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Research Article

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Tetrabutylammonium acetate catalyzed one-pot multi component synthesis of spirooxindoles from 1-methylquinoline-2,4(*1H, 3H*)-dione

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ABSTRACT

An efficient one pot synthesis of spirooxindoles by three-component reaction of isatin, malononitril/ethylcyano acetate and N-methylquinoline-2, 4-dione in water in the presence of TBA Acetate has been described. The methodology described here has the advantages of environment friendliness, higher yields, low cost, low reaction times and convenient operation.

Keywords: Spirooxindoles, TBA Acetate, Multi component reactions, Knoevenagel condensation, Michel addition

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INTRODUCTION

Multi component reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the use of hazardous solvents, reagents and purification complications. In the past decades, there has been a tremendous development in three or four component reactions and great efforts continue to be made to develop new MCRs.[1]

Indole nucleus is the most common and important feature of a variety of natural products and pharmaceuticals.[2,3] sharing of the indole 3-carbon atom for the synthesis of spirooxindole systems stimulated much interest and the unique structural array and pharmacological activities displayed by these classes of spirooxindoles have made them attractive synthetic targets.[4]

Among oxygen-containing heterocycles fused with indole ring system, chromene based structures are found to manifest diverse activities such as antidepressant, anti hypertensive, antiviral, anti-tubulin and anti oxidative etc.,[5-15] Spirooxindoles synthesis using quinolones and active methylene compounds has not been focused much using TBA Acetate as a catalyst and water as reaction medium. These type of reactions were earlier reported using L-proline,[16] $InCl_3$,[17]TEBAC,[18] NH_4Cl,[19] etc,. Minoo Dabiri *et al.* have reported the synthesis of spirooxindoles using TEBA as surfactant catalyst but mentioned that the method has the disadvantage of generation mixtures of pyrans and unsaturated nitriles. This drawback has been successfully overcome by using the TBA Acetate (Tetrabutylammonium acetate) in water at 100^0C.

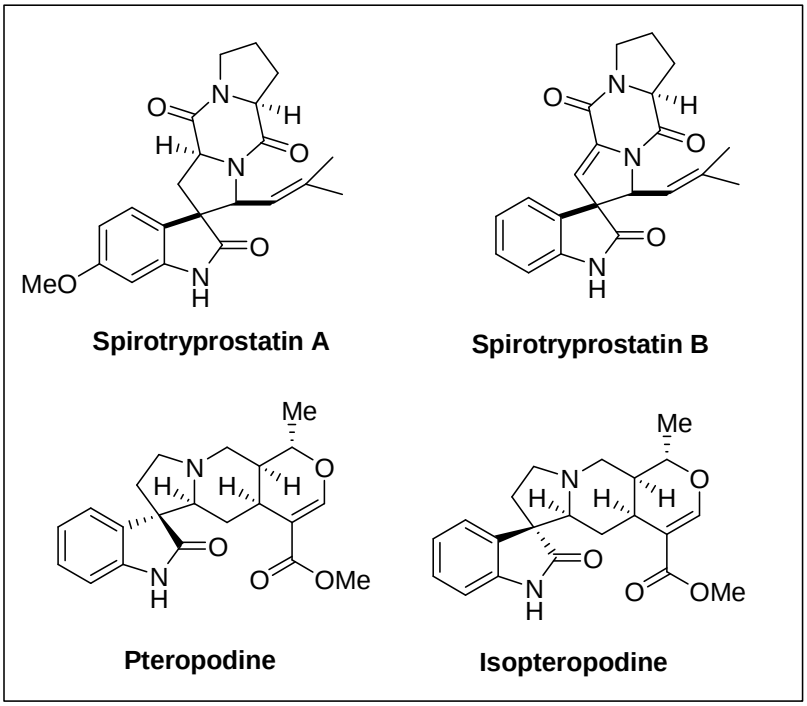


Fig 1. Illustrations of some Spirooxindole-containing compounds

Breslow[20] reported that using water as reaction medium which shows the hydrophobic effects enhances the rate of several organic reactions rediscovered the use of water as solvent during 1980's. There has been growing recognition that water is an attractive medium for several organic transformations[21] and many MCRs in aqueous medium have been reported.[22] As a consequence of our interest in synthesis of organic compounds in water, we now wish to extend our approach for the one-pot synthesis of spirooxoindoles using water and TBA Acetate as surfactant catalyst has been described.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in DMSO – d_6 using TMS as internal standard using 400 MHz spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only. Starting materials **2 & 3** were obtained from commercial sources and used as such.

General procedure for the synthesis of spirooxindole derivatives 4(a-j).
A mixture of isatin **3** (1mmol), malononitrile or cyanoacetic esters **2** (1mmol), 1,3-dicarbonyl compounds **1** (1 mmol), and TBA Acetate (0.1 mmol) in water (2 mL) was stirred at 100□C for 15-60 min. After completion of the reaction confirmed by TLC, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water and cooled ethanol to afford the pure **4(a-j)**.

