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Direct, facile synthesis of acyl azides and nitriles from carboxylic acids using bis(2-methoxyethyl)aminosulfur trifluoride

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Dedicated to Professor Hoshang E. Master on the occasion of his 60th birthday

Abstract—A mild, efficient, and practical method for the one-step synthesis of acyl azides from carboxylic acids using bis(2-methoxyethyl)aminosulfur trifluoride is described. The reaction was easily extended to the synthesis of the corresponding nitriles by the inclusion of phosphorous reagents. The method can be applied to the synthesis of optically active nitriles in high yields, and is compatible with fluorous phosphines.

The need for simple and efficient strategies to obtain complex molecules and their analogues is a driving force for the development of new methodologies. Acyl azides and nitriles are important intermediates in organic chemistry. They are extremely useful in the preparation of amides and heterocyclic compounds.[1] Moreover, nitriles can be transformed into heterocyclic compounds of significant biological importance.[2]

Over the years, a number of methods have been developed for the synthesis of nitriles, including oxidation routes from primary amines[3] and aldehydes,[4] and dehydration of amides[5] and aldoximes.[6] Nitriles can also be synthesized in a one-pot manner from alcohols using a variety of reagents.[7] There are, however, few one-pot direct methods for the synthesis of nitriles from carboxylic acids.[8]

Many single-step and multi-step methods have been developed to convert carboxylic acids to acyl azides.[9,10] Since carboxylic acids are more readily available commercially than are acyl azides and nitriles, we sought a more robust, mild, selective and highly efficient procedure for the direct conversion of carboxylic acids to acyl azides as well as nitriles.

In 1999, Lal et al. reported the synthesis and application of the fluorinating reagent bis(2-methoxyethyl)aminosulfur trifluoride (commonly known by the trade name Deoxo-Fluor) as an alternative to diethylaminosulfur trifluoride (DAST). While the reactivity profiles of these two reagents are similar, Deoxo-Fluor is more thermally stable than DAST and therefore easier to use.[11]

We recently reported efficient one-step methods for the synthesis of amides, benzoxazolines, oxazolines, oxadiazoles, aldehydes, and ketones from carboxylic acids using the Deoxo-Fluor reagent.[12] These conversions were in response to our pursuit of developing new analytical methods to locate double bonds in polyunsaturated fatty acids and to quantify free fatty acids in human plasma, inspired by an early work from the Georg lab.[13] In continuation of our work, we report here a highly efficient conversion of carboxylic acids, using Deoxo-Fluor and sodium azide, to their acyl azides in a one-pot, direct synthesis. Furthermore, the inclusion of certain phosphorous reagents allowed conversion in the same pot to the corresponding nitriles. The reactions are extremely simple and powerful, and proceed under very mild conditions.

In a typical reaction to form acyl azides, the carboxylic acid (0.43 mmol, 1 equiv) and diisopropylethylamine (DIPEA) (0.86 mmol, 2 equiv) were dissolved in CH_2Cl_2 (2 mL) in an open test tube. NaN_3 (1.3 mmol, 3 equiv) was then added as a 0.5 M DMSO solution (2.7 mL).

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The mixture was cooled to 0 °C. Because of the presence of DMSO, the reaction mixture solidifies at this temperature. Deoxo-Fluor (0.65 mmol, 1.5 equiv) was added dropwise over a 15–30 min period, converting the solid to a solution. For aliphatic carboxylic acids, the solution mixture was kept at 0 °C for the course of the reaction. For aromatic carboxylic acids, the reaction mixture was kept at 0 °C for 15 min after Deoxo-Fluor addition, and was then allowed to warm to room temperature. The reaction mixture was occasionally shaken on a vortex mixer for the times listed in Table 1. The solvent was removed in a SpeedVac (centrifugal lyophilizer) with no heating of the sample. (We should note that *the use of sodium azide in CH_2Cl_2 could possibly lead to the formation of $CH_2(N_3)_2$ and/or HN_3, which are explosive*;[14] however, in the carefully designed reaction and solvent evaporation conditions used here, no problems were encountered. The order of addition of the reagents is critical with sodium azide being added to carboxylic acid only after the amine base is present to avoid the formation of HN_3). The residue was taken up in diethyl ether and washed with water. After drying over $MgSO_4$ and filtration, the solvent was evaporated either under a stream of dry nitrogen or in a chemical fume hood (depending upon the volatility of the product) to give the crude product. The product was purified by flash silica gel column chromatography using a heptane–ether eluent.

