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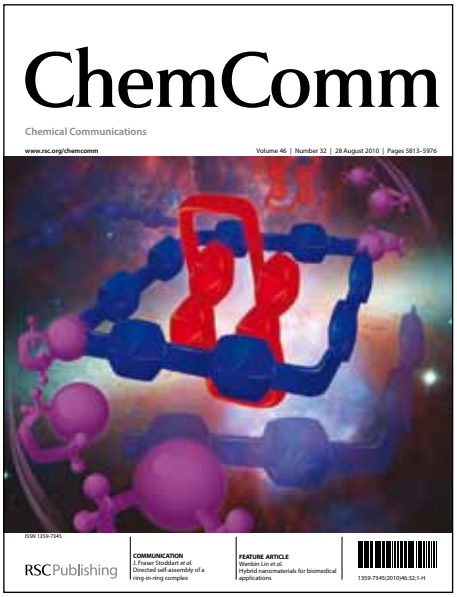

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ARTICLE TYPE

Ni^{II}-salt catalyzed activation of primary amine-sp^3C_α-H and cyclization with 1,2-diketone to tetrasubstituted imidazoles

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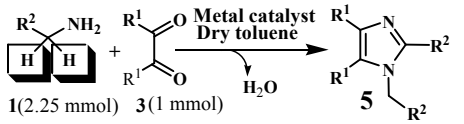
$NiCl_2.6H_2O$ and $Ni(OAc)_2.4H_2O$ were found as efficient catalysts for C-H activation of benzyl and aliphatic amines for an unprecedented multi C-N bond forming cyclization with 1,2-diketones under refluxing toluene to furnish highly substituted and polycyclic imidazoles.

C-H activation is an emerging revolutionary research area in modern science.[1,2] Although significant development was made in recent time, C-H activation of substrate bearing highly reactive functionality is still lacking. For instance, metalation of sp^3C_α-H bond of primary amine is not a simple task because the amine group has a tendency for reduction, decomplexation and chelation and also its easy oxidation to imine with metals. To date, Schafer and Jun et als. reported two pioneering research works using $[(PPh_3)_3RhCl]$ and metallaaziridine catalysts for C-C coupling of primary amines with olefins to afford cyclic amines and ketones respectively.[3] Activating and exploiting C-H for direct transformation to valuable C-N bond is challenging especially with metal catalysts.[2] In a continuous effort to study C-N bond forming cyclization reaction,[2d,e] we envisioned developing a metal catalyst which is benign to amine functionality (**1**) and selectively performs dual C_α-H bond activation with 1,2-diketones (**3**) leading to direct construction of valuable imidazoles[4] (**5**, Scheme 1). Recently tetrasubstituted[5] and polycyclic imidazoles[6] received considerable attention of researchers because of their existance in bioactive natural products and also novel antitumor, rapid fluorescence switching, photochromism and semiconducting material properties.[4-7] Tetrasubstitued imidazoles were synthesized by multicomponent condensation using HBF_4-SiO_2, supported sulfuric acid, *p*-dodecylbenzenesulfonic acid, ionic liquid, $Zn(BF_4)_2$ and $ZrCl_4$ catalyst under microwave irradiation or heating conditions,[8] and few others.[4f,5c,9] Thus, development of a new and simple strategy using readily available ingredients and inexpensive metal-salt catalyst for direct construction of 1,2,4,5-tetrasubstituted and polycyclic imidazoles will be a great contribution to a limited number of existing approaches.



