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ARTICLE TYPE

Organoiodine (III) mediated intramolecular oxidative cyclization of 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazines to 5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*] isoquinolines

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A series of 5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines, **4** were obtained by oxidative cyclization of 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazines, **3**, in the presence of hypervalent iodine oxidant (iodobenzene diacetate, IDB) and dichloromethane at ambient temperature. This methodology involves a proficient metal-free intramolecular C–N bond formation, facilitated by hypervalent iodine reagent.

Introduction

Isoquinoline, an imperative heterocyclic template of an assortment of natural products and pharmaceuticals, possess intriguing biological activity.[1,2] Further, 1,2,4-triazoles find their applications in the field of biological and pharmacological activities,[3-5] including antifungal,[6] bactericidal,[6,7] anxiolytic,[8,9] anticonvulsant,[10] or herbicidal[11] and antidepressant activities.[12] It is fascinating that hydrazine and their analogs promptly undergo annulations to the 1,2,4-triazole ring,[13] a guaranteeing biologically active compound.[14,15] Likewise, the fused heterocyclic 1,2,4-triazoles find their essentialness as CNS depressant,[16] antiallergy,[17] antimicrobial[18] and anti-inflammatory[19] drugs. In this way, it was envisaged that chemical entities with both the isoquinoline and fused or bridged 1,2,4-triazole might result in compounds with interesting biological activity. In this perspective and with our longstanding interest in the synthesis and diversification of heterocycles, particularly in quinoline and isoquinoline chemistry,[20-22] thus we report a convenient, practical and efficient hypervalent iodine mediated synthesis of bridgehead triazoles, for instance, 5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines (Scheme 1).

As of late, the triazolopyridines, triazoloquinolines and so on has been reported by oxidative cyclization from their respective hydrazones.[23-35] Few of the strategies included the utilization of dangerous reagents like lead tetracetate, phosphorus oxychloride or a moisture sensitive ferric chloride, microwave irradiation in acetic anhydride or nitrobenzene which required reflux conditions.[36-38] Likewise, few others included laborious procedures, larger amount of oxidants thereby causing environmental issues. To conquer these, alternate methods and reagents were developed.[39, 40] so that reactions are completed under the mild reaction conditions and acted as an option to the reported customary strategies. Amongst the organohypervalent iodine reagents (Fig.1),[41-46] the iodobenzene diacetate (IBD) have risen as a low toxic, readily accessible, and simplicity to handle reagent for the valuable transformations.[47-60]

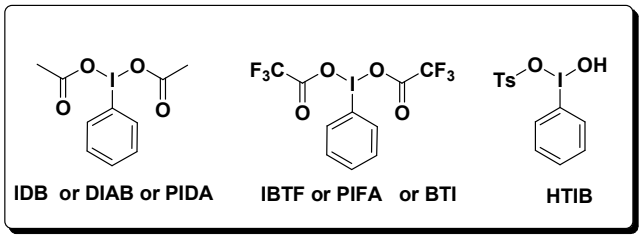
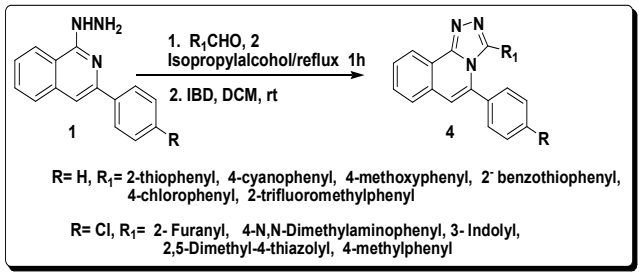


Fig. 1 Some organoiodine (III) reagents.

Results and Discussion

The synthetic pathway of **5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines, 4** is depicted in Scheme 1



Scheme 1. Synthesis of 5-aryl-3-(aryl)-[1,2,4]triazolo [3,4-*a*]isoquinolines

The imperative cyclization precursor hydrazones were promptly acquired by the condensation of 1-(3-arylisoquinolin-1-yl) hydrazine, **1** with distinctive aromatic and heteroaromatic aldehydes, **2** in isopropanol under reflux condition with a trace of glacial acetic acid. The 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazines, **3** formed were filtered, dried and utilized for further investigation on cyclization.

