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# Solvent-Free Solid Acid-Catalyzed Electrophilic Annelations: A New Green Approach for the Synthesis of Substituted Five-Membered N-Heterocycles

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**Abstract:** An effective microwave-induced, solid acid-catalyzed, environmentally benign synthesis of substituted pyrroles, indoles and carbazoles under solvent-free conditions is described. The new synthetic methodology is based on the use of a considerably strong solid acid, K-10 montmorillonite. Both the cyclialkylation of amines and annelation of pyrroles and indoles have been completed within minutes and provided excellent (75–98%) yields with practically 100% selectivity.

**Keywords:** carbazoles; indoles; K-10 montmorillonite; microwave heating; pyrroles; solid acids

## Introduction

Five-membered, nitrogen-containing heterocycles, such as pyrroles, indoles, and carbazoles are important building blocks in an extensive number of biologically active compounds.[1] These heterocyclic moieties are of exceptional interest in pharmaceutical applications as they represent the core part of several drugs. Examples include anti-inflammatory, antitumor, antiallergic, antiviral and anti-hypertensive compounds.[2] The importance of these heterocycles provides significance and actuality for developing new methods for their syntheses.[3] Due to strengthening environmental regulations and safety concerns, the development of environmentally responsible synthetic methods is also highly desirable. Although the Fischer indole synthesis and many other efficient methods had been reported,[4] the development of green synthetic methods for the preparation of these hererocycles is still in the forefront of synthesis research.

Most synthetic methods are based on the construction of the pyrrole moiety on prefunctionalized aryl precursors, which involves multiple steps.[4] Recent methods use C-3 functionalized pyrroles as starting materials for the preparation of indoles.[5] Carbazole derivatives have also been widely used for building electroluminescent materials and polymers having electrical and thermal conductivity. A recent review describes wide applications of carbazoles in drug development and natural product chemistry.[6] Methods for carbazole syntheses are usually based on transition metal-mediated reactions, for example, Diels–Alder reactions, reductive cyclization of 2-nitrobiphenyls and double arylation of primary amines.[7]

Another rapidly growing area in organic syntheses is the application of solid acid catalysis to replace the traditional effective, but harmful and corrosive mineral acids such as sulfuric acid. Solid acid catalysts, including clays, zeolites, metal oxides, and acidic ion-exchange resins, have been widely used to develop clean and environmentally benign synthetic processes.[8] Our catalyst of choice in developing a new method for the synthesis of 5-membered N-heterocycles is a synthetic clay, montmorillonite K-10.[9] It is a well-known and widely used solid acid catalyst in synthetic organic chemistry. An overwhelming number of papers, reviews and books deal with its synthetic applications.[9] As such it is considered a well-characterized, unique, solid acid *reference* catalyst. It is also a green acid catalyst, but most importantly, K-10 montmorillonite is a commercially available material and can be used without any pretreatment. It offers several advantages over classical liquid acids; it is solid, non-corrosive, inexpensive and easily reusable. Also, K-10 has high active surface area (220–270 $m^2 g^{-1}$) that ensures excellent reaction rates. The Hammett acidity ($H_o$) value for K-10 is *ca.* −8 indicating strong acidity.[9] It is also an excellent catalyst for micro-

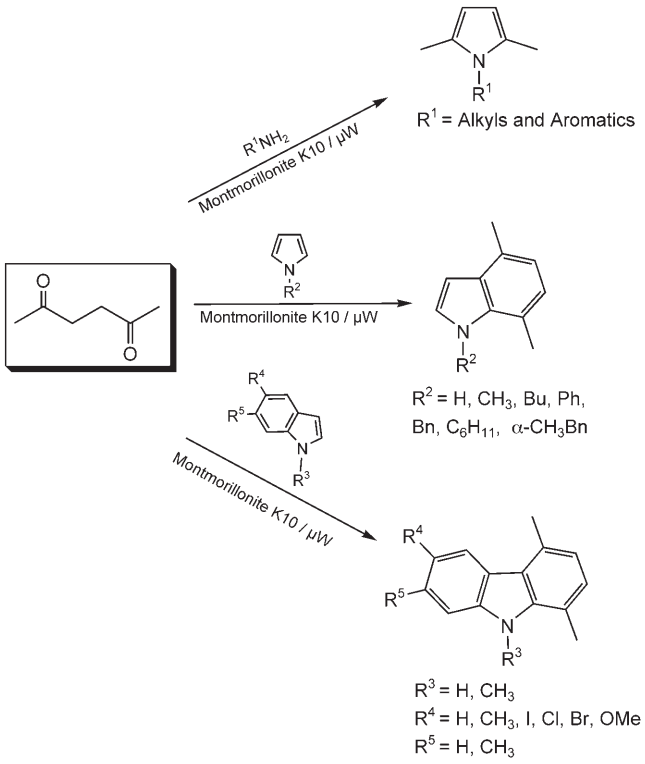
wave-assisted organic synthesis. This area has also attracted considerable attention in recent years.[10]

