

Facile one-pot synthesis of new annulated hexacyclic ring system indeno-pyrano-furo-indoles and spiro indenopyran-indoles under microwave irradiation

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Received 16 January 2008; accepted (revised) 3 March 2009

An efficient and clean procedure for the synthesis of a new hexacyclic system indeno-pyrano-furo-indoles **8** and spiroindoles incorporating pentacyclic ring system spiro[indenopyran-indoles] **6** using inorganic solid support under microwave irradiation is described.

Keywords: Spiro indole, microwaves, Knoevenagel condensation, neutral alumina

Indoles are common in nature forming the core unit of a number of bioactive substances^{1,2}. Some functionalized spiro indole derivatives were found to be potential bioactive agents³ and have been the focus of attention for chemists and pharmacologists during last two decades. The diverse biological activities reported for pyran⁴ and spiro[indolo-pyrans] as muscle relaxant and anti-inflammatory agents are well known^{5,6}. A large number of indene derivatives have been utilized as therapeutic agents⁷ and possess antibacterial activities⁸.

Earlier the reaction of 3-dicyanomethylene-2*H*-indol-2-ones **3a** with 1*H*-indene-1,3(2*H*)-dione **6** has been studied in conventional manner using ethanol as solvent and piperidine as basic catalyst in 4-6 (ref. 9). Reactions in solution phase can often be toxic and polluting, hence unacceptable in these environmentally conscious days.

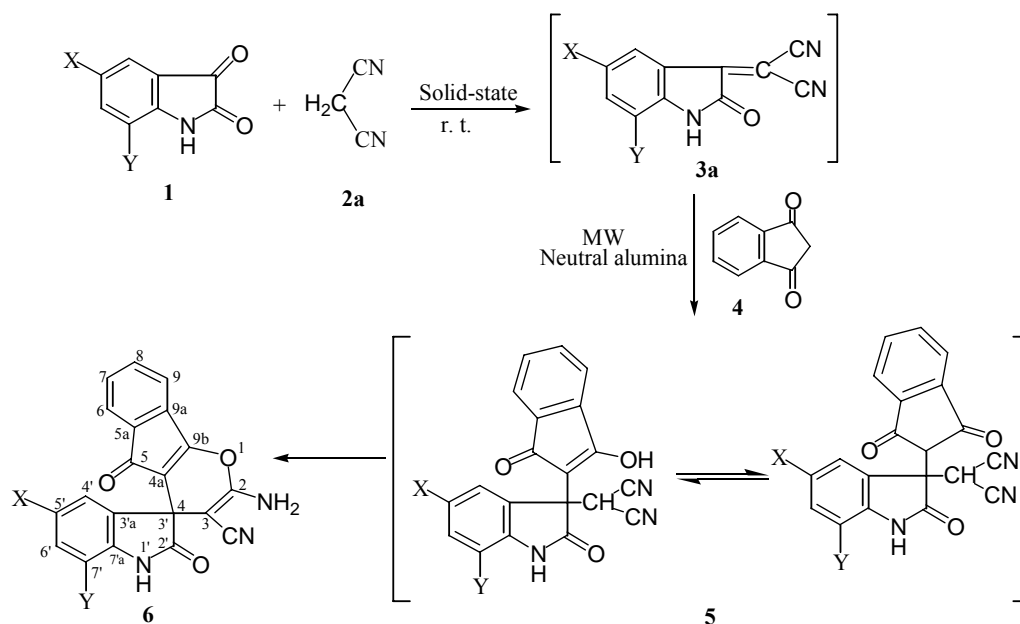
The exploitation of microwaves for assisting different organic reactions¹⁰ has blossomed into an important tool in synthetic organic chemistry with large horizon of applications. Especially interesting was the coupling with dry media conditions¹¹ which allowed reaction on a preparative scale under atmospheric pressure, avoiding the risk of high pressure and explosions, result which may from reactions carried out in closed vessels such conditions are milder, easier to work-up and give higher selectivity than similar reactions using organic reagents in solvents.

Furthermore, the role of substituents at the indole ring¹² and at the olefinic carbon of indolylidene

derivatives has been observed earlier and it has been found that substituents changed the reaction results¹³.

Hence, in continuation of the earlier interest on synthesis of biodynamic heterocycles under microwave irradiation¹⁴ and to check the role of substituents at olefinic carbon of **3a/b**, the reaction of **3a/b** with 1*H*-indene-1,3(2*H*)-diones **4** has been investigated to explore the possibility of the formation of a novel system under microwave irradiation using neutral alumina as inorganic solid support which also acts as a basic catalyst.

