ABSTRACT

In the last decades a number of pyrazole and isoxazole derivatives have been introduced in clinical practice. The therapeutic effectiveness of these agents has been bounded by a number of limiting factors. Due to this, the development of novel, selective, potent and safe agents remains in high priority in medicinal chemistry research. Synthans, such as oxoketenedithioacetals are known in the literature to offer unprecedented opportunity to a chemist in the synthesis of a wide variety of difficultly accessible heterocyclic compounds. It has been demonstrated that oxoketenedithioacetals react smoothly with smoothly with nucleophiles and offered a very facile one pot synthetic entry to five, six and seven membered heterocyclic rings. The present work describes the synthesis of oxoketenedithioacetal derivative of deoxybenzoin 1.02 and their subsequent conversion to pyrazole derivatives 1.03, 1.04 a, 1.04 b and to isoxazole derivatives, 1.05, 1.06 a, 1.06 b respectively as shown in Scheme 1.1. The structures of the compounds have been established analytically. These structures can help the medicinal chemists to use them as intermediates to design various drug candidates possessing a number of pharmacological activities

KEYWORDS: pyrazole, isoxazole, oxoketenedithioacetal, deoxybenzoin

INTRODUCTION

Oxoketenedithioacetals show considerable promise as versatile intermediates in the functional group manipulations and sequential carbon-carbon bond forming transformations. Because of this, their synthesis and reactions have attracted much attention of chemists and several reviews on its application in synthesis; have appeared in the literature1. 2. It has been shown, that these intermediates undergo facile nucleophilic displacement reactions with a variety
of bidentate nucleophiles to afford wide array of ring structures which provide an unprecedented opportunity to a chemist for a one step synthesis of difficultly accessible fused heterocyclic systems containing pyrazole, isoxazole, pyridine, pyrimidine, benzodiazepine and benzodiazepine etc. A perusal of literature on the application of these intermediates revealed that hetero-ring appended analogues from these entities have been less exploited in the literature in synthesis. This prompted us to examine the feasibility of the application of these materials, as versatile synthans in the synthesis of a wide variety of heterocyclic systems. The pyrazole and isoxazole derivatives occur abundantly in synthetic compounds of biological interest. They have been known to exhibits the anti-inflammatory activity and in this respect form interesting targets in synthesis since their structures have potential for the development of anti-inflammatory drugs. This has precisely been the reason for selecting these molecules for the present study. The present work describes the synthesis of a series of hetero ring incorporated biologically active analogues, from the oxoketenedithioacetals.

Carbonyl compounds containing an adjacent CH\(_2\) group have been known to undergo reaction with CS\(_2\) and CH\(_3\)I in presence of a base to form the corresponding oxoketenedithioacetal derivatives. This methodology was applied on deoxybenzoin to form the corresponding, oxoketenedithioacetal derivative 1.02. Treatment of 1.02 in the subsequent step with hydrazine hydrate and hydroxylamine hydrochloride generated the corresponding pyrazole and isoxazole derivatives 1.03 and 1.05 respectively whose subsequent reaction with CISO\(_3\)H followed by NH\(_3\) in succession generated 1.04 a, 1.04 b, 1.06 a and 1.06 b respectively (Scheme 1.1).

Greatly encouraged by the bioactive profiles of pyrazole and isoxazole derivatives, we aimed in the present work to synthesize the pyrazole and isoxazole derivatives on this premise that their presence in tandem along with the sulphonamide group should contribute significantly to the biological activity in the resulting molecules. The idea behind formulating such a study was to assess the favorable impact if any the presence of these produced by exercising an additive or cumulative effect on the overall bio-efficacy in the molecules. If their role to produce a positive impact on activity was established such structures were likely to form interesting targets in synthesis and for biological evaluations.

**METHODOLOGY**

**General Procedures**

All the required materials were purchased from Sigma-Aldrich. Melting points were determined in open glass capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel (G) plates. Before analysis all samples were dried for one hour under reduced pressure. \(^1\)HNMR spectra were recorded on model AC-300F (Brucker) using CDCl\(_3\) as solvent and TMS as internal reference. Chemical shifts are expressed in \(\delta\) ppm.
Experimental Procedures

Preparation of 3, 3- bis (methylthio) -1, 2-diphenyl prop-2-en-1-one (1.02): To a stirred suspension of sodium hydride (0.053 g, 2.2 mmole) in DMF (3 ml) was drop wise added a solution of deoxybenzoin 1.01 (1.0 mmole, 0.196 g) in DMF at 0 °C. The resulting mixture was allowed to warm to room temperature over 40 min and then carbon disulfide (1.5 mmol, 0.1 ml) was added drop wise. After stirring at room temperature for 30 min, the resulting orange-colored suspension was treated with methyl iodide (3.0 mmole) at room temperature. The stirring was continued at room temperature overnight, the resulting yellow suspension was refluxed on a water bath for 3 h. The mixture was then poured on crushed ice and the benzene layer was separated. The aqueous layer was extracted with benzene and then combined extract was washed with water, dried over anhydrous sodium sulphate and the solvent was removed by distillation. The crude oxoketenedithioacetal 1.02 was obtained as yellow semisolid mass 0.117 g (yield, 75%). 1HNMR [300 MHz, CDCl3]: δ 7.16-7.30 [m, 5H, Ar-H], δ 7.45-7.83 [m, 5H, Ar-H], δ 2.25 [s, 6H, each -SCH3].

