Dehydration of Amides to Nitriles: A Review

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Abstract

Over the past few decades studies on dehydration reaction of Amides have been well documented in the literature and the importance of Nitriles as intermediates in Organic Synthesis is well established. This review focuses on all the recent synthetic developments in Dehydration of amides to Nitriles.

Keywords: dehydration, amide, nitrile.

Introduction:

Nitrile functionalities are extensively applied in organic Synthesis and used for the production of pharmaceuticals, agrochemicals, and polymers[1,2]. Therefore, dehydration of amides to nitriles is an important transformation in organic syntheses[3,4,5]. Nitriles are one of the most important precursors in organic synthesis. It may be used as starting material for a large number of other functional groups like carboxylic acid, amines, ketones and a large number of molecules of commercial significance[6]. Moreover, cyano group itself is present in HIV protease inhibitor[7], 5-lipoxygenase inhibitors[8] and many other biological important molecules[9,10].

Dehydration is one of the fundamental methods to convert primary amides to nitriles[23]. Earlier strong acidic dehydrating agents like P_2O_5[24], $POCl_3$[25], $SOCl_2$[26], $TiCl_4$[27], $NaBH_4$[28] etc. were used to perform this type of reaction. But presently, a number of efficient methods have been reported for the dehydration of amides to nitriles.

Dehydration of Amides in hydrated media[3]:

Konwar et. al. developed a facile method of dehydration of amides in hydrated media. In this process dehydration of amides were carried out using $AlCl_3 \cdot 6H_2O/KI/H_2O/CH_3CN$ system.

$$R - CO - NH_2 \xrightarrow{\text{AlCl}_3.6\text{H}_2\text{O/KI/H}_2\text{O}} R - CN$$

Reaction Scheme (2.1)
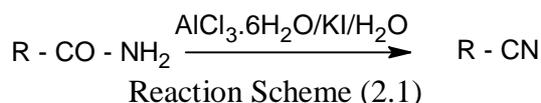
Amides were reacted with the $\text{AlCl}_3.6\text{H}_2\text{O/KI/H}_2\text{O/CH}_3\text{CN}$ system [1 equivalent of $\text{AlCl}_3.6\text{H}_2\text{O/KI}$, 1 equivalent of the amides] in a mixture of acetonitrile and water (5:1) at reflux temperature for 6 h and after workup with 5% ammonium hydroxide solution, it produced corresponding nitriles in good yields in the hydrated media. Also, when the system was treated with the cyclic amides, intramolecularcyclodehydration (BischlerNaperialski reaction) occurred[11] and resulted industrially important isoquinoline derivatives.

Zinc –Catalyzed dehydration of Primary Amides to Nitriles[1]:
Stephan Enthaler et.al.developed the zinc-catalyzed dehydration of amides with N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) as a dehydration reagent into the corresponding nitriles.. With the straightforward and commercially available zinc (II)triflate as the precatalyst and MSTFA, an excellent system has been established to afford nitriles in excellentyields and chemoselectivities.

Reaction Scheme (2.2)
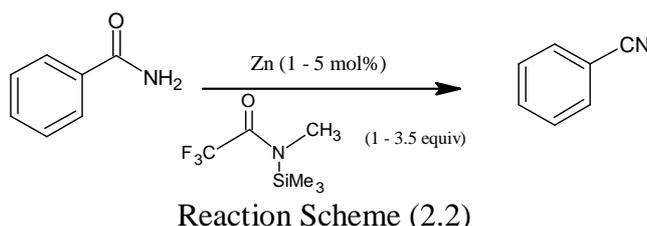
A pressure tube was charged with an appropriate amount of Zn(OTf)_2 (0.05 mmol, 5.0 mol%), the corresponding amide (1.0 mmol), and MSTFA (3.5 equivalents, 3.5 mmol). After addition of THF (2.0 mL), the reaction mixture was stirred in a preheated oil bath at 70^0C for24 h. Themixture was cooled in an ice bath and biphenyl (internal standard) was added. The solution was diluted with dichloromethane and an aliquot was taken for GC-analysis(30 m Rxi-5 ms column, 40–300^0C). The solvent was carefully removed and the residue was purified by column chromatography (n-hexane/ethyl acetate 5:1).

