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Ionic liquid supported synthesis of tricyclic pyrimido [1,2-*a*]benzimidazoles by a telescoped Michael/hetero annulation strategy†

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A telescoped sequence involves the reaction of cationic imidazolium attached 2-aminobenzimidazoles with *in situ* generated 1,1-dicyano-2-aryl ethylenes was explored for the regioselective synthesis of pyrimido[1,2-*a*]benzimidazoles. The perceived regioselectivity was presumed in terms of preferential Michael addition of 2-aminobenzimidazole followed by intramolecular annulation to the exclusive formation of 4-iminopyrimidines on an ionic liquid support. A plausible mechanistic pathway for their selective formation is discussed and fully supported by X-ray analysis. The present strategy reveals both the amine function and the ring nitrogen in substituted 2-aminobenzimidazoles are active sites for nucleophilic attack on α,β-unsaturated nitriles.

Introduction

Construction of five/six membered nitrogen heterocycles generally requires a functionalized N–C–N moiety and 2-amino nitrogen heterocycles which are the common building blocks for this purpose. Tautomerism and competing nucleophilicities are often found in 2-amino nitrogen heterocycle systems and presents challenging problems, especially when both of the nitrogens are able to react with α,β-unsaturated compounds. In particular, substituted 2-aminobenzimidazoles possess the hitherto structural features and reactivity profiles to build up a fused pyrimidine ring.[1] Pyrimido[1,2-*a*]benzimidazole is non-naturally occurring nitrogen heterocycles embedded with guanidine unit in the fused tricyclic system. These are synthesized by the reaction of 2-aminobenzimidazoles by a variety of reagents with a three carbon fragment, which can act as a double electrophile.[2] The active methylene derivative is considered as an important intermediate for the synthesis of various heterocycles due to the presence of both nucleophilic and electrophilic sites.[3] Analogs of this tricyclic system were synthesized by three component coupling under microwave irradiation and by using thiamine hydrochloride as a catalyst in aqueous conditions.[4–7] Attempts have been made in recent years to address the problem of discrimination of two regioisomeric products in the reactions of 2-aminobenzimidazoles, the origin which lies in the competing nucleophilicities of the 2-amino group and the ring nitrogen.[7] The variation on the active methylene component with ketoesters in ionic liquid medium has been reported and Sheibani *et al.* demonstrated the multi-component reaction of 2-aminobenzimidazole with ethyl-α-cyanocinnamoates in the presence of various base catalyst and the outcome of the product is differ from the present endeavor.[8,9]

These tricyclic compounds have been employed as imaging agents for detecting neurological disorders because of their unique binding ability to tau-proteins and β-amyloid peptides.[10] Introduction of an amino group on the benzimidazole ring has resulted in molecules to act as VR1 type capsaicin receptor ligands.[11] Bi-functional pyrimidines and pyrimidobenzimidazoles with *ortho*-amino and cyano groups have found their ability to act as anti-inflammatory and anthelmintic agents respectively[12,13] (Fig. 1).

In recent years, multicomponent reactions (MCR) based on telescoped/tandem procedures where the reagents added one at a time and without work up have proven to be a valuable and rapid approach in drug discovery and natural product synthesis.[14] Currently ionic liquids advanced as a soluble support and attracted considerable interest owing to their homogeneous reaction medium, simple and convenient work up protocol and conventional spectroscopic monitoring

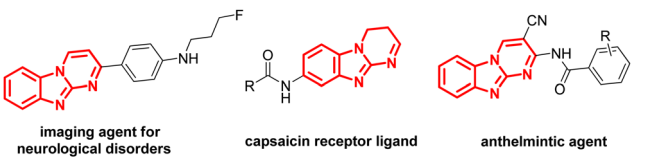

Fig. 1 Structurally related biologically active pyrimidobenzimidazoles.

