HETEROCYCLES, Vol. 89, No. 4, 2014, pp. 1017 - 1024. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 20th December, 2013, Accepted, 7th February, 2014, Published online, 18th February, 2014
DOI: 10.3987/COM-13-12920

IMPROVING THE SYNTHESIS OF SPIROPYRAN DERIVATIVES USING MICROWAVE IRRADIATION METHOD

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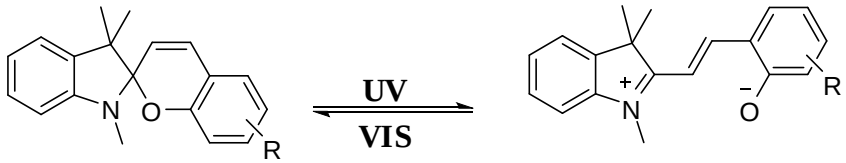
Abstract – A solvent free synthesis of spiropyran derivatives has been developed from the condensation of indoline and salicylaldehyde using a microwave irradiation method. This method starts from readily available starting materials and provides biologically interesting products. The microwave irradiation method was remarkably successful and gave spiropyran derivatives in higher yield (72–99%) with a much shorter reaction time (10–15 min) compared to the conventional heating method. The chemical structures of the compounds prepared were characterized through IR, ^{1}H NMR and ^{13}C NMR spectral data.

Among the structurally diverse photochromic compounds, spiro compounds have attracted much interest due to their remarkable properties. Spiropyrans were first synthesized and studied in early 1950's, by Hirschberg and Fisher.[1] Particular attention has been given to spiropyran due to their potential applications in optical devices and sensors[2] as well as biomedical applications.[3] Interestingly, spiropyran compound is reversible when it undergoes photo-transformation with changes in solvent polarity.[4] Scheme 1 shows the photochromism of typical spiropyran when exposes to UV light, producing an open form compound known as merocyanine.



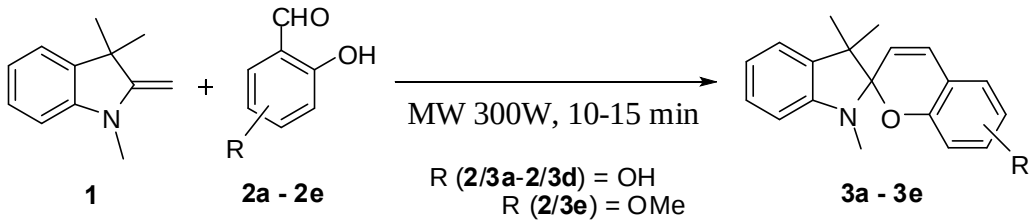
SPIROPYRAN **MEROCYANINE**

Scheme 1. Photochromism of typical spiropyran

Many techniques have been employed to synthesize spiropyran and their derivatives.[5-8] One of the most popular conventional methods was developed by the Wizinger and Wenning in 1940. It involves the condensation of 2-alkyl heterocyclic quaternary salt with the substituted salicylaldehyde in refluxing solvent such as ethanol, acetonitrile and tetrahydrofuran.[9]

In recent years, microwave irradiation has been widely used in organic chemistry synthesis.[10] Gedye and Majetich were the earliest researchers to report on the microwave irradiation especially in the preparation of various heterocyclic compounds.[11,12] This "non-conventional" synthetic method offers numerous benefits such as accelerating the synthesis of inorganic[13] and organic compounds,[14,15] shorter reaction time,[16,17] produce higher yields[18] and enhance product purities.[19] Moreover, microwave irradiation is also considered as a "green" alternative since many organic reactions can be carried out in solvent-free conditions.[20,21] Microwave irradiation method offers an efficient alternative approach although it is not extensively explored in synthesizing spiropyran and their derivatives.

