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Acetone Cyanohydrin: A Convenient Alternative of Toxic Sodium Cyanide/Acetic Acid for Oxidative Cyanation of Tertiary Amines

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Abstract Acetone cyanohydrin was found to be a facile, convenient and comparatively safer alternative to toxic sodium cyanide/acetic acid system for generating in situ HCN for the oxidative cyanation of tertiary amines to α-aminonitriles in high yields with hydrogen peroxide using $RuCl_3$ as catalyst. In addition organic nature of acetone cyanohydrin makes it more suitable for an organic transformation since it is readily soluble in reaction medium and can be added in a controlled manner.

Keywords Acetone cyanohydrin · Cyanation · Oxidation · Tertiary Amine · Ruthenium

1 Introduction

α-Aminonitriles are highly useful and versatile intermediates which exhibit dual reactivity and widely used in the preparation of a variety of biologically important compounds such as alkaloids [1–4] and functional materials. Further, they can readily be converted into other useful products such as in α-amino acids either via hydrolysis or by nucleophilic additions to the nitrile group [5]. Therefore, the synthesis of these α-aminonitriles is significantly important both in synthetic as well as medicinal chemistry. The classic method known as Strecker reaction [6] involving the one pot condensation of a carbonyl compound, an amine and cyanide in presence of homogeneous [7–9] or heterogeneous [10–13] catalysts is well documented albeit provide poor product yields. Alternatively, the oxidation of tertiary amines with stoichiometric oxidants such as chlorine dioxide [14], *m*-chloroperbenzoic acid [14, 15], hydrogen peroxide [16, 17] or mercuric acetate [18], followed by the reaction of the iminium intermediate by cyanide ion represents a simple approach for their synthesis. However, the use of stoichiometric oxidants and production of huge amounts of hazardous waste is undesirable from environmental viewpoints. Metal-catalyzed oxidative of tertiary amines by using oxidants such as O_2, H_2O_2, TBHP with NaCN in acetic acid is one of recently developed approaches for the direct synthesis of α-aminonitriles [19–24]. The generation of in situ HCN from the reaction of sodium cyanide and acetic acid is the common and critical feature of these methods. However, the major limitations with the use of sodium cyanide/acetic acid system are its hazardous nature, high cost and also the excess of dissolved cyanide ions in the reaction mixture may cause the deactivation of the catalyst. This might be explained due to the difficulties associated with the controlled addition of the solid NaCN salt; which can be overcome by using the liquid cyanation reagent.

Acetone cyanohydrin **1** as compared to the inorganic cyanide salts is one of the mild, cheap, and environmentally friendly species that can be considered as a better choice for an organic transformation [25]. Although, the use of acetone cyanohydrin for the in situ generation of HCN has recently been explored for some reactions [26, 27], however, is remained less explored for the oxidative cyanation of tertiary amines [28]. In the present

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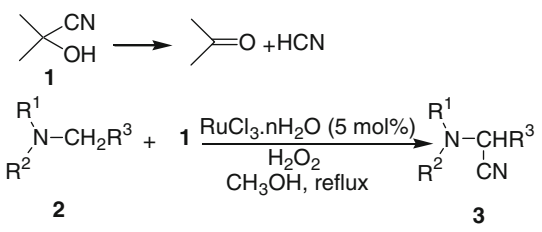
communication we wish to report a successful application of acetone cyanohydrins as a convenient and efficient source of in situ HCN for the oxidative cyanation of tertiary amines **2** to α-aminonitriles **3** by using hydrogen peroxide as oxidant and ruthenium trichloride as catalyst under mild reaction conditions (Scheme 1). Although Murahashi et al. [24] have reported the detailed results and mechanism for this transformation using ruthenium trichloride as catalyst with H_2O_2 with NaCN in acetic acid.

