Ultra Scientist Vol. 24(3)B, 399-404 (2012).

Synthesis Of 2-(-6-Aryl-[1,2,4] Triazolo [3,4b] [1,3,4] Thiadiazole-3-yl Methyl) Isoindole 1,3-Diones Involving Six Synthetic Steps For Examining Their Antimicrobial Potentials

RIDAM. MISRA, *V.K. PANDEY and SHRADHA SINHA

(Acceptance Date 4th September, 2012)

Abstract

Reaction of glycine with phthalic anhydride formed (1,3-Dioxo-1,3-dihydro-isoindol-2-yl) acetic acid (1) which on heating with phosphorous pentachloride under reflux afforded(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)acetyl chloride (2). The compound 2 on treatment with an ice-cold solution of hydrazine dehydrate gave(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)acetic acid hydrazide (3), which on reaction with carbon disulphide followed by addition of potassium hydroxide on stirring yielded potassium salt of N-2-(1.3-dioxo-1,3-dihydr-isoindole -2-yl) acetyl]hydrazine carbodithioic acid (4). Compound 4 was used as such for further reaction, which on heating with hydrazine dehydrate resulted in the formation of 2-(4-amino-5-mercapto-4H[1,2,4]triazole -yl-methyl) isoindole-1,3-diones (5). Compounds 5 on condensation with different aromatic acids and phosphorous oxychloride furnished 2-(6-aryl [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazolo-3-yl-methyl)-isoindole 1,3-diones (6). Compounds 6 were screened for their antimicrobial potentials.

Key words: Antimicrobial activity, Thiadiazoles, Triazole, Isoindoles, Diones.

Introduction

Triazolo thiadiazoles are familiar group of compounds. Although, thiadiazole derivatives find greater applications in medicines, related thiadiazoles have been less extensively studied for biological activities[1,2]. A triazole derivative, virazole (ribavirin) 1-β-ribofuranosyl-1,2,4-triazole-3-carboxamide has been claimed as the first genuine broad spectrum antiviral agent. Its synthesis and activity were first reported in 1972[3,4]. Several reports have given an adequate account of metabolism, lack of immunosuppressive activity effect on Herpes

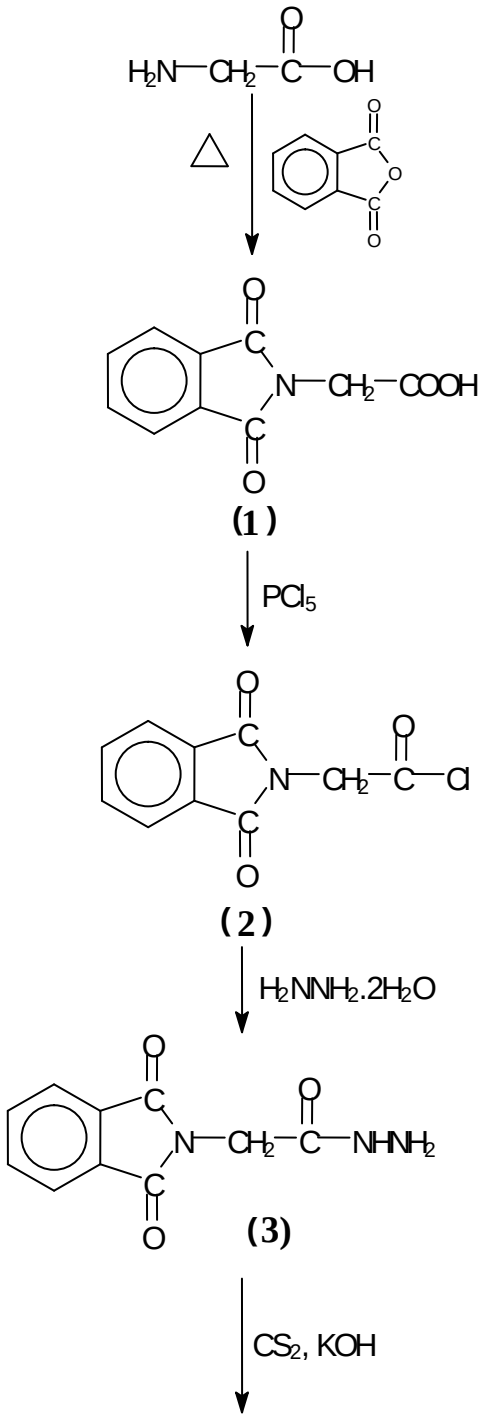
Corresponding Authors E-Mail id: ridammisra@rediffmail.com

