SHORT PAPER

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Montmorillonite catalysed synthesis of novel spiro[3H-indole-3,3′- [3*H*-1,2,4] triazol]-2(1*H*) ones in dry media under microwave irradiation†

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A new route for the one pot synthesis of novel spiro[3*H*-indole-3,3′-[3*H*-1,2,4] triazol]-2 (1*H*) ones utilizing 3-arylimino-2*H*-indol-2-ones (**3**) and thiosemicarbazide (**4**) as starting material under microwave irradiation is reported. Complete conversion was observed by TLC which also showed the formation of a single product.

Intensive research in the field of antibacterial and antifungal agents has continued to grow in the recent years because of the increasing resistance of microorganisms to antibiotics and other antimicrobial drugs.

Research on spiro indoles is of current interest due to their exceptional biological activity.[1–3]

Along with spiro indolines, the great importance of triazole derivatives in the field of biochemistry[4–6] has also attracted the attention of biochemists for some time.

In view of the useful pesticidal activity shown by 1,2,4-triazoles,[7–10] it was considered that combinations of indole and 1,2,4-triazole structures might provide more potent pesticides.

Although 1,2,4-triazole derivatives are associated with a broad spectrum of bioactivities, spiro[3*H*-indole-3,3′-[3*H*-1,2,4] triazoles] have not so far been synthesised. However, brief reports mention the classical synthesis of spiro[3*H*-indole-3,4′-[4*H*-1,2,3] triazoles] in two steps. The first step involved the synthesis of isatin-3-anils in refluxing toluene in 3–4 h followed by treatment with diazomethane in ether for 21 days in a second step.[11–12]

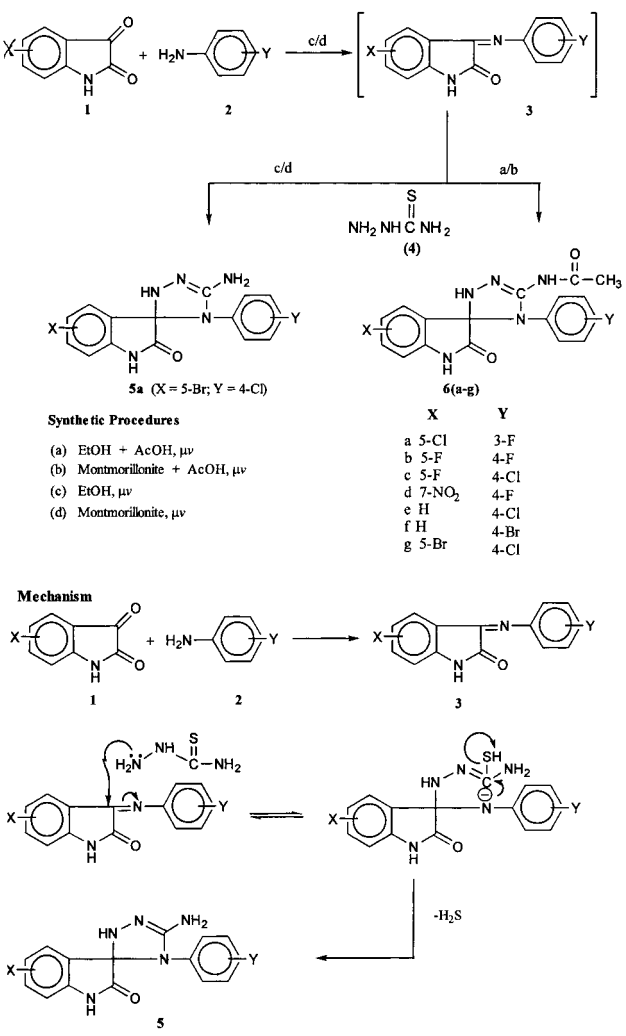
The present report describes the synthesis of a series of spiro[3*H*-indole-[3*H*-1,2,4] triazoles] by an elegant new one pot procedure. Earlier reports mention the synthesis of 1,2,4-triazole derivatives by a long process involving 3–4 steps.[13]

In these environmentally conscious days, the developments in technology are directed towards environmentally sound and cleaner procedures. Hence, present day chemists are no longer confined to use only thermal energy for driving chemical reactions. With the easy availability of microwave sources, their use in chemistry has gained momentum recently. Further, there is increasing interest in the use of environmentally benign reagents and conditions[14] and particularly in solvent free procedures[14] which lead to clean, efficient and economical technology. Safety is largely increased, work-up is simplified and cost is reduced.

