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Succinimide-*N*-sulfonic Acid Promoted Efficient, One-Pot, Three Component Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-ones

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A series of 2,3-dihydroquinazolin-4(1*H*)-ones has been synthesized using a simple, effective, one-pot, three component condensation of isatoic anhydride, aromatic aldehydes and amines in refluxing ethyl alcohol. It has been found that 15 mol% succinimide-*N*-sulfonic acid is the optimum amount of catalyst to obtain the high yield.

Keywords: Succinimide-*N*-sulfonic acid, 2,3-Dihydroquinazolin-4(1*H*)-one, One pot synthesis.

INTRODUCTION

Dihydroquinazolinones are an important class of heterocycles as they show various biological and pharmacological activities such as diuretic [1], antitumor [2], antidepressant [3], antibiotic [4], analgesic [5] and antipyretic [6] activities. Till this date various methods for the synthesis of these types of compounds have been already proposed by the researchers [7]. Among them, the condensation of anthranilamide with the substituted aldehydes in *p*-toluenesulfonic acid (PTSA) catalyst [8,9], one pot condensation of ammonium salt, aromatic aldehydes and amine derivatives using solid catalysts or mineral acids [10]. In addition to this the reductive cyclization of metallic samarium with *o*-azido benzamide or *o*-nitro benzamide has also done using iodine as a catalyst [11]. The simplest route reported for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones is the condensation of anthranilamide, with aldehyde or ketone using various catalysts such as PTSA [12], acetic acid [13], tetrabutylammonium bromide [14], gallium (III) triflate [15], ionic liquids [16], montmorillonite K-10 [17], *etc.* However, most of the above methods having various disadvantages such as toxic solvents, long reaction time, hard workup procedure and costly reagents. In this regard to develop the simple, faster and efficient method is important goal of several researchers.

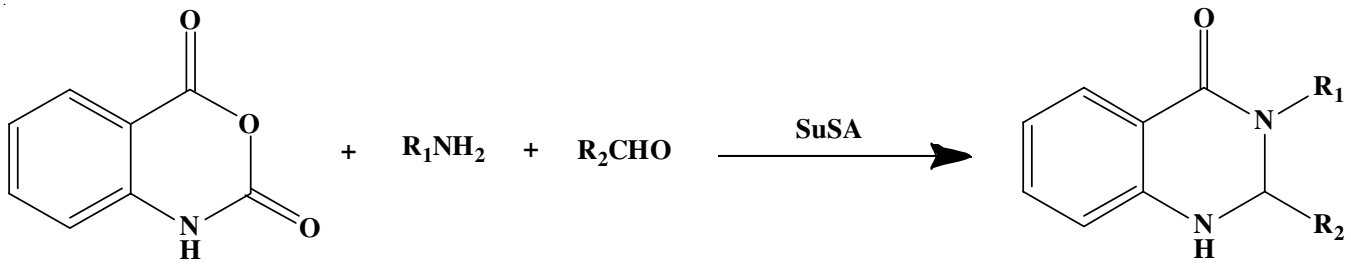
Various uses of green chemistry in the organic synthesis such as use of minimum stages in the synthesis route, use of non-toxic solvents and minimization of water are well known [18]. The use of succinimide-*N*-sulfonic acid was reported by various researchers in the different organic transformations [19-21]. Accordingly, a new simple and green route is developed for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using succinimide-*N*-sulfonic acid with short reaction time.

EXPERIMENTAL

All the chemicals were of analytical grade and used without further purification. Isatoic anhydride, primary amines and aldehydes were procured from Merck, India. The FT-IR spectra were recorded in the range of 4000-400 cm^{-1} on Perkin-Elmer 781 spectrophometer. ^1H NMR spectra were obtained from using DMSO as a solvent and TMS as an internal standard on Bruker Avance III HD. The melting points were recorded on Buchi B-545 with open capillary tubes. The TLC technique was used to monitor the progress of the reaction.

Synthesis of succinimide-*N*-sulfonic acid catalyst: The catalyst was synthesized by using chlorosulfonic acid and succinimide as per reported methods [22,23].

Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives: Succinimide-*N*-sulfonic acid (15 mol%) was added to a stirred mixture of aldehyde (1 mmol), isatoic anhydride (1 mmol) and amine (1.2 mmol) in 5 mL ethyl alcohol under reflux condition (**Scheme-I**). The TLC was used to monitor the reaction. A 30 mL cold water was added to the above mixture to solidify the obtained product. The synthesized product was filtered



Scheme-I

TABLE-1
SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES DERIVATIVES

Sample	R^1	R^2	Time (min)	Yield (%)	m.p. (°C)
1	2-$ClC_6H_4CH_2$	2-Cl-6-FC_6H_3	30	84	202-204
2	2-$ClC_6H_4CH_2$	4-$NO_2C_6H_4$	30	93	206-208
3	2-$ClC_6H_4CH_2$	2,6-$Cl_2C_6H_3$	30	96	185-187
4	2-$ClC_6H_4CH_2$	Ph	60	92	174-175
5	Ph	2-ClC_6H_4	60	94	135-137
6	Ph	2,4-$Cl_2C_6H_3$	45	93	190-192
7	Ph	3-$O_2NC_6H_4$	45	93	188-190
8	Ph	2-$O_2NC_6H_4$	45	94	180-182
9	$PhCH_2$	2,3-$Cl_2C_6H_3$	45	90	207-209
10	$PhCH_2$	Ph	30	86	159-161
11	$PhCH_2$	2-$O_2NC_6H_4$	30	86	134-136

Reaction condition: Aldehyde (1 mmol), isatoic anhydride (1 mmol), amine (1.2 mmol) and SuSA catalyst (15 mol%)

and washed with cold water. The recrystallization was carried out using ethanol as a solvent. The yield and appropriate time required is given in Table-1.

Sample 1: m.f.: $C_{21}H_{15}N_2OCl_2F$, ^{1}H NMR ($CDCl_3$) δ ppm: 4.20 (d, *J* = 16.0 Hz, 1H, CH_2), 4.84 (br, 1H, NH), 5.56 (d, *J* = 16.0 Hz, 1H, CH_2), 6.39 (s, 1H, CH), 6.70 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.90-6.94 (m, 2H, Ar-H), 7.20-7.31 (m, 4H, Ar-H), 7.29-7.50 (m, 3H, Ar-H), 7.99 (dd, *J* = 1.5 Hz, *J* = 1.3 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 50.72, 67.77, 111.77, 116.12, 117.27, 120.56, 127.43, 127.56, 128.21, 128.99, 129.11, 129.66, 129.88, 130.20, 130.57, 133.59, 133.74, 133.97, 145.87, 161.73, 163.18, 165.15.

Sample 2: m.f.: $C_{21}H_{16}N_3O_3Cl$, ^{1}H NMR ($CDCl_3$): δ = 4.00 (d, *J* = 16.0 Hz, 1H, CH_2), 4.40 (br, 1H, NH), 5.70 (d, *J* = 16.0 Hz, 1H, CH_2), 6.75 (d, *J* = 8.0 Hz, 1H, CH), 6.65 (s, 1H, Ar-H), 6.90-6.95 (m, 1H, Ar-H), 7.30-7.40 (m, 8H, Ar-H), 8.30 (dd, *J* = 1.6 Hz, *J* = 1.2 Hz, 1H, Ar-H), ppm; ^{13}C NMR ($CDCl_3$): δ = 50.30, 65.46, 112.43, 120.20, 122.32, 128.30, 130.63, 129.43, 136.12, 137.75, 137.80, 138.54, 138.86, 147.99, 166.42 ppm.

Sample-3: m.f.: $C_{21}H_{15}N_2OCl_3$, ^{1}H NMR ($CDCl_3$) δ ppm: 3.95 (d, *J* = 16.0 Hz, 1H, CH_2), 4.35 (br, 1H, NH), 5.55 (d, *J* = 16.0 Hz, 1H, CH_2), 6.60 (d, *J* = 8.0 Hz, 1H, CH), 6.80 (s, 1H, Ar-H), 6.80-6.90 (m, 1H, Ar-H), 7.20-7.50 (m, 8H, Ar-H), 8.10 (dd, *J* = 1.6 Hz, *J* = 1.2 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 44.70, 70.55, 114.43, 115.77, 120.14, 127.50, 129.36, 129.43, 129.66, 129.85, 130.10, 132.33, 133.51, 133.84, 134.80, 134.43, 136.75, 145.77, 164.66.

Sample 4: m.f.: $C_{21}H_{17}N_2OCl$, ^{1}H NMR ($CDCl_3$): δ = 3.95 (d, *J* = 16.0 Hz, 1H, CH_2), 4.35 (br, 1H, NH), 5.55 (d, *J* = 16.0 Hz, 1H, CH_2), 6.60 (d, *J* = 8.0 Hz, 1H, CH), 6.80 (s, 1H, Ar-H), 6.80-6.90 (m, 1H, Ar-H), 7.20-7.50 (m, 8H, Ar-H), 8.10 (dd, *J* = 1.6 Hz, *J* = 1.2 Hz, 1H, Ar-H), ppm; ^{13}C NMR ($CDCl_3$): δ = 40.82, 75.27, 112.12, 113.54, 121.24, 125.73, 126.67, 127.37, 127.38, 127.75, 129.23, 132.33, 147.37, 165.68 ppm.