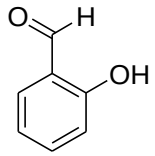
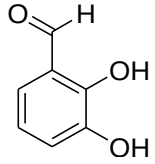
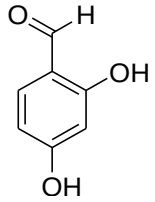
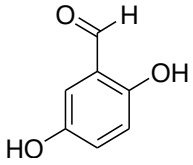
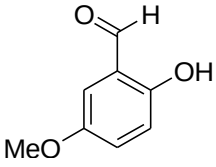
Among the synthetic conditions for preparation of spiropyran derivatives, the normal heating method (reflux) is the well known method.[6,8,22-25] In this reaction, the derivatives of spiropyrans **3a–3e** were prepared by the reaction of indole **1** and salicylaldehyde derivatives **2a–2e** under microwave irradiation technique in solvent free condition for 10–15 min at 300 W. Scheme 2 shows the synthesis of spiropyran **3a**–**3e** using a microwave irradiation method.



Scheme 2. Preparation of spiropyran **3a–3e** using microwave irradiation

The yields of the products **3a**–**3e** were improved under the microwave irradiation compared to normal approaches (Table 1).

Table 1. Yield of spiropyran **3a – 3e**

Product	Salicylaldehyde **2a–2e**	Normal Method/ % yield	time	Microwave % yield	t/min
3a		44[a,22]	4 h	93	10
3b		90[a,23]	5.5 h	99	10
3c		40[b,18]	-	No reaction	10
3d		62[a,24]	6 h	97	10
3e		58[c,20]	20 min	72	15

Conditions: a = reflux; b = room temperature; c = ultrasound

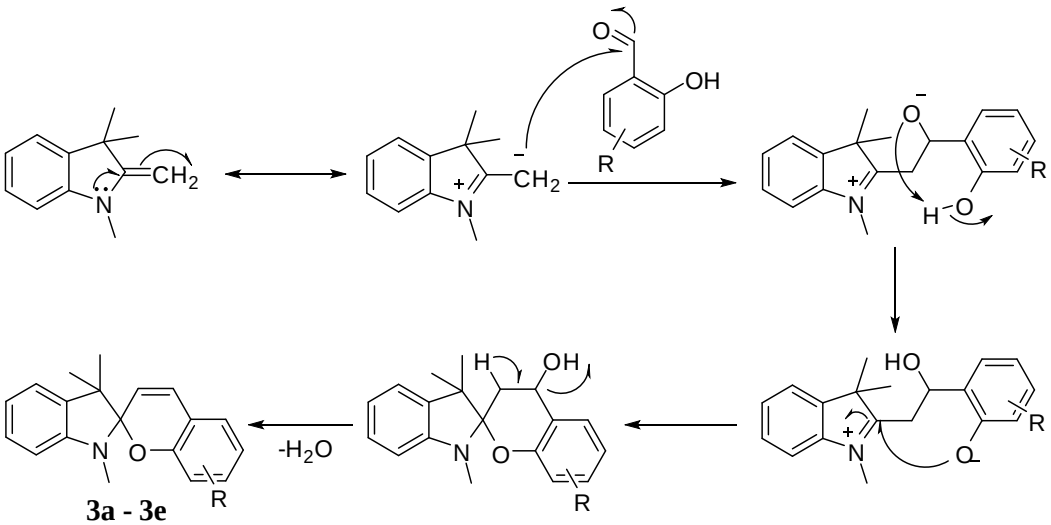
Comparison of the product were made for normal and microwave approach respectively. By using the microwave method, the yields of **3a**–**3e** products were increased in ranged of 72–99%. It is due to the low reactivity of formyl group with additional electron donating group at 4-position of 2,4-dihydroxybenzaldehyde which led to produce **3c** crude product with unidentified side product that failed to be purified.[17] Compound **3d** gives a higher yield (97%) compared to compound **3e** by the fact that a hydroxyl group at para position of salicylaldehyde which is more reactive compared to a methoxy group with respect to benzene.

