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One pot direct synthesis of amides or oxazolines from carboxylic acids using Deoxo-Fluor reagent

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Abstract—A mild and highly efficient one pot–one step condensation and/or condensation–cyclization of various acids to amides and/or oxazolines using Deoxo-Fluor reagents is described. Parallel syntheses of various free fatty acids with 2-amino-2, 2-dimethyl-1-propanol resulted with excellent yields.

Natural fatty acid amides have been detected in total lipids of microorganisms,[1,2] plants[3] and animals.[4] Very recently, both fatty acid amides and ethanol-amides have been found to be physiological signaling molecules in the brain.[5,6] GC–MS separation of fatty acid amides has been studied, mainly picolinyl esters[7] and 4,4-dimethyl-2-oxazolines (DMOX)[8] derivatives of fatty acids, and their GC–MS properties have been reviewed in detail[9]. DMOX derivatives exhibit good chromatographic properties; indeed, only slight changes in temperature programming are necessary to obtain, retention times similar to those of their corresponding fatty acid methyl esters (FAME). However, drastic thermal conditions (150–190 °C) and long reaction times (6–12 h) are necessary to obtain sufficient derivatization yield.[9]

There is considerable interest in the synthesis of amides as well as oxazolines by direct combination of carboxylic acids and amines and/or amino alcohols, as the methods employed may be utilized in peptide and natural product syntheses. Different methodologies have been reported in the literature,[10] the most common being conversion of a carboxylic acid moiety to a more reactive functional group, such as an acyl chloride, mixed anhydride, acyl azide, *N*-acylbenzotriazoles[11] or active esters, or via an in situ activation of carboxylic group by some peptide coupling reagents such as benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[12,13] and *N*,*N*′-dicyclohexylcarbodiimide (DCC).[14] More recently, new systems were developed using carbon tetrabromide/triphenylphosphine,[15] 2-chloro-1-methylpyridinium iodide (CMPI) and/or 2-bromide-1-methylpyridinium iodide (BMPI),[16] titanium and/or divalent tin reagents,[17] or a lanthanide chloride[18] as catalyst. Drawbacks of these methods include modest yields, expensive coupling reagents and difficulty in removal of excess reagent and reagent byproducts.

Comparative analysis of acyl fluorides and acyl chlorides shows that acyl fluoride possess greater stability than the corresponding acid chlorides towards neutral oxygen nucleophiles (water and methanol), yet have high reactivity toward anionic nucleophiles and amines.[19] Moreover acid fluorides react more like activated esters than acid halides (Cl, Br and I). Recently, Lal and co-workers reported a fluorinating reagent bis (2-methoxyethyl) aminosulfur trifluoride (Deoxo-Fluor) as a thermally stable alternative to the diethylaminosulfur trifluoride (DAST).[20,21] Studies by Tunoori et al. have demonstrated that Deoxo-Fluor converts carboxylic acids to acid fluorides and then into Weinreb amides in one flask.[22] In 2000, the Wipf's and Williams's groups reported the use of DAST as well as Deoxo-Fluor in cyclodehydration reactions to convert β-hydroxy amides to oxazolines under mild reaction conditions.[23]

As part of our search for new methods to quantify free fatty acids in human plasma, we sought a convenient synthesis of their free fatty amides to provide stable chromatographic behavior and high volatility. In the present work, we report the use of Deoxo-Fluor for

