Advances in the Chemistry of Nitriles and Amides

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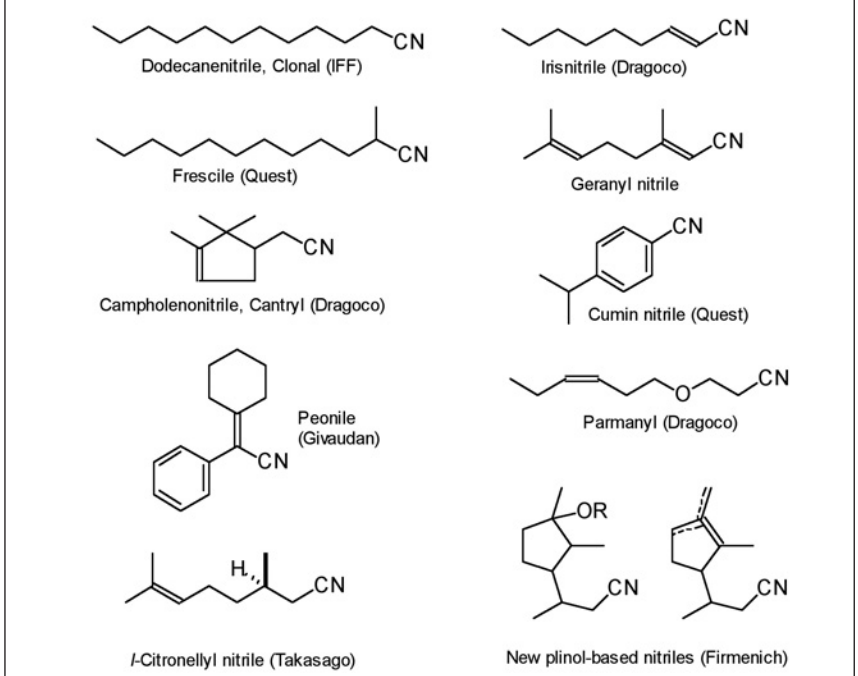
Nitriles and amides represent two important families of organic compounds containing respectively, a CN or a $CONR_1R_2$ moiety. Their chemistries are very much intertwined because either family can serve as a feedstock for the other. For instance, nitriles can be obtained by a direct dehydration of primary amides $RCONH_2$, and vice versa, primary amides — by an addition of water to nitriles. Conversions of nitriles to N-substituted secondary or tertiary amides are also quite practical, although they often require more than one chemical step.[1]

Regarding the applications of nitriles and amides, these two classes of compounds tend to occupy different functional niches. Nitriles are primarily used as fragrances, and amides as flavor and cosmetics components — coolants, sweeteners, and so forth, with some exceptions. Nitriles have long been known as more chemically stable odor alternatives for the corresponding aldehydes, but certainly have not been limited to this kind of application.[2] The current aroma chemical market features about three dozen nitriles varying greatly in their chemical structure (examples are given in Figure 1). There are saturated and unsaturated aliphatic nitriles with both linear and branched carbon skeletons, cycloaliphatic and aromatic nitriles, and also those containing combinations of aromatic and aliphatic substituents. Parmanyl (Dragoco) represents an interesting "hybrid" of leaf alcohol and a nitrile molecule obtained by addition of *cis*-3-hexenol to acrylonitrile.[3] Reflecting the growing demand for the optically active aroma chemicals, Takasago manufactures *l*-citronellyl nitrile.[4] Firmenich patented a new family of nitriles containing a plinol-based fragment.[5]

Figure 1. Examples of nitriles — aroma chemicals



There is no universal synthetic approach to all classes of nitriles used in perfumery. One of the textbook methods for obtaining nitriles consists of the alkylation of cyanide salts with alkyl halogenides.[1,2] Practical applicability of this method is limited not only by the notorious toxicity of the cyanides, but often by the commercial unavailability of starting alkyl halogenides. Another general method — ammonolysis of carboxylic acids, esters, or long-chain alcohols — is often a method of choice when the starting materials (acid, ester, alcohol) are readily available, inexpensive and relatively stable because the reaction conditions are rather harsh. For example, dodecanenitrile can be obtained in a high yield by the ammonolysis of lauric acid at 260°C over a titania/silica catalyst.[6] Condensation methods lead to α,β-unsaturated nitriles. Thus, geranyl nitrile is obtained by the condensation of methyl heptenone with acetonitrile, a method, which might present a viable alternative to the oximation-dehydration route discussed below.[7] Condensation of phenylacetonitrile with cyclohexanone produces Peonile (Givaudan).[8]

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The oximation-dehydration method remains an important tool for obtaining nitriles of various structures and is widely used in the aroma chemical industry. It will be exemplified here by the synthesis of geranyl nitrile from a readily available terpene aldehyde citral (Figure 2). In the first stage of the synthesis citral reacts with hydroxylamine producing citral oxime. The hydroxylamine can be obtained *in situ* from its salts (sulfate or hydrochloride) and a suitable base.