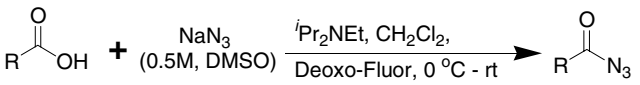
Both aromatic (Table 1, entries 1–5) and aliphatic (entries 6–12) carboxylic acids converted cleanly to azides. All reactions resulted in high isolated yields, and conversion of carboxylic acid was complete as determined by GC–MS. 4-Bromobenzoic acid (entry 2) was efficiently converted to the corresponding azide, while 4-nitrobenzoic acid (entry 3) gave the corresponding acyl azide along with 10% of the primary amine (derived from Curtius rearrangement of the acyl azide). The efficacy of this method was explored by converting *ortho*-substituted carboxylic acids, such as salicylic acid to give 2-hydroxybenzoyl azide (entry 4). This method was found applicable to α-substituted carboxylic acids such as diphenylacetic acid (entry 5). As expected,[12] no geometric isomerization of disubstituted alkenes (entries 9 and 10) was observed.

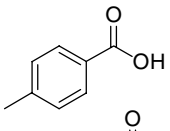
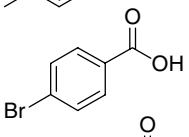
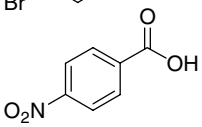
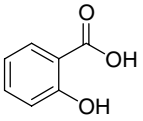
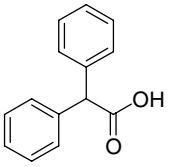
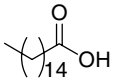
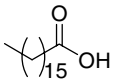
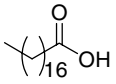
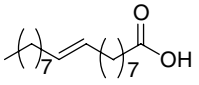
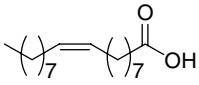
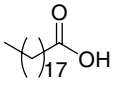
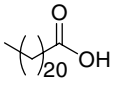
Our experiences with the Deoxo-Fluor reagent have shown that it can be exceptionally selective, depending upon the reaction conditions.[12] As triphenylphosphine (PPh_3) is known to facilitate conversion of acyl azides to nitriles,[15] we examined whether the addition of a phosphorous reagent to the single pot would allow access to nitriles directly from carboxylic acids via in situ generated acyl azides.

Preliminary experiments to this end showed that optimal reactions required a base that is less hindered than DIPEA, such as triethylamine (TEA) or pyridine, to promote the conversion to nitriles. After a detailed study of reaction conditions with palmitic acid as the example, we found that treatment of 1 equiv of carboxylic acid, 3 equiv of NaN_3 (in DMSO), and 3 equiv each of TEA and PPh_3 in CH_2Cl_2 with 1.5 equiv of Deoxo-Fluor at 0 °C led to the formation of hexadecanenitrile in 90% yield after 30 min. It should be noted that less triphenylphosphine (1.2 equiv) can be used, but only if added after conversion to the azide is complete.

