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Divergent reaction: metal & oxidant free direct C–H aryloxylation and hydride free formal reductive *N*-benzylation of N-heterocycles†

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Metal, oxidant and other additive-free novel methods for direct C–H aryloxylation of aliphatic amines are developed. In the presence of excess amine, the course of the reaction was diverted, producing various arylmethylamines *via* hydride-free formal reductive amination. Involvement of a quinone methide intermediate was revealed from mechanistic studies.

N-heterocycles and their functionalized derivatives are widespread building blocks of many natural products, biologically relevant synthetic molecules and medicinal drugs.[1] Therefore, efforts are continuing for the development of novel synthetic methods for the direct functionalization of amines.[2,3] In this context, oxazines are of particular interest due to their important pharmacological properties as well as for their use in organic synthesis.[4–6] Various methods mainly relying on the cycloalkylation strategy involving 1,3-aminoalcohol and dialdehyde were used for the syntheses of oxazines with limited substrate scope.[5] Thus, direct C–H oxygenation of aliphatic secondary amines appears to be important strategy for the syntheses of structurally diverse oxazines. In this regard, Maulide and co-workers shown that a set of oxazines can be prepared by functionalizing cyclic amines, primarily, *N*-arylated pyrrolidine.[3c] Recently, Maycock *et al.* and we have independently developed an efficient strategy for direct C–H aryloxylation to synthesize diverse ring fused oxazines by functionalizing various saturated cyclic and acyclic amines.[3a,b] However, metal based oxidants were used to promote this transformation. Herein we report a metal and oxidant free microwave assisted method for the direct C–H aryloxylation of N-heterocycles.[3d] It was also found that, the course of reaction can be diverted to provide mono- and di-arylmethylamines *via* hydride free formal reductive amination.

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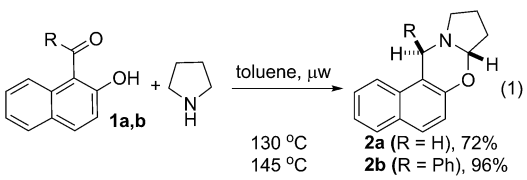
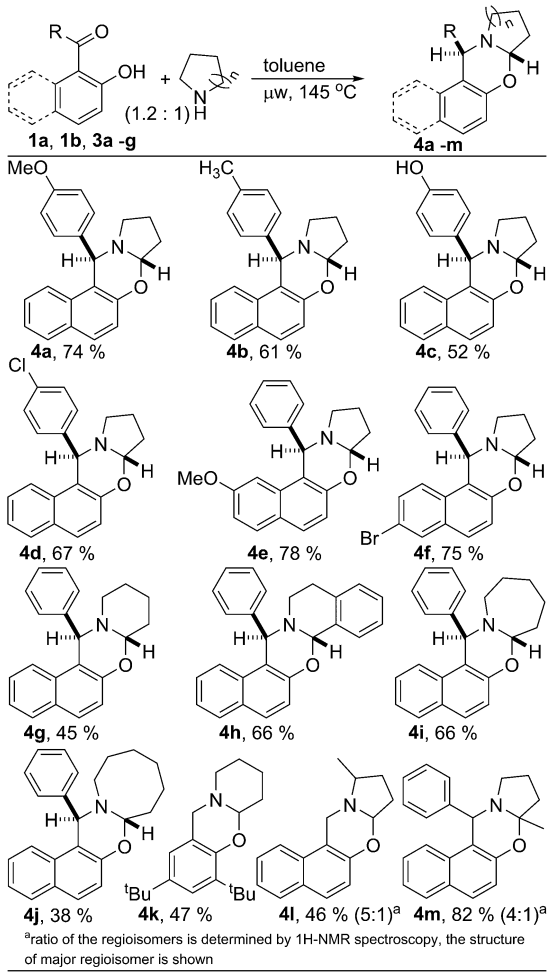
During our studies on silver promoted oxidative cyclization of Betti base, we observed that the 2-hydroxynaphthalenylmethyl pyrrolidine provided the desired oxazine.[3a] On the other hand, corresponding 2-hydroxyphenylmethyl pyrrolidine did not produce expected oxazine under the same reaction conditions. We anticipated that, in contrast to salicylaldehyde based substrate, substituents at 5 & 6 position in naphthyl based substrate probably helps to promote the cyclization.[3f] It was believed that the intramolecular cyclization producing oxazine occurred *via* an iminium ion that can be accessed through the condensation of 2-hydroxy naphthaldehyde and secondary amine.[3a,7] Therefore, we thought that the same transformation might be achieved by simply reacting 2-hydroxy naphthaldehyde with amines under metal and oxidant free reaction conditions.



