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VERSATILE BISMUTH SALTS-INDUCED REACTIONS FROM OUR LABORATORY: A PERSPECTIVE

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Abstract:

Bismuth salts-mediated reactions are developed for the synthesis of diverse organic molecules of medicinal significance. Reactions conducted with bismuth salts are environmentally friendly and these may proceed due to the release of acids in the media. Bismuth salt may also act as a Lewis acid in these reactions. Versatile organic molecules in chiral and achiral forms are synthesized using bismuth salts-induced reactions at our research laboratory.

Key Words

Bismuth salts, Catalysis, Synthesis

Introduction:

Our bismuth salts-mediated reactions have started more than 22 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 presence 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 [1–3]. 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 [4–8]. 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 [9]. An extension of this method was performed with eugenol and the reaction gave a nitro compound [10]. 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 [10]. Dinitroestradiol was not formed [11].

Indoles and Azaindoles:

Reaction of indole with carbonyl compounds in the presence of bismuth nitrate produced bisindoles [12a]. The reaction proceeded well with activated ester [12b]. Using this method, *bis*-azaindole was prepared [13]. The reaction followed an electrophilic process.

Protection of Carbonyl Compounds:

The carbonyl compounds were protected as acetal, ketal, thio ketal and mixed ketals with equal success following microwave-induced reaction using bismuth nitrate as the catalyst [14]. These studies uncovered a few basic principles. It was demonstrated that protection of aldehydes was faster than the ketones. Acetal protection was faster than other forms of protection.

Deprotection of Oximes and Hydrazones:

Oximes and hydrazones were deprotected to carbonyl compounds using bismuth nitrate-catalyzed microwave-induced reactions. In general, oxime and hydrazone deprotection reactions took longer time than an acetal and ketal deprotection. Nevertheless, these reactions were useful to create intramolecular chemoselectivity[15].

Enamination:

Reaction of amines with β -dicarbonyl molecules in the presence of catalytic amounts of bismuth nitrate in the absence of any solvent under microwave irradiation afforded the product [16].

Oxidation:

Oxidation of various alcohols, for example, primary, allylic and benzylic alcohols were performed with bismuth nitrate as the catalyst under very mild condition. This method was applied for the oxidation of baccatin to 13-keto baccatin which are highly functionalized. Oxidation of benzylic methylene groups to benzylic ketone was performed by sodium bismuthate and bismuth nitrate. These reactions proceeded well in the presence of microwave irradiation. Several polyaromatic ketones were prepared using this reagent combination. Bismuth nitrate-induced microwave-assisted synthesis of vanillin from natural spice, curcumin was developed. Selective oxidation of curcumin to vanillin was an important observation [17].

Carbohydrates:

We found that glucose can be converted to glucose per-*O*-acetate using molar proportion of acetic anhydride and catalytic amounts of bismuth nitrate under microwave irradiation [18a]. We believed peracetylation of glucose proceeds through a coordination of bismuth nitrate with acetic anhydride [18b]. In continuation of our work in this area, we prepared glycosyl chloride using a combination of bismuth chloride and bismuth nitrate [19].

Hydrolysis of amide:

Oxidation of polyaromatic compounds was performed with sodium bismuthate under microwave-mediated irradiation method. In contrast, reaction of the same compound with bismuth nitrate produced amine [20].

Pyrrole-Substituted Dihydroindole:

The keto-group of isatin derivatives was very reactive and it was used to prepare pyrrole-substituted dihydroindole through bismuth nitrate-catalyzed microwave-induced method. Reaction of isatin and its derivatives with hydroxy proline with catalytic amounts of bismuth nitrate under refluxing ethanol for 6h produced pyrrole-substituted dihydroindole as the only product [21].

Paal Knorr Reaction: Synthesis of β -Lactams:

We developed a simple method for the preparation of *N*-substituted pyrroles by reacting 2, 5-dimethoxytetrahydrofuran and amines (Clason-Kaas reaction [22], a modified Paal-Knorr method) in the presence of bismuth nitrate under microwave irradiation. Reaction of 3-keto- β -lactam with *trans*-hydroxy proline in the presence of bismuth nitrate in ethanol under microwave irradiation produced a mixture of two optically active pyrrole-substituted β -lactams [23a]. Chiral synthesis of novel pyrrole-substituted β -lactams was developed [23b].

Octahydroxanthenes:

Reaction of 1,3-cyclohexanedione with different aldehydes using several bismuth (III) salts as a catalyst was performed. Bismuth iodide in the absence of solvent was proved to be the best catalyst for this purpose [24].

