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One-pot synthesis of imidazoles from aromatic nitriles with nickel catalysts†

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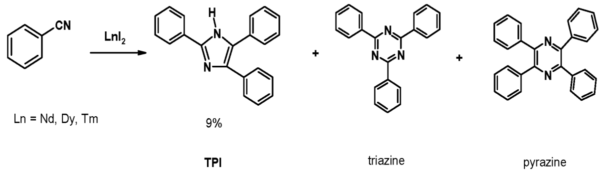
Nickel(0) catalysts were used to produce substituted imidazoles in good to high yields using benzonitrile, *p*-substituted benzonitriles and 4-cyanopyridine as starting materials.

Imidazoles are a very important family of heterocyclic compounds that possess a wide range of applications within the academic and industrial arenas. Imidazoles can be found in several types of drugs (*e.g.* anti-inflammatory, anticancer agents and blood pressure regulators), natural products and metalloenzymes.[1] Existing methodologies for the synthesis of imidazoles are limited in terms of the starting materials, conversion and product selectivity, which consistently result in low yields.[2] The use of catalysts is a potentially useful strategy to overcome low conversions of traditional synthetic methods, minimize the amount of reaction byproducts and undesired impurities, and even promote formation of complex imidazole-derivatives by incorporation of other functionalities.[3]

There are very few reports on the use of nitriles—especially aromatic ones—as starting materials for the synthesis of imidazoles; even less documented by metal-mediated or catalytic transformations. A relevant example of catalysis was disclosed by Bochkarev *et al.*, using lanthanides (Tm, Nd and Dy) for the reduction, cyclization and cyclotrimerization of benzonitrile (**BN**), which yielded 2,4,5-triphenylimidazole (**TPI**) (best isolated yield = 9% using Tm), 2,4,6-triphenyltriazine (Nd, 39%, Dy, 15%, Tm, 6%) and 2,3-,2′-3′-tetraphenylpyrazine (Nd, 10%, Dy, 3%, Tm, 2%) all in very low amounts (Scheme 1).[4]



Scheme 1

The use of alkaline metals and hydrides for the preparation of **TPI** from benzonitrile by metal-mediated reactions has also been documented: NaH yields 27% of **TPI** and 34% of the triphenyltriazine.[5] These procedures, however, are impractical for their scaling up due to the requirement of stoichiometric NaH, in addition to laborious separations needed to remove produced triazine from the reaction mixture.

The metal-mediated synthesis of **TPI** *via* tungsten–iminocarbene complexes and **BN** was reported by Wulff and co-workers.[6] This is a rather elaborate procedure with a good yield (84% **TPI**). As a downside, in addition to it not being a catalytic process, the iminocarbenes need to be prepared independently, prior to the reaction with **BN**.

There are a handful of reported catalytic processes to prepare imidazoles[3] none of which refers to the use of organic nitriles as starting materials for direct synthesis of these organics. Usually the procedures involve multi-component reactions with a variety of reagents and a metal catalyst introduced in high loads (15–20% mol) to drive the cycloaddition reactions. It is worth mentioning that a paper by Siamaki and Arndsten has been published,[7] wherein they describe the synthesis of tetra-substituted imidazoles by a palladium-catalyzed (5% mol) process involving two imines and an acid chloride under a CO atmosphere. The corresponding imidazoles are obtained in low to moderate yields.

In recent years, our group has been interested in the chemistry of nickel compounds employed for several synthetic processes relevant for academia and industry, related to nitriles.[8] In all of these processes, formation of nickel(0) compounds with a formula, $[(L\text{–}L)Ni(\eta^2\text{-}NC\text{-}R)]$ ((L–L) = chelating diphosphine; R = alkyl, aryl), was initially observed when reacting an alkyl-, aryl- or heteroarylnitrile in the presence of the nickel(I) dimer, $[(dippe)NiH]_2$ (**1**) (dippe = 1,2-bis(diisopropylphosphino)ethane).

