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Microwave-Assisted Solvent Free Synthesis of Spiro-Indole Derivative

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Abstract

A solid supported synthetic procedure has been developed for the synthesis of novel spiro indole derivatives using solid support as energy transfer medium under microwave irradiation (MWI). The results were compared with those obtained by the classical as well as solution phase method in MWI. This solvent-free technique coupled with the high yields and short reaction time makes this procedure eco-friendly for synthesis.

Keywords: *Spiro indoles, microwave irradiation, ^{1}H NMR, IR*

Introduction

The research on spiro indoles is of current interest due to their diverse biological activities.[1] If the indole ring is joined to other heterocyclic systems through a spiro carbon atom, the resulting compounds show a wider range of pharmacological activities.[2-4] Microwave heating has been used for the rapid synthesis of variety of compounds[5,6] wherein chemical reactions are accelerated because of selective absorption of microwave energy by polar molecules, non-polar molecules being inert to the microwave irradiations. The coupling of microwave irradiation (MWI) with the use of catalysts of mineral supported reagents, under solvent-free conditions, provide unique chemical processes with special advantages such as enhanced reaction rates, higher yields, greater selectivity and the ease of manipulation.[7] In addition, the limitations of the microwave-assisted reactions in solvents, like the development of high pressures and the need for specialized vessels, are circumvented via this solid state technique which enables organic reactions to occur rapidly at atmospheric pressure.[8]

In view of the above mentioned limitations of the reported methods[9,10] and growing interest in the development of environmentally benign protocols[11-13], it has been described a microwave-accelerated solid state approach for the rapid synthesis of spiro [indole-pyrazole/isoxazole/pyrimidine]-2(1H) – ones in this study.

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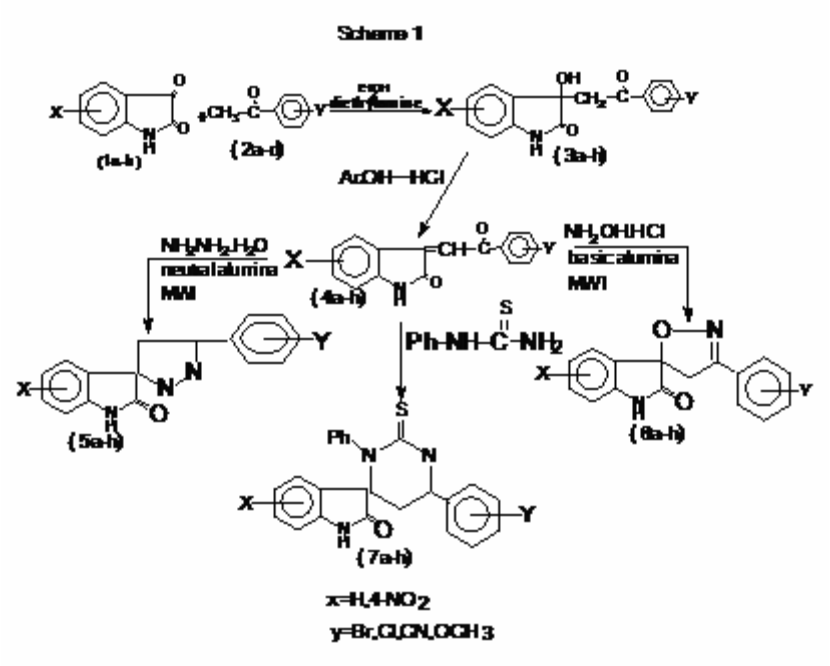
Experimental Methods

3-Hydroxy-3-phenacyl-indol-2-ones (3a-h) and 3-aroyl methylene-indole-2-ones (4a-h) were synthesized by literature method as described elsewhere (Scheme 1).[14] The spiro[indole-pyrazoles] (5a-h), spiro[indole-isoxazoles] (6a-h) and spiro[indole-pyrimidines] (7a-h) were synthesized through conventional, microwave solution phase and microwave solid phase reactions for comparative synthetic studies.



Conventional Solution Phase Reactions (Method A): Hydrazine hydrate/hydroxylamine hydrochloride/phenylthiourea (0.01 mol) was added to 3-aroyl-methylene-indol-2-ones (4a-h) (0.01 mol) in absolute ethanol (20 mL) and the mixture was refluxed under constant stirring for 4-6 h. The progress of the reaction was monitored on TLC. The reaction mixture was cooled and the product separated was filtered, dried and recrystallized from ethanol.

Microwave Solution Phase Reactions (Method B): A mixture of 3-aroylmethylene-indol-2-one (4a-h) (0.01 mol) and hydrazine hydrate/hydroxylamine hydrochloride/phenylthiourea (0.01 mol) in absolute ethanol (5-10 mL) taken in an Erlenmeyer flask and the contents were subjected to microwave irradiation for an appropriate time and worked-up as described in Method A.

