FACILE MICROWAVE-ASSISTED ONE-POT SOLID PHASE SYNTHESIS OF SPIRO[3H-INDOLE-3,4′-PYRAZOLO[3,4-b] PYRIDINES]

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Abstract: A rapid, enviro-economic protocol for the novel one-pot synthesis of a series spiro [3H-indole-3,4′-pyrazolo[3,4-b]pyridines (**7a-f**) under microwave irradiation is described. The intermediates spiro pyrazolopyran (**5**) and dicyanomethylene indole-2-one (**3**) were synthesized in situ' in quantitative yields with reasonable purity. The results obtained demonstrate the versatility of the process.

1.Introduction

The spiro indole derivatives have attracted much concern during last few decades due to their exceptional biological properties (1) and their presence in number of biologically active alkaloids (2). The spiro indole derivatives incorporating either pyran, pyridine, pyrazole or pyrazolo-pyran moieties have been synthesized in view of wide variety of medicinal applications (3). Condensed pyrazoles are also known to possess various biological activities and pyrazolo[3,4-b]pyridines are used as potential antimicrobial (4), anti-inflammatory (5), multidrug resistant for tumor cells (6), cardiovascular (7) etc. But, little attention has been paid on the synthesis of spiro indolines incorporating pyrazolo pyridine moieties, which may lead to the production of compound with altered/enhanced bioactivity. The use of solid supports together with an efficient coupling with microwave activation has received much attention in the recent years(8) because of their enhanced selectivity, milder reaction conditions and lower cost than those associated with conventional homogenous reaction procedures.

The spiro pyrazolo-pyran system (**5**) has been synthesized in two steps (9), the first involving the synthesis of 1,3-dihydro-3-dicyano-methylene-2H-indol-2-one (**3**) in 60-68% yield by refluxing **1** and **2** in ethanol using basic catalyst for 4hrs,followed by the Michael condensation of **3** with **4** in presence of base in ethanol to give **5** (yield 60-72%, time 3-4 hrs); there is only one reference to the synthesis of spiro[indole-pyrazolo-pyridines](**7**), which involves three steps conventional synthesis by another route (10).

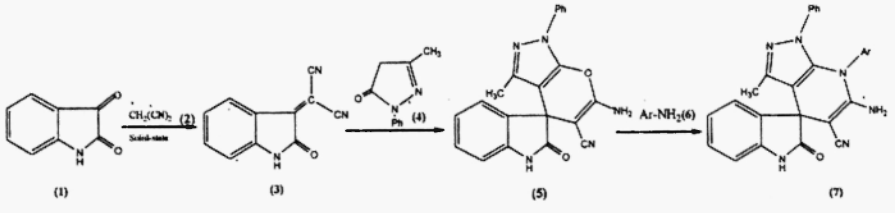
The synthesis of **3** also seems to be an important contribution towards green chemistry as it serves as an important synthon for synthesis of various heterocyclic systems, such as pyrans, pyridines, isoquinolines (11), etc. We now report an improved synthesis of alkene-nitrile derivatives (**3**) by solid-state reaction of **1** and **2** in absence of solvent or catalyst. It was obtained in quantitative yield ~100% with reasonable purity (TLC) for the first time and used for the further conversion to **5** by reaction with **4** under MWI coupled with different solid supports including silica gel, aluminas (acidic or neutral), strongly acidic montmorillonite K10 and KSF (Table 1). Further, in view of varying biological activities associated with spiro pyrazolo-pyridines, we have also developed a one-pot dry-media synthesis of spiro[3H-indole-3,4′-

pyrazolo[3,4-b]pyridines] (7) by the reaction of 5 with heterocyclic amines (6) under microwave irradiation.

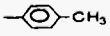
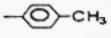
However, in some cases 3 and 5 were isolated and characterized for comparative studies.100% conversion of 1 and 2 to 3 and 3 to 5 was observed on TLC, which also showed the formation of single product.