Dehydration of Primary Amides to Nitriles in Solvent and Solvent-Free Conditions[12]:

Reaction Scheme (2.3)
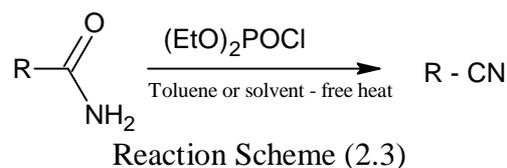
Primary alkyl and aryl amides efficiently are converted to the corresponding nitriles by heating in the presence ofdiethyl chlorophosphate in excellent yields. This method works under mild conditions with shorter reaction times.

(Method A): For each reaction, the amide (1 mmol) and toluene (1 ml)was charged into a 5 ml double-necked round-bottom flaskequipped with a magnetic stirrer and condenser. The mixturewas heated to reflux and diethyl chlorophosphate (1 mmol)was added. The reaction was heated for 5-20 min and then thereaction mixture was cooled to room temperature. The crudemixture was neutralized by 10 ml aqueous solution of sodiumhydroxide (5%) and was extracted by diethyl ether (2 × 10ml). Drying the combined ethereal layer by anhydrous sodiumsulphate and then filtration and evaporation of the solventgave the crude product, which was purified by short column ofsilica gel with *n*-hexane and ethyl acetate (9:1-1:1) to give thepure product.

(Method B):For each reaction, the amide (1 mmol) was charged into a5 ml double-necked round-bottom flask equipped with amagnetic stirrer and condenser. Then the mixture was heatedat 120 °C and diethyl chlorophosphate (1 mmol) was added.The reaction was heated for 5-25 min and then the reactionmixture was cooled to room temperature. The mixture wasextracted by diethyl ether (2 ×10 ml). The combined ethereallayer was allowed to dry by anhydrous sodium sulphate andthen filtration and evaporation of the solvent gave the crudeproduct, which was purified by short column of silica gel with*n*-hexane and ethyl acetate (9:1-1:1) to give the pure product.

Copper-Catalyzed Dehydration of Primary Amides to Nitriles[13]:

Stephan Enthaler et.al. introduced a coppercatalyzed protocol for the dehydration of primary amides to their corresponding nitriles applying N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) as silylation reagent.

Reaction Scheme (2.4)
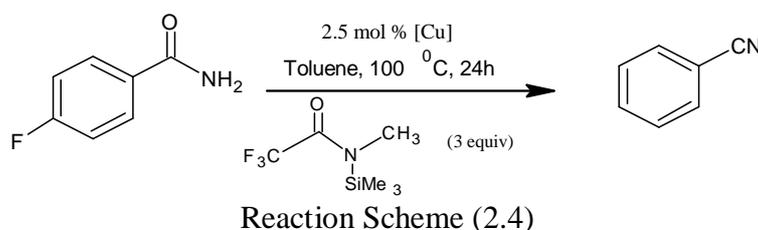
A pressure tube was charged with an appropriate amount of copper(I) chloride (0.018 mmol, 2.5 mol%), and the corresponding amide (0.72 mmol). After addition of toluene (2.0 mL) 2.0 equivalents of MSTFA (1.44 mmol) were added and the reaction mixture was stirred in a preheated oil bath at 100^0C for 24 h. The mixture was cooled to room temperature. The reaction mixturewas dissolved in diethyl ether and purified by column chromatography after that the solvents were removed under reduced pressure.

Dehydration of Primary Amides with PdCl$_2$ in AqueousAcetonitrile[14]:

A new, mild, and reversible method to convert primary amides to nitriles in good yields using PdCl$_2$ in aqueous acetonitrile is described by Sonia I. Maffioli et.al.

$$R - CO - NH_2 \xrightarrow{\text{cat. PdCl}_2 \text{ in } H_2O - MeCN} R - CN$$

Reaction Scheme (2.5)
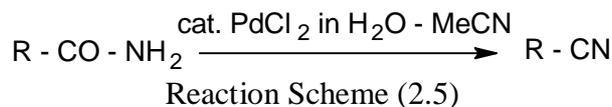
PdCl$_2$was to convert primary amides into the corresponding nitriles in aqueous organic solvents under mild conditions. It was reported that by using PdCl$_2$ in water/acetonitrile as solvent mixture, primary amides dehydrated in good yields after a few hoursat room temperature. The reaction gave satisfactory results on both aliphatic and aromatic primary amides, and in the latter case, electronic-withdrawing or -donating groups did not significantly affect the reaction rate. The reaction was shown to be reversible, and water wasfound to be formally transferred from the substrate to the acetonitrile.

