



ORIGINAL RESEARCH PAPER

Chemistry

SYNTHESIS OF SOME OF PHARMACEUTICALLY IMPORTANT OXOKETENEDITHIOACETALS ANALOGUES OF CARBAZOLO AND AZACARBAZOLO CONDENSED TRIAZINE INDOLE

KEY WORDS: carbazolo, azacarbazolo, triazine indole, enol, ether, oxoketene dithioacetal and IR, ¹HNMR and MS

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ABSTRACT

This paper describes the synthesis of oxoketenedithioacetals **2.33** (a-d) from the reaction of carbazole and azacarbazole condensed derivatives of 8-nitro-2H-[1,2,4] triazino-(5,6-b)-indole-3-(5H-one) **2.32a**, **2.32b** and 8-nitro-2H-[1,2,4]-triazino-(5,6-b)-indole-3-(5H-thione) **2.32b**, **2.32d** derivatives with CS₂/CH₃I. The structure of all the compounds have been established by elemental analysis, IR, ¹HNMR and MS spectral data.

Introduction

Oxoketene dithioacetals contain active functional groups and play an important role in variety of synthetic applications. Greatly encouraged by the impressive applications of oxoketene dithioacetals.

Several reviews have recently appeared in the literature on the synthetic utility of -oxoketene dithioacetals, as versatile three-carbon synthons. The most recorded method for the preparation of oxoketene dithioacetals involves the reaction of ketones containing an adjacent CH₂ group with carbon disulphide in the presence of base followed by alkylation of the resulting -oxodithioic acids.

The conjugated ketene dithioacetals contain a masked ester functionality and hold considerable potential as substrates for functional group manipulation and sequential carbon-carbon bond forming transformations. α-Oxoketene dithioacetals, especially the dimethyl thioacetal have recently received considerable attention due to their synthetic importance for the construction of a variety of alicyclic, aromatic and heterocyclic nucleus. The direct displacement of the methylthio group of ketene dithioacetals by nucleophiles through an addition-elimination mechanism has proved to be a convenient method for the preparation of wide variety of heterocyclic compounds¹⁻⁴. A large number of active methylene compounds have been converted in to the polarized ketene dithioacetals (**a-f**) with permutations and combinations of substituents (**fig:2.1**).

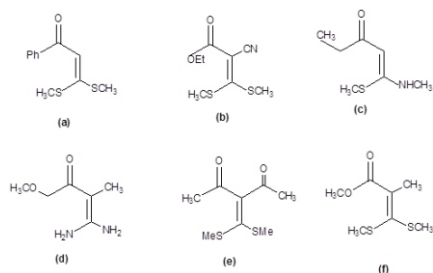


Fig.2.1

Experimental

- Melting points are determined in open glass capillaries and are uncorrected.
- The purity of the compounds were checked by TLC on silica gel (G) plates.
- IR spectra were recorded on CE (SHIMADZU) FTIR-8400S.
- ¹H NMR spectra were recorded on medel AC-300F (Brucker) using CDCl₃/DMSO-d₆ as solvent and TMS as an internal reference. Chemical shift are expressed in ppm.
- Before analysis all samples were dried for one hour under reduced pressure.
- Physical and spectral data for all the compounds are given in table **2.1** and **2.2**.

Good yield of α-oxoketene dithioacetals was obtained with NaH

and CS₂ from aromatic ketones (60-90%) and several workers have effectively employed this combination (in PhH, DMF or DMSO) for the synthesis of conjugated ketene dithioacetals from aryl and heteroaryl ketones¹⁴⁻¹⁶ and active methylene compounds.¹⁷⁻¹⁹ Potassium t-butoxide (in PhH, DMF or PhH / DMF) is also an effective base²⁰⁻²⁴ and K t-BuO / THF / CS₂ / RX combination has recently been developed as a particularly effective procedure for α-oxoketene dithioacetals.

Preparation of 8-nitro-2H-[1,2,4]triazino-5 (6-b) indole-3 (5H-one)(2.29)a

(9.0g 0.047mole) of 5-nitroisatin dissolved in 200ml. of absolute ethanol was added to a warm solution of (4.3g. 0.47mole) of thiosemicarbazide in 125ml of water and 10 ml of glacial acetic acid and the mixture was refluxed was for one hour. The aqueous ethanol solution upon cooling gave 11.5g. (92%) and m.p. 300-302°C. An analytical sample of this was obtained by recrystallization from a water-pyridine solvent pair.

