J. Braz. Chem. Soc., Vol. 19, No. 7, 1264-1269, 2008.
Printed in Brazil - ©2008 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Microwave-Promoted Synthesis of Novel *N*-Arylanthranilic Acids

Mauro A. Bueno, Larissa R. S. P. Silva and Arlene G. Corrêa*

Departamento de Química, Universidade Federal de São Carlos, 13565-905 São Carlos-SP, Brazil

Nesse trabalho é relatada a síntese de uma série de ácidos *N*-aril antranílicos inéditos, com bons a excelentes rendimentos, empregando irradiação de microondas como fonte de aquecimento para promover a reação de acoplamento de Ullmann entre ácidos antranílicos e brometos de arila contendo grupos substituintes doadores ou aceptores de elétrons.

In this paper we report the synthesis of a series of novel *N*-aryl anthranilic acids, with good to excellent yields, employing microwaves as heat source to promote the Ullmann coupling between anthranilic acids and aryl bromides possessing electron donating or withdrawing groups.

Keywords: *N*-aryl anthranilic acids, microwaves, Ullmann coupling, green chemistry

Introduction

N-Aryl anthranilic acids are an interesting class of compounds which shows antibacterial[1,2] and anti-inflammatory[3] properties. It is also employed as precursor of biologically important compounds such as acridine[4-6] and acridone alkaloids.[7-14] The synthesis of *N*-aryl anthranilic acids can be usually achieved by the Ullmann condensation[15] between a 2-halobenzoic acid and an aryl amine[16,17] or an anthranilic acid and an aryl halide.[18,19] One of the major drawback of these methodologies is the need of heating during long reaction time.[20]

One of the twelve principles of Green Chemistry is that energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized.[21] The use of unconventional energy sources, as for example ultrasound or microwave (MW) irradiation, may greatly reduce energy consumption. Methods for carried out Ullmann reaction under ultrasonic irradiation have been reported.[22,23]

The use of microwaves in organic synthesis has grown in recent years and among its advantages, when compared to the reactions carried out in conventional heating, are the reduction of reaction times and, in many cases, a significant increase in yields of desired products.[24-27] There are few reports in literature describing the Ullmann coupling employing microwave heating using water as solvent[28,29] and solvent-free conditions.[30]

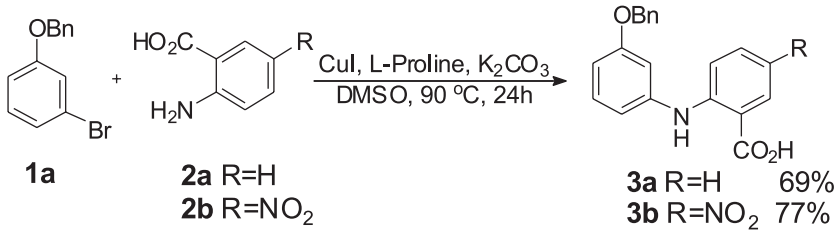
*e-mail: agcorrea@power.ufscar.br

In this paper we report the synthesis of a series of novel *N*-aryl anthranilic acids, with good to excellent yields, employing microwaves as heat source to promote the Ullmann coupling between anthranilic acids and aryl bromides possessing electron donating or withdrawing groups.

Results and Discussion

In an ongoing program on the synthesis of acridone alkaloids, we firstly investigated the Ullmann reaction of 1-benzyloxy-3-bromobenzene (**1a**) and an anthranilic acid (**2**). After a series of experiments employing several literature available procedures,[31-34] we observed that this reaction was best performed using the methodology described by Ma and co-workers[20] (Scheme 1), employing 20 mol% of Cu and L-proline, DMSO as solvent at 90 °C for 24 h.

Our attempts to obtain the desired compounds under analogous conditions in a focused microwave oven (CEM-Discover®) were unsuccessful (Table 1, entry 1). The reason for this lack of reactivity may be due to the high dielectric loss of dimethylsulfoxide which makes the microwave effect less pronounced.[26,35] Then, we performed the reaction between compound **1a** and **2a** with the same catalytic system but using *iso*-amyl alcohol as solvent and after one hour the desired compound was isolated in 78% yield (entry 2). However, reaction between aryl halide **1a** and anthranilic acid **2b** in analogous conditions furnished no product. The low solubility of **2b** in *iso*-amyl alcohol



Scheme 1. Synthesis of *N*-arylanthranilic acids.

seemed to be responsible for the unsatisfactory result, thus we performed the reaction of **1a** and **2b** in anhydrous DMF and compound **3b** was obtained in 59% yield. The yield of **3b** was improved to 82% by the use of DMF containing 10% of water (entries 6-8).