Aluminium chloride and sodium iodide (AICI$_3$-NaI):aversatile dehydrating agent[15]:

AICI$_3$-NaI is an efficient reagent for dehydration of amidesand it formsisoquinoline derivatives by cyclodehydrating amides in very good yields at roomtemperature.

$$R - CO - NH_2 \xrightarrow{\text{AlCl}_3 / \text{NaI}, \text{CH}_3\text{CN}} R - CN$$

Reaction Scheme (2.6)
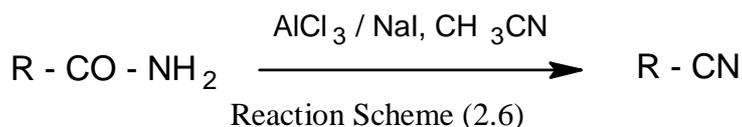
Anhydrous aluminium chloride (0.264 g,2 mmol) and sodium iodide (0.900 gm, 6 mmol) was added to dryacetonitrile (25 ml) and the mixture stirred magnetically forhalf hourat room temperature under nitrogen. Amide (1 mmol) was added and stirring was continued under reflux foranother 2.5 h. The progress of the reaction was monitored by TLC.The reaction mixture was poured into ice cold ammonical water solution(10%) and extracted with diethyl ether. The organic layer waswashed with water (2 x 100 mJ), dried and the solvent was distilledoff under reduced pressure to give nitrile.

Preparation of nitriles from Primary Amides under Swern Oxidation Conditions[16, 19]:

$$R - CO - NH_2 \xrightarrow[\text{Et}_3\text{N}]{\text{(COCl)}_2 - \text{DMSO}} R - CN$$

Reaction Scheme (2.7)
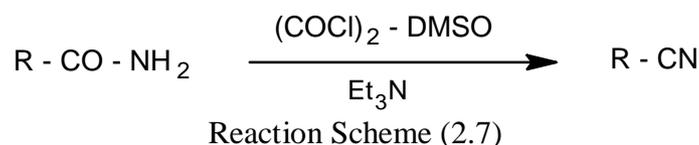
Noriyuki Nakajima and Makoto Ubukata reported a mild conversion method of primary amides to nitriles using the activated dimethyl sulfoxide (DMSO) species under the Swern oxidation conditions[17], (COCl$_2$)-DMSO and Et$_3$N.

A solution of (COCl)$_2$ (0.77 mmol) in CH$_2$Cl$_2$ (0.5 mL) was added to the solution of amide (0.55 mmol) and DMSO (1.1 mol) in CH$_2$Cl$_2$ (1.5 mL) at -78^{0}C. After stirring for15 min. at-78°C, Et$_3$N (0.23 mL, 1.65 mmol) wasadded drop wise to the mixture. After the reaction mixture was stirred for 15 min. at -78^{0}C, the mixture wasquenched by addition of water (5 mL). After this mixture was warmed to room temperature, the aqueous layerwas extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (30 mL), dried(Na$_2$SO$_4$), and then filtered. (yield 93 %).

Rapid Method of Converting Primary Amides to Nitriles[18]:

A rapid and facile method for the conversion of primary amides to nitriles using inexpensive and readily available ZnCl$_2$ in aqueous acetonitrile and their regeneration using ZnCl$_2$–H$_2$O–THF in the presence of acetamide under microwave irradiation in good yields is reported. The reactionis completed by 1 min.
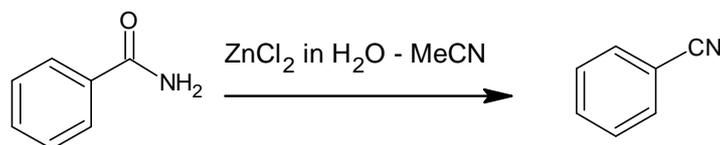
Reaction Scheme (2.8)

