Iodination of activated aromatics by using I2/ HNO_3/AcOH

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Abstract

A new reagent system consisting of I2/ HNO3 in AcOH has been found to be effective in iodinating a variety of commercially important substrates under ambient conditions. The Process leads to high yields (90-98%) at room temperature in a short reaction time. A remarkable feature of this system is that even acid sensitive functionalities like anilines can be iodinated quantitatively.

Keywords: Iodination, Aromatic, Iodoarenes, Regiospecific

Introduction

Iodination of organic compounds and the chemistry of organic iodides are of interest as they find various commercial applications.[1-2] They are able to form a large variety of stable aromatic polyvalent iodine compounds, which have found increasing application in modern synthetic procedures.[3] Also aromatic iodides have long been used in organic synthesis as versatile intermediates that can be transformed into a variety of functional groups.[4] They can be easily functionalized through metal catalyzed cross coupling reactions[5] in the synthesis of many interesting natural products[6] and bioactive materials.[7] Iodoaromatic compounds are used in medicine as drug or diagnostic aids, contractors [8] and radioactively labeled markers. They also have importance in medicinal and pharmaceutical research.[9] Finally, iodo-aromatic compounds are also been used in medicine as, biochemistry, many pharmaceuticals, metabolism, radiolabelling studies, nuclear magnetic imaging, radioimmunoassay studies, dyestuffs, organic electroluminescent, electrophotography, agricultural chemicals, antimicrobial, antibacterial, and antifungal agents. However, the low electrophilic nature of the molecular iodine compared to the molecular bromine and chlorine difficult direct iodination. The direct iodination is also hampered by the formation of HI which can cause protolytic cleavage of sensitive compounds. Hence many different synthetic methods (direct and Indirect) or their improvements have been reported for effective preparation of aryl iodide. [10]

Iodination of activated aromatic compounds has been carried out by using molecular iodine or iodide ions together with an oxidizing agent such as $ICl/in(otf)_3$[11], NIS/CF_3CO_2H[12], $NaOCl/NaI$[13], NH_4I/Oxone[14], HIO_4/H_2SO_4[15], $ICl/Ag_2SO_4/H_2SO_4$[16], I_2/NO_2[17], $KMNO_4/H_2SO_4$[18], Iodine-monochloride[19], bis(Pyridiodium(1) tetrafluoborate CF_3SO_3H[20], I_2/HgX_2[21], NIS/CF_3SO_3H [22],CF_3COOAg/I_2[23], I_2/I_2O_5[24] , NaIO4/KI/NaCl[25]. However most of these procedures suffer from major disadvantages like poor yields, long reaction time, harsh reaction conditions, and use of hazardous or toxic reagents, hence questioning the suitability for commercial production. Despite the availability of various reagents for iodination low selectivity and formation of undesired side products under mild reaction conditions continue to be problematic. There is a need to find an alternative procedure which is clean, efficient, regioselective simple to work up and cost effective. In the present investigation a new approach has been designed for the preparation of iodo-organics using molecular Iodine (I_2) as an iodinating agent and HNO_3 as oxidant and after the iodinated products in one pot reaction giving good yields . This process occurs at room temperature, within a shorter period of time, easily workable, thus minimizing the cost of production of iodoaromatics. Encouraged by the above advantages the iodination of some commercial important substrates

in good yields using I_2/HNO3 as the reagent is being reported. The results are summarized in Table-1.

