Int. J. Chem. Sci.: 8(2), 2010, 809-816

MICROWAVE ASSISTED SYNTHESIS OF SOME NEW SPIRO-[INDOLE-THIAZOLIDINE] DERIVATIVES : A GREEN CHEMICAL PATHWAY

KIRTI SHRIMALI, MANISH RAWAL, PINKI B. PUNJABI and SURESH C. AMETA

Microwave Synthesis Laboratory, Department of Chemistry, University College of Science, M. L. Sukhadia University, UDAIPUR – 313001 (Raj.) INDIA

ABSTRACT

The reaction sequence involves microwave induced preparation of N-(2-oxo-1, 2-dihydro-3'H-indol-3-ylidene) pyridine-4-carbohydrazide **(3)** from isoniazid **(1)** and isatin **(2)** followed by the cyclocondensation of **(3)** and mercaptoacetic acid under microwave conditions to achieve the synthesis of spiro-[indole-thiazolidine] compound **(4)**. The resulting compound was then allowed to react with various aromatic aldehydes to afford arylidene derivatives **(5a-d)**.

Key words: Spiro-[indole-thiazolidine], Isoniazid, Isatin, Microwave irradiation.

INTRODUCTION

Heterocyclic compounds hold a special place among pharmaceutically important natural and synthetic materials. The remarkable ability of heterocyclic nuclei to serve as reactive pharmacophores, has largely contributed to their unique values as traditional key elements of numerous drugs. By far, the most important heterocyclic systems used in pharmaceuticals are those having five and six membered rings. In a continuation of search for better and improved drugs, organic chemists investigated the synthesis of novel spiro heterocyclic compounds with the assumption that the incorporation of more than one bioactive heterocyclic moiety into a single framework may result into the production of novel heterocycles with enhanced bioactivity. Over the past decade, chemists have reported some exciting synthetic strategies for the synthesis of this exclusive class of compounds. Consequently, there is an increased interest in technologies and concepts that facilitates

*Author for correspondence; E-mail: ameta_sc@yahoo.com; kirti_shrimali2103@yahoo.com

more rapid synthesis and screening of chemical substances to identify compounds with appropriate qualities. One such high-speed technology is Microwave Assisted Organic Synthesis (MAOS).

Spiro compounds are well known to possess varied pharmacological activities[1,2]. Spiropyrans are biologically interesting compounds, with antibacterial[3], antifungal[4], antitumor[5], hypotensive[6] effects and also have potential applications to industrial fields[7-9]. Spirohydantoin derivatives showed antiepileptic[10], antipsychotic[11], antidepressant[12], antixiolytic[13], neuroprotection[14], antiproliferative[15] and anticonvulsant[16] activities.

A microwave assisted three component regioselective one pot cyclocondensation method has been developed for the synthesis of a series of novel spiro [indole-thiazolidin-ones][17] in high yields as compared to a conventional two step procedure. A green chemical synthesis of novel spiro [indole-pyrido-thiazines] was carried out under microwave conditions[18], which was reluctant to be formed under thermal conditions. A facile one pot synthesis of novel spiro-fused pyran derivatives via condensation of ninhydrin with malononitrie and active methylene compounds has been carried out by Shaker *et al.*[19] Shanthi *et al.*[20] reported a new $InCl_3$-catalyzed facile and rapid method for the synthesis of spirooxindoles. Recently, Pandey *et al.*[21] reported solvent free synthesis of 3'-substituted spiro-[indole-thiazolidine] via isotinimiries. Spiro-fused heterocycles under solvent free conditions have also been carried out by Shaabani and Bazgir[22]. Byk *et al.*[23] reported new regioselective multicomponent reaction to synthesize novel spiroheterobicyclic aliphatic ring.

In the present investigation, isoniazid is condensed with isatin using green pathway (i.e. microwave radiation) to synthesize some new spiro-[indole-thiazolidine] compounds.

