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An insight into nitromethane as an organic nitrile alternative source towards the synthesis of aryl nitriles

Rakhee Saikia,[b] Satyajit Dey Baruah,[b] Ramesh C. Deka,[b] Ashim J. Thakur*[a] and Utpal Bora*[a]

Abstract: Directed by an unusual *in situ* reduction of Cu(II), our protocol is a simple Cu(I)-mediated synthesis of aryl nitriles, with inexpensive and readily available nitromethane as the cyanating source, in moderate to good yields. Exhibiting a wide substrate scope, the method involves simple reaction conditions, is additive free with low catalyst loading. The mechanism of cyanation of aryl halides is elucidated by a congregation of three cycles, namely the *in situ* reduction of Cu(II) species by nitromethane, generation of HCN species from nitromethane and a regular organometallic pathway which releases the nitrile derivative. The detail of the mechanism of generation of CN^- from nitromethane is computationally validated. Our protocol holds the distinction of involving a rarely encountered Cu(I) catalytic species as well as facile *in situ* generation of nucleophilic CN^- to yield synthetically useful aromatic nitriles.

Introduction

The exploration of novel methodologies for the introduction of a nitrile group into an aromatic framework is a much desired endeavour, considering the broad synthetic utility of the nitrile functionality.[1] Its appearance in a number of natural heterocyclic products and easy transformation into a plethora of useful functionalities such as aromatic acids, esters, amines, amides, aldehydes and nitrogen heterocycles accounts for its popularity and applications.[2-3] Since the first nitrile synthesis, with Rosenmund-von Braun[4] and Sandmeyer[5] reactions being the breakthrough protocols, all the traditional methods of nitrile synthesis suffered from the use of stoichiometric amounts of toxic metal cyanides (M-CN; M = alkali metal, Cu, Zn, Ag), which generated a significant amount of waste. Requirement of elevated temperatures (150-250 °C) being another shortcoming of those processes. One of the practical solutions that has emerged to reduce the risk of hazardous metal cyanides, is to employ, either non-metallic cyanide sources, such as aryl(cyano)-iodonium triflates,[6] acetone cyanohydrin,[7] malononitrile,[8] AIBN,[9] benzyl cyanide,[10] acetonitrile,[11] butyronitrile,[12] ethyl (ethoxymethylene)cyanoacetate,[13] etc., or sources which can generate CN^- group *in situ* (indirect sources). Recent examples of such 'indirect sources' are nitromethane,[14] the combination of NH_4I-DMF,[15] NH_4HCO_3-DMSO or NH_4HCO_3-DMF,[16] DMF[17] and *t*-BuNC.[18]

The pioneers of employing the inexpensive, less-toxic and readily available indirect organic nitrile source CH_3NO_2, Yu and his group, successfully cyanated aryl C-H bonds with nitromethane, the mechanism of which was rationalized through a radical-cation pathway.[19] Henceforth, nitromethane was utilized to cyanate organic scaffolds with operational simplicity and economic viability.

Although, a variety of atypical transition metals, such as Pd,[20] Ni,[21] Co,[22] Zn,[14] and Rh[23] have been identified to assist the process of cyanation without the need of pre-functionalised substrates,[24] the role of Cu as an inexpensive and readily available transition metal in cyanation, cannot be overlooked.[25] Moreover, efficient and sustainable processes of cyanation of common functionalized substrates, such as aryl halides, needs further exploration.[26] The abundance of aryl halides in nature and their affinity towards a metal in a metal-catalyzed reaction, prompted us to employ them as substrates in our reaction. To the best of our knowledge, Cu-catalyzed cyanation of aryl iodides with nitromethane has been reported only once, [27] mechanistic aspects of which, is unexplored in detail.

Herein, we report a Cu(I)-catalyzed cyanation of aryl halides (iodides/bromides) with nitromethane. Our protocol highlights an unprecedented, dual role played by nitromethane in the reaction. In addition to being the cyanating source, nitromethane also helps in the *in situ* generation of active Cu(I) species by reduction of the parent Cu(II) salt. The mechanistic aspect of our protocol is explained in detail, by experimental as well as computational methods. Moreover, it involves mild reaction conditions, low catalyst loading and requires no additives.

