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Utility of iodine catalyzed tandem oxidation, cross-coupling and cyclisation reactions in organic synthesis

Titas Biswas[1]* and Swapan Kumar Biswas[2]

[1]Department of Chemistry, Gurudas College, Kolkata-700054, West Bengal, India; [2]Department of Chemistry, Sree Chaitanya College, Habra, North 24 Parganas, West Bengal, India

E-mail/Orcid Id:

TB: titas.biswas@gmail.com; https://orcid.org/0000-0001-7926-9106; *SKB:* swapaniict@gmail.com, https://orcid.org/0000-0002-2757-7702

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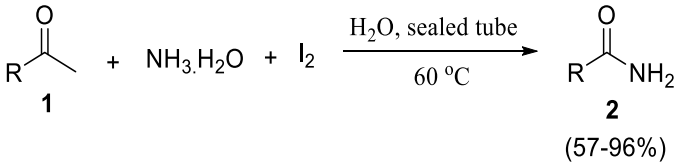
Abstract: Molecular iodine is an eco-friendly, powerful catalyst and plays an important role in pharmaceutical, medicinal and organic chemistry. For a long time, molecular iodine has been hugely applied in carbohydrate chemistry. Due to the huge application of molecular iodine in oxidation, cross coupling and cyclisation reactions, it has emerged as an elegant tool in organic synthesis. Earlier I discussed (Biswas, 2021) on iodine mediated cascade oxidative functionalisation, cyclisation and annulation reactions. In this review, I describe the utility of iodine catalysed tandem oxidation, cross coupling, and cyclisation reactions in organic synthesis. Molecular iodine catalysed mild oxidative conditions yielding desired products, and oxidising techniques applied to the efficient synthesis tolerate a wide range of starting materials with aryl or alkyl replacements. These reactions were carried out as a one-pot or multi-step eco-friendly process that could be used for a wide range of drug and pharmaceutical product synthesis.

Introduction

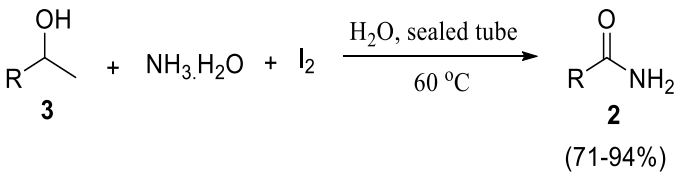
Since molecular iodine is the weakest oxidizer among the halogens, it is a more selective and efficient reagent for oxidation. Furthermore, molecular iodine is noncarcinogenic, readily available, inexpensive and a benign reagent. Due to the versatile character of molecular iodine, it has been playing an important role in organic synthesis since its discovery. Iodine mediated reactions are classified into three categories; iodine mediated domino reactions, iodine mediated tandem reactions and iodine mediated cascade reactions. This review describes the utility of iodine catalysed tandem oxidation, cross-coupling and cyclisation reactions. Iodine mediated tandem reactions are very useful to synthesize amide, imide, polyenicdiones, unsymmetrical 1, 4-enediones, oxidative cyclisation and various heterocyclic compounds.

Synthesis of amide and imide derivatives

Cao et al., (2009) developed a synthetic strategy for preparing primary amides from the direct transformation of structurally different methyl ketones (aryl, heteroaryl, vinyl, or ethynyl) in good yield (57-96%, Scheme 1). This strategy also converts secondary alcohols to primary amides in good yield (71-94%, Scheme 2). The reaction between ketone (1), ammonia and molecular iodine in water in a sealed tube at 60ºC temperature furnishes the corresponding amide (2) with a good yield. The same reaction condition is applied by taking secondary alcohol (3) instead of ketone to provide the amide (2) in good yield.



Scheme 1. Preparation of primary amide from ketone.

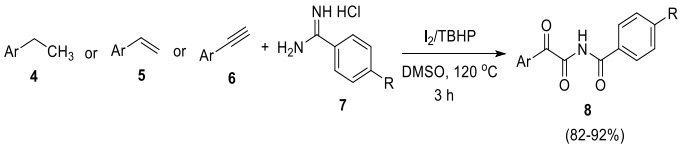


Scheme 2. Preparation of primary amide from a secondary alcohol.

***Corresponding Author:** titas.biswas@gmail.com

Kalmode et al., (2014) reported an effective synthesis approach for the manufacture of α-ketoimides using sp^3, sp^2, and sp C–H functionalization followed by oxidative cross-coupling.

