Facile One Pot Microwave Induced Synthesis of Spiro [Indole-pyrazoles] and Spiro [indol-isoxazoles]

Anshu Dandia*, Ruby Singh, Gajendra Kumar, Kapil Arya and Harshita Sachdeva

Department of Chemistry, University of Rajasthan, Jaipur - 302 004, India

Abstract

The potential of domestic microwave oven has been utilized in an elegant one step synthesis of a series of new fluorine containing spiro [indole-pyrazoles] and spiro [indol-isoxazoles] in 85-95% yields. Results were compared with those obtained following the classical method which involves synthesis in three steps. The advantages obtained by the use of microwave irradiation were demonstrated.

1. Introduction

Functionalized spiro indole derivatives are found to be potential bioactive agents and have been the focus of attention for chemists and pharmacologists during last two decades (1-3). 3-aroylmethylene-2H-indol-ones 4 has been proved as the synthetic building block for the synthesis of 3-spiro indolines (2), and have shown wide variety of biological activities (1,4). Since 4 are quite reactive compounds with an alkene system flanked on either side by two carbonyl groups, their reactions are extensively studied under classical conditions by many workers leading to the formation of different products depending upon the reaction conditions. The reaction of 4 with hydrazine hydrate in absolute ethanol resulted in the formation of spiro compounds (5) whereas similar reaction in glacial acetic acid furnished hydrazone (6). However, reaction of 4 with phenyl hydrazine surprisingly afforded a mixture of corresponding spiro compound, hydrazone and pyridazino-indole in absolute ethanol and glacial acetic acid media (7). Similar observations have also been observed in case of reaction of 4 with hydroxylamine hydrochloride (8).

The role of fluorine and perfluoro groups in heterocyclic chemistry is noteworthy as compared with their non-fluorinated analogues (9). Fluorinated heterocycles have the remarkable pesticidal, herdicidal and pharmacological activities. But the main constraint in their use for wide variety of bioactivity arises from cost effective factors and this can be overcome by the use of economic and ecofriendly microwave technology (10,11).

Hence, as a part of our extensive research programme for developing new fluorinated bioactive heterocycles (12) and encouraged by the vast potential of microwave technology over conventional methods (13), the rate enhancement capability of microwave oven has been utilized for the first time in the facile one pot synthesis of fluorinated spiro [indole-pyrazoles/isoxazoles] 5/8 by the reaction of 4

with hydrazine hydrate and hydroxylamine hydrochloride respectively. The former compound **4** was synthesized "insitu" by the reaction of substituted indole-2,3-dione **1** and fluorinated acetophenones **2**. It may be pointed out here that the conventional synthesis of spiro [indole-pyrazoles] and spiro isoxazole systems has been reported by three step procedure. (1,7,14).

The intermediate chalcone. **4** was synthesized earlier by the "Knoevenagel reaction" of **1** and substituted **2** in two steps (1) using diethylamine as catalyst giving first **3**., which on dehydration afforded **4**. However, when we studied the reaction of **1** and **2** under microwave irradiation in the absence of diethylamine **4** has been isolated instead of the expected product 1,3-dihydro-3-hydroxy-3-(2-phenyl-2-oxoethyl)-2H-indol-2-one **3** formed under classical condition.

2. Result and Discussion

The formation of spiro compounds has been confirmed on the basis of spectral studies. Spiro [indole-pyrazoles] showed characteristic IR absorption bands in the region 3300-3150 (NH), 3000-2900 (C–H), 1700-1680 (C=O), 1600 (C=N) cm^{-1} and ^1H NMR ($CDCl_3$) signals at δ 3.8-4.1 (dd, 2H, CH_2), a broad peak at 9.5 (s, 1H, NH pyrazole, 1H), 8.0-8.4 (NH indole) and 6.8-8.0 ppm (aromatic protons). The position of NH was confirmed on deuteration. Presence of >C=O absorption in IR and characteristic signal for -CH_2 in ^1H NMR spectrum rules out the possibility of the formation of either condensed product or a hydrazone. Further support was obtained from mass spectrum of **5d** as molecular ion peak at M/Z 295 exactly corresponded to the molecular weight of the spiro compound.