The products (**3a–3e**) were prepared according to the described microwave method. The structures of spiropyrans (**3a–3e**) were confirmed by FT-IR and NMR spectral data. The IR spectrum of spiropyran

showed the presence of the hydroxyl group of intramolecular H-band in substituent salicylaldehydes at 3300–3200 cm^{-1}.[26] The absorption band at 1610–1600 cm^{-1} and 1480–1460 cm^{-1} are refer to the aromatic ring C=C stretching. It is known that the presence of absorption bands at 1260–1240 cm^{-1} to 1070 cm^{-1} were attributed to the aryl C-O stretching. Furthermore, the C_{spiro}-O stretching frequencies are found to be at 930–920 cm^{-1} that signify the indolinobenzospiropyran compounds.[27]

Structural elucidations of **3a**–**3e** were also achieved by ^1H NMR spectroscopy. All the spiropyrans (**3a**–**3e**) show signals of two *gem*-dimethyl groups at 1.13±1.18 ppm and 1.28±1.32 ppm. The results indicate the methyl group is not magnetically equivalent. *N*-Methyl peak is observed as a singlet at 2.71±2.75 ppm, due to the orthogonal nature of the indoline and benzopyran halves.[28] The olefinic protons appear as a doublet at 5.67±5.72 and 6.82±6.87 ppm respectively, with large coupling constants *J* = 10.1±10.2 Hz. This is a typical value for *cis* configuration.[29] For **3b** and **3d** compounds which have a hydroxyl group attached to the aromatic ring are observed as a broad singlet peak at 5.47 ppm and 4.68 ppm. Apart from that, **3e** shows a singlet peak at 3.77 ppm which integrates for 3 protons where it indicates the methoxy group. The proton NMR spectra of (**3a–3e)** show aromatic hydrogens that appeared as multiplet from 6.49 to 7.91 ppm respectively.

All the entire signal comprising an indoline and benzopyran subunits, the common components are accordance for all the spiropyran moieties.[29] According to Natali and co-workers,[30] the reaction mechanism takes place when the Fisher base forms a carbanion caused by mesomeric effect. Thus, the nucleophiles of Fisher base attack the carbonyl group of the substituted salicylaldehydes. This allows the internal proton transfer of hydroxyl group within the ring.[31] Then, it underwent intramolecular ring closing followed by the elimination of water to form the spiro compound (Scheme 3).



Scheme 3. Proposed mechanism of compounds **3a–3e**

In summary, a series of spiropyran **3a**–**3e** were successfully prepared using a domestic microwave as irradiation source with improved yield (72–99%). This technique offers an alternative to synthesize organic compounds with a high yield and short reaction time compare to the conventional method. Furthermore, this research also demonstrated that microwave irradiation is a convenient, inexpensive and highly efficient technique which can also contributes towards the green chemistry.

EXPERIMENTAL

Microwave irradiation was carried out using the domestic microwave oven (Electrolux, model EMM2017X,PCR). Infrared (IR) spectra were recorded by using Perkin Elmer FT-IR at room temperature. The test samples were prepared by using KBr disc method and analyzed over the range of 400 – 4000 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance spectrophotometer (400MHz) using tetramethylsilane (TMS) as internal reference. Purification was performed using flash column chromatography on grade silica gel (Merck, 70-230 mesh). Analytical thin layer chromatography (TLC) was performed on precoated silica gel Merck DC Kieselgel 60 F_{254} plates and the spots were visualized with UV light. All the chemicals were obtained from commercial sources and were used without further purification.

Microwave method

To a mixture of spiroyrans (**3a–3e** (2.5 mmol)), salicylaldehyde derivatives **2a–2e** (2.5 mmol) and 1,3,3-trimethyl-2-methyleneindoline **1** (2.5 mmol) were added. The reaction mixture was taken in vial and placed in a microwave oven and irradiated at 300 W for 10–15 min. The crude product was concentrated and purified by flash column chromatography with hexane–EtOAc (4:1) as the eluent to afford the product.