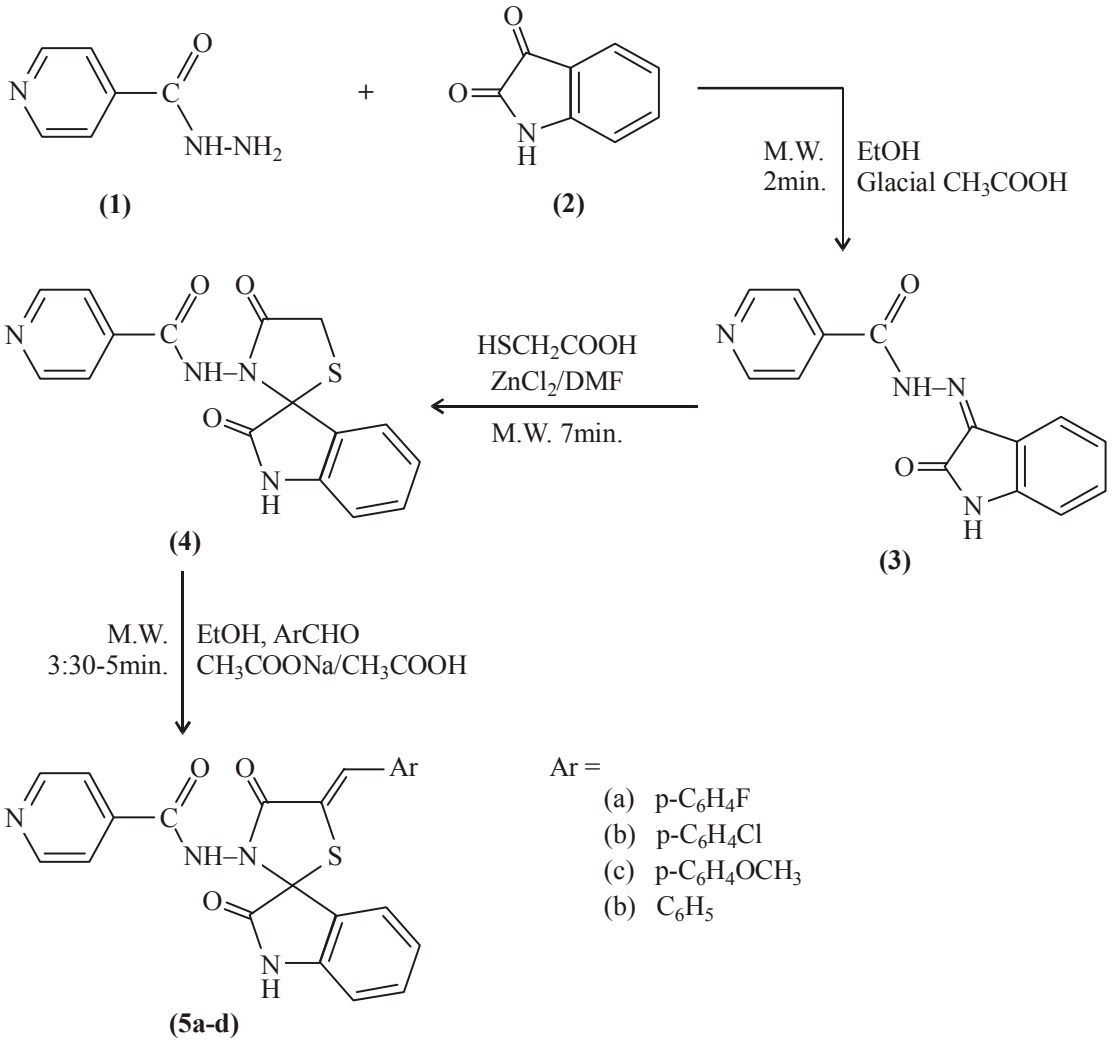
EXPERIMENTAL

All reactions were carried out in a domestic microwave oven (Kenstar, Model No. OM-26EGO). Melting points are uncorrected and determined in open capillaries. Reactions were monitored by thin layer chromatography using silica gel-G as adsorbent using ethyl acetate : n-hexane (7 : 3) as eluent and was detected by iodine vapors. IR spectra (KBr pellets) were recorded on Perkin-Elmer 1800 (FTIR) spectrophotometer. ^{1}H NMR spectra (DMSO-d_6) were taken on a Bruker DRX spectrophotometer (300 MH_Z FTNMR) using TMS as internal standard and chemical shifts are expressed in δ. Mass spectra were taken on a Jeol sx-102/PA-6000 (EI) spectrometer. Elemental analysis for C, H and N were conducted using a Perkin, Elmer C, H, N and analyzer.

Synthesis of N - (2-oxo -1, 2 - dihydro - 3'H - indol - 3 - ylidene] pyridine - 4 - carbohydrazide (3)

The reaction mixture of equimolar (0.01 mole) quantities of isoniazid **(1)** and isatin **(2)** in alcohol and catalytic amount of glacial CH_3COOH was heated for 2 min. in a microwave oven. The mixture was then allowed to cool; a yellow coloured solid separated out, which was filtered, dried and recrystallized from CH_2Cl_2.

