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MONTMORILLONITE KSF-MEDIATED FACILE SYNTHESIS OF PYRROLES

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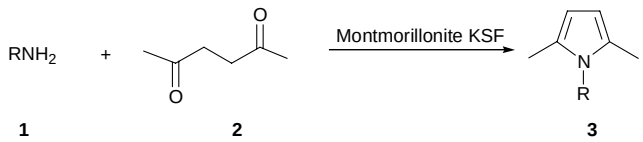
Abstract – A facile synthesis of substituted pyrroles over montmorrilonite KSF clay has been accomplished in excellent yield.

The application of clay-mediated organic reaction is currently under extensive investigation.[1] Recently, we have demonstrated clay mediated facile aromatic nitration of several hydrocarbons[2] and a structure-activity relationship study of various polyaromatic derivatives easily prepared from the corresponding amines in a projected route towards the development of novel anticancer agents.[3] Based on the biological activities of these derivatives, we became interested in the synthesis of pyrroles bound to the amines of different structures.

Although, various methods[4] are known for the synthesis of pyrroles, still Paal-Knorr's method[5] is very effective. Recently, synthesis of some pyrroles with aniline derivatives under microwave irradiation was reported.[6] We report here a convenient and facile synthesis of several pyrroles in the surface of montmorillonite without using microwave irradiation. The advantages of using solid support in chemical reactions are numerous. There is no requirement of strong acid and alkali, extraction, heating device, stirrer, and many standard glass apparatus.

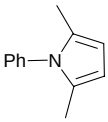
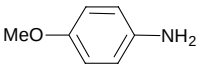
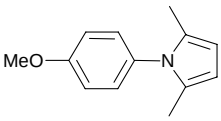
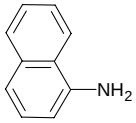
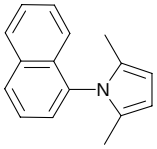
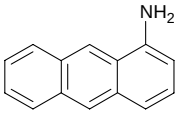
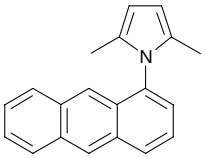
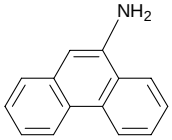
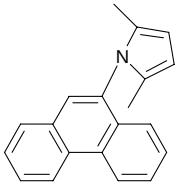
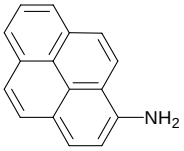
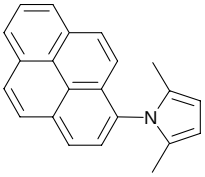
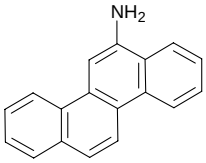
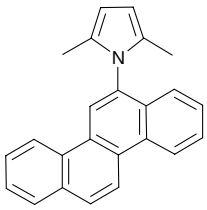
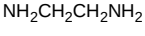
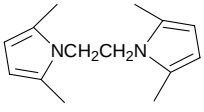
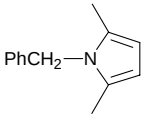
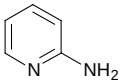
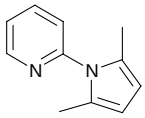
Scheme 1



1 **2** **3**

We used several amines (**1**) including monocyclic, bicyclic, tricyclic, tetracyclic aromatic amines as well as aliphatic amine, heterocyclic amines and benzylic amines for this study. The other starting material was commercially available 2, 5-hexan-di-one (**2**) (Scheme 1). At the beginning of the procedure, the solid mass was prepared by mixing the clay and a solution of the amines (**1**) and the ketone (**2**) in dichloromethane and evaporation of the solvent under reduced pressure. This solid mass was then kept at room temperature for the specified time as indicated in the Table 1. The yield of the product (**3**) is shown

Table1: Montmorillonite KSF-mediated synthesis of pyrroles

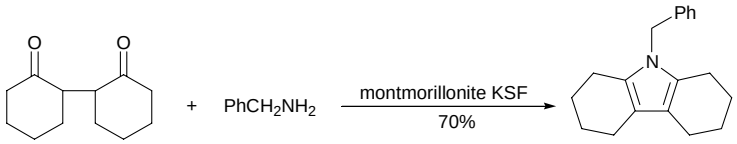
Entry	Amine	Product	Time (h)	Yield (%)
1			10	96
2			15	81
3			11	83
4			19	98
5			18	94
6			20	88
7			22	85
8			10	85
9			10	95
10			25	70

in the Table 1. The less basic aromatic amines needed longer reaction time, although the yields are comparable to the more basic amino compounds.

It is of note that, this method of pyrrole formation goes exceedingly well with comparatively less basic multicyclic aromatic systems (Table 1, Entries 3-7) and heterocyclic amine (Table 1, Entry 10) without the need for Lewis acids to activate or catalyze the process. The formation of a bis-pyrrole was observed when diamine was the starting material (Entry 8). In addition, all the reactions were successful at room temperature. Previously, even with simple aniline derivatives, high temperature and/or microwave irradiation were required.

Having an attractive route for the synthesis of pyrroles, synthesis of an octahydrocarbazole in which pyrrrole constitutes the central ring was attempted. The starting diketone (**4**) was prepared by following an oxidative coupling reaction of cyclohexanone enolate by ferric chloride.[7] Condensation of the diketone (**4**) with benzyl amine as described above afforded the tricyclic octahydrocarbazole in moderate yield (Scheme 2). Octahydrocarbazoles can be converted to the carbazoles by dehydrogenation over chloranil or palladium/charcoal. Because of considerable synthetic attention as potential carcinogens and several other interesting biological activities, *N*-substituted carbazole by clay-mediated synthesis is noteworthy. Synthesis of *N*-unsubstituted carbazoles was demonstrated earlier by Fisher's or Bucherer's method.[8] However, the reaction conditions are not mild and an alkylation step is necessary to obtain *N*-substituted product

Scheme 2



4 **5**

We investigated other solid supports, such as silica gel and alumina in this reaction. However, the reaction did not go to completion and only an insignificant amount of the starting material was consumed. The reaction did not proceed without any solid support. The use of montmorillonite, however, under identical conditions gave a cleaner reaction. This observation has strengthened the importance and nature of the solid support. . The present methodology has advantages over the Lewis acid-mediated synthesis of pyrroles[7] in terms of yield of the products, generality of the method and simple work-up without going through the extraction-chromatography for the purification of the products. In addition, unlike many other procedures, no extra energy source, like microwave irradiation or ultrasound is needed for the success of the reaction.

In summary, we have demonstrated a facile synthesis of pyrroles over a solid surface in excellent preparative yield (70-98%). We believe that our method is general since almost all kinds of primary

amino compounds can be used with remarkable success and thus this method has a more scope for the future applications. Particularly, exploitation of the carbazole strategy for the generation of novel multicyclic structures and their biological evaluation is under progress.

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11. General procedure for the synthesis of pyrroles: Montmorillonite KSF clay (1 g), hehane-2,5-dione (114 mg, 1 mmol) and the appropriate amine (1.2 mmol) were mixed together thoroughly using a little dichloromethane. The solvent was then evaporated and the mixture was kept at room temperature for a period specified in Table 1. After this period the solid mixture was washed with dichloromethane and the washings were evaporated to get pure pyrroles. An identical procedure was adopted for the preparation of **5** from the diketone (**4**) in 70% yield.