Sample 5: m.f.: $C_{20}H_{15}N_2OCl$, ^{1}H NMR ($CDCl_3$): δ = 5.20 (br, 1H, NH), 6.27 (s, 1H, CH), 6.66 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.00-7.05 (m, 1H, Ar-H), 7.22-7.29 (m, 3H, Ar-H), 7.39-7.46 (m, 1H, Ar-H), 7.52-7.63 (m, 1H, Ar-H), 8.27 (d, *J* = 8 Hz, 1H, Ar-H), 8.15 (d, *J* = 1.2 Hz, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ = 67.44, 114.67, 116.49, 122.46, 127.22, 128.79, 130.19, 130.27, 132.10, 132.49, 134.46, 135.27, 139.70, 142.34, 147.10, 166.33 ppm.

Sample-6: m.f.: $C_{20}H_{14}N_2OCl_2$, ^{1}H NMR ($CDCl_3$) δ ppm: 5.19 (br, 1H, NH), 6.57 (s, 1H, CH), 6.59 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.91-6.96 (m, 1H, Ar-H), 7.19-7.26 (m, 3H, Ar-H), 7.29-7.47 (m, 3H, Ar-H), 7.39-7.46 (m, 1H, Ar-H), 7.48-7.60 (m, 1H, Ar-H), 8.05 (d, *J* = 8 Hz, 1H, Ar-H), 8.07 (d, *J* = 1.2 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 71.55, 115.23, 117.99, 120.21, 126.22, 127.12, 130.79, 130.33, 131.87, 133.20, 134.50, 136.64, 136.70, 141.71, 145.66, 166.23.

Sample 7: m.f.: $C_{20}H_{15}N_3O_3$; ^{1}H NMR ($CDCl_3$): δ = 5.25 (br, 1H, NH), 6.60 (s, 1H, CH), 6.85 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.93-6.99 (m, 1H, Ar-H), 7.25-7.30 (m, 3H, Ar-H), 7.40-7.65 (m, 3H, Ar-H), 7.70-7.90 (m, 1H, Ar-H), 8.15 (d, *J* = 8 Hz, 1H, Ar-H), 8.20 (d, *J* = 1.2 Hz, 1H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ = 67.49, 112.39, 117.45, 120.92, 125.47, 126.36, 129.79, 130.74, 132.28, 133.76, 135.92, 135.99, 136.18, 142.35, 147.72, 166.42 ppm.

Sample 8: m.f.: $C_{20}H_{15}N_3O_3$, ^{1}H NMR ($CDCl_3$): δ = 5.20 (br, 1H, NH), 6.45 (s, 1H, CH), 6.60 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.80-6.85 (m, 1H, Ar-H), 7.21-7.29 (m, 3H, Ar-H), 7.33-7.50 (m, 3H, Ar-H), 7.41-7.47 (m, 1H, Ar-H), 7.50-7.65 (m, 1H, Ar-H), 8.20 (d, *J* = 8 Hz, 1H, Ar-H), 8.25 (d, *J* = 1.2 Hz, 1H,

Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ = 69.31, 114.15, 116.56, 119.36, 125.74, 129.57, 130.15, 132.42, 133.16, 135.50, 136.73, 137.39, 140.52, 146.43, 165.19 ppm.

Sample-9: m.f.: $C_{21}H_{16}N_2OCl_2$, ^{1}H NMR ($CDCl_3$) δ ppm: 3.59 (d, *J* = 16.0 Hz, 1H, CH_2), 4.97 (br, 1H, NH), 5.80 (d, *J* = 16.0 Hz, 1H, CH_2), 6.12 (s, 1H, CH), 6.60 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.87-6.92 (m, 1H, Ar-H), 7.20-7.51 (m, 9H, Ar-H), 8.07-8.09 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 48.26, 68.55, 115.43, 115.89, 120.21, 125.28, 126.74, 127.63, 128.92, 128.99, 129.10, 130.17, 130.51, 134.51, 134.85, 135.55, 139.85, 145.56, 164.66.