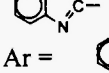
Synthesis of 7 from spiro system 5 was carried out using different types of solid supports e.g. montmorillonite K10, KSF, neutral and acidic alumina under microwave irradiation (Table 2). Reaction did not occur in neutral alumina, while lower yields were obtained on using acidic alumina or montmorillonite KSF. Further, the use of few drops of DMF together with these solid supports showed better conversion of 5 into 7 in shorter time, with improved yield and best results were obtained, when neutral alumina with few drops of DMF was used. Preliminary studies allowed us to optimize the substrate support relative amount, reaction times and to establish the convenience to use few drops of DMF as an energy transfer medium in order to permit higher temperature (12) (Table-2) In order to show the advantages in the use of neutral alumina/DMF and of microwave heating mode, Table-3 shows comparative results for the synthesis of 5a and 7a by conventional and non-conventional methods. Experiments were also carried out under classical heating in the same conditions as under microwaves indicating the existence of non-thermal microwave effect (13).

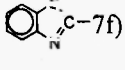
The structure of new synthesized compounds **3a-c** and **5a-c** were confirmed on the basis of spectral studies (Table5). The formation of novel system spiro[indole-pyrazolopyridine] (**7a-f**) from spiro[pyrazolo pyran] system (**5**) was indicated by the disappearance of peak due to pyran ether linkage at 1180-1170 cm^{-1} in IR spectra.



3 and 5a) X=Cl, b) X= 5,7-di CH_3,c) X=5-NO_2,d) X=H

7a) X=5-Cl , Ar =  7b) X=5-Cl, Ar=  7c) X=5-Cl, Ar =  7d) 

X–H,Ar= 

7e) X=H, Ar =  7f) X=H,Ar=

Experimental

Mps were determined in open glass capillaries and are uncorrected. Infrared spectra were recorded a Perkin-Elmer (Model-577) in KBr pellets. ^{1}H NMR and ^{13}C NMR were obtained on Jeol (Model FX 90Q) at 89.95 and 22.49 MHz, respectively using $CDCl_3$ as solvent and TMS as internal reference. Indole-2,3-diones (14) and 2-amino benzothiazole(15) were prepared according to literature procedure. Solid support were Aldrich products and used as received.

The induced microwave convection system used has microwaves generated at a frequency of 2450 MHz. The oven has a range of microwave output energy of 700 watts.

Solid-state synthesis of 1,3-dihydro-3-dicyanomethylene-2H-indol-2-ones (3) : An equimolar mixture (1 mmol) of **1** and **2** was ground thoroughly in an agate mortar for 1-2min (TLC). Alternatively **3** was also prepared by irradiation of neat mixture of **1** and **2** for 30 sec. at 640 W. The intermediates **3a-d** so obtained in reasonable purity were used as such for the next step without further purification.

Spiro[3H-indole-3,4(1H)pyrano[2,3-c]pyrazole] (5a) : A mixture of **3a** and **4** in equimolar ratio (1mmol) was adsorbed on neutral alumina (3g) with the help of methanol (3ml) and dried, irradiated inside the microwave oven at 640 W till completion of reaction (TLC). The mixture eluted with methanol gave the crystalline pure product.

The remaining compounds (**5b-d**) were synthesised in similar manner.

Spiro[3H-indole-3,4′-pyrazolo[3,4-b]pyridine] (7a) : It was synthesized by two different methods (1) Classical heating (2) Microwave assisted synthesis.

(1) Classical heating: An equimolar mixture (1 mmol) of **5a** and **6a** in glacial acetic acid (20 ml) was refluxed for 2hrs. As the reactants disappeared (TLC), the reaction mixture was poured into crushed ice. The separated solid was filtered and recrystallized from ethanol.

(2) Microwave assisted synthesis : An equimolar mixture(1 mmol) of **3a** and **4** was adsorbed on neutral alumina (3g) and irradiated at 640 W till the completion of the reaction (3min.). To this, a mixture 4-methyl aniline **6a** (1mmol) and 0.5ml DMF was added and irradiated further, the product was eluted with methanol and excess of solvent was evaporated to give a solid which was found to be pure by TLC.

