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

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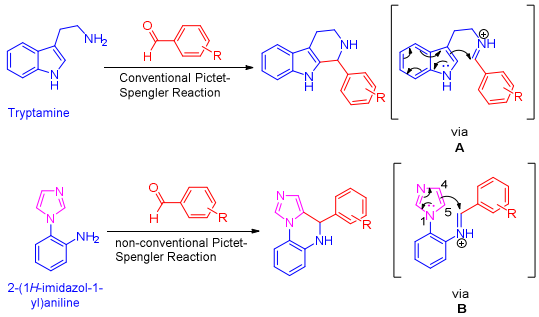
An ionic liquid (IL) supported, regioselective synthesis of imidazo[1,5-*a*]quinoxalines and methyl *N*-phenylbenzimidats under microwave conditions was reported. The IL-immobilized aromatic amines were reacted with various ketones and aliphatic aldehydes under unconventional Pictet-Spengler reaction to generate polycyclic imidazo[1,5-*a*]quinoxalines. Alternatively, aromatic aldehydes afforded auto-oxidized imidazo[1,5-*a*]quinoxalines first which further converted to novel methyl *N*-phenylbenzimidats unexpectedly during the cleavage of IL-support. In the reported strategy, rapidness is achieved through microwave condition whereas IL-support assists purification by simple precipitation.

The Pictet-Spengler reaction is one of the most efficient synthetic methods for C-C bond formation in organic chemistry.[1,2] Traditionally, it consists of a condensation of an aliphatic amine attached to an activated aromatic ring with aldehyde in the presence of acid to generate imine which then undergoes cyclization through intramolecular attack of carbon nucleophile from reactive aromatic ring. However, despite being a facile strategy, it was limited to only aliphatic amines such as tryptophan, tryptamine, histidine, histamine and dimethoxyphenethylamines.[3] Recently, a modified version of Pictet-Spengler reaction was introduced where in contrast to traditional method; aryl amines tethered with heterocycles were used (Scheme 1).[4] Aromatic amines are less reactive towards condensation with either an aldehyde or ketone to form rate-determined imine formation as compared to that of an aliphatic amines, however Schiff's base of aromatic amines **B** is more electrophilic as compared to Schiff's base of aliphatic amines **A**, which in turn facilitates C-C bond formation for aromatic amines.[5] This strategy delivers novel polycyclic frameworks which resembles structures of drug scaffolds. Development of eco-friendly, efficient and economical synthetic methods has always been a main aim of the synthetic chemists. Ionic liquid supported synthesis (ILSS)



Scheme 1. Conventional and non-conventional Pictet-Spengler reaction.

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 activities[8] 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] EAPB0203 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 (IC_{50} = 2 nM) and having good potency against T-cell proliferation (IC_{50} = 0.67 μM).[12] Recently, various synthetic routes for the preparation of imidazoquinoxalines have been published. Moarbess *et. al*

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reported the synthesis of 4-substituted imidazo[1,2-a]quinoxaline through condensation of ortho-fluoronitrobenzene with imidazole followed by cyclization and substitution with amines.[11] However, the method suffers from the use of corrosive reagents like $POCl_3$ as well as the low yield of final products. Bakherad and coworkers revealed synthesis of 1-aryl-substituted-4-chloroimidazo[1,2-a]quinoxalines *via* a $PdCl_2$-mediated Sonogashira coupling reaction.[13] 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]quinoxaline via condensation of benzyl- or picolylamines with 3-aroyl- and alkanoylbenzoylquinoxalin-2-ones.[14] Despite of being a novel approach, it comprises drawbacks like harsh reaction condition (150 °C) and low yield. Synthesis of imidazo[1,5-a]quinoxalines through acid catalyzed modified Pictet-Spengler reaction involving an aromatic amine linked to N1 of imidazole with aldehydes was demonstrated by Kundu.[15] 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]quinoxalines in terms of rapidness, simplicity and efficiency is highly demanding.

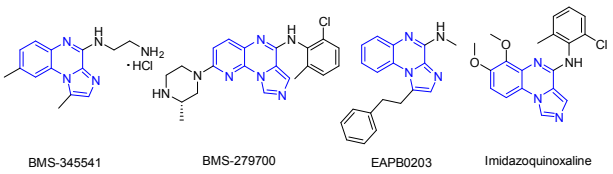
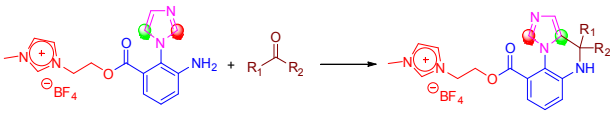


Fig. 1. Representative examples of biologically active imidazoquinoxalines.

