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KO^{t}Bu Promoted Transformation of Nitriles to Amides

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Abstract

The amide functional group is present in proteins and is essential for sustaining life. It is a synthetically versatile synthon distributed in several biologically active molecules. Although there are many synthetic methods, there is a need for the development of an ideal reaction condition, which can be performed at room temperature in a metal-free environment and be scalable for industrial applications. This chapter describes the hydration of nitriles using potassium tert-butoxide under anhydrous conditions. Potassium tert-butoxide acts as a nucleophilic oxygen source during the hydration of nitriles to give the corresponding amides under anhydrous conditions. This protocol does not need any transition-metal catalyst or any special experimental setup and is easily scalable to bulk-scale synthesis. A single-electron-transfer radical mechanism as well as an ionic mechanism are proposed for the hydration process. The reaction proceeds smoothly for a broad range of substrates under mild conditions, providing an efficient and economically affordable synthetic route to the amides in excellent yields.

Keywords: *Amide; KO^{t}Bu; Nitrile*

Introduction

Amides form one of the most important functional groups in recent chemistry. They are present in numerous natural products and pharmaceutical molecules (Patai & Rappoport, 1970) In everyday life, some common medicines are taken by us, which contain amide units. Acetaminophen (paracetamol) is used as a common analgesic and antipyretic. Lidocaine and trimecaine are known as local anaesthetics. Piracetam is a nootropic in the racetams group, with a chemical name 2-oxo-1-pyrrolidine acetamide. The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide. It is an antiepileptic drug. Pyrazinamide, the pyrazine analogue of nicotinamide, acts as an antitubercular agent. Atenolol is a selective β1 receptor antagonist, a drug belonging to the group of beta blockers.

Temodar contains temozolomide, an imidazotetrazine derivative. Penicillin is a group of antibiotics. These are amide containing drugs and are widely used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms.

Atorvastatin and diltiazem are another two important drug molecules which contain amide bonds. Atorvastatin is considered the top selling drug worldwide since 2003, and it blocks the production of cholesterol. Diltiazem is used in the treatment of angina and hypertension.

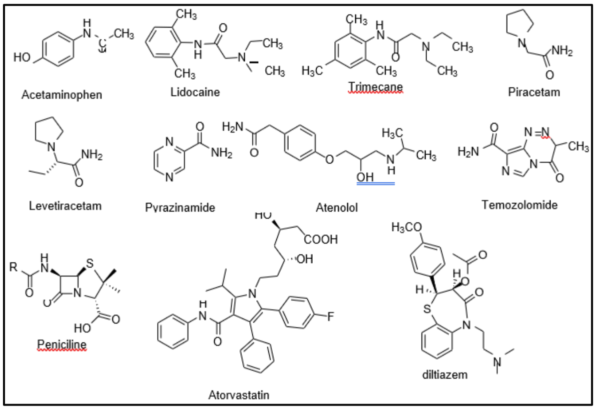


Figure 1: Amide Containing Pharmaceutical Molecules

Amide groups are present in biologically active standard amino acids like asparagines and glutamine, sphingolipids (N-acylated aminoalcohols sphingosines), nicotinamide (a vitamin, PPF) and amino sugars (all of them are N-acylated). Amides are present in linking amino acids to proteins such as enzymes. Aspartame is an amide containing compound, used as a sugar substitute in some foods and beverages. It is an artificial, non-saccharide sweetener.

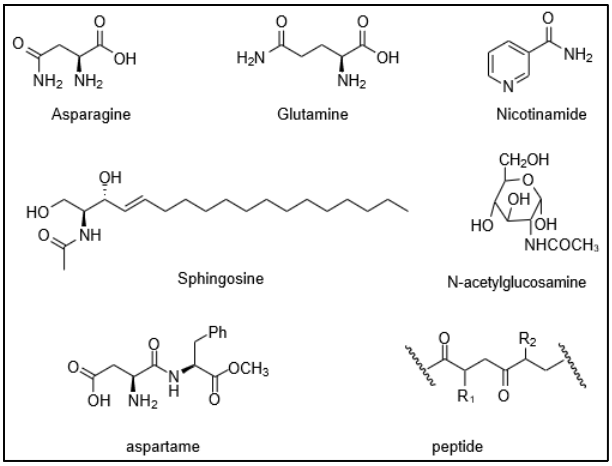
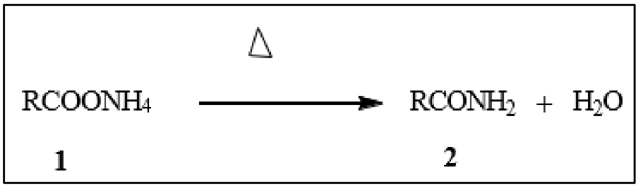


Figure 2: Amide Containing Biologically Active and Other Useful Molecules

Synthesis of Amides

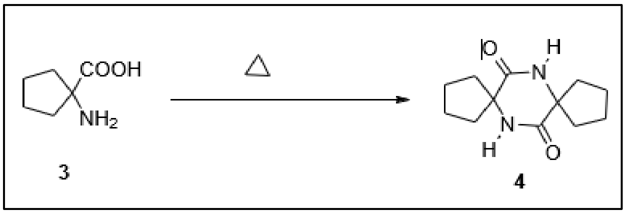
Pyrolysis of Amines and Carboxylic Acids

Heating a mixture of an amine and an acid is considered one of the common methods for preparation of amides. The salts formed by the reaction of carboxylic acids and amines lead to amide on strong heating, which is the case for the conversion of ammonium acetate 1 to acetamide 2 (Scheme 1) (Alvarado & Coleman, 1923, p.3).



Scheme 1: Formation of Amide by Heating of Ammonium Salt

Preparation of succinimide from heating ammonium succinate (Behr & Clarke, 1936, p.75) and preparation of benzanilide (Hurd & Webb, 1927, p.6) by heating benzoic acid with an excess of aniline are also known. An interesting method includes the formation of piperidinediones 4 by heating of α-amino acid (Scheme 2) (McElvain & Pryde 1949, p.326).