Results and Discussion

At first, a mixture of 4-Iodoanisole (**1a**), nitromethane (**2**) and a catalytic amount of $CuCl_2$ were made to react with each other in DMF. After 16 hours under reflux condition, the reaction offered an unexpected cyanated product in 71% yield. Allowing the reaction to proceed beyond 16 hours, however, did not increase the yield of the cyanated product.

With 4-Iodoanisole (**1a**) as the model substrate, we optimized the reaction conditions suitable for cyanation (**Table 1**). It was found that although both Cu(I) and Cu(II) salts (Table 1, entries **11-14**) could easily facilitate cyanation, the reaction proceeded best with 5 mol% of $Cu(NO_3)_2 \cdot 3H_2O$. Its complexation with 10 mol% of 1,10-Phen *in situ*, among other ligands, provided a better yield in less time (Table 1, entries **15** and **16**). Among all the organic and inorganic bases screened (Table 1, entries **7-10**), K_2CO_3 showed the best activity under the given conditions. Further study revealed a crucial role of the solvent and best results were obtained in DMSO (Table 1, entries **1-6**) at 100 °C. A decrease in temperature results in a significant decrease in product yield (Table 1, entry **17**), while further increase in temperature from 100 °C did not bring about any change in the yield of the desired product (Table 1, entry **18**).

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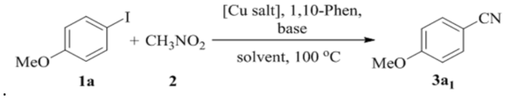


Table 1. Initial investigation of reaction conditions for the Cu(I)-catalyzed cyanation of 4-Iodoanisole (**1a**) with nitromethane (**2**).[a]

Entry	Base	Cu-salt	Solvent	Yield[b] (%)
1	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	CH_3NO_2	-
2	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	CH_3OH	67
3	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	CH_3CN	73
4	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	DMF	83
5	$\mathbf{K_2CO_3}$	$\mathbf{Cu(NO_3)_2\cdot 3H_2O}$	**DMSO**	**85**
6	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	Toluene	62
7	NaOH	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	70
8	$(C_2H_5)_3N$	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	57
9	DABCO	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	59
10	$NaHCO_3$	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	61
11	K_2CO_3	$Cu(OAc)_2\cdot H_2O$	DMSO	62
12	K_2CO_3	$CuCl_2$	DMSO	83
13	K_2CO_3	CuCl	DMSO	67
14	K_2CO_3	CuI	DMSO	64
15[c]	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	65
16[d]	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	77
17[e]	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	62
18[f]	K_2CO_3	$Cu(NO_3)_2\cdot 3H_2O$	DMSO	85

[a] Reaction conditions: 4-Iodoanisole **1a** (1 mmol), nitromethane **2** (1.5 equiv.), Cu-salt (5 mol%), Ligand (10 mol%), base (1 equiv.), solvent (3 mL), 100 °C, 16 h; 1,10-Phen = 1,10-Phenanthroline monohydrate [b] Isolated yield based on 4-Iodoanisole 1a [c] *N*,*N* Dimethylurea was used as a ligand [d] 2,2'-Bipyridyl was used as a ligand [e], [f] Reaction temperature was maintained at 80 °C and 120 °C respectively.