The use of solid phase reactions with substrates adsorbed on clay, alumina or silica gel is very important as it avoids the risk of explosions.[14] Montmorillonite clay catalyses efficient reactions on microwave irradiation even though clay by itself does not absorb microwaves.[15] Hence, in an attempt towards a non-traditional approach, because of our continuing interest in the synthesis of biodynamic spiro indolines[16] and the fact that the condensation of 3-arylimino-2*H*-2-ones (**3**) with thiosemicarbazide (**4**) has not been studied so far, we have developed a novel facile one pot synthesis of spiro [3*H*-indole-3,3′-[3*H*-1,2,4] triazole]-2(1*H*) ones under microwave irradiation using either (a) ethanol as energy transfer medium or (b) montmorillonite as inorganic solid support.

Novel spiro compounds 5 or 6 were synthesised by the condensation of 3-aryl imino-2*H*-indol-2-ones (**3**) with thiosemicarbazide (**14**) in presence or absence of acetic acid. (**3**) was synthesized in *in situ* by the reaction of indole-2,3-dione (1) with substituted anilines (**2**).

Formation of spiro compound (**5**) may be rationalized by the mechanism proposed in Scheme 1. The third carbonyl group of isatin (**1**) being more electrophilic forms the 3-arylimino derivatives (**3**) preferentially. The conversion of **3** into **5** involves the nucleophilic attack of the amino electrons of thiosemicarbazide at the electrophilic indolyl carbon accompanied by the migration of a hydrogen atom to form an intermediate thiol derivative. This is followed by cyclization



Scheme 1

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Physical and analytical data of 5′-(N-acetyl amino)-4′-aryl-2′,4′-dihydro-spiro[3H-indole-3,3′-[3H-1,2,4]triazol]-2(lH) ones (**6a–f**)

Compound	X	Y	Time[a]	Yield	Mp	Formula	Found (calcd.) %	
no.			(min)	(%)	(°C)		C	N
6a	5-Cl	3-F	4+1	83	274	$C_{17}H_{13}ClFN_5O_2$	54.55 (54.69)	18.54 (18.76)
6b	5-F	4ν	4+2	79	195	$C_{17}H_{13}F_2N_5O_2$	57.05 (57.14)	19.77 (19.60)
6c	5-F	4-Cl	2+2	80	271	$C_{17}H_{13}ClFN_5O_2$	54.68 (54.69)	18.45 (18.76)
6d	7-NO_2	4-F	5+2	76	269(d)	$C_{17}H_{13}FN_6O_4$	53.20 (53.12)	21.80 (21.87)
6e	H	4-Cl	2+2	75	252	$C_{17}H_{14}ClN_5O_2$	57.85 (57.46)	19.79 (19.71)
6f	H	4-Br	5+3	80	245	$C_{17}H_{14}BrN_5O_2$	51.50 (51.00)	17.80 (17.50)

Irradiations were carried out at 360 W using ethanol as energy transfer medium.
Irradiation time for two steps without isolation of intermediate.

and desulfurisation with the loss of H_2S to give the suggested spiro compound (**5**). In the presence of acetic acid, (**5**) undergoes acetylation to give (**6**).

Reaction occurs rapidly in both cases with the evolution of H_2S gas, the presence of which is detected by its characteristic odour and its rendering of a filter paper with lead acetate black during the progress of the reaction.

We have extensively studied the title reaction varying different parameters including medium, solid support and power level.

Montmorillonite efficiently catalysed the reaction giving the maximum yield (94–98%) with the shortest period and easier work up.

The amount of montmorillonite also plays a very important role. Reaction occurs rapidly along with enhanced yields when an optimum quantity (20% by weight) of montmorillonite is used. However, an excess of solid support (2g) reduces the yield with an increase in reaction time.