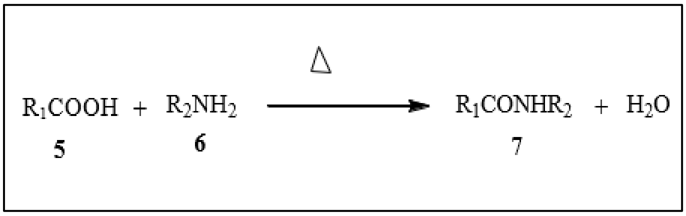


Scheme 2: Formation of Piperidinediones by Heating of A-Amino Acid

In 1931 Mitchell and co-workers (p.1879) reported that when ammonia gas is passed through an aliphatic carboxylic acid corresponding to aliphatic amide is formed. Temperature is maintained in such a way that the water formed is continually removed, and hence the equilibrium point of the reaction is shifted to the amide, side leading to a high yield. A drawback of this method is that the reaction is not suitable for carboxylic acids with a longer alkyl chain length than butyric acid. The rate of the reaction decreased considerably with increasing chain length of the carboxylic acid. On the other hand, as it requires high temperature to heat the acid, this high temperature leads dehydration of the longer chain amides to nitriles.

In 1993 Jursic and Zdravkovski (P. 2761) reported that a range of amides 7 can be synthesised by heating a mixture of different amines 5 and carboxylic acids 6 without any catalyst or coupling agent (Scheme 3). The optimum condition for the pyrolysis of amide-carboxylic acid mixture is heating at 160 - 180°C for 10-30 minutes. This method of preparing amides has so many advantages: it requires no catalysts or solvents; the procedure is simple, and the reaction times are short. On the other hand, there are several drawbacks to the method. Both the amines and carboxylic acids used should be thermally stable and should have a melting point below 200 °C. They should be non-volatile. Both the amine and acid have high boiling points. As the process

requires high temperature for completion, sometimes extreme heating can lead to tar formation. These reasons have limited this method from not to being a widely used general method for direct amide formation. This method is also not susceptible to small scale reactions and high value reactants.

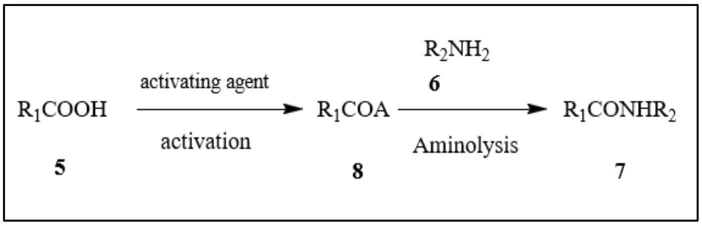


$$\underset{5}{R_1COOH} + \underset{6}{R_2NH_2} \xrightarrow{\Delta} \underset{7}{R_1CONHR_2} + H_2O$$

Scheme 3: Formation of Amide by Direct Heating A Mixture of Acid and Amine

Amide Formation by Acid-amine Coupling

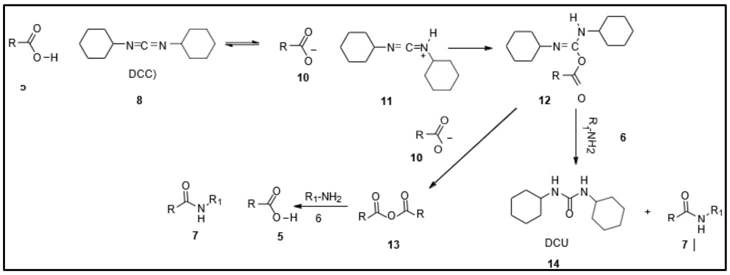
Typical methods of amide bond formation are reactions between amine and activated carboxylic acid derivatives such as acid chlorides (which are generally prepared from thionyl or oxalyl chloride), anhydrides, or by using the carboxylic acid directly with stoichiometric amounts of coupling reagents such as carbodiimides (Montalbetti & Falque, 2005, p.10827) (Scheme 4).



$$\underset{5}{R_1COOH} \xrightarrow[\text{activation}]{\text{activating agent}} \underset{8}{R_1COA} \xrightarrow[\text{Aminolysis}]{\underset{6}{R_2NH_2}} \underset{7}{R_1CONHR_2}$$

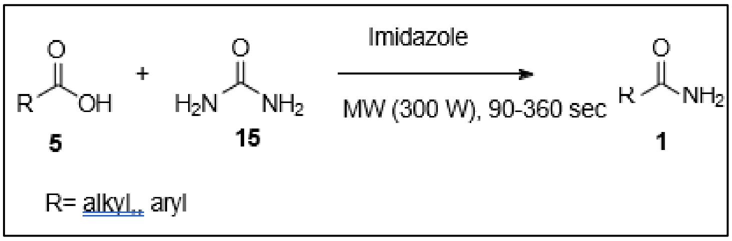
Scheme 4: Coupling Using Carbodiimides N,N'-Dicyclohexylcarbodiimide (DCC) 9

N,N'-Dicyclohexylcarbodiimide (DCC) 9 has been widely used as a coupling reagent since 1955(Sheehan & Hess, 1955, p.1067). N,N'-Dicyclohexylcarbodiimide (DCC) 9 first reacts with carboxylic acid 5 to form the active species O-acyl urea 11. Then either direct coupling with the amine 6 leads the desired amide along with dicyclohexylurea (DCU) 14 as a by-product, or reaction of another acid unit leads carboxylic anhydride 13, which reacts with amine 5 to give amide 7. With DCC, oxazolone formation can take place after generation of the O-acylurea leading to epimerisation. Koenig and Geiger (1970, P.788) reported that in a coupling reaction with carbodiimides as coupling reagents, 1-hydroxy-1H-benzotriazole (HOB^t) acts as an additive and reduces epimerisation.



