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Synthesis Charecterization and biological evaluation of 4-nitro-N-phenyl benzamide and (4-nitrophenyl) (piperidin-1-yl) methanone

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A B S T R A C T

Synthesis of mannish bases derivatives containing aromatic rings were synthesized by the condensation 4-nitrobenzoyl azide [2] with mannich bases to form (4-nitrophenyl) (piperidin-1-yl) methanone [3]. In the same way 4-nitrobenzoyl azide [2] treated with substituted aniline to form 4-nitro-N-phenylbenzamide [4]. The purification of these compounds is monitored by T.L.C. The structure of these newly synthesized compounds were characterized by ^{1}H NMR, ^{13}CNMR, Mass, IR, and elemental analysis**.**

Keywords: Mannich Bases, DMF, Acetone, Substituted Aniline

A R T I C L E I N F O

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1. Introduction

Dermatophytes are infections of keratinized tissue, that is, the epidermis, hair and nails, caused by a group of specialized fungi. The dermatophytes do not invade subcutaneous or deep tissue. *Dermytophyte-Trichophyton schoenleinii* was the first microorganism that was proven to cause an infectious disease of humans [1]. The dermatophytes species can be categorized as an ecological basic as being geophilic, zoophilic or anthrophilic [2].

The geophilic species are natural habitats in the soil, natural habitats of the zoophilic dermatophytes are domestic and wild animals [3]. *Geotrichum candidum* was believed to be part of the normal flora of human skin and gastrointestinal tract. *Geotrichum* is frequently isolated from milk and is recorded as a spoilage organism on dairy products [4]. Some fungi are parasitic, especially on plants and others are symbiotic with roots and algae [5].

Fungi cells are quite different from plant cells not only by lacking chloroplasts but also by having a cell wall that contains chitin and not cellulose [6]. Acyl azides, in general, and *N*-protected a-amino acid azidesin particular, have occupied a place of their own importance in organic [7], and peptide as well as peptidomimetic [8], syntheses. They are extensively used in the preparation of amides and peptides and a wide range of other compounds such as nitriles, and several classes of heterocycles. [7, 9].

The Curtius rearrangement of acyl azides into isocyanatesis of paramount value in synthetic chemistry. It is widely used in the preparation of amines, ureas and carbamates. A number of natural products and pharmacologically important compounds containing uriedo linkages, [10], ureidopeptidomimetics, [11] partially modified retro-inverso (PMRI) peptides, form amides and unnatural amino acids have been prepared *via* this rearrangement. [8,12], Due to such vast utility of acid azides, the development of efficient routes for their synthesis is important. The two well known routes for the preparation of acid azides are there action of NaN3 with an acid chloride [13] or mixed anhydride. [14],

The acid chloride method offers disadvantages at the preparation of acidchloride itself. These include e prolonged reaction duration, incompatibility with acid cleavable groups, and storage and stability problems associated with moisture sensitive acid chlorides. Also the poor solubility of NaN3 inorganic reaction medium requires the usage of a phase transfer catalyst, [15],or catalysts such as ZnI2 [16], to improve the yield of acid azides.

Alternately, protocols for the *in situ* generation of acid chlorides using SOCl2/DMF–NaN3,[17], cyanuric chloride /*N*-methyl morpholine, [18], triphosgene [19], *N*,*N* chloromethyl ene dimethyl ammonium chloride, [20], followed by coupling with an azide have also been reported. But these methods are not suitable for acids such as *N*-Boc/Z-a-amino acids whose acid chlorides are unstable. Preparation of acid azides *via* mixed anhydrides has been used to advantage. Yet, this method uses chloroformates which are inconvenient for handling. Katritzky *et al.*,recently prepared acid azides from acids in atwo step route involving *N*-acyl benzotriazoles as stable and reactive intermediates.[21], Acid azides, such as Boc/Z-amino acidazides, have also been prepared through a multi-step route starting from acids by hydrazinolysis of the methyl/ethyl esters followed by reaction of the resultant hydrazide with nitrosyl donors like HNO2.