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† Electronic supplementary information (ESI) available: Spectroscopic data (^{1}H, ^{13}C NMR, LRMS, HRMS, FT-IR) of essential intermediates, compounds **5** and X-ray data of compound **5i**. CCDC 936241. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra42658k

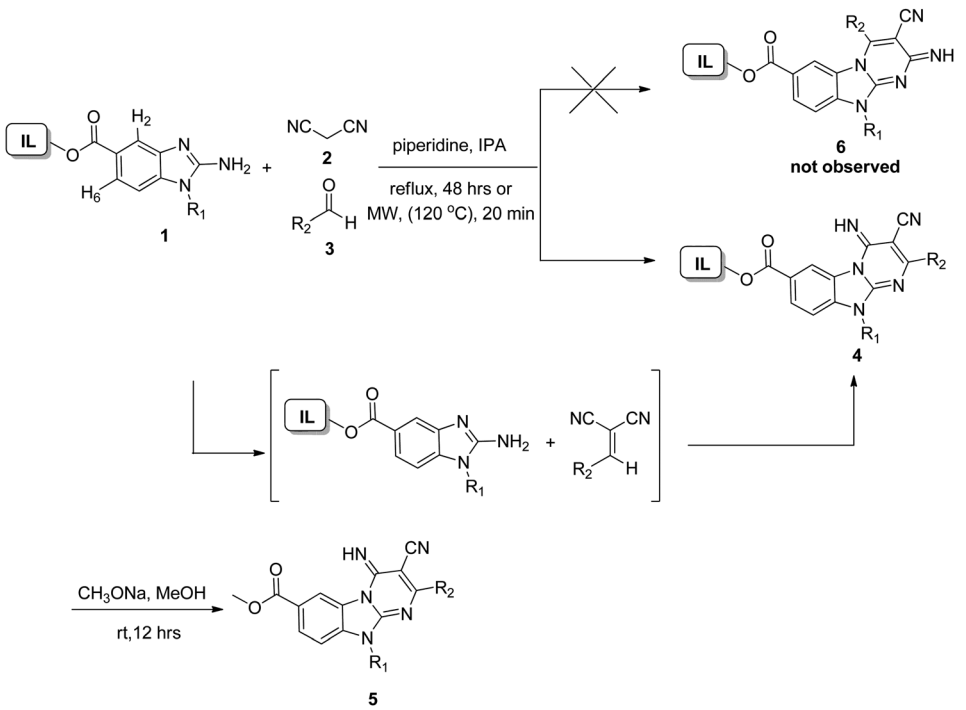
reaction progress.[15] Application of microwave (MW) as an energy source in coupled with ionic liquid support greatly diminishes the in-pot reaction time and thus accelerates the reaction rates.[16] We have developed MW assisted soluble PEG supported synthesis of 2-amino bis-benzimidazoles because of their potential binding property with DNA minor groove.[17,18] Recently we reported a novel *in situ* 1,3-sigmatropic rearrangement of Povarov reaction by PEG supported 2-aminobenzimidazoles under MW irradiation leading to the formation of 4,10-dihydropyrimido[1,2-*a*]benzimidazoles and also the application of ionic liquid as a soluble support in designing new green chemistry route to privileged β-carboline structures.[19,20] The present paper employs *n*-hydroxyethylmethylimidazolium fluoroborate as an ionic liquid support to explore an unique regioselective, telescoped route for the multicomponent synthesis of pyrimido[1,2-*a*]benzimidazoles.

