



CLAY-SUPPORTED REACTIONS FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE MOLECULES

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Abstract:

Clay has been used successfully to perform diverse reactions to prepare a variety of organic compounds. In some instances, the acidity of the clay is responsible for the success of these reactions. Some reactions require clay in combination with other acidic catalysts.

Key words:Clay, Impregnated, Heterocycles and Microwave

Introduction:

Clay is a solid substance of phyllosilicate group. Two tetrahedral silica and octahedral alumina are the fundamental substances present in clay. It is formulated as sodium calcium aluminium magnesium silicate hydroxide $(\text{Na,Ca})_{0.33}(\text{Al,Mg})_2(\text{Si}_4\text{O}_{10})(\text{OH})_2 \cdot n\text{H}_2\text{O}$. Bentonite clay mostly consists of montmorillonite. Clay absorbs water efficiently.

Montmorillonite is stable, economical and readily available clay. In our research program, we conducted numerous montmorillonite-mediated reactions successfully. Many of these reactions were performed in dry conditions. Microwave-induced reactions were able to accelerate montmorillonite-induced reactions. In this perspective, some of our studies on clay-supported reactions are discussed.

Results and Discussions:

Solid surfaces act as Lewis acids or bases during the reactions. Montmorillonite, silica gel, florisil, molecular sieves and alumina are used. We have conducting research on the synthesis and biological evaluation of a number of organic compounds. These studies have identified medicinally active beta lactams, polyaromatic compounds and heterocycles. A concise description of some of the clay-induced methods that are developed in our laboratory is discussed.

Nitration of Aromatic Hydrocarbons:

Polyaromatic molecules are widely distributed in nature. To introduce nitrogen-containing functional group in the aromatic ring, the most widely accepted reaction is nitration. Electrophilic nitration of the aromatic hydrocarbon is an important reaction. This reaction requires strong nitric acid-sulfuric acid, fuming nitric acid or nitric acid-acetic acid, nitronium fluoborate and many other highly corrosive reagents.

Montmorillonite-impregnated with bismuth nitrate was able to nitrate aromatic hydrocarbons effectively. Naphthalene, anthracene, phenanthrene, pyrene, chrysene and dibenzofluorene were nitrated with montmorillonite-impregnated with bismuth nitrate at room temperature [1]. Ferric nitrate and cupric nitrate were also used, but the success of nitration was very weak. Silica gel and alumina were used as surface, but with poor results. The nitration of aromatic hydrocarbons was highly regiospecific. No other compounds were obtained.

Nitration of Estrogens:

Estrone and Estradiol have the ability to control fundamental functions of human life. Nitration of estrone with nitric acid was a difficult task and the synthesis of nitro derivative in good yield was not possible using this method. Montmorillonite-impregnated with bismuth nitrate was a suitable reagent for the nitration of estrone [2]. The activation created by the phenolic hydroxy group was helpful to obtain isomeric nitro estrones. Other side reactions did not take place.

The phenolic hydroxy group of estradiol is not active. Therefore, alkylation with a base and alkylating agent was not easy. But, nitro estradiol was alkylated without any problem in the presence of potassium carbonate and a side chain to produce phenolic ethers [3]. An oxidation of the aromatic system, alcoholic hydroxyl group or dehydration and further alkylation at the 5-membered ring of estradiol was not observed. These new compounds with the aromatic nitro group at the 3-position was active against a number of tumor cell lines.

Nitration of β -Lactams:

Montmorillonite-bismuth nitrate impregnated method was used to nitrate aromatic ring that are part in β -lactam ring. It was found that that *p*-anisyl group of a β -lactam ring is nitrated with this reagent without rupturing the ring [4]. This work was stimulating since nitric acid breaks the ring to form complex molecules. Oxidation of the *p*-anisyl ring to other products (quinones or N-unsubstituted β -lactam) was not detected. Non-activated other aromatic rings in β -lactams were not reacted.