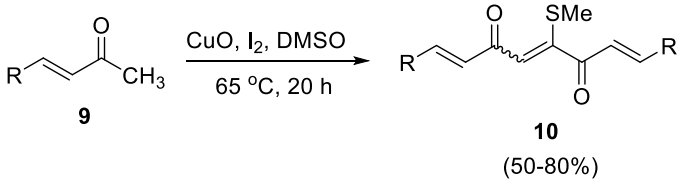
Various sp^3 (4), sp^2 (5) and sp (6) C–H functionalised compounds were treated with benzamidines hydrochloride (7) employing catalytic iodine and TBHP using DMSO solvent at 120 ºC and obtained the respective α-ketoimides (8) in yields that range from decent to outstanding (82-92%, Scheme 3).



Scheme 3. Preparation of α-ketoimides.

Synthesis of enediones

Gao et al., (2009) mentioned a method of forming a double bond from two methyl sp^3 C–H bonds to synthesise polyenicdiones directly from α, β-unsaturated methyl ketones. Treatment of α, β-unsaturated methyl ketone (9) with copper (II) oxide and molecular iodine in DMSO at 65ºC gave the expected product polyenicdione (10) in good yield (50-80%, Scheme 4). α-Iodinated ketone intermediate is formed as the key step from the enol form of methyl ketone, which is stagnated by conjugation. The reaction provided the mixture of Z/E products having Z-isomer as the major product.

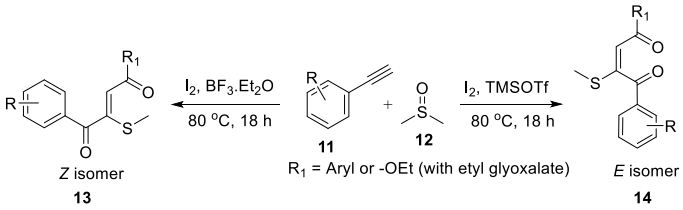


Scheme 4. Synthesis of polyenicdiones.

Devari et al., (2015) established two different paths to synthesize stereospecific (*E*) or (*Z*)-2-methylthio-1,4-diones using Bronsted (TMSOTf) acid or Lewis acid (BF_3Et_2O) in the company of molecular iodine (Scheme 5). Similarly, treatment of phenyl acetylene with ethyl glyoxylate in the presence of molecular iodine gives (*E*) and (*Z*) isomers (Scheme 6).

Path I- I_2: TMSOTf , 18 h, 80^{0}C, DMSO

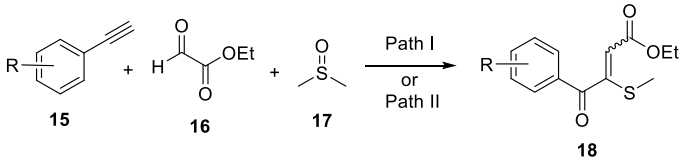
Path II- I_2: $BF_3.Et_2O$, 18 h, 80 ^{0}C, DMSO



Scheme 5. Synthesis of 2-thio-1,4-enediones.

Path I- I_2: TMSOTf, 18 h, 80 ^{0}C, DMSO

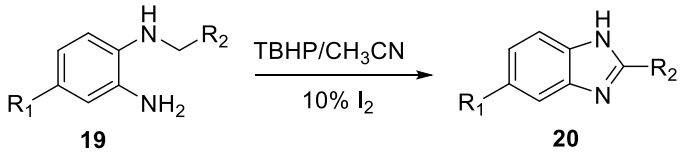
Path II-I_2: BF_3. Et_2O, 18 h, 80^{0}C, DMSO



Scheme 6. The reaction of alkynes with ethyl glyoxylate.

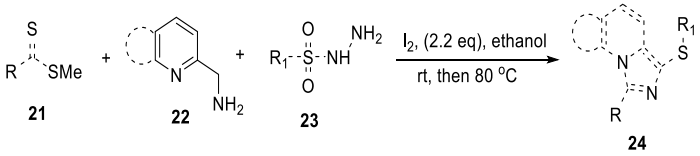
Synthesis of imidazole derivatives

Patil et al., (2016) established a synthetic strategy to prepare substituted benzimidazole by sp^3 C–H functionalization. They treated N-benzylbezene-1,2-diamine (19) with tert-butyl hydroperoxide (TBHP) oxidant using acetonitrile solvent in the presence of 10% molecular iodine to obtain substituted benzimidazole (20) (Scheme 7). The mild reaction conditions of this method are applicable for different substrates. The yields of 2-substituted benzimidazole obtained are (65-94%).



