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AN EFFICIENT SYNTHESIS OF [1,2,4] TRIAZOLO-QUINAZOLINONE DERIVATIVES USING TIN (II) CHLORIDE DIHYDRATE UNDER MILD REACTION CONDITIONS

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Abstract: In present protocol, we have developed an efficient and environmentally benign protocol for the synthesis of [1, 2, 4] triazolo-quinazolinone derivatives by the condensation of 3-amino-1, 2, 4-triazole as amine sources, with aromatic aldehydes and dimedone in the presence of 10 mol % of $SnCl_2 \cdot 2H_2O$ in acetonitrile at 80 ^oC. The key advantages of these reaction is low cost, non toxic, excellent yield, shorter reaction time, eco-friendly nature, mild reaction condition and no need of column chromatographic separation.

Keywords: Tin (II) chloride dihydrate, Aromatic aldehydes, dimedone, 3-amino-1,2,4 triazole, Mild reaction condition.

Introduction

In medicinal chemistry azoles heterocycles are important structural moiety due to their wide range of pharmaceutical and therapeutic activities. In this regard many methods have been reported and reviewed[i]. Fused heterocyclic compounds triazolo-quinazolinone derivatives are gained much more synthetic attention due to found in their most of the biological activity such as anticancer[ii], antitumour[iii], antihypertensive,[iv] analgesic and anti-inflammatory,[v] antihistaminic,[vi] and antiHIV[vii] activities. Because of their importance from industrial, synthetic and pharmaceutical point of view, few methods have been reported for the synthesis of triazolo-quinazolinone derivatives in the literature. The one pot multi-component condensation reaction of dimedone, different aldehydes with 3-amino-1,2,4-triazole by microwave irradiation[viii], conventional[ix] and conventional solvent free methods such as Microwave-assisted silica-promoted[x], Nafion-H®[xi], $H_6P_2W_{18}O_{62} \cdot 18H_2O$[xii] and $H_4[W_{12}SiO_{40}]$ grafted on magnetic chitosan[xiii], DMF/TsOH[xiv] Nafion-H®[xv], molecular iodine[xvi], Amberlyst-15® in PEG[xvii], DMF[xviii], $H_6P_2W_{18}O_{62}.18H_2O$[xix], acetic acid[xx].

However, among these many methods experience from one or more of the disadvantages such as requirement of strong acidic conditions, longer reaction times, low yields, tedious work-up procedures, excess amount of catalyst, and the use of toxic reagents, catalysts, or

solvents. As a results, the researcher have strong demand to developed better methodology for the synthesis of 1,2,4-triazoloquinazolinone derivatives in terms of simplicity, environmentally benign method, economic viability, highly efficient and high yielding which is achieved by using stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$).

In recent literature, $SnCl_2 \cdot 2H_2O$ is commonly used as a catalyst in organic synthesis[xxi] because of their properties such as non-toxic nature, easy availability, inexpensiveness and easy handling. It also played very important role for the synthesis of biologically active heterocycles such as benzimidazoles[xxii], quinoxalines[xxiii], functionalization of 4,5-diaminopyrazoles[xxiv] and meso-substituted dipyrromethanes[xxv].

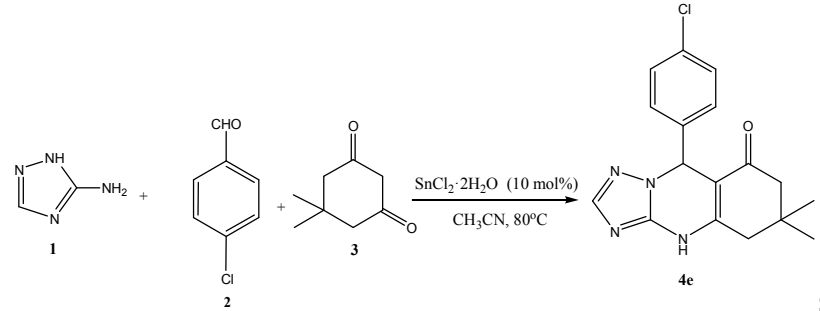
Result and Discussion

To explore the use of stannous chloride dihydrate ($SnCl_2 \cdot 2H_2O$) for the synthesis of 1,2,4-triazolo-quinazolinone by the condensation reaction of 4-chloro benzaldehyde, dimedone and 3-amino 1,2,4-triazole as a amine source in acetonitrile at 80 ^oC is consideration as a model reaction (Scheme 1). Initially, we have investigated the amount of catalyst required for this organic transformation. During this study, we have carried out the model reaction without/absence of catalyst for 120 min. but did not any desired product formed. It means initiation of the reaction was must to adding the catalyst. We realize the exact requirement of concentration and amount of catalyst for the reaction. Throughout the study, we have observed that the 10 mol% $SnCl_2 \cdot 2H_2O$ proved to be an efficient catalyst for the smoothly conversion of reaction (Table 1, Entry 8). All the [1,2,4]triazolo-quinazolinone derivatives were obtained in excellent yields with good purity. With this study of reaction conditions, we have also optimized the effect of various solvents on the reaction conditions such as water, methanol, ethanol, aqueous ethanol and acetonitrile was investigated. The acetonitrile was found to be the best solvent than the other tested solvents in terms of both yield of the product and reaction time (Table 1 Entry 8) for this transformation.