2. Materials and Methods:

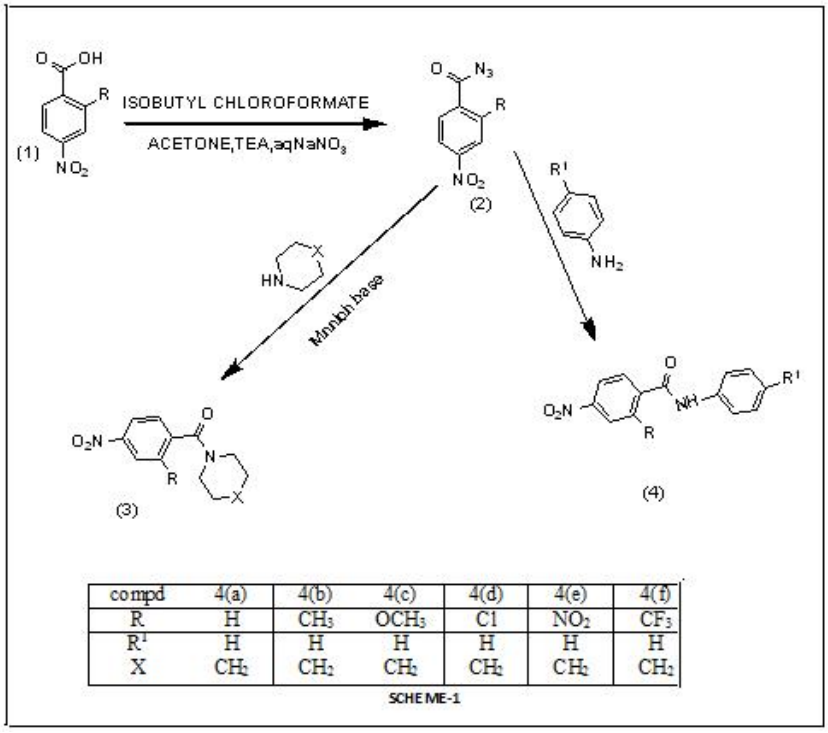
Melting points were determined on open capillaries using a Centex melting point apparatus .T.L.C. analysis were performed on precoatedsilicagel (E-Merck Kieselgel 60 F_{254}) plates and visualization was done by exposing to iodine vapour. Solvent were purified by standard procedures before use. Column chromatography was conducted by using Silica gel with different solvent systems as elutes.

IR Spectra were recorded KBr on Perkin –Elmer spectrum BX series FTIR spectrometer.H^1-NMR spectrum were recorded on Varian Gemini 300MHz and 200MHz spectrometers using TMS as internal standard(chemical shifts in & ppm) C^{13}NMR spectra were recorded on a bucker 75MHz spectrometer . Mass spectra were scanned on a Varian MATCH -7 and Joel JMSD-300 mass spectrometer at 70 ev. Elemental analysis were carried out on caroler 106 and per kin –analyzer. All the chemicals used in the present investigation were purchased from Aldrich chemicals; U.S.A.

Synthesis of 4-nitrobenzoyl azide (2)

At this instance to a solution of 4-nitrobenzoyl azide (2) (1eq) in acetone, TEA (3eq) was added and stirred at -15^{0}C for 20min.To this reaction mixture Isobutyl Chloro Formate (1:1eq) was added and stirred for 30 min.To the above reaction mixture aq NaN_3(3eq) was added and stirred for 20min at 0^{0}C. The progress of the rection was monitered by TLC with acetone. Ethyl acetate (6:4) as mobile phase .

The rection mixture was cooled poured on ice cold water(20ml),extracted with 10ml diethyl ether (5timesThe organic layer was separated, washed with water, dried over anhydrous Na_2SO_4 . The dried organic layer was filtered and evaporated under vaccum to give crude oil. The crude oil was purified by column chromatography by using 60-120 mesh silica gel. The 10% ethyl acetate-pet Ether solvent mixture was used as eluent. After the evaporation of the solvent under vaccum it affords pure 4-nitrobenzoyl azide [2].



compd	4(a)	4(b)	4(c)	4(d)	4(e)	4(f)
R	H	CH_3	OCH_3	Cl	NO_2	CF_3
R^1	H	H	H	H	H	H
X	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2

SCHEME-1

3. Results and Discussion

The structures of these newly synthesized compounds were characterized by H-NMR and IR spectral data.