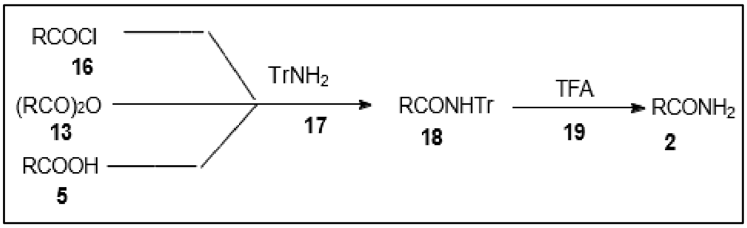
Scheme 5: Coupling of Acid and Amine in Presence of Coupling Agent DCC 9

In 2003 Khalafi-Nezhad, Mokhtari and Rad reported (p.7325) microwave assisted method for synthesising primary amides. Under microwave irradiation, carboxylic acid 5 reacts with urea 15 in the presence of imidazole to yield primary amide 2 (Scheme 6).



Scheme 6: Synthesis of Primary Amide Using Imidazole

In 2009 Theodorou *et al*. (p.277) developed another method of preparation of primary amides. Carboxylic acids 5 or it's activated derivatives undergo acylation reactions to obtain N- tritylamides 18, which undergo deprotection reactions with trifluoroacetic acid 19 at room temperature to the desired primary amides 2 (Scheme 7).



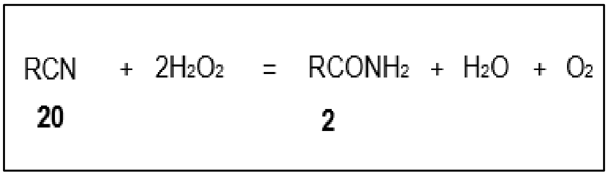
Scheme 7: Synthesis of Primary Amides Via Tritylamides Formation

Hydrolysis of Nitrile to Amide

Though there are many methods for the synthesis of amides, the hydration of nitriles is a straightforward, atom-economical and classical transformation. Traditional processes are based on acid- or base-catalysed hydrolysis, which requires harsh conditions and gives low yield due to further hydrolysis of the amides to the carboxylic acids. Therefore, the limitation of acid- or base-catalysed hydrolysis demands sustainable methods. Subsequently, metalloenzyme (Drauz & Waldmann, 2002) and transition metal catalysts (Murahashi *et al*., 1992, p.2521) were developed for the hydrolysis of nitriles.

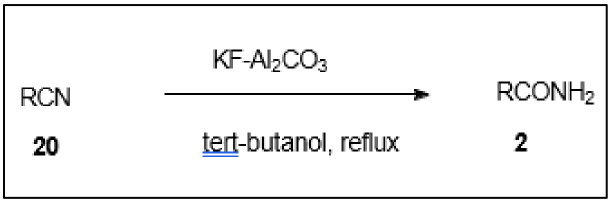
Metal Free Hydrolysis of Nitrile to Amide

Although metal-catalysed reactions are efficient protocols for the synthesis of amides, the use of expensive and toxic metal catalysts limits the exploitation of these methods. Therefore, the development of a metal-free protocol is highly demanding in chemical research. Hydrogen peroxide was reported as a hydrolytic agent for converting nitriles 20 into amides 2 (Scheme 8) by McMaster and Langreck (1917). McMaster and Langreck (1917, p.103) found that the reaction took place more smoothly when a small amount of alkali was present and at a temperature of 40 °C.



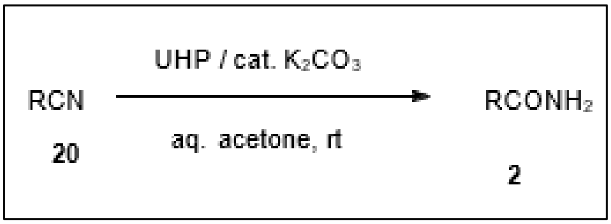
Scheme 8: Hydrogen Peroxide as Hydrolytic Agent for Conversion of Nitrile to Amide

In 1982 Rao (p. 177) described alumina coated potassium fluoride as useful catalyst for transformation of nitriles 20 to amides 2 in tert-butyl alcohol (Scheme 9).



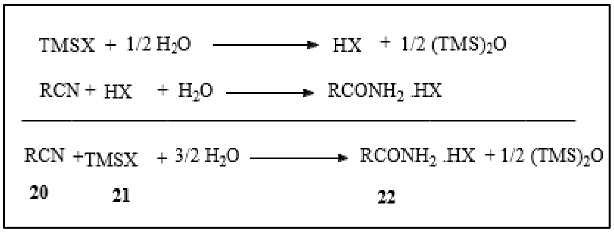
Scheme 9: Conversion of Nitriles to Amides by Alumina Coated Potassium Fluoride

In 1993, Balicki and Kaczmarek (P. 3149) developed a mild and efficient protocol where urea-hydrogen peroxide (UHP) adduct in combination with catalytic amount of K_2CO_3 easily hydrolyses a variety of aliphatic and aromatic nitriles 20 to amides 2 in aqueous acetone at room temperature (Scheme 10). This catalytic system is inexpensive, stable and easy to handle.



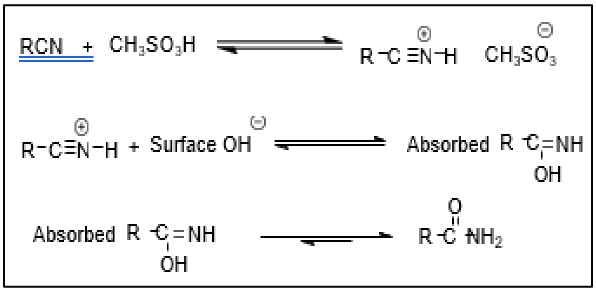
Scheme 10: Use of Urea-hydrogen Peroxide (UHP) Adduct and Potassium Carbonate

Basu and Luo, in 1998 (p.3005), reported that a variety of aliphatic and aromatic nitriles can smoothly be transformed to amides by hydrogen halide generated in situ by reaction of TMSX 21 and water at 0°C to 25°C for 2 to 4 h. They proposed that first the nitrile 20 gets protonated by HCl, generated in situ from TMSX 21 and half an equivalent of H_2O, the protonated nitrile then undergoes nucleophilic attack by another equivalent of H_2O to form the amide salt (Scheme 11).