Sample 10: m.f.: $C_{21}H_{18}N_2O$, ^{1}H NMR ($CDCl_3$): δ = 3.65 (d, *J* = 16.0 Hz, 1H, CH_2), 5.05 (br, 1H, NH), 5.65 (d, *J* = 16.0 Hz, 1H, CH_2), 6.09 (s, 1H, CH), 6.55 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.90-6.97 (m, 1H, Ar-H), 7.15-7.45 (m, 9H, Ar-H), 8.10-8.15 (m, 1H, Ar-H), ppm; ^{13}C NMR ($CDCl_3$): δ = 50.55, 70.67, 116.76, 117.73, 121.81, 124.82, 127.72, 130.15, 136.42, 134.14, 137.55, 140.78, 147.56, 165.27 ppm.

Sample-11: m.f.: $C_{21}H_{17}N_3O_3$, ^{1}H NMR ($CDCl_3$) δ ppm: 3.19 (d, *J* = 16.0 Hz, 1H, CH_2), 5.27 (br, 1H, NH), 5.59 (d, *J* = 16.0 Hz, 1H, CH_2), 6.33 (s, 1H, CH), 6.60 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.85-6.90 (m, 1H, Ar-H), 7.30-7.37 (m, 6H, Ar-H), 7.48-7.50 (m, 2H, Ar-H), 7.60-7.62 (m, 1H, Ar-H), 8.06-8.09 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$) δ ppm: 49.55, 66.29, 114.63, 115.15, 120.32, 126.12, 127.70, 127.92, 128.12, 128.20, 129.34, 130.60, 134.10, 135.17, 145.66, 146.43, 164.63.

RESULTS AND DISCUSSION

The reaction between isatoic anhydride, benzaldehyde and aniline was optimized by using various solvents. The ethyl alcohol was observed to be the solvent which gives highest yield (Table-2). The reactant ratios was also optimized and observed as isatoic anhydride (1 equiv.), benzaldehyde (1 equiv.) and aniline (1.2 equiv.). The catalyst effect is also studied on the reaction rate by varying the amount of succinimide-*N*-sulfonic acid catalyst (Table-3). It was also observed that the 15 mol% succinimide-*N*-sulfonic acid catalyst is sufficient for the synthesis. The enhancement in the quantity of catalyst also not shows increase in the yield. ^{1}H and ^{13}C NMR spectrum was used to characterize the synthesized products.

TABLE-2
SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES UNDER DIFFERENT REACTION CONDITIONS[a]

Entry	Solvent	Time (min)	Yield (%)
1	CH_3CN	60	33
2	CH_3NO_2	60	40
3	DMF	45	27
4	EtOH	30	93
5	DMSO	40	45
6	H_2O	35	63

[a]Reaction condition: Aldehyde (1 mmol), isatoic anhydride (1 mmol), amine (1.2 mmol) and SuSA catalyst (15 mol%)

The aromatic amines with nitro and halogen group substitution also used in the study of the reaction. The reaction also studied for various halogens substituted and unsubstituted aromatic aldehydes. The enhanced yield was observed in most of the cases. Being an environmentally benign catalyst succinimide-*N*-sulfonic acid was studied to synthesize various organic transformations [24]. Therefore, succinimide-*N*-sulfonic acid shows remarkable results due to its milder reaction conditions to make it the useful catalyst for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one.

TABLE-3
OPTIMIZATION OF THE SUCCINIMIDE-*N*-SULFONIC ACID (SuSA) CATALYST FOR THE SYNTHESIS OF 2,3-DIHYDROQUINAZOLIN-4(1*H*)-ONES DERIVATIVES

Entry	SuSA (mol%)	Time (min)	Yield (%)
1	5	120	59
2	8	100	75
3	12	60	81
4	15	30	90
5	18	45	87
6	20	90	84
7	0	240	Trace

At the onset of present research work, the model condensation reaction of isatoic anhydride, benzaldehyde and aniline in the presence of succinimide-*N*-sulfonic acid catalyst under different reaction media is also studied. Among the various organic solvents, ethanol is observed as the best solvent. After comparing with the other solvents under similar reaction conditions, the condensation reaction in the presence of ethyl alcohol shows 93% yield and the required time is 30 min.

Conclusion

This works reports a simple, environmentally benign and efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-one by one pot reaction of aldehydes, amines and isatoic anhydride in the presence of catalytic amount of succinimide-*N*-sulfonic acid and ethyl alcohol as solvent. This synthetic route offers several advantages compared to previous reported procedures like high yield, low-cost catalyst, easy workup, simple procedure, non-toxic solvent and environmental friendliness. Moreover, the catalyst is easy to synthesize as well as efficiently.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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