Table 1 Optimization of solvent and catalyst in synthesis of 1,2,4-triazoloquinazolinone derivatives under mild reaction conditions at 80^oC[a]

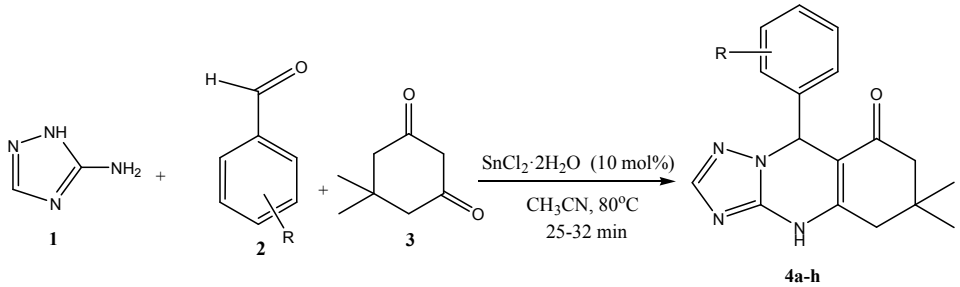
Entry	Solvent	Catalyst (mol %)	Time (min.)	Yield[b] (%)
1	-	-	120	Trace
2	H_2O	10	60	50
3	CH_3OH	10	60	72
4	EtOH	10	60	85
5	EtOH:H_2O	10	60	65
6	CH_3CN	5	60	70
7	CH_3CN	7	50	82
8	**CH_3CN**	**10**	**25**	**94**
9	CH_3CN	15	30	94

[a]**Reaction conditions:** Dimedone (1 mmol), 4-Chlorobenzaldehyde (1 mmol), 3-amino-1,2,4 triazole (1 mmol), stannous chloride dihydrate (10 mol%) in acetonitrile (3 mL) at 80 ^oC. [b]Isolated yield.



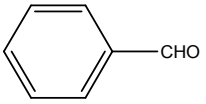
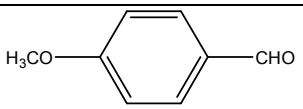
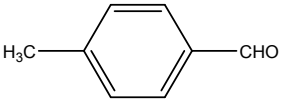
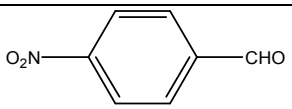
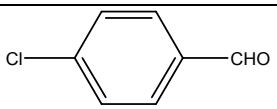
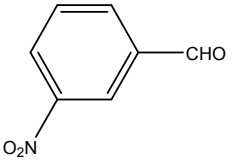
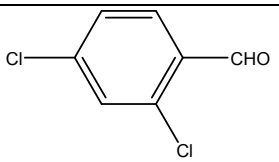
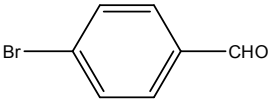
Scheme-1

Encouraging by this results, in further set of experiments, with both electron-donating or electron-withdrawing groups of various aromatic aldehydes were converted to 1,2,4-triazoloquinazolinone derivatives in good to excellent yields. The entire results are summarized in (Table 2).



Scheme 2

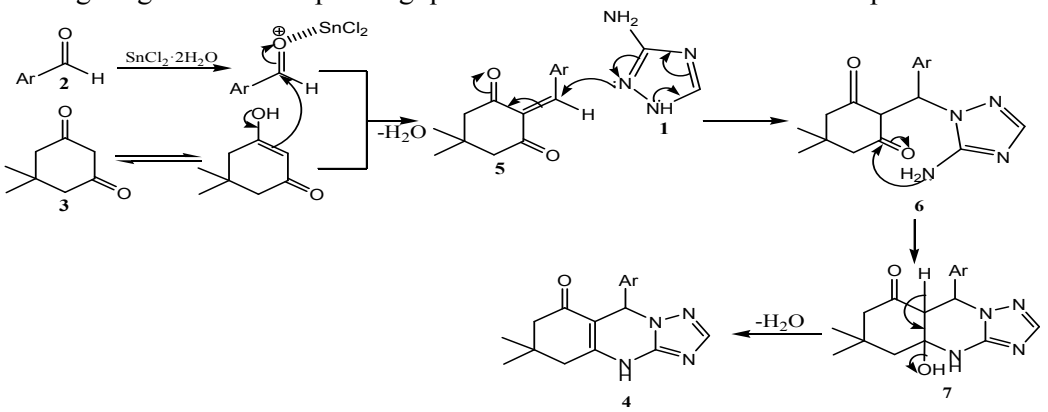
Table 2 synthesis of 1,2,4-triazoloquinazolinone derivatives using stannous chloride dihydrate under mild reaction conditions[a]