(1) (1)

To test the feasibility of our thought, commercially available 2-hydroxy 1-naphthaldehyde **1a** was reacted with pyrrolidine under different reaction condition (ESI, Table S1†). We were delighted to observe that the desired cyclic oxazine **2a** was formed with 72% yield by heating a mixture of **1a** and pyrrolidine at 130 °C under microwave irradiation (eqn (1)). The best result for the C–H functionalization of pyrrolidine was obtained using phenyl 2-hydroxynaphthyl ketone **1b**. The desired oxazine **2b** was isolated as single diastereoisomer with 96% yield.

Next, the scope of the metal and oxidant free C–H aryloxylation of secondary aliphatic amine was investigated employing the optimized reaction condition (Scheme 1). Various 2-hydroxy naphthyl 1-aryl ketones **3a–f** were examined for functionalization of pyrrolidine. Similar to ketone **1b**, ketones **3a–f** having substituted aryl & naphthyl moiety also serve as good substrates



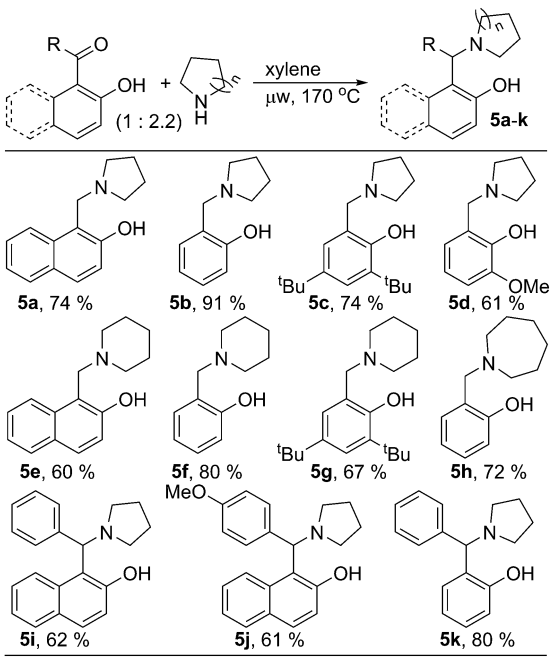
Scheme 1 Substrate scope of C–H aryloxylation.

for C–H functionalization of pyrrolidine. Little less yield found for oxazine **4c** was probably due to the lower solubility of ketone **3c** in toluene. Different 2-hydroxy aryl-aldehydes and ketones were also utilized to functionalize various aliphatic secondary amines producing structurally diverse ring fused oxazines. However, ketones were found to be better substrate than the corresponding aldehydes. Ketones containing both electron donating and withdrawing groups are equally suited for the C–H functionalization of N-heterocycles. Both benzylic C–H and non-benzylic C–H containing N-heterocycles are efficiently functionalized. Substituted pyrrolidine was also functionalized efficiently. 2-Methyl pyrrolidine was reacted with aldehyde **1a** to produce oxazine **4l** with 46% yield. As usual, the reaction of 2-methyl pyrrolidine with ketone **1b** was much efficient in producing functionalized product **4m** with very good yield (82%). For both the cases, the product was isolated as the mixture of regioisomers, interestingly, with reversed selectivity.

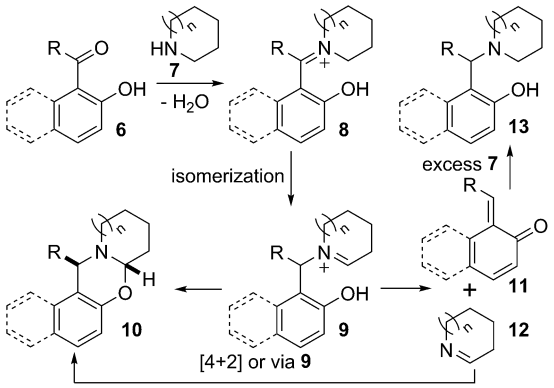
During the optimization of reaction condition for metal and oxidant free C–H aryloxylation of saturated amines, we noticed that, for most of the cases, significant amount of *N*-benzylated amine was formed along with desired ring fused oxazine (ESI†). *N*-Benzylation of amines is common in organic synthesis to protect the free nucleophilic amine functionality. Moreover, different biologically relevant natural or unnatural compounds including medicinal drugs contain arylmethylamine as main structural motif.[8] Reductive amination of aldehyde & ketone using stoichiometric amount of metal hydride based reagent is one of the main way for *N*-benzylation.[9] Similar transformation without using metal hydride would be advantageous and elegant in synthetic chemistry as well as in industry. Therefore, we looked further and optimized the process of arylmethylamine formation (ESI, Table S2†). We observed that, the reaction could be drawn towards *N*-benzylation by changing the relative stoichiometry of amine and carbonyl compound. 2-Hydroxy naphthaldehyde (**1a**) was reacted with two equivalent of pyrrolidine in xylene under microwave irradiation to give 2-hydroxy 1-naphthylmethyl amine **5a** as the major product (74%, Scheme 2). Similarly, various aldehydes and ketones were reacted with different cyclic saturated amine producing structurally diverse mono- or di-arylmethylamines **5b–k**. Hydroxyphenyl based carbonyl compounds gave better results in comparison to hydroxy-naphthyl based substrates.

