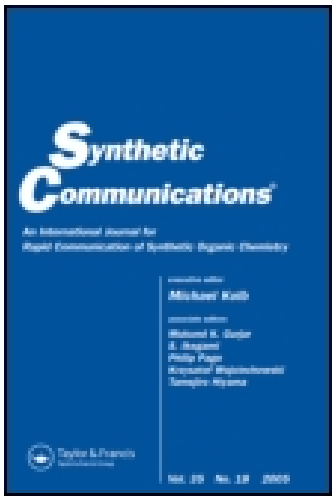

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Microwave-Assisted Solvent-Free Synthesis of the Substituted Spiroindolinonaphth[2,1-b][1,4]oxazines

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ABSTRACT

The synthesis of the substituted spiroindolinonaphth[2,1-b][1,4]oxazines **3a**–**e** is developed through the condensation of 2-methylene-1,3,3-trimethylindoline derivatives and 1-nitroso-2-naphthol under microwave irradiation. In the same conditions, in presence of morpholine the 6′-morpholinosubstituted compounds **4a**, **b**, **d**, **e** are formed. The main

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advantages of the method are the short reaction time, solvent-free reaction condition, cleaner reaction products and the higher product yields in comparison with known methods of synthesis.

Key Words: Microwave irradiation; Spirooxazines; Solvent-free synthesis.

Among many classes of organic photochromic compounds, spirooxazines have been proven to be one of the most useful due to possible practical applications.[1a,b] The aminosubsitution of spirooxazines gives rise to remarkable depth of photoactivated coloration and generally to relatively large hypsochromic color shifts.[2] By now, the widely applied method to synthesize the spironaphthoxazines consists in the condensation of methylenic base with 1-nitroso-2-naphthol.[3] The reaction leads generally to low yields of spiro-compounds even if optimization of experimental conditions allowed to improve them in some case.[4]

The same reaction of the respective 2-methyleneindoline with 4-morpholino-1-nitroso-2-naphthol being formed in situ from the reaction of 1-oximino-naphthoquinone (tautomeric form of 1-nitroso-2-naphthol) with a morpholine, results in the formation of 6′-morpholino spirooxazines (method developed by Rickwood et al.)[5] The general synthetic scope of method is rather limited by low yield for the spiro compound and by the lack of reactivity of the 2-methyleneindolines containing electronegative substituted groups. Otherwise, the advantages of the approach are the simplicity and the possibility to avoid the preliminary synthesis of the 4-amino substituted 1-nitroso-2-naphthols.[2,5]

In the present paper, in order to improve the reaction condensation of 2-methylene-1,3,3-trimethylindoline derivatives **1a**–**e** with 1-nitroso-2-naphthol with (reaction B) or without the presence of morpholine (reaction A), the effect of microwave irradiations has been studied (Sch. 1). It is known, that reactions promoted by microwave irradiation have received considerable attention because of their high efficiency, convenient work-up conditions. Several reactions of synthetic importance such as alkylation, condensation, oxidation etc., have been satisfactorily done under microwave irradiation.[6a–f]

In a typical reaction, the equimolar mixture of 1-nitrosonaphthol **2** with indoline derivatives **1a**–**e** was irradiated in a microwave oven Synthewave 402®[6f] for 15 min to produce **3a**–**e**. In the same reaction in presence of morpholine the compounds **4a**, **b**, **d**, **e** were formed. The temperature of the reactions, yields of the products are summarized in Table 1. The bases **1d**, **e** were generated in situ from corresponding salts by addition of Et_3N. It was

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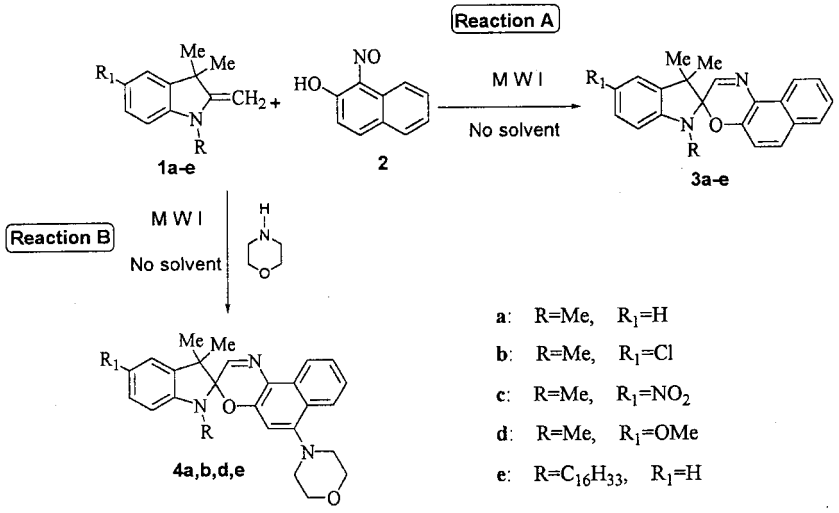

Scheme 1.

observed that **3a** forms with practically the same yields from **1a** or hydroperchlorate of **1a** in presence of Et_3N (Table 1). The spirooxazine **3a**–**e** yields obtained according to the known method (heating in EtOH)[7] are given in Table 1 for comparison. For compounds **4a**, **b**, **d**, **e** the yields obtained by method developed by M. Rickwood et al.[5] are also indicated.

