Molecular Iodine-Catalyzed Reactions

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In continuation of our research on the synthesis of diverse organic molecules, we report here molecular iodine-catalyzed diverse synthetic processes. These methods are efficient and produce products in high yield. The success of molecular iodine-catalyzed reactions depends on the release of hydroiodic acid in the reaction media.

Molecular Iodine | Catalysis | Synthesis | Organic Compounds

Introduction

Catalytic methods are crucial in organic synthesis. Due to the demand of the catalytic procedures, scientists are developing new procedures. We have been conducting molecular iodine-catalyzed reactions for the preparation of diverse organic molecules. Notably, synthesis of compounds in optically active and achiral form is performed by iodine-catalyzed reaction. In addition, almost all iodine-catalyzed processes are performed successfully using microwave. A few important reactions that are developed in our laboratory are discussed here.

Results

The principal goal of our research is to develop organic compounds as anticancer and antibacterial agents. Important pertinent reactions are investigated to prepare diverse analogues. In some instances, mechanism of the reactions is discussed to explain the formation of products. To know the each individual subjects in great detail, related papers and references cited therein can be consulted.

Glycosylation

A nucleophilic reaction of alcohol with substituted carbohydrate in the presence of a catalyst is important because of the medicinal properties of O-glycosides. This reaction may produce products through multiple mechanisms. Therefore, this process may proceed through a stereoselective or non-stereoselective pathways. Moreover, this method may become an asymmetric process because of the chirality present in the carbohydrate.

A molecular iodine-catalyzed reaction of hydroxyl beta lactam with substituted glycal was performed. This reaction produced two separable O-glycosides sterospecifically [1]. The success of the reaction depends on the

stereochemistry of the hydroxyl beta lactam and nature of the glycal. For example, *cis* hydroxyl beta lactams react with D-glycal protected with acatoxy group. Such a reaction with *trans* hydroxyl beta lactam was not successful. However, the *trans* compound reacted with a glycal obtained from a L-sugar. After separation of the isomeric glycosides, O-glycoside linkage was removed by aqueous acid solution to the respective hydroxy beta-lactams in enantiomeric forms. After realization of this objective, this method was used for the preparation of four enantiomeric forms of 3, 4-disubstituted beta lactams. Application of this method was successful in the synthesis of Taxol and Thienamycin side chains. Iodine-catalyzed glycosylation reaction was successful in the presence of acid-sensitive functional groups.

Mechanistically, a formation of an oxonium cation was suggested. The attack of hydoxy beta lactam to the glycal was only possible from the axial side of the cation due to severe repulsive electronic effects of the sugar ring oxygen and the oxygen of the alcohol component. The stereochemistry of the glycosides was confirmed by conducting hydrogenation experiment and preparing saturated derivatives. During hydrogenation experiment, a number of new observations were noted. Allylic deacetoxylation and reductive cleavage were observed in some instances.

Pyrroles

Molecular iodine-catalyzed reactions of primary amine with hexane 2,4-dione produced N-substituted pyrroles. Aromatic and aliphatic primary amino compounds produced pyrroles in good yield. A high basicity of the amines was helpful for the success of this reaction. On this basis, electron donating groups in the aromatic rings assisted the reactions favorably. Sterically hindered primary amines reacted slowly compared to the amines which were not crowded. The mechanism of this process was not established. It was speculated that the reaction proceeds through the protonation of the carbonyl group and the liberated hydroiodic acid is responsible for this attack [2]. After the initial protonation, nucleophilic attack by the amino group was highly possible. A series of intermediate steps finally produced pyrroles in excellent yield. Pyrroles-fused with beta lactams were prepared following this method.

Protected Carbonyl Compounds

Protection and deprotection of the aldehydes and ketones are important chemical methods in synthetic organic chemistry. Mild acidic reagents were found to catalyze acetal, ketals, thioketals, and mixed ketals formation. Molecular iodine was found to catalyze these processes very well [3]. Methanol, ethanol, ethylene glycol, ethylene thiol, ethylene thioalcohol were used as the other starting compounds in anhydrous tetrahydrofuran, dichloromethane, dioxane, and dimethylsulfoxide. Most of these processes were successful at room temperature. Intramolecular selectivity of protection was achieved in certain examples. Reactive and less sterically hindered carbonyl groups were protected preferentially.