Spectral data for selected compounds
4a (R = H, X = CN): Yield: 92%; M.P.: > 300^{0}C; (Lit. M.P.: >300^{0}C)

4b (R = F, X = CN): Yield: 88%; Time: 8 min; M.P.: >300^{0}C; IR (KBr): 3499, 3326 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2190 (sharp, medium, -CN), 1720, 1674cm^{-}1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS): δ 2.78 (s, 3H, -NCH_3), 6.86 (s, 2H, -NH_2), 6.75-7.60 (m, 7H, Ar-H), 10.15 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 389.

4c (R = Cl, X = CN): Yield: 85%; Time: 10 min; M.P.: > 280^{0}C; IR (KBr): 3489, 3336 (unequal doublet, asymmetric & symmetric stretching's of -NH2), 2229 (sharp, medium, -CN), 1721, 1672cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS) : δ 2.65 (s, 3H, -NCH_3), 6.91 (s, 2H, -NH_2), 7.05-7.59 (m, 7H, Ar-H), 10.23 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 405.

4d (R = Br, X = CN): Yield: 90%; Time: 7 min; M.P.: > 300^{0}C; IR (KBr): 3487, 3322 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2180 (sharp, medium, -CN), 1719, 1670cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS) : δ 2.70 (S, 3H, -NCH_3), 7.02 (s, 2H, -NH_2), 6.95 - 7.70 (m, 7H, Ar-H), 10.12 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1) : 449.

4e (R = I, X = CN): Yield: 94%; Time: 10 min; M.P.: > 300^{0}C; IR (KBr): 3479, 3198 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2205 (sharp, medium, -CN), 1720, 1673cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS) : δ 2.65 (S, 3H, -NCH_3), 6.96 (s, 2H, -NH_2), 6.85 - 7.64 (m, 7H, Ar-H), 10.09 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 497.

4f (R = H, X = $COOC_2H_5$): Yield: 92%; M.P.: > 300^{0}C; (Lit. M.P: >300^{0}C)

4g (R = F, X = $COOC_2H_5$): Yield: 87%; Time: 7 min; M.P.: 184-186^{0}C; IR (KBr): 3374, 3253 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2199 (sharp, medium, -CN), 1698, 1656, 1630cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS): δ 1.20 (t, 3H, CH_3), 2.85 (s, 3H, -NCH_3), 3.43 (q, 2H, -CH_2), 6.82 (s, 2H , -NH_2), 6.76 - 7.70 (m, 7H, Ar-H), 10.22 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 436.

4h (R = Cl, X = $COOC_2H_5$): Yield: 88%; Time: 8 min; M.P.: 268-70^{0}C; IR (KBr): 3372, 3250 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2197 (sharp, medium, -CN), 1697, 1650, 1628cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS) : δ 1.18 (t, 3H, CH_3), 2.76 (s, 3H, -NCH_3), 3.85 (q, 2H, -CH_2), 6.79 (s, 2H, -NH_2), 6.95 - 7.64 (m, 7H, Ar-H), 10.24 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 452.

4i (R = Br, X = $COOC_2H_5$): Yield: 86%; Time: 8 min; M.P.: 284-86^{0}C; IR (KBr): 3379, 3258 (unequal doublet, asymmetric & symmetric stretching's of -NH2), 2220 (sharp, medium, -CN), 1701, 1660, 1631cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS) : δ 1.03 (t, 3H, CH_3), 2.69 (s, 3H, -NCH_3), 3.90 (q, 2H, -CH_2), 6.82 (s, 2H, -NH_2), 6.89 - 7.72 (m, 7H, Ar-H), 10.21(s, 1H, -NH, D_2O exchangeable). m/z (M^++1) : 496.