Results and discussion

Methylhydroxyethyl imidazolium fluoroborate (**IL**) readily prepared from 1-methylimidazole and 2-bromoethanol was chosen as the suitable ionic liquid support for the present investigation. The first part of the synthetic sequence is the preparation of ionic liquid conjugated 2-aminobenzimidazoles which commenced with the formation of an ionic liquid–ester conjugate with 3-nitro-4-fluorobenzoic acid which was able to directly monitor the reaction progress by proton NMR. The parent IL exhibited $-OCH_2$ protons at 4.25 ppm which underwent a downfield shift to 4.85 ppm. Subsequent steps involved an *ipso*-fluoro displacement by various primary amines, followed by neutral reduction of nitro group. The ring closure to 1-substituted 2-aminobenzimidazoles **1** was accomplished by cyanogen bromide as a source of one carbon and a masked amino function by [4 + 1] approach (Scheme 1). Construction of pyrimidine required a three carbon electrophile and α,β-unsaturated nitriles were thought to be ideal for this step in view of their dual roles as double electrophiles and a masked imino functional groups. We investigated the three component reaction of 2-aminobenzimidazole–IL conjugates **1** with malononitrile **2** and benzaldehyde **3** with a variety of different solvents, bases and the temperature. Subsequently, the ideal reaction condition was optimized with piperidine as a base catalyst in refluxing isopropanol for 48 h. To further improve the synthetic efficiency, we took advantage of ionic liquid support for its good microwave absorption by their highly polar, ionic nature and the reaction was completed in 20 min under microwave irradiation. The synergic coupled microwave and ionic liquid support drastically reduced the in-pot reaction time from 48 h under conventional reflux conditions to 20 min. The tolerance of different functionalities such as ester, nitro and fluoro under this harsh condition provides a wide scope to decorate the target molecule with various substituent groups.

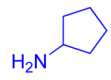
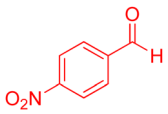
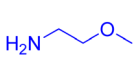
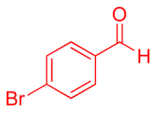
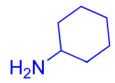
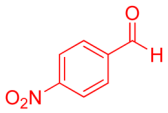
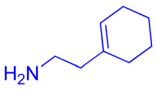
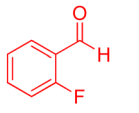
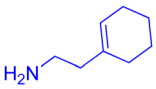
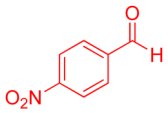
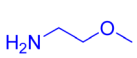
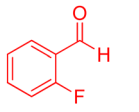
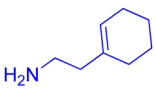
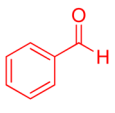
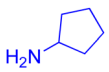
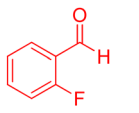
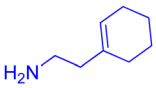
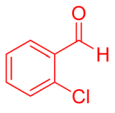
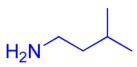
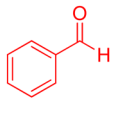
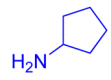
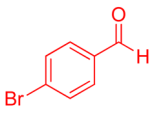
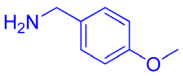
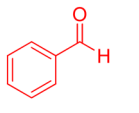
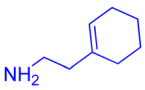
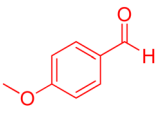
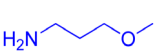
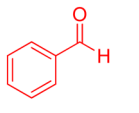
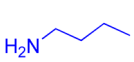
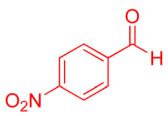
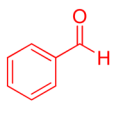
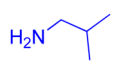
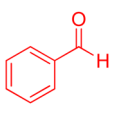
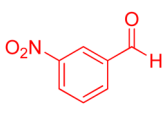
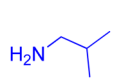
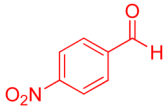
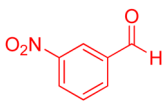
Irrespective of the electronic nature of the substituents, all the reactions were occurred very fast within 20 minutes followed by the exclusion of water molecule as the sole by-product. Detachment of the ionic liquid support was accomplished by treating the IL-conjugates **4** with sodium methoxide in methanol for 12 h at room temperature. Release of the desired compounds **5** from the support was confirmed by TLC monitoring of the reaction (Table 1).