Regarding the data presented in Table 1, it can be concluded that the yields obtained by new reaction A are always higher than those in classic heating, and moreover, the compounds formed are much clean. It is important to note that the studied method can be applied to a large set of substitutions.

The results obtained in the case of the reaction B demonstrated the success in carrying out the one-pot synthesis of 6′-morpholino substituted spironaphthoxazines with mild yields. The method failed only in case of compound **1c**, containing the strong acceptor nitro group. In contrast, in comparison with reaction developed by M. Rickwood et al. the improved yield is observed in all cases.

Thus, a simple method using a dry media and short time of reaction has been described to synthesize substituted spironaphthoxazines. The obtained compounds were cleaner and formed with higher yields compared to the usual methods of condensation.

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Table 1. The conditions of the reactions A, B and the yields of the compounds **3a–e**, **4a**, **b**, **d**, **e**.

	Reaction A				Reaction B			
Indoline derivatives	Temperature, °C under M W I	Product	Yields (in %)	Classic heating, yield (%), (ref)	Temperature, °C under M W I	Product	Yields (%)	Rickwood method, yield (%), (ref)
1a	110	**3a**	67	53[6]	90	**4a**	27	15[5]
1a[a]	65	**3a**	58	51[7,8]	65	**4a**	19	—
1b	65	**3b**	50	31[7]	65	**4b**	34	14[c]
1c	110	**3c**	27	10[7]	110	**4c**	0	0
1d[a]	65	**3d**	64	40[7]	65	**4d**	25	12[c]
1e[a]	65	**3e**	37	32[b]	65	**4e**	32	15[c]

[a]The methylenic bases were generated in situ from corresponding salts by addition of Et_3N.
[b]Compound was prepared by known procedure.[7]
[c]Compounds were prepared by known procedure.[5]

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EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker BM 250 P spectrometer (250 MHz). Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. $CDCl_3$ was used as solvent for all probes.

Thin-layer chromatography (TLC) were performed on 0.2-mm precoated plates of Silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm). For preparative column chromatography was used silica gel 60 Merck with 0.043–0.060 mm particles.

Reactions under microwave irradiation were performed in a Prolabo Synthewave 402® (2.45 GHz) monomode microwave reactor, the reaction temperature was monitored at the values given in Table 1 by means of an IR-captor.[6f] All solvents and reagents were purchased from Acros Organics and Aldrich Chimie and used without further purification.

Reaction A. A mixture of 1 mmol of indoline compound (**1a**–**e**) and 1 mmol of 1-nitroso-2-naphthol in a vessel (Ø = 1 cm) was heated for 3 min to reach the reaction temperature in the microwave oven. Reaction temperature was indicated in Table 1. If the bases were generated in situ from corresponding salts 1.5 equivalent of Et_3N are added per acid equivalent. The vessel was irradiated at the reaction temperature for 12 min under continuous stirring. After the reaction, the product was purified by column chromatography on silica gel (pentane-diethyl ether mixtures from 100 : 1 to 1 : 1 were used as eluents). The yields of the prepared compounds **3a**–**e** are indicated in Table 1.

1,3,3-Trimethylspiro[indolino-2,3′-[3H]naphth[2,1-b]oxazine] (3a). m.p. 125°C, lit.[3] 125–127°C.

5-Chloro-1,3,3-trimethylspiro[indolino-2,3′-[3H]naphth[2,1-b]oxazine] (3b). m.p.174–176°C, lit.[4] 177–178°C.

5-Nitro-1,3,3-trimethylspiro[indolino-2,3′-[3H]naphth[2,1-b]oxazine] (3c). m.p. 225°C, lit.[7] 225°C.

5-Methoxy-1,3,3-trimethylspiro[indolino-2,3′-[3H]naphth[2,1-b]oxazine] (3d). m.p. 128–131°C, lit.[4] 130–132°C.

3,3-Dimethyl-1-hexadecylspiro[indolino-2,3′-[3H]naphth[2,1-b]oxazine] (3e). m.p. 56–57°C. ^{1}H NMR (δ, ppm, J, Hz) 0.88 (t, 3H, $J = 7.5$, CH_3), 1.22 (m, 26H, $13CH_2$), 1.33 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.65 (m, 2H, CH_2), 3,17 (s, 2H, N–CH_2), 6.59 (d, 1H, $J = 7.7$, H-7), 6.87 (dd, 1H, $J = 7.4$ and 7.3, H-5), 6.99 (d, 1H, $J = 8.8$, H-5′), 7.08 (d, 1H, $J = 7.1$, H-4), 7.20 (ddd, 1H, $J = 7.6$, 7.4 and 1.2, H-6), 7.39 (ddd, 1H, $J = 7.6$, 7.5 and 1.2, H-8′), 7.57 (ddd, 1H, $J = 7.5$, 7.5 and 1.2, H-9′), 7.66 (d, 1H, $J = 8.8$, H-6′), 7.73 (s, 1H, H-2′), 7.74 (d, 1H, $J = 8.4$, H-7′), 8.54 (d, 1H, $J = 8.4$, H-10′). Anal. Calcd for $C_{37}H_{50}N_2O$: C, 82.48; H, 9.35; N, 5.20. Found: C, 82.63; H, 9.91; N, 5.05.