Entry	Nickel catalyst(mol%)	Temperature, Time (h)	Yield (%)
1	$Ni(COD)_2$ (8)	reflux, 18	25
2	$NiCl_2(PPh_3)_2$ (10)	reflux, 18	40
3	$NiBr_2$ (10)	reflux, 19	30
4	$Ni(OAc)_2.4H_2O$(10)	reflux, 18	69
5	$Ni(OAc)_2.4H_2O$(10), dppe (15)	reflux, 18	69
6	$Ni(OAc)_2.4H_2O$(10)	rt, 30	30
7	**$NiCl_2.6H_2O$ (8)**	**reflux, 12**	**90**
8	$NiCl_2.6H_2O$(8), dppe (15)	reflux, 15	89
9	$NiCl_2.6H_2O$ (10)	rt, 30	45

Scheme 1. Development and optimization of C-H activated annulation

Our initial experiment between benzyl amine (**1a**, 2.25 mmol) and benzil (**3a**, 1 mmol) was screened with several readily available potential transition metal catalysts ($[Ir(COD)Cl]_2$,$PdCl_2$, $AuCl_3$, $PtBr_2$, $FeCl_3$ etc.).[2] Unsatisfactory results were found for the desired C-H activation cum cyclization process to afford 1-benzyl-2,4,5-triphenyl imidazole (**5a**). Recently, Sunoj et al. and others reported some leading functionalization and cyclization reactions using Ni(0) catalysts for aromatic C-H activation.[10] It prompted us to examine the sp^3C_α-H metalated cyclization reaction using nickel compounds. In the very first experiment, tetrasubstituted imidazole **5a** was obtained with $Ni(COD)_2$ catalyst (8 mol%) in 25% yield and it was improved slightly (40%-69%) on use of Ni(II) compounds (entries 2-4). In order to improve the yield we further examined the reaction using different solvents (dioxane, DMF, ethylenedichloride, xylene and toluene), reaction temperatures (ambient to refluxing) and ligands [dppe (entries 5,8), tricyclohexyl phosphine, COD and cyclopentadiene] which were unsuccessful. Inspired by the recent use of Ni^{II}-catalysts[11] we employed an inexpensive and readily available $NiCl_2.6H_2O$ (8 mol%) and yield was significantly improved (90%, entry 7). It was consistantly low (30-45%) when studied at ambient temperature (entries 6,9).

With the optimized condition in hand, we next examined the scope of this oxidative cyclization reaction of benzyl amine derivatives with 1,2-aromatic, aliphatic and cyclic diketones

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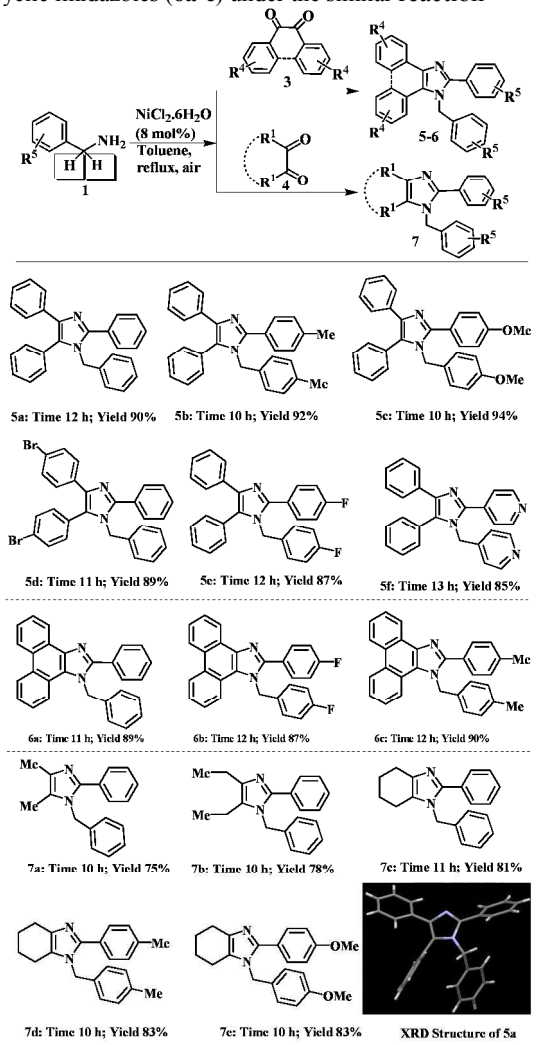
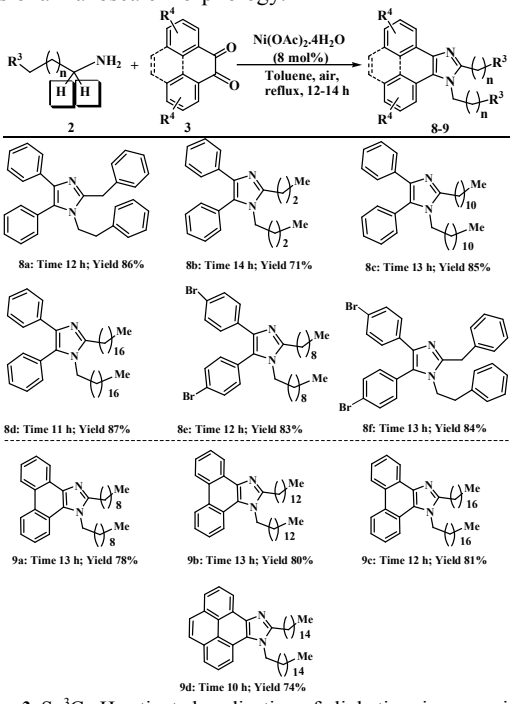
(Scheme 2). Notably, excellent yield (89-94%) of 1,2,4,5-tetrasubstitued imidazoles (**5a-d**) was obtained for benzyl amine and its derivatives bearing a strong electron-donating groups. In addition, when electron-withdrawing group containing 4-fluorobenzylamine and 4-pyridylmethylamine were used as the starting material, slightly lower yields (85-87%) were obtained for the desired products **5e**,**f**. Polycyclic imidazoles are bioactive alkaloids present in marine sponges which were synthesized by multistep approaches.[6] A simple and direct synthesis of their analogues is desirable for research in medicinal and material science toward launching new products for our society. Satisfactory results were also obtained for direct construction of polycyclic imidazoles (**6a-c**) under the similar reaction



