Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8811–8815

Microwave-assisted Friedländer synthesis of quinolines derivatives as potential antiparasitic agents

Gisela C. Muscia, Mariela Bollini, Juan P. Carnevale, Ana M. Bruno and Silvia E. Asís*

Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956 (1113) Buenos Aires, Argentina

Received 31 July 2006; revised 11 October 2006; accepted 12 October 2006

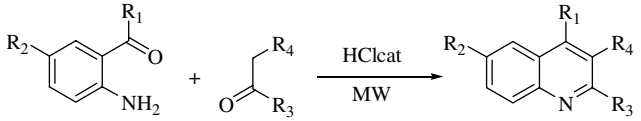
Abstract—A series of substituted quinolines was developed via the Friedländer reaction employing microwave irradiation (MW), in the presence of a catalytic amount of hydrochloric acid. The products were obtained in good yields in 1.5–12 min and were tested in vitro against the parasites causative of malaria, leishmaniasis, sleeping sickness and Chagas' disease (TDR, WHO). Some of these compounds exhibited activity against *Plasmodium falciparum* and others resulted moderately active against *Trypanosoma cruzi*.

Malaria is a major parasitic disease affecting over 100 countries of the tropical and subtropical regions of the world. Around 300–500 million clinical cases of malaria are reported every year of which around 2–3 million die due to complicated cases.[1] *Plasmodium falciparum* is the parasite responsible for most of the malarial deaths. Chloroquine remains a main antimalarial drug but the efficacy of it and other chemotherapeutic agents as mefloquine is being steadily lessened by the spread of resistant parasites. Thus, the development of alternative drugs is a continuing and urgent requirement.[2] In this regard, we have synthesized a series of 3-aminoquinolin-2-one derivatives[3] and they exhibited weak to moderate in vitro activity against *P. falciparum*.[4]

In this work, we report the synthesis under the microwave irradiation of substituted quinolines via the Friedländer reaction. Although it has been known for more than a century, it is still the most useful method for the preparation of such class of compounds. *ortho*-Acylanilines condense with a ketone or an aldehyde (which must contain an α-methylene group) by base or acid catalysis to yield quinolines. In many cases acid catalyzed Friedländer condensations have been found to be more effective than those by bases, especially one of the reactants being 2-aminoarylketone.[5]

Recently, much attention has focused on microwave-assisted organic synthesis (MAOS) in the absence of a solvent. Often, thermal demanding reactions take hours in solution. However, with microwave irradiation these same reactions may be completed in minutes.[6] Sabitha et al. reported the preparation of polycyclic quinoline derivatives in good yields under dry conditions using microwave irradiation (MW) and the reagents were adsorbed on Montmorillonite KSF clay.[5] Furthermore, the Friedländer coupling condensation products between 2-aminoacetophenone or benzophenone and substituted acetophenones were obtained under MW irradiation in the presence of 0.1–0.5 equiv of diphenylphosphate (DPP) as an acid catalyst.[7]

Herein, the preparation of a series of nine quinoline derivatives (**3a–j**) in good yields by the reaction of 2-aminoacetophenone or benzophenones (**1**) with a variety of ketones and keto esters (**2**) and a catalytic amount of concentrated hydrochloric acid is described (Scheme 1). The synthesis were carried out in a MW domestic oven



1 **2** **3a-j**

1a $R_1 = CH_3$, $R_2 = H$
1b $R_1 = Ph$, $R_2 = NO_2$
1c $R_1 = Ph$, $R_2 = Cl$

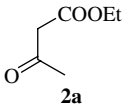
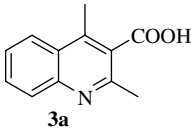
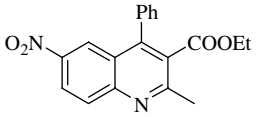
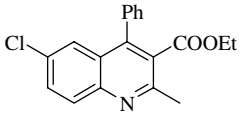
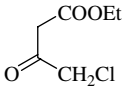
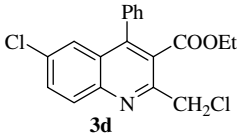
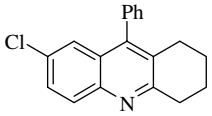
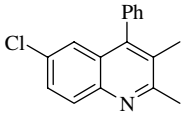
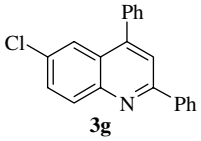
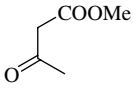
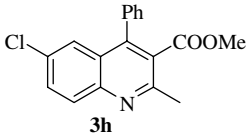
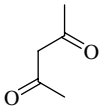
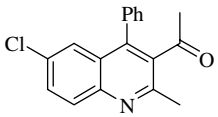
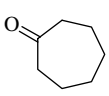
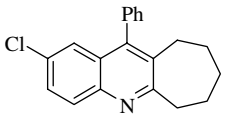
Scheme 1.