Scheme 7. Synthesis of substituted benzimidazole

One-pot three-component I_2-mediated preparation of 3-sulfenylimidazo-pyridines from dithioesters, 2-aminopyridines, and sulfonyl hydrazides has been established by Ramesha et al., (2016). In this tandem method a C–H bond is functionalized to form C–N and C–S bonds under oxidant free conditions. The tandem reaction is carried out by treatment of dithioesters (21), 2-aminopyridines (22) and sulfonyl hydrazides (23) in the presence of iodine catalyst using ethanol as solvent from room temperature to 80ºC to obtain the 3-sulfonylimidazo-pyridines (24). The sulfur-nitrogen and sulfur-oxygen bond cleavage is the key step of this reaction mechanism, which applies to the wide range of alkyl and aryl sulfonyl hydrazides, and diverse imidazopyridines (Scheme 8).



Scheme 8. Synthesis and application of 3-sulfenylimidazo[1,5-a]pyridines

The reaction was extended without using sulfonyl hydrazides (23) and only using a variety of dithioesters (21) and 2-methylamino pyridine or hydrazine pyridine (25). This tandem reaction between dithioesters and methyl-aminopyridine readily provided the intermediate imidazo[1,5-a]pyridine (Scheme

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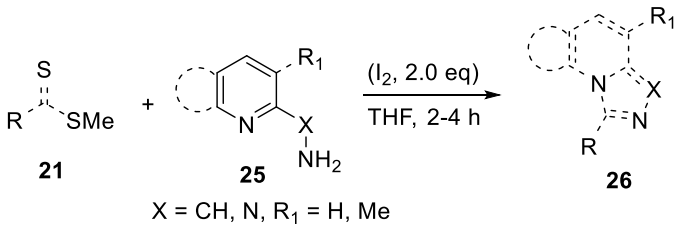
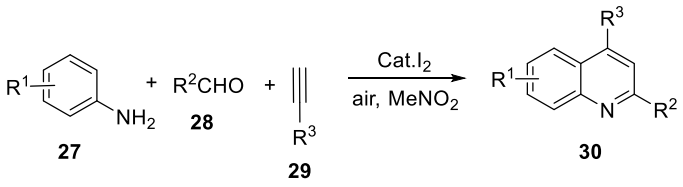
9).



Scheme 9. Synthesis and application of imidazolo[1,5-a]pyridines and [1,2,4]-triazolo[4,3-a]pyridines

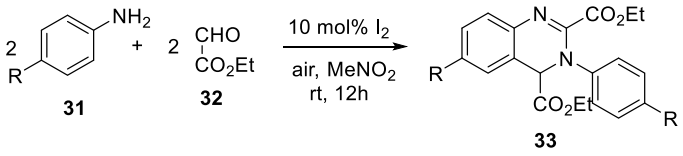
Synthesis of quinoline derivatives

Li et al., (2011) described a one-pot tandem procedure to synthesize quinolines taking amines, aldehydes and alkynes as starting materials, molecular iodine as a catalyst in air and nitromethane solvent (Scheme: 10). 10 mol % iodine was sufficient to catalyze the reaction for the preparation of desired product where iodine plays the role of mild Lewis acid. Treatment of aromatic amine (27), aldehyde (28), and alkyne (29) in the air using nitromethane solvent at room temperature gave the quinoline derivative (30).



Scheme 10. Three-component synthesis of quinolines

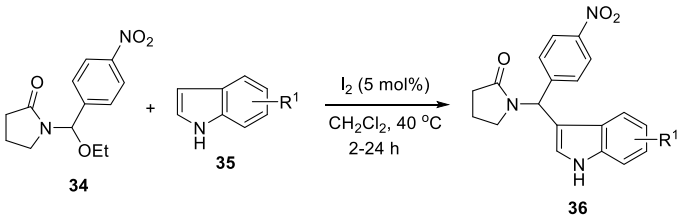
The methodology is also useful for the synthesis of quinazoline derivatives (33) from two molecules of amines (31) and two molecules of glyoxalates (32) (Scheme: 11).