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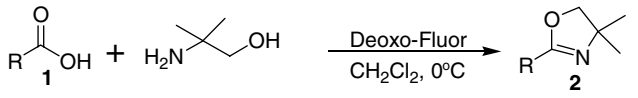
the one pot and direct conversion of carboxylic acids into their corresponding amides and/or oxazolines under mild conditions with excellent yields. We first examined the reported procedure.[22] The carboxylic acid (1 equiv) was dissolved in CH_2Cl_2, cooled to 0 °C and treated with diisopropylethylamine (DIPEA) (1.5 equiv) and Deoxo-Fluor (1.2 equiv). After 30 min (acid fluoride formation), an amine (1.5 equiv) was added. After 15 min, the reaction was warmed to room temperature and stirred for 3–8 h. While the yields of amides were good to excellent, the duration of the reaction was long, making it tedious for use with high sample volumes in clinical studies. Based on previous reports[23,24] of the efficiency and mild nature of the Deoxo-Fluor reagent in condensation and dehydration cyclization reactions, we hypothesized that it could be used for the direct conversion of carboxylic acid moiety to an oxazoline. We explored the possibility of mixing the acids and amines together before adding the Deoxo-Fluor reagent. After a series of experimentation, it was established that the oxazoline could be readily obtained by treatment of a mixture palmitic acid and 2-amino-2-methyl-1-propanol with Deoxo-Fluor at 0 °C for 30 min. Encouraged by this result, we incorporated various aliphatic (saturated and unsaturated), and aromatic carboxylic acids with a variety of amines using this methodology giving the results shown in Tables 1 and 2.

The carboxylic acid (1 equiv), amine (1.8 equiv) and diisopropylethylamine (2.2 equiv) were dissolved in CH_2Cl_2, cooled to 0 °C, and treated with Deoxo-Fluor (2.2 equiv). After 30 min, the reaction was quenched with saturated sodium bicarbonate and extracted with *n*-heptane. The combined organic layer was then dried over $MgSO_4$, filtered, and concentrated. The GC analysis showed the compound was $\geqslant 93\%$ pure without any purification. The excellent yields, ease of reaction setup and mild reaction condition of this method, encouraged us to utilize it for parallel synthesis of five different amides as well as oxazoline of free fatty acids (Fig. 1a–d).

In conclusion, we have developed a new, very mild and efficient one pot/one step method to a range of amides and oxazolines from various carboxylic acids (aliphatic, unsaturated aliphatic and aromatic acids) with various amines. The utility of this highly efficient method for

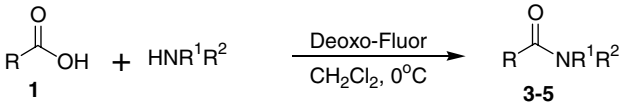
Table 1. Deoxo-Fluor direct cyclization of carboxylic acids to oxazolines



Entry	Carboxylic acid	Product (yield%)[a,b]	Reaction time (min)
1	**1a**, palmitic acid	**2a**, 98	30
2	**1b**, stearic acid	**2b**, 99	30
3	**1c**, oleic acid	**2c**, 96	30
4	**1d**, linoleic acid	**2d**, 96	30
5	**1e**, benzoic acid	**2e**, 97	30
6	**1f**, *p*-toluic acid	**2f**, 97	30
7	**1g**, *p*-nitrobenzoic acid	**2g**, 96	30

[a] Yield of isolated pure product.
[b] Products were characterized by NMR, MS and by comparison with authentic samples.