Entry	Aldehyde	Time (min)	Yield (%)[b]	Melting point °C
4a		30	92	248-250
4b		25	94	224-226
4c		28	92	264-266
4d		25	94	303-304
4e		25	94	302-304
4f		30	92	266-268
4g		32	87	324-325
4h		28	92	284-285

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

The probable mechanism of the stannous chloride dihydrate catalyzed conversion is shown in Schemes 3. In this regard to reaction mechanism, we suggest that initially, the

stannous chloride dihydrate catalyst protonates the carbonyl group of aromatic aldehyde **2**, 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**. Further intermediate **6** undergoes intra-molecular cyclisation followed by loss of water molecule giving rise to corresponding quinazolinones derivatives **4** via compound **7**



Scheme 3

Experimental

All chemicals and solvents purchased from S.D. Fine, Spectrochem and Loba chemical companies. Formation of products monitored by thin layer chromatography (TLC) and melting points were 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 electro-spray ionization (ESI) method.

General procedure for the synthesis of 1,2,4-triazolo-quinazolinone derivatives

The condensation reaction of aromatic aldehydes (1.0 mmol) and dimedone (1.0 mmol) with amine source 3-amino-1,2,4-triazole (1.0 mmol) in the presence of 10 mol % of $SnCl_2{\cdot}2H_2O$ in acetonitrile at 80 ^{o}C for appropriate time period. The progress of reaction was monitored by TLC. After completion of reaction, then solid product separated by filtration and resultant solids repeatedly wash with water. Solid products were recrystallization from ethanol.

Selected spectral data:

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

Pale yellow solid, yield—92%, mp-248-250 ^{o}C; IR (KBr): 3090, 2962, 1650, 1594, 1373, 1252, 721 cm^{-1}; ^{1}H NMR (DMSO-D_6, 500 MHz): δ = 0.95 (s, 3H, -CH_3), 1.03 (s, 3H, -CH_3), 2.05(d, *J* = 16Hz, 1H,-CH_2), 2.19 (d, *J* = 16Hz, 1H,-CH_2), 2.52-2.59 (m, 2H,-CH_2), 6.19 (s, 1H, -CH), 7.17-7.29 (m, 5H, Ar–H) 7.68 (s, 1H, NH) 11.14 (s, 1H, NH); ^{13}C NMR (DMSO-D_6, 125 MHz) δ 26.77, 28.45, 32.16, 49.74, 57.89, 105.55, 126.92, 127.69, 128.23, 141.55, 146.82, 150.24, 150.39, 192.96; MS m/z (ESI): 295 $[M+H]^{+}$.

6,6-Dimethyl-9-p-tolyl-5,6,7,9-tetrahydro-[1,2,4]triazolo[5,1-b]quinazolin-8(4H)-one (Table 2, entry 4c)

White solid; Yield 92%; mp 264–265 ^{o}C; IR (KBr): 3091, 2924, 1649, 1581, 1368, 1253, 756 cm^{-1};^{1}H NMR (500 MHz, DMSO-d6): δ 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.20 (d, J = 11.52 Hz, 2H, –CH_2), 2.39 (s, 3H, –CH_3), 2.50-2.58 (m, 2H, –CH_2), 6.16 (s, 1H, –CH), 7.07 (S, 4H, Ar-H), 7.67 (s, 1H, Ar-H), 11.10 (s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): d

192.2, 148.9, 148.6, 145.8, 137.3, 136.0, 127.7, 125.7, 105.2, 56.9, 59.1, 31.2, 37.7, 26.0, 19.7; MS m/z (ESI); 309 $[M+H]^+$.

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

Pale yellow solid, yield—94%, mp-302–304 ^oC; IR (KBr): 3124, 3088, 2962, 1649, 1579, 1367, 1253, 795 cm^{-1}; ^1H NMR (DMSO-D_6, 500 MHz): δ = 0.96 (s, 3H, -CH_3), 1.08 (s, 3H, -CH_3), 2.07(d, *J* = 16Hz, 1H,-CH_2), 2.27 (d, *J* = 16Hz, 1H,-CH_2), 2.50-2.58 (d, *J* =16Hz, 2H,-CH_2), 6.22 (s, 1H, -CH), 7.19–7.37 (m, 4H, Ar–H) 7.71 (s, 1H, NH) 11.19 (s, 1H, NH); ^{13}C NMR (DMSO-D_6, 125 MHz) δ 193.48, 151.06, 150.68, 147.29, 141.01, 132.77, 129.38, 128.76, 105.69, 57.86, 50.24, 32.69, 31.73, 28.86, 27.40; MS m/z (ESI): 329 $[M+H]^+$.

Conclusion

In summary, we have developed highly efficient and environmentally benign protocol for the synthesis of 1,2,4-triazoloquinazole derivatives using $SnCl_2 \cdot 2H_2O$ as a catalyst by the condensation reaction of dimedone, 3-amino 1,2,4-triazole as a amine source and various aromatic aldehydes in acetonitrile as a solvent at 80 ^oC. These protocol has few advantages is inexpensive and non-toxic catalyst, easily handling, simple procedure, mild reaction conditions eco-friendly, high yield and no need of chromatographic separation.

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