Post optimization, the results of scope exploration of the Cu(I) catalyzed cyanation of aryl iodides and bromides is presented in **Table 2**. Various *o*-, *m*- and *p*-substituted aryl iodides and bromides (Table 2, entries **1-15**) have reacted with nitromethane **2** under the optimized condition (Table 1, entry **4**) to give the respective cyanated product in moderate to good yields. A decent range of electron withdrawing and electron donating groups have reacted to afford the desired product, **3a₁-p**, in 52-85% yields. Nitromethane (**2**) cyanated all the substituted aryl iodides and bromides selectively at the aryl C-X (X = I/Br) bond. Electron releasing groups have shown a higher reaction yield in comparison to electron withdrawing groups. This can be attributed to the positive inductive effect of the electron-releasing substituents. The optimized reaction conditions tended to favour

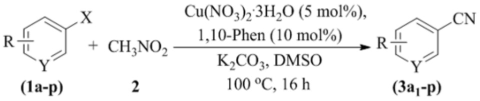
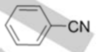
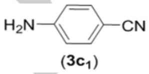
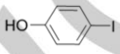
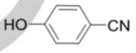
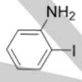
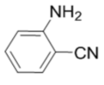
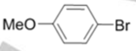
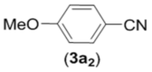
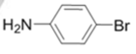
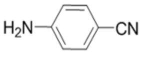
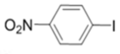
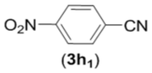
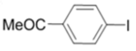
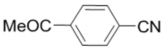
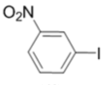
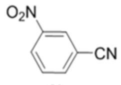
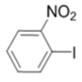
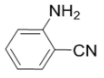
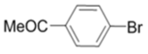
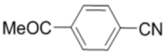
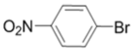
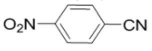
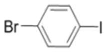
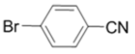
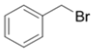
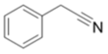
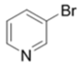
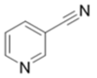


Table 2. Scope exploration of the Cu(I)-catalyzed cyanation of aryl iodides and bromides with nitromethane as the cyanating source [a]

Entry	Substrate [**1**]	Product [**3**]	Yield[b] [%]
1	 (**1b**)	 (**3b**)	50
2	 (**1c**)	 (**3c₁**)	72
3	 (**1d**)	 (**3d**)	80
4	 (**1e**)	 (**3e₁**)	52
5	 (**1f**)	 (**3a₂**)	68
6	 (**1g**)	 (**3c₂**)	65
7	 (**1h**)	 (**3h₁**)	78
8	 (**1i**)	 (**3i₁**)	70
9	 (**1j**)	 (**3j**)	61
10	 (**1k**)	 (**3e₂**)	73
11	 (**1l**)	 (**3i₂**)	54
12	 (**1m**)	 (**3h₂**)	72
13[b]	 (**1n**)	 (**3n**)	65
14	 (**1o**)	 (**3o**)	75
15	 (**1p**)	 (**3p**)	63

[a] Reaction conditions: Aryl halide (1 mmol), nitromethane (1.5 equiv.), $Cu(NO_3)_2\cdot 3H_2O$ (5 mol%), 1,10-Phen (10 mol%), K_2CO_3 (1 equiv.), DMSO (3 mL), 100 °C, 16 h (the reaction time was not optimized for each substrate), [b] 4-Iodobenzonitrile was obtained as a minor product (GC yield = 31%).

p-substituted aryl halides more than the *o*- and *m*-substitutes.

We are yet to establish a plausible reason for this inconsistency. Interestingly, 1-Iodo-2-nitrobenzene underwent cyanation, with simultaneous reduction of the nitro group in 73% yield (Table 2, entry **10**).When nitrobenzene was made to react under the same reaction conditions; aniline was obtained. This may be due to the reducing tendency of DMSO.[28] However, no such transformation was observed for the *m*- and *p*- analogues. (Table 2, entries **7**, **9** and **12**).

The mechanistic study of the reaction began with the isolation of a $[Cu(phen)_2]^{2+}$ complex (ESI-S21).The obtained $[Cu(phen)_2]^{2+}$ complex was then reacted with 4-Iodoanisole (**1a**) and nitromethane (**2**) to give the cyanated product (**3a**). Interestingly, we found that the active catalyzing species of the reaction is its cuprous analogue formed through an unusual *in situ* reduction of $[Cu(phen)_2]^{2+}$ in the presence of nitromethane.

