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Synthesis of Enol ether, α,β-unsaturated carbonyl compound, Oxoketenedithio acetal and Dimethyl aminomethylene ketone derivatives of s-Triazines as Intermediates for Synthesis of Fused Heterocycles

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Abstract

The synthesis of enol-ether, α,β-unsaturated carbonyl compound, oxoketenedithio acetal and dimethyl aminomethylene ketone derivatives of quinazoline and pyrimidine containing trisubstituted s-triazines. Apart from this, quinazoline and pyrimidine containing trisubstituted s-triazine template has also been used to synthesize quinoline-4-carboxylic acid moiety and diazepinone derivatives by adopting the Pfitzinger reaction and Beckmann rearrangement methodology. The structures of all the compounds have been confirmed by elemental analysis and spectral data.

Keywords: Synthesis, enol ether, α,β-unsaturated carbonyl compound, Oxoketenedithio acetal, dimethyl aminomethylene ketone derivatives, s-Triazines, intermediates, fused heterocycles.

Introduction

Various active intermediates such as enol ethers[1-4], α,β-unsaturated carbonyl compounds (chalcones)[5-7], oxoketenedithio acetals[8-11] and dimethyl aminomethylene ketones[12-15], *etc.* are known in the literature to undergo nucleophilic displacement with bidentate nucleophiles to form five-, six- and seven-membered fused heterocycles and thus provide unprecedented opportunities to a chemist for a one step synthesis of heterocyclic compounds such as condensed pyrazoles, isoxazoles, pyrimidines, benzodiazepines, benzoxazepines, benzothiazepines, *etc*. Incorporation of these pharmacophores on to the quinazoline, pyrimidine and piperidone containing s-triazine derivatives from corresponding active intermediates such as enol ethers, α,β-unsaturated carbonyl compound, oxoketenedithio acetals and dimethyl aminomethylene ketones have been reported. The present work is described the synthesis of quinoline-4-carboxylic acid (SS-2015-005) and diazepinone (SS-2015-006) along with active intermediates enol ethers (SS-2015-007), α,β-unsaturated carbonyl compounds (SS-2015-008), oxoketenedithio acetals (SS-2015-009) and dimethyl aminomethylene ketones (SS-2015-010) as per Scheme-1 which have been used as starting materials in synthesis fused novel heterocycles. The compound SS-2015-004 has been synthesized already and used as key starting material to synthesize above-mentioned active intermediates.

Material and Methods

Experimental: Melting points were determined in open glass capillaries and are uncorrected. The progress of the reaction was confirmed by TLC on silica gel (G) plates. IR spectra were recorded on FTIR-8400S, ^{1}H NMR spectra were recorded on AC-300F using CDCl3 /DMSO-d_6 as solvent. Chemical shift are expressed in δ ppm. Physical and spectral data are given along with respective compound.

Preparation of 2-[4-(2-Chloro-6,7-dimethoxy-quinazolin-4-ylamino)-6-(pyrimidin-2-yl amino)-[1,3,5]triazine-2-yl]-1,2,3,4- tetrahydro-benzo[b][1,6]naphthyridine-10-carboxylic acid (SS-2015-005): A solution of **SS-2015-004** (0.004mol), isatin (0.005mol) and KOH (1.2 g. in 5ml. of ethanol) was refluxed for 24 hours. After distillation of most of the solvent, water was added, the neutral impurities were removed by ether extraction and the aqueous layer was acidified with acetic acid and solid **SS-2015-005** was isolated by repeated crystallization from ethanol. FT-IR (KBr) ν_{max}/cm-^{1}: 2850 (COOH str.), 3260 (N-H str.), 2920 (C-H str.), 1600 (C=N str.), 1470, 1375 (C=C str.).; ^{1}H NMR (300 MHz, $CDCl_3$): 12.54 (1H, s, COOH), 8.06-7.43 (4H, m, ArH), 7.33-6.83 (3H, m, ArH), 4.06 (2H, s, NH), 3.88 (6H, s, CH_3), 2.67-2.59 (2H, t, CH_2), 2.56-2.48 (2H, t, CH_2).

