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Synthesis and Antimicrobial Activity of Azepine Analogue of Lignan

Ashok Kumar Singh*

Department of Chemistry, Tri-Chandra Multiple Campus, Tribhuvan University, Nepal
Email: asokksingh@yahoo.co.in

Abstract

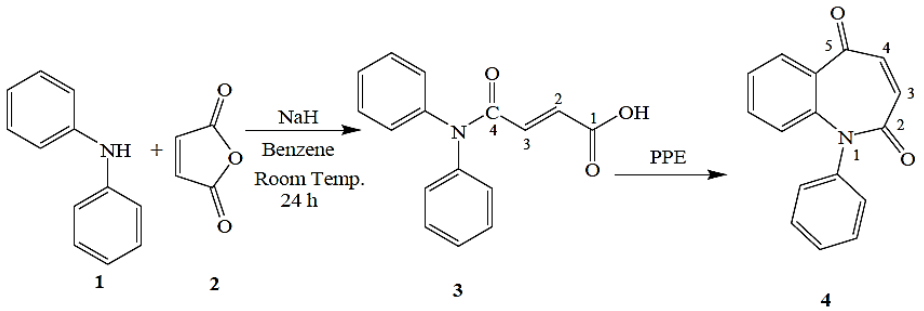
*Diphenylamine (**1**) was condensed with maleic anhydride (**2**) in the presence of sodium hydride and dry benzene, 4-N,N-diphenyl amine-4-oxo-2-butenoic acid (**3**) was achieved. Intramolecular cyclization of compound **3** with PPE afforded 1-phenyl-1H-benzo[b] azepine-2,5 dione (**4**).*

Keywords: *Diphenylamine, azepine, podophyllotoxin,*

Introduction

Seven membered heterocycles constitute an important class of compounds that have found many applications in medicinal chemistry[1,2] Some aza analogues of podophyllotoxin bearing an extended ring have been reported in literature, which are named as azapines[3] and they have exhibited low cytotoxic activity[4]. 2,3-benzodiazepine analogues act as highly selective noncompetitive antagonists and also possess anticonvulsant activity. Structure activity relationship study pointed out that the anticonvulsant activity of compounds depends on dimethoxy benzene moiety[5]. Benzazepine analogues are of significant interest due to their pharmacological activity against dopamine and other biological receptors[6]. Recently 1,3,4,5-tetrahydro-2*H*-3-benzazepine-2-one was synthesized from 2-(4-hydroxy-3-methoxy-phenyl)-N-(2-hydroxy-2-phenyl-ethyl)-N-methyl-acetamide using methanesulphonic acid[7].

Benzodiazepine is a type of psychotropic drug, which affect the mind and can also alter mood. Benzodiazepine has been used therapeutically as anxiolytic (drug to relieve anxiety), as tranquilizer and exhibited advantageous anticonvulsant properties[8, 9]. In view of extensive biological activities of benzazepine analogues, a facile synthesis of 1-phenyl-1H-benzo[b] azapine-2,3-dione (**4**), from diphenylamine-4-oxo-2-butenoic acid (**3**) using PPE has been undertaken and tested for antimicrobial activity against the pathogens.(**scheme-1**).



Scheme 1

* ***Corresponding author***

Experimental

A typical procedure for 4-N,N-Diphenyl amine-4-oxo-2-butenoic acid (3)

Sodium hydride (0.24 g, 0.01 mol) in dry benzene (15 ml) was stirred for 15 min. Then Powdered maleic anhydride (**2**, 1.0 g, 0.01 mol) was added to the reaction mixture and stirred for 24h. The reaction mixture was diluted with equal volume of water. The benzene layer along with precipitate was separated from aqueous layer. The benzene layer was extracted with 5% of $NaHCO_3$ and acidified with 2N HCl. The precipitate was filtered and the crude solid was recrystallized from ethanol to achieve **3** as white solid in 70% (1.87 g) yield.

M.P. 130-131°C

IR (Nujol): 1650 (C=O), 1720 (acid C=O), 3320-3430 cm^{-1} (OH)

^{1}HNMR (DMSO-d_6): 6.4 (d, *J*=6Hz, 1H, C_2-H), 7.2 (d, *J*=6Hz, 1H, C_3-H), 7.3-7.65 (m, 10H, Ar-H), 9.8 (bs, 1H, COOH)

MASS (m/z, % abundance): 268 (M^++1, 100), 267 (M^+, 16), 250 (55), 222 (33), 170 (44), 99 (11)

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24; **Found:** C, 71.99; H, 4.80; N, 5.35%.