The formation of Cu(I) in the reaction medium was confirmed by UV-Vis spectroscopy, cyclic voltammetry and EPR spectroscopy. The broad absorption band at 420 nm is a characteristic of the MLCT electronic transition in $[Cu(phen)_2]^{+}$ complex corresponding to the transfer of an electron from a 3d orbital of Cu to antibonding π^* orbital of 1,10-Phen ligand (**Figure 1a**).[29] X-band EPR spectra before the start of reaction, shows a sharp band with $g_{||} = 2.26$ and $g_{\perp} = 2.17$ which is characteristic of Cu(II) ion (**Figure 1b**).[30] The decrease in intensity of the EPR signal recorded for the reaction mixture after 16 hours confirms the irreversible reduction of Cu(II) to Cu(I) during the reaction. Cu(I) being a d^{10} ion, is diamagnetic.

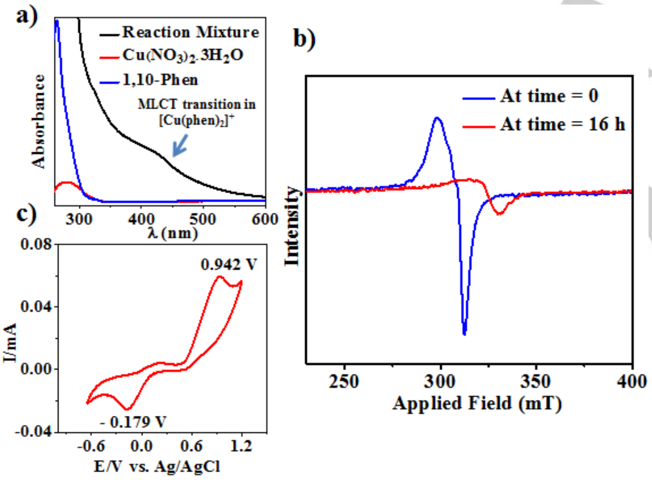
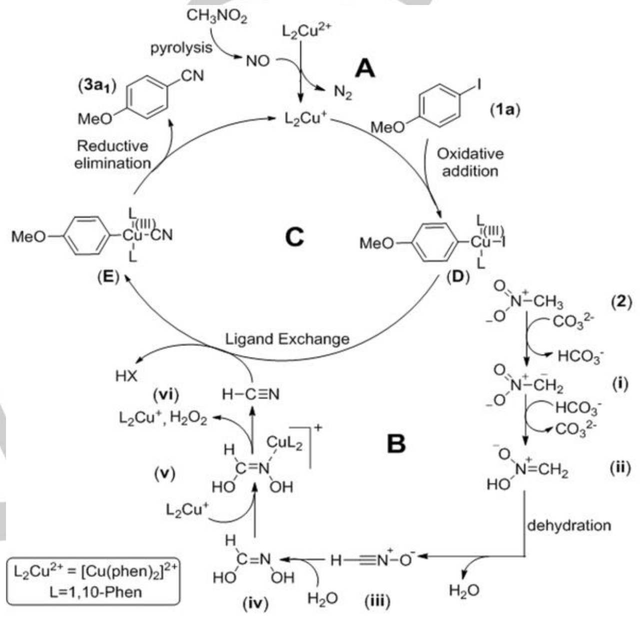


Figure 1. (**a**) UV-Vis spectra of [black: *in situ* generated Cu(I) complex; blue: 1,10-Phen; red: $Cu(NO_3)_2{\cdot}3H_2O$] in DMSO;(**b**) X-band EPR spectra of [blue: reaction mixture before the start of reaction; red: reaction mixture at the end of reaction i.e. 16 hours] in DMSO at 100 K; (**c**) Cyclic Voltammogram of the reaction mixture in DMSO.