Spiro [2*H*-1-benzopyran-2,2'-(1',3',3'-trimethylindoline)] (3a)

IR υ_{max} (KBR)/cm^{-1}: 2941, 1605, 1444, 1250, 951; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.18 (3H, s, C*H*$_3$), 1.33 (3H, s, C*H*$_3$), 2.75 (3H, s, N-C*H*$_3$), 5.69 (1H, m, *J* = 10.2, C=C*H*), 6.54 (1H, m, *J* = 7.8, H_{Ar}), 6.72 (1H, m, *J* = 8.4, H_{Ar}), 6.83 (1H, m, *J* = 7.2, H_{Ar}), 6.85 (1H, m, *J* = 7.8, H_{Ar}), 6.87 (1H, m, *J* = 10.2, C=C*H*), 7.06 (1H, m, *J* = 7.8, H_{Ar}), 7.10 (1H, m, *J* = 7.8, H_{Ar}), 7.11 (1H, s, H_{Ar}), 7.19 (1H, m, *J* = 7.8, H_{Ar}); ^{13}C NMR (150 MHz, $CDCl_3$) δc 20.2 (C-*C*H$_3$), 25.8 (C-*C*H$_3$), 28.9 (N-*C*H$_3$), 51.7 (CH$_3$-*C*-CH$_3$), 104.1 (N-C_{spiro}-O), 106.8 (*C*H$_{Ar}$), 115.0 (*C*H$_{Ar}$), 118.8 (C_{Ar}), 119.1 (*C*H$_{Ar}$), 119.3 (*C*H$_{Ar}$), 120.0 (*C*H$_{Ar}$), 121.5 (*C*H$_{Ar}$), 126.6 (H*C*=), 127.6 (H*C*=), 129.4 (*C*H$_{Ar}$), 129.6 (*C*H$_{Ar}$), 136.8 (C_{Ar}), 148.2 (C_{Ar}) and 154.4 (C_{Ar}). All the spectral data were in accordance to the literature.[22]

Spiro [2*H*-1-benzopyran-2,2'-(8'-hydroxy-1',3',3'-trimethylindoline)] (3b)

IR υ_{max} (KBR)/cm^{-1}: 3513, 2962, 1650, 1466, 1248, 931; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.17 (3H, s, CH_3), 1.29 (3H, s, CH_3), 2.74 (3H, s, N-CH_3), 5.47 (1H, s, O*H*), 5.67 (1H, m, *J* = 10.2, C=C*H*), 6.53 (1H, m, *J* = 8.0, H_{Ar}), 6.63 (1H, m, *J* = 8.0, H_{Ar}), 6.73 (1H, m, *J* = 8.0, *J* = 7.5, H_{Ar}), 6.76 (1H, m, *J* = 8.0, H_{Ar}), 6.78 (1H,m, *J* 8.0, H_{Ar}), 6.85 (1H, m, *J* = 10.2, C=C*H*), 7.07 (1H, m, *J* = 8.0, H_{Ar}), 7.18 (1H, m, *J* = 8.0, H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δc 19.9 (C-*C*H_3), 25.9 (C-*C*H_3), 28.9 (N-*C*H_3), 51.8 (CH_3-*C*-CH_3), 105.4 (N-C_{spiro}-O), 107.0 (*C*H_{Ar}), 115.6 (*C*H_{Ar}), 118.1 (CH_{Ar}), 119.0 (C_{Ar}), 119.3 (*C*H_{Ar}), 119.5 (*C*H_{Ar}), 120.4 (*C*H_{Ar}), 121.7 (*C*H_{Ar}), 127.7 (H*C*=), 129.5 (H*C*=), 136.5 (C_{Ar}), 140.8 (C_{Ar}), 143.2 (C_{Ar}) and 147.9 (C_{Ar}). All the spectral data were in accordance to the literature.[23]

Spiro [2*H*-1-benzopyran-2,2'-(7'-hydroxy-1',3',3'-trimethylindoline)] (3c)

All the spectral data were in accordance to the literature.[18]

Spiro [2*H*-1-benzopyran-2,2'-(6'-hydroxy-1',3',3'-trimethylindoline)] (3d)

