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Regioselective Synthesis of Imidazo[1,5-α]quinoxalines and Methyl N-Phenylbenzimidats on Ionic Liquid Support

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Development of eco-friendly, efficient and economical synthetic methods has always been a main aim of the synthetic chemists. Ionic liquid supported synthesis (ILSS) has been extensively used as a powerful tactic for the rapid generation of bioactive compounds.6,7 In general, ionic liquid (IL) immobilized compounds are purified by easy work-up through simple precipitation and filtration to avoid time consuming chromatographic separations. Progress of the reaction is monitored by regular proton NMR without cleavage of the IL-support. The technique is compatible with microwave irradiation which increases efficiency of the synthesis of bioactive small molecules.

Imidazoquinoxaline is an important class of heterocycles possessing significant biological activities8 as depicted in Figure 1. For examples, BMS-345541 is a significant cytotoxic compound on melanoma and also is a selective inhibitor of IκB kinase.9 BMS-272900 is an orally active inhibitor with anti-inflammatory activity.10 EAP80203 exhibits an important cytotoxicity in vitro on HTLV-I-infected CD4þ T-cell lines HUT-102 and its amine derivative demonstrated significant activities against human melanoma cell line A375.11 Furthermore, imidazoquinoxaline scaffold was identified as an enzymatic inhibitor of Lck (IC50 = 2 nM) and having good potency against T-cell proliferation (IC50 = 0.67 μM).12 Recently, various synthetic routes for the preparation of imidazoquinoxalines have been published. Moarbess et. al

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Evaluation procedures, characterization data and copies of spectral data. See DOI: 10.1039/c6ra11861e

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reported the synthesis of 4-substituted imidazo[1,2-a]quinoline through condensation of ortho-fluoronitrobenzene with imidazole followed by cyclization and substitution with amines. However, the method suffers from the use of corrosive reagents like POCI₃ as well as the low yield of final products. Bakherad and coworkers revealed synthesis of 1-aryl-substituted 4-chloroimidazo[1,2-a]quinolines via a PdCl₂-mediated Sonogashira coupling reaction. Even though the use of water as a reaction medium is environmentally friendly, the described method suffers from limited substrate scope. Mamedov developed the synthesis of imidazo[1,5-a]quinoline via condensation of benzyl- or picolylamines with 3-arylo- and alkanoylbenzylquinolazin-2-ones. Despite of being a novel approach, it comprises drawbacks like harsh reaction condition (150 °C) and low yield. Synthesis of imidazo[1,5-a]quinolines through acid catalyzed modified Pictet-Spengler reaction involving an aromatic amine linked to N1 of imidazole with aldehydes was demonstrated by Kundu. Nevertheless, the aforementioned methods suffer from various drawbacks such as longer reaction times, lack of regioselectivity, limited substrate scope and low yield; consequently, the improvement of synthetic strategy for the synthesis of imidazo[1,5-a]quinolines in terms of rapidness, simplicity and efficiency is highly demanding.

A careful literature study revealed that regioselective synthesis of imidazo[1,5-a]quinolines starting from aromatic amine with ketones on ionic liquid support has not been reported to date (Scheme 2).

In continuation of our effort towards novel synthesis of biologically interesting heterocycles herein, we report IL-supported synthesis of imidazo[1,5-a]quinolines by unconventional Pictet-Spengler reaction. This new reaction was performed regioselectively at C-5 position of imidazole with various ketones and aliphatic aldehydes under microwave irradiation. In the case of aromatic aldehydes, surprisingly, unusual imidazo[1,5-a]quinolazine ring opening reaction was observed to deliver interesting molecules. To the best of our knowledge, there is no report on this serendipitous transformation.

Initially all our attempts for the preparation of 12a via Pictet-Spengler reaction using variety of Lewis acids in the solution phase were failed. Hence, we then carried out the synthesis of 12a using ionic-liquid support. A synthetic route for the preparation of intermediate 6 is described in Scheme 3. The ionic liquid support, 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([hydemim] [BF₄]) 2 was prepared in two steps according to the literature.

Coupling of commercially available 4-fluoro-3-nitro benzoic acid 1 with ionic liquid 2 was carried out in refluxing acetonitrile by DCC and a catalytic amount of DMAP to provide the IL-supported ester 3 in 95% yield. Displacement of the fluoro group of IL-supported ester 3 with substituted imidazoles was achieved via S Ar reaction to obtain IL-bound imidazonitrobenzene 5. Reduction of nitro group of the IL-bound imidazonitrobenzene 5 by zinc and ammonium formate afforded IL-immobilized amine 6 in quantitative yield. The progress of the reaction was monitored by proton NMR directly (Supporting Information). An aliquot of the reaction mixture was precipitated and washed with cold diethyl ether. With the IL-supported amine 6 in hand, synthesis of 8a from intermediate 6 was studied (Scheme 4). In a model reaction, intermediate 6a was refluxed in acetonitrile to react with ketone 7a with TFA and MgSO₄ which failed to deliver 8a. Subsequently, we attempted microwave condition (130 °C) using toluene for 20 min to afford desired product in 89% yield (Scheme 4). In this step, imine intermediate was formed in situ and underwent nucleophilic attack by 4-methyl imidazole moiety to form C-C bond with electron rich C-5 of the imidazole ring. Finally cleavage of the ionic liquid support of 8a was accomplished by KCN in methanol at room temperature to yield the desired cyclized product 12a in 89% yields. The ORTEP diagram (Supporting Information) of methyl 3,4,4-trimethyl-4,5-dihydroimidazo[1,5-a]quinolazine-7-carboxylate

![Scheme 2](image_url)

**Scheme 2. A strategy for unconventional Pictet-Spengler reaction.**

![Scheme 3](image_url)

**Scheme 3. A General strategy for the synthesis of ionic liquid-supported amine 6.**

![Scheme 4](image_url)

**Scheme 4. A model reaction for the synthesis of imidazo[1,5-a]quinoline 12a.**
12a clearly revealed the selectivity of reaction at C-5 position of imidazole with its non-planar nature. 