Scheme



Synthesis of N-(2, 4'-dioxo-1, 2-dihydro-3'H-spiro [indole-3, 2'-[1, 3] thiazolidin]-3' yl) pyridine-4-carbaxamide (4)

To a mixture of **(3)** (0.01 mole) and mercaptoacetic acid (0.01 mole) in DMF, a pinch of anhydrous $ZnCl_2$ was added and the mixture was irradiated for 7 min. It was cooled to room temperature and then poured into crushed ice. The solid separated was filtered, washed and recrystallized from alcohol.

Synthesis of N-{5'-[(4-substituted phenyl) methylidene]-2, 4'-dioxo-1, 2-dihydro-3'H-spiro [indole-3, 2'-[1,3] thiazolidin]-3'-yl} pyridine-4-carboxamide (5a-d)

Compound **(4)** (0.01 mole) was suspended in minimum quantity of ethanol. To this, aromatic aldehyde (0.01 mole), anhydrous sodium acetate (0.02 mole) and glacial acetic acid (5 mL) were added and irradiated for 3:30-5 minutes under microwave irradiation. The reaction mixture was cooled to room temperature and then poured into ice cold water. The separated solid was filtered, washed with water and recrystallized from alcohol.

RESULTS AND DISCUSSION

Isoniazid **(1)** on condensation with isatin **(2)** in presence of catalytic amount of glacial acetic acid furnished N-(2-oxo-1,2-dihydro-3'H-indol-3-ylidene) pyridine-4-carbohydrazide **(3)**, which showed characteristic IR absorption bands at 3236 (N-H str.), 1705 (C=O str.) and 1619 cm^{-1} (C=N str.) and two sharp singlets at δ 9.2 (-NH of indole ring) and δ 8.5 (-CONH). Compound **(3)** underwent spirocyclisation upon its reaction with mercaptoacetic acid in presence of anhydrous $ZnCl_2$ to form spiro-[indole-thiazolidine] compound **(4)**. Its IR spectrum showed the absence of C=N absorption of 1619 cm^{-1} and presence of a band at 1730 cm^{-1} corresponding to C=O str. of thiazolidinone ring and also appearance of a new singlet at δ 3.5 ($S-CH_2-C$) in ^1H NMR favours the formation of spiro compound **(4)**. Compound **(4)** was then condensed with aromatic aldehydes to give arylidene derivatives **(5a-d)**, which were characterized by IR and ^1H NMR spectral data. The IR spectrum showed the absence of carbonyl absorption of thiazolidinone at 1730 cm^{-1} and the presence of a chalcone carbonyl absorption (-C=C-C=O) at 1682 cm^{-1}. Its ^1H NMR spectrum displayed a new singlet at δ 6.2 attributed to chalcone moeity (C=CH-Ar) proton. The mass spectrum also supported the proposed structure by the presence of molecular ion peak at m/z 446. All the above compounds were also confirmed by their elemental analyses. Physical and analytical data are presented in Table 1 and spectral data are given in Table 2.

Table 1: Physical and analytical data of synthesized compounds

Compd.	Ar	M.P (°C)	Yield (%)	Mol. formula	Mol. weight	Calculated/Found (%)		
						C	H	N
3	-	280	88	$C_{14}H_{10}N_4O_2$	266	63.15 (62.09)	3.79 (3.68)	21.04 (21.03)
4	-	242	85	$C_{16}H_{12}N_4O_3S$	340	56.46 (56.39)	3.55 (3.47)	18.46 (18.43)
5a	p-C_6H_4F	190	82	$C_{23}H_{15}FN_4O_3S$	446	61.88 (61.79)	3.39 (3.28)	12.55 (12.52)
5b	p-C_6H_4Cl	164	78	$C_{23}H_{15}ClN_4O_3S$	463	59.68 (59.57)	3.27 (3.21)	12.10 (12.03)
5c	p-$C_6H_4OCH_3$	186	79	$C_{24}H_{18}FN_4O_3S$	458	62.87 (62.79)	3.96 (3.89)	12.22 (12.18)
5d	-C_6H_5	138	75	$C_{23}H_{16}FN_4O_3S$	428	64.47 (64.38)	3.76 (3.68)	13.08 (13.02)