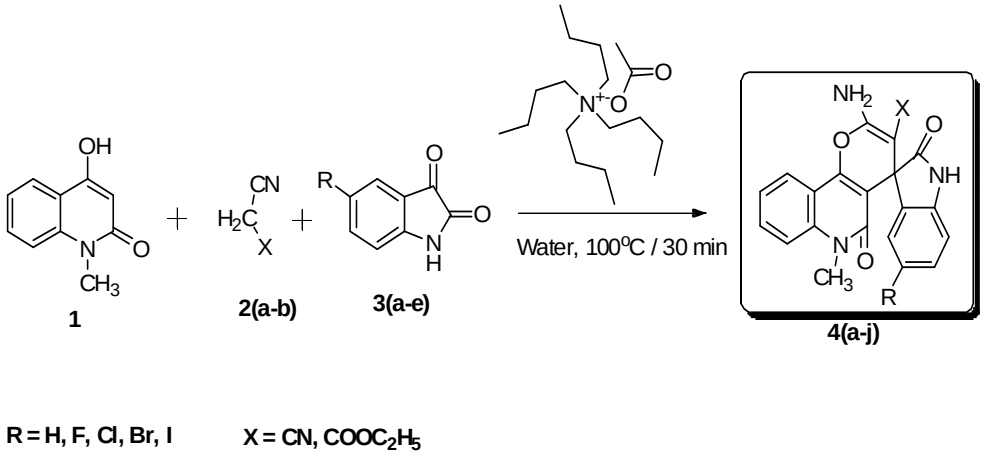
4j (R=I, X=$COOC_2H_5$): Yield: 90%; Time: 6 min; M.P.: 220-22^{0}C; IR (KBr): 3389, 3268 (unequal doublet, asymmetric & symmetric stretching's of -NH_2), 2202 (sharp, medium, -CN), 1700, 1665, 1635cm$^-$1 (-CO- group, broad) ; ^{1}H- NMR (DMSO d_6/TMS): δ 1.02 (t, 3H, CH_3), 2.71 (s, 3H, -NCH_3), 3.88 (q, 2H, -CH_2), 6.79 (S, 2H, -NH_2), 6.94 - 7.82 (m, 7H, Ar-H), 10.22 (s, 1H, -NH, D_2O exchangeable). m/z (M^++1): 544.

RESULTS AND DISCUSSION

In the present work, the reaction of 2,4-dicarbonyl compound (**1**), Isatin (**2a-b**) and active methylene compounds (**3a-e**) in a molar ratio of 1: 1: 1 in the presence of TBA Acetate catalyst (10 mol%) in water at 80-100^{o}C for 30 min resulted Spirooxindoles **4(a-j)** in good yields (Table 3). Initially, for the synthesis of spirooxindoles, we have evaluated different solvents and catalytic systems (mostly surfactant catalysts) and we have found that TBA Acetate has a unique capability to enhance the rate of the reaction in aqueous medium. The results were summarized in Table 1 and 2.

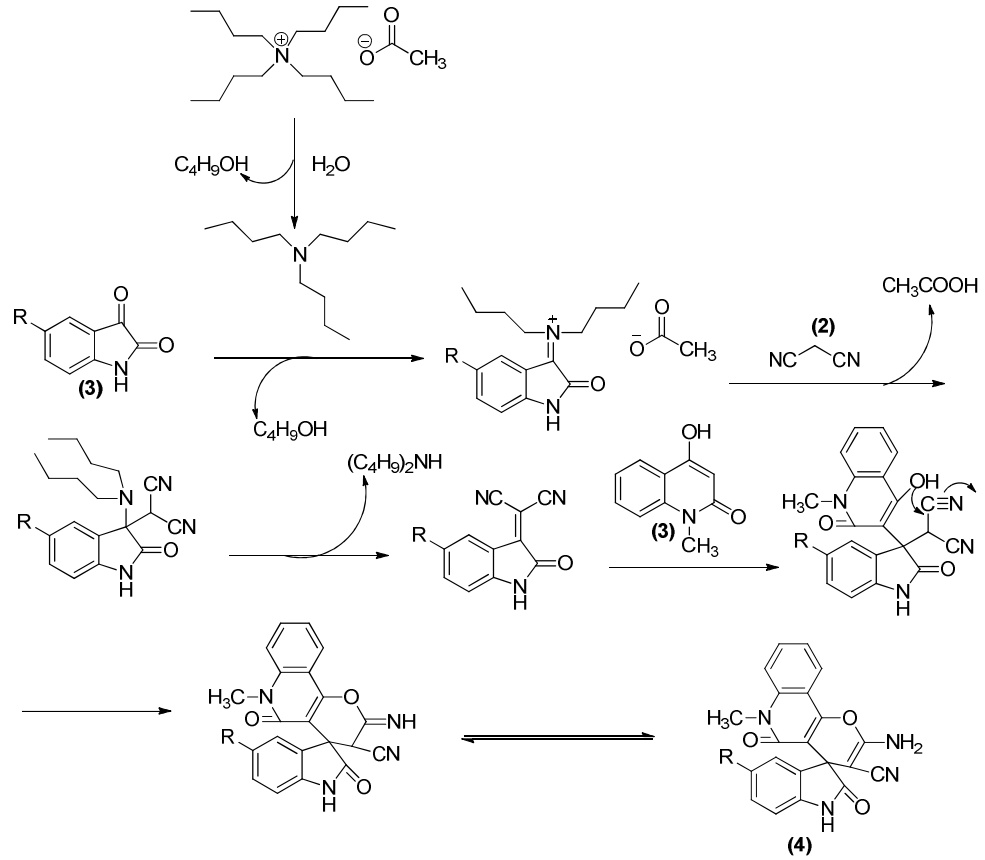
It was found that when the reaction carried out without using any catalysts, only trace amounts of the product is isolated (Entry 1, Table 2). When we use other surfactant catalysts like TBAB (Entry 2, Table 2), TEBAC (Entry 3, Table 2), CTAB (Entry 4, Table 2), CTAC (Entry 5, Table 2), SDS (Entry 6, Table 2) and TBAB melt (Entry 7, Table 2), we detected and isolated in moderate yields (50-70%). The best results were obtained when we used TBA Acetate (Entry 8, Table 2). The amount of the catalyst was optimized using 10-20 mol % and 10 mol % is suitable for under reaction conditions. The reaction temperature is also optimized by increasing form 50-100^{O}C and every time on refluxing at 100^{O}C gave maximum yield (92%). From the above studies finally the optimum conditions for the synthesis of spiroxindoles were obtained as 2,4-dicarbonyl compound (**1**), Isatin (**2a-b**) and active methylene compounds (**3a-e**) in a molar ratio of 1: 1: 1 in the presence of TBA Acetate catalyst (10 mol%) in water (10ml) at 100^{O}C for 30 min gave 92% yield (Entry 8, Table 2).