Having optimized condition in hand, we then explored the scope of the reaction using a variety of aliphatic, aromatic as well as cyclic ketones; and the results are summarized in the Table 1. All reactions were proceeded smoothly and efficiently to deliver desired products in good to excellent yields. To elaborate the skeletal diversity, we decided to exploit various

Table 1. Reaction scope for the synthesis of substituted imidazo[1,5-a]quinazolines 12

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Ketones</th>
<th>yield (%)</th>
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<tbody>
<tr>
<td>12a</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>89</td>
</tr>
<tr>
<td>12b</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>85</td>
</tr>
<tr>
<td>12c</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>90</td>
</tr>
<tr>
<td>12d</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>81</td>
</tr>
<tr>
<td>12e</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>88</td>
</tr>
<tr>
<td>12f</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>12c</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>O</td>
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<td>12h</td>
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<td>H</td>
<td>O</td>
<td>82</td>
</tr>
<tr>
<td>12i</td>
<td>H</td>
<td>H</td>
<td>O</td>
<td>87</td>
</tr>
<tr>
<td>12j</td>
<td>H</td>
<td>CH₃</td>
<td>O</td>
<td>85</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1) 6 (0.32 mmol), 7 (0.96 mmol), TFA (0.01 mL), MgSO₄ (0.1 g), toluene (2 mL), MW (130 °C), 20 min. 2) 8 (0.227 mmol), KCN (1.59 mmol), MeOH (10 mL), rt, 2 h. | Isolated yield.

Scheme 5. A model reaction of IL-teathered amine 6 with benzaldehyde 9c.

NMR spectroscopic study of the obtained product indicated the presence of additional peak corresponds to ~3.9 ppm and ~5.5 ppm respectively. These highly deshielded value of –CH₃ group was not in accordance with the speculated product 15c, but the peak at 336 in mass analysis suggested the same molecular formation. Finally, X-ray crystallographic study revealed the novel open structured product 13c (Figure 2). We further explored the scope of this unusual ring opening reaction by employing a variety of aromatic and aliphatic aldehydes. As summarized in the Table 2, aromatic aldehydes having either electron donating or withdrawing substituents and heteroaryl aldehydes afforded the ring-opening compound 13.

When aliphatic aldehydes were applied, only auto-oxidized imidazo[1,5-a]quinazolines 14 were obtained in good yields. A plausible mechanism for the ring opening reaction of substituted imidazo[1,5-a]quinazolines is illustrated in Scheme 7. In the first step, nucleophilic addition of methoxide anion on the iminium carbon of A affords intermediate B. The neutralization of negative charge on N atom of B by HCN produces C. The C-C bond breaking of C by the lone pair of N generates D which is further stabilized by Ar group; and the negative charge on the imidazole moiety is stabilizes by
potassium cation through N-/C-metallation. Finally, abstraction of NH proton of D and intermolecular proton exchange of E with HCN affords product F.

Table 2. Synthesis of methyl N-phenylbenzimidats 13 and imidazo[1,5-a]quinoxalines 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>H</td>
<td>85</td>
</tr>
<tr>
<td>13b</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>13c</td>
<td>CH₂</td>
<td>85</td>
</tr>
<tr>
<td>13d</td>
<td>H</td>
<td>79</td>
</tr>
<tr>
<td>13e</td>
<td>H</td>
<td>84</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1) (a) 6 (0.25 mmol), 9 (0.75 mmol), TFA (0.01 mL), MgSO₄ (0.1 g), CH₃CN (10 mL), reflux, 48 h (b) 11 (0.18 mmol), KCN (1.32 mmol), MeOH (20 mL), rt, 2.5 h. 2) (a) 6 (0.25 mmol), 9 (0.75 mmol), TFA (0.1 mL), MgSO₄ (0.2 g), CH₃CN (10 mL), reflux, 48 h (b) 11 (0.18 mmol), KCN (1.32 mmol), MeOH (20 mL), rt, 2.5 h.*

In conclusion, we have developed a rapid and efficient method for the synthesis of imidazo[1,5-a]quinoxalines regioselectively and unusual methyl N-phenylbenzimidats through unconventional Pictet-Spengler reaction employing aromatic amine 6 and various ketones under microwave irradiation. In an attempt to elaborate diversity, various aliphatic and aromatic aldehydes were utilized. Aliphatic aldehydes generated auto-oxidized imidazo[1,5-a]quinoxalines, conversely in the case of aromatic aldehydes, removal of the IL-support in the ultimate step surprisingly led to novel methyl N-phenylbenzimidats. The synergic effect of IL-support and microwave irradiation made the present strategy facile, efficient and economical to synthesize novel polycyclic heterocycles which are closely associated with privileged structures.

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Notes and references


17 CCDC 891457 (**12a**) and CCDC 891458 (**13c**) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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An ionic liquid (IL) supported, regioselective synthesis of imidazo[1,5-α]quinoxalines and methyl N-phenylbenzimidats under microwave was explored under unconventional Pictet-Spengler reaction to generate polycyclic imidazo[1,5-α]quinoxalines and novel methyl N-phenylbenzimidats unexpectedly during the cleavage of IL-support.