

Facile clay-induced Fischer indole synthesis: A new approach to synthesis of 1,2,3,4-tetrahydrocarbazole and indoles

Amarajothi Dhakshinamoorthy, Kasi Pitchumani*

School of Chemistry, Madurai Kamaraj University, Madurai 625021, India

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Abstract

Preparation of 1,2,3,4-tetrahydrocarbazole and substituted indoles, using a solid acid catalyst (namely K-10 montmorillonite clay) via Fischer indole synthesis in methanol medium, is described. The results obtained by the thermal method are compared with those from microwave irradiation. Active participation by adjacent acidic and basic sites of clays is proposed.

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1. Introduction

Clay minerals are hydrous silicates of aluminium, magnesium, potassium and iron. Heterogeneous catalytic organic transformations using clays and clay-based reagents find extensive applications in organic synthesis [1–5]. Cation-exchanged montmorillonite clays are used as efficient solid acid catalysts and clay-supported reagents find a wide range of applications from catalysis to molecular devices. K-10 montmorillonite clay, an inexpensive acidic industrial catalyst, is considered as a good support compared to other forms of clays, sand, silica gel, titanium dioxide and acidic alumina. It has been reported to be an excellent support and solid acid catalyst for a number of reactions, such as oxidations [6], epoxidation [7], enantioselective cyclopropanation [7], Friedel–Crafts benzylation [8], nitrations [9], halogenation [10], rearrangements [11], photophysical studies [12] and photochemical reactions [13].

One of the interesting properties of clays is their acidity, which originates from the interlayer cations; some of these may be protons or polarizing cations (e.g. Al^{3+}), which give rise to strong Bronsted acidity [14]. The higher the electronegativity of the M^{n+} , the stronger the acidic sites

generated. The surface acidity of natural clays with Na^+ and NH_4^+ as cations ranges from +1.5 to –3 (in H_0 scale). Washing of the clay with mineral acid, brings down H_0 to –6 to –8, which is between the value for conc. HNO_3 (–5) and that for conc. H_2SO_4 (–12). The above solid acid catalysts are thermally stable up to 200 °C. Our interest in “environmentally safer” reaction conditions and in exploring the utility and development of solid acid catalysts using clays, prompted us to explore Fischer indole synthesis using different cyclic and acyclic ketones and aldehydes.

Fischer indole [15] synthesis has been one of the few heterocyclic syntheses studied in great detail, due to its versatility and broad applicability in the synthesis of a number of biologically active natural and synthetic products like reserpine, strychnine, yohimbine, indomethacin and also in the synthesis of essential amino acids, such as tryptamine [16], photoconductors [17], antioxidants [18] and of clausenamine-A [19] (which exhibits various biological activities including anti-tumor, anti-inflammatory and cytotoxic activities). A wide variety of catalysts have been used for affecting the cyclization of arylhydrazones of ketones and aldehydes. The reaction conditions range from warming with acetic acid [20,21] to fuming with zinc chloride [22] and refluxing with polyphosphoric acid (PPA) [23]. PCl_3 [24] in benzene has been recommended as a mild and effective system for such cyclization. Non-catalytic indolization has

* Corresponding author. Tel.: +91 452 2456614; fax: +91 452 2459181.
E-mail address: pit12399@yahoo.com (K. Pitchumani).

also been reported in high temperature aqueous media [25] as well as in different solvents [26] like ethylene glycol, diethylene glycol, tetralin and in ionic liquids [27]. Recently, a facile zeolite-induced Fischer indole synthesis of bioactive natural product rutaecarpine [28] is reported. This multistep synthesis uses H-mordenite in acetic acid as a catalyst under refluxing condition. Fischer indole synthesis on a solid support [29] is also reported.

1,2,3,4-Tetrahydrocarbazole (THC) has also been synthesized by various routes (i) using zeolite [30] catalysts such as H-ZSM-12, H-mordenite, H-Y, H-ZSM-22, H-EU-1, H-ZSM-5 by Fischer method with phenylhydrazine and cyclohexanone (the zeolite catalyst needs activation at 823 K in air for 8 h); (ii) when cyclohexanone phenylhydrazone is treated with 96% formic acid in a Parr microwave bomb [31]; (iii) by the reaction of *N*-(4-chlorophenyl)benzophenonehydrazone with cyclohexanone in presence of *p*-toluenesulfonic acid monohydrate [32]; (iv) by reduction of the coupling product obtained in the reaction between *o*-halonitrobenzene and α -haloanones in the presence of 10% Pd on carbon as the catalyst [33].