Deprotection of the acetal, ketal, thioketal and mixed ketals were performed with molecular iodine [4]. Compounds with these types of protective groups yield the original carbonyl compounds in the presence of iodine. This was possible because protection and deprotection of aldehydes and ketones are reversible reactions.

Protection and deprotection reactions with molecular iodine were used in beta-lactam chemistry. These methods were necessary for preparation of amino sugars, amino acids, alkaloids and polycyclic beta-lactams.

Condensed Heterocycles

Molecular iodine was successful in catalyzing the reaction between isatin and hydoxyproline derivatives to form pyrrole-fused oxoindoles in high yield [5]. It was believed that the amino acid group of proline reacted with the keto group of isatin and formed a cyclic intermediate. This unstable intermediate then finally produced the product through the activation exerted by iodine. It was remarkable that the iodine-catalyzed reaction between 3-keto-beta lactams on reaction with hydroxy proline produced 3-pyrrole substituted beta lactams [6]. Several optically active beta lactams with defined absolute stereochemistry were prepared by this method. The stereochemistry of the hydroxyl proline was able to influence the configuration of the products.

Samarium-Induced Reactions

Samarium-induced chemistry in the presence of iodine was useful to study reduction of carbonyl compounds and imines and reductive dimerization of carbonyl compounds and imines. These reactions did not proceed in the absence of iodine [7]. The success of these reactions was not due to the formation of bivalent samarium species. The course of samarium diiodide-mediated reaction in many of these example was different. Such dimerization by samarium metal-iodine induced reactions produced specific ratios of dl and meso compounds.

Alkaloid Synthesis

Molecular iodine was able to catalyze Michael reaction between indoles and 2, 3-unsatuated carbonyl compounds in excellent yield in the absence of any solvents [8]. A variety of substituted indoles were used with success. An extremely rapid and convenient microwave-assisted method for the synthesis of indoloquinolines using molecular iodine as a catalyst in one-pot was developed [9]. The mixture of indole-3-carboxyaldehyde and two equivalents of aniline in presence of 10 mol% of iodine produced indoloquinolines. An effective iodine-catalyzed method for the synthesis of quinoxalines by the condensation of 1,2-diamines with 1,2-dicarbonyl compounds was developed [10].

Optically Active Polyaromatic Alcohol

Racemic dibenzofluorenol on reaction with a glycal in the presence of catalytic amounts of iodine afforded two diastereomers. These were separated and cleaved to the optical isomers of dibenzofluorenol [11]. Our laboratory had demonstrated synthesis and studied biological activity of polyaromatic compounds for the past many years [12].

Microwave-induced, Green Chemistry and Catalytic Method

The reactions described above were conducted under microwave irradiation method [13]. It was crucial to observe that all these reactions were successfully performed in domestic or automated microwave oven. In some example, limited amount of solvent was used. Solventless reactions were also performed with equal success. Clearly the microwave-induced iodine-catalyzed method was very fast, economical and produced products with better purities. Several of the above methods and related procedures were also performed following green chemistry and catalytic principles [14][15].

Conclusion

We demonstrated iodine-catalyzed reactions for the synthesis of diverse compounds. Most of the iodine-catalyzed reactions as described above produced products with high yields. Isolation of products from the reaction mixture was very convenient. Some reactions proceeded in the absence of any solvent with 1 mol% iodine. Considering the budgetary restrictions, our iodine-catalyzed reactions are the perfect examples to cut down the cost of research maintaining the standard of good publications. In addition, it was also found that iodine-catalyzed reactions can tolerate microwave-irradiation. On this basis, some of the iodine-catalyzed reactions under microwave irradiation were completed within minutes instead of hours/days. A few compounds prepared by iodine-catalyzed reactions demonstrated anticancer and antibacterial activities [14].

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