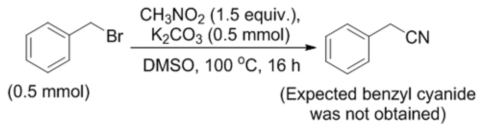
In 0.1 M KCl, the reaction mixture showed an anodic peak potential at 0.936 V *vs* Ag/AgCl suggesting oxidation of Cu(I) to Cu(II) and a cathodic peak potential at −0.173 V *vs* Ag/AgCl suggesting reduction of Cu(II) to Cu(I), at a scan rate of 50 mV/s (**Figure 1c**).[31] The UV-Vis, CV, and EPR data confirms the change in oxidation state of Cu from +2 to +1 during the reaction. The reaction mechanism can be divided into three stages, viz., (**A**) the reduction of $[Cu(phen)_2]^{2+}$ to $[Cu(phen)_2]^{+}$ by nitromethane; (**B**) generation of HCN from nitromethane and (**C**) the general organometallic cycle involving oxidative addition, ligand exchange and reductive elimination to yield the desired nitrile derivative (**Scheme 1**).



Scheme 1. Plausible mechanism of cyanation

Studies on the thermochemistry of nitromethane show that its decomposition at high temperatures can be subdivided into many phases with different products in each stage. Two of such important decomposition products are CO and NO[32] i.e. oxidation of the carbon atom of CH_3NO_2 to CO with subsequent reduction of the nitrogen atom to N_2 *via* the formation of NO.[33] The released NO interacts with Cu(II) in the reaction medium, causing the reduction of $[Cu(phen)_2]^{2+}$ to $[Cu(phen)_2]^{+}$ (**A**).[34] Control experiments suggest that reduction of Cu(II) to Cu(I) takes place only in the presence of nitromethane.

From previous literature, the process of generation of HCN from nitromethane (**B**) can be rationalized through proton abstraction (**i**) (The reaction does not proceed in the absence of a base), followed by dehydration of (**ii**) to form a nitrile oxide (**iii**). The generated nitrile oxide, HCNO, undergoes addition of a water molecule, to form a hydroxyformaldoxime species (**iv**). The *in situ* generated Cu^{+} species preferentially coordinates to the N-donor atom of (**iv**) causing labilization of the C-O and N-O bonds (**v**). Thereafter, the HCN species (**vi**) is generated, releasing a molecule of hydrogen peroxide.[35] Controlled experiment supports the involvement of Cu in the facile release of CN^{-} (**Scheme 2**).



Scheme 2. No cyanation of benzyl bromide in the absence of Cu.

Since the formation of benzyl cyanide from benzyl bromide does not involve the usual organometallic cycle, failure to yield the cyanated product in absence of Cu, suggests that Cu plays an important role in the evolution of CN^- from nitromethane. The *in situ* generation of CN^- is further supported by the picrate paper test (ESI-S20).[36] The generated HCN species then enters the organometallic cycle (**C**) at the stage of ligand exchange. The representative 4-Iodoanisole oxidatively adds to the active Cu(I) complex, forming an arylCu(III) species (**D**). It undergoes ligand exchange with HCN to form (**E**), which on reductive elimination yields 4-Methoxybenzonitrile with simultaneous regeneration of $[Cu(phen)_2]^+$ complex.

Along with the experimental analysis, to look into the heart of the electronic structure at an atomistic level, DFT calculations have been performed to gain an in-depth mechanistic insight for the *in situ* generation of HCN (**Figure 2**). A potential energy surface (PES) is constructed to investigate the detailed mechanism with energetics (**Figure 3**).

The potential energy surface was built by considering the ground state energies of initial reactants as zero. The absolute energies and relative energies are presented in Table S1, ESI-S23.