Table 2. Deoxo-Fluor direct condensation of carboxylic acids to amides



Entry	Carboxylic acid	Amine	Product (yield%)[a,b]	Reaction time (min)
1	**1a**, palmitic acid	Pyrrolidine	**3a**, 94	45
2	**1b**, stearic acid	Pyrrolidine	**3b**, 94	45
3	**1c**, oleic acid	Pyrrolidine	**3c**, 91	45
4	**1d**, linoleic acid	Pyrrolidine	**3d**, 90	45
5	**1e**, benzoic acid	Pyrrolidine	**3e**, 96	45
6	**1f**, *p*-toluic acid	Pyrrolidine	**3f**, 94	45
7	**1g**, *p*-nitrobenzoic acid	Pyrrolidine	**3g**, 93	45
9	**1a**, palmitic acid	Diethyl amine	**4a**, 99	30
10	**1b**, stearic acid	Diethyl amine	**4b**, 99	30
11	**1c**, oleic acid	Diethyl amine	**4c**, 98	30
12	**1d**, linoleic acid	Diethyl amine	**4d**, 95	30
13	**1e**, benzoic acid	Diethyl amine	**4e**, 99	30
14	**1f**, *p*-toluic acid	Diethyl amine	**4f**, 97	30
15	**1g**, *p*-nitrobenzoic acid	Diethyl amine	**4g**, 97	30
16	**1a**, palmitic acid	Dimethyl amine	**5a**, 99	30
17	**1b**, stearic acid	Dimethyl amine	**5b**, 99	30
18	**1c**, oleic acid	Dimethyl amine	**5c**, 96	30
19	**1d**, linoleic acid	Dimethyl amine	**5d**, 94	30
20	**1e**, benzoic acid	Dimethyl amine	**5e**, 98	30
21	**1f**, *p*-toluic acid	Dimethyl amine	**5f**, 97	30
22	**1g**, *p*-nitrobenzoic acid	Dimethyl amine	**5g**, 97	30

[a] Yield of isolated pure product.
[b] Products were characterized by NMR, MS and by comparison with authentic samples.