Results and Discussion

when the iodination of 4-nitroaniline was carried out with I_2 as the iodine source, and HNO3 as the oxidant in AcOH . Iodination occurred within 4 hrs at room temperature to give 2-iodo-4-nitroaniline in 89% yield. 2-iodo-4-nitro aniline has been found useful in the treatment of ubiquitin conjugation associate disorder particularly hyper proliferative disorder. [24] Johnson et al[25] have reported the formation of 2-iodo-4-ntroaniline at 0^oC with a reported yield 70%. This shows that present method is more useful. To establish the scope of the methodology, we subjected a variety of activated aromatic compounds to nuclear iodination. As can be seen, activated aromatic compounds were converted to mono or poly-iodo aromatics in quantitative yields within a short period of time at room temperature. The iodination of vanillin (1.b) affording 5-iodovaniline in good yield 80 % with no detectable ortho or para compounds, 5-iodovaniline is widely used as aqueous ink composition in ink jet printer which gives reliable printing performance and rapidly drying printed images.[21] Kometani et al have reported preparation of 5-iodovaniline at 0^oC, in 3hrs. Phenol (1.d) shows a much greater reactivity and were triiodonated affording the 2,4,6-triiodophenol in excellent yields (82%). Emmanuvel et al[23] have reported that 2,4,6-tri-iodophenol formation under harsh reaction condition(50^0C) .Kometani et al have reported 2, 4, 6-triiodophenol at 0^oC in 3h. 2,4,6-triiodophenol is used as a potent anti-inflammatory and analgesic and at the same time as a potent antiantherosclerotic hypocholesteronemic, hypolipemic, vasodilator and fluidifying aggregate agent. Deactivated anilines (1h,1c,1a) were smoothly iodinated to their iodo derivatives in good yield. Another commercial important compound 3, 5-diiodosalicyclic acid (1.c) was also prepared in excellent yield (85%) in 4hrs at room temperature from salicylic acid. This substrate undergo iodination at high temperature and longer reaction time**.** The product (1c) acts as an intermediate for veterinary anthelmintic agents. The iodination of acetanilide (1.j) was also carried out under similar reaction condition and p-iodoacetanilide was obtained in excellent yield (92 %). It is used as intermediate for medical drugs, agricultural chemical,dyestuffs, photosensitive material etc. Yushbov et.al have reported synthesis of 4-iodoacetanilide under very harsh condition(105^0C) and reported poor yield(47%). The iodination of 2-nitroaniline (1.h) was carried out at room temperature giving excellent yield 90%. It is used for making proton conducting membranes in fuel cell.Emmanuvel et.al [23] have reported the formation of 4-iodo-2-nitroaniline in excellent yield but using longer duration (8hrs).

Conclusion

It can be concluded that I_2/HNO3 act as an efficient iodinating agent for a variety of organic molecules. This method can be performed in acidic condition providing a practical alternative to other procedures by avoiding the use of harsh reaction conditions like high temperature, long reaction time, costly metal catalyst, and problematic halogenated solvents. Furthermore, ambient conditions and simple work-up, procedure and commercially viable route for synthesis of iodo-organics make present method an attractive procedure in comparison to other iodination protocols.

Experimental

Typical Procedure for Iodination

Preparation of 4-Iodoacetanilide (1.d)

Into a100 ml round bottom flask were charged acetanilide (0.01 mol) and AcOH (10 ml), Iodine 0.01 mole) and HNO3 (2ml) solution was added rapidly to the acetanilide. The reaction mixture was stirred at 30^{o}C. The reaction was monitored using TLC. After completion of the reaction the mixture was poured into ice-cold water to precipitate the product. The precipitated mass was separated from the mother liquid by vacuum filtration utilizing a Buchner funnel and then washed twice with deionised water and dried. The total isolated yield was 92%.

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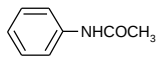
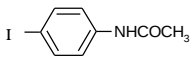
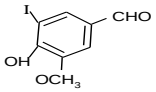
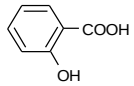
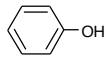
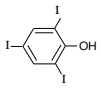
Table 1 : Iodination of aromatic compounds by I_2/HNO3/AcOH

Entry	Substrate	Product	Time(hrs)	Yield(%)
1			4	92
2.			4	80
3			4	85
4			4	82
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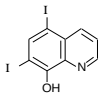
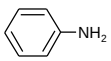
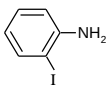
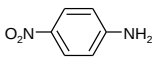
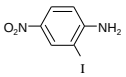
6			4	46
7			4	80
8			4	90
9.			4	89