A mixture of ZnCl$_2$ (0.136 g, 1 mmol) in 1:1 water/acetonitrile (1 ml) was taken into a Pyrexcylindrical tube; benzamide (0.121 g, 1 mmol) was then added. The mixture was homogenized and irradiated in a commercial microwave oven (320 W). At the end of irradiation (30 s), the mixture was cooled to room temperature and extracted with dichloromethane (5 ml). The organic layer was dried over anhydrous sodium sulphate, and the solvent was removedunder vacuum. The crude product was chromatographed on a short column of silica gel using 2.5% EtOAc in light petroleum as eluent to get benzonitrile (0.097 g, 94%).

N-Protected Chiral α-Aminonitriles from N-Protected s-Amino Acid Amides[20,21]:

Marc Rodriguez et al. reported the dehrdrationof N-protected α -amino-acid amides toN-protected α-aminonitriles in goodyields and with excellent purities by reaction of the corresponding primary amides with cyanuricchloride in DMF.
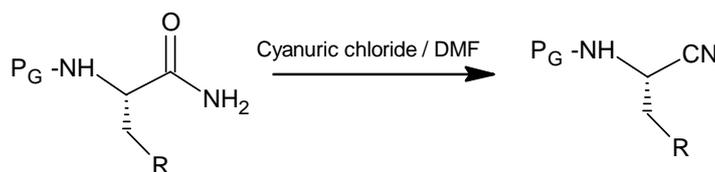
Reaction Scheme (2.9)

To a stirred solution of a N-protected α-amino-acid amide (10mmol.) in

dimethylformamide(10 ml) at room temperature was added at once cyanuric chloride (Aldrich, 922mg, 5 mmoi.). Upon completion of the reaction (monitored by TLC, generally not more than 30 min.), water(c.a. 100 ml) was added. When the expected compound precipitated, the solid was collected by filtration on asintered glass funnel, washed with 5% aqueous sodium bicarbonate, then with water, and dried in vacuum.When the expected product did not precipitate, the reaction mixture was partitioned between water and ethylacetate, the organic layer washed with 5% aqueous sodium bicarbonate, then with water, dried over sodiumsulfate and concentrated under reduced pressure. The product was then crystallized from the appropriatesolvent.

Catalytic properties of iron complexes: dehydration of amides to nitriles[22]:

Matthias Beller et al. reported various iron carbonyl clusters such as $Fe_2(CO)_9$ or$[Et_3NH][HFe_3(CO)_{11}]$ to catalyze the dehydrationof amides into the corresponding nitriles in the presence ofsilanes in high yields. Nagashima and co-workers[29] reported similar type of reaction with ruthenium.
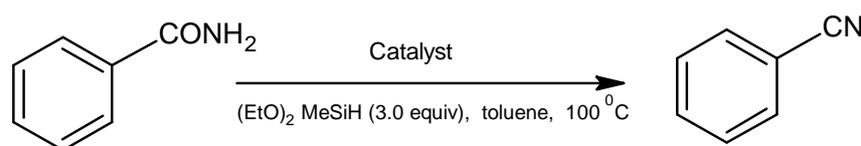
Reaction Scheme (2.10)

They selected benzamide tobenzonitriles as a model system to identify andoptimize critical reaction parameters. Here, $(EtO)_2MeSiH$ isused as a comparably cheap and stable silane in toluene in thepresence of various iron catalysts. Thereaction did not occur in the absence of any catalyst. However, to our delight 5 mol% of non-toxic iron(II)acetate catalyzed the desired transformation and affordedbenzonitrile in 83% yield. No reaction isobserved applying 5 mol% of either $Fe(CO)_5$, $FeCl_2$ or $FeCl_3$. On the other hand, higheractivities and good yields (83–92%) are observed in thepresence of 2–3 mol% of $[CpFe(CO)_2]_2$, $Fe_3(CO)_{12}$ and

[Et_3NH] [HFe_3(CO)_{11}]. Nearlyquantitative yield (97%) is obtained applying $Fe_2(CO)_9$. Other iron sources, such as $Fe(acac)_3$, alsogave reasonable yield of benzonitrile.