Keywords: Microwave; Friedländer quinolines; Antiparasitic activity.
* Corresponding author. Tel.: +54 11 49648251; fax: +54 11 4508 3645; e-mail: elizabet@ffyb.uba.ar

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.073

adapted for the use of a reflux condenser, at constant power (400 W). All the reactions proceed to completion between 1.5 and 12 min (Table 1) and a longer time did not increase the yield.[8,9]

Table 1. Reaction times, yields and melting points of compounds **3a–j**

Entry	Substrate **1**	Substrate **2**	Product **3**	Time (min)	Yield (%)[a]	Mp (Lit) (°C)
1	**1a**	 **2a**	 **3a**	6	60	270–272
2	**1b**	**2a**	 **3b**	6	68	139–142
3	**1c**	**2a**	 **3c**	6	55	98–100 (108)[10]
4	**1c**		 **3d**	6	50	106–108
5	**1c**		 **3e**	12	52	225–227
6	**1c**		 **3f**	12	89	221–223 (127)[10]
7	**1c**		 **3g**	12	50	206–208 (102)[10]
8	**1c**		 **3h**	6	55	132–134
9	**1c**		 **3i**	1.5	64	221–223 (151)[10]
10	**1c**		 **3j**	7	45	193–195 (175)[10]

[a] Yields refer to pure products.

Theoretically, the Friedländer reaction with unsymmetrical ketones such as ethyl methyl ketone can have two possible modes of cyclization giving rise to two regioisomers. In the Brønsted acid catalyzed reaction, 2,3-dimethylquinoline was reported to be the major product, whereas under basic conditions, 2-ethylquinoline was the major product.[10] In our case, the same tendency was observed (entry 6).

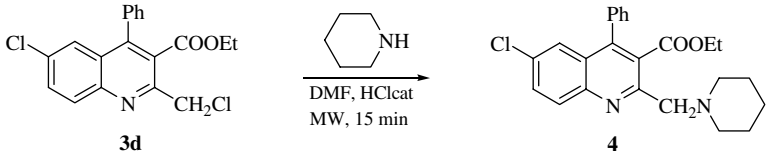
Compounds **3c**, **3e**, **3f**, **3g**, **3i** and **3j** were reported in 2003 but their synthesis was ionic liquid-promoted and carried out with prolonged heating at 100 °C.[10] However, although the spectroscopical data of our products agree this previous work, their melting points are quite different (Table 1).

Very recently, the synthesis of analogous quinoline compounds prepared by the same reaction type and catalyst but utilizing water as the solvent was published. Although this reaction medium has a number of advantages, the reaction temperature was 90 °C and the times were extended to 6 h.[11] In addition, polysubstituted quinolines were prepared at room temperature in the presence of a catalytic amount of yttrium triflate, thus compound **3i** was also obtained by this last method in 6 h.[12]

Pyperidil derivative **4** was prepared in a good yield from compound **3d** employing MW (Scheme 2). It was achieved in only 15 min instead of the 3 h with conventional heating.[13]

Eight of the synthesized products were selected for a primary in vitro screening at Tropical Disease Research (TDR) Program, World Health Organization (WHO, Switzerland). Compounds **3a**, **3c**, **3e**, **3f–i** and **4** were tested in vitro against *P. falciparum*, *Leishmania donovani*, *Leishmania infantum*, *Trypanosoma cruzi* and *T. b. rhodesiense*, causative agents of malaria, leishmaniasis, Chagas' disease and sleeping sickness, respectively, and cytotoxicity was tested on the cell line L6. The activity data are given as micromolar concentration that produces 50% inhibition (IC_{50}) in the assays used and are shown in Tables 2[14] and 3.[15] Compounds **3c** and **4** presented activity against *P. falciparum*, and compounds **3h** and **3i** exhibited moderate activity against *L. infantum*. On the other hand, pyperidil derivative **4** was almost as active for Chagas' disease as the reference drug benznidazole and it was selected for a secondary in vivo screening.[14,16] In addition, compounds **3c**, **3f** and **3g** also resulted moderately active against *T. cruzi*. The remaining compounds lacked of antimalarial activity, taking in account their IC_{50} values were quite close to the upper limit.