The formation of species (**i**) proceeds *via* a transition state, **TS1** (imaginary frequency = 1146*i* cm^{-1}) where, one of the C-H bonds of nitromethane interacts with K_2CO_3 and undergoes an elongation from 1.09 Å to 1.35 Å to release HCO_3^{2-}. This step has an activation barrier of 11.27 kcal/mol and is spontaneous, with Gibbs free energy change (ΔG) of -0.9 kcal/mol. **TS2** marks the elongation of the O-H bond of HCO_3^{2-} from 0.976 Å to 1.35 Å resulting in the formation of (**ii**), a new O-H bond with a bond distance of 1.12 Å. Only one imaginary frequency (680*i* cm^{-1}) is obtained with an activation barrier of 11.35 kcal/mol and ΔG value of 13.53 kcal/mol. Species (**ii**) then undergoes dehydration to generate HCNO (**iii**). This step is a barrierless transition (barrier of activation is -0.5 kcal/mol, imaginary frequency = 278*i* cm^{-1}) which may be due to the presence of a good leaving group (H_2O) in the transition state (**TS3**). The resultant HCNO species (**iii**) is quite stable, as represented in the PES (**Figure 3a**). The process is spontaneous with ΔG = -14.07 kcal/mol. The addition of a molecule of H_2O to HCNO species to form hydroxyformaldoxime (**iv**) passes through **TS4** (imaginary frequency of 105*i* cm^{-1}) with a very low barrier of 1.01 kcal/mol; the process is spontaneous with ΔG = -0.20 kcal/mol. TD-DFT spectrum of $[Cu(phen)_2]^+$ confirms formation of the Cu(I)complex with λ_{max} obtained at 417 nm (ESI-S22) in correlation to the experimental absorption intensity (λ_{max}) at 420 nm. The metal to ligand charge transfer (MLCT) is depicted by the metal-centered HOMO and the ligand-centered LUMO of $[Cu(phen)_2]^+$ complex (ESI-S22). $[Cu(phen)_2]^+$ complex interacts with species (**iv**) to form (**v**) (pre-reaction complex).

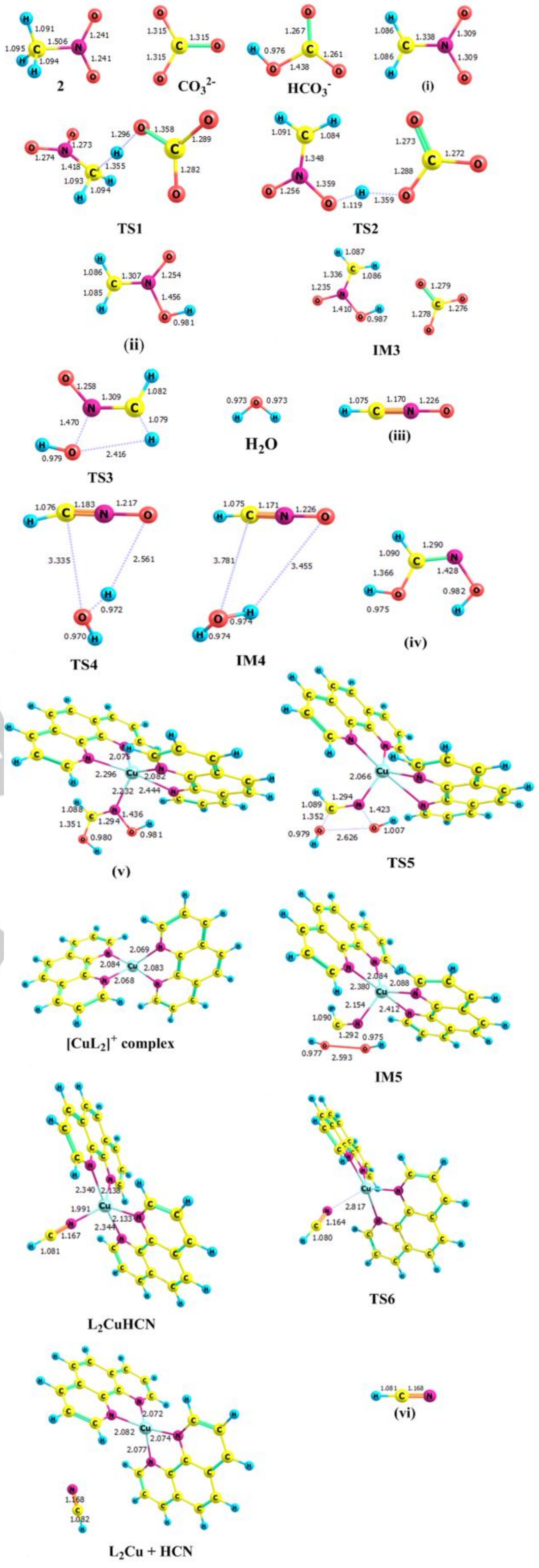


Figure 2. Optimized geometries of all the species involved in the generation of HCN from nitromethane at RPBE/DNP level of theory (ball and stick model).