Supported monomeric vanadium catalyst for dehydration of amides to form nitriles[30]:

KiyotomiKaneda et al. reported that Monomeric vanadium oxide specieswhich is created on the surface ofhydrotalcite (V/HT), acts as a reusable solid catalyst forthe highly efficient dehydration of amides into the correspondingnitriles.

Reaction Scheme (2.11)
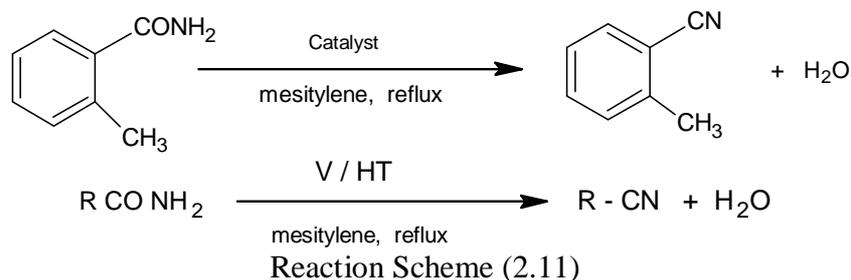
Hydrotalcites (HTs, $Mg_6Al_2(OH)_{16}CO_3$) are layered anionicclays consisting of positively charged two-dimensional brucitelayers and anionic species, such as hydroxide and carbonate, located in the interlayer. HTs have attracted much attention as catalysts because of their multifunctionality, includingtheir cation and anion exchange ability, surface tunable basicity and metal adsorption capacity[31].

Synthesis of V/HT : HT (1.0 g) was added to100 mL of an aqueous VCl_3 solution (4 mM) and then themixture was stirred at room temperature for 3 h. The obtainedslurry was filtered, washed with deionized water and driedovernight at room temperature in vacuo to yield V/HT (V: 1.9 wt%) as a pale gray powder.

Dehydration of Amides by Silazanes, Chlorosilanes, Alkoxysilanes, and Aminosilanes[32]:

William E. Dennis reported the dehydration of amides to nitriles with the help of Silazanes, aminosilanes, alkoxysilanes, and chlorosilanes.

$$3\ R\ CO\ NH_2\ +\ (HNSiMe_2)_3\ \longrightarrow\ 3\ RCN\ +\ 3\ NH_3\ +\ (OSiMe_2)_x$$

(where R = Me, Ph)

$$4\ Ph\ CO\ NH_2\ +\ (HNSiMe_2)_4\ \xrightarrow{heat}\ 4\ Ph\ CN\ +\ 4\ NH_3\ +\ (OSiMe_2)_x$$

$$Ph\ CO\ NH_2\ +\ (n\text{-}BuO)_4\ Si\ \xrightarrow{heat}\ Ph\ CN\ +\ n\text{-}BuOCOPh\ +\ [(n\text{-}BuO)_3\ Si]_2O$$

Reaction Scheme (2.12)
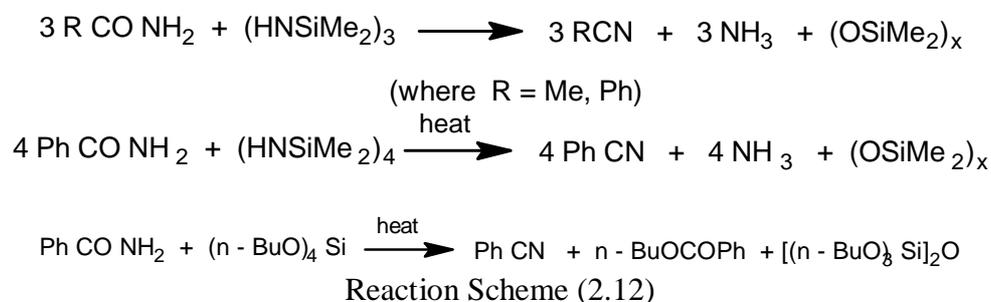
CatalyticSynthesis of Nitriles from Amides[33]:

Matthias Beller et al. reported the fluoride - catalyzed dehydrationof amides to nitriles.Basically they highlighted the catalytic dehydration of aromatic and aliphatic amides using silanes in the presence of catalyticamounts of fluoride. The synthesis of aliphatic and aromatic nitriles proceeds with high selectivity under mild conditions.