Formation of spiro [indole-isoxazoles] in the reaction of **4** with hydroxylamine hydrochloride instead of other possible products was also confirmed on the basis of spectral studies. IR bands have been observed in the region of 1730-1700 (C=O), 1660-1600 (C=N), 3000-2900 (C–H) and 3300-3150 (NH) cm^{-1}. In ^1H NMR (DMSO-d_6), signals were observed at δ 2.5-2.3 (s, 2H, CH_2), δ 6.6-7.8 (aromatic protons) and δ 8.0-8.4 (NH indole) ppm. The presence and position of NH was confirmed on deuteration. In ^{13}C NMR spectrum **8d** (X=5-Br, Y=H), sharp signals have been observed at δ 164 (C=O), 162 (C=N), 152, 146, 143, 138, 124, 118, 117.9, 117.6, 116, 115, 114 and 112 (12 aromatic ring carbons), 111.6 (spiro carbon), 28 (CH_2) ppm. In the mass spectrum of **8c** (X=5-CH_3, Y=3-CH_3, 4-F), though molecular ion peak was not observed at m/z 310 but the base peak was observed at 175 by the loss of $C_{10}H_6FNO$ moiety. Other characteristic peaks were observed at m/z 296 (10.8%), 294 (5.3%), 281 (10.8%), 267 (6.1%), 266 (25.6%), 224 (19.9%), 176 (13.0%), 159 (42.8%), 158 (16.7%), 156 (11.0%), 152 (11.2%), 147 (11.3%), 131 (67.4%), 129 (11.4%), etc. The ^{19}F NMR spectrum of **8c** shows singlet δ-119.2 ppm due to fluorine attached at the aryl ring.

3. Experimental

Melting points were determined in open glass capillary and were uncorrected. IR spectra were recorded on a Perkin Elmer (model 577) in KBr pellets. ^{1}H NMR and ^{19}F NMR were recorded on model DRX300 using DMSO d_6 + $CDCl_3$ as solvent at 300.13 and 282.37 MHz, respectively, TMS was used as internal reference for ^{1}H NMR and hexafluorobenzene as external reference for ^{19}F NMR. Mass spectra were recorded on Kratos 30 and 50 mass spectrometers. All compounds were found homogeneous on TLC in various solvent systems. The Induced Microwave Convection system has been used, where microwaves are generated at a frequency of 2450 MHz. The oven has a range of microwave output energy upto 1200 W.

1,3-Dihydro-3-[2-phenyl-2-oxoethylidene]-2H-indol-2-ones 4

In view of immence biological and synthetic importance some **4a-d** compounds have been isolated and for comparative studies synthesised by both conventional and microwave irradiation method.

I. Conventional method : Compounds have been synthesised in two steps

(i) Synthesis of fluorinated 1,3-dihydro-3-hydroxy-3-[2-phenyl-2-oxoethyl]-2H-indol-2-ones 3 : An equimolar mixture of 1 and 2 (0.01 mol) in absolute ethanol (30 ml) containing 2 drops of diethylamine as catalyst was refluxed on steam bath for 50 minutes and left at room temperature overnight, when light coloured crystals were obtained, which were filtered, dried and recrystallised from ethanol.

(ii) Synthesis of 1,3-dihydro-3-[2-phenyl-2-oxoethylidene]-2H-indol-2-ones 4 : A mixture of 3 (0.01 mole), conc. hydrochloric acid (0.5 ml) and acetic acid (20 ml) was heated on a steam bath for 30 minutes. On cooling the reaction the reaction mixture, red needles were obtained which were filtered, dried and recrystallised from ethanol, to give tittle compounds in 50-60% yield.

II. Microwave irradiation method

4a-d have been synthesised in one step in the absence of any catalyst.

An equimolar mixture of 1 and 2 (0.01 mol) in minimum quantity of absolute ethanol was irradiated inside the microwave oven at 240 watts for appropriate time till the completion of the reaction. Progress of the reaction was checked by TLC. On cooling needles separated out, which were filtered and found to be pure on TLC.

Synthesis of Spiro [indole-pyrazoles] 5

All compounds **5a-d** have been synthesised in one step without isolation of intermediate chalcone 4 under microwave irradiation.

An equimolar mixture of **1** and **2** (0.01 mole) in minimum quantity of absolute ethanol was irradiated at 240 watts. As the reactants disappeared (TLC), hydrazine hydrate (0.01 mol) was added to the reaction mixture and again irradiated for appropriate time till the completion of the reaction. On cooling crystals separated out, which were found to be pure on TLC.

Synthesis of Spiro [indol-isoxazoles] 8

An equimolar mixture of **1** and **2** (0.01 mol) in minimum quantity of absolute ethanol was irradiated at 240 watts for appropriate time. As the reactants disappeared (TLC), hydroxylamine hydrochloride (0.01mol), KOH (1 gm) and aqueous ethanol was added to the reaction mixture and again irradiated till the completion of the reaction. On cooling, crystals separated out which were filtered and found to be of sufficient purity.

For comparative studies **5a,b** and **8a,b** compounds have also been synthesised by **conventional method** from **4** as follows :-

A mixture of **4** (0.01 mol) and hydrazine hydrate/hydroxylamine hydrochloride (0.01 mol) in absolute ethanol (50 ml)/KOH (1 gm) in ethanol (60 ml) respectively was refluxed for 5/4 hrs. The resulting precipitate obtained on concentration and cooling was filtered and showed a formation of mixture of products along with 5/8 on TLC. The solid obtained was recrystallised from suitable solvent to give major yield (45-55%) of 5/8 respectively.

