Organic Chemistry: An Indian Journal

Research | Vol 12 Iss 5

Organoiodine (III) Mediated One-Pot Synthesis of Several New Coumarinyl-Triazolo-Triazines

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Received: September 22, 2016; **Accepted:** October 14, 2016; **Published:** October 26, 2016

Abstract

The study foregrounds the efficacy of organoiodine (III) reagent, [hydroxy(tosyloxy)iodo]benzene (PhI(OH)OTs) in the synthesis of new derivatives of coumarinyl containing N-bridgehead heterocyclic compounds namely, 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4] triazines (4) from the reaction of 3-(α-tosyloxyacetyl)coumarins (2) and 5-aryl-3,4-diamino-s-triazoles (3). The umpolung compounds 2 are, in turn, obtained by the α-tosyloxylation of 3-acetylcoumarins 1 with PhI(OH)OTs. The reaction was also carried out in one-pot starting from enolizable ketones 1 by generating the tosyloxyketones 2 *in situ*. In one-pot procedure, the ketones 1 are first treated with PhI(OH)OTs and then with diaminotriazoles 3 to furnish the expected title compounds 4 in better yields than the stepwise procedure.

***Keywords:** 3-Acetylcoumarins; [hydroxy(tosyloxy)iodo]benzene; One-pot, 3-(α-tosyloxyacetyl)coumarins; 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines; 5-aryl-3,4-diamino-s-triazoles;*

Introduction

Coumarin (2H-chromen-2-one) and its derivatives are considered as privileged compounds in modern heterocyclic era because of their role in synthetic organic chemistry. Coumarins, belonging to a large class of molecules known as benzopyrans, are biodynamic chemotypes showing significant pharmacological and physiological properties [1,2]. In the present study, the 3-acetylcoumarin derivatives 1, possessing the enolizable ketonic group, are employed to prepare the umpolung compounds, 3-(3-(α-tosyloxyacetyl) coumarins 2 on reaction with the organoiodine (III) reagent, [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent). HTIB is established to be a versatile reagent for the synthesis of various classes of heterocyclic compounds via α-tosyloxylation of enolizable carbonyl compounds [3-8]. The present work involves the cyclocondensation of 3-(3-(α-tosyloxyacetyl) coumarins and 5-aryl-3,4diamino-1,2,4-triazoles 3 to furnish the title compounds. 1,2,4-Triazole nucleus has been incorporated into a wide range of drugs because of their ability to bind a variety of enzymes and receptors in biological systems via diverse non-covalent interactions [9-11]. Keeping in view the tremendous potential of HTIB in the synthesis of heterocyclic compounds [12-14] and our ongoing research work on the synthesis and biological evaluation of triazole fused heterocycles [15,16], we are reporting here in the synthesis of some new N-containing bridgehead heterocyclic compounds namely, 3-aryl-6-(3-coumarinyl)-[1,2,4] triazolo[4,3-b][1,2,4]triazines 4.

Citation: Pundeer R, Kiran V. Organoiodine(III) Mediated One-Pot Synthesis of Several New Coumarinyl-Triazolo-Triazines. Org Chem Ind J. 2016;12(5):106.

Materials and Methods

Melting points were taken in open capillaries in an electrical apparatus and are uncorrected. IR spectra in KBr were recorded on Perkin-Elmer 1800 FT-IR spectrophotometer. The ^{1}H NMR and ^{13}C spectra were recorded on Bruker instrument at 300 MHz and 75 MHz respectively. The chemical shifts were expressed in ppm units downfield from an internal TMS standard. Purity of the compounds was checked by thin layer chromatography (TLC) using silica gel aluminium sheets of Merck and UV lamp was used for the visualization of the compounds. Elemental analyses were carried out in Perkin-Elmer 2400 instrument. All the chemicals were purchased from commercial suppliers and were used without further purification. The acetylcoumarins 1 were prepared by stirring a mixture of corresponding salicylaldehydes and ethyl acetoacetate in the presence of piperidine [17]. α-Tosyloxylation of 1 was then, performed with HTIB in DCM [18]. For the synthesis of triazoles 3, a mixture of thiosemicarbazide and aryl carboxylic acids was refluxed in the presence of concentrated H_2SO_4 to obtain thiadiazoles; which on treatment with hydrazine hydrate in ethanol gave the required triazoles 3 [19,20].