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Reaction B. A mixture of 1 mmol of indoline compound **1a**–**e**, 1 mmol of 1-nitroso-2-napthol and 1 mmol of morpholine in a vessel ($\varnothing = 1$ cm) was heated for 3 min to the reaction temperature in the microwave oven. Reaction temperature was indicated in Table 1. If the bases were generated in situ from corresponding salts 1.5 equivalent of Et_3N are added per acid equivalent. The vessel was irradiated at the reaction temperature for 12 min under continuous stirring. After the reaction, the product was purified by column chromatography on silica gel, pentane-diethyl ether mixtures from 100 : 1 to 1 : 1 were used as eluents. The yields of the prepared compounds **4a**, **b**, **d**, **e** are indicated in Table 1.

6′-Morpholino-1,3,3-trimethylspiro[indolino-2,3′-[3H]naphth[2,1-b] oxazine] (4a). m.p. 198–200°C, lit.[5] 196°C.

5-Chloro-6′-morpholino-1,3,3-trimethylspiro[indolino-2,3′-[3H] naphth[2,1-b]oxazine] (4b). m.p. 205–207°C, lit.[2] 196°C. ^{1}H NMR (δ, ppm, J, Hz) 1.34 (s, 6H, $C(CH_3)_2$), 2.73 (s, 3H, N–CH_3), 3.08 (m, 4H, $N(CH_2)_2$), 3.95 (m, 4H, $O(CH_2)_2$), 6.48 (d, 1H, $J = 8.2$, H-7), 6.60 (s, 1H, H-5′), 7.04 (d, 1H, $J = 2.0$, H-4), 7.16 (dd, 1H, $J = 8.2$ and 2.2, H-6), 7.39 (ddd, 1H, $J = 8.2$, 8.2 and 1.2, H-8′), 7.57 (ddd, 1H, $J = 8.2$, 8.2 and 1.2, H-9′), 7.62 (s, 1H, H-2′), 8.05 (d, 1H, $J = 8.1$, H-7′), 8.55 (d, 1H, $J = 8.4$, H-10′). Anal. Calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.63; H, 5.91; N, 9.35.

5-Methoxy-6′-morpholino-1,3,3-trimethylspiro[indolino-2,3′-[3H] naphth[2,1-b]oxazine] (4d). m.p 170–172°C, lit.[2] 172–173°C. ^{1}H NMR (δ, ppm, J, Hz) 1.35 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 2.70 (s, 3H, N–CH_3), 3.06 (m, 4H, $N(CH_2)_2$), 3.80 (s, 3H, OCH_3), 3.94 (m, 4H, $O(CH_2)_2$), 6.48 (d, 1H, $J = 8.7$, H-7), 6.63 (s, 1H, H-5′), 6.74 (m, 2H, H-4, H-6), 7.38 (dd, 1H, $J = 7.2$ and 7.8, H-8′), 7.57 (dd, 1H, $J = 7.6$ and 7.3, H-9′), 7.64 (s, 1H, H-2′), 8.05 (d, 1H, $J = 8.3$, H-7′), 8.55 (d, 1H, $J = 8.6$, H-10′). Anal. Calcd for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 73.01; H, 6.68; N, 9.39.

3,3-Dimethyl-1-hexadecyl-6′-morpholinospiro[indolino-2,3′-[3H] naphth[2,1-b]oxazine] (4e). violet oil. ^{1}H NMR (δ, ppm, J, Hz) 0.88 (t, 3H, $J = 6.5$, CH_3), 1.23 (m, 26H, $13CH_2$), 1.34 (s, 6H, $C(CH_3)_2$), 1.63 (m, 2H, CH_2), 3.07 (m, 4H, $N(CH_2)_2$), 3.14 (t, 2H, $J = 7.5$, N–CH_2), 3.95 (m, 4H, $O(CH_2)_2$), 6.59 (m, 2H, H-5′ and H-7), 6.87 (dd, 1H, $J = 7.3$ and 7.4, H-5), 7.08 (d, 1H, $J = 7.1$, H-4), 7.19 (dd, 1H, $J = 7.6$ and 7.6, H-6), 7.38 (ddd, 1H, $J = 8.2$, 8.2 and 1.3, H-8′), 7.55 (ddd, 1H, $J = 8.4$, 8.1 and 1.3, H-9′), 7.65 (s, 1H, H-2′), 8.04 (d, 1H, $J = 8.1$, H-7′), 8.54 (d, 1H, $J = 8.4$, H-10′). Anal. Calcd for $C_{41}H_{57}N_3O_2$: C, 78.93; H, 9.21; N, 6.73. Found: C, 78.84; H, 9.30; N, 6.69.

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