In conclusion, microwave-assisted solvent-free reactions were employed to synthesize quinoline derivatives. This method has a short reaction time and is an economical procedure to enlarge this family of compounds. Regarding the biological evaluation, these molecules are useful for further optimization of the antimalarial and antichagasic activities, specially compound **4** owing to its remarkable performance.



Scheme 2.

Table 2. Antiprotozoal activity of compounds **3a**, **3c**, **3f**, **3g** and **4** (IC_{50} values are given in μg/mL)[a]

Compound	*P. falciparum*	*L. donovani*	*T. cruzi*	*T.b. rhodesiense*	Cytotoxicity L6 cell line
	Chloroquine 0.04	Miltefosine 0.2	Benznidazole 0.25	Melarsoprol 0.005	Podophyllotoxin 0.007
3a	>5	>30	>30	40.5	>90
3c	4.47	13.2	13.6	13.6	49.8
3f	>5	12.89	10.44	12.7	39.5
3g	>5	13.38	8.42	22.4	>90
4	2.56	12.19	0.98	11.4	24.1

[a] IC_{50} = 50% growth inhibition.

Table 3. Antiprotozoal activity of compounds **3e**, **3h** and **3i** (IC_{50} values are given in μg/mL)[a]

Compound	*P. falciparum*	*L. infantum*	*T. cruzi*	*T. b. rhodesiense*	Cytotoxicity L6 cell line
	Chloroquine 0.026	Pentostam 2.4	Benznidazole	Suramin 0.13	Tamoxifen 4.9
3e	>18.8	>18.8	nt[b]	>18.8	>18.8
3h	>20	3.4	nt	>20	>20
3i	>18.9	11.8	nt	>18.9	>19

[a] IC_{50} = 50% growth inhibition.
[b] nt: not tested.

Melting points were determined in a capillary Electrothermal 9100 SERIES-Digital apparatus and are given uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at rt using a Bruker 200 MHz spectrometer with TMS as the internal standard. The chemical shifts (δ) are given in ppm. Infrared spectra were recorded on a FT Perkin Elmer Spectrum One from KBr discs. Analytical TLC were performed on DC-Alufolien Kiesegel 60 F_{254} Merck. Microwave-assisted reactions were carried out in a household MW oven BGH-QUICK Chef 15240. This apparatus was modified for laboratory applications adapting an external Liebig condenser.

Acknowledgement

We wish to thank Dr. Foluke Fakorede, TDR, WHO (Switzerland). We are grateful for the financial support from Universidad de Buenos Aires (UBACyT B-020).