3-(3-aryl-[1,2,4]triazolo[3,4-b][1,2,4]triazin-6-yl)-2*H*- chromen-2-ones (4a-i): General Procedure

Procedure A: (via isolation of tosyloxyketones)

Step I: 3-(α-Tosyloxyacetyl) coumarins (2): To a stirred solution of 3-acetylcoumarin (1, 10 mmol) in DCM (50 ml) was added HTIB (10 mmol). The resulting mixture was allowed to stir at 40°C to 50°C temperature. HTIB was initially insoluble in DCM, but gradually disappeared as the reaction proceeded. The stirring was allowed to continue for about 4 h. The solvent was evaporated under vacuum and the gummy mass so obtained, was triturated with pet ether (60°C to 80°C) to remove iodobenzene. The resulting colourless solid was thoroughly washed with water. The solid was recrystallized from ethanol to obtain the pure tosylate compound.

Step II: 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines(4): To a mixture of 3-(α-tosyloxyacetyl)coumarin (2, 10 mmol) and the triazole (3, 10 mmol) in ethanol (20 ml) was added a pinch of anhydrous K_2CO_3 and the reaction mixture was heated under reflux for about 4 h to 5 h. About half of the solvent was removed under vacuum and the reaction mixture was cooled to room temperature. The solid, separated out, filtered and recrystallized from ethanol to give pure product 4.

Procedure B: One-pot preparation of 4 starting from 3-acetylcoumarin

Typical procedure: To a mixture of 3-acetylcoumarin 1 (10 mmol) in DCM was added HTIB (10 mmol) and the reaction mixture could stir for 4 h to 5 h. The progress of the reaction was checked by TLC. Excess of the solvent was distilled off under reduced pressure. To the residual mixture was added 5-phenyl-3,4-diamino-1,2,4-triazole (10 mmol), ethanol (20 ml) and a pinch of anhydrous K_2CO_3. The reaction mixture was heated under reflux for 4 h to 5 h. About half of the solvent was removed under vacuum and the reaction mixture was cooled to room temperature. The solid, separated out, filtered and recrystallized from ethanol to obtain the pure product 4.

Characterization Data of 3-aryl-6-(3-Coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines (4a-4i)

6-(3-coumarinyl)-3-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4a)

IR (νmax, in KBr): 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.34-7.43 (m, 3H), 7.50-7.61 (m, 5H), 69-7.71 (m, 1H), 8.51 (s, 1H), 8.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz δ): 110.20, 116.37, 118.38, 119.64, 120.93, 121.77, 122.09, 123.36, 124.57, 128.29, 129.57, 131.33, 138.88, 144.08, 152.91, 160.73; Elemental analysis: Calculated for $C_{19}H_{11}N_5O_2$: C 66.86, H 3.25, N 20.52; Found: C 66.78, H 3.18, N 20.34.

3-(4-chlorophenyl)-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4b)

IR (νmax, in KBr): 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.39-7.43 (m, 3H), 7.47-7.59(m, 3H), 7.98-8.02 (d, 2H), 8.51 (s, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz δ): 110.23, 117.25, 119.23, 119.61, 121.86, 124.58, 128.29, 130.25, 131.32, 133.39, 137.61, 138.81, 143.99, 152.75, 159.71, 164.65; Elemental analysis: Calculated for $C_{19}H_{10}ClN_5O_2$: C 60.73, H 2.68, N 18.64; Found: C 60.87, H 2.77, N 18.48.

6-(3-coumarinyl)-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4c)

IR (νmax, in KBr): 1713cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, δ): 7.35-7.38 (m, 2H), 7.48-7.63 (m, 4H), 7.66-7.69 (m, 2H), 8.55 (s,1H), 9.35 (s, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz δ): 110.11, 116.13, 116.38, 119.57, 120.90, 121.01, 124.61, 128.32, 131.41, 138.91, 143.99, 152.91, 156.05, 159.68, 161.36, 164.37; Elemental analysis: Calculated for $C_{19}H_{10}N_6O_4$: C 59.07, H 2.61, N 21.75; Found: C 58.95, H 2.53, N 21.94.