Reaction Scheme (2.13)
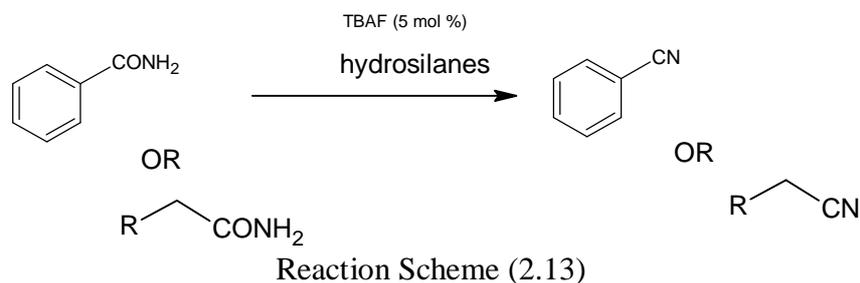
Conversion of substituted amides to nitriles[34]:

Mahajan et al. reported the synthesis of 2-amino – 5- chlorobenzonitrile from 2-amino -5- chlorobenzamide using phosphorous pentoxide:

Reaction Scheme (2.14)
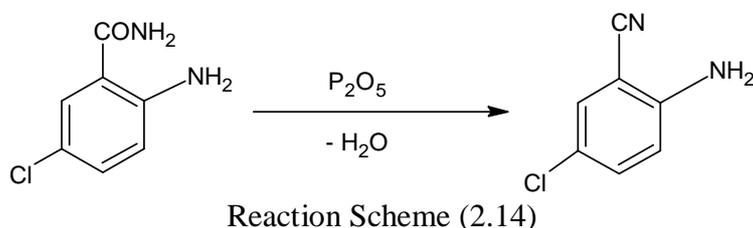
Phosphorous pentoxide (14 mmoles) and 2-amino-5-chlorobenzamide (6 mmoles) were taken in a round botton flask. The reaction mixture was shaken for 30 min and then vacuum distilled for 1 h. The distillate containing 2-amino-5-chlorobenzonitrile and phosphoric acid was collected. It was filtered off to separate the solid product, 2-amino-5-chlorobenzonitrile, from phosphoric acid. It was washed with cold water and recrystallized from aqueous ethanol.

A convenient new procedure for converting primary amides into nitriles[35]:

An operationally simple and high-yielding procedure has been developed for the conversion of primary amides to the corresponding nitriles, using ethyl dichlorophosphate/DBU as the mild dehydrating agent.

Reaction Scheme (2.15)
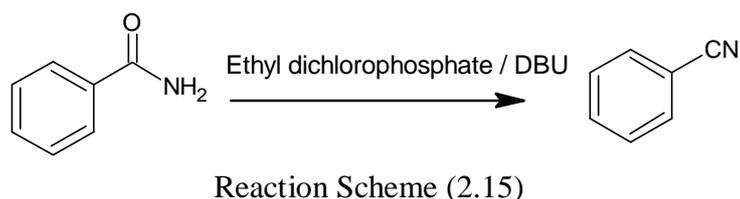
Procedure: Amide (1.0 mmol) was treated with 3 equivalents of DBU (0.457 g, 3.0 mmol) in dichloromethane (5 mL) at room temperature for 10 min, at which time 2 equivalents of ethyl dichlorophosphate (0.326 g, 2.0 mmol) was then added, and the reaction was continued at the same temperature for additional 50 min. Addition of

aqueous NH$_4$Cl followed by dichloromethane extraction and flash chromatography (silica gel, 10% ethyl acetate in n-hexane) afforded the corresponding nitrile (98%). When the reaction was repeated with phenyl dichlorophosphate in place of ethyl dichlorophosphate, 97% yield of the pure product was isolated.

Conclusion:

This article summarizes the recent development of dehydration of amides to nitriles since nitriles functionalities are extremely applied in organic synthesis.

Acknowledgement:

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