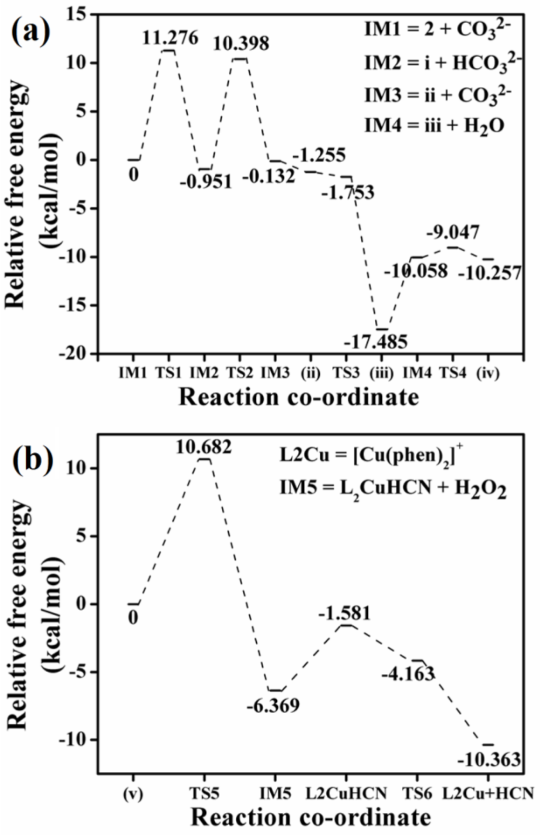


Figure 3. Potential energy surface depicting the generation of HCN from nitromethane at RPBE/DNP level of theory.

In (**v**), two Cu-N bonds of $[Cu(phen)_2]^+$ elongates from 2.08 Å to 2.30 Å and 2.44 Å respectively. Moreover, the bond distances of O-H groups from each other in (**iv**) changes from 2.65 Å to 2.13 Å in (**v**). Thus, transition (**TS5**) takes place with an activation barrier of 10.68 kcal/mol, (imaginary frequency = 499*i* cm^{-1}) and Gibbs free energy change (∆G) of -6.36 kcal/mol to form **IM5**. The formation of H_2O_2 in IM4 triggers the generation of HCN. This transition (**TS6**) is barrierless with Gibbs free energy change of ∆G = - 8.7 kcal/mol. From the PES (Figure 3), it is observed that the post reaction complex (**L_2Cu + HCN**) is a reasonably stable species. Only one imaginary frequency provides testimony of the transition states connecting the reactants and products.

Conclusions

To summarize our work, we have developed a simple Cu(I) catalyzed methodology for the generation of synthetically and pharmaceutically important aryl nitriles, with nitromethane as the cyanating source. Easily synthesizable $[Cu(phen)_2]^{2+}$ catalyst ensures homogeneity of the reaction medium, surpassing the risk of catalyst deactivation. Operational simplicity of the method overcomes most drawbacks associated with usual cyanation processes. We have demonstrated the first detailed outlook on the unusual mechanism of generation of a CN^- species from nitromethane, with simultaneous *in situ* reduction of Cu(II) to Cu(I). We believe our study will lead to newer avenues on nitromethane and its extensive utilization in synthetic organic chemistry.