Water effect was also observed in the reaction of anthranilic acid **2b** with *p*-bromoanisol (**1b**). In anhydrous DMF, compound **3c** was obtained in 39% while it was isolated in 76% when performed in DMF/water (entries 9 and 10). Reaction of **1a** and **2a** in DMF/water resulted in the formation of a complex mixture of by-products; additionally use of *iso*-amyl alcohol/water resulted in the recovery of starting materials (entries 4 and 5). Formation of by-products in DMF/water system may be attributed to the higher reaction temperature. By the other hand, the lack of reactivity in *iso*-amyl alcohol/water system may be due to the lower solubility of the reagents, however this effect is not clear yet since the solvent dramatically affect the Ullmann reaction and inhibition of the cooper catalytic species should also be considered.[36]

After optimization of the Ullmann reaction we performed the coupling of different anthranilic acids and aryl halides possessing electron donating and electron withdrawing groups to evaluate the scope of this protocol (Table 2). Good to excellent isolated yields were obtained in all cases, excepting with difluor-substitute anthranilic acid **2f**, which afforded relatively low yield probably due to its low reactivity once starting material was recovered.

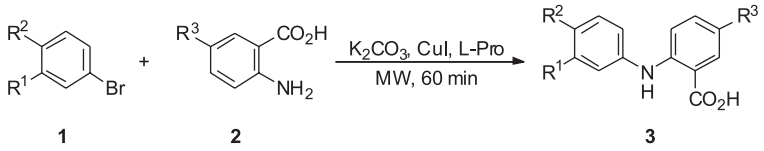
Conclusions

In summary, we have demonstrated that Ullmann coupling reaction between anthranilic acids and aryl bromides employing microwave heating is an advantage method since desired products can be obtained in good yields and shorter reaction time when compared to the conventional heating. Employing this protocol we prepared a series of novel *N*-arylanthranilic acids with good to excellent yields.

Experimental

Unless otherwise noted, all commercially available reagents were purchased from Aldrich Chemical Co. Reagents and solvents were purified when necessary according to the usual procedures described in the literature. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-200 (200 and 50 MHz respectively). The IR spectra refer to films and were measured on a Bomem M102

Table 1. Ullmann coupling employing microwave irradiation

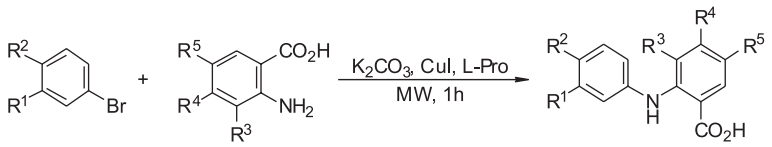


1 2 3

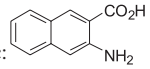
Entry	Aryl bromide	Anthranilic acid	Solvent	Temperature / (°C)	Product, yield / (%)[a]
1	**1a**: R^1=BnO; R^2=H	**2a**: R^3=H	DMSO	90	NR
2	**1a**	**2a**	*iso*-amyl alcohol	140	**3a**: R^1=BnO, R^2=R^3=H (78%)
3	**1a**	**2a**	DMF	160	NR
4	**1a**	**2a**	*iso*-amyl alcohol/H_2O	140	NR
5	**1a**	**2a**	DMF/H_2O	160	NR
6	**1a**	**2b**: R^3=NO_2	*iso*-amyl alcohol	140	NR
7	**1a**	**2b**	DMF	160	**3b**: R^1=BnO; R^2=H; R^3=NO_2 (59%)
8	**1a**	**2b**	DMF/H_2O	160	**3b** (82%)
9	**1b**: R^1=H; R^2=MeO	**2b**	DMF	160	**3c**: R^1=H; R^2=MeO; R^3=NO_2 (39%)
10	**1b**	**2b**	DMF/H_2O	160	**3c** (76%)

[a]Isolated yield after purification.