Microwave Solid Phase Reactions (Method C): Neutral and basic alumina as mentioned in the scheme 1, (18 g) was added to the solution of 1,3-dihydro-3-[2-(sub/nsub)phenyl)-2-oxoethylidene]-2H -indol-2-one (4a-h) and hydrazine hydrate/hydroxylamine hydrochloride/phenylthiourea in ethanol. The reaction mixture was dried, placed in alumina bath[15] inside the microwave oven at 560 W for 40-60 seconds. Progress of the reaction was monitored through TLC at the interval of 10 s. On completion of the reaction, the mixture

was cooled at room temperature, the product was extracted using ethanol (4 x 5 mL) and the solvent was removed under reduced pressure which yields the corresponding title compounds 5-7(a-h).

Results and Discussion

The 3-aroylmethylene-indole-2-ones (4a-h) were synthesized from their corresponding isatin and acetophenone derivatives according to literature method.[14] The condensation of 3-aroylmethylene-indole-2-one (4a-h) with hydrazine hydrate was carried out using neutral alumina as energy transfer medium under MWI which afforded spiro [indole-pyrazoles] (5a-h) in 90-97% yield. The formation of compounds was confirmed on the basis of IR and ^{1}H NMR spectral data. IR bands have been observed in the region of 3350-3150 (NH), 1700-1680 (C=0) and 1600 cm^{-1} (C=N). In ^{1}H NMR spectra signals were observed at δ 3.8-4.1 (s, 2H, -CH_2), 6.9-7.6 (m, Ar-H), 8.9 (brs, 1H, -NH of indole) and 10.1 (brs, 1H, -NH pyrazole). Spiro [3H-indole-3, 5'- isoxazole]-2(1H)-ones (6a-h) were synthesized by the reaction of (4a-h) and hydroxylamine hydrochloride. IR bands observed in the region 1730-1700 (C=0) and 1660-1600 cm^{-1} (C=N) and signals in ^{1}H NMR spectra at δ 2.3 (s, 2H, -CH_2) and 6.6-8.6 (m. Ar-H) confirmed the formation of compounds (6a-h).

Similarly using basic alumina the condensation of phenylthiourea and (4a-h) yielded corresponding spiro [indole-pyrimidine] derivatives (7a-h) under MWI, which were characterized by the appearance of IR bands at 3230-3100 (-NH), 1715 (NHCO), 1660 (C=N) and 1240 cm^{-1} (C=S). ^{1}H NMR of compounds (7a-h) showed peaks at δ 6.40(d, 2H, -CH_2), 6.20-7.65 (m, 12H, Ar-H) and 9.35 (brs, 1H, -NH), appearance of C=0 absorption ruled out the formation of condensed system.

Conclusions

All the compounds have been synthesized by classical methods in 3-6 h, synthesis under MWI involves 3-6 min in solution phase while using solid support reaction was completed within 40-60 s with improved yield from 60-70 to 90-96% (Table 1). So that this method was developed an easy and convenient synthetic procedure for preparation of Spiro compounds by coupling microwaves under solvent free conditions keeping modernization and simplification of classical procedure, to avoid volatile or toxic solvents and external use of bases.

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Table1: Physical data of compounds (5-7).

Compd. No.	M. P. (^{o}C)	Yield (%)			Reaction Period (h/min/s)		
		Method A	Method B	Method C	Method A (h)	Method B (min)	Method C (s)
5a	249-250	68	78	92	4	3	40
5b	239-240	58	74	90	4	3	50
5c	235-236	47	65	92	6	5	50
5d	232-233	48	72	93	4	6	60
5e	225-226	52	66	91	5	6	50
5f	229-230	56	72	94	4	3	40
5g	222-223	59	78	96	6	4	50
5h	260-261	62	79	92	5	3	60
6a	255-256	60	75	92	6	5	40
6b	248-249	62	73	90	6	6	40
6c	242-243	53	73	92	5	6	60
6d	240-241	54	72	91	4	6	50
6e	223-224	48	69	90	4	3	50
6f	255-256	57	72	92	7	5	50
6g	228-229	59	75	94	6	6	60
6h	230-231	62	79	95	5	4	40
7a	315-316	52	75	92	6	4	60
7b	292-293	54	74	95	5	5	50
7c	285-286	62	77	95	6	5	50
7d	307-308	55	75	93	6	6	50
7e	310-311	67	79	94	5	4	40
7f	296-297	59	72	92	5	4	50
7g	294-295	54	68	90	5	5	40
7h	303-304	57	72	90	5	4	40

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