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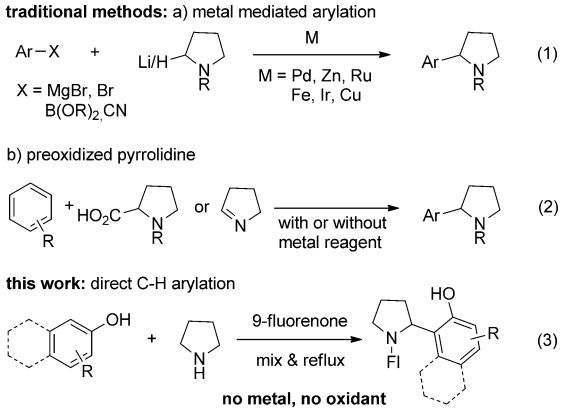
Metal- and Oxidant-Free Direct sp^3 C–H Arylation of Pyrrolidine

Surajit Haldar, Sujit Mahato, and Chandan K. Jana*[a]

Abstract: Arylated aliphatic *N*-heterocycles, and particularly arylated pyrrolidines, have a wide range of applications in medicine as well as in chemistry. Arylation of pyrrolidines mainly relies on metal-mediated couplings, which produce unwanted toxic metal waste. In this Communication, we report an oxidant- and metal-free method for direct sp^3 C–H arylation of pyrrolidine employing a highly atom economic three-component reaction. The method, operating under very simple and mild conditions, is highly selective and very efficient in producing single regioisomer of the arylated product even on a multigram scale. As an alternative to the metal-mediated reaction, this method has the potential to be used in production at an industrial scale. Moreover, a new approach for C–H arylation based on a novel reactivity that differs from the reactivity in Mannich or Betti reactions of iminium ion is presented.

The dependence of human society on functional molecules that serve as advanced materials and medicine is increasing tremendously with time. Accordingly, huge progress has been made for the development of novel methods and strategies to synthesize those functional molecules. During synthesis, excess atomic units in the form of reactants, reagents, solvents or catalysts required to achieve chemical selectivity and molecular complexity are eliminated as chemical waste, which becomes a major problem for the environment. Enormous effort is ongoing to modify known methods and/or to develop new methods for minimizing the production of the chemical waste. Various concepts such as atom economy,[1] redox economy,[2] and step economy[3] were introduced and accepted by the synthetic chemistry community as some of the important parameters for evaluating the practicability of synthetic methods.[4] In this respect, the reaction that involves simple addition of reactants without any other aid from metal-based catalysts, oxidants, and so on, and provides the desired product would be better suited. A very few reactions of this kind (e.g. Diels–Alder,[5] Mannich,[6] Betti reactions,[7] and so on), in comparison with the pool of known chemical processes, are precedented in literature. Therefore, innovative design for the development of new reactions or reformatting the known ones to minimize the waste, keeping the essential features intact (selectivity, yields etc.), is intensely needed.

In view of such development, evolutionary efforts are continuing in the context of direct C–H-arylation of saturated *N*-heterocycles, as α-arylated heterocycles such as arylated pyrrolidines have a wide range of applications in chemistry as well as in medicine.[8,9] All of the known protocols for efficient direct arylation of saturated *N*-heterocycles generally involve the use of organometallic reactants either in stoichiometric and/or catalytic amount (Scheme 1,



Scheme 1. Direct C–H arylation of pyrrolidine.

Eq. (1)).[10,11] The metal-mediated reactions are highly efficient in terms of selectivity and reactivity in producing wide variety of valuable C–H arylated heterocyclic compounds. However, considerable interest has been shown in recent years for developing metal-free transformations to exclude the traces of toxic metal contamination in pharmaceutically important compounds, as well as to avoid the unwanted metal-based chemical waste.[12] In an another approach, preoxidizied starting materials were used for the arylation with or without metal-based reagents (Scheme 1, Eq. (2)).[13] Therefore, all of these known processes produce toxic chemical waste, which are a burden to the environment. In addition, not easily achievable reaction conditions (such as moisture free, air free etc.) in metal based reaction