Scheme 11. Aniline and ethyl glyoxalate are condensed together.

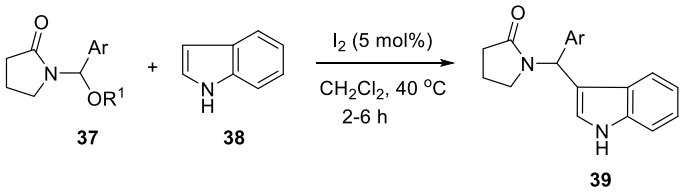
Synthesis of indole derivatives

I_2-catalyzed C–O activation of 1-[ethoxy(4-nitrophenyl)methyl]pyrrolidin-2-one (34) for the synthesis of indeno[1,2-b]indoles (36) is reported by Xu et al., (2012). This method is one pot sequential reaction that produces various indeno[1,2-b]- indole derivatives in good yields (Scheme 12).



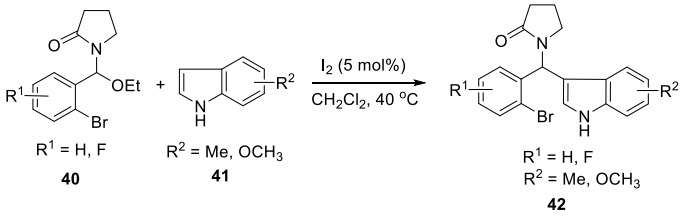
Scheme 12. The C–O activation of 1-[ethoxy(4-nitrophenyl)methyl]pyrrolidin-2-one with indoles in presence of molecular iodine catalyst.

The reaction between the pyrrolidine-2-one derivative (37) and indole (38) using molecular iodine catalyst in dichloromethane solvent at 40ºC provided the indeno[1,2-b]indole (39) (Scheme 13).



Scheme 13. Synthesis and application of Indeno[1,2-b]indole derivatives.

Similarly, treatment of 2-bromo-phenenyl-pyrrolidin- 2-one (40) and indole derivative (41) in the presence of molecular iodine catalyst in dichloromethane solvent at 40ºC furnished the pyrrolidin-2-one derivative (42) (Scheme 14).



Scheme 14. I_2-catalyzed C–O bond activation of 2-bromo-phenenyl-pyrrolidin-2-one derivatives with indoles.

Synthesis of 2-aminothiazole derivatives

Zhu et al., (2012) used an I_2/CuO catalytic media to develop a one-pot tandem technique for synthesising 2-aminothiazoles. Treatment of methyl ketones (43) or unsaturated methyl ketones (46) and thiourea (44) in presence of I_2/CuO catalytic medium undergo cyclization to form 2-aminothiazoles (45) (Scheme 15) or 2-amino-4-ethenylthiazoles (47). The method was found to be stereo-selective in obtaining the *E*-isomers of 4-ethenyl-2-aminothiazoles (Scheme: 16).

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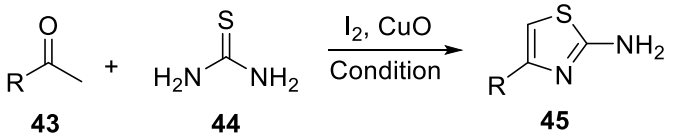
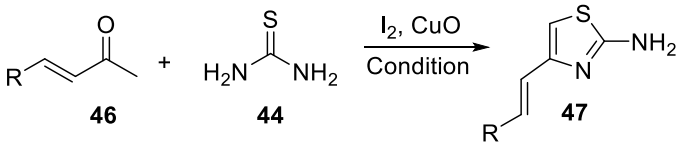


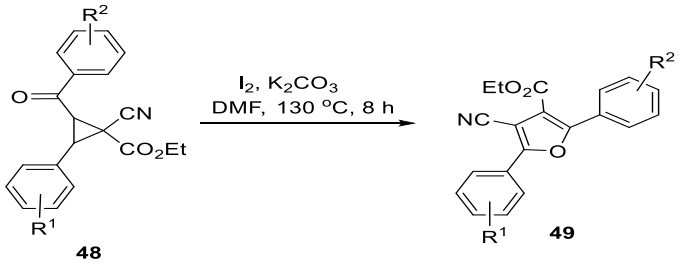
Scheme 15. Formation of 2-aminothiazole derivatives



