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Controlled conversion of phenylacetic acids to phenylacetonitriles or benzonitriles using bis(2-methoxyethyl)aminosulfur trifluoride

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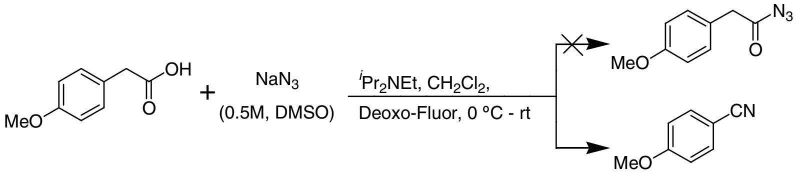
Abstract

A mild, efficient, and practical method for the one-step synthesis of benzonitriles from phenylacetic acids using bis(2-methoxyethyl)aminosulfur trifluoride is described. The reaction was easily extended to the synthesis of the corresponding phenylacetonitriles by inclusion of triethylphosphine.

Aromatic and aliphatic nitriles are important intermediates in organic synthesis, widely used as starting materials for the synthesis of carboxylic acids, amides, amines, aldehydes, and ketones.[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] On the other hand, aromatic nitriles are generally prepared from the corresponding aryl halides with or without metal catalysis.[8] However, the synthesis of aromatic nitriles from carboxylic acids, particularly one-pot direct methods, has been reported only once.[9]

Recently, we reported a facile and mild conversion of various carboxylic acids into acyl azides using the Deoxo-Fluor reagent in a one-pot direct manner.[10] In that study, the model compound 4-methoxyphenylacetic acid failed to convert to the corresponding acyl azide. Instead, what formed was the one carbon atom loss product, 4-methoxybenzonitrile (Scheme 1). Intrigued by this result, we envisioned that by applying appropriate conditions, aromatic nitriles could be made directly from phenylacetic acids via this one carbon atom loss. During the course of the work, we found that inclusion



Scheme 1.

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of triethylphosphine (PEt_3) in the reaction allowed for retention of the carbon, and that the phenylacetonitrile corresponding to the starting phenylacetic acid was the major product. Both reactions, carried out in the presence of sodium azide (NaN_3), can be performed under very mild conditions.

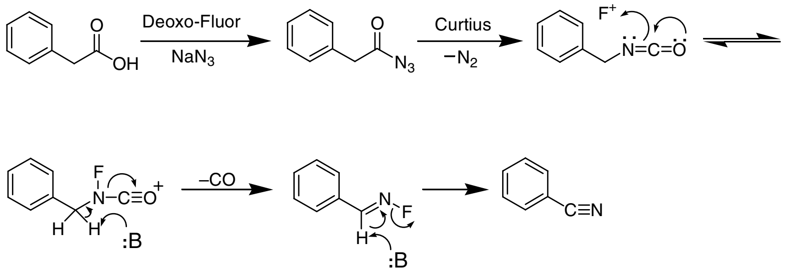
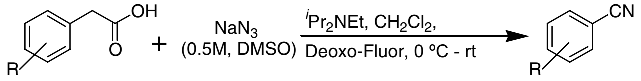


Fig. 1. Proposed mechanism for conversion of phenylacetic acids to benzonitriles.

Table 1
One-pot synthesis of benzonitriles from phenylacetic acids



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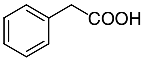
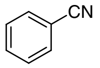
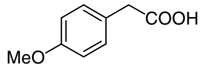
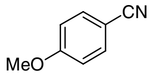
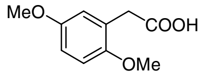
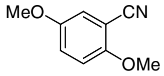
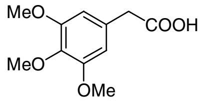
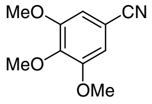
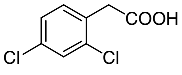
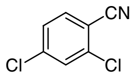
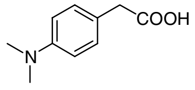
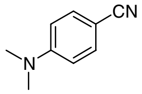
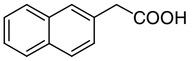
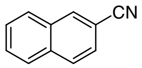
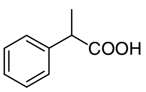
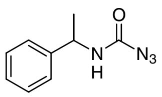
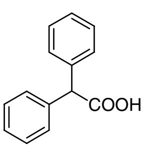
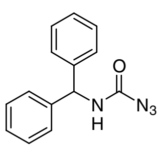
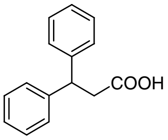
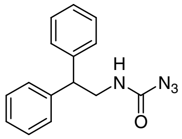
1			88	3.5
2			90	4
3			78	4
4			85	4
5			90	3
6			80	5
7			90	4
8			90	1
9			90	1
10			92	1

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

A proposed mechanism for the formation of the benzonitrile is shown in Figure 1. Initial reaction of the acyl fluoride (formed in situ from reaction of the acid with the Deoxo-Fluor reagent) with sodium azide provides in situ generation of an acyl azide, which undergoes Curtius rearrangement.

The interaction of the nitrogen atom of the isocyanate with electrophilic fluorine (from Deoxo-Fluor) provides an intermediate that loses carbon monoxide through β-elimination, yielding the unstable fluoroimine intermediate that also readily undergoes β-elimination to give the more stable benzonitrile as the final product. The enhanced acidity at benzylic protons most likely explains the difference in reactivity.[11]

When the reaction was carried out with cyanuric chloride instead of Deoxo-Fluor, the product was the acyl azide.[12] This clearly demonstrated the role of Deoxo-Fluor in the Curtius rearrangement, deprotonation, and loss of carbon monoxide.