Table 2: Spectral data of synthesized compounds

Compd.	Spectral data		
3	**IR (cm^{-1})**	:	3236 (N-H str.), 3100 (C-H str., aromatic), 1705 (C=O str.), 1768 (C=O str. of CONH), 1619 (C=N str.)
	^{1}H NMR (δ)	:	9.2 (s, 1H, NH), 7.0-7.8 (m, 4H, Ar-H), 8.5 (s, 1H, CONH), 8.38 (d, 2H, Ar-H of pyridine ring), 6.6 (d, 2H, Ar-H of pyridine ring).
4	**IR (cm^{-1})**	:	3360 (N-H str.), 3110 (C-H, aromatic), 1705 (C=O str.), 1730 (C=O of thiazolidinone ring)
	^{1}H NMR (δ)	:	9.2 (s, 1H, NH), 6.9-7.5 (m, 4H, Ar–H),8.55 (s, 1H, CONH), 8.36 (d, 2H, Ar-Hof pyridine ring), 6.62 (d, 2H, Ar-H) of pyridine ring), 3.5 (s, 2H, S-CH_2-C)

Cont…

Compd.			Spectral data
5a	**IR (cm^{-1})**	:	3318 (N-H str.), 3065 (C-H str.,aromatic) 1720 (C=O str.), 1682 (C=O str. of thiazolidinone ring), 1118 (C-F str.)
	^{1}H NMR (δ)	:	9.1 (s, 1H, NH), 6.9-7.4 (M, 8H, Ar-H), 8.62 (s, 1H, CONH), 8.35 (d, 2H, Ar-H) of pyridine ring), 6.5 (d, 2H, Ar-H of pyridine ring), 6.2 (s, 1H, C=CH-Ar)
	MS (m/z)	:	446$[M]^+$, 340 $(C_{17}H_{11}N_3O_2SF]^+$ $[C_9H_6N_2SOF]^+$, 131 $[C_8H_5NO]^{+\cdot}$, 114 $[C_3H_2N_2SO]^{+\cdot}$, 78 $[C_5H_4N]^{+\cdot}$, 95 $[C_6H_4F]^{+\cdot}$, 28$[CO]^+$
5b	**IR (cm^{-1})**	:	3310 (N-H str.), 3072 (C-H str., aromatic) 1715 (C=O str.), 1685 (C=O str. of thiazolidinone ring), 749 (C-Cl str.)
	^{1}H NMR (δ)	:	9.28 (s, 1H, NH), 7.1-7.5 (M, 8H, Ar-H), 8.59 (s, 1H, CONH), 8.34 (d, 2H, Ar-H) of pyridine ring), 6.6 (d, 2H, Ar-H of pyridine ring), 6.3 (s, 1H, C=CH-Ar)
	MS (m/z)	:	465 $[M+2]^{+\cdot}$, 463 $[M]^{+\cdot}$, 356 $[C_{17}H_{11}N_3O_2SCl]^{+\cdot}$, 225 $[C_9H_6N_2SOCl]^{+\cdot}$, 131 $[C_8H_5NO]^{+\cdot}$, 114 $[C_3H_2N_2SO]^{+\cdot}$, 111$[C_6H_4Cl]^{+\cdot}$,78 $[C_5H_4N]^{+\cdot}$, 28 $[CO]^{+\cdot}$
5c	**IR (cm^{-1})**	:	3315 (N-H str.), 3078 (C-H str., aromatic) 1712 (C=O str.), 1680 (C=O str. of thiazolidinone ring), 1160 (C-O str.)
	^{1}H NMR (δ)	:	9.3 (s, 1H, NH), 7.0-7.5 (m, 8H, Ar-H), 8.6 (s, 1H, CONH), 8.38 (d, 2H, Ar-H) of pyridine ring), 6.75 (d, 2H, Ar-H of pyridine ring), 6.28 (s, 1H, C=CH-Ar),3.5 (s, 3H, $–OCH_3$)
	MS (m/z)	:	458 $[M]^{+\cdot}$, 352 $[C_{18}H_{14}N_3O_3S]^{+\cdot}$, 221$[C_{10}H_9NO_2S]^{+\cdot}$, 131 $[C_8H_5NO]^{+\cdot}$, 114$[C_3H_2N_2OS]^{+\cdot}$, 107 $[C_7H_7O]^{+\cdot}$,78$[C_5H_4N]^{+\cdot}$, 28 $[CO]^+$
5d	**IR (cm^{-1})**	:	3325 (N-H str.), 3088 (C-H str.,aromatic) 1705 (C=O str.), 1680 (C=O str. of thiazolidinone ring)
	^{1}H NMR (δ)	:	9.1 (s, 1H, NH), 7.1-7.6 (m, 9H, Ar-H), 8.62 (s, 1H, CONH), 8.36 (d, 2H, Ar-H) of pyridine ring), 6.8 (d, 2H, Ar-H of pyridine ring), 6.1 (s, 1H, C=CH-Ar)
	MS (m/z)	:	428 $[M]^{+\cdot}$, 322 $[C_{17}H_{12}N_3O_2S]^{+\cdot}$, 191$[C_9H_7N_2SO]^{+\cdot}$, 131 $[C_8H_5NO]^{+\cdot}$, 114 $[C_3H_2N_2SO]^{+\cdot}$, 78$[C_5H_4N]^{+\cdot}$, 77$[C_6H_5]^{+\cdot}$, 28 $[CO]^{+\cdot}$