Continuing our efforts in developing environmentally benign processes, herein we report an effective, new, one-step process to synthesize substituted pyrroles, indoles and carbazoles. Our approach is based on a new pathway, namely a solid acid-catalyzed Friedel–Crafts cyclialkylation/annelation. The combination of solid acid catalysis, solvent-free conditions and microwave irradiation results in excellent yields, reduces the reaction times and represents a highly eco-friendly approach.

## Results and Discussion

The Friedel–Crafts reaction is one of the most important C–C bond forming methodologies.[11] Friedel–Crafts cyclization reactions, either of intramolecular or intermolecular nature, can lead to useful carbocyclic compounds, such as quinolines, lactones, condensed aromatics, and cyclic aromatic ketones.[12,13] The intramolecular pathway involves a substituted aromatic substrate, which undergoes cyclization due to the close spatial arrangement of two reacting centers. In contrast, bimolecular Friedel–Crafts cyclizations of a single aromatic moiety with bifunctional electrophiles are more difficult to carry out as competitive intermolecular reactions might significantly decrease the selectivity of cyclization. However, due to the higher reactivity of N-heterocycles, the use of a bifunctional substrate is appealing for the formation of indoles and carbazoles. Our basic idea is that a selective electrophilic annelation on pyrroles can provide indoles, and eventually lead to carbazoles (Scheme 1). A similar method had been reported for the synthesis of the target compounds, however, the use of *p*-toluenesulfonic acid or HCl as catalyst, benzene as solvent, 40 h reaction time and the at best moderate yields (average yield 45–55%) did not represent a novel approach.[14] Our own experiments with sulfuric acid as catalyst showed even worse features (less than 10% yield). Besides their corrosive and harmful nature, the low yields and significant polymerization of pyrrole clearly indicated that these liquid acids cannot be the catalyst of choice for the above detailed electrophilic annelation process.

In order to show the general nature and efficiency of our new method we initially carried out the synthesis of substituted pyrroles using aromatic and aliphatic primary amines and 2,5-hexanedione in a K-10 montmorillonite-catalyzed, microwave-assisted reaction. This process, an efficient modification of the Paal–Knorr synthesis,[15] is formally a solid acid-catalyzed cyclialkylation on the nitrogen of the amines. The general procedure involves the adsorption of reactants on the catalyst surface with a minimum amount




**Scheme 1.**

of solvent. Evaporation of the solvent gives the dry mixture of catalyst and reactants adsorbed on its surface. The dry mixture is then irradiated by microwaves for the specified time. The results are summarized in Table 1.

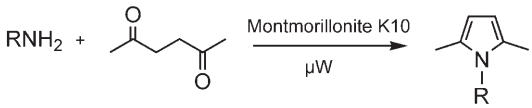
As the data indicate, the reactions provide practically quantitative yields in very short reaction times. The reactivity of different amines plays only a minor role in the process, even the longest reaction takes place within 6 min providing a 98% yield. In addition, the reaction proceeds with 100% selectivity without by-product formation. It was observed that the product did not undergo secondary reactions even after an extended time of irradiation.

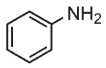
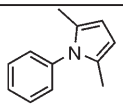
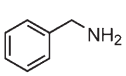
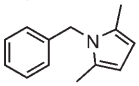
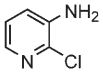
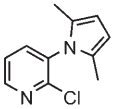
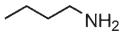
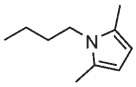
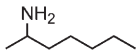
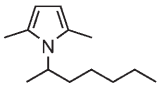
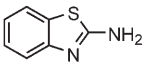
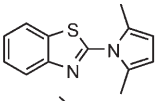
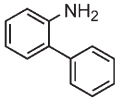
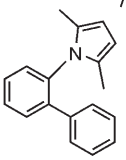
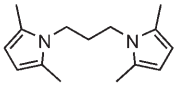
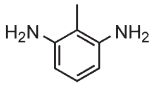
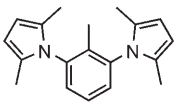
The excellent results obtained with primary amines prompted us to extend the scope of the reaction to synthesize higher analogues such as indoles and carbazoles. The same methodology has been applied using pyrroles as starting materials to obtain substituted indoles. The results are tabulated in Table 2.