References and notes

1. *WHO Drug Inf. Bull.* **1999**, *13*, 9.
2. Ayad, F.; Tilley, L.; Deady, L. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2075.
3. Asís, S. E.; Bruno, A. M.; Dominici, D.; Bollini, M.; Gaozza, C. H. *J. Heterocycl. Chem.* **2003**, *40*, 107.
4. Muscia, G. C.; Bollini, M.; Bruno, A. M.; Asís, S. E. *J. Chil. Chem. Soc.* **2006**, *51*, 859.
5. Sabitha, G.; Babu, R. S.; Subba Reddy, B. V.; Yadav, J. S. *Synth. Commun.* **1999**, *29*, 4403.
6. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
7. Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. *Tetrahedron Lett.* **2003**, *44*, 255.
8. *Typical procedure for compounds* **3a–j**: A mixture of **1a–c** (2.16 mmol) and α-methyleneketone **2** (10.90 mmol) with 0.15 mL concd HCl in a 50 mL round-bottomed flask was subjected to microwave irradiation. After completion of the reaction (TLC), the reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with satd soln $NaHCO_3$ (10 mL) and brine (10 mL). This was then dried (Na_2SO_4) and concentrated under reduced pressure to give a solid product which was triturated with EtOH.
9. Spectra data for products: *2,4-dimethylquinoline 3-carboxylic acid* (entry 1, **3a**): ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 3H), 2.44 (s, 3H), 7.21–7.83 (m, 4H), 11.99 (s, 1H). IR (cm^{-1}): ν 3468, 2930, 2848, 1692, 1655, 1432, 749. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.42; H, 5.77; N, 6.60. *Ethyl 2-methyl-6-nitro-4-phenylquinoline-3-carboxylate* (entry 2, **3b**): ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 2.73 (s, 3H), 4.05–4.09 (q, 2H), 7.40–8.52 (m, 8H). IR (cm^{-1}): ν 3089, 2981, 1728, 1620, 1526, 1339, 1224, 1065, 707. Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.79; H, 4.91; N, 8.21. *Ethyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate* (entry 3, **3c**): ^{1}H NMR (DMSO-d_6): δ 0.88 (t, 3H), 2.68 (s, 3H), 3.99–4.10 (q, 2H), 7.35–8.10 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 13.31, 23.21, 61.14, 124.41, 125.21, 127.66, 128.47, 128.89, 128.99, 130.84, 130.97, 131.33, 134.13, 144.67, 145.46, 154.53, 167.06. IR (cm^{-1}): ν 3035, 2928, 1722, 1221, 1069, 840, 712. Anal. Calcd for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30. Found: C, 70.28; H, 5.28; N, 4.39. *Ethyl 6-chloro-2-chloromethyl-4-phenylquinoline-3-carboxylate* (entry 4, **3d**): ^{1}H NMR (DMSO-d_6): δ 0.85 (t, 3H), 3.99–4.03 (q, 2H), 5.02 (s, 2H), 7.37–8.21 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 13.15, 45.46, 61.40, 124.70, 126.27, 126.57, 128.53, 128.92, 129.02, 131.36, 131.80, 132.93, 134.10, 145.10, 146.89, 152.96, 166.20. IR (cm^{-1}): ν 2956, 1720, 1471, 1317, 1223, 1069, 835, 703. Anal. Calcd for $C_{19}H_{15}Cl_2NO_2$: C, 63.35; H, 4.20; N, 3.89. Found: C, 63.24; H, 4.38; N, 3.73. *7-Chloro-9-phenyl-1,2,3,4-tetrahydroacridine* (entry 5, **3e**): ^{1}H NMR ($DCCl_3$): δ 1.85 (m, 2H), 2.03 (m, 2H), 2.69 (m, 2H), 3.72 (m, 2H), 7.21–8.98 (m, 8H). IR (cm^{-1}): ν 3019, 2942, 1630, 1580, 1478, 1178, 717. Anal. Calcd for $C_{19}H_{16}ClN$: C, 77.68; H, 5.49; N, 4.77. Found: C, 77.74; H, 5.85; N, 4.99. *6-Chloro-2,3-dimethyl-4-phenylquinoline* (entry 6, **3f**): ^{1}H NMR ($DCCl_3$): δ 2.30 (s, 3H), 3.30 (s, 3H), 7.12–7.80 (m, 7H), 9.00 (d, 1H). IR (cm^{-1}): ν 3083, 1641, 1482, 1375, 1024, 702. Anal. Calcd for $C_{17}H_{14}ClN$: C, 76.26; H, 5.27; N, 5.23. Found: C, 76.01; H, 5.37; N, 5.34. *6-Chloro-2,4-diphenylquinoline* (entry 7, **3g**): ^{1}H NMR ($DCCl_3$): δ 7.69–8.40 (m, 13H), 9.77 (d, 1H). IR (cm^{-1}): ν 3053, 1611, 1162, 754, 705. Anal. Calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44. Found: C, 79.70; H, 4.49; N, 4.72. *Methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate* (entry 8, **3h**): ^{1}H NMR ($DCCl_3$): δ 2.76 (s, 3H), 3.58 (s, 3H), 7.32–8.04 (m, 8H). IR (cm^{-1}): ν 3067, 2911, 1736, 1585, 1480, 1448, 1210, 828, 710. Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49. Found: C, 69.68; H, 4.86; N, 4.41. *3-Acetyl-6-chloro-2-methyl-4-phenylquinoline* (entry 9, **3i**): ^{1}H NMR ($DCCl_3$): δ 1.98 (s, 3H), 3.12 (s, 3H), 7.62–7.96 (m, 7H), 9.09 (d, 1H). IR (cm^{-1}): ν 3035, 1704, 1480, 1385, 840, 711. Anal. Calcd for $C_{18}H_{14}ClNO$: C, 73.10; H, 4.77; N, 4.74. Found: C, 73.31; H, 5.04; N, 4.93. *2-Chloro-11-phenyl-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline* (entry 10, **3j**): ^{1}H NMR ($DCCl_3$): δ 1.5–1.7 (m, 2H), 1.75–1.95 (m, 4H), 2.65–2.75 (m, 2H), 3.2–3.4 (m, 2H), 7.19–7.25 (m, 3H), 7.51–7.56 (m, 3H), 7.99 (d, 1H). IR (cm^{-1}): ν 2955, 2889, 1489, 831, 707. Anal. Calcd for $C_{20}H_{18}ClN$: C, 78.04; H, 5.89; N, 4.55. Found: C, 78.20; H, 6.06; N, 4.83.
10. Palimkar, S. S.; Siddiqui, S. A.; Rajgopal, T. D.; Lahoti, J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371.
11. Wang, G.; Jia, C.; Dong, Y. *Tetrahedron Lett.* **2006**, *47*, 1059.
12. De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1647.
13. *Typical procedure for compound* **4**: A mixture of **3d** (0.40 g, 1.10 mmol), pyperidine (0.11 mL, 1.10 mmol) and K_2CO_3 (0.15 g, 1.10 mmol) with 0.15 mL concd HCl and 0.3 mL DMF in a 50 mL round-bottomed flask was subjected to microwave irradiation for 15 min. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with water, 5% HCl (10 mL) and brine (10 mL). This was then dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow solid product. This was triturated in benzene to give a white solid powder (mp 211–213 °C, yield 70%). The same reaction was carried out with conventional heating for 3 h in AcOH as the solvent and the yield was 50%. *Ethyl 6-chloro-4-phenyl-2-(pyperidil)methylquinolin-3-carboxylate* ^{1}H NMR (DMSO-d_6): δ 0.81 (t, 3H), 1.74–1.87 (m, 6H), 3.19–3.22 (m, 2H), 3.63–3.69 (m, 2H), 4.02–4.05 (q, 2H), 4.76 (s, 2H), 7.37–8.30 (m, 8H). IR (cm^{-1}): ν 2941, 1722, 1562, 1480, 1222, 1081, 833, 680. Anal. Calcd for $C_{24}H_{25}ClN_2O_2$: C, 70.49; H, 6.16; N, 6.85. Found: C, 70.40; H, 6.50; N, 7.14.
14. The in vitro protocols and activity criteria can be found at WHO website (www.who.int/tdr/grants/workplans/pdf). For antimalarial activity (K1 strain is used), if the IC_{50} is >5 μg/mL, the compound is classified as inactive. If the IC_{50} is 0.5–5 μg/mL, the compound is classified as moderately active. If the IC_{50} is <0.5 μg/mL, the compound is classified as active and is further evaluated using

two strains, K1 and NF54. For Chagas disease, if the IC_{50} is >30 μg/mL, the compound is classified as inactive. If the IC_{50} is between 2 and 30 μg/mL, the compound is classified as moderately active. If the IC_{50} is <2 μg/mL, the compound is classified as active and is further evaluated in an in vivo screen.

15. Antwerp University, LMPH, standard procedures used for the TDR in vitro screening. For antimalarial activity GHA strain is used and for antileishmanial activity MHOM/MA(BE)/67 strain is used. The compound is classified as inactive when the IC_{50} is higher than 16 μg/mL. When IC_{50} lies between 16 and 1 μg/mL, the compound is regarded as being moderately active. When the IC_{50} is lower than 1 μg/mL, the compound is classified as active and is evaluated in a secondary screening.
16. Compound **4** was active at 50 mg/kg per ip route in a Chagas model (preliminary in vivo assay, WHO), under evaluation.