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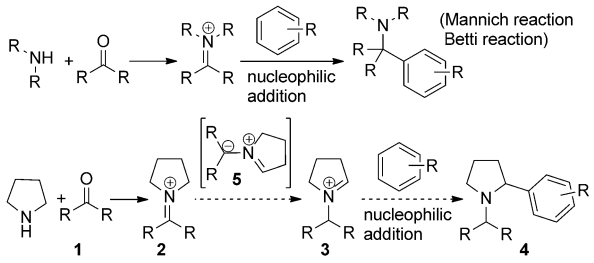
creates difficulty, especially in industrial-scale production. Herein, we present a metal-free, oxidant-free, atom-economic, and operationally simple method for direct α-C–H arylation of pyrrolidine from a three component reaction, without any additional aid (Scheme 1, Eq. (3)). The method is highly regioselective and very efficient even on a gram scale.

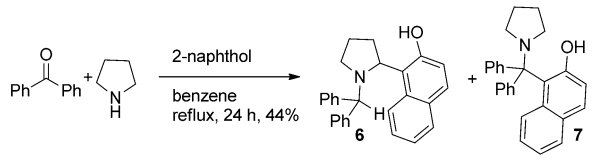
Alkylation or arylation of aldehydes and ketones by nucleophilic addition to the corresponding iminium ions (the Mannich reaction, Scheme 2) is a very efficient carbon-



Scheme 2. Two different modes of iminium ion reactivity.

carbon bond-forming reaction. Thus, the reaction has been extensively applied in organic synthesis to produce various functional molecules.[6] In the context of α-C–H arylation of amines, we anticipated that by the judicious design of a carbonyl compound **1**, one could isomerize the initial iminium ion **2** into **3**, which will react subsequently with a nucleophilic aromatic compound to give the arylated product **4**. The azomethine ylide **5** may be involved in mediating this isomerization.[14] A perfect design of the carbonyl compound would stabilize the negative charge of the zwitterion **5**.

In this context, we chose benzophenone, which is cheap and commercially available, as the carbonyl partner to test our mechanistic hypothesis. The choice was based on our perception that the initial iminium ion (**2**, R = Ph) will be sterically hindered for nucleophilic attack, and the anion in the corresponding azomethine ylide (**5**, R = Ph) will be stable because of delocalization through the two phenyl groups present. Accordingly, we set the first reaction of benzophenone with pyrrolidine in the presence of 2-naphthol as the nucleophile in benzene at reflux. Indeed, we were delighted to isolate desired α-arylated pyrrolidine **6** in 44% yield (Scheme 3). The product was formed as a sole regioisomer without producing Betti or Mannich adduct **7**. Encouraged by this initial result, we performed the same

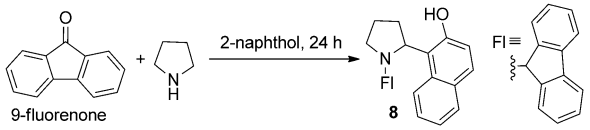


Scheme 3. Naphthylation of pyrrolidine in the presence of benzophenone.

reaction at an elevated temperature (140 °C for 48 h) to increase the yield of the reaction. However, the desired compound was isolated in a lower yield of 18%.

At that point, we had to turn our attention to search for a different carbonyl compound that can serve to provide a high yield as well as exclusive regioselectivity. Ready availability of that carbonyl compound was also considered during our planning. Accordingly, we selected 9-fluorenone as suitable carbonyl partner, keeping in mind that extra benefit may be obtained due to the aromatic nature of the anion in the corresponding azomethine yield. The reactivity of 9-fluorenone was tested by treating it with pyrrolidine in benzene at reflux in the presence of 2-naphthol. As expected, the arylated pyrrolidine **8** was isolated as a single regioisomer with very good yield of 80% (Table 1, entry 1). Dif-

Table 1. Variation of solvents and temperature.



