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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Free Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2014, Vol. 30, No. (1):
Pg. 319-323

A Multistep Preparation of 3-Aryl-8-methoxythiazolo [3', 2' : 2, 3] [1, 2, 4] triazino [5, 6-b] indoles Under Microwave IR-radiations

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http://dx.doi.org/10.13005/ojc/300141

(Received: October 16, 2013; Accepted: November 11, 2013)

ABSTRACT

The different 3-Aryl-8-methoxythiazolo [3', 2' : 2, 3] [1, 2, 4] triazino [5, 6-b] indoles having antihistaminic, antithyroid, antitubercular, antifungal & antibacterial activities are synthesized through a multistep preparation in high yield in shorter reaction time under microwave irradiations.

Key words: Indole, Microwave, Aryl, heterocyclic.

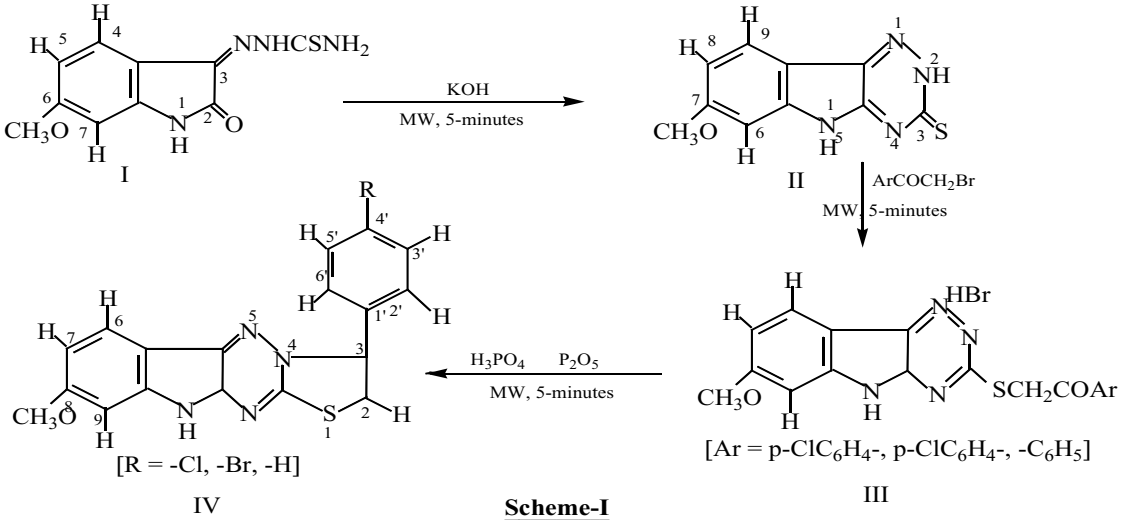
INTRODUCTION

Bridgehead nitrogen heterocycles containing thiazole and related heterocycles (thiadiazole and thiadiazine) exhibit antihistaminic, antithyroid, antitubercular, antifungal & antibacterial activities[1-3] and their synthetic importance has been greatly enhanced by the recent uses of their condensed bridgehead nitrogen heterocycles as anthelminitics, antidepressants, platelet aggregation inhibitors, antineoplastic, vulcanization accelerators and photographic sensitizers[4-11]. The indoles are already been synthesized by different method But they requires longer reaction time and tedious workup[12-21]. Microwave assisted reactions are gaining much more importance in synthetic organic chemistry due to dramatic reduction in time from days to hours and hours to minutes or seconds[22-24].

The present work reports the synthesis of 3-Aryl-8-methoxythiazolo[3', 2' : 2, 3][1, 2, 4] triazino[5, 6-b]indoles in a multi step preparation in high yield in shorter reaction time(Scheme 1).

Our work started by reacting 6-methoxyisatin with thiosemicarbazide in Anhyd. ethanol under microwave irradiation at 560W for 5-minutes to give 6-Methoxyisatin-3-thiosemicarbanzone (I). After separation, the 6-Methoxyisatin-3-thiosemicarbanzone(I) reacts with 5% KOH under microwave irradiation at 560W for 5-minutes to give 7-Methoxy-5H-2,3-dihydro [1, 2, 4] triazino [5, 6-b] indole-3-thione (II).

The compound 7-Methoxy-5H-2,3-dihydro [1, 2, 4] triazino [5, 6-b] indole-3-thione (II) further reacts with p-chlorophenacyl bromide under



I II III IV

Scheme-I

microwave irradiation at 560W for 5-minutes to give 5H-3-(p-chlorophenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide (IIIa; Ar = p-C1C_6H_4). Similarly, 7-Methoxy-5H-2,3-dihydro [1, 2, 4] triazino [5, 6-b] indole-3-thione(II) was also irradiated with p-cholorophenacyl bromide, phenacyl bromide, under microwave irradiation at 560W for 5-minutes to give 5H-3-(p-bromophenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide(IIIb, Ar = p-Br C_6H_4) and 5H-3-(phenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide (IIIa; Ar = C_6H_5) respectively. The results are shown in Table-1.