3-Dicyano/Carboethoxycyanomethylene-2*H*-indol-2-ones **3a/b** have previously been synthesized in a conventional manner by the Knoevenagel condensation of **1** and **2a/b** in refluxing ethanol in the presence of few drops of piperidine¹⁵. This synthesis has been improved by the solid-state reaction of **1** with malononitrile **2a** at RT¹⁶. While the solid-state reaction of **1** with ethylcyanoacetate **2b** failed to occur at RT, it was carried out under microwave irradiation by irradiating the neat reaction mixture at 640 W for 30-60 sec. Intermediates **3a/b** were used as such for the next conversion. The new improved synthesis of **3a/b** neither require basic catalyst nor solvent and the products were obtained with reasonable purity (TLC) and in quantitative yield. Knoevenagel condensation of acyclic aldehyde and ketones with active methylene compounds either in solid-state or using various supported reagent under microwave irradiation have been extensively studied by various workers^{17,19}. However, there is no report on



Scheme I

Knoevenagel condensation of heterocyclic ketones in absence of any base and solvent.

The Michael reaction of **3a** having an electron attracting group on the exomethylene carbon is interesting as it can afford either adduct **5** which can exist as such, or a spiro pyran system of oxindole. The Michael reaction of **4** with **3a** with leads to the formation of spiro system spiro[indenopyran-indoles] (Scheme I).

But the reaction of **3b** leads to the exclusive synthesis of hexacyclic ring system novel 2-imino-3,10-dioxindeno[3'',2'';5',6']pyrano[4',3';3,4]furo[2,3-b]indoles **8** (Table I). The formation of **8** was assumed to involve the cycloaddition of indole -OH on the ester group of spiro compound (Scheme II). These observations are in agreement with the earlier work on reaction of **3b** with 1-phenyl-2-thiohydantion¹⁸ and also report of Latif *et al.* on reaction of **3b** with and 3-methyl-1-phenyl-2-pyrazolin-5-one²⁰.

Finally, to check the possible intervention of specific (non-thermal) microwave effects, the reactions (in case of **6a** and **8a**) were carried out using a pre-heated oil-bath at the same time and same final temperature (126-29°C) as measured at the end of exposure during microwave experiments (Table II). It has been found that only traces of the product were obtained under thermal conditions, demonstrating that the effect of microwave irradiation is not purely thermal as yet evidenced in several cases^{21,23}.

In conclusion, the synthesis of novel hexacyclic ring system and pentacyclic ring system in open

vessels involving the Michael and Knoevenagel condensations under microwave irradiation is a rapid, economic, manipulating simple, selective and environmentally benign protocol and proceeds under mild neutral conditions.

The structure of spiro compound **6** and novel condensed system **8** has been confirmed on the basis of spectral studies. IR spectra of **6a, b** showed characteristic absorption bands at 3400-3180 (NH₂ and NH) 2200-2195 (C≡N), 1720-1680 cm⁻¹ (two C=O). In the mass spectrum of **6b** the molecular ion peak obtained at 369 (100%) showed the formation of spiro compound. IR spectra of novel system **8a-c** showed characteristic absorption bands at 3350-3360 (NH), 1740-1700 (two C=O)²⁰ and 1610 cm⁻¹(C=N). In the ¹H NMR of **8a-c** signals were obtained at 5.04-5.07 (s, CH), 6.78-7.70 (m, Ar-H) and 9.04-9.08 (bs, NH, exchangeable with D₂O). ¹³C NMR spectrum of **8a** showed signals at 196.0 (C=O), 175.1 (C=O), 161.1 (C=N), 159.8 (C=N), 158.1(14b-C), 142.0 (5a-C), 137.2 (14a-C), 135.1 (10a-C), 134.8-121.0 (other aromatic carbons), 104.2 (9c-C), 52.5 (methine carbon, CH), 38.3 (9b-C). An inspection of IR, ¹H and ¹³C NMR provides no evidence for the formation of spiro compound as ester absorption band in IR and signals due to ethyl moiety were absent in ¹H and ¹³C NMR. Formation of condensed product has been further confirmed on the basis of mass spectrum of **8a**. The molecular ion peak was observed at m/z 342 (15%) corresponding to molecular weight of condensed system **8a**, not of expected spiro system **7**