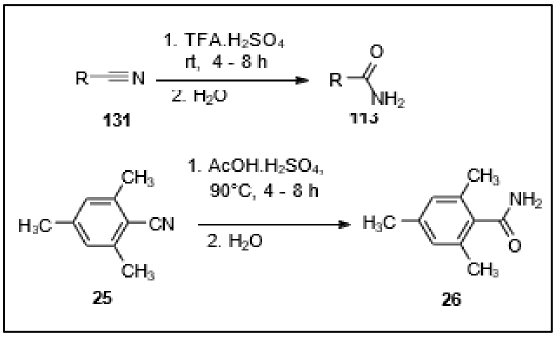
Scheme 11: Transformation of Nitriles to Amides Using in Situ Generated Hydrogen Halide

In 2003, Sharghi and Hosseini Sarvari reported (p. 207) that $Al_2O_3/MeSO_3H$ (AMA) system can be used for the hydrolysis of nitriles to the amides. The reaction proceeded smoothly within 10–15 min when nitrile was heated at 120°C with AMA. The polar Al_2O_3 surface contains a layer of hydroxyl groups which serve as the source of water in the reaction (Scheme 12).



Scheme 12: Transformation of Nitriles to Amides by $Al_2O_3/MeSO_3H$

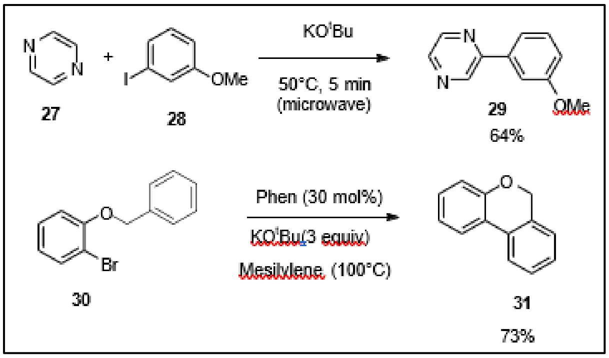
Later, Moorthy and Singhal (2005, p.1926) developed a reagent system consisting of TFA-H_2SO_4 mixture, which converts both aliphatic and aromatic nitriles 20 to the corresponding amides 2 (Scheme 13). Transformation of sterically hindered nitriles 25 needed higher temperatures (>90°C) and AcOH was used instead of TFA to obtain the corresponding amides 26 (Scheme 13).



Scheme 13: Conversion of Nitriles to Amides Using TFA- H_2SO_4 or AcOH- H_2SO_4 Mixture

Although these processes offer improved yields and selectivity, each of these protocols has its own set of disadvantages. There is a need for the development of an ideal reaction condition, which can be performed at room temperature in a metal-free environment and scalable for industrial applications.

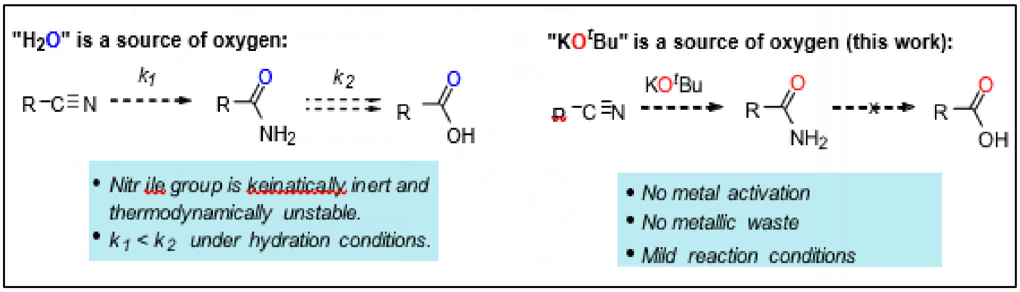
Recently the use of KO^{t}Bu has attracted much more attention, which provides a cheap and green alternatìve to several metal-catalysed organic reactions. In 2008, Yanagisawa and co-workers (p. 4673) reported KO^{t}Bu promoted synthesis of biaryls 29 by coupling reaction between electron- deficient arene 27 with aryl halide 28 (Scheme 14). Liu group (2010) independently reported KO^{t}Bu mediated biaryl synthesis in 2010 (p.16737).



Scheme 14: Potassium tert-butoxide Promoted Synthesis of Biaryls

In 2011, a special role of KO^{t}Bu was observed during iron-catalysed head-to-head dimerisation of terminal aryl alkynes to give the corresponding (E) selective conjugated enynes (Midya *et al*., 2011, p.6698) These new modes of reactivity of KO^{t}Bu raise concerns within the synthetic community. Therefore, the goal was to gain more mechanistic insights into the reactivity of KO^{t}Bu. It has been reported by Kataoka and co-workers (2002, p. 5553) that the nitrile group can be activated via coordination with the potassium ion.

In this chapter we describe an efficient protocol for the hydrolysis of organonitriles to the corresponding amides using potassium tertiary butoxide (KO^{t}Bu) as an oxygen source (Scheme 15).



Scheme 15: Potassium Tertiary Butoxide Promoted Transformation of Organonitriles to Amides

Results and Discussion

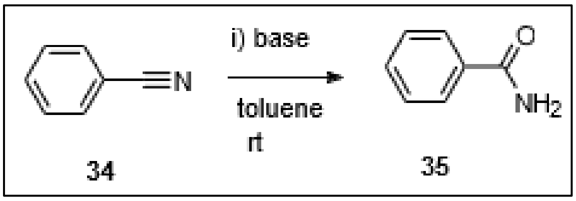
KO^{t}Bu Promoted Transformation of Organonitriles to Amides Under Metal Free Condition

It was previously reported that the nitrile group can be activated via coordination of the nitrile group to the potassium ion (Liu *et al*., 2010, p.16737) The possibility of nucleophilic addition of *tertiary* butoxide to the electrophilic carbon atom of the activated nitrile group was explored. When 50 mol% of KO^{t}Bu was added to the solution of benzonitrile 34 in toluene under anhydrous conditions (Table 1, entry 1), 42% of the amide 35 was formed. This preliminary result inspires investigate this reaction in detail. Benzonitrile 34 was used as a model substrate to optimise the reaction conditions.

