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One pot direct synthesis of oxazolines, benzoxazoles, and oxadiazoles from carboxylic acids using the Deoxo-Fluor reagent

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Abstract—A one-pot, high yield direct synthesis of various 2-substituted oxazolines, benzoxazoles, and 2-oxadiazoles from carboxylic acids using Deoxo-Fluor reagent is described.

In recent years, considerable interest has been devoted to finding a new methodology for the synthesis of oxazoline and oxadiazole building blocks.[1,2] These five-membered heterocycles belong to an important class of compounds due to their biological activities.[3,4] Oxazoline moieties have a wide variety of applications such as chiral auxiliaries, synthetic intermediates, and protecting groups.[5–7] On the other hand, oxadiazole rings are important class of heterocycles with a wide range of pharmaceutical and biological activities (anti-inflammatory, anticonvulsant, and analgesic activities).[8]

Numerous methods for the synthesis of oxazolines have been reported. Widely used methods are (i) reaction of amino alcohols with carboxylic acids[9] or carboxylic acid derivatives (*ortho* esters, nitriles, imino ether hydrochlorides, and acyl benzotriazoles);[10] and (ii) cyclodehydration of β-hydroxyamides with a number of reagents including the Burgess reagent, diethylaminosulfur trifluoride (DAST), PPh_3/DEAD, and the Vilsmeier reagent.[11] Oxadiazoles have been prepared by (i) cyclodehydration of diacylhydrazines with various anhydrous reagents and oxidation of acylhydrazones with different oxidizing agents;[12] and (ii) direct reaction of an acid chloride and/or a carboxylic acid with an acid hydrazide and hydrazine.[13] Drawbacks of these methods include drastic thermal conditions (160–220 °C), long reaction times (12–18 h), modest yield, expensive coupling reagents and difficulty in removal of excess reagent and by-products.

As part of our program to develop new analytical methods for location of double bonds in polyunsaturated fatty acids, as well as new methods to quantify free fatty acids in human plasma, we discovered a highly efficient conversion of carboxylic acids to related oxazolines and oxadiazoles, namely a one-pot synthesis using the Deoxo-Fluor reagent.

Recently, we reported the use of the Deoxo-Fluor reagent for the one step synthesis of amides and oxazolines.[14] Here, we demonstrate that this reagent is very efficient at promoting the coupling and/or coupling/cyclodehydration of carboxylic acids with amines and/or 2-amino alcohol, giving amides and/or oxazolines, respectively, in high yields and purities ($\geqslant$93%). The simplicity and mildness of this protocol compared to the reported methods led us to examine the applicability of the process in a number of other cases. Typically, the reaction is run by addition of the Deoxo-Fluor reagent into a mixture of the carboxylic acid and amino alcohol in CH_2Cl_2 at 0 °C. When other amino alcohols (chiral and aromatic) were explored, we found that in all cases we obtained the desired cyclized products (oxazolines and benzoxazoles) in high yield, along with the bis(methoxyethyl)amide (less than 10%) (Scheme 1).[15]

To eliminate this impurity, we made a slight modification to our procedure. The carboxylic acid (1 equiv), 2-aminophenol (2.2 equiv), diisopropylethylamine (DIPEA) (2.6 equiv) and potassium carbonate (K_2CO_3)

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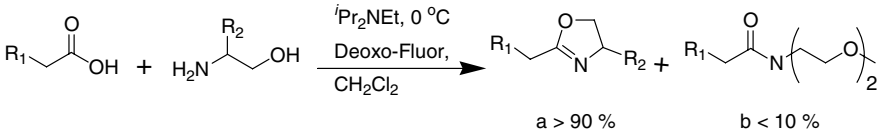
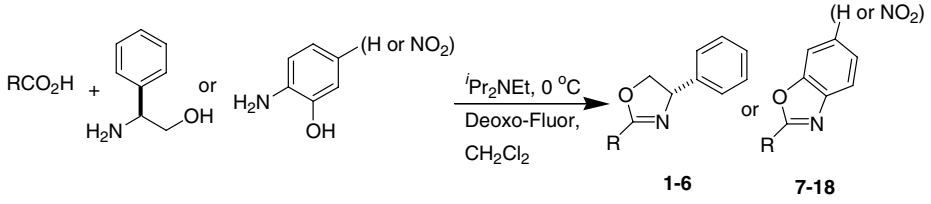


Scheme 1.

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



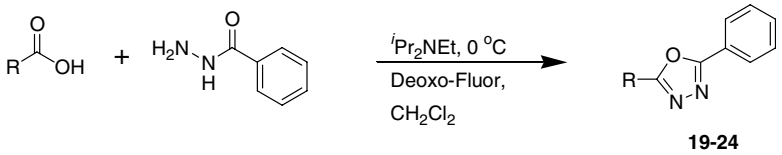
	(*S*)-Phenylglycinol	2-Aminophenol	5-Nitro-2-aminophenol
Palmitic acid	**1** (95%)[a,b]	**7** (99%)[a,b]	**13** (98%)[a,b]
linoleic acid	**2** (95%)[a,b]	**8** (98%)[a,b]	**14** (97%)[a,b]
Elaidic acid	**3** (97%)[a,b]	**9** (97%)[a,b]	**15** (98%)[a,b]
Benzoic acid	**4** (97%)[a,b]	**10** (99%)[a,b]	**16** (98%)[a,b]
p-Toluic acid	**5** (94%)[a,b]	**11** (98%)[a,b]	**17** (98%)[a,b]
p-Nitrobenzoic acid	**6** (98%)[a,b]	**12** (95%)[a,b]	**18** (98%)[a,b]

[a] Yield of isolated pure product.
[b] The purity of all products was determined to be >95% by ^{1}H and ^{13}C NMR spectroscopy and GC–MS analysis.