6-(3-(6-chlorocoumarinyl))-3-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4d)

IR (νmax, in KBr): 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.10-7.14(m, 1H), 7.40-7.43 (m, 4H), 7.59-7.61 (m, 1H), 7.61-7.73 (m, 2H), 8.51 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 116.44, 119.59, 119.87, 121.02, 124.67, 126.75, 128.48, 129.04, 130.39, 131.59, 133.32, 139.75, 148.65, 153.13, 159.87, 167.39; Elemental analysis: Calculated for $C_{19}H_{10}ClN_5O_2$: C 60.73, H 2.68, N 18.64; Found: C 60.65, H 2.62, N 18.75.

6-(3-(6-chlorocoumarinyl))-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4e)

IR (νmax, in KBr): 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, δ): 7.23 (d, 2H, J=7.8 Hz), 7.31-7.40 (m, 3H), 7.53-7.64 (m, 2H), 8.60 (s, 1H), 8.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 109.91, 116.35, 119.19, 119.59, 120.86, 124.55, 128.28, 130.10, 131.29, 133.38, 137.59, 138.80, 143.97, 152.83, 159.70, 164.63; Elemental analysis: Calculated for $C_{19}H_9Cl_2N_5O_2$: C 55.63, H 2.21, N 17.07; Found: C 55.50, H 2.12, N 17.25.

6-(3-(6-chlorocoumarinyl))-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4f)

IR (νmax, in KBr): 1720 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, δ): 7.40-7.61 (m, 3H,), 7.79-7.96 (m, 4H), 8.61 (s, 1H), 9.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 116.37, 119.53, 119.96, 121.12, 124.69, 126.84, 128.57, 129.14, 130.44, 131.67, 133.37, 139.85, 148.78, 153.25, 159.96, 167.48; Elemental analysis: Calculated for $C_{19}H_9ClN_6O_4$: C 54.24, H 2.16, N 19.97; Found: C 54.39, H 2.04, N 19.78.

6-(3-(6-bromocoumarinyl))-3-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4g)

IR (νmax, in KBr): 1705 cm^{-1}; ^1H NMR (DMSO-d6, 300 MHz, δ): 7.44-7.48 (m, 3H), 7.62-7.67 (m, 2H), 7.78-7.89 (m, 3H), 8.63 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 114.45, 118.89, 119.67, 121.27, 124.61, 127.05, 128.63, 129.28, 130.42, 131.66, 133.58, 139.81, 148.73, 153.84, 160.04, 167.53; Elemental analysis: Calculated for $C_{19}H_{10}BrN_5O_2$: C 54.31, H 2.40, N 16.67; Found: C 54.18, H 2.31, N 16.83.

6-(3-(6-bromocoumarinyl))-3-(4-chlorophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4h)

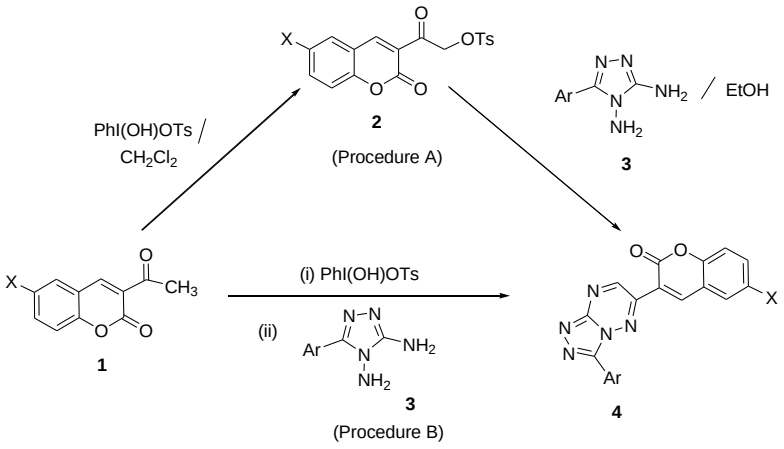
IR (νmax, in KBr): 1713 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, δ): 7.34-7.43(m, 3H), 7.50-7.72 (m, 2H), 8.08 (d, 2H, *J*=4.5 Hz), 8.51 (s, 1H), 8.93 (s, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz, δ): 112.44, 119.45 119.64, 121.22, 124.67, 126.45, 128.65, 129.14, 130.46, 131.72, 133.52, 138.75, 147.65, 154.13, 159.07, 164.34. Elemental analysis: Calculated for $C_{19}H_9BrClN_5O_2$: C 50.19, H 2.00, N 15.40; Found: C 50.07, H 1.93, N 15.26.