At the outset, the reaction was done utilizing a mixture of 1-(3-phenylisoquinolin-1-yl)-2-(thiophen-2-ylmethylene) hydrazine, **3a** (1mmol) without the iodine reagent and solvent under heating condition at 100 °C, however, the reaction did not continue to give the sought 5-phenyl-3-(thiophen-2-yl)-[1,2,4]triazolo[3,4-a]isoquinoline, **4a** (Scheme 1, Table 1, entry 1), whereas 17-30% of **4a** is formed in the presence of iodine reagents in acetonitrile solvent (Table 1, entries 2-4). The results demonstrated that both the solvent and iodine reagents are essential for the reaction. Further, we shifted the solvents from CH_3CN, toluene and CH_2Cl_2 (Scheme 1, Table 1, entries 5-10). Among the investigated conditions, in the presence of IBD, CH_2Cl_2, the reaction offered the desired product, **4a** with a yield of 87% (Scheme 1, Table 1 and entry 8). Likewise, the IBTF and HTIB proceeded to offer the desired product in low yield of 20-46% after delayed reaction time (Scheme 1, Table 1, entries 5-7, 9, 10). Energized by these results, further improvement was carried out by altering iodine reagent loading under CH_2Cl_2 solvent reflux conditions. Amongst the different catalysts loading, good yields of 92% were obtained utilizing 1.1 equiv. of IBD/ CH_2Cl_2 system (Table 2, entry 13) and other trials gave moderate yields (Table 2, entries 1-12). Treatment of 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazine, **3** with iodobenzenediacetate (IBD) in dichloromethane for 1 h at room temperature brought out the cyclization in the establishment of a solitary product.

The oxidative cyclization of hydrazones brought about the formation of 5-aryl-3-(aryl/heteroaryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines, **4** (see Table 3). The oxidative transformation is clean and proficient. The 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazine, **3** of aromatic and heteroaromatic aldehydes, **2** with both electron-withdrawing and electron-donating substituent were oxidized to give the corresponding 5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines, **4** in high yields (Table 3). The aliphatic aldehyde hydrazones did not proceed well to give the desired triazoles due to their immediate cleavage and oxidation of aldehyde functionality. The experimental procedure is exceptionally simple. The high yield transformation did not form any undesirable by-products. Furthermore, the products were procured with a higher degree of purity which obliged no further purification. The critical advantages of this strategy are operational straightforwardness, short reaction time, pure products, ecnomical, and nontoxicity of the reagent and remarkable yields. The structures of every 5-aryl-3-(aryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines, **4a–k** were confirmed by their spectral data.

Table 1. Optimization of the cyclization conditions using diverse reagent[a]

Entry	Iodine (III) reagent (equiv)	Solvent	Yield (%)[b]
1	Nil	NIL	No reaction
2	IBD	CH_3CN	30
3	IBTF	CH_3CN	21
4	HTIB	CH_3CN	17
5	IBD	Toluene	25
6	IBTF	Toluene	20
7	HTIB	Toluene	28
8	IBD	CH_2Cl_2	87
9	IBTF	CH_2Cl_2	46
10	HTIB	CH_2Cl_2	32

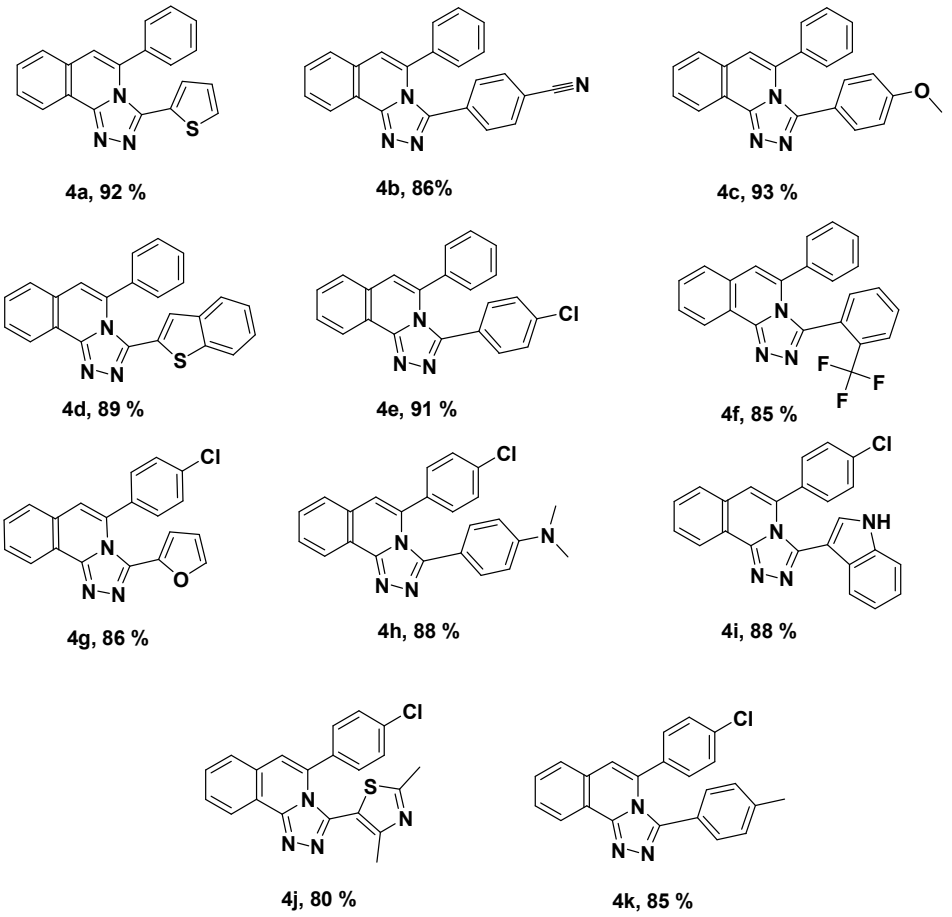
[a]Reaction Conditions: i) 1-(3-phenylisoquinolin-1-yl)-2-(thiophen-2-ylmethylene) hydrazine**, 3a** (1 mmol, 1.0 equiv.), iodine reagent (1.0 equiv.) in solvent (10 ml) at room temperature for 1 h. [b]Isolated yields.