7b-c was also prepared by following the same procedure under microwave irradiation.

The identity of the compounds synthesised by various methods was established by their mixed melting points and spectral studies (Table 4,5).

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Table 1. Effect of solid support in dry media for the synthesis of **5a** under microwave irradiation

Support	Temp* (°C)	Reaction Time (min.)	Isolated Yield (%)
Neutral alumina	128-126	3	94
Acidic alumina	126-124	4	84
Montmorillonite KSF	115-113	4	68
MontmorilloniteK10	120-118	4	65
Silica gel	120-117	3	64

Table 2. Synthesis of **7a** under classical heating (A) and microwave irradiation (B)

Heating Mode	Support/Solvent	Temp* (°C)	Time (min.)	Isolated Yield (%)
B	Neutral alumina	115-113	15	Nil
B	Neutral alumina +DMF	140-138	5	90
B	Acidic alumina	112-110	8	25
B	Acidic alumina +DMF	135-132	6	76
B	Montmorillonite KSF	112-109	10	30
B	Montmorillonite KSF+DMF	128-126	6	72
A	Glacial AcOH	reflux	120	50

Table 3. Comparative results obtained for the synthesis of compounds **3a**, **5a** and **7a** using conventional method (Δ), solid state reaction (S.S.) and microwave activation (MW).

Cmpd	Method	Solvent/Support	Reaction Time (min.)	Temp.* (°C)	Yield (%)
3a	Δ	EtOH + Piperidine	180	reflux	60
3a	S.S.	Solid-State	1	r.t.	≥98
5a	Δ	EtOH + Piperidine	180	76-74	70
5a	MW	Neutral alumina	3	128-126	≥94
5a	Δ	Neutral alumina	3	128-126	≤10[a]
5a	Δ	Neutral alumina	20	128-126	50[b]
7a	Δ	Glacial AcOH	120	108-110	60
7a	MW	Neutral alumina + DMF	5	140-138	≥90
7a	Δ	Neutral alumina +DMF	5	140-138	≤15[a]
7a	Δ	Neutral alumina +DMF	25	140-137	60[b]

a) Complements to 100% are starting materials

b) Conversions are >90% Complements is constituted of decomposition and uncyclised products.

* Final temperature was measured by immersion of a glass thermometer at the end of exposure to microwave irradiation (approximate temperature range)

Table 4. Physical and Analytical data of synthesized compounds

Cmpd	Yield* (%)	Time (min.)	m.p.(°C)	Lit. mp (°C)	Molecular formula	N analysis (%) Found (Calcd)
3a[x]	99	1	225-227	-	$C_{10}H_4N_3OCl$	18.30 (18.25)
3b[x]	99	1	196-198	-	$C_{12}H_9N_3O$	23.33 (23.40)
3c[x]	96	2	205-207	-	$C_{10}H_4N_4O_3$	18.83 (18.78)
3d[x]	99	1	192-195	191-193[16]	$C_{10}H_5N_3O$	21.53 (21.59)
5a[y]	94	4	230-232	-	$C_{21}H_{14}N_5O_2Cl$	17.63 (17.68)
5b[y]	89	3	218-221	-	$C_{23}H_{19}N_5O_2$	17.34 (17.30)
5c[y]	90	4	226-228	-	$C_{21}H_{14}N_6O_4$	20.28 (20.33)
5d[y]	90	3	273-275	272-275[9]	$C_{21}H_{15}N_5O_2$	18.97 (18.92)
7a[y]	90	4 + 5	215-218	-	$C_{28}H_{22}N_6O$	17.05 (17.09)
7b[y]	86	3 + 7	230-232	-	$C_{28}H_{19}N_7OS$	18.30 (18.35)
7c[y]	88	3 + 5	216-218	-	$C_{27}H_{21}N_7O$	19.85 (19.79)
7d[y]	90	3 + 5	168-170	-	$C_{28}H_{21}N_6OCl$	18.34 (18.39)
7e[y]	87	3 + 6	228-231	-	$C_{28}H_{18}N_7OSCl$	19.56 (19.52)
7f[y]	88	4 + 5	260-264	-	$C_{27}H_{20}N_7OCl$	21.35 (21.31)