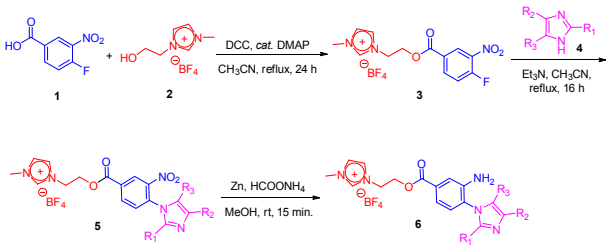
A careful literature study revealed that regioselective synthesis of imidazo[1,5-*a*]quinoxalines starting from aromatic amine with ketones on ionic liquid support has not been reported to date (Scheme 2).



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

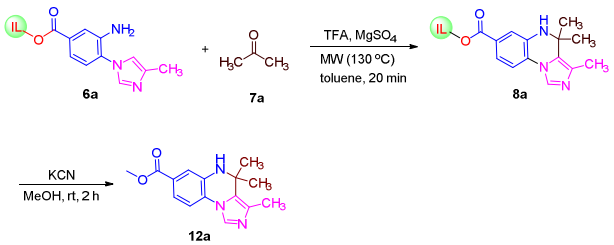
In continuation of our effort towards novel synthesis of biologically interesting heterocycles herein, we report IL-supported synthesis of imidazo[1,5-*a*]quinoxalines by unconventional Pictet-Spengler reaction. This new reaction was performed regioselectively at C-5 position of imidazole with various ketones and aliphatic aldehydes under microwave irradiation. In the case of aromatic aldehydes, surprisingly, unusual imidazo[1,5-*a*]quinoxazoline 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] [BF_4]) **2** was prepared in two steps according to the literature.[16]



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

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_NAr 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



Scheme 4. A model reaction for the synthesis of imidazo[1,5-*a*]quinoxaline **12a**.

directly (Supporting Information). An aliquot of the reaction mixture was precipitated and washed with cold diethyl ether. With the IL-bound 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 $MgSO_4$ which failed to deliver **8a.** Subsequently, we attempted microwave condition (130 °C) using toluene for 20 min to afford desired product in 89% (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*]quinoxaline-7-carboxylate

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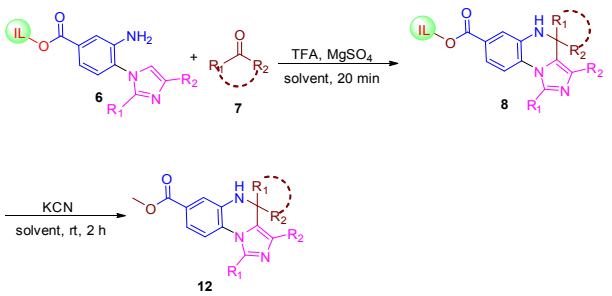
12a clearly revealed the selectivity of reaction at C-5 position of imidazole with its non-planar nature.[17]

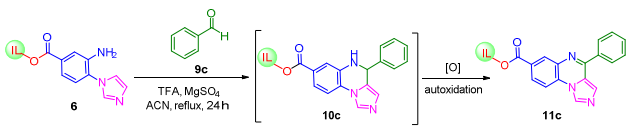
Having optimized condition in hand, we then explored the scope of the reaction using a variety of aliphatic, aromatic as well as cyclic ketones; and the results are summarized in the Table 1. All reactions were proceeded smoothly and efficiently to deliver desired products in good to excellent yields. To elaborate the skeletal diversity, we decided to exploit various aldehydes for the similar cyclization. In our first attempt, IL-bound amine **6** was reacted with benzaldehyde in the presence of TFA and $MgSO_4$ in refluxing acetonitrile for 24 h. In this case, the formation of more stable fully aromatic compound **11c** by oxidation was evident by the disappearing of expected N-H and adjacent C-H protons in the proton NMR spectrum; this was further confirmed by mass spectroscopy (Scheme 5). Finally, removal of the ionic liquid support from **11c** was performed by KCN in methanol at room temperature (Scheme 6).

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

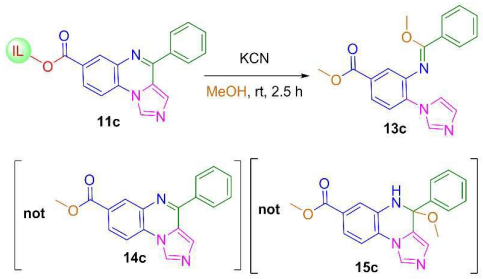


Entry	R^1	R^2	Ketones	yield[b] (%)	Entry	R^1	R^2	Ketones	yield[b] (%)
12a	H	CH_3		89	12k	H	CH_3		80
12b	H	H		85	12l	H	CH_3		86
12c	H	H		90	12m	H	CH_3		84
12d	H	H		81	12n	CH_3	H		71
12e	H	H		88	12o	CH_3	H		70
12f	H	H		89	12p	CH_2CH_3	CH_3		91
12g	H	H		87	12q	CH_2CH_3	CH_3		90
12h	H	H		82	12r	CH_2CH_3	CH_3		88
12i	H	H		76	12s	CH_2CH_3	CH_3		87
12j	H	CH_3		85					

[a]Reaction conditions: 1) **6** (0.32 mmol), **7** (0.96 mmol), TFA (0.01 mL), $MgSO_4$ (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. [b]Isolated yield.



