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Facile access to 3-cyano-4-azaindoles via a modified Madelung indole synthesis

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ABSTRACT

An unprecedented methodology for the facile synthesis of 2-substituted 3-cyano-4-azaindoles using modified Madelung synthesis is described. The methodology relies on acid and amine coupling under very mild conditions.

Aza-heterocycles represent important scaffolds in drug discovery platforms, including the azaindoles which have been referred to as privileged structures, since they are structural motifs present in biologically active natural products, pharmaceuticals and diverse synthetic intermediates.[1] As azaindole differs from indole only by the presence of an additional ring nitrogen, it shows excellent potential as a bioisostere of the indole ring. Amongst various classes of azaindoles, 4-azaindoles[2] are of particular interest because they are used as modulators of kinase activity[3] and are frequently used in the treatment of allergic, autoimmune, inflammatory, antiproliferative and hyperproliferative diseases including the rejection of transplanted organs or tissues and AIDS.[4] As it is a common structural scaffold for drug targets, development of new diversity tolerant synthetic protocols to this privileged structure continues to be a vibrant area of research. The classical methods for the synthesis of azaindole include aza-Fischer reaction,[5] Reissert-type procedure,[6] Batcho–Leimgruber reaction,[7] Lorenz-type cyclization[8] and Bartoli sequence.[9] The most notable limitations in many of these procedures include harsh reaction conditions, long reaction times and sometimes unavailability of appropriate substrates. Many recent advances in one pot azaindole synthesis have focused on metal mediated procedures employing palladium,[10a] copper[10b,c] and zirconium[10d] as catalysts. However, the significant cost associated with many of these metals and their tendency to remain intact on organic products has been a major obstacle in implementing these procedures on large-scale applications. Thus, development of expeditious synthetic approach for the synthesis of 4-azaindoles from easily available precursors in a single pot is highly warranted.

The Madelung synthesis is one of the most versatile and extensively employed routes for the synthesis of indoles.[10b,11] The Madelung synthesis involves intramolecular cyclization of an *N*-(2-alkylphenyl)alkanamide with a strong base at elevated temperatures. The most common conditions employed include sodium amide or sodium/potassium alkoxide at temperatures of 300–400 °C[12] and also use of stronger bases like LDA or ^{n}BuLi.[13] In the context of our research on the utility of cascade reaction in the synthesis of indoles,[14] we envisaged the feasibility of applying the modified Madelung type approach for the preparation of 3-cyano-4-azaindoles under milder reaction conditions. Our interest in this class of compounds stems from their therapeutic potential as modulators of large conductance calcium-activated potassium channels (BK_{Ca}).[15] To pursue our objective, we sought to explore the synthetic reactivity of easily accessible (3-aminopyridin-2-yl) acetonitrile for the generation of the 4-azaindoles. We thought that use of carboxylic acid as an electrophile would allow the direct installation of a substituent at C_2 of the azaindole ring offering considerable structural diversity. From a synthetic perspective, we rationalized that use of a basic condition would allow anticipated conversion through amidation of (3-aminopyridin-2-yl)acetonitrile followed by tandem cyclization thereby providing a facile access to 4-azaindoles under milder conditions (Scheme 1).

To test the validity of the proposed hypothesis, a preliminary survey of reaction conditions was conducted using (3-aminopyridin-2-yl)acetonitrile (**1a**), isonicotinic acid and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) as model substrates with

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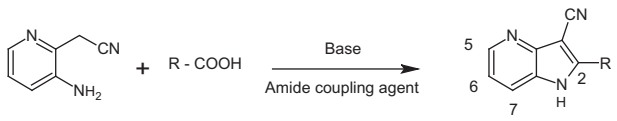


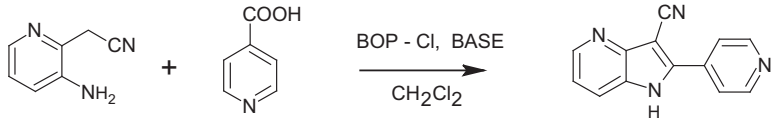
Scheme 1.

several bases in CH_2Cl_2 (Table 1). The reactions were conducted at low temperatures to avoid inter or intra molecular condensation of **1a** with excess of base. To our surprise, the catalytic performance of inorganic bases such as sodium hydride and potassium *tert*-butoxide proved to be ineffective as the desired 4-azaindole was scarcely obtained after prolonged reaction time (Table 1, entries 1 and 2). We focused our attention towards organic bases (Table 1, entries 3–6). Unfortunately, triethyl amine and pyridine were unable to initiate the reaction (Table 1, entries 4 and 5) while ^{n}BuLi was not able to mediate the reaction to a synthetically useful degree (Table 1, entry 3). In fact, use of *N*,*N*-diisopropylethylamine (DIPEA) caused a more drastic increase in the yield of desired 4-azaindole (Table 1, entry 6).

