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MY SILVER JUBILEE WITH BISMUTH SALTS

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Abstract:
Our research group has studied bismuth salts-mediated reactions extensively for the synthesis of diverse organic molecules of medicinal significance. These reactions performed with bismuth salts are environmentally benign. Bismuth salts are capable of releasing acids during the course of the reactions. Nitrate salt generates cationic nitronium ion as an electrophile. These salts are suitable to act as Lewis acids in these reactions too. These properties are exploited in the synthesis of versatile organic molecules in chiral and achiral forms in our research laboratory.

Key Words
Bismuth Salts, Catalysis, Organic Synthesis, Environmentally Friendly

Introduction:

Our bismuth salts-mediated reactions have started more than 25 years ago. These methods have proved to be extremely rewarding and challenging since then. Bismuth salts produce products through acid-induced process. They generate mineral acids in the reaction media and or co-ordinate with electronegative atoms. Because of the bigger size, bismuth is not bound to anions very tightly. Thus, in the present of solvents or under forcing conditions, acids are generated from most of the available bismuth salts. The vacant 6p-orbital present in bismuth is used by electronegative elements through coordination, if necessary. Bismuth salts-induced chemical reactions are reviewed [1a-c]. The principal aim of this perspective is to highlight bismuth salts-induced reactions that our laboratory has conducted for the 22 years.

Nitration of Aromatic Compounds:

Aromatic nitration is a crucial reaction in chemistry. Therefore, many methods are known for this purpose. A facile and simple method of aromatic nitration with bismuth nitrate impregnated with clay was developed [2a-2f]. This reaction proceeded well at high temperature or under microwave. The regioselectivity of bismuth nitrate-mediated nitration was identical with the other known methods. The nitration was then extended to nitrate the aromatic rings present in β-lactams. Nitration of the aromatic group present at the N- of the β-lactam ring proceeded well using bismuth nitrate-impregnated with clay under the influence of microwave. In some examples, a dinitro compound was also obtained. An extension of this method was performed with eugenol and the reaction gave a nitro compound [3a-3b]. No isomerization of

the alkene group was observed in this reaction. The nitration was conducted with estrone and estradiol. The reaction of estrone produced 2-nitro and 2, 4-dinitro estrone. Oxidation of the aromatic ring was not noted. Dinitroestradiol was not formed. This method avoids the use of corrosive nitric acid.

Indoles and Azaindoles:

A reaction of indole with carbonyl compounds using bismuth nitrate produced bisindoles [4a]. The reaction proceeded well with activated ester containing compound [4b]. Using this method, *bis*-azaindole was prepared in god yield [5]. The reaction followed an electrophilic mechanism.

Protection of Carbonyl Compounds:

The carbonyl compounds were protected easily as acetal, ketal, thio ketal and mixed ketals following microwave-mediated reaction using bismuth nitrate as the catalyst [6]. It was demonstrated that protection of aldehyde groups was faster than that of the ketones. Acetal group protection was faster than other groups of protection.

Deprotection of Oximes and Hydrazones:

Oximes and hydrazones were deprotected to their carbonyl compounds using bismuth nitrate-induced microwave-mediated reactions. However, oxime and hydrazone deprotection reactions took longer time then acetal and ketal deproection. These reactions demonstrated excellent intramolecular chemoselectivity [7].

Enamination:

Reaction of amines with β-dicarbonyl compounds in the presence of catalytic amounts of bismuth nitrate without solvent under microwave irradiation afforded the products in good yield [8].

Oxidation:

Oxidation of various alcohols, for example, primary, allylic and benzylic alcohols were performed with bismuth nitrate as the catalyst under mild condition. This method was applied for the oxidation of baccatin to 13-keto baccatin which is the core of Taxol. Oxidation of benzylic methylene group to benzylic ketone connected to multiple aromatic rings was performed by sodium bismuthate and bismuth nitrate. These reactions proceeded well in the presence of microwave irradiation. Many polyaromatic ketones were synthesized using this reagent combination. Bismuth nitrate-mediated microwave-induced synthesis of vanillin from curcumin was developed [9].

Carbohydrates:

Glucose was converted to glucose per-*O*-acetate using acetic anhydride and catalytic amounts of bismuth nitrate under microwave irradiation [10a]. This peracetylation of glucose proceeded through a coordination of bismuth nitrate with acetic anhydride [10b]. Following this method, glycosyl chloride using a combination of bismuth chloride and bismuth nitrate was synthesized [11].

Hydrolysis of amide:

Oxidation of polyaromatic compounds was conducted with sodium bismuthate under microwave-mediated irradiation method. In contrast, reaction of the same compound with bismuth nitrate produced amine [12].

Pyrrole-Susbtituted Dihydroindole:

The keto-group of isatins was reactive and it was used to make pyrrole-substituted dihydroindole using bismuth nitrate-catalyzed microwave-induced method. Reaction of isatin and its derivatives with hydroxy proline in presence of bismuth nitrate produced pyrrole-substituted dihydroindole as the only product [13].