The identity of the product synthesised by both methods i.e. (a) one pot synthesis under microwave irradiation (b) three step conventional synthesis has been checked by mixed m.p's, IR and ^{1}H NMR spectral studies.

All the compounds **5** and **8** have been synthesised in one step without isolation of intermediate chalcone **4** under microwave irradiation because 100% conversion was observed on TLC and a crystalline product was separated which does not require further purification and recrystallisation.

Acknowledgement

Financial assistance from U.G.C., New Delhi is gratefully acknowledged and we are also thankful to Central Drug Research Institute, Lucknow for providing spectral data.

References

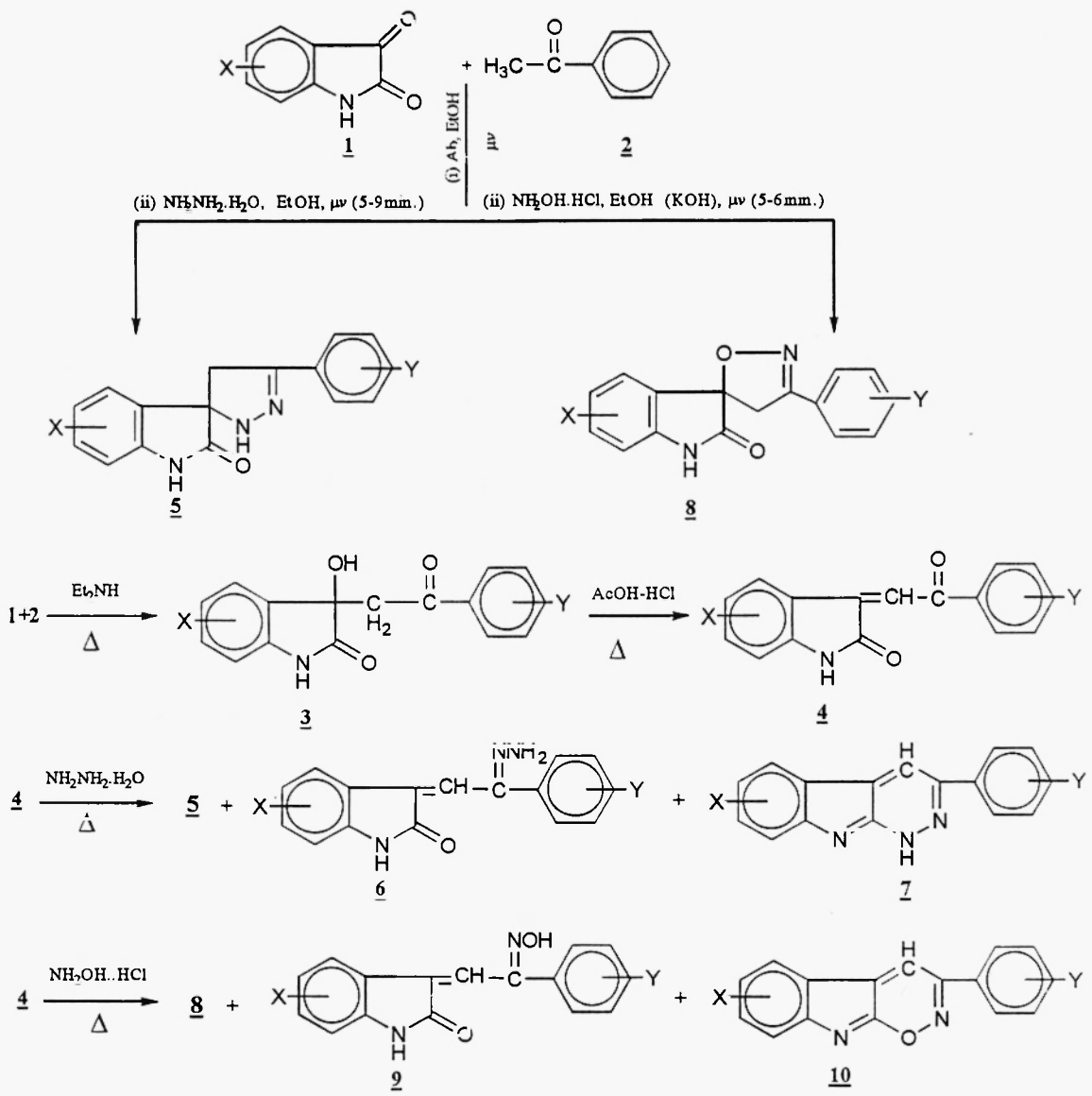
(1) K.C. Joshi, R. Jain and P. Chand, *Heterocycles*, **23**, 957 (1985).