It is noteworthy to mention that all the crude products after the cleavage are subjected to HPLC analysis and shows the



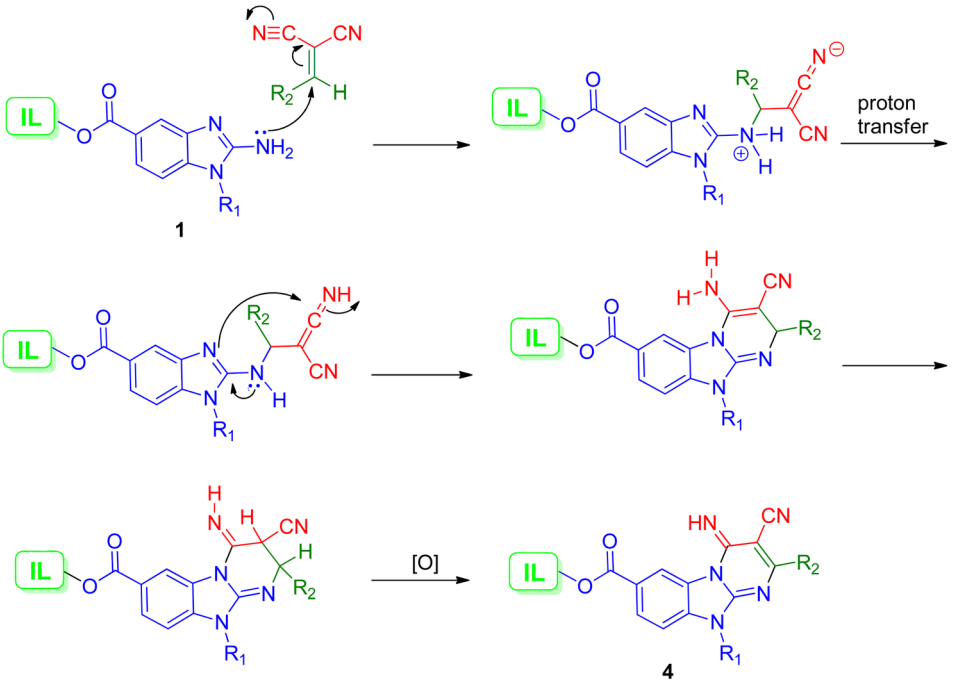
Scheme 1 Ionic liquid supported synthesis of pyrimidobenzimidazoles.

Table 1 Synthesis of 4,10-dihydropyrimido[1,2-*a*]benzimidazoles **5**

Entry	R_1NH_2	R_2CHO	Purity[a] (%)	Yield[b] (%)	Entry	R_1NH_2	R_2CHO	Purity[a] (%)	Yield[b] (%)
5a			93	89	**5k**			86	73
5b			78	88	**5l**			90	74
5c			89	85	**5m**			85	78
5d			96	81	**5n**			93	69
5e			82	78	**5o**			90	74
5f			79	79	**5p**			87	79
5g			93	71	**5q**			88	67
5h			68	85	**5r**			82	84
5i			82	79	**5s**			80	81
5j			96	86	**5t**			97	72

[a] Purity of the crude compounds. [b] Yields were determined on the weight of purified samples.

crude purity around 67–96% which enables the atom economic and synthetic efficiency of the developed protocol. The infrared spectra of target compounds **5** shows bands around 1715, 2200 and 3300 cm^{-1} indicating the presence of ester, carbonyl and nitrile and NH groups. A significant feature of the ^{1}H-NMR of all the compounds is the appearance of a downfield doublet around 9.5 ppm of H_2 (J_{meta} = 1–2 Hz with H_6). The downfield shift is due to the presence of azomethine group, and it is possible that H_2 is located inside the de-shielding zone of the C=N π bond. This observation is highly supportive of the structure **5**. The other possible isomeric structure **6** arising from the Michael addition by the ring nitrogen was not observed in the present work. However, such isomeric compounds have both been reported in the literature as mixture of products.[7] It is likely that the *N*-alkylation (R_1) probably enhances the nucleophilicity of the 2-amino group, which forms the basis for the observed regioselectivity and exclusive formation of the 4-iminopyrimidine tautomer. Role of imino tautomer is also proposed in the biochemical mechanistic pathways of thiamine and its T-like structure in the understanding Hoogsteen pairings and stacking interactions in DNA pyrimidine bases.[21–23] On the basis of the above observations, the possible mechanism for the formation of compounds **5** is proposed in Scheme 2. The malononitrile and the aldehyde are first condensed to generate



