

Direct Synthesis of Weinreb Amides from Carboxylic Acids Using Triphosgene

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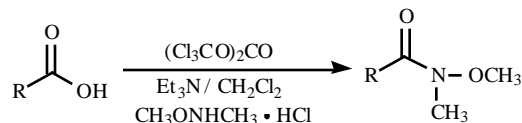
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Abstract: Weinreb amides were conveniently prepared in high yields by reaction of carboxylic acids with *N,O*-dimethylhydroxylamine hydrochloride at room temperature using triphosgene as an acid activator in the presence of triethylamine.

Keyword: Weinreb amides, triphosgene, carboxylic acids, *N,O*-dimethylhydroxylamine hydrochloride.

Since the first report by Nahm and Weinreb [1] on the use of *N*-methoxy-*N*-methylamides (Weinreb amides) in the synthesis of ketones this functional group has been widely used as versatile synthetic intermediates in organic synthesis [2]. A number of synthetic methods are available for the direct conversion of carboxylic acids to the corresponding Weinreb amides [2, 3]. The direct conversion relies on *in situ* activation of carboxylic acids to attack of *N,O*-dimethylhydroxylamine. Some of these methods suffer from drawbacks, which include the preparation of commercially unavailable reagent, long reaction time, low yields, and tedious work up procedure. The use of triphosgene as a synthetic auxiliary in the preparation of many important classes of organic compounds has been investigated intensively in the last twenty years [4]. This white crystalline compound has proved as a safe and stable replacement of phosgene. Triphosgene is known to react with carboxylic acids to produce carboxylic acid chlorides or carboxylic acid anhydrides [5]. To the best of our knowledge, no reports have yet appeared in the literature on the conversion of carboxylic acids into Weinreb amides using triphosgene. We wish to report herein a simple one-pot procedure for the direct conversion of carboxylic acids to Weinreb amides using triphosgene as an acid activator as shown in Scheme 1.



Scheme 1.

This method involves the reaction of carboxylic acid with triphosgene to form an acid chloride or anhydride, followed by addition of *N,O*-dimethylhydroxylamine to yield the desired Weinreb amide [6]. The reaction proceeded rapidly and smoothly in CH_2Cl_2 at room temperature. In all cases, the formation of Weinreb amide was monitored by disappearance of the starting acid by TLC analysis. The reaction was completed within an hour at room temperature. After completion of reaction, 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. A variety of Weinreb amides were obtained from aromatic carboxylic acids and aliphatic carboxylic acids in high yields [7]. The results are summarized in Table 1. We have tested various benzoic acids with electron-donating and electron-withdrawing groups on the aryl ring (entries 1-5). The electronic effect of substituents on the benzoic acids does not affect much the reaction yield. The reaction of nicotinic acid,

Table 1. Synthesis of Weinreb Amides from Carboxylic Acids

| Entry | Carboxylic Acids | Products | Yield ^a |
|-------|------------------|----------|--------------------|
| 1 | | | 98 % |
| 2 | | | 94 % |

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(Table 1). contd...

| Entry | Carboxylic Acids | Products | Yield ^a |
|-------|------------------|----------|--------------------|
| 3 | | | 93 % |
| 4 | | | 98 % |
| 5 | | | 96 % |
| 6 | | | 96 % |
| 7 | | | 98 % |
| 8 | | | 94 % |
| 9 | | | 92 % |
| 10 | | | 90 % |

a) Yields refer to isolated products.

5-nitro-2-furoic acid, and 1-naphthoic acid with triphosgene and the subsequent addition of equimolar amounts of *N,O*-dimethylhydroxylamine hydrochloride and triethylamine afforded the desired Weinreb amides (entries 6-8). Just as in the reaction of aromatic carboxylic acids by this procedure, aliphatic carboxylic acids reacted smoothly to afford the corresponding Weinreb amides in high yields (entries 9, 10).

In summary, we have developed a mild and efficient one-pot procedure for the conversion of various carboxylic acids to their corresponding Weinreb amides using triphosgene as an acid activator. The present procedure described here offers high yields of products, short reaction time, and operational simplicity.

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- [6] General experimental procedure: To a stirred solution of the carboxylic acid (2 mmol) in CH₂Cl₂ (10 ml) at 0 °C were added triphosgene (1 mmol) and triethylamine (10 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 disappearance of the acid, as determined using TLC. After 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.

- [7] All the products prepared were characterized ^1H NMR, ^{13}C NMR, IR, and MS analysis. The spectroscopic data were in agreement with the structures of the products. Data for unknown compound *N*-Methoxy-*N*-methyl-5-Nitro-2-furamide **7**: mp 106-107 °C; TLC Rf 0.60 (50% ethyl acetate in hexane); IR (KBr): 3166, 3100, 1644, 1576, 1530, 1426, 1373, 1355, 1252, 1214, 1118, 1041, 987, 969, 947, 841, 812, 748 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, $J = 3.6$ Hz, 1H), 7.26 (d, $J = 3.6$ Hz, 1H), 3.87 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 156.9, 151.7, 146.5, 118.4, 111.4, 62.0, 33.1; HRMS (EI) m/z : calcd for ($\text{C}_7\text{H}_8\text{N}_2\text{O}_5$): 200.0433, found 200.0426 [M].