(excess) were dissolved in CH_2Cl_2, cooled to 0 °C, treated with the Deoxo-Fluor reagent (2.2 equiv) and vortexed. The reaction took place rapidly and cleanly within 30–120 min.[16] To the best of our knowledge, this is the first example of a one-pot method for the efficient generation of benzoxazoles from carboxylic acids at 0 °C. Table 1 shows the results we obtained for the direct reaction of various carboxylic acids with various amino alcohols. The products were generally obtained in high purity and high yield. Aliphatic carboxylic acids (entries **1**–**3** saturated and unsaturated (cis and trans)) as well as aromatic acids (entries **4**–**6** electron-rich and electron poor) were all reacted with aromatic amino alcohols (2-aminophenol and 2-amino-5-nitrophenol) to give equally excellent results. When a chiral amino alcohol (*S*)-phenylglycinol was employed, less than 2% racemization was observed.[17] These results illustrate the general applicability of this method to the preparation of various oxazolines and benzoxazoles under very mild condition and short reaction times.

The efficiency and the ease of the reaction setup led us to speculate that a one pot process for the synthesis of oxadiazoles might be possible. The same procedure was in fact successfully applied to the preparation of oxadiazoles. The carboxylic acid (1 equiv), benzhydrazide (2.2 equiv), diisopropylethylamine (DIPEA) (2.6 equiv) and potassium carbonate (K_2CO_3) (excess) were dissolved in CH_2Cl_2, cooled to 0 °C, and treated with Deoxo-Fluor reagent (2.2 equiv) for 2 h to furnish the desired products, 2,5-disubstituted 1,3,4-oxadiazoles in excellent yields (Table 2). We would like to mention that when the alkyl instead of aryl acid hydrazide was applied, the yield of the reaction was low (less than 45%).[18]

Table 2. Deoxo-Fluor direct cyclization of carboxylic acids to oxadiazoles



Entry	Carboxylic acid	Product (Yield)[a,b]	Reaction time (h)
1	Palmitic acid	**19** (82%)[a,b]	3
2	Linoleic acid	**20** (80%)[a,b]	3
3	Elaidic acid	**21** (79%)[a,b]	3
4	Benzoic acid	**22** (95%)[a,b]	2
5	*p*-Toluic acid	**23** (94%)[a,b]	2
6	*p*-Nitrobenzoic acid	**24** (90%)[a,b]	2

[a] Yield of pure isolated products.
[b] The purity of all products was determined to be >95% by ^{1}H and ^{13}C NMR spectroscopy and GC–MS analysis.

In conclusion, we have developed an efficient, straightforward and common method for the synthesis of oxazolines, benzoxazoles, and oxadiazoles from various carboxylic acids using the Deoxo-Fluor reagent. The reaction is carried out in one-pot and is operationally simple, mild, and gives products with high yields and purity. Moreover, short reaction times, ease of work-up and high degree of chemoselectivity are other noteworthy advantages of this new method.

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15. According to the literature bis(methoxyethyl)amine is generated along with SO_2, in acyl fluoride formation using the Deoxo-Fluor reagents, see: White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, *69*, 2573–2576.
16. *Representative procedure*: The elaidic acid (49.4 mg, 0.175 mmol, 1 equiv), diisopropylethylamine (DIPEA) (80 μL, 0.46 mmol, 2.6 equiv), 2-aminophenol (42.10 mg, 0.385 mmol, 2.2 equiv), and potassium carbonate (K_2CO_3) (excess) were dissolved in 2 mL CH_2Cl_2. The solution was cooled to 0 °C, and the Deoxo-Fluor reagent (71 μL, 0.385 mmol, 2.2 equiv) was added dropwise. After 2 h the reaction mixture was quenched with saturated aqueous sodium bicarbonate at 0 °C. After warming to room temperature, the biphasic mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (silica gel, 1.5×20 cm, $10 \rightarrow 50$ EtOAc/hexanes) provided **9** (60.3 mg, 97%) as a light yellow solid.
17. Shimadzu HPLC (Model LC-10AT vp); Waters UV detector (Model 486); Chiralcel OD column; 15% 2-propanol–hexane; 0.5 mL min^{-1}; at a stable ambient temperature (21 °C) were used.
18. GC–MS analysis of the crude cyclized products 1,3,4-oxadiazoles as well oxazolines and benzoxazoles showed that the products generally were $\geqslant$90% pure.