Optimisation of Bases

Improvement of the yield was observed when the amount of base was increased to 1.0 equivalent (entry 2, Table1). Using 2 equiv of base, the yield was further improved to 80% (entry 3, Table 1) and 91% benzamide 35 was obtained when 3.0 equivalent of KO^{t}Bu was added and the reaction was stirred for 5 h at room temperature (entry 4).

Table 1: Screening of Bases for Hydrolysis Reaction of Benzonitrile 34 to Benzamide 35



Entry[a]	Base (eqv.)	Yield (%), time
1	KO^{t}Bu (0.5)	42,5 h
2	KO^{t}Bu (1.0)	60, 5 h
3	KO^{t}Bu (2.0)	80, 5 h
4	KO^{t}Bu (3.0)	91, 5 h
5	KO^{t}Bu (3.0)	96, 3 h[b]
6	KO^{t}Bu (3.0)	89, 5 h[c]
7	NaO^{t}Bu (3.0)	NR, 5 h
8	LiO^{t}Bu (3.0)	NR, 5 h
9	K_2CO_3 (3.0)	NR, 5 h[d]
10	Cs_2CO_3 (3.0)	NR, 5 h
11	K_3PO_4 (3.0)	NR,5 h

[a]all reaction were carried out under nitrogen atmosphere, [b]heating at 60°C, [c] purity of KO^{t}Bu 99.99%, sigma-aldrich, [d]heating at 130°C.

A slight improvement in yield (96%) as well as shorter reaction time (3 h) was noticed when it was carried out at 60 °C (entries 4-5). To avoid contamination from the glassware and reagents, hydration of benzonitrile 34 was performed using 99.99% pure KO^{t}Bu (Sigma

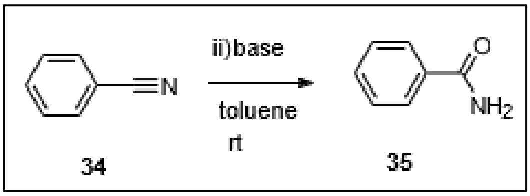
Aldrich) in thoroughly clean glassware. The benzamide was obtained in similar yield in toluene and ^{t}BuOH (entry 6, Table 1). To investigate the importance of the positive counter cation, sodium and lithium tertiary butoxide were used.

Surprisingly, no product formation was observed in the crude NMR analysis (entries 7-8). This experimental data proves that potassium cation plays an important role in this transformation. Next, several inorganic bases (K_2CO_3, Cs_2CO_3 & K_3PO_4) containing different counter anions were screened and none of these bases afforded the desired product (entries 9-11). Running the reaction in presence of K_2CO_3 at higher temperature did not improve the result after 5 h (Table 1, entry 9).

Optimisation of Solvents

Next, various solvents were screened to further improve the yield. At first, different aprotic solvents were used. Benzonitrile (34) yielded benzamide 35 in 91% yield, when it was treated with 3.0 equivalents of KO^{t}Bu in toluene (Table 2, entry 1). While moderate yield (55%) of the amide 35 was obtained in both THF and xylene (entries 3-4).

Table 2: Screening of Solvent for Hydrolysis Reaction Benzonitrile 34 to Benzamide 35



Entry[a]	solvent	Yield (%), time
1	Toluene	91, 5 h
2	Toluene	15, 5 h[b]
3	Xylene	55, 5 h
4	THF	55, 5 h
5	Dioxane	27, 5 h
6	DMF	NR, 5 h
7	DMSO	NR, 5 h
8	DMAc	NR, 5 h
9	DCE	NR, 5 h
10	DCM	traces, 5 h
11	$CHCl_3$	NR, 5 h
12	EtOH	65, 5 h
13	^{i}PrOH	75, 5 h
14	^{t}BuOH	›99, 4 h
15	^{t}BuOH	51, 4 h[b]

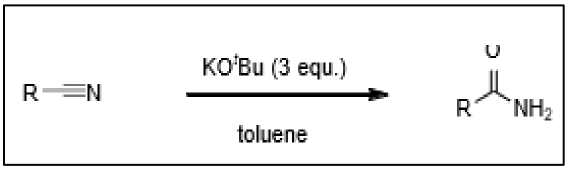
[a]all reaction were carried out under nitrogen atmosphere, [b] 2% of H_2O (v/v) was added.

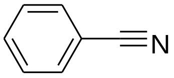
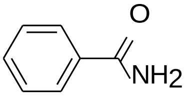
In case of polar aprotic solvents (DMF, DMSO and DMAc) no product formation was observed (entries 6-8). Halogenated solvents like dichloroethane (DCE) and chloroform failed to afford the desired amide 35 (entries 9 and 11) while dichloromethane (DCM) managed to give the desired amide 35 only in trace amounts (entry 10). When hydration was performed in polar protic solvents (entries 12-14), the desired product was obtained in 65%, 75%, and >99% yield in ethanol, isopropanol and tertiary butanol (^tBuOH) respectively. It might seem that air moisture is the source of the Oxygen atom in the amide. But in the presence of small amounts of water (2 % H_2O (v/v)) yield of the amide reduced significantly. The presence of 2 % H_2O (v/v) in toluene reduced the yield to 15%, and the same reduced the yield to 51 % in ^tBuOH (Table 2, entries 2 and 15). It implies that KO^tBu is the source of the Oxygen atom of the amide. Hence, 3 equivalent KO^tBu was proved to be the optimal base. The yield of each of these substrates was determined in both toluene (Table 3) and ^tBuOH (Table 4).