Paal Knorr Reaction: Synthesis of β-Lactams:

A simple method for the synthesis of *N*-substituted pyrroles by reacting 2, 5-dimethoxytetrhydrofuran and amines (Clauson-Kaas reaction [14], a modified Paal-Knorr method) in the presence of bismuth nitrate under microwave irradiation was developed. Reaction of 3-keto-β-lactam with *trans*-hydroxy proline with bismuth nitrate under microwave irradiation produced two optically active pyrrole-substituted β-lactams [15a]. This method was extended for the chiral synthesis of novel pyrrole-susbtituted β-lactams [15b-c].

Octahydroxanthenes:

Octahydroxanthenes were prepared by reacting 1,3-cyclohexanedione with different aldehydes using several bismuth (III) salts as a catalyst. Bismuth iodide was proved to be the best catalyst for this method [16].

Michael Reaction:

Bismuth nitrate was used for a facile Michael reaction with indoles, pyrroles, carbamates, and heterocyclic amines [17a]. The reaction occurred at the 3-position of indole system. Pyrroles produced 2-substituted compounds in good yield. Importantly, this reaction proceeded with electron deficient carbamates. Attempted reaction of carbamates with various Lewis acids either failed or produced products in low yield. The success of this reaction helped to understand the coordinating role of bismuth with the oxygen. This reaction was conducted in aqueous media and in the presence of ultrasound [17b-17d].

Hantzsch Reaction:

Numerous dihydropyridines were synthesized following microwave-induced bismuth nitrate-mediated reaction of amines, aldehydes and dicarbonyl compound under solventless conditions. The oxidation to pyridines was not observed [18].

Biginelli Reaction:

Microwave-mediated bismuth nitrate-induced synthesis of dihydropyrimidones following Biginelli reaction was developed [19]. Reaction of aldehyde, urea and dicarbonyl compound with bismuth nitrate under microwave irradiation produced dihydropyrimidines in excellent yield.

Ferrier Rearrangement:

Bismuth triflate-catalyzed microwave-mediated process for the preparation of both enantiomers of thienamycin side chain was developed. The reaction of hydroxyethyl group present in racemic thienamycin side chain was performed with sugar derivative using bismuth triflate. Two glycosides were formed and these on separation and acid-induced process produced chiral isomers of thienamycin side chain [20].

Peachman Condensation:

Pechman condensation reaction is an important method for the synthesis of coumarin [21]. Bismuth nitrate-catalyzed reactions and microwave-induced method was used for a facile Pechmann condensation toward a few coumarin compounds.

Diels-Alder Reaction:

Diels-Alder reaction is used for the preparation of polycyclic systems starting from dienes and dienophiles. Tricyclic molecules were prepared using imines derived from citranellal and aromatic amines in the presence of bismuth nitrate under microwave-induced reactions [22].

Quinoxalines, Quinolines, Polyhydroquinolines, Benzimidazoles and Amino Phosphonates:

An excellent and environmentally friendly method for the preparation of quinoxalines and *bis*-quinoxalines was realized by reacting *o*-phenylene diamines with 1,2-dicarbonyl compounds using 5 mol% of bismuth nitrate under microwave irradiation. A number of bismuth salts (bismuth chloride, bismuth triflate, bismuth iodide, bismuth subnitrate, bismuth bromide, and bismuth nitrate pentahydrate) were used in cataylyic amounts for this purpose.

An efficient microwave-induced bismuth nitrate-catalyzed method for the preparation of quinolones was developed. The amino ketone was mixed with ketone in the presence of

bismuth nitrate and then the reaction mixture was irradiated in a domestic microwave oven. A green method for the synthesis of substituted polyhydroquinolines using bismuth nitrate, in aqueous medium under sonochemical irradiation was developed. A coupling reaction of a diamine with aldehyde using bismuth nitrate and oxidation of the carbon-nitrogen bond to benzimidazole derivatives was performed. Bismuth halides, bismuth triflate, bismuth subnitrate, and bismuth nitrate pentahydrate were used in automated CEM microwave irradiation conditions and bismuth nitrate pentahydrate was found to be the best. Using this method, amino phosphonates were prepared [23].

Conclusions:

Bismuth salts-induced reactions have become a powerful method for the synthesis of diverse compounds of medicinal significances. Many bismuth nitrate-induced processes can be highly accelerated using domestic and automated microwave irradiation under solventless reaction conditions. Mechanistically, bismuth nitrate or bismuth triflate released nitric acid or triflic acid in the media during the reaction. A direct coordination of bismuth to the electronegative atom was observed in NMR study. Synthesis of intermediates for biologically active molecules is presented here. Many products as described herein can be used to prepare other molecules of complex structures.

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