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SUCCINIMIDE-*N*-SULPHONIC ACID CATALYZED SYNTHESIS OF [1,2,4]-TRIAZOLO-QUINAZOLINONE DERIVATIVES UNDER SOLVENT FREE CONDITIONS

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Abstract: Herein, we report succinimide-*N*-sulphonic acid (SuSA) as an efficient, low cost, reusable and environmentally benign protocol for the synthesis of 1,2,4-triazoloquinazolinone derivatives from the reaction of aromatic aldehydes and dimedone with 3-amino-1,2,4 triazole as a amine source under solvent free reaction conditions. The synthesized compounds were confirmed by IR, ^{1}HNMR, ^{13}CNMR and Mass spectral analysis.

Keywords: SuSA, Aromatic aldehydes, dimedone, 3-amino-1,2,4 triazole, Solvent free.

Introduction

Nitrogen containing heterocyclic compounds played important role in the pharmaceutical and agrochemical industries due to their frequently massive physiological properties which have results several applications[i]. Among these quinazoline derivatives have important pharmacological activities such as anti-HIV[ii], anticancer[iii], anticonvulsant[iv], antifertility[v], anti-inflammatory[vi], antidiabetics[vii], antihypertensive[viii]. In addition, triazoles are the important structural parts in the skeleton of some bioactive compounds[ix-xi].

In recent years chemist more attention to the synthesis of 1,2,4-triazoloquinazolinone derivatives due to their wide range of synthetic and pharmacological application. Hence, several synthetic methodologies have been developed for the synthesis of 1,2,4-triazoloquinazolinone derivatives in the literature. Among these methods are the condensation of dimedone, aldehydes with 3-amino-1,2,4-triazole in the presence of sulfamic acid[xii], molecular iodine[xiii] and anthranilic acid[xiv], reusable DABCO-based ionic liquids[xv].

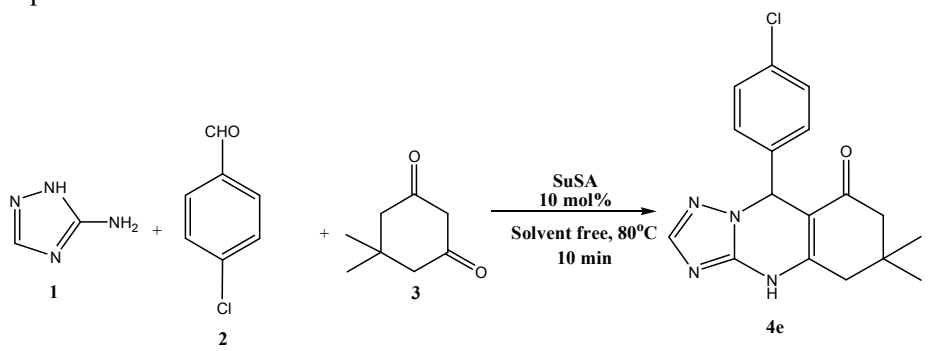
However, some of these methods are suffered from one or more disadvantages such as harsh reaction conditions, use of expensive and hazardous catalyst or solvent, longer reaction time and unsatisfactory yield. Therefore, for the synthesis of 1,2,4-triazolo-quinazolinone derivatives is a need to develop a rapid, efficient, and environmentally benign synthetic protocol.

Based on the previous studies the use of catalysts bearing sulfonic acid functionality for carrying synthesis of 1,2,4-triazolo-quinazolinone derivatives, our efforts were directed for finding out sulphonic acid based organocatalysts, which should be mild in nature. In this endeavor, succinimide -*N*- sulphonic acid perfectly stood out as a mild acid catalyst. Due to the experimental simplicity in recent years, succinimide-*N*-sulfonic acid (SuSA) has drawn much interest in different organic synthesis[xvi-xx].

Results and Discussion

To explore the use of succinimide-*N*-sulfonic acid as a catalyst for the reaction of 4-chlorobenzaldehyde and dimedone with 3-amino-1,2,4 triazole for 10–15 min under solvent free condition to give the formation of 6,6-dimethyl-9-(4-chlorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one in 94 % yield (Table 1 Entries 5). Interestingly, when we carried out same reaction with absence of catalyst did not give any desired product. It means initiation of the reaction was must to intervention of catalyst. We find out exact requirement of catalyst and concentration of catalyst in the reaction. During this study, 10 mol% succinimide-*N*-sulfonic acids proved to be an efficient catalyst for the reaction transformation smoothly (Table 1 Entries 5). All the [1,2,4]triazolo-quinazolinone derivatives were obtained in excellent yields with good purity.

