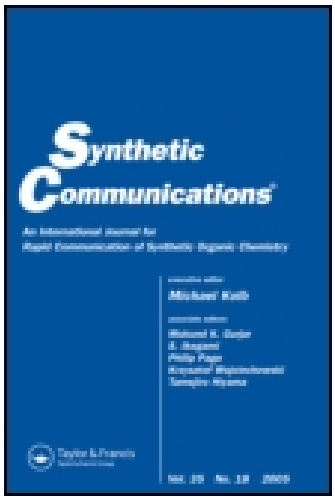

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An Efficient One-Pot Synthesis of *N*-Methoxy-*N*-methylamides from Carboxylic Acids

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ABSTRACT

Several *N*-methoxy-*N*-methylamides were prepared by the reaction of the corresponding carboxylic acids with *N*,*O*-dimethylhydroxylamine hydrochloride at room temperature using trichloromethyl chloroformate in the presence of triethylamine in excellent yields.

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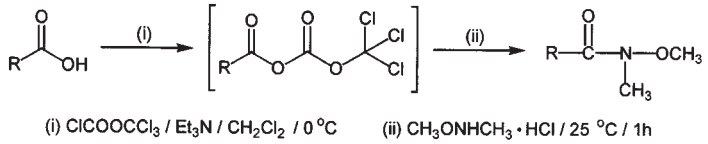
Key Words: Carboxylic acids; *N*-Methoxy-*N*-methylamides; Weinreb amides; Trichloromethyl chloroformate; *N*,*O*-Dimethylhydroxylamine hydrochloride.

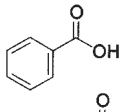
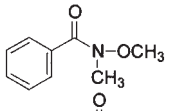
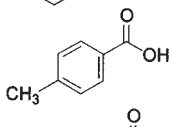
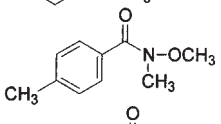
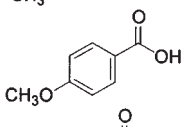
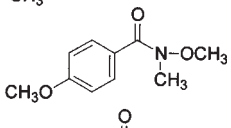
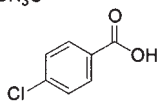
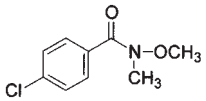
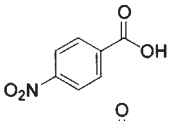
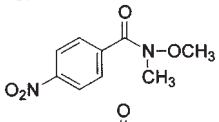
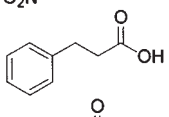
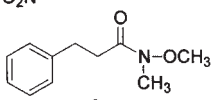
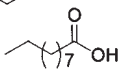
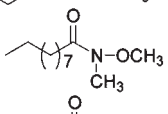
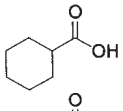
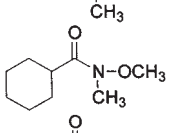
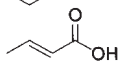
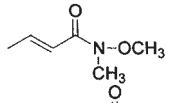
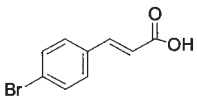
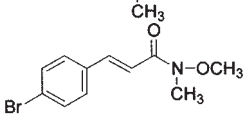
N-methoxy-*N*-methylamides (Weinreb amides) have widely used as versatile synthetic intermediates in organic synthesis since they react with Grignard and organometallic reagents to give ketones.[1–4] Over the last 20 years, a number of methods for the conversion of carboxylic acids to *N*-methoxy-*N*-methylamides have been appeared in Lit.[5–18] In spite of numerous methods available for the synthesis of *N*-methoxy-*N*-methylamides there still exists scope to develop better synthetic methods. We wish to report herein a simple one-pot procedure for the conversion of carboxylic acids to *N*-methoxy-*N*-methylamides using trichloromethyl chloroformate as shown in Sch. 1.

The *N*-methoxy-*N*-methylamides can be conveniently prepared from carboxylic acids and *N*,*O*-dimethylhydroxylamine hydrochloride at room temperature using trichloromethyl chloroformate in the presence of triethylamine. The carboxylic acid undergoes reaction with trichloromethyl chloroformate in the presence of triethylamine to give a mixed carbonic anhydride as activated intermediate. Nucleophilic attack of the *N*-methoxy-*N*-methyl amine on the carbonyl carbon in the activated anhydride affords desired Weinreb amide, concomitant with the formation of phosgene, carbon dioxide, and hydrogen chloride by a concerted process. As shown in Table 1, excellent yields of the products were obtained from each of the carboxylic acids examined. The reaction was found to proceed smoothly at room temperature and usually completed within 1 h. The reaction mixture was monitored by TLC until the starting material was consumed. After completion, the triethylamine hydrochloride was removed by suction filtration, and the filtrate was concentrated under reduced pressure. The crude products were purified by short path silica gel column chromatography. Not only aliphatic carboxylic acids but also aromatic carboxylic acids reacted smoothly to afford the corresponding *N*-methoxy-*N*-methylamides in excellent yields. Neither electron-releasing (Entries **1–3**) nor electron-withdrawing substituents



Scheme 1.

