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Revisiting the synthesis of aryl nitriles: a pivotal role of CAN†

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Facilitated by the dual role of Ceric Ammonium Nitrate (CAN), herein we report a cost-effective approach for the cyanation of aryl iodides/bromides with CAN–DMF as an addition to the existing pool of combined cyanation sources. In addition to being an oxidant, CAN acts as a source of nitrogen in our protocol. The reaction is catalyzed by a readily available Cu(II) salt and the ability of CAN to generate ammonia in the reaction medium is utilized to eliminate the additional requirement of a nitrogen source, ligand, additive or toxic reagents. The mechanistic study suggests an evolution of CN[−] leading to the synthesis of a variety of aryl nitriles in moderate to good yields. The proposed mechanism is supported by a series of control reactions and labeling experiments.

Introduction

The ubiquity of nitrile-containing frameworks and their growing demand in the clinic are attributed to the biocompatibility of the nitrile functionality.¹ Around 30 nitrile-containing compounds were suggested in a variety of medications in 2010 and an additional 20 were being considered as leads for clinical development.² Benzonitriles and heteroaromatic nitriles also form substructures of various fine chemicals and agrochemicals.³ They are commercially utilized in high-performance rubbers, polymers, molecular electronics and in the synthesis of heterocycles and can be easily transformed into a number of synthetically important functionalities.⁴ Hence, the search for sustainable and cost-effective processes of nitrile synthesis is always an important area of research. Transition metal-catalyzed synthesis of benzonitrile and its derivatives occupies a significant domain of synthetic organic chemistry. Although Mn,⁵ Fe,⁶ Co,⁷ Ni,⁸ Zn,⁹ Pd,¹⁰ Rh,¹¹ and Ru¹² have all been utilized to mediate the process of cyanation, a plethora of cyanation processes have been efficiently catalyzed by Cu, in its various homogeneous and heterogeneous modifications. This is on account of its economy and versatility.¹³ The lethal effects caused by the stoichiometric use of metal cyanides and high temperature (approx. 150–250 °C) employed in the classi-

cal approaches of cyanation by Sandmeyer¹⁴ and Rosenmund-von Braun¹⁵ prompted the utilization of either indirect cyanide sources or *in situ* generated cyanide. Apart from the recently established indirect cyanation sources such as nitromethane,¹⁶ acetone cyanohydrin,¹⁷ DMF,¹⁸ *t*-BuNC,¹⁹ NaN₃,²⁰ dimethylmalononitrile,²¹ formamide,²² K₄[Fe(CN)₆],²³ AIBN,²⁴ acetonitrile,²⁵ and ethyl(ethoxymethylene)cianoacetate,²⁶ the extensive establishment of combinations of sources of carbon and nitrogen to generate aryl nitriles is gaining increasing importance. The combinations of NH₃(aq)–DMF,²⁷ NH₄I–DMF,²⁸ NH₄HCO₃–DMSO,²⁹ and NH₄HCO₃–DMF³⁰ are some standout examples. In this regard, the cyanation of readily available aryl iodides/bromides with these combined-reagents enables easy access to aryl nitriles. 4-(Trifluoromethyl)benzonitrile as a critical intermediate of the antidepressant ‘Fluvoxamine’ is readily synthesized from 4-chlorobenzotrifluoride on a ton-scale.³¹

Known to participate as a one-electron oxidant in a number of carbon–carbon bond formation reactions,³² the importance of Ceric Ammonium Nitrate (CAN) is highlighted in the pioneering works by Trahanovsky³³ and Heiba–Dessau.³⁴ As a most extensively used cerium(IV) reagent, the wide popularity of CAN is based on its easy handling, cost-effectiveness, high reduction potential value (+1.61 V vs. NHE), low toxicity and high solubility in many organic solvents.³⁵

In addition to its use as an oxidant, herein, we present a report of its capability to act as a nitrogen atom donor. Together with DMF as a carbon source (and solvent), the two easily available precursors modulate into an efficient cyanating agent for aryl iodides/bromides. The presented methodology highlights a dual role of CAN and requires no additives, no toxic reagents and involves a ligand-free Cu(II) catalyst (Fig. 1).

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