Encouraged by this result, in further set of experiments, in order to build the generality of the reaction, variety of aromatic aldehydes with either electron-withdrawing or electron-donating groups were converted into 6,6-dimethyl-9-(4-chlorophenyl)-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one derivatives in good to excellent yields. All the results are presented in **Table 2**.

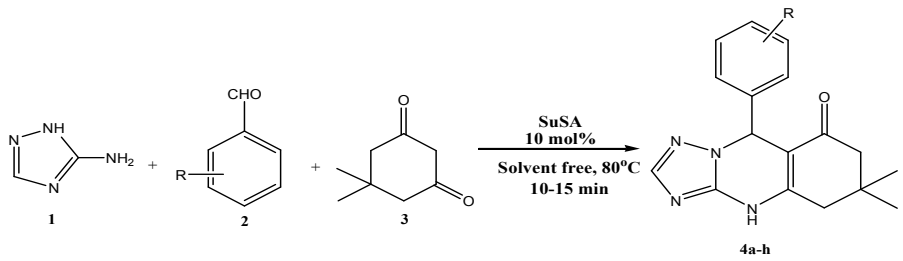


Scheme-1

Table-1 Optimization of catalyst

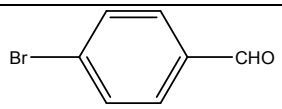
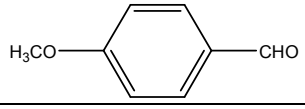
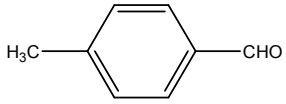
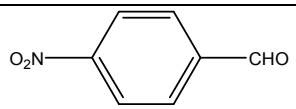
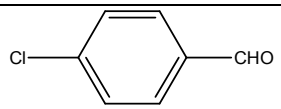
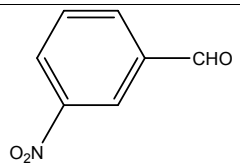
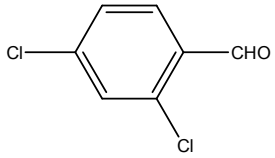
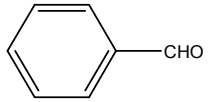
Entry	Amount of catalyst	Time (min)	Yield (%)[b]
1	-	120	Trace
2	2	60	35
3	5	45	70
4	7	25	82
5	**10**	**10**	**94**
6	15	10	94

[a]**Reaction conditions:** Dimedone (1 mmol), 4-chlorobenzaldehydes (1 mmol), 3-amino-1,2,4-triazole (1 mmol), SuSA (10 mol%) at 80 ^{o}C. [b]Isolated yield.



Scheme-2

Table-2 synthesis of 1,2,4-triazoloquinazolinone derivatives using SuSA under solvent free conditions[a]

Entry	Aldehydes	Time (min)	Yield (%)[b]	Melting point °C
4a		12	90	284-286
4b		10	92	225-227
4c		12	93	264-266
4d		10	94	302-304
4e		10	94	301-303
4f		12	92	265-268
4g		15	85	322-324
4h		15	92	250-252

[a]**Reaction conditions:** Dimedone (1 mmol), Aromatic aldehydes (1 mmol), 3-amino-1,2,4 triazole (1 mmol), SuSA (10 mol%) at 80 °C. [b]Isolated yield.

The reusability of the catalyst is one of the main advantages and makes it useful for practicable applications. Therefore the, recovery and reusability of SuSA were investigated. In order to explore the reusability of SuSA, the reaction of 4-chloro benzaldehyde and dimedone with 3-amino-1,2,4 triazole under solvent free condition was selected as a model reaction. After completion of the reaction, the SuSA was washed with ethyl acetate dried and