Preparation of 8-amino-2H-[1,2,4]triazino-5 (6-b) indole-3 (5H-one)(2.30)a

Compound **2.33a** (1.0g 0.0114) mole in methanol (30ml) and conc. HCl (6ml) were taken in 250ml round bottom flask and the mixture was heated on the water bath. To it iron powder (0.5g 0.020mole) was added pinch by pinch for an hour with continuous stirring. The reaction mixture was further refluxed for 1 hour and then filtered hot. The filtrate was neutralized with aqueous ammonia(50%) until the brown solid had completely separated out which was recrystallized from ethanol to give 1.40g (60%) fine dark brown powder **2.30a** m.p., 215-217°C. Similarly compound **2.30b** was prepared.

Preparation of 1,2,4- triazin- 3(2H) -one 3,4 dihydro-2H-carbazol-1 (9H)-one-2.32a

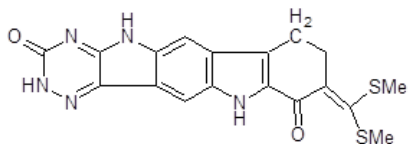
A solution of **2.30a** (1.0g 0.003mole) in aq. HCl (conc. HCl 10ml in 10ml water) was treated with a cold saturated solution of sodium nitrite (2g in 5ml water), while the temp. was kept at 0-5°C. The solution was kept aside for 10 min. It was then added portion wise to an ice-cooled mixture containing 2-hydroxymethylidene cyclohexanone (prepared in situ) from (**2.31a**), HCOOEt, NaOEt, CH₃OH and water by stirring over a period of 1 hour. The contents were allowed to stand for further half an hour and were poured in ice cold water. The resulting solid was filtered, washed with water, dried over night and was recrystallized from ethanol. The product (hydrazone) was dissolved in acetic acid (20ml) and dil. HCl (5ml). It was refluxed on an oil bath for half an hour. Contents were poured in ice cold water with continuous stirring which resulted 2.32a 4.5g (70%) m.p., 230-232°C. Similarly compound 2.32b,c,d were prepared.

Preparation of 1,2,4- triazin- 3(2H) -one 3(bis(methyl thio) methylene)- 2,3- dihydroacridin -4 (1H,9H,10H) -one (2.33a)

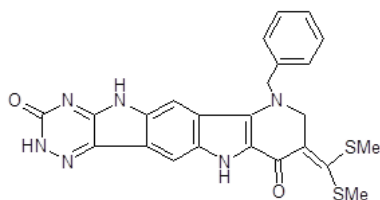
A mixture of 2.32a (1.0g 0.005moles) and CS₂ (2ml) was added to a well stirred and cooled suspension of t-BuOK (2g 0.009moles) in dry benzene (180ml) and DMF (120ml). The reaction mixture was allowed to stand at room temp. for 4 hours. Methyl iodide (2ml 0.006moles) was gradually added with stirring and external

cooling (exothermic reaction). The reaction mixture was allowed to stand for further 4 hour at room temp with occasional shaking. It was then refluxed on a water bath for 3 hour. The mixture was poured on crushed ice and the benzene layer was collected. The aqueous portion was extracted with benzene and the combined extracts were washed, dried on sodium sulphate to give **2.33a** 0.61g yield 65% and m.p. 250-252°C.

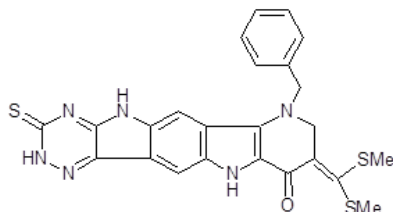
Similarly compound **2.33b,c,d** were prepared. Yield and melting point of these compounds are given in table **2.2**.