2 Results and Discussion

Acetone cyanohydrin was synthesized by using the standard method [27] and stored at room temperature without taking any special care. Initially the oxidative cyanation of *N,N*-dimethylaniline was studied for comparing the efficiency of acetone cyanohydrin with NaCN/CH_3COOH under the similar reaction conditions as developed by Murahashi et al. at room temperature. The results of these experiments are summarized in Table 1 (entry 1). The use of acetone cyanohydrin was found to be as efficient as NaCN/acetic acid system and afforded comparable results. The important advantage of the acetone cyanohydrin was its slow and controlled addition to the reaction mixture, which provided an improved and efficient cyanation of tertiary amines in the present reaction. By using a syringe pump acetone cyanohydrin could easily be added to the reaction mixture continuously in a slow and controlled manner, which further avoids the accumulation of excess cyanide into the reaction mixture. At the end the reaction, the reaction mixture was quenched with 1 N HCl in order to decompose excess acetone cyanohydrin. The aqueous layer was extracted with dichloromethane and subjected to usual work-up, afforded the corresponding nitrile selectively without any by-product being observed.

While at 50 °C the reaction was found to be faster and afforded better product yield without any significant effect on the selectivity of the desired product. However, further increase in reaction temperature affected the product selectivity adversely (Table 1, entry 1). It is worthy to mention that we did not use acetic acid in case of acetone cyanohydrin, whereas, with NaCN the presence of acetic acid is essential. We have used methanol as solvent for this reaction, albeit the reaction could be proceeded well with comparable results under solvent free conditions as shown in Table 1, entry 1. The effect of catalyst was confirmed by carrying out a blank experiment without using any catalyst under otherwise similar reaction conditions. The reaction did not occur in the absence of catalyst even after prolonged reaction time (24 h). In addition, the drop wise addition of hydrogen peroxide to the reaction mixture was found to be better than its addition in one portion.



Scheme 1 Oxidative cyanation of tertiary amines

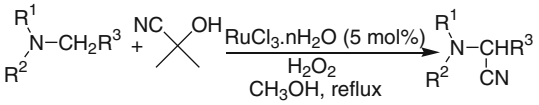
Further, we extended the scope of the developed method by using various tertiary amines **2** as substrates with acetone cyanohydrin **1** under described reaction conditions at 50 °C. As shown in Table 1, all the substrates were efficiently converted into the corresponding α-aminonitriles, affording higher product yields with selective formation of the desired products. Reaction of substituted *N,N*-dimethylanilines having both electron-donating and electron-withdrawing substituents were gave better yields of corresponding cyanated products (entries 2–5) without any evidence of the formation of by-products. Similarly, the reaction could also be applied efficiently to cyclic amines: Piperidine, pyrrolidine, and tetrahydroisoquinoline derivatives under described reaction conditions (Table 1, entries 6–8). Tertiary amines such as tributylamine did not undergo any reaction under these reaction conditions and the substrates could be recovered at the end (Table 1, entry 9). We also repeated the selected experiments at room temperature and compared with the results reported in the literature by using NaCN/acetic acid as shown in Table 1 (entries 1, 2, 4, 6).

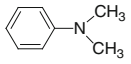
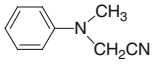
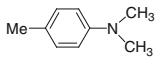
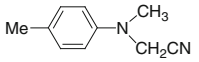
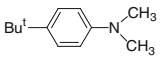
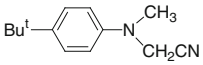
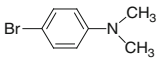
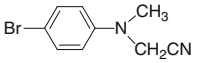
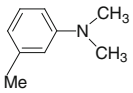
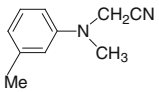
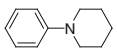
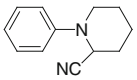
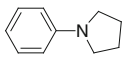
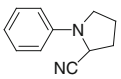
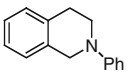
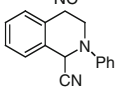
Although, the mechanism of reaction is not clear at this stage, the probable mechanistic pathway for the reaction will be in analogy with the mechanism proposed by Murahashi et al. [24] as shown in Scheme 2.