IR υ_{max} (KBR)/cm^{-1}: 3296, 2959, 1606, 1466, 1249, 938; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.14 (3H, s, CH_3), 1.28 (3H, s, CH_3), 2.71 (3H, s, N-CH_3), 4.68 (1H, s, O*H*), 5.68 (1H, m, *J* = 10.2, C=C*H*), 6.49 (1H, m, *J* = 8.0, H_{Ar}), 6.51 (1H, m, *J* = 9.5, H_{Ar}), 6.54 (1H, m, *J* = 8.0, H_{Ar}), 6.57 (1H, m, *J* = 8.0, H_{Ar}), 6.59 (1H, m, *J* = 8.0, H_{Ar}), 6.75 (1H, m, *J* = 10.2, C=C*H*), 7.07 (1H, m, *J* = 7.0, H_{Ar}), 7.18 (1H, m, *J* = 8.0, H_{Ar}); ^{13}C NMR (400 MHz, $CDCl_3$) δc 20.3 (C-*C*H_3), 25.9 (C-*C*H_3) ,29.0 (N-*C*H_3), 51.7 (CH_3-*C*-CH_3), 106.8 (N-C_{spiro}-O), 112.9 (*C*H_{Ar}), 115.6 (2 x *C*H_{Ar}), 116.4 (CH_{Ar}), 119.0 (CH_{Ar}), 119.3 (C_{Ar}), 120.5 (*C*H_{Ar}), 121.5 (*C*H_{Ar}), 127.6 (H*C*=), 129.1 (H*C*=), 136.8 (C_{Ar}), 148.2 (C_{Ar}), 148.6 (C_{Ar}) and 148.7 (C_{Ar}). All the spectral data were in accordance to the literature.[24]

Spiro [2*H*-1-benzopyran-2,2'-(7'-methoxy-1',3',3'-trimethylindoline)] (3e)

IR υ_{max} (KBR)/cm^{-1}: 2833, 1644, 1468, 1240, 922; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 1.17 (3H, s, CH_3), 1.32 (3H, s, CH_3), 2.74 (3H, s, N-CH_3), 3.77 (3H, s, OCH_3), 5.72 (1H, m, *J* = 10.2, C=C*H*), 6.53 (1H, m, *J* = 7.8, H_{Ar}), 6.62 (1H, s, H_{Ar}), 6.66 (1H, s, H_{Ar}), 6.68 (1H, m, *J* = 8.4, H_{Ar}), 6.82 (1H, m, *J* = 10.2, C=C*H*), 6.85 (1H, m, *J* = 7.8, H_{Ar}), 7.09 (1H, m, *J* = 7.2, H_{Ar}), 7.19 (1H, m, *J* = 7.8, H_{Ar}); ^{13}C NMR 150 MHz, $CDCl_3$) δc 20.2 (C-*C*H_3), 25.8 (C-*C*H_3), 28.9 (N-*C*H_3), 51.6 (CH_3-*C*-CH_3), 55.8 (O*C*H_3), 103.8 (C_{Ar}), 106.7 (N-C_{spiro}-O), 111.4 (*C*H_{Ar}), 115.2 (*C*H_{Ar}), 115.5 (*C*H_{Ar}), 119.0 (*C*H_{Ar}), 119.1 (*C*H_{Ar}), 120.3 (*C*H_{Ar}), 121.5 (*C*H_{Ar}), 127.5 (2 x H*C*=), 129.3 (*C*H_{Ar}), 136.6 (C_{Ar}), 148.2 (C_{Ar}), 148.6 (C_{Ar}) and 153.1 (C_{Ar}). All the spectral data were in accordance to the literature.[20]

ACKNOWLEDGEMENTS

The authors thank the School of Chemical Sciences and Food Technology, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, Bangi and Centre for Research and Instrumentation Management UKM for instrumental facilities as well as grants GGPM-2011-054 and FRGS/1/2013/ST01/UKM/03/4 for funding the project.

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