A mechanistic proposal for this divergent reaction is presented in Scheme 3. Carbonyl compound **6** on reaction with secondary amine **7** produced iminium ion **8**. The isomeric ion **9** could be formed from **8**.[10] The iminium ion **9** could either intramolecularly cyclise to give desired oxazine **10** or undergo dissociation to give the quinone methide **11** and cyclic imine **12**. Diastereoselective intermolecular reaction occurred, probably *via* 4 + 2 cycloaddition or *via* **9**, between the quinone methide **11** and imine **12** to furnish stable oxazine **10**.[3b,6a]

On the other hand, quinone methide **11** could react with nucleophile present in the reaction mixture.[11] Therefore, when the reaction was carried out in the presence of excess amine **7**, quinone methide **11** was trapped by the secondary amine providing formally reduced product **13**. However, the reduced



Scheme 2 Substrate scope of formal reductive amination.



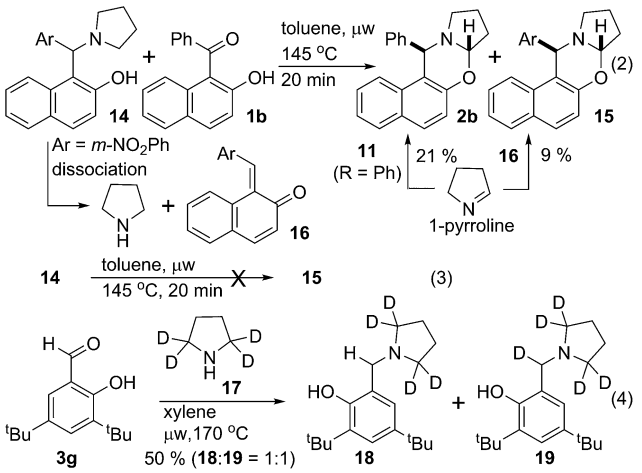
Scheme 3 Mechanistic proposal.

product can also be formed through direct reduction of iminium ion **8** or any of its mesomer by intermolecular hydride transfer from excess amine **7**.[12]

Experiments in Scheme 4 were performed to better understand the course of the reaction. Hydroxy ketone **1b** was reacted with arylmethylamine **14** in toluene at 145 °C under microwave irradiation. Two oxazines **2b** & **15** were isolated with 21% & 9% yield respectively (eqn (2)). However, no cyclized product **15** was formed from **14** under the same conditions (eqn (3)). To explain this observation, we reasoned that, **14** dissociated to pyrrolidine and quinone methide **16** under thermal condition.[6b] Pyrrolidine then reacted with ketone **1b** to produce isomerized iminium ion similar like **9** that dissociated to quinone methide equivalent to **11** and 1-pyrroline. 1-Pyrroline then partitioned during its subsequent reaction with quinone methide **11** (R = Ph) & **16** to give corresponding oxazines **2b** & **15**. This observation supported our mechanistic proposal that the reaction or a part of it proceeded through intermolecular pathway *via* quinone methide intermediate. However, the possibility also remained for the reaction to occur through intramolecular process.

Isotope labelling experiment was performed to probe the novel *N*-benzylation reaction (eqn (4)). Deuterated pyrrolidine **17** was reacted with aldehyde **3g** under the standard reduction conditions producing a mixture of unlabelled and labelled benzyl amine **18** & **19**, respectively, with 1 : 1 ratio.[13] Partial incorporation of the deuterium at the benzylic position accounts for the azomethine ylide intermediate for the conversion of iminium ion **8** to its isomer **9**.[14] Thus the observation of ~50% deuterium incorporation eliminated the possibility of intermolecular hydride transfer process for the formation of reduced product.

Direct C–H aryloxylation of secondary aliphatic amine was achieved *via* a microwave assisted metal, oxidant and other additive free method. Structurally diverse oxazines were obtained by simply heating a mixture of suitable carbonyl compound and amine. We have also showed that the course of the reaction can be altered by changing the relative stoichiometry of carbonyl compound and amine. Upon using one fold excess amine, a formal reductive *N*-benzylation occurred producing a set of biologically relevant mono- or diarylmethylamines. Mechanistic investigation suggested that quinone methide was involved as the intermediate for the reaction.



Scheme 4 Experiments performed for mechanistic investigation.

Acknowledgements

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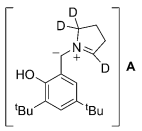
13 Ratio was determined 1H-NMR spectroscopy; see ESI.†

14 Deuterium lebelling at benzylic position of **19** occurred probably *via* the deuteration of zwitterionic intermediate **A**.



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