2.33b

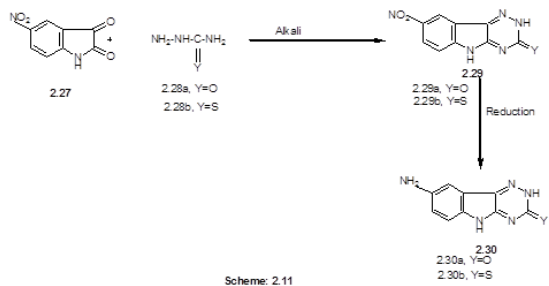


2.33c

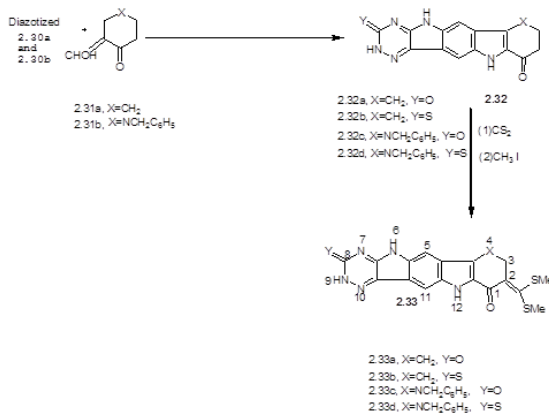


2.33d

Fig:2.2



Scheme: 2.11

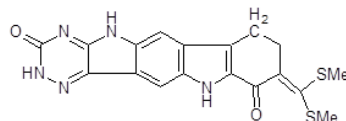


Scheme:2.12

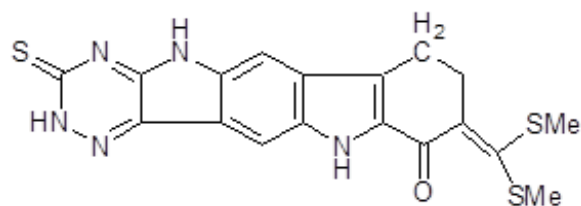
2.4 Results and discussion

In the present work synthesis of oxoketenedithioacetals **2.33(a-d)** were carried out in accordance with the literature procedure which consisted of the condensation of 5-nitroisatin **2.27(a,b)** with semicarbazide or thiosemicarbazide **2.28(a,b)** followed by their reduction with Fe+HCl in methanol in the subsequent step to give **2.30a,b** respectively (scheme:2.11). Diazotized **2.30a-b** underwent Japp-Klingemann reaction with 2-hydroxymethylidene cyclohexanone (and N- substituted 3-hydroxymethylidene piperidone) (**2.31**) (which were generated in situ from the reaction of cyclohexanone or N- substituted piperidone with ethyl formate in presence of NaOEt) to give corresponding hydrazones. This underwent concomitant ring closure with acid to furnish **2.32a,b,c,d** which in the subsequent step was treated with CS₂/CH₃I to give oxoketene dithioacetals **2.33a,b,c,d** respectively (scheme:2.12). Physical and spectral data of these compounds are given in table 2.1 and 2.2 respectively.

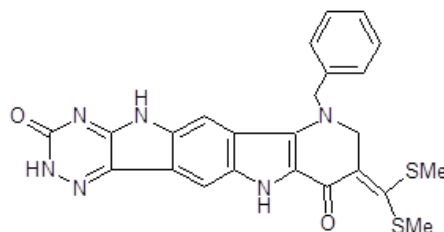
Adopting this procedure following four oxoketenedithioacetals were prepared in this chapter (**fig:2.2**).



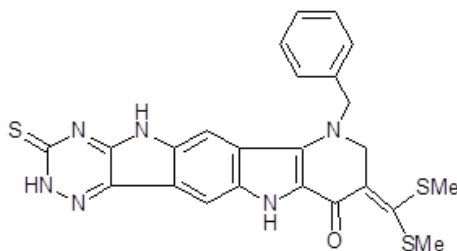
2.33a



2.33b



2.33c



2.33d
Fig:2.2

Conclusion

In conclusion, an efficient methodology for the synthesis of oxoketenedithioacetals from the reaction of carbazole and azacarbazole condensed derivatives of triazine indole derivatives was developed with CS₂/CH₃I. Heterocyclic scaffolds bearing these structures have been widely studied because of their impressive pharmaceutical activities. It was, therefore, reasoned

that the presence of pyrimidine, carbazole or azacarbazole in tandem with the same molecular framework could produce the novel heterocyclic scaffolds with interesting biological activities.

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