Scheme 2. Direct synthesis of varied tetrasubstituted imidazoles

conditions. Next, we turned our attention for applicability of the protocol toward synthesis alkyl substituted imidazoles (**7**). Interestingly, dialkyl and cyclic 1,2-diketones underwent the cyclization reaction smoothly to afford desired product **7a-e** in 10-11 h with good yield (75-83%). The single-crystal XRD structure[12] of **5a** is displayed in Scheme 2.

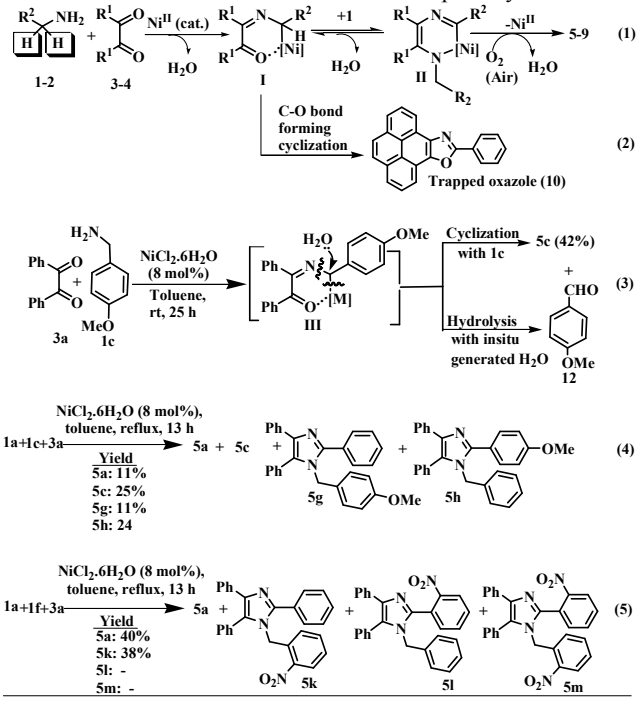
In an ongoing project in nanoscience and nanotechnology, we designed imidazole molecule bearing long chain hydrocarbon to fabricate unidirectionally packed nanomaterials for organic electronics.[13] However, its direct insertion is very challenging due to presence of relatively unactivated sp^3C_α-H in the aliphatic amines bearing long chain hydrocarbons. On use of $NiCl_2.6H_2O$ (10 mol%) **8a** (Scheme 3) was obtained only in 54% yield. Pleasingly, we found a more efficient catalyst $Ni(OAc)_2.4H_2O$ (8 mol%) to furnish imidazole derivatives (**8a-f**) in good yield (71-87%). Long chain hydrocarbon decorated polycyclic imidazoles (**9a-d**) were also obtained under similar reaction condition in good yield (74-81%). Interestingly, on use of $CuX_2.H_2O$ (X= OAc, Cl, Br) **5a** and **8a** were also obtained in moderate yield (48-25%) under the reaction conditions. The compounds are solid in nature and showed excellent fabricated textures *via* molecular aggregation. Spin coater fabricated material of **9d** was imaged in a scanning electron microscope and displayed disc-like two dimensional nanoscale morphology.