Experimental Section

General Information

All the chemicals used for the reactions were procured commercially and used without further purification. The progress of the reaction was monitored through thin layer chromatography on Merck Kieselgel Silica gel 60 F_{254} plates using short wave UV light (λ=254 nm). The products were purified by column chromatography using Silica gel (60-120 mesh and 100-200 mesh). The identification of the purified products was done by NMR spectroscopy. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz JEOL NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C spectroscopy). Chemical shifts for both ^{1}H (δ_H) and ^{13}C (δ_C) NMR are assigned in parts per million (ppm) using TMS (0 ppm) as the internal reference and $CDCl_3$ and DMSO-d_6 as solvent ($CDCl_3$: δ_H = 7.25 ppm and δ_C = 77.1 ppm; DMSO-d_6: δ_H = 2.5 ppm, DMSO-d_6 absorbed water = 3.3 ppm and δ_C = 40.0 ppm). The multiplicities of the signals are assigned as: s = singlet, d = doublet, t = triplet, br = broad and m = multiplet. HRMS data were recorded in Q-TQF mass analyzer by electron spray ionization technique.

All the computation was performed as in Dmol^3 program package.[37-38] Generalized gradient approximation (GGA) using revised Perdew-Burke-Ernzerhof exchange-correlation functional has been used to optimize the electronic structures of the reactants, pre-reactive complexes (RCs), transition states (TSs) and products with double numerical with polarization (DNP) basis set for our calculations.[39] DNP basis set used for our calculations is comparable to Gaussian 6-31G**, but DNP is more accurate than a Gaussian basis set of the same size.[40-41] For the vibrational frequency calculations, same level of theory was used. We have obtained stable minima which correspond to the real and positive values and the first order saddle points (transition states) are characterized by imaginary frequency. To improve computational performance, a global orbital cutoff of 4.5 Å was employed. Self-consistent field (SCF) procedures are done with tolerances of the energy, gradient, and displacement convergences: $1.0*10^{-5}$ Ha, $2*10^{-3}$ Ha Å and $5*10^{-3}$ Å respectively. RPBE functional has been preferred for the calculations as it displays better results with good accuracy comprehensive for improved adsorption energies of small molecules on transition metal complexes, which is the ultimate goal of this study. The effect of solvent continuum, in DMSO is incorporated using conductor-like screening model (COSMO) in Dmol^3 module. Temperature ranging from 25 K to 1000 K at an interval of 25 has been carried out. Analysis of 373 K in correlation to the experimental run to simulate the same environment has been performed.

General experimental procedure

An oven-dried 50 ml round-bottomed flask, with a magnetic stirring bar, was charged with $Cu(NO_3)_2.3H_2O$ (5 mol%, 0.05 mmol, 0.0123 g), 1,10-Phenanthroline monohydrate (10 mol%, 0.1 mmol, 0.0199 g), 2 (1.5 equiv., 1.5 mmol, 80 µL) substrate 1a (1 mmol, 0.235 g), K_2CO_3 (1 equiv., 0.138 g) in DMSO (3 mL). It was then fitted to a condenser and stirred at 100 °C under reflux conditions in an oil bath. After 16 h, the crude mixture was extracted with EtOAc and washed with crushed ice. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting reaction mixture was purified by column chromatography using hexane-EtOAc mixture as eluent to afford product 3a.

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Keywords: aryl nitrile • copper • cyanation • *in situ* reduction • nitromethane

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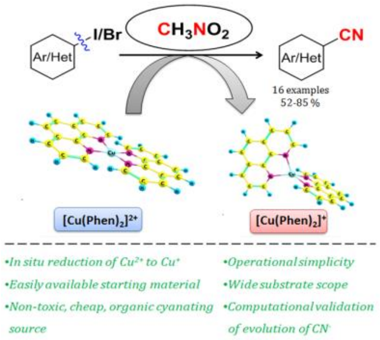
Entry for the Table of Contents

Layout 1:

FULL PAPER

An experimental and computational study into the synthesis of aryl nitriles with nitromethane as an organic and non-toxic alternative of traditional cyanating sources is investigated. The mechanistic pathway of cyanation is the highlight of the current study.



cyanation • nitromethane *

Rakhee Saikia, Satyajit Dey Baruah, Ramesh C. Deka, Ashim J. Thakur * *and Utpal Bora*[*]

Page No. 1– Page No. 7

An insight into nitromethane as an organic nitrile alternative towards the synthesis of aryl nitriles