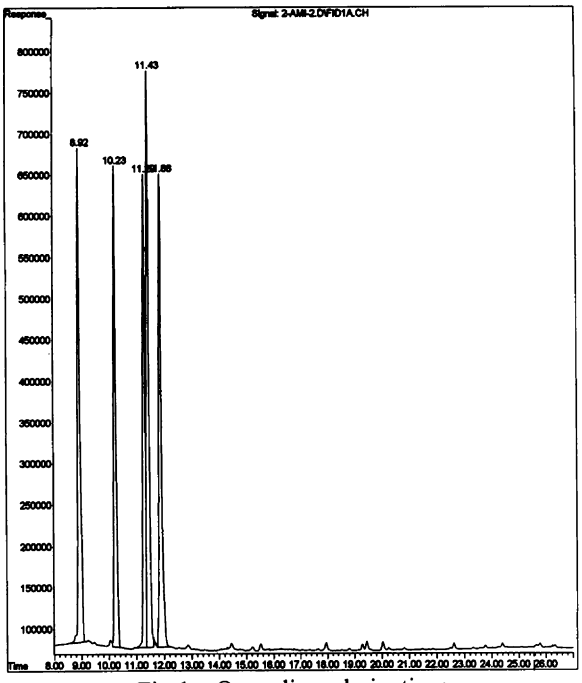


Fig.1a. Oxazolines derivatives

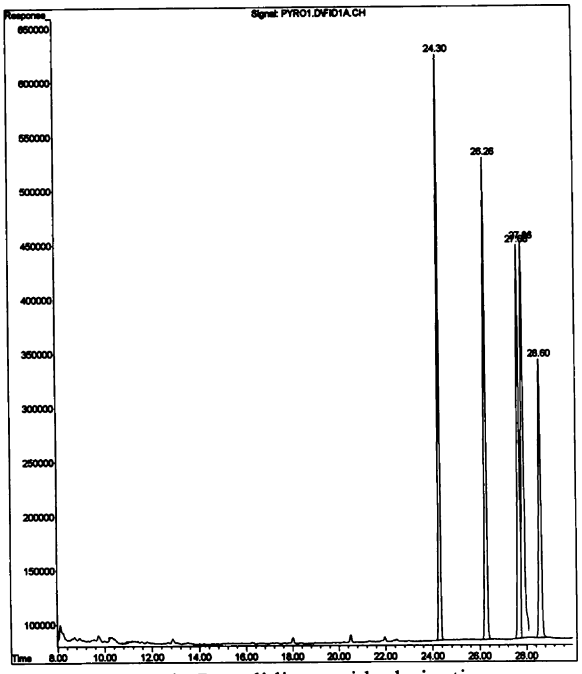


Fig.1b. Pyrrolidine amide derivatives

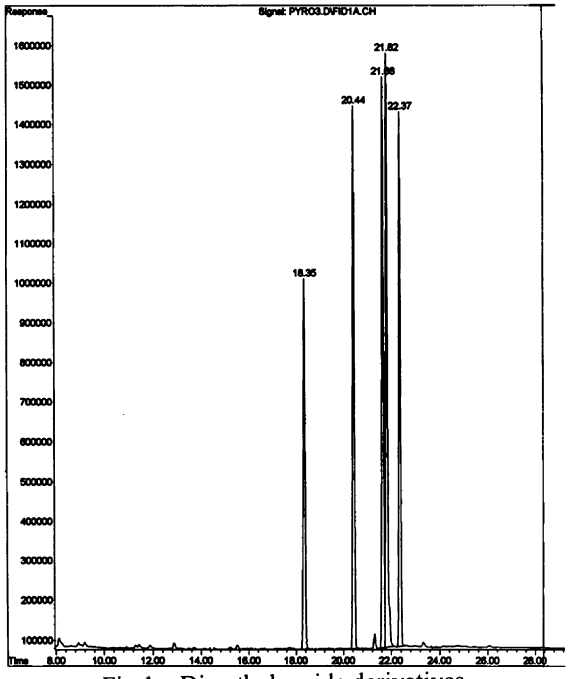


Fig.1c. Dimethyl amide derivatives

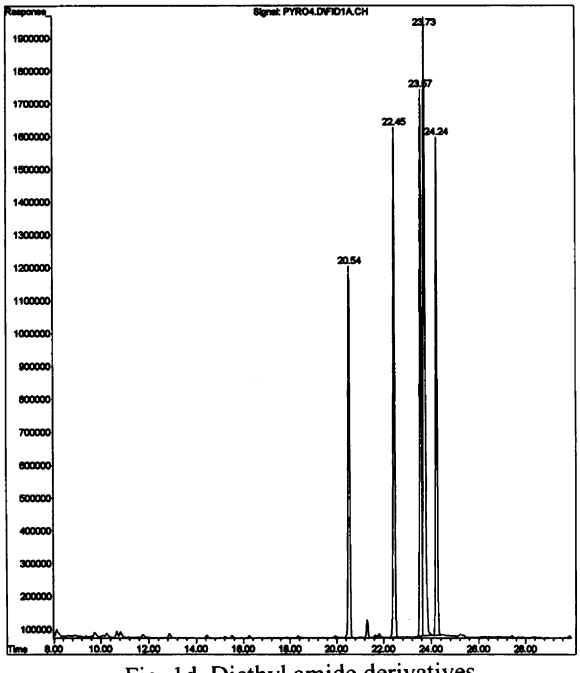


Fig. 1d. Diethyl amide derivatives

Figure 1. GC chromatograms of the reaction products of C16:0 (palmitic acid), C17:0 (heptadecanoic acid), C18:0 (stearic acid), C18:1 (oleic acid), and C18:2 (linoleic acid) with 2-amino-3-methyl-1-propanol, pyrrolidine, dimethyl amine and diethylamine, respectively. Conditions: GC-FID (Agilent GC-6890) the flow rate of carrier gas (He) was set at 5 mL/min. The oven temperature was programmed to initiate at 160 °C and held for 2 min. The temperature was raised to 200 °C at a rate of 20 °C and held for 4 min, and finally increased to 270 °C at a rate of 5 °C and held for 23 min. Column: SPD-1 fused-silica capillary column (30 m × 0.53 mm I.D., 0.10 μm film thickness; Supelco, Bellefonte, CA, USA). (a) Oxazolines derivatives; (b) pyrrolidine amide derivatives; (c) dimethyl amide derivatives; (d) diethyl amide derivatives.

combinatorial solution-phase synthesis was demonstrated. The ease, efficiency, and mild conditions of this reaction make it superior to the existing methods. We are currently using this method for the estimation of free fatty acids in plasma of patients.

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