6-(3-(6-bromocoumarinyl))-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4i)

IR (νmax, in KBr): 1705 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz, δ): 7.34-7.43 (m, 2H), 7.48 (d, 2H, *J*=8.7 Hz), 7.56-7.71 (m, 1H), 8.01 (d, 2H, *J*=8.7 Hz), 8.51 (s, 1H), 8.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz, δ): 112.38, 118.19, 119.87, 121.36, 124.84, 126.84, 128.69, 129.37, 130.45, 131.59, 133.48, 139.75, 148.60, 153.23, 159.63, 167.57; Elemental analysis: Calculated for $C_{18}H_{11}NO_2S$: C 49.05, H 1.95, N 18.06; Found: C 48.91, H 1.84, N 18.23.

Results and Discussion

Initially the reaction of the tosylate compound, 3-(α-tosyloxyacetyl)coumarin (2a) and the *s*-triazole, 3,4-diamino-5-phenyl-1,2,4-triazole (3a) was examined. Taking clues from the literature reports and after making several attempts under different conditions, the reaction proceeded successfully in ethanol under reflux conditions in the presence of catalytic amount of K_2CO_3. The progress of the reaction was monitored through thin layer chromatography and a single product was obtained in very good yield (85%) which was identified as the cycloadduct, 6-(3-coumarinyl)-3-phenyl-[1,2,4]triazolo[4,3-b][1,2,4]triazine (4a). Encouraged by the fruitful outcome of the attempt, it was considered worthwhile to extrapolate the reaction for the synthesis of variously substituted new derivatives of 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines by taking different 6-halosubstituted 3-(α-tosyloxyacetyl)coumarins and 5-aryl-3,4-diamino-1,2,4 triazoles. Fortunately, in all the examples, the expected products 4a-4i were obtained, in 78% to 85% yield (SCHEME 1, TABLE 1). Therefore, the HTIB mediated reaction evidenced to be an efficient method for the synthesis of several new coumarinyl-triazolo-triazines.



SCHEME 1. **Synthesis of 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines (4).**

All the newly synthesized coumarin substituted triazolotriazines 4a-4i are new compounds and their structure has been confirmed through appropriate analysis of the spectral and elemental data. The C=O stretch originally present around 1684 cm^{-1} in the IR spectra of tosylates2 was disappeared in the IR of 4. Also, the singlets positioned around δ 2.47 and 5.40 due to CH_3 and CH_2 in the ^1H NMR spectra of 2, were absent in 4 as expected. Moreover, the $_1H$ NMR spectra of the title products (4a-4i) displayed a characteristic singlet in the region δ 8.8-9.3 due to C_7–H. All other protons appeared in the aromatic region.