Table 2. Optimization of the IBD reagent load[a]

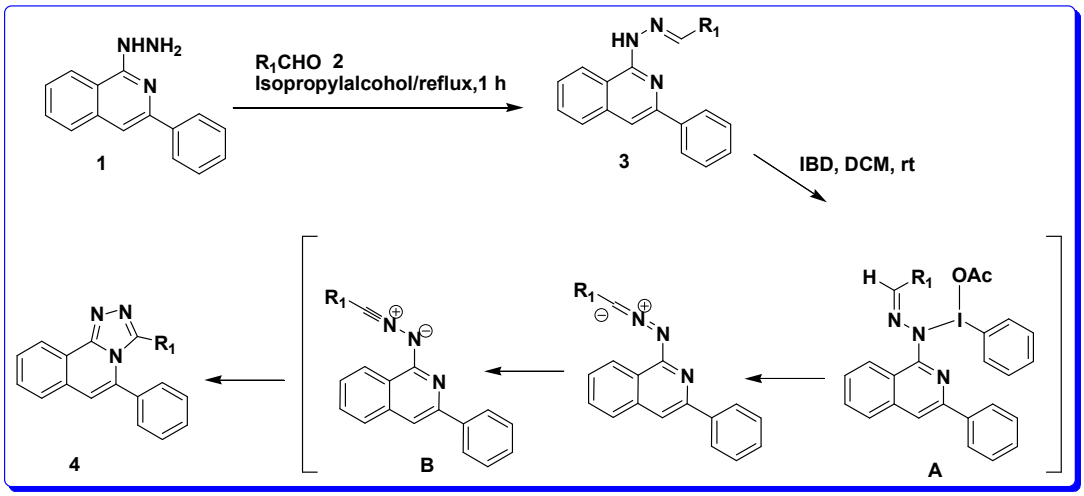
Entry	Iodobenzene diacetate, IBD (equiv)	Solvent	Yield (%)[b]
1	1	NIL	12
2	1	DMF	30
3	1	DIOXANE	30
4	1	THF	30
5	1	Toluene	25
6	1	CH_3CN	30
7	1	CH_2Cl_2	87
8	0.1	CH_2Cl_2	30
9	0.3	CH_2Cl_2	55
10	0.5	CH_2Cl_2	70
11	0.7	CH_2Cl_2	74
12	0.9	CH_2Cl_2	80
13	1.1	CH_2Cl_2	92

[a]Reaction Conditions: i) 1-(3-phenylisoquinolin-1-yl)-2-(thiophen-2-ylmethylene) hydrazine**, 3a** (1 mmol, 1.0 equiv.), iodine reagent in solvent (10 ml) at room temperature for 1 h. [b]Isolated yields.

Table 3 Synthesis of 5-aryl-3-(aryl/heteroaryl)-[1,2,4]triazolo[3,4-*a*]isoquinolines[a]



[a]Reaction Conditions: i) 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene) hydrazine**,** **3** (1 mmol, 1.0 equiv.), iodine reagent, IBD (1.1 equiv.) in dichloromethane (10 ml) at room temperature for 1 h.



Scheme 2 Possible mechanism of the reaction

A conceivable mechanism is delineated in Scheme 2. The principal step includes the electrophilic attack of IBD on 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene) hydrazine**,** **3** to form an organoiodine (iii) intermediate, **A**. Consequently, **A** creates an alternate intermediate nitrile imide, **B** alongside ejection of molecules of iodobenzene and acetic acid. The nitrile amide, **B** experiences cyclization to give the 5-aryl-3-(aryl)-[1,2,4]triazolo [3,4-*a*]isoquinolines, **4**.