The possible existence of a specific (non-thermal) microwave effect has been studied by carrying out the reactions using a preheated oil bath at the same time and same final temperature (78°C) as that absorbed during the microwave experiment (360 W).

It has been found that lower yields have been obtained using a preheated oil bath which indicate that the effect of microwave irradiation is not purely thermal (Table 3).

Reaction of indole-2,3-dione and fluorinated anilines with thiosemicarbazide in the absence of acetic yielded light yellow or cream coloured compounds **5**. The IR spectra of **5** synthesised by both conventional and microwave irradiation showed strong absorption bands at 3400 and 3350 corresponding to asymmetric and symmetric stretching of a free NH_2 group, 3240, 3182 (two NH), 1743 (C=O) and 1625 (C=N) cm^{-1}. The shifting of the indole NHCO band to higher frequency as compared to the NHCO of anil (1680 cm^{-1}) in **3** indicated the disappearance of conjugation to the carbonyl group present in anil **3**. In the ^1H NMR, signals were observed at δ 6.85-8.85 (m, Ar-H, NH of triazole and NH_2) and 11.09 (br, indole NH) ppm. The presence and position of NH and NH_2 were confirmed on deuteration. The presence of NH_2 group was further confirmed by a diazotisation test.

The structure of compounds **5** has been further confirmed on the basis of ^{13}C NMR spectra. In the ^{13}C NMR spectrum of **5a** (X = 5-Br; Y = 4-Cl), sharp signals have been observed at δ 164.02 (C-O), 152.08 (N-C=N), 147.28, 146.31, 142.10, 132.34, 130.39, 124.15, 120.35, 119.39, 118.06, 117.22, 116.51, 115.4 (12-aromatic ring carbons), 111.62 (spiro-carbon.

However, the product **6** obtained by the reaction of 3-aryl imino-2H-indol-2 ones with thiosemicarbazide in the presence of acetic acid with the evolution of H_2S gas was not found to be identical with the previous compound **5** synthesised in the absence of acetic acid by TLC, melting point and spectral studies.

The IR spectra of **6** showed characteristic absorption bands at 3417, 3242, 3182 (three NH stretching bands), 2993 (C–H stretching), 1730(C=O) and 1614 (C=N) along with one additional band at 1697 cm^{-1} indicating the presence of one more

Table 2 Comparative results of the synthesis of **5** and **6** under microwave irradiation

Compd no.	X	Y	Microwave method				Mp(°C)	Mol. formula	Found (calcd.) %	
			a		b				C	N
			Time (min)	Yield (%)	Time (Min) (i)/(ii)	Yield (%) (i)/(ii)				
5a	5-Br	4-Cl	4+1	65	2+2 / 4+3	98.2 / 90.5	280	$C_{15}H_{11}Br\,ClN_5O$	46.16 (45.91)	17.85 (17.85)
6g	5-Br	4-Cl	4+2	71	2+2 / 4+2	87.7 / 80.0	296	$C_{17}H_{13}BrClN_5O_2$	47.20 (47.00)	16.25 (16.12)

In method (a) irradiations were carried out at 360 W using ethanol as energy transfer medium.
Method b(i) Montmorillonite 20% by weight (ii) 2g montmorillonite, at 480 W.
Irradiations were carried out at 360 W using ethanol as energy transfer medium.
Irradiation time for two steps without isolation of an intermediate.

C=O group. The stretching bands corresponding to a free NH_2 group were absent.

In the ^{1}H NMR spectrum, expected signals were observed at δ 6.85–9.79 (m, Ar-H triazole NH and NH $COCH_3$) and 11.05 (br, indole NH) ppm along with additional signals at δ 2.11 ($COCH_3$) ppm. The position of NH protons was confirmed on deuteration.

Formation of spiro compound **6** has been further confirmed on the basis of ^{13}C NMR and mass spectra.

In the ^{13}C NMR spectrum of **6a**, (X = 5-Cl; Y = 3-F) sharp signals were observed at δ 162.50 (*C* = O), 179.18 (C = O), 152.28 (N–C=N) 146.19, 143.25, 141.89, 132.34, 130.89, 124.05, 120.35, 119.39, 117.64, 116.54, 116.12 & 115.14 (12 aromatic ring carbons) 110.78 (spirocarbon) 38.62 (CH_3).