Table I — Physical and analytical data of **6a,b** and **8a-c**

Compd	X	Y	Time* (min)	Yield [#] (%)	m.p. (°C)	Mol. Formula	Found (Calcd) (%)	
							C	N
6a	H	H	5	93	245 (Ref 9)	C ₂₀ H ₁₁ N ₃ O ₃	70.22 (70.38)	12.28 (12.31)
6b	CH ₃	CH ₃	4	90	240	C ₂₂ H ₁₅ N ₃ O ₃	71.40 (71.54)	11.36 (11.38)
8a	H	H	5	92	210	C ₂₀ H ₁₀ N ₂ O ₄	70.01 (70.08)	8.21 (8.18)
8b	Br	H	6	88	220	C ₂₀ H ₉ BrN ₂ O ₄	56.91 (57.03)	6.62 (6.65)
8c	F	H	5	90	238	C ₂₀ H ₉ FN ₂ O ₄	66.54 (66.67)	7.75 (7.78)

*Indicates the time for synthesis of final products from **3a/b** under microwave irradiation using neutral alumina.

[#] Isolated yield

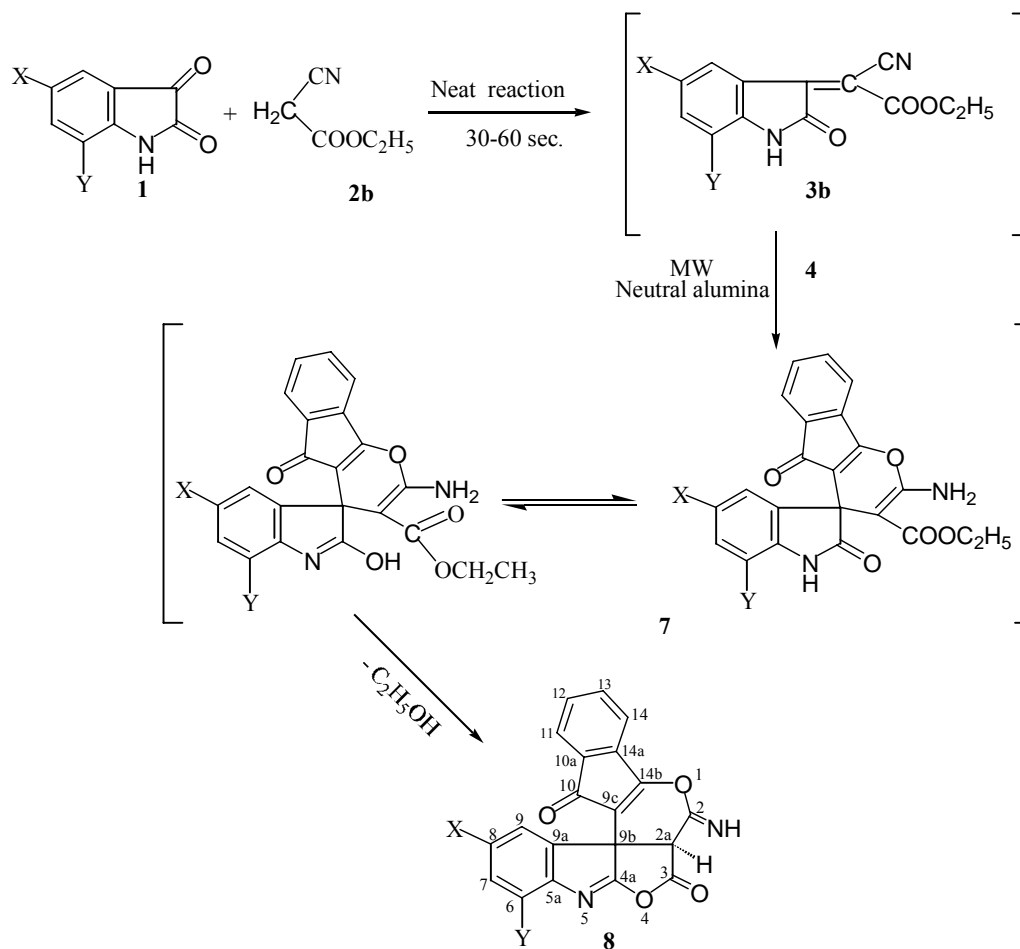
**Scheme II**

Table III — Spectral data of **6a,b** and **8a-c**

Compd	¹ H NMR (δ, ppm)	¹³ C NMR (δ, ppm)
6a	δ 6.56-7.50 (m, 8H, Ar-H), 7.9 (br, 2H, NH ₂ *), 9.15 (br, 1H, NH*).	182.2, 170.1 (two C=O), 168.5 (C-NH ₂), 157.2 (9b-C), 143.3 (7a'-C), 135.5 (9a-C), 133.8 (5a-C), 129.1-121.4 (other aromatic carbons), 116.9 (C≡N), 103.7 (4a-C), 50.8 (spiro carbon), 60.4 (3-C).
6b	δ 2.14 (s, 3H, CH ₃), 2.32 (s, 3H, CH ₃) 6.51-7.49 (m, 6H, Ar-H), 7.85 (br, 2H, NH ₂ *), 9.14 (br, 1H, NH*).	180.1, 171.2 (two C=O), 169.1 (C-NH ₂), 156.8 (9b-C), 141.1(7a'-C), 136.2 (9a-C), 134.2 (5a-C), 132.3-125.1 (other aromatic carbons), 115.7 (C≡N), 102.6 (4a-C), 51.1 (spiro carbon), 59.6 (3-C), 21.5, 12.1 (two CH ₃).
8a	δ 5.04 (s, 1H, CH), 6.76-7.69 (m, 8H, Ar-H), 9.04 (br, 1H, NH*).	196.0, 175.1 (C=O), 161.1, 159.8 (two C=N), 158.1 (14b-C), 142.0 (5a-C), 137.2 (14a-C), 135.1 (10a-C), 134.8-121.0 (other aromatic carbons), 104.2 (9c-C), 52.5 (methine carbon, CH), 38.3 (9b-C).
8b	δ 5.07 (s, 1H, CH), 6.78-7.70 (m, 7H, Ar-H), 9.08 (br, 1H, NH*).	194.0, 177.1 (C=O), 162.3, 160.2 (C=N), 159.1(14b-C), 143.2 (5a-C), 138.2 (14a-C), 135.5-122.2 (other aromatic carbons), 103.1 (9c-C), 52.8 (methine carbon, CH), 36.2 (9b-C).
8c	δ 5.06 (s, 1H, CH), 6.75-7.68 (m, 7H, Ar-H), 9.05 (br, 1H, NH*).	195.8, 178.2 (C=O), 163.1, 161.2 (two C=N), 158.9 (14b-C), 155.4 (8-C), 143.8 (5a-C), 136.3 (14a-C), 136.2-124.4 (other aromatic carbons), 104.9 (9c-C), 53.1 (methine carbon, CH), 37.8 (9b-C).

* NH and NH₂ are D₂O exchangeable

thus establishing the condensed system unequivocally. Other fragments were observed at 276 (100%), 248 (48%), 227 (28%), 147 (50%), 77 (74%). The spectral data of all synthesized compounds are given in **Table III**.