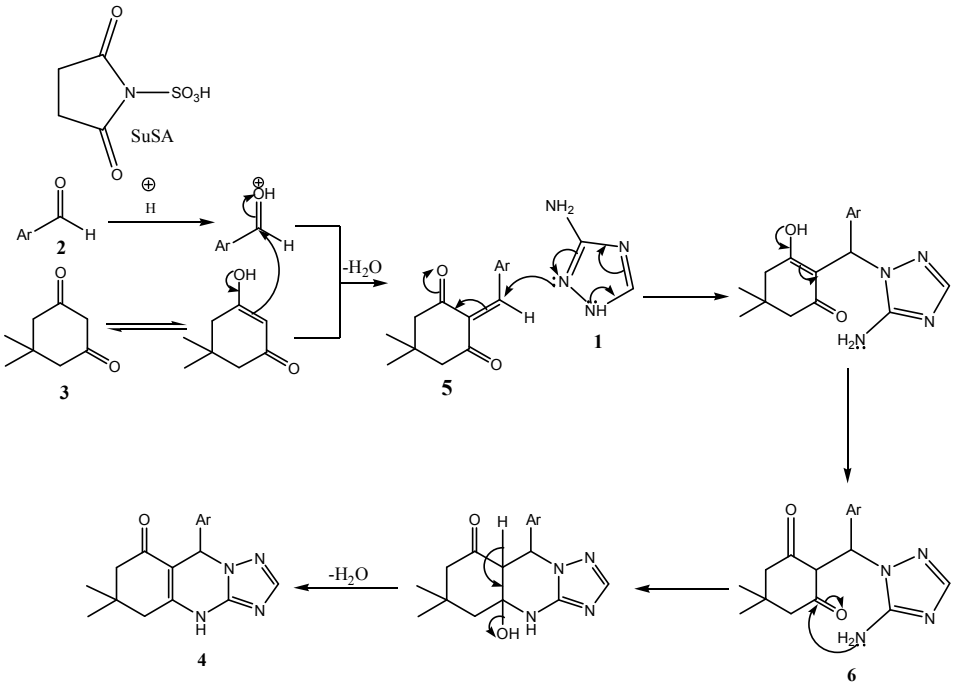
store for another consecutive reaction. This process repeatedly for next three runs. It means SuSA is stable and reused without significant loss of catalytic activity (**Table 3**)

Table-3 Reusability of the SuSA

No. of Runs	Fresh	Run 1	Run 2	Run 3
Yield (%)[b]	94	94	92	91

[b]Isolated Yield

The possible mechanism for the SuSA catalyzed transformation is shown in following **Schemes 3.** In regard to reaction mechanism, we suggest that initially, the solid acid catalyst protonates the carbonyl group of aromatic aldehyde, which then condenses with dimedone to produce the intermediate product **5**. Michael addition reaction takes place undergoing more nucleophilic endocyclic nitrogen attack in the 3-amino-1,2,4-triazole **1** to α, β-unsaturated carbonyl compound **5** creates acyclic intermediate **6**. Due to, the endocyclic nitrogen is more nucleophilic than the primary amino group[xxi-xxii]. Further intermediate **6** undergoes intra-molecular cyclisation followed by loss of water molecule giving rise to corresponding triazolo-quinazolinones derivatives **4.**



Scheme-3

Experimental

All chemicals and solvents obtained from S. D. Fine, Spectrochem and Loba chemical companies. Formation of products monitored by thin layer chromatography (TLC) and melting points determined by open capillary and are uncorrected. ^{1}HNMR and ^{13}CNMR spectra were characterized by using Bruker Avance spectrometer 500 MHz and 125 MHz respectively in $CDCl_3$ solvent. Chemical shift (δ) values expressed in parts per million (ppm) and tetramethylsilane (TMS) used as internal standard. Mass spectra were recorded on a macro mass spectrometer, applying electrospray ionization (ESI) method.

General Procedure for the Preparation of Succinimide-N-sulfonic acid

Succinimide-N-sulphonic acid as a stable reagent is easily prepared as reported by the reaction of succinamide with chlorosulphonic acid (Yield 94%).[xxiii]

General procedure for the synthesis of [1,2,4] triazolo-quinazolin–8(4H)-ones

A mixture of the aromatic aldehyde (1 mmol), 3-amino-1,2,4 triazole (1 mmol), dimedone (1 mmol), SuSA (10 mol %) was heated at 80 °C under solvent- free conditions for the appropriate time. Progress of the reaction was monitored by TLC (*n*-hexane: ethyl acetate, 75:25). After completion of reaction, it was cooled to room temperature and 5 mL of cold water was added to the mixture. The SuSA was dissolved in water and filtered for separation of the crude product and the separated product was washed twice with ethanol (2 × 5 mL) to afford the title compounds (4a–4h) with excellent yield and good purity.

Selected Spectral data:

6,6-dimethyl-9-(4-bromophenyl)-5,6,7,9-tetrahydro[1,2,4]-triazolo[5,1b] quinazolin-8 (4H)-one (Table 2, 4a)

Pale yellow solid; Yield 90%; mp 284-286 °C; IR(KBr): 3082, 2956, 2886, 1642, 1580, 1364, 1252, 835, 765cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6): δ 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.20 (q, J = 10.38, 16.43 Hz, 2H, –CH_2), 2.55 (s, 2H, –CH_2), 6.21 (s, 1H, –CH), 7.14-7.16 (d, J = 8.30 Hz, 2H, Ar-H), 7.48-7.50 (d, J = 8.30 Hz, 2H, Ar-H), 7.71 (s, 1H, Ar-H), 11.19 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d6): δ 27.40, 28.86, 32.69, 50.24, 57.94, 105.64, 121.33, 129.73, 131.69, 141.43, 147.29, 150.69, 151.07, 193.49; MS m/z (ESI): 373 $[M+H]^+$.