In order to understand one pot amidation followed by tandem cyclization of **1a** with isonicotinic acid using DIPEA could occur more efficiently under different conditions, we tested many of the common solvents (Table 2). The use of mixture of CH_2Cl_2 and DMF (4:1 v/v) gave excellent yield of corresponding product (Table 2, entry 7). The solvents such as $CHCl_3$, CH_3CN and DMF furnished the desired azaindole in moderate yields (Table 2, entries 2, 3 and 6). On the contrary, THF and 1,4-dioxane were ineffective in initiating the transformation (Table 2, entries 4 and 5).

With DIPEA as a base of choice and CH_2Cl_2:DMF (4:1 v/v) as a solvent, the substrate scope was investigated by reacting (3-aminopyridin-2-yl)acetonitrile with commercially available carboxylic acids of diverse electronic and steric nature. The results summarized in Table 3 clearly demonstrate the generality of the protocol. The aromatic as well as heteroaromatic carboxylic acids were directly converted into corresponding azaindoles in 30–80% yields (Table 3, entries 1–8). Notable is the tolerance of the reaction to the presence of halogen (Table 3, entry 2) and azide (Table 3, entry 5) substituents on the heteroaromatic ring of carboxylic acids, thus providing a handle for additional synthetic manipulation. To further probe the scope of the procedure, aliphatic carboxylic acid such as butanoic acid (Table 3, entry 9) and heteroaromatic aldehyde such as thiophene-2-carboxylic acid (Table 3, entry 10) were scrutinized as substrates. The reaction preceded giving 20% yield of the corresponding products. The attempts to increase the yields of the products of these substrates failed even by performing the reactions at elevated temperature of 120 °C. The lack of reactivity in case of these substrates may be rationalized on the basis of tentative mechanistic rationale postulated in Scheme 2. The BOP-Cl plays a crucial role in catalysis by acting as acid–amine coupling agent as well as excellent dehydration reagent.[17] Initially, BOP-Cl and carboxylic acid form a highly

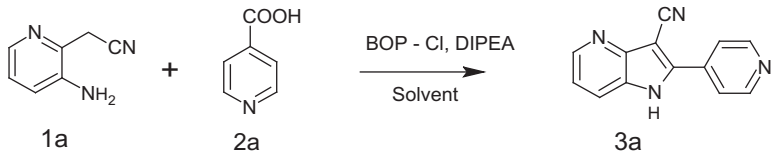
Table 1
Optimization of base in the synthesis of 3-cyano-4-azaindoles[a]



Entry	Base	Time (h)	*T* (°C)	Yield[b] (%)
1	NaH	14	rt	16
2	K^{t}OBu	16	rt	28
3	^{n}BuLi	5	rt	10
4	TEA	9	rt	0
5	Pyridine	10	rt	0
6	DIPEA	4	rt	60

[a] Optimal reaction conditions: **1a** (1 equiv), BOP-Cl (1.5 equiv), carboxylic acid (**2a**, 1 equiv), base (3 equiv), CH_2Cl_2(10 mL).
[b] Isolated yields after column chromatography.

Table 2
Solvent optimization in the synthesis of 3-cyano-4-azaindoles[a]



Entry	Solvent	Time (h)	*T* (°C)	Yield[b] (%)
1	CH_2Cl_2	4	rt	60
2	$CHCl_3$	10	rt	30
3	CH_3CN	11	rt	10
4	THF	9	rt	0
5	1,4-Dioxane	14	rt	0
6	DMF	3	rt	50
7	CH_2Cl_2: DMF	2.5	rt	80

[a] Optimal reaction conditions: **1a** (1 equiv), BOP-Cl (1.5 equiv), carboxylic acid (**2a**, 1 equiv), DIPEA (3 equiv), CH_2Cl_2: DMF (10 mL).
[b] Isolated yields after column chromatography.