(2) K.C. Joshi, R. Joshi, *J. Indian Chem Soc.*, 76 (11-12) 515-766 (1999).

(3) M. Martin, G. Nadler, R. Gimmermann, *Eur. Pat.*, (1989) 303418; *Chem. Abstr.*, **111**, 97293u (1989).

(4) S.M. Kupchan, M.A. Eakinonal and A.M. Thomson, *J. Med. Chem.*, **14**, 1147 (1971).

(5) H. Otomasu, T. Tanaka and A. Aoyagi, *Chem. Pharm.Bull.*, **24(4)**, 782 (1976).



3a ;	7-NO,	X H	Y	5a ;	7-NO, X 3-Cl, 4-F Y
3b;	7-NO$_2$	4-F		5b;	5-CH, 3-CH$_3$, 4-F
3c;	7-NO$_2$	3-Cl, 4-F		5c;	7-NO$_2$ H
3d;	5-CH$_3$	3-CH$_3$, 4-F		5d;	5-CH$_3$ H
4a ;	7-NO$_2$	H		8a ;	7-NO$_2$ 4-F
4b;	7-NO$_2$	4-F		8b;	7-NO$_2$ 3-CH$_3$, 4-F
4c;	7-NO$_2$	3-Cl, 4-F		8c;	5-CH, 3-CH$_3$, 4-F
4d;	5-CH,	3-CH$_3$, 4-F		8d;	5-Br H

Scheme

(6) G. Kobayashi and S. Furukawa, *Chem. Pharm. Bull.*, **12(10)**, 1129 (1964).

(7) K.C. Joshi, A. Dandia and S. Bhagat, *Ind. J. Chem.*, **31B**, 98-104 (1992).

(8) K.C. Joshi, R. Jan, K. Sharma and S.C. Jain, *J. Ind. Chem. Soc.*, **65(9)**, 640-2 (1988).

(9) R. Filler, *Chem. Tech.*, **4**, 752 (1974).

(10) A.K. Bose, B.K. Banik, N. Lavlinskaia, M. Jayaraman and M.S. Manhas, *Chem. Tech.*, 18-23 (1997).

(11) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathe, Synthesis, 1213-1234 (1998).

(12) (a) A. Dandia, M. Upreti, B. Rani and U.C. Pant, J. Chem. Res (M), 3348-3335 (1998); J.C.R. (s) 752-753 (1998). (b) A. Dandia, M. Saha and H. Taneja, *J. Fluorine Chem.*, **90**, 17-21 (1998).

(13) (a) A. Dandia, H. Sachdeva and R. Singh, *J. Chem. Res.* (S), 272-275 (2000). (b) A. Dandia, H. Sachdeva and R. Singh, *Synth. Commun.*, **29 (13)**, 1879-1892 (2001).

(14) G.I. Zhungictu, G.A. Dragalina and G.N. Dorofeenko, Khim. Getereotsikl. Soedin., **40**, 1973, *Chem. Abstr.*, 78, 111201w (1973).

Table 1 : Physical and analytical data of **3** and **4**

Compound no.	Time (min)	Yield (%)	m.p. (°C)	Molecular Formula
3_a	50	70	140	$C_{16}H_{12}N_2O_5$
3_b	50	69	137	$C_{16}H_{11}N_2O_5F$
3_c	60	76	135	$C_{16}H_{10}N_2O_5ClF$
3_d	55	74	200	$C_{18}H_{16}NO_3F$
4_a	5	63[#]	174	$C_{16}H_{10}N_2O_4$
4_b	8	64[#]	187	$C_{16}H_9FN_2O_4$
4_c	9	70[#]	138	$C_{16}H_8ClFN_2O_4$
4_d	6	73[#]	135	$C_{16}H_{14}FNO_2$

Compounds **3a-d** synthesized bv coventional method and **4a-d** bv microwave method.

Table 2 : Physical and analytical data of 5 and 8

Compound no.	Time* (min)	Yield[#] (%)	m.p. (°C)	Molecular Formula
5_a	9+5	74.4	138	$C_{16}H_{10}ClFN_4O_3$
5_b	6+4	84.5	215	$C_{18}H_{16}FN_3O$
5_c	5+7	65	142	$C_{16}H_{12}N_4O_3$
5_d	6+2	78	265	$C_{17}H_{14}FNO_3$
8_a	8+6	88	90	$C_{16}H_{10}FN_3O_4$
8_b	7+3	65	110	$C_{17}H_{12}FN_3O_4$
8_c	6+3	73	260	$C_{18}H_{15}FN_2O_2$
8_d	5+3	75	278	$C_{16}H_{11}BrN_2O_2$

*Time correspond to one pot synthesis of **5** and **8** without isolation of intermediate **4** #Isolated yield in single step. All Compounds given in table 1 and 2 gave satisfactory elemental analyses.

Received on October 15, 2001