6,6-dimethyl-9-(4-methoxyphenyl)-5,6,7,9-tetrahydro[1,2,4]triazolo[5,1b]quinazolin-8-(4H)-one (Table 2, 4b)

Colourless solid; Yield 92%; mp 225-227 °C; IR (KBr): 765, 829, 1252, 1364, 1580, 1635, 2950, 3095 cm^{-1}. ^{1}H NMR (DMSO-D_6, 500 MHz): δ 0.75 (s, 3H). 0.82 (s, 3H), 2.07(d, *J* = 16Hz, 1H), 1.83 (d, *J* = 16Hz, 1H), 1.98 (d, *J* =16Hz, 1H), 2.28-2.37 (m, 2H), 3.47 (s, 3H), 5.93 (s, 1H), 6.60 (d, *J* = 8Hz, 2H), 6.87 (d, *J* = 8Hz, 2H), 7.45 (s, 1H), 10.87 (s, 1H), ^{13}C NMR (DMSO-D_6, 125 MHz): δ 26.79, 28.49, 32.15, 49.78, 54.99, 57.30, 105.71, 113.54, 128.09, 133.82, 146.72, 150.14, 158.66, 192.94; ESI-MS: *m/z* 325 $[M+H]^+$.

6,6-dimethyl-9-(4-nitrophenyl)-5,6,7,9-tetrahydro[1,2,4]triazolo[5,1b]quinazolin-8-(4H)-one (Table 2, 4d)

Pale yellow solid; Yield 94%; mp 302-304 °C; IR (KBr): 852, 1252, 1346, 1593, 1643, 2961, 3080, 3105 cm^{-1}. ^{1}H NMR (DMSO-D_6, 500 MHz): δ 0.96(s, 3H). 1.05 (s, 3H), 2.07(d, *J* = 16Hz, 1H), 2.21 (d, *J* = 16Hz, 1H), 2.57 (d, *J* =16Hz, 1H), 2.50 (d, *J* = 16Hz, 1H), 6.37 (s, 1H), 7.50 (d, *J* = 8Hz, 2H), 7.74 (s, 1H), 8.17 (d, *J* = 8Hz, 2H), 11.31 (s, 1H), ^{13}C NMR (DMSO-D_6, 125 MHz): δ 27.45, 28.78, 32.72, 50.17, 58.01, 105.24, 124.06, 128.97, 147.33, 147.43, 148.90, 150.92, 151.48, 193.52; ESI-MS: *m/z* 340 $[M+H]^+$.

6,6-dimethyl-9-(3-nitrophenyl)-5,6,7,9-tetrahydro[1,2,4]-triazolo[5,1b]quinazolin-8(4H)-one (Table 2, 4f)

Yellow solid; Yield 92%; mp 265-268 °C; IR(KBr): 3082, 2956, 1649, 1580, 1344, 1252, 807cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6): δ 0.75 (s, 3H, CH_3), 0.829 (s, 3H, CH_3), 1.86 (d, J = 16 Hz, 1H, –CH_2), 1.99 (d, J = 16 Hz, 1H, –CH_2), 2.28-2.40 (m, 2H, –CH_2), 6.20 (s, 1H, –CH), 7.37-7.44 (m, 2H, Ar-H), 7.52 (s, 1H, Ar-H), 7.84-7.90 (m, 2H, Ar-H), 11.09 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d6): δ 26.85, 28.31, 32.23, 49.65, 57.39, 104.5, 121.66,

122.81, 130.04, 133.71, 143.45, 146.77, 147.58, 150.42, 151.13, 193.09; MS m/z (ESI): 340 $[M+H]^+$.

Conclusion

In summary, in this protocol we report the synthesis of [1,2,4] triazolo-quinazolin–8(4H)-ones derivatives from the condensation of aromatic aldehydes and dimedone with 3-amino-1,2,4 triazole by using succinimide-*N*-sulfonic acid as a catalyst under solvent-free conditions. This protocol offers several noteworthy advantages such as mildness of the reaction conditions, short reaction times, and high to excellent yields, simple procedure and reusability of the catalyst.

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