ACKNOWLEDGEMENTS

The authors are thankful to Prof. G. L. Talesara, Head, Department of Chemistry, M. L. Sukhadia University, Udaipur (Raj.) for providing laboratory facilities and are also thankful to the Director, RSIC, CDRI, Lucknow for spectral and analytical studies.

REFERENCES

1. P. Kathylan and D. Apostolos, J. Org. Chem., **62**, 4164 (1997).
2. M. J. Kukla, H. J. Breslin, C. J. Diamond and P. A. J. Jansen, J. Med. Chem., **34**, 3187 (1991).
3. J. Zamocka, E. Misikova and J. Durinda, Pharmazie, **41**, 610 (1991).
4. T. Ohira and M. Yatagi, Wood Res. Soc., **39**, 237 (1993).
5. S. J. Mohr, M. A. Chirigos, F. S. Fuhrman and J. W. Pryor, Cancer Res., **35**, 3750 (1975).
6. V. K. Tandon, M. Vaish, S. Jain, D. S. Bhakuni and R. C. Shrimal, Indian J. Pharm. Sci., **53**, 22 (1991).
7. J. T. C. Wojtyk, P. M. Kazmaier and E. Buncel, Chem. Commun., 1703 (1998).
8. Y. Abe, K. Sumioka, R. Nakao, T. Horii and T. Kitao, Chem. Express, **6(9)**, 679 (1991).
9. B. Scaudel, C. Guermeur, C. Sanchez and K. Delaire, Mater. J. Chem., **7**, 61 (1997).
10. H. U. Stilz, W. Guba, M. Just, O. Klingler, W. Konig and G. J. Zoller, J. Med. Chem., **44**, 1158 (2001).
11. K. Faghihi, K. Zamani and A. Mobinikhaledi, Turk. J. Chem., **28**, 345 (2004).
12. E. Naydenova, N. Pencheva, J. Popova, N. Stoyanov and B. Aleksiev, Farmaco, **57**, 189 (2002).
13. H. Byrtus, M. Pawloski, B. Duszynska and A. J. Bojarski, Polym. J. Pharm., **53**, 395 (2001).
14. E. G. Maestrup, S. Fischer, C. Wieser, D. Schepmann, A. Hiller, W. D. Conrad, J. Steinbach and P. Brust, J. Med. Chem., **52(19),** 6062 (2009).
15. J. Vinsova, K. Kosar and E. Kasafirek, Collect. Czech. Chem. Commun., **58**, 2987 (1993).

16. M. A. Davis, S. O. Winthrup, R. A. Thomas, F. Herr, M. P. Charset and R. Gaudry, J. Med. Chem., **7(4)**, 439 (1964).

17. A. Dandia, R. Singh, S. Khaturia, C. Merienne, G. Morgant and A. Loupy, Biorg. Med. Chem., **14**, 2409 (2006).

18. A. Dandia, K. Arya, M. Sati and S. Gautam, Tetrahedron, **60**, 5253 (2004).

19. R. M. Shaker, A. F. Mahmoud and F. F. A. Latif, J. Chinese Chem. Soc., **52**, 563 (2005).

20. G. Shanthi, G. Subbulakshmi and P. T. Perumal, Tetrahedron, **63**, 2057 (2007).

21. M. Pandey, D. Singh and K. N. Single, J. Heterocycl. Chem., **46**, 49 (2009).

22. A. Shaabani and A. Bazgir, Tetrahedron Lett., **45**, 2575 (2004).

23. G. Byk, H. E. Gottlieb, J. Herscovici and F. Mirkin, J. Comb. Chem., **2(6)**, 732 (2000).

Accepted : 23.11.2009