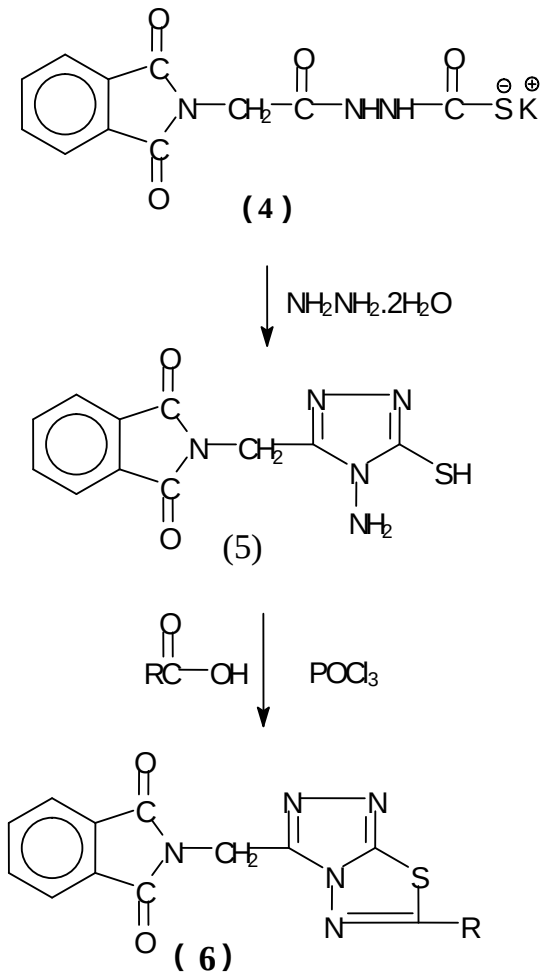
Simplex Virus type-1, inability to develop resistant strains of herpes virus, effect on viral hepatitis in animals and on influenza in human, mice and primates[5]. In addition, triazoles viz., itraconazole, ketoconazole and fluconazole are in clinical use against fungal diseases. Itraconazole has very strong activity against Aspergillus and Torulopsis. 1,2,4 triazolo-[3,4 b] thiadiazoles are interesting fused systems derived from 4-amino-5-substituted-1,2,4-triazole-3-thiols[6,7]. These fused systems are reported to possess significant antibacterial, antifungal, herbicidal, diuretic and anthelmintic activities[8-12]. Diencka[13] in 1977 found that 0.05mg/kg of sulphonamido thiadiazole butamide when administered to rabbits once a day for 8 hour decreased the blood glucose level. These observations gave me an impetus to undertake the synthesis of substituted triazolo thiadiazoles 6a-f (Scheme -I) for studying their antimicrobial potentials.

Experimental

The melting points of the compounds were determined in a Toshniwal electric melting point bath and are uncorrected. The infrared (IR) spectra of the compounds were recorded in the region of 4000-400 cm^{-1} using KBr on a FT-IR Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrometer in $CDCl_3$ solvent. The values of the chemical shifts are expressed in units. The ^{13}C NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrometer. All the compounds were checked for purity by thin layer chromatography (TLC).

1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid (N-Phthaloylglycine)(1): A





Scheme-I

mixture of finely powdered phthalic anhydride (0.1 mole) and glycine (α -aminoacetic acid (0.1 mole) was heated in such a way that the temperature did not exceed 185 ^{0}C for a period of half an hour. The hot melt was allowed to stand at room temperature for 30 minutes. The solidified material thus obtained, was treated with a solution of sodium-bicarbonate (10%) with stirring. Addition of sodium bicarbonate solution was continued till there was no any observable degree of effervescence. It was filtered off and the residue was rejected. The filtrate was neutralized with diluted hydrochloric acid. A white colored precipitate, separated out on complete neutrali-zation. The precipitate was allowed to settle down, filtered off and washed with cold water. It was dried at 100^{o}C and recrystallized from hot water as white crystalline solid. It melted at 190^{o}C [191-192^{o}C][14], yield, 95%.

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl) acetyl chloride (2): In order to prepare the compound named as (2), a mixture consisting of (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetic acid (0.07 mole) and phosphorus pentachloride (PCl_5) (0.08 mole) in dry benzene (100 ml) was heated under reflux for two hours in such a manner that the reaction mixture remained free from moisture for the entire period of reaction. Subsequently, the solvent benzene and phosphorus oxychloride ($POCl_3$) formed were removed by distillation under diminished pressure. The acid chloride thus obtained, was used for the further reaction without any purification.

(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid hydrazide (3): The acid chloride (2) (0.07 mole) *i.e.* (1,3-dioxo-1,3-dihydro-isoindol-2-yl) acetyl-chloride was cooled and a solution of previously cooled hydrazine dihydrate (1.50 mole) was added in instalments with vigorous stirring. When the addition was completed, the resultant mixture was further stirred mechanically for half an hour. It was left as such undisturbed for one hour and filtered off. The solid was washed with cold water repeatedly and dried at 100^{o}C. It was

recrystallized from diluted ethanol as white crystalline mass, m.p. 210^{0}C, yield 75%.
Anal. for $C_{10}H_9N_3O_3$ N Calcd. 21.91%, Found 21.54%

Potassium salt of N-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetyl]-hydrazine carbodithioic acid (4): (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid hydrazide (3) (0.05 mole) was dissolved in a solution of potassium hydroxide (10%) (~25 ml) by stirring. On getting a homogenous solution, previously cooled carbon disulphide (CS_2) (0.1 mol) in absolute ethanol (50 ml) was added dropwise with constant stirring. When the process of addition was completed, the resultant solution was further stirred. A semi-solid material was obtained which did not solidify even after prolonged cooling and therefore was used as such for the further reaction.

