



Synthesis of Indole Annulated Benzazepine Derivative of Medicinal Interest

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ABSTRACT

The ubiquity of benzazepines in medicinal chemistry is undoubtedly a consequence of the multifarious biological response which they elicit in combating a variety of body ailments. A benzazepine derivative- 'Fenoldopam mesylate' has emerged as a vasodilator in peripheral arteries and as a diuretic in the kidneys. This discovery provided an optimism for the search of other novel agents from benzazepine class of compounds which could show a higher level of medicinal efficacy. The proposed synthesis (scheme-1), in its first step was propelled forward with the formation of compound 1.3 (which resulted from the reaction of succinyl chloride and p-fluoroaniline). The reaction of 1.3 with ethyl formate in the presence of a base formed 1.4 which underwent Japp-Klingemann reaction with aryl diazonium chloride followed by cyclocondensation with acid under the conditions of Fischer indolization to give indole substituted derivative 1.5.

Key words: P-fluoroaniline, Succinyl chloride, Japp-Klingemann reaction, Fischer Indolization, Spectral study.

INTRODUCTION

Benzazepine moiety occurs frequently in both natural and synthetic drugs and is of highly biological interest. The use of this class of compound is not merely confined to the management of stress related conditions and for their use as antibacterial agents^{1,3}, but their additional applications are continuously emerging. Galantamine (Galanthamine), a benzazepine derived from norebelladine, has been studied in the treatment for Alzheimer disease⁴. In a quest to develop easily accessible routes to the synthesis of some novel heteroring annulated benzazepine derivatives, the present investigation aims to examine the operational feasibility of

the proposed strategy outlined in scheme-1 for the synthesis of compounds 1.6-1.7.

MATERIALS AND METHOD

P-fluoroaniline and succinyl chloride were the product of Fischer Scientific. All the chemicals employed for synthesis were of analytical grade and were used as supplied without further purification. All the solvents were dried and distilled before use. 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. The visualization of spot was carried in an iodine chamber. IR spectra were recorded on

CE(SHIMADZU)FTIR-8400S.1 H NMR spectra were recorded on model AC-300F(Bruker) using CDCl₃/DMSO-d₆ as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm.

Synthesis of (7-fluoro-3,4-dihydro-1H-benzo[b]azepine-2,5-dione) (compound-1.3)

Acylation

Compound 1.1 (2.20g) was mixed with succinyl chloride 1.2(1.64g) and dry pyridine(5ml). The mixture was refluxed for 10-15 mins. Cooled reaction mixture was poured slowly with stirring in 150-200ml ice cold water. The resulting solid reactant which was settled was filtered, washed with cold water, recrystallized from hot water containing few drops of methanol.

Friedel craft reaction

Compound above prepared(2.58 g) was mixed with PPA(5g) and heated at 150-160°C for 4hr (the process of the reaction was monitored by TLC). The reaction mixture was cooled to 20°C and concentrated salt of Na₂CO₃ was added to make it alkaline. The product was extracted with ethyl acetate (3x10 ml). The extract was dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column chromatography of silica gel with CHCl₃ as an eluent to give compound 1.3. yield 60%, m.p. 120-122 °C.

Synthesis of 4-(ethoxymethylene)-7-fluoro-3,4-dihydro-1H-benzo[b]azepine-2,5-dione (compound-1.4)

To a solution of 10% sodium ethoxide(10 ml) in benzene (50ml) at 0°C, a solution of ethyl formate (10 ml) in dry benzene (25 ml) was added. To this mixture compound 1.3 (2.25g) in benzene (25ml) was added. The mixture was stirred for 4 hrs 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 (1.4) was recrystallized from ethanol to give pure compound 1.4. yield 50%, m.p. 298-300°C.

Synthesis of 8-fluorobenzo[6,7]azepino[4,3-b]indole-6,12(5H,1H)-dione (compound-1.5)

Preparation of hydrazone

A solution of Compound 1.4a (3.26) was kept aside for 10 minutes. It was then added portionwise

to an ice cold mixture containing compound 1.4 (4.0ml), sodium acetate(6g), methanol(37.0ml) and water(20.0ml) over a period of 0.5 hours with stirring. The contents were allowed to stand for further 0.5 hours and the resulting solid mass was filtered, washed with water, dried and crystallized from ethanol.

Cyclization of hydrazone

A solution of hydrazone above prepared (3.18g) in a mixture of acetic acid(19.0ml) and hydrochloric acid(4.7 ml) was refluxed on an oil-bath preheated to 125-130°C for 0.5 hours. The contents were then cooled and poured into cold water with stirring. The separated brown solid was purified by passing through a column of silica gel using 50% benzene in petroleum ether as eluent. yield 66%, m.p. 133-135°C.