Scheme 2 A proposed mechanism for the regioselective synthesis of IL-conjugated 4-iminopyrimidine fused benzimidazoles **4**.

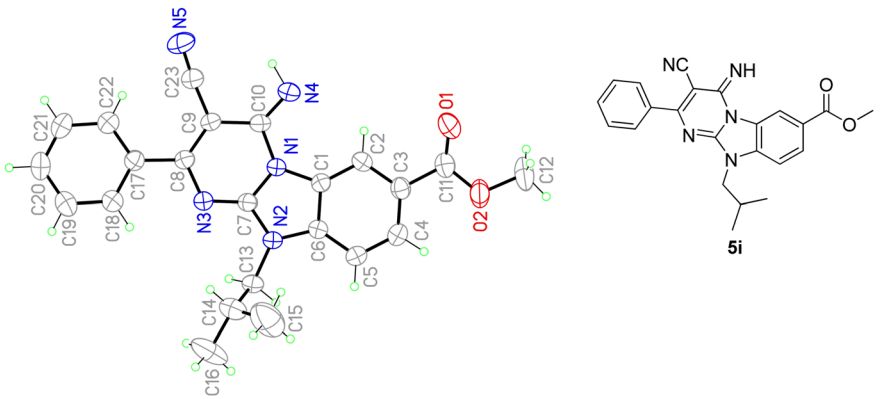


Fig. 2 ORTEP diagram and structure of compound **5i**.

the α, β-unsaturated nitrile intermediate. The next step involves the preferential nucleophilic attack of the 2-amino group at the β-carbon of the nitriles in a typical Michael addition. Subsequently, the ring nitrogen attacks the imino carbon leading to a zwitterionic intermediate, where compound **5** is obtained by proton exchange and facile oxidation. The driving force for the facile dehydrogenation is the generation of a highly conjugated pyrimidine ring system and it is pertinent to mention that the recently observed aerobic α,β-dehydrogenation of carbonyl compounds may support for this proposed autoxidation step.[24]

The proposed structure is unequivocally supported by X-ray analysis† and the ORTEP diagram for **5i** is presented (Fig. 2). The C_{10}–N_4 distance of 1.27 Å is the shortest among all the C–N bond distances and clearly supports the exocyclic imine structure. The *cis* orientation of C_{10}–N_4 bond with C_1–C_2 bond brings the C_2 proton in close spatial proximity, which accounts for its de-shielding effect on H_2, consistently observed in all the compounds **5**.

Conclusion

In conclusion, we have developed a three component telescoped synthesis of novel benzimidazole iminopyrimidines with high regioselectivity. The reaction process involves Knoevenagel condensation, Michael type addition followed by intramolecular six-membered heterocyclization sequence. The selective formation can be rationalized in terms of the preferential reactivity between the ylidenic double bond and the 2-amino functionality. The convenient one-pot operation, atom economic and exclusive regioselectivity are the salient features of this novel protocol. The synergic coupled microwave and ionic liquid support in the synthetic protocol drastically reduced the in-pot reaction time

and accelerated the rapid generation of the functionalized 4-iminopyrimidines. Regioselective synthesis of this novel framework bearing benzimidazole, cyano and exocyclic azomethine functionalities may open a new avenue to discover interesting biologically active compounds.

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