To explore the generality and scope of the one-pot method, various carboxylic acids were examined (Table

Table 1. One-pot synthesis of acyl azides from carboxylic acids

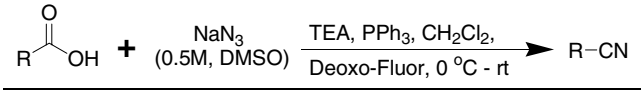


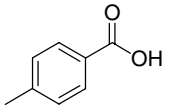
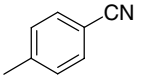
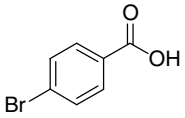
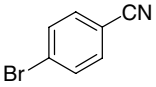
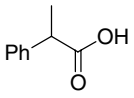
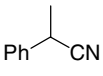
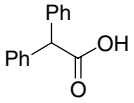
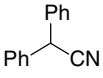
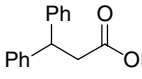
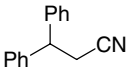
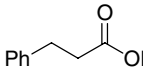
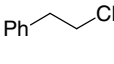
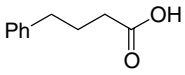
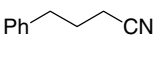
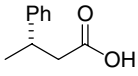
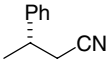
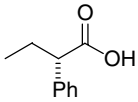
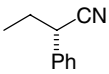
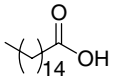
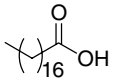
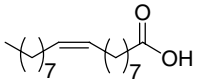
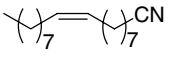
Entry	Carboxylic acid	Product	(Yield,[a] %) Reaction time, min
1		**1**	(90) 75
2		**2**	(92) 60
3		**3**	(87) 60
4		**4**	(83) 75
5		**5**	(90) 50
6		**6**	(94) 30
7		**7**	(92) 30
8		**8**	(95) 30
9		**9**	(85) 30
10		**10**	(90) 30
11		**11**	(96) 30
12		**12**	(94) 30

[a] Yield of pure, isolated products (characterized by GC–MS, and ^1H and ^{13}C NMR).

2). Both aromatic and aliphatic carboxylic acids were smoothly and efficiently converted to nitriles within 30–60 min under these reaction conditions. Note that the reaction was accelerated as compared to acyl azide formation, perhaps due to TEA and/or the presence of PPh_3. Benzoic acids with electron-withdrawing and -releasing groups (entries 1 and 2), and hindered carboxylic acids (entries 3–5 and 9) provided high yields of nitriles. Since optically active nitriles are important synthetic intermediates for a number of biologically active compounds,[16] we applied this method for the synthesis of nitriles with chiral centers α and β to the original carbonyl system (Table 2, entries 8 and 9). No racemization was observed by chiral GC analysis. This is the first report of chiral nitriles being synthesized directly from their corresponding chiral carboxylic acids.

Table 2. One-pot synthesis of nitriles from carboxylic acids



Entry	Carboxylic acid	Product	(Yield,[a] %) Reaction time, min
1			**13** (90) 60
2			**14** (92) 50
3			**15** (87) 50
4			**16** (88) 50
5			**17** (90) 50
6			**18** (85) 60
7			**19** (90) 60
8			**20** (90) 60
9			**21** (85) 30
10			**22** (90) 30
11			**23** (91) 30
12			**24** (90) 30

[a] Yield of pure, isolated products (characterized by GC–MS, and ^1H and ^{13}C NMR).

The pathway for conversion of the acid to the nitrile is envisioned to proceed as follows (Fig. 1). Deoxo-Fluor is known to convert carboxylic acid to acyl fluoride,[13] whose fluoride is displaced by azide to give acyl azide. Reaction between acyl azide and PPh_3 results in the formation of acyl triazaphosphadiene. This cyclizes to oxaphosphatriazine, which loses N_2 in a concerted fashion to yield nitrile and Ph_3PO.[17] Amide (and the associated acyl iminophosphorane) is an unlikely intermediate, because when we replaced the acid with amide and used the same reaction conditions, the conversion to the nitrile was incomplete (⩽50%), even with longer reaction times and in the presence of excess Deoxo-Fluor (up to 10 equiv). The pathway as given in Figure 1 does not, however, provide an explanation for the previously mentioned accelerated nitrile formation, the need for excess TEA and PPh_3, nor the fact that Ph_3PS is also an abundant by-product of the reaction, so the mechanism will require further examination.