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



Scheme 6. Cleavage of the ionic liquid support of compound **11c**.

NMR spectroscopic study of the obtained product indicated the presence of additional peak corresponds to $-CH_3$ group at ~3.9 ppm and ~55.0 ppm respectively. These highly deshielded value of $-CH_3$ 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[17] 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**.

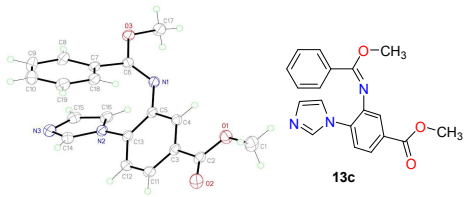


Fig. 2. A ORTEP diagram of (*Z*)-methyl 4-(1*H*-imidazol-1-yl)-3-((methoxy(phenyl)methylene)amino)benzoate **13c**.

When aliphatic aldehydes were applied, only auto-oxidized imidazo[1,5-*a*]quinoxalines **14** were obtained in good yields. A plausible mechanism for the ring opening reaction of substituted imidazo[1,5-*a*]quinoxalines 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

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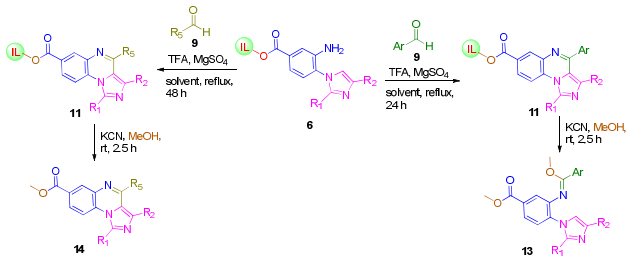
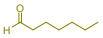
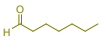
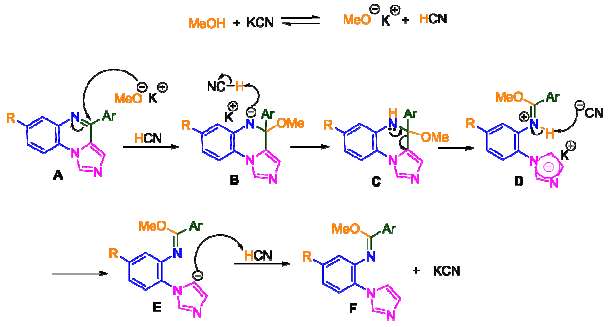
potassium cation through *N*-/*C*-metallation. Finally, abstraction of NH proton of **D** and intermolecular proton exchange of **E** with HCN affords product **F**.

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



Entry	R^1	R^2	Aldehyde	yield[b] (%)	Entry	R^1	R^2	Aldehyde	yield[b] (%)
13a	H	H		85	13g	H	H		83
13b	H	H		80	13h	H	H		89
13c	H	H		85	13i	CH_3	H		86
13d	H	H		79	14a	CH_3	H		80
13e	H	H		81	14b	H	H		77
13f	H	H		84	14c	H	H		76

[a]Reaction conditions: 1) (a) **6** (0.25 mmol), **9** (0.75 mmol), TFA (0.01 mL), $MgSO_4$ (0.1 g), CH_3CN (10 mL), reflux, 24 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), $MgSO_4$ (0.2 g), CH_3CN (10 mL), reflux, 48 h (b) **11** (0.18 mmol), KCN (1.32 mmol), MeOH (20 mL), rt, 2.5 h. [b]Isolated yield.



Scheme 7. A plausible mechanism for the ring opening reaction of imidazo[1,5-*a*] quinoxalines.

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

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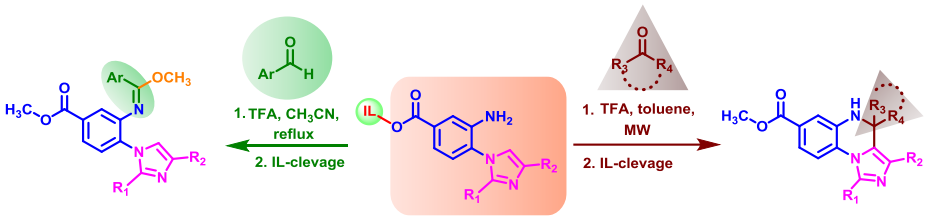

An ionic liquid (IL) supported, regioselective synthesis of imidazo[1,5-*a*]quinoxalines and methyl *N*-phenylbenzimidats under microwave was explored under unconventional Pictet-Spengler reaction to generate polycyclic imidazo[1,5-*a*]quinoxalines and novel methyl *N*-phenylbenzimidats unexpectedly during the cleavage of IL-support.