In the mass spectrum of **6a** (X = 5-Cl; Y = 3-F), a very weak molecular ion peak was observed at *m/z* 373 (M^+, 3.5%). Another peak at 375 was not observed, as expected in case of this molecule. However, the presence of a strong peak at 59(95.3%) for $NH(CO^+)CH_3$, as observed by Popp and Piccirilli[17] in the case of *N*-acetylated heterocycles, along with other spectral data and elemental analyses supports the formation of the suggested compound.

The presence of fluorine was confirmed by ^{19}F NMR spectra. The fluorine attached to the aryl ring was observed at δ -115.48 ppm.

On the basis of spectral studies, the compounds **5** and **6** have been identified as the novel 5′-amino-4′-aryl-2′,4′- dihydro spiro[3*H*-indole3,3′-[3*H*-1,2,4]-triazole]-2 (1*H*) ones (**5**) and 5′-(*N*-acetylamino)-4′-aryl-2′,4′-dihydro-spiro[3*H*-indole3,3′-[3*H*-1,2,4]-triazole]-2 (1*H*) ones (**6**).

Experimental

Melting points (mp) in °C were determined in open glass capillary and are uncorrected; IR spectra were recorded on Testscan Shimadzu FTIR 8000 series. ^{1}H NMR and ^{19}F NMR were recorded on a Jeol (model FX-90Q) using ($CDC1_3$ + $DMSOd_6$) as solvent at 89.55 and 84.25 MHz, respectively. ^{13}C NMR was recorded on model dpx200 using DMSO as solvent at 50.3 Mhz. TMS was used as internal reference for ^{1}H NMR and ^{13}C NMR and hexafluorbenzene as external reference for ^{19}F NMR. Mass spectra were recorded on Kratos 30 and 50 mass spectrometers. All compounds were found homogeneous by TLC in various solvent systems

The Induced Microwave Convection system was used, where microwaves are generated at a frequency of 2450 MHz. The oven has a range of microwave output energy up to 1200 W.

General procedure for the preparation of 5′-amino/N-acetylamino-4′-aryl-2′,4′-dihydro-spiro[3H-indole-3,3′-[3H-1,2,4] triazol]-2(1H) ones (**5**/**6**) *under microwave irradiation*: Compounds **5** and **6** have been synthesised in one step without isolation of the intermediate anil (**3**) using either (a) ethanol as energy transfer medium or (b) montmorillonite K10 as an inorganic solid support.

Table 3 Comparative results obtained in the synthesis of the compounds **5a** and **6g** by conventional method (A) and microwave method (B) using ethanol as energy transfer medium

Compound no.	Method	Reaction time/(min)	Final temperature(°C)[a]	Yield (%)
5a	B	4+1	78	65
	A(i)	4+1	78	Nil
	A(ii)	15+2	78	Trace
	A(iii)	15+8	78	30
6g	B	4+2	78	70.8
	A(i)	4+2	78	Nil
	A(ii)	15+3	78	Trace
	1A(iii)	15+5	78	35

[a]Final temperature measured at the end of exposure to microwave irradiation.

(a) Equimolar mixture (0.01 mole) of appropriate indole-2,3-dione (**1**) and substituted anilines (**2**) in the minimum quantity of ethanol (5–10 ml, required to form a slurry) was irradiated intermittently for an appropriate time (Table 1) inside a microwave oven at 360 watts until the completion of the reaction. As the reactants disappeared (TLC), thiosemicarbazide (**4**) (0.01 mole) or thiosemicarbazide (**4**) and acetic acid (2–3 drops) were added to the reaction mixture which was again irradiated for required time (Table 1) to give **5** or **6**.

On cooling, crystals separated out which were found to be of sufficient purity.

The compounds obtained in the absence of presence of acetic acid were found to be **5** and **6** respectively.