Other phosphorous reagents were also examined for suitability in the conversion of palmitic and 4-bromobenzoic acids to their corresponding nitriles (Table 3). Although the reaction with PPh_3 was efficient, removal of its oxide and sulfide (the major non-volatile by-products of the reaction) was difficult and required two or three column chromatographic purifications.

We therefore tested phosphorous reagents that, along with their oxides and sulfides, could be more easily removed. Triethylphosphine and triethylphosphite, which are, along with their oxides and sulfides, sufficiently volatile to be removed on a SpeedVac, served this purpose well, providing good yields of nitriles.

Phosphine reagents more sterically hindered than PPh_3 such as tri-*tert*-butylphosphine or tri-*o*-tolylphosphine did not give nitriles, yet did not interfere with acyl azide formation. Use of a phosphorus ylide, (carbethoxymethylene)triphenylphosphorane, in the reaction gave nitriles, but in low yield and the reactions required a long

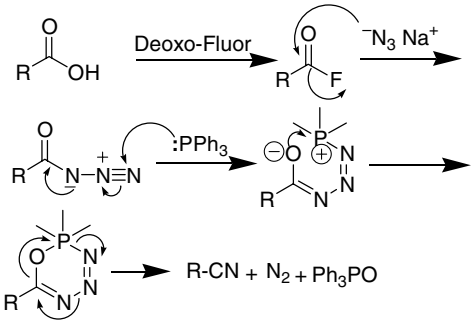
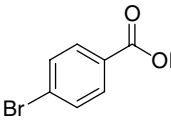
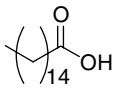
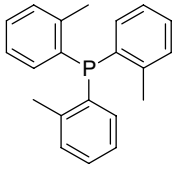
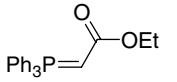
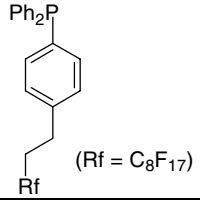


Figure 1. Proposed mechanism for the conversion of carboxylic acids to nitriles.

Table 3. Reaction compatibility with various phosphorus reagents

Phosphorous reagent	Carboxylic acid	
		
Et_3P	(100%),[a] 30 min	(100%),[a] 30 min
$(EtO)_3P$	(100%),[a] 90 min	(100%),[a] 90 min
$^tBu_3P$	No product	No product
	No product	No product
	(35%),[a] 24 h	(50%),[a] 24 h
	(100%),[a] 50 min	(100%),[a] 30 min

[a] Percent conversion as determined by GC–MS. All reactions completely consumed the carboxylic acids. Where the values are <100%, the remaining materials were the respective acyl azides.

time (24 h) and excess phosphorus reagent (10 equiv). A fluorous analogue of PPh_3, whose unreacted form and by-products can be removed by selective solvent or solid phase partitioning,[18] was found to be on par with PPh_3 for the conversion to nitriles.

In summary, an efficient new one-pot direct method for the synthesis of various acyl azides from carboxylic acids was found. The method provides excellent yields in short reaction times. Inclusion of certain phosphorous reagents in the reaction provides a simple and efficient method for the direct conversion of carboxylic acids to nitriles, in high yield and without racemization. The compatibility with volatile phosphorous reagents as well as a fluorous phosphine provides means to simplify purification of nitrile from the reaction mixture.

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Supplementary data

Supplementary data (a description of the general methods, GC–MS, and spectroscopic data (^1H and ^{13}C NMR) for all products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.119.

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