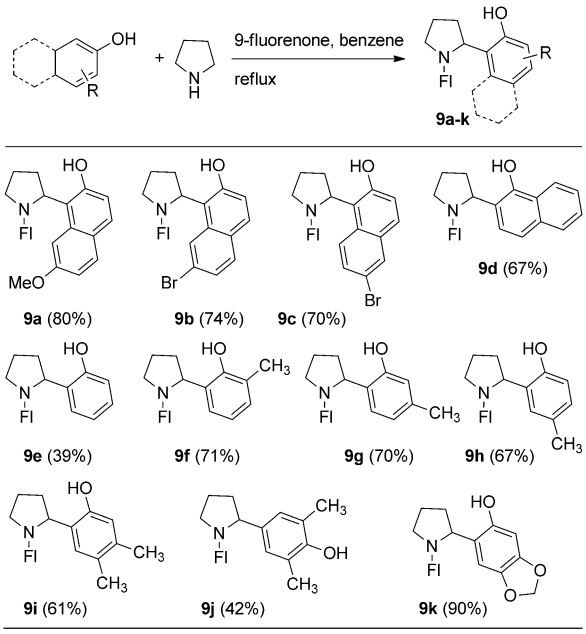
Entry	Solvent	*T*	Yield [%][b]
1	benzene	reflux	80
2	benzene	RT	27
3	toluene	reflux	32
4	dichloromethane	reflux	16
5	THF	reflux	39
6	EtOAc	reflux	23

[a] Reactions were carried out with 2-naphthol (0.7 mmol), pyrrolidine (1.2 equiv.) and 9-fluorenone (1.2 equiv.). For additional experiments see the Supporting Information. [b] Yield of isolated product.

ferent reaction conditions, by varying reaction temperatures and solvents, were examined for further improvement in the yield of the desired product. Although, other solvents, such as toluene, THF, dichloromethane, and so on, are suitable for the reaction, benzene at reflux was the most suitable solvent.

The scope of this new reaction was then investigated under the optimized reaction conditions (Scheme 4). At first, different commercially available naphthol derivatives were examined as potential nucleophiles. Reaction with methoxy and bromo-substituted 2-naphthols gave the desired products **9a** (80%), **9b** (74%), and **9c** (70%), in very good yields. 1-Naphthol reacted similarly to provide the α-naphthylated pyrrolidine derivative **9d**. In every case, only the C–H arylated compound was formed without producing the Betti product

Next, we considered phenol and its derivatives as the potential nucleophilic substrates. Phenol derivatives can react through the *ortho* as well as the *para* position. Thus, this creates the possibility of producing at least two regoisomeric products. Surprisingly, a single regioisomer was formed from the reactions of phenol and its derivatives. The regiochemistry of representative compounds were confirmed from their X-ray crystal structures (Figure 1). Phenol react-



Scheme 4. Arylation of pyrrolidine with naphthol and phenol derivatives. Yields of **9a**–**f** are after 24 h reaction; yields of **9g**–**k** are after 36 h reaction.

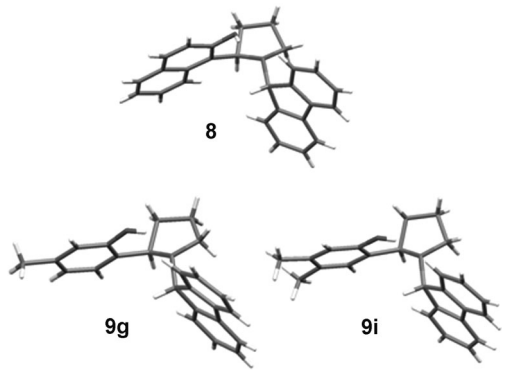
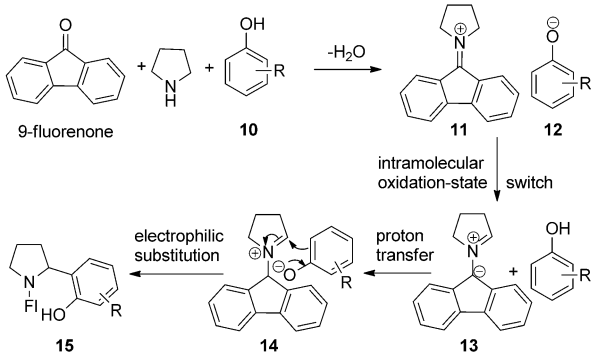