Recently we reported a study dealing with the hydrogenation of aryl-nitriles and aryl-dinitriles or dicyanobenzenes, DCB (1,2-, 1,3- and 1,4-DCB), using nickel(0) catalysts and THF as solvent.[9] The reactions took place under relatively mild conditions and the corresponding products of condensation for each substrate were obtained. In particular, the hydrogenation of **BN** produced a mixture of *N*-benzylbenzylimine (**BBI**) and the total hydrogenation product, dibenzylamine (**DBA**; the major product), with overall

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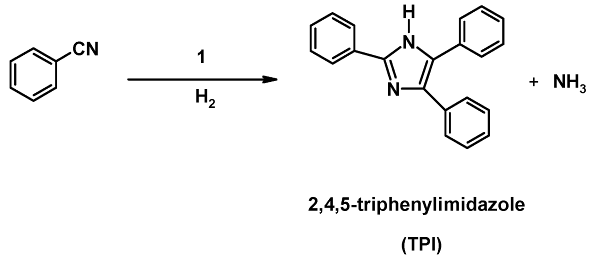
† Electronic supplementary information (ESI) available: Includes detailed experimental procedures, relevant analytical and spectroscopic data (1D-, 2D-NMR spectra and MS) of produced imidazoles. See DOI: 10.1039/c1cc13497c



Scheme 2

Table 1 Catalytic cyclization of BN: synthesis of TPI

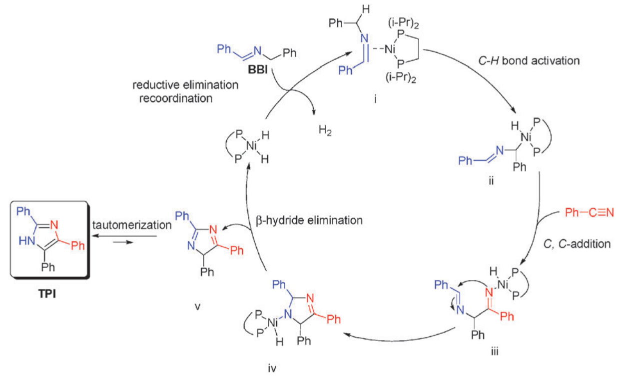
Entry	Time/h	Temp./°C	H_2 pressure/psi	Yield of TPI (%)
1	24	180	60	54
2	48	180	60	93
3	24	230	120	66
4	48	230	120	98
5	48	180	120	98
6^a	48	180	60	92

General reaction conditions: a stainless steel autoclave pressurized at the indicated pressure (psi) of H_2. Reaction mixtures were charged in a dry-box under neat conditions (no solvent added). Catalyst loading: 0.5 mol% of **1** relative to the nitrile. ^{a} Mercury drop test.

conversion above 95%. Herein we disclose our findings relative to the efficient catalytic, one-pot preparation of 2,4,5-trisubstituted imidazoles using simple aromatic nitriles as starting materials. Reactions are run under H_2 pressure and under neat conditions.

It is well known that the reaction of $[(\text{dippe})\text{Ni}(\mu\text{-H})]_2$ (**1**) with aromatic nitriles yields the formation of the Ni(0) complex[10] $[(\text{dippe})\text{Ni}(\eta^2\text{-}NC\text{-Ar})]$. The synthesis of **TPI** was made *via* the *in situ* hydrogenation of **BN** using complex **1** as a catalyst precursor under a variety of reaction conditions (Scheme 2). Relevant experimental details are summarized in Table 1.

From the data in Table 1, high yields of **TPI** can be obtained at 180 °C and 60 psi of H_2 over 48 h (entry 2). An increase of temperature (230 °C) and pressure (120 psi) allows to improve the yield of such product, although only slightly with respect to the same reaction times under milder conditions (entries 4 and 5). In all cases just minute amounts of triazine were observed ($<1\%$), and it was barely observed on using high H_2 pressure. A mercury drop experiment was performed to test the homogeneity of the catalytic process (entry 6), without any inhibition observed in its presence. Formation of NH_3 (see Scheme 2) was verified in all reactions by gently bubbling a stream of gases released from the reactor after completion of the respective runs, into a saturated aqueous solution of $CuSO_4$. A distinctive color change to deep blue is attributed to formation of the ammonia–copper(II) complex, $[Cu(NH_3)_6][SO_4]$.[11]