Experimental Section

Infrared spectra were recorded on Perkin-Elmer (Model-577) Shimadzu instrument in KBr pellets. ¹H and ¹³C NMR spectra were recorded on Jeol Model FX-90Q at 89.55 MHz (CDCl₃ + TFA) and on Bruker WM-300 at 75.47 MHz (CDCl₃+DMSO-*d*₆), respectively using TMS as internal reference. Melting points are uncorrected (**Table I**). All the compounds were found homogeneous on TLC in various solvent systems.

Synthesis of 2-amino-3-carbonitrile-spiro[(indeno-[1,2-*b*]pyran)-4(5*H*),3'-[3*H*]-indole] 2',5(1'*H*)-diones, **6a,b**

An equimolar mixture (0.01 mole) of indole-2,3-dione **1** and malononitrile **2a** was ground thoroughly in an agate mortar for 1-2 min (TLC). The corresponding intermediates **3a** was obtained in reasonable purity. The compound **4** (0.01 mole) was adsorbed on neutral alumina (2 g) *via* a methanolic solution and swirled for a while followed by removal of the solvent under gentle vacuum. The dry powder thus obtained was placed into a pyrex-glass open vessel and irradiated in a microwave oven at 640 W until the completion of reaction. The product was extracted with methanol and the methanolic extract was

concentrated on rota-evaporator and left in the refrigerator when a crystalline solid separated out and was filtered and found homogenous on TLC. For analytical studies and biological screening it was purified by re-crystallization from appropriate solvent.

The formation of **3a** and **6a** was confirmed by mixed m.p.s with authentic samples prepared conventionally according to literature method⁹.

Synthesis of 2-imino-3,10-dioxoindeno[3'',2'';5',6']-pyrano[4',3';3,4]furo[2,3-*b*]indoles, **8a-c**

A neat equimolar mixture (0.01 mole) of indole-2,3-dione **1** and ethylcyanoacetate **2b** was irradiated under microwave irradiation for 30-60 sec (TLC, 100% conversion, compared with authentic sample⁹. To this **6** (0.01 mole) was added and the reaction mixture was adsorbed on neutral alumina and irradiated for appropriate time. The product was extracted from methanol.

Acknowledgement

Financial assistance from CSIR, New Delhi is acknowledged and one author (RS) also gratefully acknowledge same for providing Research Associateship.

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