Conclusions

The iodine (III)-mediated oxidative cyclization of 1-(3-aryllisoquinolin-1-yl)-2-(arylmethylene) hydrazine**, 3** to 5-aryl-3-(aryl)-[1,2,4]triazolo [3,4-*a*]isoquinolines, **4** is significant as the strategy is eco-friendly, included gentle conditions, and there is a plausibility of utilizing this methodology for the synthesis of a wide variety of heterocyclic compounds of potential biological interest.

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Experimental

Typically, the condensation of 1-(3-phenylisoquinolin-1-yl) hydrazine, **1a** (1mmol), 2- thiophene-2-carboxaldehyde, **2a** (1mmol**)** in isopropanol (10mL) under reflux condition with a trace of glacial acetic acid gave 1-(3-phenylisoquinolin-1-yl)-2-(thiophen-2-ylmethylene) hydrazine, **3a,** which was filtered, dried and utilized for further investigation on cyclization.

To a stirred solution of 1-(3-phenylisoquinolin-1-yl)-2-(thiophen-2-ylmethylene) hydrazine, **3a** (1 mmol) in DCM (10 ml) at room temperature, IBD (1.1 mmol) was added in portions during 5 min. The resulting mixture was agitated for 1 h at room temperature. The solvent was evaporated and the residual mass containing product and iodobenzene triturated with petroleum ether to give the solid product, which was recrystallized from methanol to yield pure 5-phenyl-3-(thiophen-2-yl)-[1,2,4]triazolo[3,4-a]isoquinoline, **4a**.

5-Phenyl-3-(thiophen-2-yl)-[1,2,4]triazolo[3,4-a]isoquinoline, (4a)

Brown solid, mp 195.1 °C, IR (KBr-ν cm^{-1}): 3061,1724, 1636, 1522, 1451, 1374, 1294, 1224, 1150, 844, 777, 762, 705, 538, 491. ^{1}H NMR (400 MHz, DMSO-D_6, 25 °C) δ ppm: 8.66 (d, *J* = 5.04 Hz, 1H), 7.99 (d, *J* = 7.12 Hz, 1H), 7.79 (m, 2H), 7.51 (d, *J* = 5.08 Hz, 1H), 7.34-7.15 (m, 6H), 6.66 (m, 1H), 6.50 (d, *J* = 3.60 Hz,1H); ^{13}CNMR (100 MHz DMSO-D_6) δ ppm: 149.93, 143.71, 135.21, 133.32, 131.43, 130.83, 130.54, 129.49, 129.32, 128.97, 128.89, 128.17, 128.07, 127.84, 127.24, 123.38, 120.69, 117.36. Calcd for $C_{20}H_{13}N_3S$, HRMS (EI) 327.0830; found, 327.1192 (M+).

Notes and references

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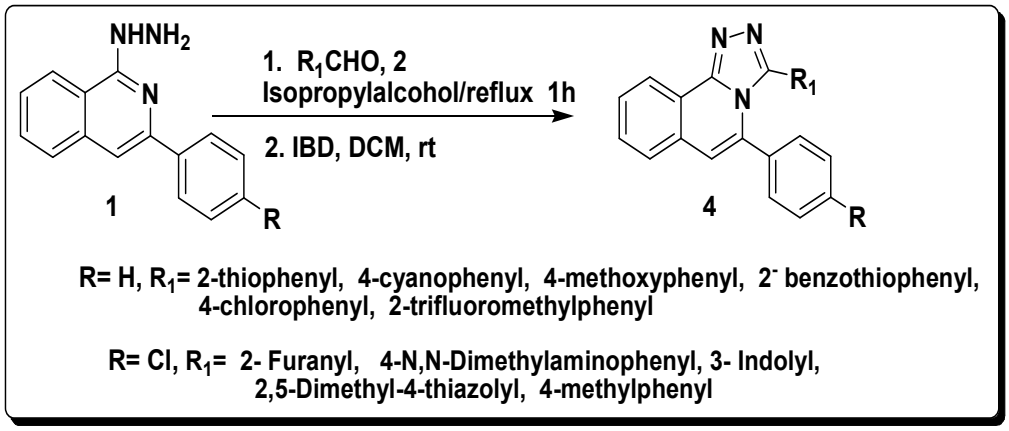

Intramolecular C–N bond formation is achieved through oxidative cyclization of 1-(3-arylisoquinolin-1-yl)-2-(arylmethylene)hydrazines, **3**, in the presence of hypervalent iodine oxidant and dichloromethane at ambient temperature.