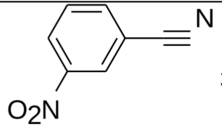
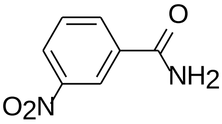
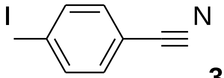
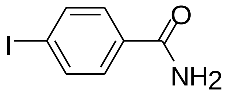
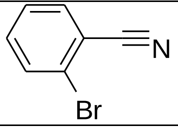
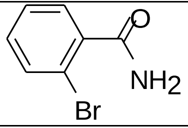
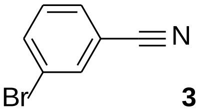
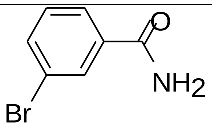
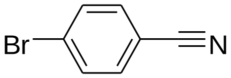
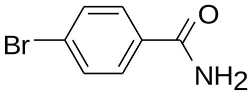
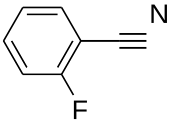
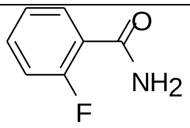
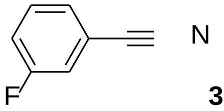
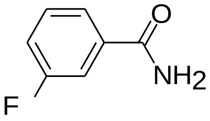
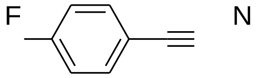
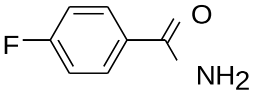
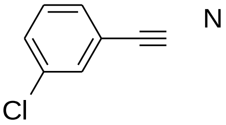
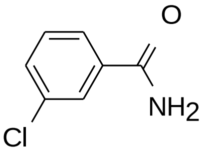
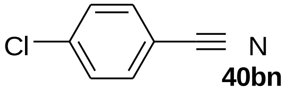
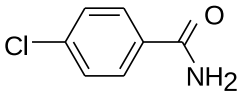
Generalisation of Reaction

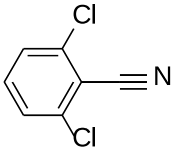
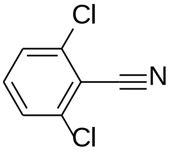
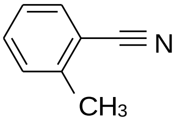
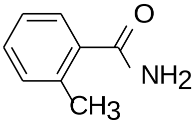
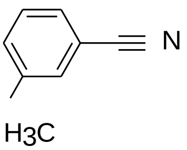
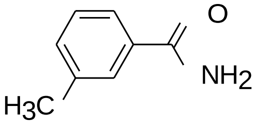
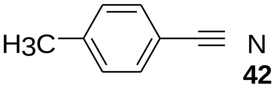
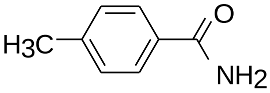
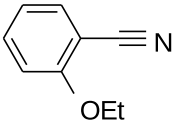
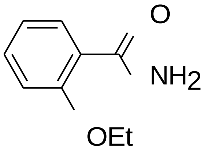
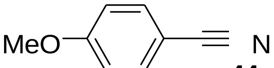
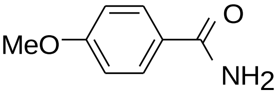
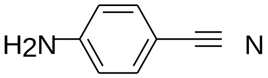
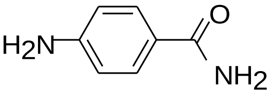
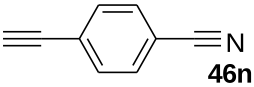
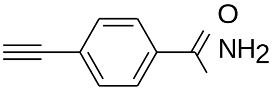
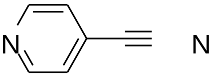
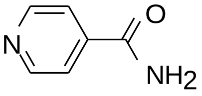
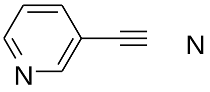
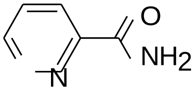
Having established optimal conditions for this reaction, expansion of the substrate scope was explored. Electron-deficient aromatic nitriles provided corresponding amides (36–41) in good to excellent yields (Table 3). Hydration of m-nitrobenzonitrile worked extremely well in ^tBuOH and the corresponding amide 36 was isolated in nearly quantitavie yields (>99%). Reactivity of para-substituted halobenzonitriles is higher in both the solvents (^tBuOH and toluene) and the corresponding amides (37, 38c, 39c, 40b) were obtained in excellent yields (Table 3 & Table 4). On the other hand meta- and ortho-substituted halobenzonitriles reacted slowly in toluene (Table 3). The desired amides (38a, 38b, 39a, 39b, 40a, 41) are obtained in good to excellent yields when the hydration was carried out in tBuOH. Improved reactivity in ^tBuOH compared to toluene could be due to the strong hydrogen bonding ability of ^tBuOH with the heteroatom present in the aryl moiety. Para-substituted electron-rich aromatic nitriles afforded the corresponding amides (42c, 44, 45) in moderate to good yields in both toluene and ^tBuOH (Table 3 and Table 4).

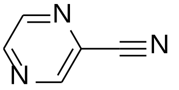
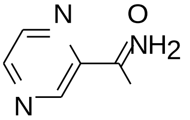
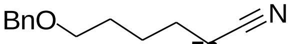
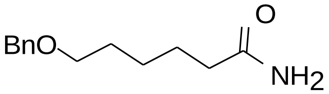
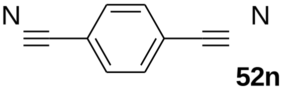
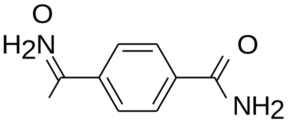
Table 3: KO^tBu Promoted Hydrolysis of Nitriles to Amides in Toluene



Entry	Substrate	Product	Time, Temperature, Yield
1	 **34**	 **35**	5 h, rt, 91%

2	 **36n**	 **36**	5 h, rt, no reaction 5 h, 85 ˚C, 40%
3	 **37n**	 **37**	5 h, rt, 93%
4	 **38an**	 **38a**	9 h, rt, 80%
5	 **38bn**	 **38b**	9 h, rt, 85%
6	 **38cn**	 **38c**	9 h, rt, 90%
7	 **39an**	 **39a**	5 h, rt, 85%
8	 **39bn**	 **39b**	12 h, rt, 86%
9	 **39cn**	 **39c**	5 h, rt, 95%
10	 **40an**	 **40a**	12 h, rt, 79%
12	 **40bn**	 **40b**	5 h, rt, 84%

13	 **41n**	 **41**	5 h, rt, 58%
14	 **42an**	 **42a**	9 h, rt, no reaction 5 h, 60 ˚C, 45%
15	 **42bn**	 **42b**	9 h, rt, 45%
16	 **42cn**	 **42c**	9 h, rt, 79%
17	 **43n**	 **43**	5 h, rt, no reaction 5 h, 60 ˚C, 95%
18	 **44n**	 **44**	9 h, rt, 71%
19	 **45n**	 **45**	5 h, 85 ˚C, 56%
20	 **46n**	 **46**	5 h, rt, 85%
21	 **47n**	 **47**	5 h, rt, 95%
22	 **48n**	 **48**	5 h, rt, 70%