^{1}H NMR spectra (300MHZ, $(CD)_2$ SO,TMS): 7.10-7. 25 (m, 4H, due to 4H of Benzene ring,)

IR spedtra: The compound (2) shows signals at, 1690(C=N), 1790 (-C=O), 2110(N=N)

Synthesis of (4-nitrophenyl) (piperidin-1-yl) methanone (3)

^{1}H NMR spectra(300MHZ,$(CD)_2$ SO,TMS): 7.25-7.75 (m,4H attached to the nitro benzene ring), 2.65(m,2H,of CH_2 attached to piper dine ring),1.83(m,2H,of CH_2 attached to piper dine ring),1.79(t,2H t,2H,of CH_2 attached to piper dine ring).

IR spedtra: The compound (3) shows signals at, 1660 (C=N), 1750 (-C=O), 2950(-CH sreching)

Synthesis of 4-nitro-N-phenylbenzamide (4)

To a mixture of pure of (4-nitrophenyl)(piperidin-1-yl) methanone [3] (1eq), in benzene (1eq) was added and refluxed for 16hrs.progress of the reaction was monitored by TLC with acetone. Ethyl acetate (6:4) as mobile phase. After completion of reaction solvent was evaporated under vacuum to give crude residue, purified by column chromatography 60-120 mesh silica gel to give 4-nitro-N-phenylbenzamide(4).

The structures of this newly synthesized compounds 4(a-f) were characterized by[1] H-NMR and IR spectral data.

^{1}H NMR spectra (300MHZ, $(CD)_2$ SO,TMS): 8.55 (S, 1H, due to the-NH attached to keto group), 6.75-7.75 (m,4H attached to the nitro benzene ring),6.55-7.45(s,5H attached to benzene ring)

IR spedtra: The compound (4) shows signals at, 1690 (C=N), 1720 (-C=O), 3150(-NH)

Table 1: Charactrization of above compounds

Compound	Molecular Formulae	Yield	M.P.O^0 C	% of Analysis					
				C		H		N	
				Calcd	Found	Calcd	Found	Calcd	Found
1	$C_7H_5NO_4$	60%	210	68.85	68.82	6.05	6.01	7.65	7.64
2	$C_7H_4N_4O_3$	54%	223	69.47	69.44	6.36	6.31	7.4	7.36
3	$C_{12}H_{14}N_2O_3$	65%	215	66.66	66.64	6.1	6.06	7.5	7.07
4	$C_{13}H_{10}N_2O_3$	62%	205	63	62.91	5.28	5.25	7.00	6.99

Anti-Bacterial Activity:

The anti bacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcusaureus NCCS 2079 and Bacillus cereus NCCS 2106. The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200. The synthesized compounds were used at the concentration of250 µglml and 500µglml using DMSO as a solvent the cefaclor 10µglml disc was used as a standard. (Himedia, Laboratories Ltd, Mumbai).

The test results presented in the table -2, suggest that 4a, 4d, 4e exhibit high activity against the tesed bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity

The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of aspergillus niger NCCS1196 and candida albicans NCCS3 4471 Compounds were treated at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was clotrimazole 50µglml against both organisms. The test results were presented in the table-3.

Table 2: Antibacterial activity by disc diffusion method for phenyl benzamide 4(a.f)

Compound	Zone of inhibition (mm)			
	Staphylococcus aureus	**Bacillus cereus**	**Escherichia coli**	**Pseudomonas aeruginosa**
4a	12	17	16	14
4b	14	11	15	10
4c	13	12	10	09
4d	16	17	12	11
4e	18	16	15	17
4f	11	14	13	12
Cefaclor	19	22	19	20

Table 3: Antifungal activity by disc diffusion method for phenyl benzamide 4(a.f)

Compound	Zone of inhibition (mm)	
	Asperigillus niger	**Candida albicans**
4a	11	13
4b	12	11
4c	16	17
4d	19	19
4e	21	21
4f	17	23
Clotrimazole	25	25

4. Conclusion

- Furthermore the substitution with phenyl group having a chloro group at p-position showed better activities.
- Mannish bases and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, antiflammatory.

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