Preparation of 1-[4-(2-chloro-6,7-dimethoxy-quinazoline-4-ylamino)-6-(pyrimidine-2-ylamino)-[1,3,5]triazin-2-yl]-[1,4]diazepam-5-one (SS-2015-006): Preparation of oxime from SS-2015-004: To mixture of **SS-2015-004** (0.137mol), hydroxylamine hydrochloride (0.150mol), sodium hydroxide (1.0g in 0.2ml.of rectified spirit and 1 ml water) was added in portions with shaking. As the reaction became too vigorous, the flask was cooled in running tap water. When all the sodium hydroxide was added, reflux condenser was attached to the flask, and the mixture was refluxed for 20 min. Cooled and poured the contents of the flask into a solution of 0.2 ml of concentrated HCl in 3 ml of water. Filtered the precipitate, washed and recrystallized it from methanol to give oxime of **SS-2015-004.**

Table-1
Physical data of the Compounds

Compound No.	Molecular formula	M. W.	Yield (%)	M.P. (°C)	Elemental Analysis Cald. / Found	
					N	S
SS-2015-005	$C_{30}H_{24}CIN_{11}O_4$	638.04	70	252-254	24.15/23.95	----
SS-2015-006	$C_{22}H_{22}CIN_{11}O_3$	523.90	72	293-294	29.41/29.10	----
SS-2015-007	$C_{25}H_{25}CIN_{10}O_4$	565.00	60	296-298	24.79/24.48	----
SS-2015-008	$C_{29}H_{25}CIN_{10}O_3$	597.00	63	301-304	23.46/23.16	----
SS-2015-009	$C_{25}H_{25}CIN_{10}O_3S_2$	613.10	64	289-291	22.85/22.51	10.46/10.16
SS-2015-010	$C_{25}H_{26}CIN_{11}O_3$	564.00	60	310-311	27.32/26.91	----

Rearrangement of oxime into SS-2015-006: 2,4,6-Trichloro[1,3,5]triazine (10mmol) was added to DMF (2ml), maintained at 25ºC. After the formation of white solid, the reaction was monitored (TLC) until complete disappearance of TCT, then oxime of **SS-2015-004** (10.0mmol in DMF) was added. After the addition, the mixture was stirred at room temperature, monitored (TLC) until the completion of reaction, water was added. Organic phase was washed with 15 ml of a saturated solution of Na_2CO_3 followed by HCl and brine. The organic layer was dried and solvent was evaporated to give **SS-2015-006.** FT-IR (KBr) ν_{max}/cm-^{1}: 3180 (N-H str.), 2945, 2877 (C-H str.), 1580 (C=N str.), 1525, 1456 (C=C str.).; ^{1}H NMR (300 MHz, $CDCl_3$): 8.05 (1H, s, NH), 7.21 (2H, s, ArH), 8.33-6.54 (3H, m, ArH), 4.06 (2H, s, NH), 3.61 (6H, s, CH_3).

Preparation of 1-[4-(2-Chloro-6,7-dimethoxy-quinazolin-4-ylamino)-6-(pyrimidin-2-yl amino)-[1,3,5]triazin-2-yl]-3-ethoxymethylene-piperidin-4-one (SS-2015-007): To a solution of 10% sodium ethoxide (10mmol) in dry benzene (50ml) at 0ºC, a solution of ethyl formate (10mml) in dry benzene (25ml) was added. To this mixture **SS-2015-004** (10mmol) in benzene (25ml) was added. The mixture was stirred for 4 hours at room temperature and allowed to stand overnight. It was then diluted with cold water, acidified with dil. HCl and extracted with ether. The solvent was evaporated and the resultant compound was recrystallized from ethanol to give pure **SS-2015-007**. FT-IR (KBr) ν_{max}/cm-^{1}: 3230 (N-H str.), 2978, 2830 (C-H str.), 1700 (C=O str.), 1587 (C=N str.), 1534, 1459 (C=C str.).; ^{1}H NMR (300 MHz, $CDCl_3$): 8.03-6.55 (3H, m, ArH), 7.4 (1H, s, ArH), 7.21 (2H, s, ArH), 4.1 (2H, s, NH), 3.9 (2H, q, CH_2), 3.8 (6H, s, CH_3), 3.5 (2H, s, CH_2), 3.07 (2H, t, CH_2), 3.22 (2H, t, CH_2), 1.3 (2H, t, CH_3).

Preparation of 3-Benzylidene-1-[4-(2-chloro-6,7-dimethoxy-quinazolin-4-ylamino)-6-(pyrimidin-2-ylamino)-[1,3,5]triazin-2-yl]-piperidin-4-one (SS-2015-008): A mixture of **SS-2015-004** (0.01mol), benzaldehyde (0.01mol) and fused sodium acetate (0.015mol) in glacial acetic acid was refluxed for 5 hrs. The reaction mixture was cooled in an ice water. The resulting solid was filtered, washed with water and recrystallized from aq. ethanol to give pure compound **SS-2015-008**. FT-IR (KBr) ν_{max}/cm-^{1}: 3219 (N-H str.), 2995, 2880 (C-H str.), 1710 (C=O) 1548 (C=N str.), 1570, 1495 (C=C str.).; ^{1}H NMR (300 MHz, $CDCl_3$): 8.33-8.11 (3H, m, ArH), 7.44-7.20 (4H, m, ArH), 7.18 (1H, s, ArH), 7.12 (1H, s, ArH), 7.09 (1H, s, ArH), 4.00 (2H, s, NH), 3.89 (6H, s, CH_3), 3.59 (2H, s, CH), 3.17 (2H, t, CH_2), 3.06 (2H, t, CH_2).