[x] = compounds Synthesized by solid-state reaction, *Isolated yield

[y] = compounds Synthesized by microwave irradiation

b : All compounds gave satisfactory elemental analyses (C and H) within 0.25 ± % of theoretical value.

Compounds 5a-d and 7a-f was synthesized in one- pot, e.g. 7a 4+5 indicates, first irradiation for 4 min gives compound 5a (detected by TLC) and then further irradiation after adding p-toluidine for 5 min yield 7a.

Table 5. ^{1}H NMR and ^{13}C NMR Spectra of compounds 3a-c, 5a-c and 7a-f

Cmpd	^{1}H NMR (δ) ppm
3a	7.50-8.10 (m, 3H, Ar-H), 9.68 (br, 1H, indole NH)
3b	2.18-2.29 (bs, 6H, 2×CH_3), 7.75-8.01 (m, 2H, Ar-H), 9.59 (br, 1H, indole NH)
3c	7.15-8.02 (m, 3H, Ar-H), 10.02 (br, 1H, indole NH)
5a	2.02 (s, 1H, CH_3), 7.50-8.40 (m, 8H, Ar-H), 8.85 (br, 2H, NH_2), 10.92 (br, 1H, indole NH)
5b	2.02 (s, 1H, CH_3), 2.17-2.23 (br, 6H, 2×CH_3), 7.25-8.50 (m, 7H, Ar-H), 8.82 (br, 2H, NH_2), 11.02 (br, 1H, indole NH)
5c	2.05 (s, 1H, CH_3), 7.15-8.42 (m, 8H, Ar-H), 8.80 (br, 2H, NH_2), 11.08 (br, 1H, indole NH)
7a	1.96 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 6.92-7.48 (m, 12H, Ar-H), 8.80 (br, 2H, NH_2), 11.09 (br,1H,
7b	indole NH)
7c	1.99 (s, 3H, CH_3), 6.92-7.80 (m, 12H, Ar-H), 8.85 (br, 2H, NH_2), 11.04 (br, 1H, indole NH)
7d	2.01 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 6.90-7.50 (m, 11H, Ar-H), 8.82 (br, 2H, NH_2), 11.09 (br, 1H, indole NH)
7e	1.95 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 6.95-7.90 (m, 13H, Ar-H), 8.84 (br, 2H, NH_2), 11.12 (br, 1H, indole NH)
7f	1.98 (s, 1H, CH_3), 6.92-7.80 (m, 13H, Ar-H), 8.84 (br, 2H, NH_2), 11.13 (br, 1H, indole NH)
	1.96 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.92-7.48 (m, 12H, Ar-H), 8.85 (br, 2H, NH_2), 11.14 (br, 1H, indole NH)

^{13}C NMR (δ) ppm ; 5a : 8.2 (CH_3), 59.2 (C–C≡N), 71.4 (spiro carbon), 117.2 (C≡N), 118.2, 119.4, 122.3, 126.0, 128.0, 128.8, 129.1, 129.9, 130.4, 132.2, 139.7, 140.2, 151.0 (aromatic ring carbons), 169.2, 175.1 (C=O and C–NH_2)

7a : 8.4, 20.9 (two CH_3), 57.6 (C–C≡N), 71.1 (spiro carbon), 117.2 (C≡N), 115.0, 118.4, 119.1, 122.3, 126.0, 127.7, 128.1, 129.1, 129.9, 130.4, 131.8, 132.6, 139.4, 140.2, 143.7, 149.6, 150.1 (aromatic ring carbons), 168.2, 173.8 (C=O and C–NH_2)

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