Scheme 3. Sp^3C_α-H activated cyclization of aliphatic primary amines

Recently Ji et al. has reported CuI-$BF_3.Et_2O$ cocatalyzed oxidative cyclization of acetophenones and amine to trisubstituted imidazoles through formation of 1,2-diimine.[14] Formation of no desired product (**5a**) was observed with the diimine whereas monoimine of 1,2-diketone (**3a**) underwent smoothly to **5a**. Herein, Ni^{II}-salt is expected to perform selective dual activation of C_α-H bonds of the primary amines (**1**,**2**). It leads to formation of an intermediate **I** with 1,2-diketones (**3**,**4**) and subsequently amine insertion (**II**). Eventually C-N coupled reductive elimination of the catalyst in the cyclization process afforded 1,2,4,5-tetrasubstituted imidazoles (**5-9**, eq. 1, Scheme 4). The reaction was incomplete in absence of oxygen. Progress of the reaction by 1,5-proton shift (**I**) was not observed in presence of both organic and inorganic bases. We also trapped corresponding oxazole (**10**, eq. 2) on use of strongly aromatic pyrenedione and benzyl amine which was formed in the reaction from **I** through C-O coupling. The nickel salt is a powerful activator for C_α-H of 4-methoxybenzylamine (**1c**) even at room temperature to construct **5c** (eq. 3). However, low yield (42%)

was attributed due to formation of the byproduct anisaldehyde (**12**) from hydrolysis of **III**, (eq. 3) in presence of insitu generated water. The involvement of 1,2-diketone with primary aliphatic amine and Ni^{II}-catalyst is crucial in the reaction process because it was unsuccessful on use of acetophenone and 1,3-diketones (acetylacetone, ethylacetoacetate or acetoacetanilide). Primary amine is the essential partner for the reaction assembly as we observed no reaction on use of dibenzylamine whereas mixture of the secondary amine and primary amine (1:1) leads to formation of **5a**. These studies support the C_α-H activation with the Ni^{II}-salt is crucial for the direct annulation reaction of primary amines.



Scheme 4. Studies on possible reaction path of the annulation reaction

Next, we sought for investigating the electronic influence in the cyclization process by means of cross coupling reaction. Reaction between unsubstituted benzylamine (**1a**) and activated 4-methoxybenzylamine (**1c**) afforded major products **5c** and **5h** (25 and 24%, eq. 4) bearing 4-methoxyphenyl group at C_2. Whereas deactivated 2-nitrobenzyl amine (**1f**, eq. 5) afforded **5a** and **5k** without formation of **5l** and/or **5m** bearing 2-nitrophenyl ring at C_2. These cross over experiments clearly indicate that formation of intermediates **II** and **III** are more favoured with the initial attack of electron-rich vs electron-defficient benzyl amines.

In conclusion, for the first time we have demonstrated nickel(II)-salt as a catalyst for activating and exploiting sp^3C_α-H of primary amines for multi C-N bond-forming robust annulation to 1,2,4,5-tetrasubstituted and polycyclic imidazoles in a single operation. The simple, efficient and new strategy, sp^3C-H activation with Ni^{II}-salts, its unprecedented catalytic activity and diverse scope will find immense application in chemical sciences.

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