23	 **49n**	 **49**	9 h, rt, 50%
24	 **50n**	 **50**	5 h, 50 °C, no reaction 3 h, 130 °C, 83%
25	 **52n**	 **52**	12 h, rt, 58%

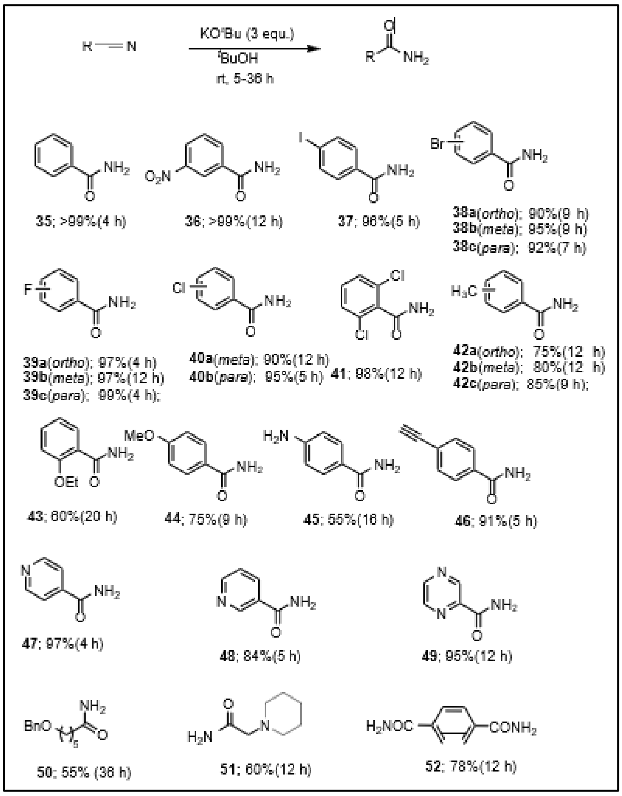
On the other hand, ortho substituted benzonitriles having electron-donating functional groups are less reactive under standard hydration conditions in toluene at rt (Table 3). These benzonitriles can be transformed into the corresponding hydration products (amides 42a and 43) in synthetically useful yields either by heating for a few hours or by performing the hydration reaction in ^{t}BuOH. The protocol is successfully applied for the hydration of para- and meta-cayano pyridine to give the corresponding amides (47, 48) in 97% and 84% yield, respectively. Antitubercular agent pyrazinamide 49 is prepared in 95% yield by hydration of the corresponding nitrile, protocol has been utilised by us. Meta-cayano pyridine and pyrazine nitrile show higher reactivity in ^{t}BuOH than toluene.

Higher reactivity can also be explained by hydrogen bonding model. As compared to aromatic nitriles, aliphatic nitriles seem to be less reactive under specific reaction conditions due to the absence of cation-π stabilisation (Scheme 16). Under optimised reaction conditions, amide 50 and 51 are obtained in 55% and 60% yield, when hydration is performed in ^{t}BuOH. Yield of amide 50 is improved significantly, when the reaction is performed in toluene at 130 °C. This reaction system can also be applied to 1,4-dicyanobenzene. It is delightful to observe the formation of the desired dicarboxamide product 52 as a single product in 78% yield.

These results indicate that the newly developed hydration methodology exhibits general substrate scope (electron-rich, electron-deficient aromatic, heteroaromatic, aliphatic and dicyano nitriles). These reactions can be performed in the air atmosphere without any change in yield of the amide products. The outcome of this protocol depends on both the electronic nature and sterics of the substrates.

In case of ortho- and meta- methylbenzonitriles, ortho-ethoxy benzonitrile and ortho-dichlorobenzonitrile, the hydration is less efficient in toluene at room temperature (Table 4, entries 13-15, 17) and carried out at higher temperature. But these substrates react efficiently in ^{t}BuOH at room temperature (Table 3) to give the corresponding amides.

Table 4: KO^{t}Bu Promoted Hydrolysis of Nitriles to Amides in ^{t}BuOH



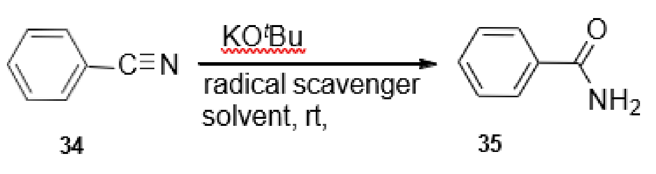
The yields were enhanced from 58% (toluene) to 98% (tBuOH) for the amide 41, 0% (toluene) to 75% (^{t}BuOH) for the amide 42a, 45% (toluene) to 80% (^{t}BuOH) for the amide 42b, 0% (toluene) to 60% (^{t}BuOH) for the amide 43. Similar enhancement of reactivity is also observed in case of meta- nitrobenzonitrile; the yield was enhanced from 0% (toluene) to >99% (^{t}BuOH) for the amide 36 at room temperature.

Mechanistic Study

To gain further mechanistic information, radical quenching experiment was performed in both toluene and ^{t}BuOH, since most of the KO^{t}Bu promoted reactions go through the radical process (Liu *et al.*, 2010, p.16737) (Table 5). When hydration of benzonitrile was performed in the presence of nucleophilic radical trap 2,2,6,6-tertamethylpiperidine (TEMPO), only 78% product formation was observed in toluene, while in the same reaction 82% product formation was observed in ^{t}BuOH. Furthermore, in both the solvents, around 30% inhibition of product formation was observed in presence of 1,1-diphenyl ethylene.