Scheme 16. Formation of 2-amino-4-ethenylthiazole derivatives

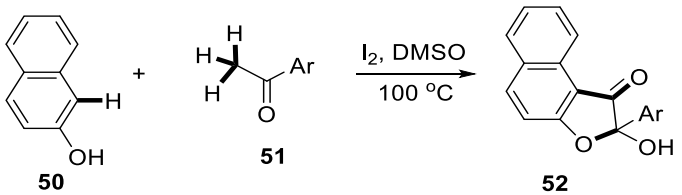
Synthesis of furan derivatives

Liu et al., (2017) reported a strategy for the preparation of 4-cyanofuran-3-carboxylate derivatives via iodine/potassium carbonate-promoted ring-opening / cyclization/rearrangement domino reaction. The starting material for this synthesis was 1-cyanocyclopropane-1-carboxylate derivatives (48) which, on treatment with I_2/K_2CO_3 in DMF solvent at 130ºC provided the 4-cyanofuran-3-carboxylate derivatives (49) (Scheme: 17).



Scheme 17. Synthesis of 4-cyanofuran-3-carboxylate derivatives

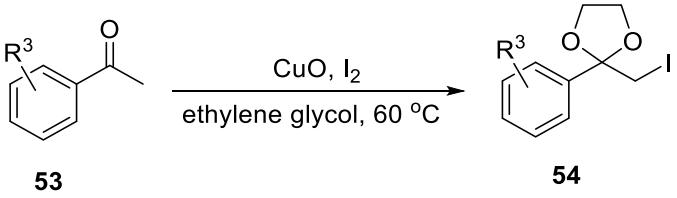
Gao et al., (2014) reported a one-pot, molecular iodine promoted oxidative cross-coupling between 2-naphthols and methyl ketones. This tandem methodology involves sequential iodination/ Kornblum oxidation/Friedel-Crafts/ oxidation/cyclization cascade reaction. 2-Napthol (50) was treated with methyl ketone (51) in the presence of molecular iodine in DMSO at 100ºC and obtained Naphtho[2,1-b]furan-1(2H)-ones (52) (Scheme 18).



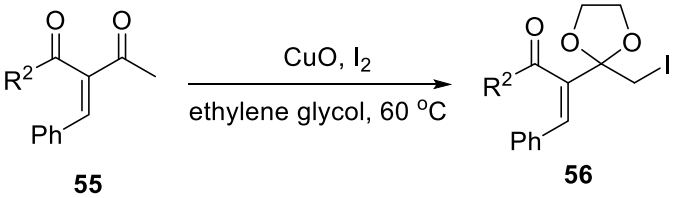
Scheme 18. Synthesis and application of Naphtho[2,1-b]furan-1(2H)-ones

Synthesis of iodoketal derivatives

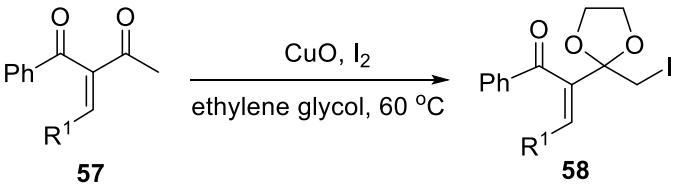
Yang et al., (2013) derived an effective technology for the direct synthesis of α-iodoketals from methyl ketones: The iodination reaction catalysed by copper (II) oxide and the subsequent regioselective ketalization reaction catalysed by iodine which is used in excess or can be regenerated. Treatment of methyl ketones (53) with copper(II) oxide in presence of molecular iodine in ethylene glycol at 60ºC furnished the iodoketals (54) in good yield (Scheme 19). They derived a tandem integration technique for the direct prepation of α-iodoketals in ethylene glycol using copper (II) oxide in presence iodine catalyst. Treatment of compounds 55 and 57 with copper(II) oxide in presence of iodine using ethylene glycol as solvent provides the corresponding molecules 56 and 58 in good yields (Scheme 20, 21).



Scheme 19. Aryl methyl ketones are used in the synthesis and application of α-iodoketals.



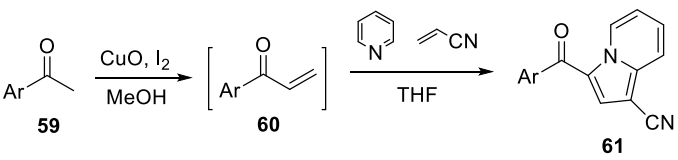
Scheme 20. Synthesis and application of α-iodoketals from (*Z*)-2-benzylidene-1-arylbutane-1,3-dione.