(b) I and II (0.6 mmole) were adsorbed separately on montmorillonite K10 (20% by weight) with the help of methanol, mixed thoroughly and irradiated for an appropriate time at 480 watts until the completion of the reaction. As the reactants disappeared, thiosemicarbazide **4** (0.6 mmole) or **4** and two drops of acetic acid were adsorbed on montmorillonite K10, added to the reaction mixture, mixed thoroughly. Irradiation gave **5** or **6**. The product was extracted with methanol and the excess solvent was evaporated on a rotary evaporator, to give a solid which was found to be of sufficient purity.

Compounds **6a–f** have been synthesised by method (a) while **6g** and **5a** have been synthesised by methods (a) and (b). Results are summarised in Tables 1 and 2.

The identity of the products was established by their mixed mp's, IR and ^{1}H NMR spectral studies.

Spectral data of **5a** and **6a–g** are as follows:

5a: δ_H ($CDCl_3$ + $DMSOd_6$): 6.85–7.65 (m, 9H, Ar–H and NH_2) 8.85 (s, 1H, NH), 11.09 (Ibs, 1H, NH); δ_C (DMSO) 164.02, 152.08, 147.28, 146.31, 142.10, 132.34, 130.39, 124.15, 120.35, 119.39, 118.06, 117.22, 116.51, 115.14, 111.62; ν_{max}/cm^{-1}(KBr) 3400, 3350, 3240, 3182, 1743, 1625, 528.

6a: δ_H ($CDC1_3$ + $DMSOd_6$) : 2.11 (s, 3H, CH_3), 6.88–7.50 (m, 7H, Ar–*H*) 8.75 (s, 1H, NH) 9.22 (bs, 1H, NH), 11.05 (bs, 1H, N*H*); δ_C (DMSO) 179.18, 162.50, 152.28, 146.19, 143.25, 141,89, 132.34, 130.89, 124.05, 120.35, 119.39, 117.64, 116.54, 116.12, 115.14, 110.78, 38.62; ν_{max}/cm^{-1}(KBr) 3417, 3242, 3182, 2993, 1730, 1697, 1614, 1295, 1115, 740.

6b: δ_H ($CDC1_3$ + $DMSOd_6$) : 2.12 (s, 3H, CH_3), 6.89–7.55 (m, 7H, Ar-H) 8.77 (s, 1H,NH) 9.24 (bs, 1H, NH), 11.06 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3419, 3246, 3198, 2995, 1722, 1698, 1615, 1269, 1201, 1120.

6c: δ_H ($CDC1_3$ + $DMSOd_6$) : 2.13 (s, 3H, CH_3), 6.90–7.59 (m, 7H, Ar–H) 8.80 (s, 1H,NH) 9.24 (bs, 1H, NH), 11.07 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3400, 3268, 3153, 2979, 1720, 1696, 1616, 1336, 745, 690.

6d: δ_H ($CDCl_3$ + $DMSOd_6$) : 2.12 (s, 3H, CH_3), 6.90–7.59 (m, 7H, Ar–H) 8.80 (s, 1H,NH) 9.24 (bs, 1H, NH), 11.07 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3410, 3245, 3190, 2992, 1725, 1699, 1619, 1520 and 1321.

6e: δ_H ($CDCl_3$ + $DMSOd_6$) : 2.10 (s, 3H, CH_3), 6.86–7.46 (m, 8H, Ar–H) 8.74 (s, 1H,NH) 9.20 (bs, 1H, NH), 11.04 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3405, 3238, 3198, 2989, 1726, 1698, 1617, 746, 705.

6f: δ_H ($CDCl_3$ + $DMSOd_6$) : 2.09 (s, 3H, CH_3), 6.87–7.46 (m, 8H, Ar–H) 8.74 (s, 1H,NH) 9.21 (bs, 1H, NH), 11.05 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3409, 3240, 3180, 1728, 1699, 1620, 570, 515.

6g: δ_H ($CDCl_3$ + $DMSOd_6$) : 2.15 (s, 3H, CH_3), 6.87–7.57 (m, 7H, Ar–H) 8.79 (s, 1H,NH) 9.25 (bs, 1H, NH), 11.08 (bs, 1H, NH); ν_{max}/cm^{-1}(KBr) 3418, 3243, 3123, 2989, 1730, 1697, 1622, 769, 742, 632, 580.

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