Figure 1. X-ray crystal structures of **8**, **9g**, and **9i**.[15]

ed exclusively through *ortho* position and the product **9e** was isolated in moderate yield. Furthermore, a 71% yield of **9f** and exclusive regioselectivity was obtained for *ortho*-cresol. *meta*-Cresol and *para*-cresol reacted similarly to furnish the desired products **9g** (70%) and **9h** (67%) respectively. Slightly lower yields were obtained for sterically demanding disubstituted phenols. The reaction of 3,4-dimethylphenol gave desired product **9i** in 61% yield. The reaction was forced to occur through the *para* position of 2,6-dimethylphenol as both of its *ortho* positions were blocked. However, the *para*-product **9j** was isolated in slightly lower yield. The highly oxygenated phenol derivative sesamol also reacted very efficiently. The desired product **9k** was isolated in the highest yield of 90% in this series. Expectedly, the reaction of electron deficient *meta*-bromophenol provided the desired product in trace amounts. Also, no desired product was formed from *para*-nitrophenol.

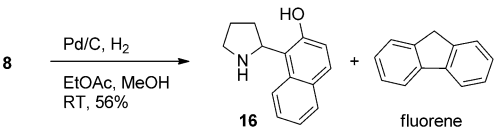


Scheme 5. Proposed mechanism of metal-free arylation of pyrrolidine.

A mechanistic proposal for the metal- and oxidant-free atom-economic α-C–H arylation of pyrrolidine is presented in Scheme 5. Pyrrolidine condenses with 9-fluorenone with the assistance of the phenolic OH group (**10** as a proton source) to form the corresponding iminium cation **11**, which is accompanied by phenolate anion **12**. Base-(pyrrolidine or phenolate) aided isomerization of parent iminium ion **11** occurs to produce the azomethine ylide **13**, which has a fluorenyl anion moiety that is stabilized by its aromaticity. A secondary iminium ion **14** is probably formed through protonation of azomethine ylide **13**. [16] The oxidation-state switch from the fluorenone carbon in **11** to the C2 position of pyrrolidine in **14** eliminates the possibility of Mannich or Betti product formation. Then, the secondary iminium ion **14** reacts with the phenolic compound by an aromatic electrophilic substitution reaction to provide the α-arylated product **15**. The close association (as shown in Scheme 5) of the electrophilic iminium ion **14** with the nucleophilic phenolate anion probably directs the reaction entirely through the *ortho* position and consequently brings the exclusive regioselectivity.[13d]

The cleavage of the *N*-fluorenyl moiety of the arylated pyrrolidine was investigated next. Accordingly, compound **8**, when treated under standard hydrogenolysis conditions for 24 h, provided the desired 2-naphthylpyrrolidine **16** in 56% yield along with 34% of the unreacted starting material (Scheme 6). Therefore, the fluorenyl moiety which is installed in the C–H arylation process can serve as a protecting group similar to a benzyl protecting group for amines. Furthermore, fluorene produced by reductive cleavage can be oxidized and recycled.

In conclusion, we have discovered a metal-, oxidant-, and other-additive-free method for direct sp^3 C–H arylation of pyrrolidine by an operationally simple, and highly atom



Scheme 6. Cleavage of the *N*-fluorenyl moiety of the arylated pyrrolidine.

economic three-component reaction. Importantly, a new approach for direct C–H arylation based on a novel reactivity of iminium ions, which differs from the traditional reactivity in Mannich or Betti reaction, is presented. As an alternative to the metal-mediated reaction, the method is highly regioselective and efficient, even in a multigram scale reaction. Therefore, this method will be highly compatible for industrial-scale synthesis of valuable arylated pyrrolidines for practical application.[8h] A detailed mechanistic investigation is ongoing in our laboratory.

Experimental Section

The phenol or naphthol derivative (0.5 mmol, 1.0 equiv.) was added to a solution of pyrrolidine (1.2 equiv.) and 9-fluorenone (1.2 equiv.) in benzene (2 mL) at room temperature. Then the reaction mixture was stirred at reflux for 24 h or 36 h depending on the substrates. Then the mixture was cooled to room temperature, the organic solvents were removed under vacuum, and the crude product was purified by column chromatography to provide analytically pure 2-aryl pyrrolidines. Some of the compounds (e.g. **8**, **9b**, and **9c**) crystallize from the reaction mixture, and thus do not require column chromatographic purification.

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Keywords: arylation · C–H activation · iminium ions · metal-free reaction · pyrrolidines

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