Preparation of 5-(methylthio)-3, 4- diphenyl-1H-pyrazole (1.03): Hydrazine hydrate (0.16 g, 5 mmole) and 1.02 (0.3 g, 1 mmole) were taken in 50 ml of ethanol and refluxed for 3 h. The solvent was removed and the residue was treated with 20 ml of chloroform and extracted with water. The chloroform layer was concentrated. At the end of complete evaporation of chloroform 1.03 was obtained as yellow crystalline solid 0.190 g (yield 72%, m.pt. 172-174 °C). 1HNMR [300 MHz, CDCl3]: δ 13.7 [s, 1H, pyrazole], δ 7.16-7.30 [m, 5H, Ar-H], δ 7.45-7.83 [m, 5H, Ar-H], δ 2.25 [s, 3H, -SCH3]

Preparation of 4-(5-(methylthio)-3, 4- diphenyl-1H-pyrazole-3-yl) benzene-1-sulphonyl chloride 1.04 (a) and 4-(5-(methylthio)-3, 4-diphenyl-1H-pyrazole-3-yl) benzene-1-sulphonamide 1.04(b): Chlorosulfonic acid (4 ml, 0.06 mole) was cooled in ice bath and treated with 1.03 (0.26 g, 1 mmol) at such a rate that the reaction temperature could be maintained between 10-15 °C for almost 30 minutes. The ice bath was removed and the solution was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane and the solution was slowly added to ice water with stirring. Out of the two phases which were separated, dichloromethane portion was concentrated (containing 1.04 a) and cooled to 5°C and treated with conc. NH4OH and stirred at 15°C for 15 min. The mixture was then extracted with dichloromethane, filtered and concentrated to give 0.25 g of yellow oil (yield 70%) 1HNMR, 1.04 (b) [300 MHz, CDCl3]: δ 13.7 [s, 1H, pyrazole], δ 7.16-7.30 [m, 5H, Ar-H], δ 7.45-7.83 [m, 4H, Ar-H], δ 2.25 [s, 3H, -SCH3], δ 2.0 [s, 2H, -NH2 gp.]

Preparation of 5-(methylthio)-3,4-diphenylisoxazole (1.05): Hydroxyl amine hydrochloride (0.34 g, 5 mmole) and 2.02 (0.26 g, 1 mmole) were taken in ethanol (50.0 ml) and refluxed for 3 h. The solvent was removed and the residue was treated with 20 ml of chloroform and extracted with water. The chloroform layer was concentrated. After complete evaporation of chloroform 1.03 was obtained as colorless crystalline solid 0.192 gm (yield 72%), m.pt. 181-183 °C. 1HNMR [300 MHz, CDCl3]: δ 7.16-7.30 [m, 5H, Ar-H], δ 7.45-7.83 [m, 5H, Ar-H], δ 2.25 [s, 3H, -SCH3]

Preparation of 4-(5-(methylthio)-4-phenylisoxazol-3-yl) benzene-1-sulphonyl chloride 1.06(a) and -(5-(methylthio)-4-phenylisoxazol-3-yl) benzene-1-sulphonamide 1.06(b): Chlorosulfonic acid (4 ml, 0.06 mole) was cooled in ice bath and treated with 2.03 (0.27 g, 1 mmole) at such a rate the reaction temperature was maintained between 10-15 °C for almost 35 minutes. The ice bath was removed and the solution was stirred at room temperature for 16 h. The mixture was diluted with dichloromethane and the solution was slowly added to ice water with stirring. From the two phases which were
separated, the DCM portion was collected and cooled to 5°C and then treated with conc. NH₄OH and stirred at 15°C for 15 min. The mixture was then extracted with dichloromethane, filtered and concentrated to give 2.06 ± 0.26 gm of yellow solid. It was dissolved to 2-butanol and then recrystallised using isopropyl alcohol 0.25 g (yield, 71%), m. pt. 185-187°C. \textsuperscript{1}HNMR, 1.06(b) [300 MHz, CDCl₃]: δ 7.16-7.30 (m, 5H, Ar-H), δ 7.45-7.83 (m, 4H, Ar-H), δ 2.25 (s, 3H, -SCH₃), δ 2.0 (s, 2H, -NH₂ gp.]

Schematic presentation of the synthesis of oxoketenedithioacetal from deoxybenzoin and their subsequent conversion to pyrazole and isoxazole derivatives:

\[ \text{O} \quad \text{O} \quad \text{S} \quad \text{C} \quad \text{H}_3 \quad \text{S} \quad \text{C} \quad \text{H}_3 \]

\[ \text{C}_2 \quad \text{H}_5 \quad \text{I} \]

1.01

\[ \text{NH}_2\text{NH}_2 \]

1.02

\[ \text{NH}_2\text{OH}. \text{HCl (base)} \]

1.03

\[ \text{ClSO}_3\text{H} \]

1.05

\[ \text{ClSO}_3\text{H} \]

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RESULT AND DISCUSSIONS

In view of the impressive biological activities shown by pyrazole and isoxazole nuclei it was thought of interest in the present work to construct intermediates consisting of these ring systems. The idea behind building such a system was to establish the synthesis of these intermediates. It was envisaged that the precursors which could fulfill this synthetic requirement and were accessible easily, could be, oxo-ketenedithioacetal of deoxybenzoin 1.02 from which pyrazole 1.03 and isoxazole 1.05 could be obtained easily in one step. The synthesis of the desired intermediates was conceived in the present work from oxo-ketenedithioacetal of deoxybenzoin 1.02 following the strategy shown in scheme-1.1. Oxo-ketenedithioacetal reacted smoothly with hydrazine hydrate and hydroxylamine hydrochloride in alcohol to afford the corresponding pyrazole (1.03) and isoxazole (1.05) derivates respectively. The subsequent reactions of 1.03 and 1.05 with CISO₃H and NH₃ in succession generated 1.04 b and 1.06 b respectively as shown in Scheme 1.1. Structures of these compounds were unambiguously established from their spectral data. These pyrazole and isoxazole derivatives can be used as intermediates to design new heterocyclics as potential bioactive agents.

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