Nitration of Eugenol:

Eugenol was nitrated to a single nitro compound with montmorillonite-bismuth nitrate [5]. The 4-position of the aromatic system with respect to methoxy group was nitrated. Phenolic hydroxy group had no effect. No oxidation of the aromatic rings, alkene group, dinitration or non-regioselective nitration was detected.

One-Pot Synthesis of β -Lactams:

In continuation of the beta-lactam research, montmorillonite was used for the preparation of imines derived from aromatic amines and aromatic aldehydes [6]. The reactants were mixed with montmorillonite without solvent. The time of the reaction varied because the reactivity of the amines and carbonyl compounds are not the same. Electron donating groups were able to accelerate while electron withdrawing groups retarded the formation of imines. This reaction clearly indicated that montmorillonite acts as a dehydrating agent by absorbing water.

3, 4-Disubstituted β -lactams by the reaction of the imine with acid chloride in the presence of a tertiary base was conducted. Acid chloride (acetoxyacetyl chloride, benzyloxyacetyl chloride, crotonyl chloride and phenoxyacetyl chloride) and triethylamine (or N-methylmorpholine) was added to the clay-containing imine and the reaction mixture was thoroughly mixed. The stereochemistry of the β -lactams was predictable. No differences of the configuration of the resulting products were seen from those reactions conducted following Staudinger cycloaddition reaction.

Glycosylations:

A facile montmorillonite-catalyzed or montmorillonite/bismuth nitrate was used for glycosylation of numerous alcohols with glycals derived from glucose [7]. Many catalysts or acidic reagents failed to produce products with galactose glycal even with favorable leaving group present in the nucleophilic compounds. However, alcohols react with galactose glycal in the presence of montmorillonite and produce glycosides.

Paal-Knorr Method:

Montmorillonite-mediated pyrrole synthesis by reacting primary amines and hexane 2, 5-dione was performed [8]. A nucleophilic reaction exerted by the amine on the keto group and subsequent dehydration was the mechanism of this process. The stronger basic amines were much more reactive in this reaction. The sterically hindered amines reacted slowly than non-crowded amines.

Oxidation:

Montmorillonite-impregnated bismuth nitrate was used to oxidize allylic and benzylic alcohols to carbonyl compounds. Bismuth nitrate alone was not effective [9]

Deprotection of Oximes:

Carbonyl compounds were regenerated from oximes with montmorillonite-supported bismuth nitrate. A molar proportion of bismuth nitrate was required. An excess amount of bismuth nitrate was required to deprotect oximes to carbonyl compounds in the absence of montmorillonite [10].

Reduction of Aromatic Nitro Compounds:

Clay-induced samarium metal-mediated reduction of aromatic nitro compounds to aromatic amines was achieved in good yield [11].

Synthesis of Enamines:

Enamine, the intermediate for ketone alkylation and acylation were prepared in the presence of clay [12]. The reaction was smooth and the yield of the product was very high.

Synthesis of Dihydropyridines:

The clay-mediated reaction was successful for the preparation of dihydropyridines in excellent yield [13].

Microwave-Induced Method:

Some of the reactions described herein with montmorillonite or montmorillonite-bismuth nitrate were performed in domestic and automated microwave oven. It was also found that montmorillonite-induced reactions under microwave were slower than montmorillonite-bismuth nitrate-induced microwave-mediated reactions. Although the cause of rate acceleration by montmorillonite-bismuth nitrate under microwave or without microwave was not studied systematically, we believe the free hydroxyl group present in montmorillonite can bind bismuth nitrate very effectively. As a result of this binding synergistic effects were possible. It appeared that the montmorillonite-bound reactants or montmorillonite-bismuth nitrate-bound reactants react at a much faster rate than those reactions in which such a suitable solid surface is absent [14].

Conclusion:

We demonstrated montmorillonite-supported diverse reactions for the synthesis of compounds under environmentally benign conditions. Most of the montmorillonite-mediated reactions produced required products in excellent yields. Some of the products as described herein are medicinally active.

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