Table 2. Ullmann reaction of different anthranilic acids and aryl halides[a]



1 **2** **3**

Entry	Aryl bromide	Anthranilic acid	Product, yield / (%)[b]
1	**1c**: R^1=NO_2; R^2=BnO	**2a**: R^3=R^4=R^5=H	**3d**, 83
2	**1d**: R^1=MeO; R^2=BnO	**2a**	**3e**, 85
3	**1e**: R^1=H; R^2=BnO	**2b**: R^3=R^4=H; R^5=NO_2	**3f**, 69
4	**1f**: R^1; R^2=H	**2b**	**3g**, 82
5	**1c**		**3h**, 54
6	**1d**	**2c**:	**3i**, 81
7	**1c**	**2d**: R^3=MeO; R^4=R^5=H	**3j**, 92
8	**1d**	**2d**	**3k**, 70
9	**1c**	**2e**: R^3=R^4=R^5=MeO	**3l**, 83
10	**1d**	**2f**: R^3=H; R^4=R^5=F	**3m**, 38
11	**1c**	**2f**	**3n**, 54

[a]All reactions were performed in anhydrous *iso*-amyl alcohol as solvent at 140 °C, except for anthranilic acid **2b** which was performed in DMF/H_2O 90% at 160 °C. [b]Isolated yield after purification.

spectrometer. Mass Spectra were recorded on a Shimadzu GCMS-QP5000 or Mass Spectrometer QuatroLC-Micromass. Elemental analyses were performed on a Fisons EA 1108 CHNS-O. Analytical thin-layer chromatography was performed on a 0.25 μm film of silica gel containing fluorescent indicator UV_{254} supported on an aluminum sheet (Sigma-Aldrich). Flash column chromatography was performed using silica gel (Kieselgel 60, 230-400 mesh, E. Merck). Gas chromatography was performed in a Shimadzu GC-17A with H_2 as carrier and using a DB-5 column. Melting points were performed in Microquimica MQAPF-301.

General procedure

Aryl bromide (0.84 mmol), anthranilic acid (0.42 mmol), CuI (0.084 mmol), L-proline (0.084 mmol), K_2CO_3 (0.42 mmol) and solvent (1 mL) (Tables 1 and 2) were placed in a glass tube, purged with oxygen-free nitrogen during 10 min sealed and irradiated during 1h in a focused microwave oven (CEM Discover®).

*2-(3-Benzyloxy-phenylamino)-benzoic acid (**3a**)*[37]

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (90:10:0.3) as eluent; white solid; mp 134.8 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.11 (s, 1H), 6.96-6.76 (m, 4H), 7.51-7.24 (m, 8H), 8.10 (dd, J_1 8.1, 1.4 Hz, 1H), 9.35 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 70.0, 109.3, 110.4, 110.6, 114.4, 115.3, 117.3, 127.4 (2C), 127.9, 128.5 (2C), 130.1, 132.5, 135.2, 136.8, 141.6, 148.5, 159.7, 173.8. Anal. Calc. for $C_{20}H_{17}NO_3$: C 75.22; H 5.37; N 4.39. Found: C 75.02; H 5.40; N 5.20.

*2-(3-Benzyloxy-phenylamino)-5-nitrobenzoic acid (**3b**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 194.3 °C (dec.); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.07 (s, 2H), 6.94-6.77 (m, 1H), 7.06 (d, *J* 9.4 Hz, 1H), 7.38-7.21 (m, 7H), 8.06 (dd, *J* 9.4, 2.7 Hz, 1H), 8.93 (d, *J* 2.7 Hz, 1H), 10.42 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 69.8, 76.3, 77.0, 77.6, 110.4, 110.8, 112.1, 112.7, 16.3, 127.1 (2C), 127.8, 128.4 (2C), 128.8, 129.2, 130.2, 136.3, 137.0, 139.5, 152.5, 159.5, 169.3. Anal. Calc. for $C_{20}H_{16}N_2O_5$: C 65.93; H 4.43; N 7.69. Found: C 65.13; H 4.50; N 7.03.

*2-(4-Methoxy-phenylamino)-5-nitrobenzoic acid (**3c**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 230.8 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.77 (s, 3H), 6.84-7.27 (m, 6H), 8.08 (dd, *J* 9.0, 4.0 Hz, 1H), 8.66 (d, *J* 4.0 Hz, 2H), 10.71 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.2, 110.1, 112.7, 114.9 (2C), 126.4 (2C), 128.4, 129.1, 130.6, 136.0, 137.0, 153.4, 157.5, 168.6. Anal. Calc. for $C_{14}H_{12}N_2O_5$: C 58.33; H 4.20; N 9.72. Found: C 58.09; H 4.33; N 9.72.

