Microwave-assisted synthesis of quinolones and 4*H*-1,4-benzothiazine 1,1-dioxides

Jaime Charris*, Arthur Barazarte, José Domínguez and Neira Gamboa

Laboratorio de Síntesis Orgánica, Facultad de Farmacia, Universidad Central de Venezuela, Aptdo. 47206, Los Chaguaramos, 1041-A Caracas, Venezuela

A rapid method for the preparation of *N*-aryl-2-methylthio-4-oxo-1,4-dihydroquinoline-3-carbonitriles (**2a–e**) and *N*-aryl-3-methylthio-4*H*-1,4-benzothiazine-2-carbonitrile 1,1-dioxides (**2f–o**) is reported. The cyclization is accelerated by microwave irradiation under solvent free conditions in the presence of K_2CO_3.

Keywords: quinolones, 1,4-benzothiazines, ketene *S*,*N*-acetals

The quinolone and benzothiazine nuclei are often found in biologically active molecules, and a large variety of methods have been employed for their synthesis.[1,2] Generally, these synthetic routes have been carried out in solution. These methods have their merits, but all have drawbacks such as the use of large amounts of volatile and poisonous solvents. Moreover, the reaction times are long and the yields not impressive. In recent years, microwave dielectric heating technology combined with solvent-free conditions have been used in many organic reactions, leading to shorter reaction times, higher yields, cleaner reaction products and environmentally more benign conditions compared with the classical heating.[3, 4]

In connection with our research program directed toward the synthesis of novel quinolone and benzothiazine derivatives with potential antimalarial activity,[5] we describe the synthesis of quinolones **2a–e** and 1,4-benzothiazine dioxides **2f–o** rapidly and efficiently, from 3-(*N*-arylamino)-3-methylthio-2-(*o*-chlorobenzoyl)acrylonitriles (**1a–e**) or 3-(*N*-arylamino)–3-methylthio-2-(*o*-chlorobenzenesulfonyl)acrylonitriles (**1f–o**) that could be easily cyclised under solvent-free conditions using microwave technology.

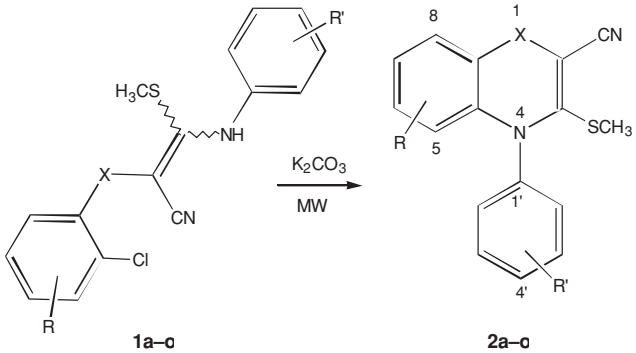
We have first prepared ketene *S*,*N*-acetals **1a–o** by reaction of the *o*-chlorobenzoylacetonitriles or *o*-chlorobenzenesulfonylacetonitriles with aryl isothiocyanates, followed by treatment with methyl iodide and potassium hydroxide in 1,4-dioxan, as previously described.[5,6] The respective ketene *S*,*N*-acetals were mixed with potassium carbonate and irradiated without solvent in a domestic microwave oven to afford compounds **2a–o** (Scheme 1). The results are reported in Table 1. The identities of compounds **2a–j** were established by comparison of their physical and spectroscopic properties with those earlier reported.[5, 6]

In conclusion, from our experimental results it is evident that the solvent-free reaction using microwave heating proceeds with significant decrease in reactions times and comparably high chemical yields. It is thus a rapid and convenient method for the preparation of compounds of type **2a–o**.

Experimental

Melting points were determined with a Fischer-Johns micro hot-stage apparatus. IR spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Jeol Eclipse 270 MHz spectrometer in DMSO-d_6 with tetramethylsilane as internal standard. Elemental analyses were performed by Atlantic Microlab, Norcross, GA, USA. All the products have been previously described except the ^{1}H NMR spectra of **2k–o**.[5,6] A White-Westinghouse microwave oven equipped with a turntable and operating 2450 MHz was used at its full power, 750 W, for all the experiments. An alumina batch (aluminium oxide 60 G neutral, type E, Merck: 50g; batch 4.0 cm diameter) was used as a sink inside the MW oven during irradiation of the reaction mixtures.