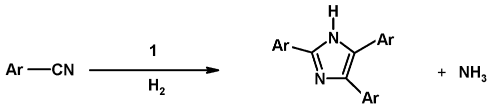


Scheme 3

A mechanistic proposal for this transformation is based on our previous findings for the catalytic reduction of **BN** using H_2 and a variety of solvents;[9] from which studies, formation of the Schiff base, **BBI**, as the main product was established. To a much lesser extent, **BBI** underwent further reduction to *N*-dibenzylamine. In perspective, the synthesis of **BBI** constituted a definite proof of a catalytic tandem hydrogenation–condensation process during which NH_3 is also extruded. In the current work we envision **BBI** to act as a key organic intermediate towards the final cyclization product, **TPI**, *via* a series of basic reactions depicted in Scheme 3.

Initial η^2-coordination of **BBI** to nickel(0) through the C=N bond is proposed in Scheme 3 as intermediate (i), inspired in closely related complexes displaying a coordinated fluorinated imine reported by our group.[12] The latter complexes were structurally characterized and later on also used in catalysis under low pressure of hydrogen, coupled to a hydrogen-transfer system in methanol.[13] In the current catalytic cycle we propose a C–H bond activation from the related iminic-nickel(0) species (i), to give the alkyl-hydrido intermediate (ii). Insertion of a second nitrile molecule to give a C,C-addition reaction is then proposed to give intermediate (iii),

Table 2 Catalytic cyclization of aromatic nitriles to yield imidazoles



Entry	Substrate	Time/h	Temp./°C	H_2 pressure/psi	Yield of imidazole (%)
1	4-Methyl-benzonitrile	48	180	120	98
2	4-Methoxy-benzonitrile	48	180	120	97
3	4-Fluoro-benzonitrile	48	180	120	83
4	4-Cyanopyridine	48	180	60	77
5	4-Cyanopyridine	48	180	120	91

General reaction conditions: a stainless steel autoclave pressurized at the indicated pressure (psi) of H_2. Reaction mixtures were charged in a dry-box under neat conditions (no solvent added). Catalyst loading: 0.5 mol% of **1** relative to the nitrile.

which is followed by an intramolecular cyclization reaction to form (iv). A β-hydride elimination reaction leads to the free organic (v) with concomitant formation of a nickel dihydride (the hydride source), from which reductive elimination of H_2 with re-coordination of **BBI** completes the turnover by reforming of (i). Ultimately, tautomerization of (v) produces **TPI**.

Using the optimized conditions in Table 1 we decided to extend the scope of this reaction to *p*-substituted aryl-nitriles (R_p–C_6H_4–CN) and 4-cyanopyridine. The results are summarized in Table 2.

Very good yields of the corresponding imidazoles were obtained in all cases, under the optimized reaction conditions. Only in the case of 4-cyanopyridine was the initial yield low (entry 4), due to the unexpected production of the corresponding triazine. The latter was overcome by increasing the pressure of H_2 (entry 5), which substantially disfavors cyclotrimerization. No inhibition of the activity of nickel(0) was observed on using mercury with any of the substrates listed in Table 2. The latter is consistent with examples of homogeneous catalysis, similarly to **BN**.

Further studies to extend the scope of this reaction to asymmetric imidazoles were made. These experiments were also intended to provide mechanistic insights of the current cyclization reaction. The independent preparation of **BBI** and its use in the reaction, employing the conditions described in Table 1, entry 2, produced always pure **TPI**, confirming the intermediacy of **BBI** for the **TPI** formation. Similarly, the independent preparation of asymmetric analogs to **BBI** under the very same reaction conditions gave mixtures where the production of the symmetrical imidazole (*via* **BBI**) was always the favored product, due to the use of an excess of the corresponding nitrile (neat conditions).

The catalytic one-pot cyclization of aromatic nitriles to yield 2,4,5-trisubstituted imidazoles in high yield using single-site nickel catalysts is reported for the first time. This synthetic method can be used to prepare a variety of valuable imidazoles from cheap raw materials such as *p*-substituted benzonitriles and *N*-heterocycles such as 4-cyanopyridine under neat conditions and relatively low H_2 pressure. The generation of byproducts such as triazines can be substantially or totally inhibited by increasing the pressure of H_2 in the system. Current studies are underway to extend the scope of this reaction to other hetero-aromatic and alkyl nitriles.

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