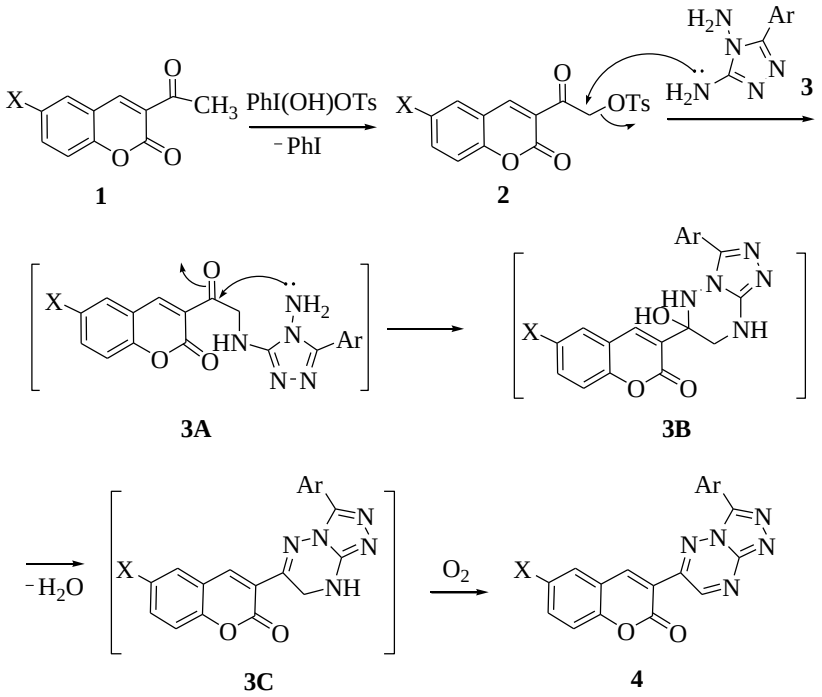
It is well documented that the advantage of tosyloxyketones (TK) mediated syntheses is that it is possible to carry out the reaction in one-pot starting from ketones, by generating the TK *in situ*, without its isolation. Hence, to further extend the utility of the present synthetic approach, the conversion 1 → 3 was performed in one-pot without isolating the intermediate 3-

(α-tosyloxyacetyl)coumarins 2 (SCHEME 1). The title compounds 4 were obtained in all the cases in overall yields (90% to 94%) better than the stepwise procedure. The physical data of the compounds 4 is summarized in TABLE 1. The probable mechanism of the synthetic reaction is outlined in SCHEME 2. HTIB being moderately electrophilic at iodine attacks 3-acetylcoumarins (1) to give the tosylate derivatives 2 with the reductive loss of iodobenzene. 3-(α-Tosyloxyacetyl)coumarins (2) undergo nucleophilic substitution by the attack of amino group of the triazole 3 to give an intermediate 3A. The intermediate 3A, cyclizes to furnish the triazolotriazines 4 by subsequent loss of water molecule and aerial oxidation.

TABLE 1. **Physical data of the products 4 prepared according to Scheme 1.**

Compounds	X	Ar	M.P. (°C)	Yield[a] (%)	
				Stepwise	One-pot
4a	H	C_6H_5	186-187	85	94
4b	H	4-ClC_6H_4	226-228	78	90
4c	H	4-$NO_2C_6H_4$	284-286	83	92
4d	Cl	C_6H_5	235-236	81	92
4e	Cl	4-ClC_6H_4	218-219	80	93
4f	Cl	4-$NO_2C_6H_4$	290-291	82	95
4g	Br	C_6H_5	241-242	79	91
4h	Br	4-ClC_6H_4	184-186	81	94
4i	Br	4-$NO_2C_6H_4$	308-309	82	90

[a]Yield (%) of isolated pure product 4 were calculated w.r.t. 1.



SCHEME 2. **Plausible mechanism for the synthesis of title compounds 4.**

Conclusion

The present study provides organoiodine (III) mediated simplistic synthesis of new derivatives of 3-aryl-6-(3-coumarinyl)-[1,2,4]triazolo[4,3-b][1,2,4]triazines (4) starting from the reactants 3-acetylcoumarins 1 and triazoles 3 through the intermediacy of tosylates 2. The efficacy of the reaction was further extended by adopting the single vessel procedural development without isolating the intermediate TK. The one reactor procedure was proved to be superior in terms of experimentation, time duration and yield.

Acknowledgements

We thank University Grants Commision (UGC), New Delhi for providing the financial assistance to accomplish the work and to Kurukshetra university, Kurukshetra, Haryana for providing the necessary research facilities.

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