2-(4-Amino-5-mercapto-4H[1,2,4] triazol-3-yl-methyl]isoindol-1,3dione(5): A mixture consisting of potassium salt of N-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)acetyl] hydrazine carbodithioic acid (4) (0.05 mole) hydrazine dihydrate (0.12 mole), water (20 ml) and n-hexane (50 ml) was heated under reflux for four hours. Subsequently, the reaction mixture was cooled and the insoluble material was filtered off. The clear filtrate was acidified with acetic acid and the solid which separated out after neutralization was washed with minimum quantity of cold water and dried at 100^{o}C. Recrystallization from ethanol afforded a white crystalline solid which melted at 282^{o}C, yield 70%.

Anal. for $C_{11}H_9N_5O_2$; N Calcd. 28.80%, Found: 28.72%

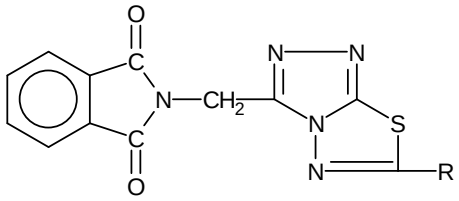
2-(6-Aryl [1,2,4] triazolo [3,4-b][1,3,4] thiadiazolo-3-yl-methyl)-isoindol-1,3-diones (6): Synthesis of target compounds (6) involved cyclization leading to the formation of nitrogen bridge head compounds. Thus, an intimate mixture of a carboxylic acid (0.02 mole), 2-(4-amino-5-mercapto-4H[1,2,4] triazol-3-yl-methyl)-isoindol-1,3-dione (5) (0.02 mole) and phosphorus oxychloride (0.1 mole) was heated under reflux for five hours under anhydrous reaction conditions. Subsequently, the contents were poured into cold water slowly with stirring. A solid immediately separated out which was filtered off and was washed with a solution of sodium bicarbonate (10%) in order to remove any unreacted acid. It was finally washed with cold water and dried in vacuo for 24 hours. The compounds of this category thus synthesized were recrystallized from ethanol (containing decolourizing charcoal) and recorded in Table VI alongwith their characterization data.

IR (KBr) (ν_{max} in cm^{-1}): 1705 (imide C=O), 1640 (C=N).
^{1}H NMR (DMSO-d6) (in δ ppm): 7.22-7.75 (m, 9H, Ar$\underline{H}$), 3.95 (s, 2H, N-C$\underline{H_2}$).
^{13}C NMR (DMSO-d_6 (in δ ppm): 45.25 (C-9), 115.25, 117.62, 125.36, 129.24, 131.55, 133.75 (C-1 to C-6, C-13 to C-18), 168.52 (C-10), 170.25 (C-11, C-12), 172.64 (C-7, C-8).

Conclusion And Discussion

All the four compounds were evaluated for their antimicrobial activity by the established methods as recommended by National Committee for Clinical Laboratory Standards. One compound of the series having 2-hydroxy phenyl substituent showed antibacterial activity

Table I



Characterization data of 2-(6-aryl[1,2,4] triazolo [3,4-b][1,3,4] thiadiazol-3-yl methyl) isoindol-1,3-diones (6)

Compd. No.	R	m.p. (°C)	Yield (%)	Color	Mol. formula	Mol. Wt.	Analysis Nitrogen, %	
							Calcd.	Found
6a.	phenyl	>300	65	Brown	$C_{18}H_{11}N_5O_2S$	361	19.39	19.38
6b..	2-hydroxyphenyl	300	50	White	$C_{18}H_{11}N_5O_3S$	377	18.57	18.55
6c..	2-chlorophenyl	>300	62	Pink	$C_{18}H_{10}N_5O_2SCl$	396.5	17.65	17.60
6d..	3-aminophenyl	>300	45	Brown	$C_{18}H_{12}N_6O_2S$	376	22.34	22.29
6e..	4-pyridyl	298	50	White	$C_{17}H_{10}N_6O_2S$	362	23.20	23.16

against *Escherichia coli* while the same compound showed antifungal activity against four fungal strains *viz. Candida albicans, Cryptococcus neoformans, Sporothrix schenkii and Trichophyton mentagrophyte.* However, these compounds could not provoke any measurable degree of antiviral activity against Japanese encephalitis virus (JEV) *in vitro* when tested in 1-3 days old suckling Swiss albino mice[15].

Acknowledgement

The authors are thankful to the Head of the Department of Chemistry, University of Lucknow, Lucknow for providing necessary laboratory facilities and to the Director, Central Drug Research Institute (CDRI), Lucknow, for providing elemental, spectral and biological activity data.

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