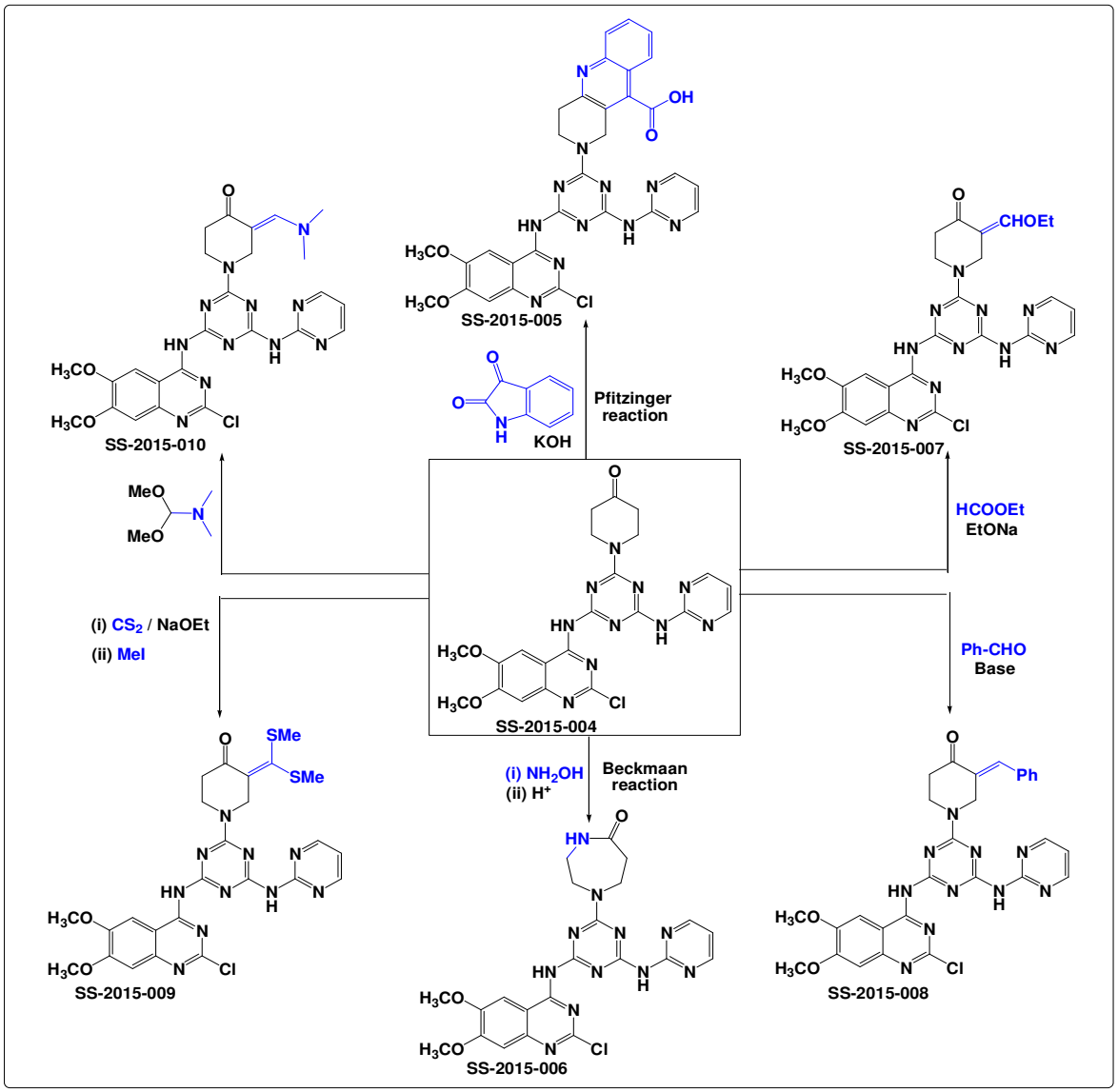
Preparation of 1-[4-(2-Chloro-6,7-dimethoxy-quinazolin-4-ylamino)-6-(pyrimidin-2-yl amino)-[1,3,5]triazin-2-yl]-3-dimethylaminomethylene-piperidin-4-one (SS-2015-009): A mixture of **SS-2015-004** (0.003mol) and CS_2 (3ml) was added to a well stirred and cooled suspension of t-BuOK(0.006mol) in dry benzene (15ml) and DMF (10ml). The reaction mixture was allowed to stand at room temperature for 4 hour. Methyl iodide (3ml) was gradually added with stirring and with external cooling. The reaction mixture was allowed to stand for further 4 hours at room temp. with occasional shaking. It was then refluxed on a water bath for 3 hours. The mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extracts were washed, with water dried on anhydrous sodium sulphate to give **SS-2015-009**. FT-IR (KBr) ν_{max}/cm-^{1}: 3220 (N-H str.), 2965, 2830 (C-H str.), 1690 (C=Ostr.), 1587 (C=N str.), 1534, 1459 (C=C str.).; ^{1}H NMR (300 MHz, $CDCl_3$): 8.33-8.01 (3H, m, ArH), 7.84 (1H, s, ArH), 7.44 (1H, s, ArH), 4.22 (2H, s, NH), 3.75 (6H, s, CH_3), 3.54 (2H, s, CH_2), 3.66 (2H, t, CH_2), 3.32 (2H, t, CH_2), 2.23 (6H, s, CH_3).