We further explore our work by irradiated 5H-3-(p-chlorophenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide (IIIa; Ar = p-C1C_6H_4) in a mixture of H_3PO_4/P_2O_5 under microwave irradiation at 560W for 5-minutes to give 3-(p-chlorophenyl-8-methoxythiazolo[3', 2' : 2, 3][1, 2, 4] triazino[5, 6-b]indole(IVa, R = Cl). Similarly, 5H-3-(p-bromophenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide (IIIb; Ar = p-BrC_6H_4) and 5H-3-(phenacylthio-7-methoxy [1, 2, 4] triazino [5, 6-b] indole hydrobromide (IIIa; Ar = C_6H_5) were also irradiated in a mixture of H_3PO_4/P_2O_5 under microwave irradiation at 560W for 5-minutes to give 3-(p-bromophenyl-8-methoxythiazolo[3', 2' : 2, 3][1, 2, 4] triazino[5, 6-b]indole(IVa, R = Br) and 3-(phenyl-8-methoxythiazolo[3', 2' : 2, 3][1, 2, 4] triazino[5, 6-b] indole(IVa, R = H) respectively. The results are shown in Table-2.

EXPERIMENTAL

All the melting points reported are uncorrected. Infrared spectra (ν_{max} in cm^{-1}) were recorded in nujol mull or KBr on a Perkin-Elmer 842/Beckman IR-20 / Hitachi 215 spectrometers. The proton magnetic resonance spectra were recorded on a VXR-200 MHz or R-32 Perkin-Elmer 90 MHz spectrometer in $CDC1_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal reference stadnard. The chemical shifts are expressed in d (ppm) units downfield from TMS. Mass spectra were scanned on a Jeol JMX-DX-300 spectrometer operating at 70 eV. Carbon, hydrogen and nitrogen analyses were carried out on a Yanaco MT-3 (JAPAN) instrument. Thin layer chromatography (TLC) were performed on silica-gel plates using acetone-benzene (1 : 3 or 1 : 2) as solvent system and iodine chamber as visualizing agent.

Typical procedure for the synthesis of 6-Methoxyisatin-3-thiosemicarbanzone(I)

A mixture of 6-methoxyisatin(0.18g, 0.001 mol) in Anhyd. ethanol (2ml) and thiosemicarbazide (0.1g, 0.0011 mol) in a mixture of water (2 ml) and glacial acetic acid (0.5 ml) was irradiated under microwave irradiation at 560W for 5-minutes. A yellow coloured solid formed during irradiation. The solid was filtered, washed well with water and crystallized from ethanol-DMF furnishing yellow crystals. yield 0.247g (95%), m.p. 265^{O}C.[Found : N, 22.68, S,

12.62. $C_{10}H_{10}N_4O_2S$ requires N, 22.40; S, 12.80%]; IR : 825, 860 (1, 2, 4-trisubstituted benzene ring), 1115 (C=S), 1125 & 1370 (C-O-C stretching), 1620 (C=N), 1700 (C=O), 3200, 3280, 3400 (NH, NH_2).

Typical procedure for the synthesis of 7-Methoxy-5H-2,3-dihydro [1, 2, 4] triazino [5, 6-b] indole-3-thione(II)

6-Methoxyisatin-3-thiosemicarbazone (I, 0.125g, 0.0005 mole) in 5% KOH (3.5 ml) was irradiated under microwave irradiation at 560W for 5-minutes. The reaction mixture was cooled and the insoluble material removed by filtration. The filtrate on neutralisation with dil. HCl gave a yellow solid which was filtered, washed well with water and crystallised from aq. DMF furnishing yellow crystals, yield 0.108 g (92%), m.p. > 260^{O}C [Found : C, 51.91; H, 3.57; N, 23.84; S, 13.58. $C_{10}H_8N_4SO$ requires C, 51.72; H, 3.45; N, 24.13; S, 13.79%]; IR : 810, 860 (1, 2, 4-Trisubstituted benezene ring), 1150 (C=S), 1170, 1370 (C-O-C stretching), 1590, 1610 (C=N), 3200 (N-H stretching).