As shown, the reactions provide the expected substituted indoles in good to excellent yields. The substituents on the pyrrole ring significantly affect the rate and the reactivity of substrates. Pyrrole itself undergoes cyclialkylation in a very short (2 min) reaction providing practically quantitative yield. *N*-Alkylpyrroles also react readily and give good to excellent yields, however, in longer reactions. The nature of the substituent clearly affects the reaction rates and

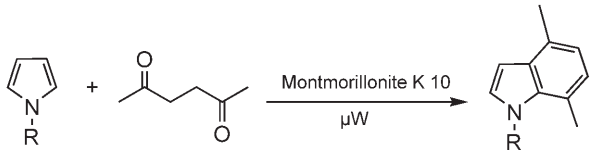
**Table 1.** K-10 montmorillonite catalyzed synthesis of substituted pyrroles under microwave irradiation at constant (90 °C) temperature.

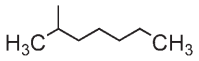
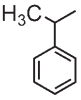



| Entry | Amine | Irradiation Time [min] | Product | Yield [%][a] |
|---|---|---|---|---|
| 1 |  | 3 |  | 98 |
| 2 |  | 4 |  | 96 |
| 3 |  | 2 |  | 98[b] |
| 4 |  | 3 |  | 91 |
| 5 |  | 2 |  | 97[b] |
| 6 |  | 6 |  | 98[b] |
| 7 |  | 2 |  | 96[b] |
| 8 |  | 3 |  | 98[b] |
| 9 |  | 3 |  | 97[b] |

[a] Yields of the isolated products after flash chromatography, 100% selectivity for all products observed by GC-MS.
[b] New compounds.

**Table 2.** K-10 Montmorillonite catalyzed synthesis of substituted indoles under microwave irradiation at constant (90 °C) temperature.




| Entry | R | Irradiation Time [min] | Yield [%][a] |
|---|---|---|---|
| 1 | H | 2 | 98 |
| 2 | $CH_3$ | 6 | 82 |
| 3 | Bu | 12 | 80[b] |
| 4 |  | 12 | 85[b] |
| 5 |  | 9 | 91[b] |
| 6 |  | 25 | 75[b] |
| 7 |  | 9 | 79[b] |
| 8 |  | 8 | 75[b] |

[a] Yields of the isolated products after flash chromatography, 100% selectivity for all products observed by GC-MS.
[b] New compounds.

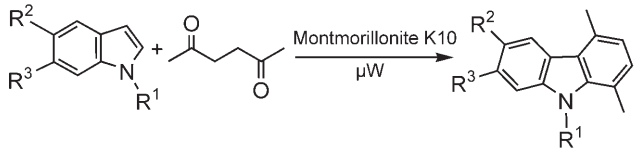
yields. In the presence of electron-donating substituents (e.g., entry 5) the rate is higher than with electron-withdrawing substituents (e.g., entry 6) following the general rules of Friedel–Crafts chemistry. The selectivity is excellent, the expected indoles exclusively form in the reaction. Interestingly, this selectivity remains very high even at increased (2:1) diketone/pyrrole ratios, indicating that the theoretical one-pot process from pyrroles to carbazoles does not occur. As a limitation of the method, it is worth mentioning that pyrroles having strong electron-withdrawing substituents (e.g. 2-acetyl or 2-formyl) provide the corresponding indoles only in traces even after extended reaction times (25–30 min).

To further widen the scope of the process, several substituted indole derivatives were used as substrates in the reaction, expecting the corresponding carbazole derivatives. A wide variety of indoles possessing electron-donor and electron-withdrawing substituents have been studied. The results are summarized in Table 3.