Table 1. Preparation of *N*-methoxy-*N*-methylamides from carboxylic acids.

Entry	Acid	Product	Yield[a] (%)
1			97
2			94
3			92
4			96
5			98
6			95
7			93
8			96
9			92
10			93

[a]Yields refer to isolated products.

(Entries **4** and **5**) on the benzoic acids disturbed the facile formation of *N*-methoxy-*N*-methylamides. The reaction of saturated aliphatic, unsaturated aliphatic, and cyclic acids (Entries **6–10**) gave the corresponding *N*-methoxy-*N*-methylamides in excellent yields.

The *N*-methoxy-*N*-methylamides can be also prepared from the mixed carbonic anhydride generated from the treatment of carboxylic acids with

alkyl chloroformates in the presence of base followed by subsequent addition of *N*,*O*-dimethylhydroxylamine hydrochloride.[19] Even though the trichloromethyl chloroformate used here is somewhat more expensive reagent than other acid activating agents such as alkyl chloroformates, the use of this reagent offers some significant advantages compared to the use of routine alkyl chloroformates. Perhaps the advantage of the procedure is the fact that pure Weinreb amides can be obtained without the need to separate by-product. The reaction took place in shorter reaction times and better yields compared to the alkyl chloroformates.[19b,d]

Although trichloromethyl chloroformate has been used to be an excellent activating reagent in several organic reactions such as dehydration of formamides,[20] dehydration of aldoximimes,[21] oxidation of alcohols,[22] acylation of α-aminoalcohols,[23] and formation of isocyanates[24] and dioxolanediones,[25] we did not find where this reagent was used to prepare Weinreb amides from carboxylic acids.

In summary, we have developed an efficient one-pot procedure for the conversion of various carboxylic acids to their corresponding *N*-methoxy-*N*-methylamides using trichloromethyl chloroformate. The present procedure described here has the advantages of mild reaction condition, high yields of products, shorter reaction times, and operational simplicity.

EXPERIMENTAL SECTION

Trichloromethyl chloroformate was purchased from Fluka and used as received. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F254 TLC plate. Purification was performed by flash column chromatography by using Merck 230–400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectral data were obtained on a Jeol JNM-ECP 400 MHz NMR spectrometer. Infrared spectra were recorded using a Jasco FT/IR-410 spectrophotometer with internal calibration. Mass spectra were recorded on a Jeol JMS-700 High Resolution mass spectrometer. The products were characterized by comparison of their ^{1}H NMR spectra with those of known compounds (Entries **1–6** and **8–10**).[9,17,26–28] Otherwise, an unknown product was fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and HRMS analysis (Entry **7**).

General Procedure

To a stirred solution of the carboxylic acid (2 mmol) in CH_2Cl_2 (10 mL) at 0°C were added trichloromethyl chloroformate (2 mmol)

and triethylamine (6 mmol). Then *N*,*O*-dimethylhydroxylamine hydrochloride (2 mmol) was added to the solution and the ice bath was removed. The reaction mixture was stirred at room temperature until completion. The triethylamine hydrochloride was removed by suction filtration. Removal of the filtrate by rotary evaporation followed by short path silica gel column chromatography purification using 20% ethyl acetate in hexane as the mobile phase afforded the pure product.

The characterization of *N*-methoxy-*N*-methyldecanamide (Entry 7). IR (thin film): 2925, 2854, 1670, 1465, 1412, 1382, 1177, 1124, 1003, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.18 (s, 3H), 2.41 (t, $J = 7.32$ Hz, 2H), 1.63 (t, $J = 7.32$ Hz, 2H), 1.20–1.35 (br, 12H), 0.88 (t, $J = 6.96$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 61.3, 32.2, 32.0, 29.6, 29.5, 29.3, 24.7, 22.7, 14.2. HRMS (EI) *m*/*z*: Calcd. for ($C_{12}H_{25}NO_2$): 215.1885. Found: 215.1880 [M^+].

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