* Correspondent. E-mail: charrisj@camelot.rect.ucv.ve



Scheme 1

Table 1 Synthesis of quinolones and 4*H*-1,4-benzothiazine derivatives under microwave irradiation

No.	*R*	X	*R*'	Yield /%	t/min
2a	H	CO	H	92	10
2b	H	CO	*p*-OMe	87	7
2c	H	CO	*m*-OMe	90	11
2d	H	CO	*o*-OMe	83	8
2e	H	CO	*p*-Cl	89	13
2f	7-Cl	SO_2	H	81	7
2g	7-Cl	SO_2	*p*-OMe	90	6
2h	7-Cl	SO_2	*m*-OMe	87	9
2i	7-Cl	SO_2	*o*-OMe	90	8
2j	7-Cl	SO_2	*p*-Cl	79	11
2k	6-Cl	SO_2	H	79	7
2l	6-Cl	SO_2	*p*-OMe	94	8
2m	6-Cl	SO_2	*m*-OMe	90	10
2n	6-Cl	SO_2	*o*-OMe	92	9
2o	6-Cl	SO_2	*p*-Cl	81	12

General procedure for preparation of **2a–o**: **1a–e** or **1f–o** (5 mmol) and potassium carbonate (10 mmol) were mixed thoroughly in an agate mortar. The mixture was then placed in a 5 ml beaker. Then the beaker was placed in the microwave oven and irradiated for the specified time under solvent-free conditions until the mixture became liquid. The time required for each reaction is indicated in Table 1. The reaction mixture was cooled and suspended in water (2 ml). The solid was collected by suction filtration and washed with cold ethanol, then with water. The crude product was recrystallised from ethanol-water to give a pure sample. The physical and spectra data of the compounds **2k–o** are as follows.

6-Chloro-3-methylthio-4-phenyl-1,4-benzothiazine-2-carbonitrile 1,1-dioxide (**2k**): m.p. 202–204 °C. IR (cm^{-1}): 2192 (CN), 1315 (SO_2). ^{1}H NMR δ: 2.68 (s, 3H, SCH_3), 6.61 (d, 1H, H_5, J = 1.8Hz), 7.56 (dd, 1H, H_7, J_1: 1.7, J_2: 8.4Hz), 7.68 (m, 5H, Ar), 8.09 (d, 1H, H_8, J = 8.4Hz). ^{13}C NMR δ: 20.7, 88.0, 112.4, 120.6, 124.2, 126.0, 127.6, 129.8, 131.25, 131.5, 138.3, 138.7, 140.05, 166.1. Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S_2$: C, 52.96; H, 3.06; N, 7.68. Found: C, 52.86; H, 3.07; N, 7.68 %.

6-Chloro-4-(4-methoxyphenyl)-3-methylthio-1,4-benzothiazine-2-carbonitrile 1,1-dioxide (**2l**): M.p. 144–146 °C. IR (cm^{-1}): 2192 (CN), 1309 (SO_2). ^{1}H NMR: δ 2.68 (s, 3H, SCH_3), 3,86 (s, 3H, OCH_3), 6.68 (d, 1H, H_5, J = 1.9Hz), 7.19 (d, 2H, $H_{3',5'}$, J = 8.9Hz), 7.47 (d, 2H, $H_{2',6'}$, J = 8.9Hz), 7.67 (dd, 1H, H_7, J_1 = 1.9, J_2 = : 8.6Hz), 8.07 (d, 1H, H_8, J = 8.6Hz). ^{13}C NMR: δ 20.6, 56.2, 87.5, 112.4, 116.2, 120.7, 124.1, 126.0, 127.5, 131.05, 131.1, 138.3, 140.4, 161.0, 167.0. Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S_2$: C, 51.97; H, 3.33; N, 7.13. Found: C, 51.84; H, 3.28; N, 7.18 %.