3 Conclusion

In summary, we have demonstrated the first successful application of acetone cyanohydrin as the convenient source of in situ HCN for the oxidative cyanation of various tertiary amines to the corresponding α-aminonitriles without using acetic acid as solvent. The presented method is more advantageous than the existing methods since acetone cyanohydrin is cheap and comparatively safer in handling than NaCN/acetic acid for an organic reaction which not only avoids the use of toxic reagent but also its liquid nature provides the controlled addition of the cyanide in the reaction mixture. We believe that the presented work will provide new opportunities and open up new possibilities for the use of acetone cyanohydrin as a convenient source of HCN for other organic transformations.

Table 1 $RuCl_3$ catalyzed oxidative cyanation of tertiary amines **2**



Entry	Substrate	t (h)		Product	Conv.(%)[c]/ Yield (%)[d]	
		[a]	Ref. [25][b]		[a]	Ref. [25][b]
1		2.5	2.0		90/85[e] 98/92[f] 98/62[g] -[h] 90/82[i] 98/94[j, f]	90[c]
2		2.0	1.5		87/82[e] 98/92[f]	81
3		2.5			95/90[f]	
4		3.0	3.0		78/72[e] 89/84[f]	67
5		6.0			18[e] 30[f]	
6		3.5	2.0		73/65[e] 86/80[f]	69
7		3.5			82/76[e] 85/80[f]	
8		3.0	1.5		88/80[e] 92/89[f]	76
9	$(t\text{-Bu})_3N$	5.0	-	-	-	-

[a] *Conditions* substrate (1 mmol), catalyst (5 mol %), 35% aq. H_2O_2 (2.5 mmol, added drop wise), acetone cyanohydrin (2 ml) MeOH (4 mL)

[b] Comparison with the method reported in Ref. [24]

[c] Determined by GC–MS

[d] Isolated yields

[e] At room temperature

[f] At 50 °C

[g] Under refluxing

[h] Blank experiment, reaction time 24 h

[i] Addition of hydrogen peroxide in one portion

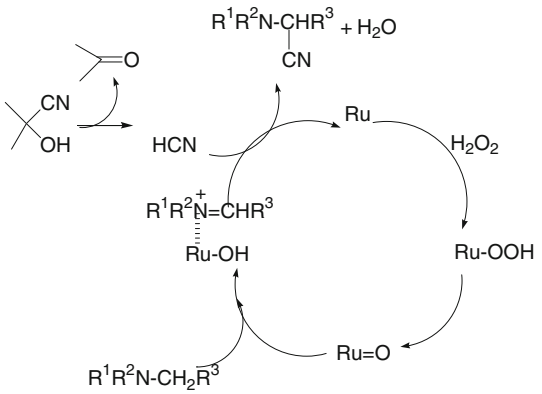
[j] Under solvent free conditions

4 Experimental Section

All tertiary amines are commercially available and used as received. $RuCl_3.nH_2O$ was purchased from Aldrich and used as received. Acetone cyanohydrin was prepared as following the literature procedure [29]. The conversions and selectivity of the products were determined by high resolution GCMSD, EI, quadrapole mass analyzer, EM detector.

4.1 General Experimental Procedure for Oxidative Cyanation of Tertiary Amines

A 25 mL round bottomed flask equipped with a magnetic stirrer bar was charged with tertiary amine (1 mmol), MeOH (2 mL), $RuCl_3{\cdot}nH_2O$ (5 mol%, 0.05 mmol) and the resulting reaction mixture was stirred. The reaction mixture was refluxed and the acetone cyanohydrin (2.0 mL) was added via a syringe. The aqueous hydrogen peroxide



Scheme 2 Probable mechanistic pathway

(2.5 mmol, 35 wt%) was added drop wise to the stirred mixture under reflux and the progress of the reaction was monitored by TLC (SiO2). After completion of the reaction, the reaction was quenched with 1 N HCl and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate followed by the usual work-up to yield corresponding nitrile. The crude product was purified by column chromatography. The conversion of the tertiary amine and selectivity for the desired product was determined by GC–MS and the identity of the products was established by comparing their spectral data with authentic samples.

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