In the second stage, the oxime is converted to the nitrile using dehydrating agents, most commonly acetic anhydride.[2] It is well known, however, that the acetic anhydride technology has a couple of significant drawbacks. First is the formation of an equimolar amount of spent acetic acid; second is the fact that the process is often accompanied by side reactions. In the case of the dehydration of citral oxime, an acid catalyzed side reaction gives isohexenyl isoxazoline (Figure 2).[9]

The search for better dehydration agents for oximes remains a very active field in modern synthetic organic chemistry, and a number of publications on this topic appear in scientific and patent literature every year.[10] Among them, patent applications by Kao Corp. and BASF deal with relatively inexpensive basic agents such as alkali hydroxides, salts and oxides.[11,12] A significant share of the cost of the entire process still belongs to that of the hydroxylamine salt used in the first stage for the introduction of a C-N bond.

Figure 2. Synthesis of geranyl nitrile via citral oxime

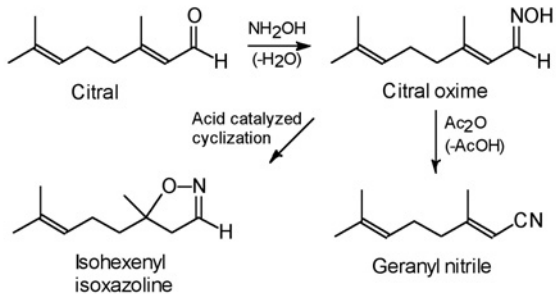


Figure 3. Synthesis of geranyl nitrile using ammonia and hydrogen peroxide

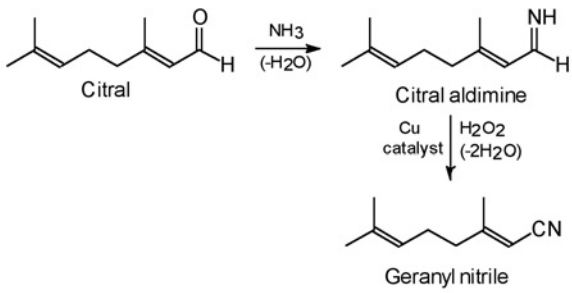
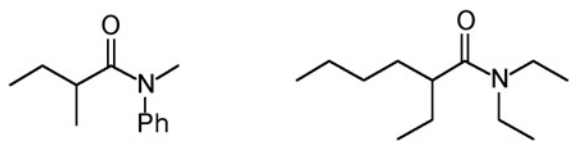


Figure 4. Examples of aroma chemicals — tertiary amides



A new method developed in our laboratory consists of the reaction of citral with ammonia and hydrogen peroxide in the presence of a copper catalyst (Figure 3).[13] In this process, a hypothetical intermediate aldimine initially formed from citral and ammonia undergoes further oxidative dehydrogenation with hydrogen peroxide to produce geranyl nitrile.[14]

In general, this method can be successfully applied to other α,β-unsaturated and aromatic substrates like sorbic aldehyde, cinnamaldehyde or anisaldehyde, but gives poor yields of nitriles from aldehydes with unconjugated carbonyl group such as citronellal or dimethyl octanal.[13,14] Therefore, the oximation-dehydration method retains its importance for the synthesis of this class of nitriles. It is worth noting here that

citronellyl and tetrahydrogeranyl nitriles can be obtained by a selective hydrogenation of geranyl nitrile over Ni, Co, or Pd catalysts.[15]

Aroma chemicals N,N-Disubstituted (tertiary) amides are represented in Figure 4 by Gardamide (Quest) and Rosaliptus (Rhodia). Gardamide also possesses insect repellent properties.[16]

Dipeptides, a special group of amides that includes the widely used Aspartame, have been discussed in many articles and reviews, and will not be considered here. [17]

The developing market for secondary (N-monosubstituted) amides is mostly due to their rapidly growing applications in flavors and cosmetics as physiological cooling compounds. According to publications, their cooling effect is based on the "chemical action at or near those nerve endings which are associated with the sensation of cold." [18] The advantages of the amide coolants over menthol are low volatility and the absence of a strong odor. The two most widely used cooling amides are WS-3 and WS-23. Synthesis of WS-3 starts with l-menthol, and goes through intermediates menthyl chloride, menthyl magnesium chloride and menthane carboxylic acid (Figure 5).[19] An alternative, shorter method for the conversion of the menthyl magnesium chloride into WS-3 is its reaction with ethyl isocyanate.[20]