6-Chloro-4-(3-methoxyphenyl)-3-methylthio-1,4-benzothiazine-2-carbonitrile 1,1-dioxide (**2m**): M.p. 150–152 °C. IR (cm^{-1}): 2192 (CN), 1306 (SO_2). ^{1}H NMR: δ 2.76 (s, 3H, SCH_3), 3.85 (s, 3H, OCH_3), 6.77 (m, 2H, $H_{5,2'}$), 6.91 (dd, 1H, $H_{6'}$, J_1 = 3.2, J_2 = 7.3Hz), 7.25 (dd, 1H, $H_{4'}$, J_1 = 3.2, J_2 = 7.3Hz), 7.43 (dd, 1H, H_7, J_1 = 1.9, J_2 = 8.6Hz), 7.52 (t, 1H, $H_{5'}$, J = 7.3Hz), 7.97 (d, 1H, H8, J = 8.6Hz). ^{13}C NMR: δ 20.6, 57.0, 87.9, 112.2, 114.95, 117.8, 121.0, 121.7, 124.0, 125.2, 128.1, 132.1, 136.2, 139.65, 140.2, 161.4, 166.4. Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S_2$: C, 51.97; H, 3.33; N, 7.13. Found: C, 51.62; H, 3.34; N, 6.99 %.

6-Chloro-4-(2-methoxyphenyl)-3-methylthio-1,4-benzothiazine-2-carbonitrile 1,1-dioxide (**2n**): M.p. 181–183 °C. IR (cm^{-1}): 2186 (CN), 1317 (SO_2). ^{1}H NMR: δ 2.66 (s, 3H, SCH_3), 3,90 (s, 3H, OCH_3), 6.16 (dd, 1H, $H_{3'}$, J_1 = 3.5, J_2 = 7.9Hz), 6.68 (d, 1H, H_5, J = 1.9Hz), 7.21 (t, 1H, $H_{4'}$, J = 7.9Hz), 7.41 (t, 1H, $H_{5'}$, J = 7.8Hz), 7.50 (dd, 1H, $H_{6'}$, J_1 = 3.2, J_2 = 7.6Hz), 7.67 (dd, 1H, H_7, J_1 = 1.9, J_2 = 8.4Hz), 8.0 (d, 1H, H_8, J = 8.4Hz). ^{13}C NMR: δ 20.8, 56.3, 87.9, 112.4, 115.4, 117.3, 120.6, 121.6, 124.2, 125.8, 127.6, 132.0, 138.4, 139.5, 139.85, 161.2, 166.05. Anal. Calcd. for $C_{17}H_{13}ClN_2O_3S_2$: C, 51.97; H, 3.33; N, 7.13. Found: C, 51.56; H, 3.30; N, 7.05 %.

6-Chloro-4-(4-chlorophenyl)-3-methylthio-1,4-benzothiazine-2-carbonitrile 1,1-dioxide (**2o**): M.p. 236–238 °C. IR (cm^{-1}): 2192 (CN), 1318 (SO_2). ^{1}H NMR: δ 2.68 (s, 3H, SCH_3), 6.72 (d, 1H, H_5, J = 1.8Hz), 7.61 (d, 1H, $H_{3',5'}$, J = 8.6Hz), 7.68 (dd, 1H, H_7, J_1 = 1.8, J_2 = 8.4Hz), 7.75 (d, 1H, $H_{2',6'}$, J = 8.6Hz), 8.10 (d, 1H, H_8, J = Hz). ^{13}C NMR: δ 20.7, 88.7, 112.3, 120.6, 124.3, 125.9, 127.7, 131.3, 131.9, 136.1, 137.5, 138.5, 139.9, 165.9. Anal. Calcd. for $C_{16}H_{10}Cl_2N_2O_2S_2$: C, 48.37; H, 2.53; N, 7.05. Found: C, 48.42; H, 2.60; N, 6.92 %.

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