Typical procedure for the synthesis of 5H-3-(p-chlorophenacylthio-7-methoxy[1, 2, 4]triazino [5, 6-b] indole hydrobromide (IIIa; Ar = p-C1C_6H_4)

A mixture of II(0.232 g, 0.001 mol) and p-cholorophenacyl bromide (0.234 g, 0.001 mol) in DMF (6 ml) was irradiated under microwave irradiation at 560W for 5-minutes, and poured into ice-water. The solid thus separated, was filtered, washed with water and crystallized from aq. DMF to give IIIa as yellow crystals, yield 0.415 g (94%), m.p. > 260 [Found: N, 12.20; S, 6.92. $C_{18}H_{14}N_4O_2$ SBrCl requires N, 12.03; S, 6.87%]; IR : 810, 860 (1, 2, 4-trisubstituted benzene ring), 1170, 1370 (C-O-C stretching), 1570 (C-N stretching), 1590, 1610 (C=NO, 1690 (C=O), 3180 (N-H stretching).

Table 1: **3-p-Chlorophenyl-8-methoxythiazolo [3', 2' : 2, 3][1, 2, 4] triazino [5, 6-b] indole**

S. No.	Substrate(R)	Time(in minutes)	Yield(%)	m.p.(°C)
1.	-pClC_6H_4-(IIIa)	5	94	> 260^{O}C
2.	-pBrC_6H_4-(IIIb)	5	91	> 260^{O}C
3.	-C_6H_5(IIIc)	5	98	> 260^{O}C

Table 2: **3-p-Chlorophenyl-8-methoxythiazolo [3', 2' : 2, 3][1, 2, 4] triazino [5, 6-b] indole**

S. No.	Substrate(R)	Time(in minutes)	Yield(%)	m.p.(°C)
1.	-Cl(IVa)	5	91	> 250^{O}C
2.	-Br(IVb)	5	90	> 250^{O}C
3.	-H(IVc)	5	96	> 250^{O}C

Following members of the series were also prepared in a similar way

IIIb (Ar = p-BrC_6H_4-), yield (91%), m.p. > 260^{O}C [Found : N, 11.23; S, 6.38, $C_{18}H_{14}N_4O_2SBr_2$ requires, N, 10.98; S, 6.27%]; IR: 1570 (C-N stretching), 1610 (C=N), 1690 (C=O), 3190 (N-H). IIIc (Ar = C_6H_5), yield (98%) m.p. > 260^{O}C [Found : N, 14.62; S, 8.18.$C_{18}H_{15}N_4O_2SC1$ requires N, 14.49; S, 8.27%]; IR : 1575 (C-N stretching), 1600 (C=N), 3240 (N-H stretching).

Typical procedure for the synthesis of 3-p-Chlorophenyl-8-methoxythiazolo[3', 2' : 2, 3][1, 2, 4] triazino [5, 6-b] indole(IVa, R = C1)

Ketone IIIa(0.1g) in a mixture of H_3PO_4 (0.3ml) and P_2O_5 (0.4g) was irradiated under microwave irradiation at 560W for 5-minutes. The reaction mixture was poured into water and neutralised with aq. K_2CO_3 solution. The solid, thus separated, was filtered, washed well with water and crystallised from aq. DMF to furnish IVa as dark red crystals, yield 0.071 g (91%), m.p. > 250^0 [Found :

C, 59.17; H, 3.11; N, 15.16; S, 8.91.$C_{18}H_{11}N_4SOCl$ requires C, 58.93; H, 3.01; N,15.27; S, 8.73%]; IR; 1515 (C-N stretching) 1600 (C=N). PMR (DMSO-d_6) : 3.95 (3H, s, C_8-OCH_3), 7.40 [2H, d (J=7.5Hz), H-3' and H-5'], 7.70 [2H,d (J = 7.5.Hz), H-2' and H-6'], 7.90 (1H,s,C_2-H), 6.9-8.1 (3H, m, aromatic protons of indole moiety).

Following members of the series were also prepared in a similar way

IVb (R = Br): yield (90%), m.p. > 250^{O}C [Found : C, 52.38; H, 2.76; N, 13.42; S, 7.51. $C_{18}H_{11}N_4SOBr$ requires C, 52.55; H, 2.67; N, 13.62; S, 7.78%]; IR : 1520 (C-N stretching), 1610 (C = N).

IVc (R = H) : yield (96%), m.p. > 250^{O}C[Found : C, 64.92; H, 3.68; N, 16.64; S, 9.87.$C_{18}H_{11}N_4SO$ requires C, 65.06; H, 3.61; N, 16.86; S, 9.63%]; IR : 1520 (C-N stretching), 1610 (C = N).

ACKNOWLEDGMENTS

We thank Professor D. Villemin (France), Dr. R. Sharma (Dayton, USA) and Professor A.J. Bellamy (Swindon, UK) for inspiration.

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