A typical procedure for 1-Phenyl-1H-benzo[b] azepine-2,3dione

Compound (**3**, 1.34 g, 5 m mol) in PPE (20 ml) was refluxed for 3h at 80°C and then stirred at room temperature for overnight. The reaction mixture was diluted with cold water and extracted with chloroform (3x20 ml). The organic layer was washed with 5% sodium bicarbonate (3x20 ml) and washed with water (3x20 ml). The organic layer was dried over anhydrous sodium sulphate and evaporated to dryness. The crude solid was recrystallized with ethanol to achieve **4** as a pale green solid in 72% (0.9 g) yield.

M.P. 110-112˚C

IR (Nujol): 1655 cm^{-1} (C=O)

^{1}HNMR ($CDCl_3$): 7.05 (d, *J*=6Hz, 1H, C_3-H), 7.1-7.85 (m, 9H, Ar-H), 7.6 (d, *J*=6Hz, 1H, C_4-H)

MASS (m/z, % abundance): 250 (M^++1, 30), 249 (M^+, 5), 221 (100), 205 (30)

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62; **Found:** C, 77.20; H, 4.50; N, 5.72%.

Results and Discussion

The strategy in the synthesis of desired compounds is as follows. Diphenylamine (**1**) was condensed with maleic anhydride (**2**) in the presence of sodium hydride and dry benzene, 4-N,N-diphenyl amine-4-oxo-2-butenoic acid (**3**) achieved. Intramolecular cyclization of compound **3** with PPE afforded 1-phenyl-1*H*-benzo[b] azepine-2,5 dione (4).

4-N,N-Diphenyl amine-4-oxo-2-butenoic acid (**3**) was obtained in good yield, by heating a mixture of diphenyl amine (**1**), maleic anhydride (**2**) and sodium hydride in presence of dry benzene. PPE has been used as a good cyclodehydrating agent in many heterocyclic syntheses. The compound **3** was cyclized to the corresponding azepine derivative **4** by heating with PPE.

The structure of all compounds was supported by IR, ^{1}NMR data and microanalysis. The IR spectrum of compound **3** showed keto carbonyl, acid carbonyl and OH stretching frequencies at 1650, 1720 and 3320-3430 cm^{-1} respectively. On the other hand, ^{1}H NMR spectrum showed absorption as two doublets at δ 6.4 and 7.2 and a multiplet in the range δ 7.0-7.65 assigned to C_2-H, C_3-H and aromatic protons respectively. In addition, it showed a broad singlet at δ 9.8 assigned to hydroxy protons. Mass spectrum of compound **3** showed the molecular ion peak at 267

In IR spectra compound **4** showed absorption at 1655 due to keto group stretching. Similarly in ^{1}H NMR spectra it showed two doublets at δ 7.05 and 7.6 due to C_3 and C_4 protons of azepine dione ring. In addition, it showed a multiplet in the range δ 7.1-7.85 due to aromatic protons. In mass spectra of compound **4** showed the molecular on peak at 249.

Antimicrobial activity

The compound **4** was screened for antimicrobial activity using cup plate method[10,11]. The activity was carried out against three pathogenic bacteria, *B. Cereus, S. Aureus* and *E. Soli* and two fungal culture, *F. Solani, A. Favus*. The standard drugs used were Chloromycetin and Griseofulvin. The compound was tested in dimethyl formaide. The zone of incubation was compared with standard drug after 43 hr of incubation at 37^0 for antibacterial activity and 36 hr at 37^0 antifungal activity. Antimicrobial activity screening results are summarized in Table 1 and 2.

Table 1: *Antibacterial activity*

	B. cereus		***S. aureus***		***E. coli***	
Compd.	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative% of inhibition
89	353	96	420	91	100	98

Table-2*:* *Antifungal activity of Compound **4***

	F. Solani		***A. Flavus***	
Compd.	Area of inhibition mm^2	Relative % of inhibition	Area of inhibition mm^2	Relative % of inhibition
4	226	78	256	88

Conclusion

The compound 1-phenyl-1*H*-benzo[b]azepine-2,5-dione has shown considerable activity against *F. Solani* and *A. Flavus* fungal strains.

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