RESULTS AND DISCUSSION

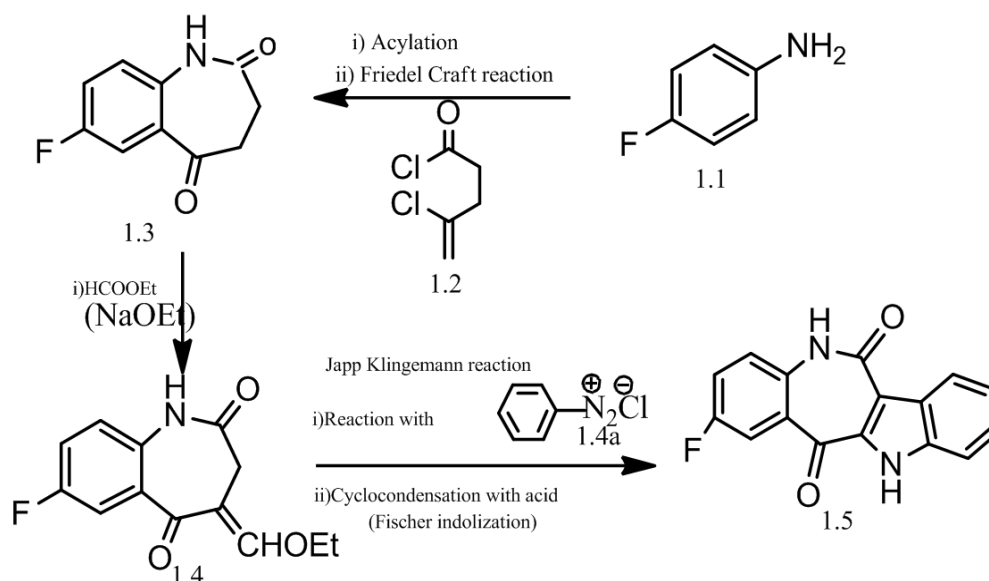
Scheme – 1 envisaged that the reaction of 1.3 with ethyl formate in presence of a base formed 1.4 which undergo Japp-Klingemann reaction with aryl diazonium chloride followed by cyclocondensation with acid under the conditions of Fischer indolization to give indole ring substituted derivative 1.5

IR spectra

Infrared spectra of compound 1.3 on KBr pellet exhibited strong absorption bands at 1660cm⁻¹ and 1700cm⁻¹ for the carbonyl group of CONH and CO groups respectively, along with this IR spectrum also exhibited bands at 3400cm⁻¹ (NH), [2970, 1430cm⁻¹ (CH₂ next to C=O)], 2970cm⁻¹ (C-H), 1590cm⁻¹ (C=C)..

Infrared spectra of compound 1.4 on KBr pellet exhibited peaks at 3068cm⁻¹ (C-H str. of C₆H₅F), 1550cm⁻¹ (C=C str. of C₆H₅F), 3280cm⁻¹ (NH str.) [CONH], 1680cm⁻¹ (C=O)[CONH], 1610cm⁻¹ (C=O str.), 1620cm⁻¹ (C=C).

Infrared spectra of compound 1.5 on KBr pellet exhibited peaks 3068cm⁻¹ (C-H str. of C₆H₅F), 1550cm⁻¹ (C=C str. of C₆H₅F), 3280cm⁻¹ (NH str.) [CONH], 1680cm⁻¹ (C=O)[CONH], 1610cm⁻¹ (C=O str.), 3300cm⁻¹ (NH sec. amine). The formation of compound 1.5 was confirmed by appearance of peak at 3300 cm⁻¹ (NH of indole ring).



Scheme 1:

¹H NMR spectra

¹H NMR spectrum of compound 1.3 in CDCl₃+DMSO-d₆ displayed signals for the presence of 8 protons. Appearance a downfield broad singlet for 1H at δ 8.0 was attributed to NH group. Appearance of multiplet at δ 7.40-7.87 was assigned to the three protons of fluorobenzene ring. A singlet for four protons which appeared at δ 2.93 and δ 2.42 was attributed to two CH₂ groups of azepanedione ring.

¹H NMR spectrum of 1.4 in CDCl₃+DMSO-d₆ exhibited a downfield broad singlet for 1H at δ 8.0 which was attributed to NH group of azepanedione ring. Another singlet for 1H at δ 6.95 was assigned to the protons of CH group attached to ether group on one side and α, β-unsaturated carbonyl group on other side. Presence of a triplet for 3H at δ 1.21 and quartet for 2H at δ 4.49 were assigned to the ethyl group of enolic ether. Appearance of multiplet at δ 7.45-7.98 was assigned to the three protons of fluorobenzene ring. A singlet for two protons which appeared at δ 2.90 was attributed to CH₂ group of azepanedione ring.

¹H NMR spectrum of 1.5 in CDCl₃+DMSO-d₆ exhibited a downfield broad singlet for 1H at δ 8.0

which was attributed to NH group of azepanedione ring. Appearance of multiplet at δ 7.45-7.98 was assigned to the three protons of fluorobenzene ring. Another singlet for 1H at δ 11.63 was assigned to NH group of indole. Appearance of multiplet at δ 6.91-8.47 was assigned to the four protons of benzene ring.

Mass spectra

Mass spectrum of compound 1.3 gave peaks at m/z 193.05(100.0%), 194.06(11.0%) which provided a strong evidence to its molecular weight(193.17).

Mass spectrum of compound 1.4 gave peaks at m/z 249.08(100.0%), 250.08(14.5%) which provided a strong evidence to its molecular weight(249.24).

Mass spectrum of compound 1.5 gave peaks at m/z 310.32(100.0%), 218.363(15.5%), 239.99(11.1%), 279.552(9.8%), 291.112(5.4%) provided strong evidence to its molecular weight(310.32).

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