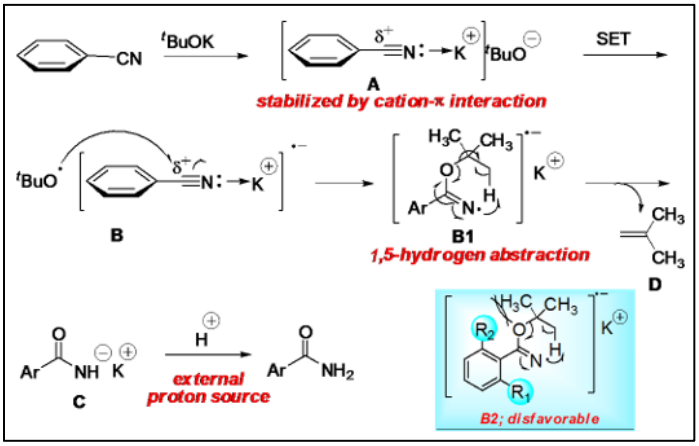
But in the presence of galvinoxyl as electrophilic radical trap, complete inhibition of nitrile hydration was observed in toluene (Table 5). In ^{t}BuOH, nearly 30% inhibition of product formation was observed using galvinoxyl as the radical trap. Radical quenching experiments suggest the radical pathway of the hydration process.

Table 5: Hydration of Nitriles in the Presence of Radical Scavengers



Radical Scavenger	***Yield***	
	Toluene(5 h)	*^{t}BuOH(4 h)*
none	*91%*	>99%
TEMPO	*78%*	82%
1,1-diphenyl ethylene	*68%*	*70%*
galvinolxyl	*trace*	*75%*

Based on this data, a single-electron transfer mechanism was proposed for the hydration of organonitriles (Scheme 16). Lewis basic nitrile will coordinate with potassium cation in the presence of KO^{t}Bu. This kind of complexation was initially observed by Kataoka and co-workers (2002, p. 5553) Complex A can be further stabilised by intermolecular cation-π interaction as well as π-π* stacking (Jonkheijm *et al*., 2006, p.80) Next radical ion pair B will be generated via single electron transfer between the cationic complex A and tertiary butoxide anion. Nucleophilic addition of tert-butoxy radical to the electrophilic carbon atom of the nitrile would then form iminyl radical intermediate B1, which upon 1,5-hydrogen abstraction followed by elimination of isobutylene D would lead to the formation of potassium amidate C. Finally, protonation of C by any external proton source would lead to the formation of the amide. Based on this mechanism, working model B2 has been proposed to explain the lower yield in toluene in the case of ortho-substituted substrates. Formation of intermediate B1 is unfavourable due to the steric interaction between the ortho-substitution and 6 membered cyclic intermediate. As a result, hydration of ortho-substituted aryl nitriles does not undergo hydration at room temperature in toluene, these transformations occurred upon heating at 60 °C to give moderate yields of the corresponding products (Scheme 16).



Scheme 16: Proposed Mechanism for KO^{t}Bu Mediated Hydrolysis of Organonitriles

However, in ^{t}BuOH hydrogen bonding partially locks the conformation (B3) (Figure 3), as a result, free rotation of C(aryl)-C(CN) is minimised and hence, hydration takes place at room temperature. But in the case of ortho-dichloro benzonitrile slightly better yield of the amide 41 is observed in toluene due to higher electrophilicity of the nitrile group. In ^{t}BuOH, intermolecular hydrogen bonding increases the effective steric bulk at the two ortho-positions hence conformation of B4 is locked (Figure3). As a result, hydration of ortho-dichloro benzonitrile proceeds through a lower energy transition state and provides amide 41 with nearly quantitative yield at room temperature. Similar trends were also observed during the formation of 38b, 39b, and 40a in ^{t}BuOH having hydrogen acceptor substituents at the meta-position. The involvement of intermediate B5 is anticipated in these cases (Figure 3). In the case of ortho- flurobenzonitrile comparatively higher yield of the amide 39a was obtained due to the smaller size and strong electron withdrawing effect of the fluoro group (Table 3 & Table 4).

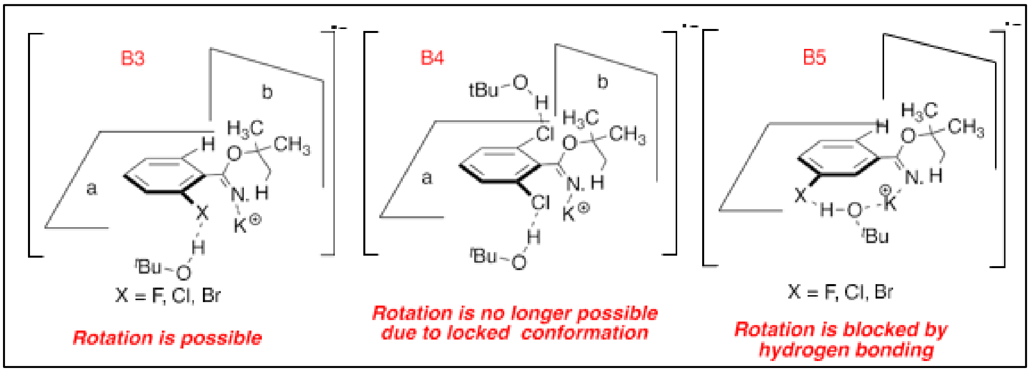


Figure 3: Hydrogen-bonding Model and Reactivities of Different Substituted Nitriles

Conclusion

Classical hydration of nitriles is carried out under acid and base catalysed conditions. However, major limitations of these hydration protocols include a) the formation of corresponding acids by over-hydrolysis, b) the requirement of high temperature and pressure, c) poor functional group tolerance and narrow substrate scope and d) inability to hydrolyse substrates having more than one nitrile functional group. Moreover, organonitriles are the major industrial waste, which falls into the rivers and seas, causing a major environmental threat. So, potassium tertiary butoxide mediated hydration of organonitriles under mild reaction conditions is a suitable alternative to acids and base catalysed methods. Various electron-rich, electron-deficient nitriles as well as cyanopyridines have been transformed into nitriles in excellent yields. Ortho substituted substrates provide the corresponding amides in synthetically useful yields in tert-BuOH. Aliphatic nitriles work well under this reaction condition. None of these substrates underwent over-hydrolysis under this hydration condition. Very high selectivity is observed towards double hydration during hydrolysis of dicyanobenzene.

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