In a typical reaction, 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). 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, converting the solid to a solution. The reaction mixture was kept at 0 °C for 15 min, and then allowed to warm to room temperature. Within seconds, gas evolution, presumably N_2, occurred. The reaction mixture was occasionally shaken on a vortex mixer for the times listed in Table 1. After removal of solvent in a SpeedVac (centrifugal lyophilizer) with no heating of the sample, the residue was taken up in diethyl ether and washed with water. After drying over $MgSO_4$ and filtration, the solvent was evaporated to give the crude product, which was purified by silica gel column chromatography using a heptane–ethyl acetate eluent. [**Caution:** *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*;[13] however, we have employed these carefully designed reactions and solvent evaporation conditions many times, and no such problems have been encountered.]

Various substituted phenylacetic acids were examined (Table 1) to explore the generality and scope of this method. Electron-rich (entries 2–4) and -poor (entry 5) acids were smoothly and efficiently converted to benzonitriles in excellent yields. In the case of hindered phenylacetic acids (entries 8–10), the benzonitrile did not form; instead, the resulting products were the phenyl carbamoyl azides.[14]

Recently, we reported synthesis of nitriles from carboxylic acids via reduction of in situ formed acyl azides using triphenylphosphine and the Deoxo-Fluor reagent. We therefore next examined the suitability of the model 4-methoxyphenylacetic acid under these conditions (NaN_3 0.5 M in DMSO, 3 equiv each of TEA and PPh_3 in CH_2Cl_2, 1.5 equiv of Deoxo-Fluor). Although the reaction

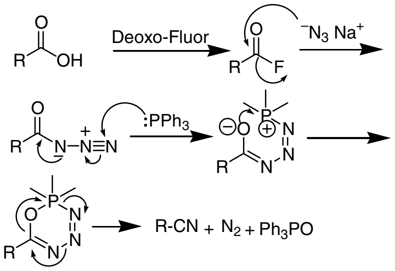
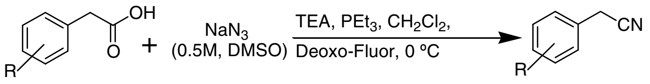


Fig. 2. Proposed mechanism for conversion of carboxylic acids to nitriles.

Table 2
One-pot synthesis of phenylacetonitriles from phenylacetic acids



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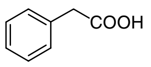
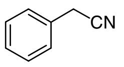
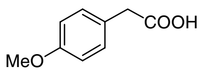
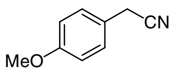
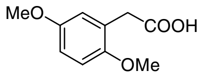
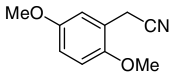
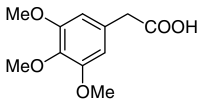
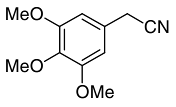
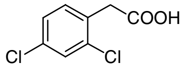
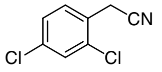
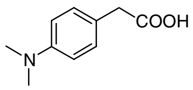
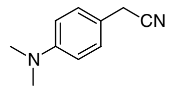
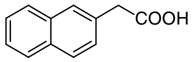
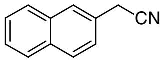
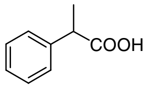
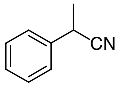
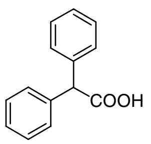
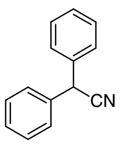
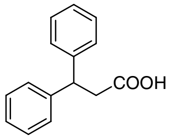
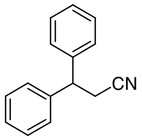
1			88	30
2			90	30
3			80	50
4			88	50
5			92	30
6			86	60
7			90	40
8			85	30
9			90	30
10			90	30

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

with PPh_3 progressed rapidly to completion in 60 min to give the desired 4-methoxyphenylacetonitrile, about 20% of the product formed was the one carbon atom loss product 4-methoxybenzonitrile.

To expand the applicability of this conversion to the phenylacetonitrile, optimal experimental conditions, including examination of other phosphorous reagents, were developed.

We postulated that the Curtius rearrangement would more readily occur at higher temperatures, so the reaction was performed at low temperature in hopes of favoring formation of the acyl triazaphosphadiene, which further cyclizes to an oxaphosphatriazine that loses N_2 in a concerted fashion to yield the nitrile and Ph_3PO (Fig. 2). Triethylamine (TEA) was found to be superior to DIPEA and, among the phosphines examined, triethylphosphine provided the highest selectivity and yield of the desired phenylacetonitrile (typically in a 49:1 ratio of phenylacetonitrile to benzonitrile). An added benefit of using triethylphosphine is that its oxide is volatile, unlike Ph_3PO.

Using the optimized condition, the scope of this new methodology was examined. As shown in Table 2, both electron-poor and -rich phenylacetic acids were converted to the corresponding phenylacetonitriles very efficiently and in high yield (entries 1–7). Gratifyingly, we found that the hindered phenylacetic acids (entries 8–10) could also be efficiently converted to their respective phenylacetonitriles with these conditions.

In conclusion, we report the synthesis of benzonitriles from the corresponding phenylacetic acids by a one carbon atom loss process via Curtius rearrangement, deprotonation, and loss of carbon monoxide. This process is based on the use of Deoxo-Fluor and sodium azide, which presumably convert the phenylacetic acid into an isocyanate that is converted to the benzonitrile through a two-step β-elimination process. Also, the reaction can be controlled to give phenylacetonitriles by the inclusion of triethylphosphine in the reaction mixture. The ease, efficiency, and mild conditions of this reaction make it an attractive alternative to the existing methods.

Acknowledgments

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Supplementary data

Experimental procedures and spectroscopic data for the new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.090.

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