Michael Reaction:

Our endeavor with bismuth nitrate demonstrated a facile Michael reaction with Indoles, pyrroles carbamates, and heterocyclic amines [25a]. The reaction took place at the 3-position of indole system. The reaction proceeded at 2-position with 3-substituted indole. Pyrroles produced 2-substituted products in excellent yield. Interestingly, this reaction proceeded with carbamates which were electron deficient. Reaction of carbamates with other Lewis acid either failed or produced products with very low yield. On this basis, the theory of coordination of bismuth with the oxygen was further strengthened. However, the coordinating effect of bismuth with the oxygen was very high due to its bigger size. This reaction was conducted in water and in the presence of ultrasound [25b-25d].

Hantzsch Reaction:

Numerous dihydropyridines were prepared following microwave-induced bismuth nitrate-catalyzed reaction of amines, aldehydes and dicarbonyl compound under solventless conditions. The crucial part was that oxidation to pyridines was not observed [26].

Biginelli Reaction:

Microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones following Biginelli reaction was developed [27]. Reaction of aldehyde, urea and a dicarbonyl compound in the presence of catalytic amount of bismuth nitrate under microwave irradiation produced dihydropyrimidines in excellent yield.

Ferrier Rearrangement:

We developed bismuth triflate-catalyzed microwave-induced method for the preparation of both enantiomers of thienamycin side chain, The reaction of hydroxyethyl group present in racemic thienamycin side chain was performed with glycal in the presence of bismuth triflate and two glycosides were formed in almost equal ratios [28].

Pechman Condensation:

Pechman condensation reaction is the most important reaction for the synthesis of coumarin [29]. In continuation of our research on bismuth nitrate-catalyzed reactions and microwave-induced method we reported a facile Pechmann condensation toward a few coumarins.

Diels-Alder Reaction:

Diels-Alder reaction is used extensively for the construction of several polycyclic systems starting from dienes and dienophiles. We prepared tricyclic molecules using imine derived from citranellal and aromatic amines in the presence of catalytic amounts of bismuth nitrate under microwave-induced reactions [30].

Quinoxalines:

To overcome these limitations, an excellent and environmentally friendly procedure for the synthesis of quinoxalines and *bis*-quinoxalines was developed by reacting *o*-phenylene diamines with 1,2-dicarbonyl compounds using catalytic amount (5 mol%) of bismuth nitrate under microwave irradiation [31]. A number of bismuth salts, e.g., bismuth chloride, bismuth triflate, bismuth iodide, bismuth subnitrate, bismuth bromide, and bismuth nitrate pentahydrate were used in catalytic amounts in a reaction between *o*-phenylene diamine and phenyl glyoxal monohydrate ethanol under automated CEM microwave irradiation conditions.

Quinolines:

We developed an efficient method of microwave-induced bismuth nitrate-catalyzed method for the synthesis of quinolones. The amino ketone was mixed with ketone in the presence of bismuth nitrate pentahydrate very thoroughly and then the reaction mixture was irradiated in a domestic microwave oven.

Polyhydroquinolines:

As a part of our ongoing research for the development of green strategies to target novel pharmacophores, a green and expeditious method for the synthesis of diversely substituted polyhydroquinoline derivatives using bismuth nitrate pentahydrate, in aqueous medium under sonochemical irradiation at room temperature was developed.

Benzimidazoles:

Our method depended on a coupling reaction of a diamine with aldehyde using bismuth nitrate under microwave irradiation and oxidation of the carbon-nitrogen bond to benzimidazole derivatives. Bismuth iodide, bismuth bromide, bismuth chloride, bismuth triflate, bismuth subnitrate, and bismuth nitrate pentahydrate were tested in automated CEM microwave irradiation conditions (300 Watts, 80°C, 5 min) and bismuth nitrate pentahydrate (10 mol%) was found to be the best.

Conclusions:

Bismuth salts-mediated reactions have become a powerful tool for the synthesis of diverse compounds of medicinal and pharmaceutical significances. It has been shown that many bismuth nitrate-induced processes can be highly accelerated using domestic and automated microwave irradiation and under solventless reaction conditions. Mechanistically, it appears bismuth nitrate or bismuth triflate released nitric acid or triflic acid in the media during the reaction. However, this argument can also be challenged in reactions where direct coordination of bismuth to the electronegative atom was observed in NMR study. In many instances, synthesis of an intermediate for biologically active molecules is presented. Many products obtained from this study can be used to prepare other molecules of interests.

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