The synthesis of WS-23 begins with an alkylation of propionitrile with two molecules of isopropyl bromide to give diisopropyl propionitrile, DIPPN. In the next stages, DIPPN is converted to diisopropyl propionic acid, DIPPA, and further to WS-23 using thionyl chloride and monomethyl amine (Figure 6, method A).[21]

In the recent years, the search for more economical methods for obtaining WS-3 and WS-23 has intensified. IFF patented a method for a direct, one-step conversion of DIPPN into WS-23 in approximately 70 percent theory yield using dimethyl sulfate as a source of a methyl group and triacetin as a co-reagent (Figure 6, method B). [22] This process is accompanied by the formation of by-product methyl acetate.

Millennium Specialty Chemicals has developed an alternative method for the synthesis of WS-23 in up to quantitative yield by reacting DIPPN with methylating agents in the presence of acids (Figure 6, method C). [23] This method allows the use of a great variety of methylating agents, for example methanol, trimethyl borate, dimethyl carbonate and trimethyl phosphate. Even weak methylating agents such as dimethyl oxalate or methyl acetate give substantial yields of WS-23. Among the acids are: polyphosphoric (PPA), methanesulfonic, chlorosulfonic, and sulfuric. The method is also applicable to the synthesis of WS-3 from the corresponding nitrile and ethylating agents, and to the synthesis of functionally substituted amides containing an additional alkoxycarbonyl group.[23] The physiological properties of the latter compounds need to be investigated.

To conclude, the chemistry of nitriles and amides continues to develop towards new methodologies for the synthesis of known and traditionally used compounds, and also broadens access to new types of products possessing potentially useful properties.

Figure 5. Synthesis of WS-3

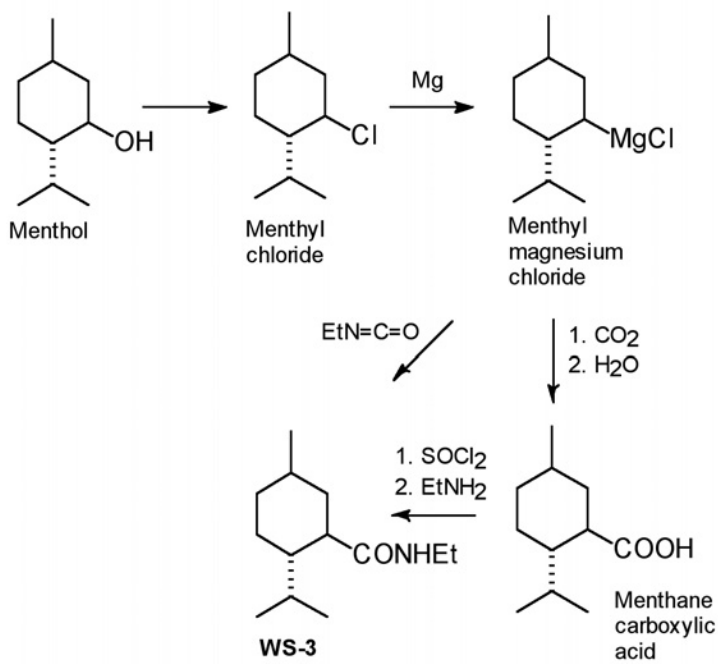
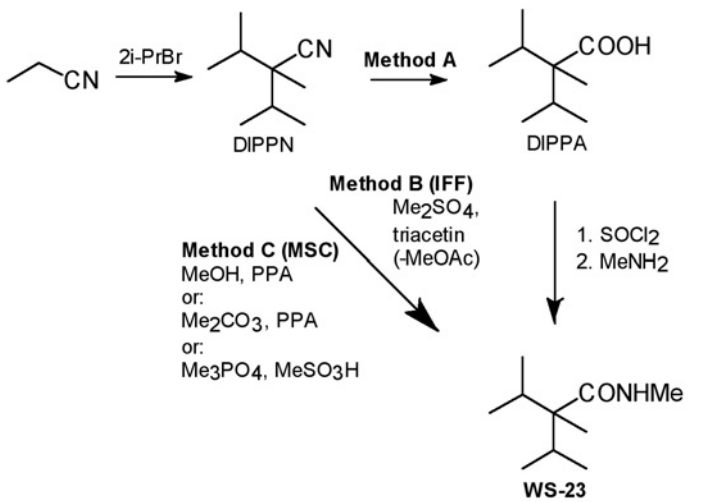


Figure 6. Synthesis of WS-23



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