Scheme-1. Synthesis of Spirooxindoles 4(a-j) using TBA Acetate as catalyst and water as solvent



R = H, F, Cl, Br, I **X = CN, $COOC_2H_5$**

Scheme-2. Plausible mechanism for the formation of Spirooxindoles using TBA Acetate



After evaluating the reaction conditions, the synthesized the products were obtained in a simple workup process as the catalyst is directly soluble in water and the product is insoluble and can be directly separated after cooling to room temperature. The filtrate contain the catalyst can be recovered and recycled.

The proposed mechanism for the formation of spirooxindoles was shown in Scheme 2. We suggest that TBA Acetate forms an iminium ion with isatin in presence of water which facilitates the Knoevenagel condensation of malononitrile with isatin, forms an intermediate which further after losing the molecules of TBA Acetate. This intermediate attacked by N-methylquinoline-2,4-dione via Michel addition followed by the cycloaddition of

hydroxyl group on cyano moiety to form the desired product. In this study all products were characterized by melting point, IR, ^{1}H-NMR spectral data as well as HRMS.

Table-1. Solvents effect on the reaction of N-methylquinoline-2, 4-dione (1) Isatin (2a) and malononitrile (3a) in the presence of 10 mol% of TBA Acetate

Entry	Solvent[a]	Time (min)[b]	Yield (%)[c]
1	CH_3OH	360	60
2	C_2H_5OH	240	70
3	CH_3CN	360	30
4	DMF	240	70
5	DMSO	360	<30
6	$CHCl_3$	360	<30
7	CH_2Cl_2	360	<30
8	Solvent free	180	Trace
9	Water	30	92

[a]refers to solvent 10 ml was used
[b]refers to the maximum time used for the completion of the reaction.
[c]refers to the Isolated Yields.

Table-2. Synthesis of Spirooxindoles using various Surfactant catalysts

Entry	Catalyst	Temp	Time(min)	Yield (%)
1	None	100	60	10
2	TBAB	100	120	60
3	TEBAC	100	120	70
4	CTAB	100	180	50
5	CTAC	100	180	55
6	SDS	100	180	65
7	TBAB melt	100	180	60
8	TBA Acetate (10 mol %)	100	30	92
9	TBA Acetate (10 mol %)	80	40	88
10	TBA Acetate (10 mol %)	70	50	80
11	TBA Acetate (10 mol %)	60	60	82
12	TBA Acetate (15 mol %)	50	80	80
13	TBA Acetate (20 mol %)	50	120	80
14	TBA Acetate (10 mol %)	100	140	80
15	TBA Acetate (10 mol %)	100	160	80
16	TBA Acetate (10 mol %)	100	180	80

Table -3. Syntheses of Spirooxindoles 4(a-e) using N-methylquinoline-2,4-dione (1), Isatin 3(a-e) and active methylene compounds 2(a-b) using TBA Acetate as catalyst Water as solvent at 100^{0}C

Entry	Product	Time(min)	Temp(^{o}C)	Yield(%)[c]
1	**4a**	30	100	90
2	**4b**	30	100	92
3	**4c**	30	100	92
4	**4d**	30	100	90
5	**4e**	30	100	94
6	**4f**	30	100	90
7	**4g**	30	100	92
8	**4h**	30	100	90
9	**4i**	30	100	90
10	**4j**	30	100	92

[c]refers to Isolated Yields.

CONCLUSION

In conclusion, we have described spirooxindole derivatives using TBA Acetate as recyclable catalyst in aqueous medium. This new method has the advantages of higher yields, mild reaction conditions, shorter reaction times, convenient procedure and environmental friendliness.

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