Scheme 21. Synthesis and application of α-iodoketals from (*Z*)-2-arylidene-1-phenylbutane-1,3-dione.

Synthesis of indolizine derivatives

Cai et al., (2013) described a convenient and facile one-pot synthesis of indolizine derivatives. The reaction mechanism proceeded by integrating iodination, pyridinium ylide synthesis, and 1,3-dipolar cycloaddition in the MeOH-THF double-solvents system. The aryl methyl ketone (59) on treatment with copper(II) oxide and iodine provided the α, β-unsaturated carbonyl compounds (60), which on reaction with pyridine and vinyl cyanide in MeOH-THF double solvents provided the indolizine derivatives (61) in good yield (Scheme 22).



Scheme 22. Synthesis and application of indolizine derivatives

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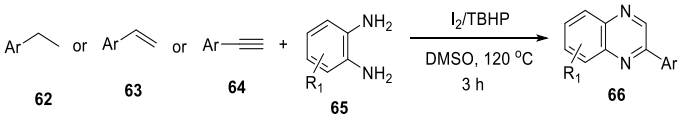
Preparation of quinoxaline derivatives

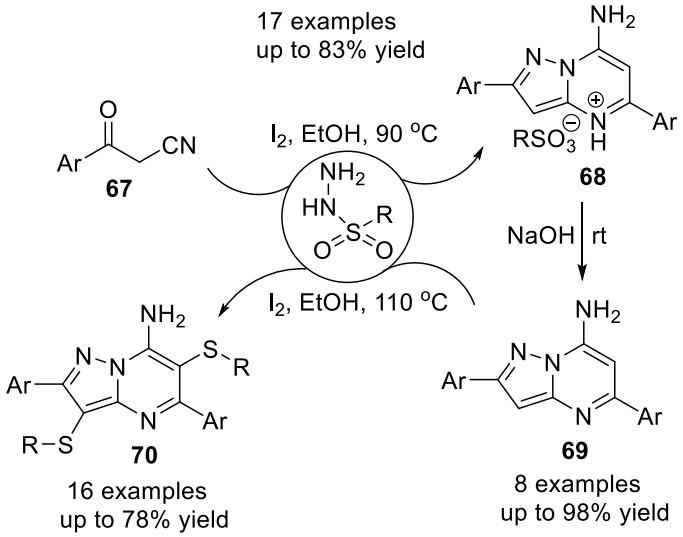
Vadagaonkar et al., (2014) described a one-pot, atom-economic synthesis of quinoxalines. The reaction was carried out by treatment of ethylarenes (62) or ethylenearenes (63) or ethynearenes (64) with o-phenylenediamines (65) in the presence of the catalytic amount of I_2 and TBHP oxidant in DMSO at 120ºC to obtain the quinoxaline derivatives (66) yielding an excellent result (Scheme 23). The mechanism proceeds by C-H functionalization and oxidative cyclization.



Scheme 23. Preparation of quinoxalines

Synthesis of pyrazolo[1,5-a] pyrimidine derivatives

Sun et al., (2016) established a unique, iodine-catalyzed three-component bi-cyclization of β- ketonitriles with sulphonyl-hydrazides, by which a wide range of functionalized pyrazolo[1,5- a]pyrimidin-4-ium sulfonates could be synthesized in a highly regioselective manner. Treatment of β- ketonitriles (67) with sulphonyl-hydrazides using iodine catalyst in ethanol at 60ºC provided the compound 68 which on reaction with NaOH at room temperature furnished the desulphonated compound 69. The compound 69 was subjected to I_2 catalyst in ethanol at 110 ºC to obtain the product 70 in good yield (Scheme 24).



Scheme 24. Preparation of pyrazolo[1,5- a]pyrimidin-4-ium sulfonates

Conclusion

In conclusion, iodine mediated tandem reactions are very useful for synthesising a variety of amide and imide derivatives, enediones, imidazole derivatives, quinoline derivatives, indole 2-aminothiazole derivatives, furan derivatives, iodoketal derivatives, indolizine derivatives quinoxaline derivatives and pyrazolo[1,5-a] pyrimidine derivatives. Due to the wide application of this procedure, it may be applicable for the construction of various pharmaceutically and medicinally active compounds.

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