Preparation of 3-(Bis-methylsulfanyl-methylene)-1-[4-(2-chloro-6,7-dimethoxy-quinazolin-4-ylamino)-6-(pyrimidin-2-ylamino)-[1,3,5]triazin-2-yl]-piperidin-4-one (SS-2015-010): **SS-2015-004** (15.7mmol) was dissolved in *N, N*-dimethylformamide dimethyl acetal (15ml) and the solution was

heated under refluxed for 4 hours and concentrated. The residue was triturated with hexane, filtered, and washed with hexane to give **SS-2015-010**. FT-IR (KBr) ν_{max}/cm^{-1}: 3250 (N-H str.), 2990, 2860 (C-H str.), 1715 (C=O str.), 1610 (C=N str.), 1481, 1451 (C=C str.).; ^1H NMR (300 MHz, $CDCl_3$): 8.27-7.96 (3H, m, ArH), 7.86 (1H, s, ArH), 7.74 (1H, s, ArH), 7.52 (1H, s, ArH), 3.01 (2H, s, NH), 2.99 (6H, s, CH_3), 2.99 (6H, s, CH_3), 2.85 (2H, s, CH), 2.84 (2H, t, CH_2), 2.82 (3H, s, CH_3), 2.00 (3H, s, CH_3).

Results and Discussion

The synthesis of quinoline-4-carboxylic acid (SS-2015-005) and diazepine derivatives (SS-2015-006) were carried out from trisubstituted s-triazine (SS-2015-004) by reactions of isatin in presence of base and hydroxylamine hydrochloride in presence of acid. The key synthon SS-2015-004 was also utilized to synthesize the reactive intermediates SS-2015-007, SS-2015-008, SS-2015-009, SS-2015-010 with reaction of i. ethyl formate and sodium ethoxide ii. benzaldehyde and sodium ethoxide iii. CS_2/MeI and base iv. *N, N*-dimethylformamide dimethylacetal respectively. The formation all the compounds was confirmed by physical and spectral data. IR peak of the compound SS-2015-004 at 3250cm^{-1} was disappeared in the compound SS-2015-005 and new broad peak around 2550-2850cm^{-1} appeared due to carboxylic acid group. Presence of carboxylic acid was also confirmed by appearance of ^1H NMR signal a singlet at 12.54 δ ppm. Formation of all other compounds (SS-2015-006 to SS-2015-010) was also confirmed by observation of similar spectral data.



Scheme-1

Synthesis of Quinoline-4-carboxylic acid moiety, 1,4-Diazepinone, Enol ether, α,β-unsaturated carbonyl compound, Oxoketene dithioacetal and N,N-Dimethyl aminomethylene ketone of trisubstituted s-triazine

Conclusion

Enol-ether, α,β-unsaturated carbonyl compound, oxoketenedithio acetal and dimethyl aminomethylene ketone derivatives of quinazoline and pyrimidine containing trisubstituted s-triazines as well as quinoline-4-carboxylic acid moiety and diazepinone derivatives have been synthesized successfully. The structures of all the compounds have been confirmed by elemental analysis and spectral data.

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