The development of one-pot approaches to carbazoles or indoles is a subject of considerable interest because of their significance in both economical and ecological points of view. Reported literature in this context are listed below: (i) a one-pot synthesis of 5-substituted *N,N*-dimethyltryptamine from 4-substituted hydrazines using 4% sulfuric acid [34]; (ii) one-pot synthesis of THC by thermal cyclization of *N*-trifluoroacetyl enehydrazines [35] involving use of trifluoroacetic anhydride and retake of trifluoroacetic acid; (iii) one-pot synthesis of THC by using one equivalent of ionic liquid such as choline chloride-2ZnCl₂ [36]; (iv) recently, synthetically important indolo[2,3-*a*]carbazoles are obtained in a one-pot reaction via Fischer indole synthesis starting from 2-amino-cyclohexanone hydrochloride and substituted arylhydrazine hydrochlorides in the presence of 95% CH₃COOH–TFA mixture [37]. However, the above methods involve use of corrosive liquid acids such as sulfuric acid, hydrochloric acid and trifluoroacetic anhydride, which are not environmentally friendly. Thus, with a view to overcome the difficulties involved in the above methods involving corrosive acids, we have chosen an environmentally safe, benign catalyst namely K-10 montmorillonite to synthesis indole derivatives. This method has advantages over the conventional Fischer indolization routes from three perspectives. First, it would obviate the need to prepare or isolate potentially sensitive arylhydrazones. Second, it would provide a potentially general means to the requisite *N*-arylhya-zones for Fischer indolization from a single, commercially available precursor. Third, the crucial rearrangement proceeds under mild conditions to give carbazoles in moderate to excellent yields.

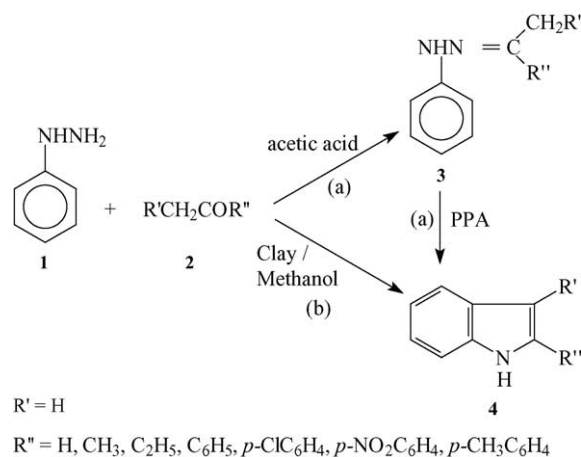
A survey of the literature has shown that the preparation of indoles from phenylhydrazones of aldehydes and ketones having α -methylene group has been carried out with the aid of a number of acidic reagents. However, the phenylhydrazones generally have undergone the reaction under the

influence of vigorous reaction conditions. For example, previous studies of cyclization of arylhydrazones involve difficulties associated with catalysts like PCl₃ and polyphosphoric acid, which are environmentally unfriendly, hazardous or difficult to handle, and also such catalysts are required in large amounts. PCl₃ is needed in equimolar amount, polyphosphoric acid in 8–9-fold excess by weight and zinc chloride is used in as large as 3-fold excess. Also Fischer indole synthesis to give indoles is unsuccessful with acetaldehyde with a variety of catalysts. A similar negative result is also obtained when the non-catalytic method using refluxing monoethyleneglycol is employed. Thus, in spite of the diverse synthetic routes developed so far, a more concise, environmentally friendly one-pot option that eliminates the potential hazards is desirable. In this context, there is no report on the use of acidic clay namely K-10 montmorillonite, which is a versatile solid acid catalyst. In order to test the utility of this catalyst, in the present study Fischer indole synthesis involving both cyclic and acyclic ketones is reported in the presence of solid acid catalysts, namely K-10 montmorillonite and H⁺- and Na⁺-exchanged montmorillonite clays (Scheme 1). This transformation has also been carried out using microwave irradiation.

2. Experimental

2.1. Preparation of the catalysts

K-10 montmorillonite (surface: 220–270 m²/g; bulk density: 300–370 g/l) was purchased from Fluka. Na⁺ exchange was carried out with a sample of 1 g of K-10 montmorillonite clay stirred with 25 mL of 1 M sodium chloride solution for 3 days and then filtered, and washed repeatedly with water to remove excess sodium chloride. It was then dried overnight in an oven at 90 °C. A similar exchange with HCl yielded H⁺-exchanged K-10 montmorillonite.



Scheme 1. Schematic representation of Fischer indole synthesis by (a) conventional method and (b) clay-catalyzed route.

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