The data indicate the usefulness of our method. Indole and substituted indole derivatives readily undergo electrophilic annelation under the same reaction conditions providing a wide variety of substituted carbazoles. The reaction times and yields do not show significant substituent effects, the yields are excellent

**Table 3.** K-10 montmorillonite catalyzed synthesis of substituted carbazoles under microwave irradiation at constant (90 °C) temperature.




| Entry | $R^1$ | $R^2$ | $R^3$ | Irradiation Time [min] | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | H | H | H | 12 | 95 |
| 2 | H | I | H | 7 | 86[b] |
| 3 | H | Cl | H | 4 | 94[b] |
| 4 | H | Br | H | 3 | 90 |
| 5 | H | Me | H | 3 | 94[b] |
| 6 | H | H | Me | 3 | 96[b] |
| 7 | H | COOMe | H | 5 | 88[b] |
| 8 | Me | H | H | 10 | 89[b] |
| 9 | H | OMe | H | 3 | 96 |

[a] Yields of the isolated products after flash chromatography, 100% selectivity for all products observed by GC-MS.
[b] New compounds.

in most cases and the reactions are completed within 3–12 min. Similarly to the previous examples (Table 1 and Table 2), the exclusive formation of carbazoles has been observed.

While the synthesis of pyrroles (Table 1) follows the general Paal–Knorr-type mechanism there are two possibilities to describe the mechanism of indole and carbazole formation. The first is a step by step alkylation, the second is a concerted reaction path. The concerted cyclization is highly unlikely under the extremely polar conditions and due to the surface bound active intermediate serious steric hindrance applies. Considering the polarity, acid strength and heterogeneous nature of K-10 montmorillonite we suggest that the annelation occurs in two consecutive alkylation-dehydration reactions. This is partially supported by the reaction of pyrrole with a monofunctional reagent, 2-hexanone, which showed the exclusive formation of the C=C bonded product even at low conversion values, while the hydroxyalkylated product has not been detected at all. This suggests that water elimination occurs immediately after the hydroxyalkylation, the second cyclization step only takes place after dehydration.

## Conclusions

In conclusion, a new, effective, solid acid-catalyzed synthesis of substituted pyrroles, indoles and carbazoles is described. This method provides the products in very high yields and excellent selectivities in very short reaction times. In addition to efficiency, the solvent-free environment, solid acid catalysis, very limited energy consumption, and waste-free nature makes the process very attractive for the environmentally benign synthesis of these important heterocycles. Our work represents the first effective method that is based on successive electrophilic annelation for the synthesis of all three classes of these N-heterocycles.

## Experimental Section

### Materials

All starting materials were purchased from Aldrich and were used without further purification. Solvents used were all Fisher products with a minimum purity of 99.5%. K-10, a solid acid catalyst is commercially available from Aldrich and was used as received.

### NMR Analysis

Many of the products synthesized during this study are known (8 out of 26) and their spectral characterization showed satisfactory agreement with former literature data. Nevertheless, we have provided full spectral characterization of all products synthesized in this study. The $^1H$, and $^{13}C$ spectra were obtained on a 400 MHz superconducting Varian Innova400 NMR spectrometer, in $CDCl_3$ solvent with tetramethylsilane as internal standards. The temperature was 25 °C (accuracy ±1 °C) and controlled by the Varian control unit.

### GC-MS analysis

The mass spectrometric identification of the products has been carried out with a Shimadzu QP5050 and an Agilent 6850 gas chromatograph-5973N mass spectrometer system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J&W Scientific).

### General Experimental Procedure for the Microwave-Assisted K-10 Montmorillonite-Catalyzed Electrophilic Annelation of Pyrroles and Indoles

The reactions have been carried out in a focused CEM Discover Benchmate microwave reactor, using the open vessel technique. After optimization the system has been set up to a standard temperature (90 °C) for the reactions. The tem-

perature has been measured and kept constant using an infrared temperature controller.

Pyrrole (1 mmol) and 2,5-hexanedione (1.5 mmol) were dissolved in 10 mL of dichloromethane. 500 mg of K-10 montmorillonite were added to the mixture which was then stirred for 2 min. The solvent was evaporated under vacuum. The dry mixture was then transferred into a vial and inserted to the cavity of the microwave reactor. All reactions have been carried out under atmospheric pressure. The progress of the reaction was monitored by GC-MS. When the reaction was completed the product was dissolved in $CH_2Cl_2$, separated from catalyst by filtration and the solvent was removed under vacuum. The crude 4,7-dimethylindole was purified by flash chromatography to obtain the pure product.

Similar procedures were followed in case of pyrrole and carbazole syntheses except amines and indoles served as starting materials, respectively.

The complete spectroscopic characterization of the products is provided in the Supporting Information.

### Supporting Information

Details of reaction conditions and full spectroscopic characterization of each product are provided in the Supporting Information.

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