*2-(4-Benzyloxy-3-nitro-phenylamino)-benzoic acid (**3d**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 197.2 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ

5.28 (s, 2H), 6.80 (t, *J* 8.0 Hz, 1H), 7.09 (d, *J* 8.0 Hz, 1H), 7.63-7.56 (m, 9H), 7.77 (d, *J* 2.0 Hz, 1H), 7.90 (d, *J* 8.0 Hz, 1H), 9.55 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 70.7, 104.7, 112.9, 113.6, 116.8, 117.8, 118.2, 127.3 (2C), 128.0, 128.1, 128.4 (2C), 131.8, 133.8, 134.2, 136.0, 139.9, 146.8, 168.6. Anal. Calc. for $C_{20}H_{16}N_2O_5$: C 65.93; H 4.43; N 7.69. Found: C 66.20; H 4.70; N 8.11.

*2-(4-Benzyloxy-3-methoxy-phenylamino)-benzoic acid (**3e**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; yellowish solid; mp 182.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.76 (s, 3H), 5.05 (s, 2H), 6.65-6.87 (m, 2H), 6.99 (d, *J* 2.0 Hz, 2H), 7.28-7.46 (m, 7H), 7.86 (dd, *J* 8.0, 2.0 Hz, 1H), 9.45 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.7, 70.3, 108.3, 111.4, 113.1, 114.6, 114.8, 116.3, 127.6 (2C), 127.7, 128.2 (2C), 131.6, 133.8, 134.1, 137.2, 144.5, 148.3, 149.9, 169.9. Anal. Calc. for $C_{21}H_{19}NO_4$: C 72.19; H 5.48; N 4.01. Found: C 71.94; H 5.92; N 4.44.

*2-(4-Benzyloxy-phenylamino)-5-nitrobenzoic acid (**3f**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (60:40:0.3) as eluent; yellow solid; mp 202.5 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.12 (s, 2H), 6.92-7.44 (m, 13H), 8.10 (dd, *J* 10.0, 4.0 Hz, 1H), 8.70 (d, *J* 4.0 Hz, 1H), 10.42 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 69.4, 111.2, 112.6, 115.8 (2C), 126.2 (2C), 127.6 (2C), 127.8, 128.3 (2C), 128.4, 138.9, 131.0, 135.9, 136.8, 153.3, 156.4, 168.7. Anal. Calc. for $C_{20}H_{16}N_2O_5$: C 65.93; H 4.43; N 7.69. Found: C 66.22; H 4.75; N 7.94.

*5-Nitro-2-phenylaminobenzoic acid (**3g**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 241.3 °C (dec.); ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.09-7.50 (m, 7H), 8.15 (dd, *J* 8.0, 2.0 Hz, 1H), 8.69 (d, *J* 2.0 Hz, 1H), 10.36 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 110.9, 113.1, 123.9 (2C), 125.7, 128.3, 129.2, 129.7 (2C), 136.5, 138.1, 152.3, 168.5. Anal. Calc. for $C_{13}H_{10}N_2O_4$: C 60.47; H 3.90; N 10.85. Found: C 60.59; H 4.02; N 10.89.

*3-(4-Benzyloxy-3-nitro-phenylamino)-2-naphthoic acid (**3h**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 209.5 °C (dec.); ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.05 (s, 2H), 7.26-7.29 (m, 14H), 8.64 (s, 1H), 9.38 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 70.8, 99.5, 103.5, 108.0, 116.4, 116.9, 117.4, 123.4, 125.7, 126.2, 127.4 (2C), 128.0, 128.4 (2C), 128.8, 133.7, 134.6, 136.1, 136.3, 140.1, 142.2, 146.4, 169.4. Anal. Calc. for $C_{24}H_{18}N_2O_5$:C 69.56; H 4.38; N 6.76. Found: C 69.73; H 4.61; N 6.92.

*3-(4-Benzyloxy-3-methoxy-phenylamino)-2-naphthoic acid (**3i**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 198.9 °C (dec.); ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.80 (s, 3H), 5.09 (s, 2H), 6.85-7.08 (m, 3H), 7.19-7.63 (m, 10H), 7.86 (d, *J* 10.0 Hz, 1H), 8.62 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.8, 70.4, 99.58, 106.7, 107.7, 114.1, 114.8, 115.4, 122.7, 125.5, 125.5, 127.7 (2C), 128.3 (2C), 128.7, 128.9, 133.6, 134.5, 136.6, 137.3, 143.8, 144.1, 150.0, 169.7. Anal. Calc. for $C_{25}H_{21}NO_4$: C 75.17; H 5.30; N 3.51. Found: C 74.90; H 5.15; N 3.73.

*2-(4-Benzyloxy-3-nitro-phenylamino)-3-methoxybenzoic acid (**3j**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (75:25:0.3) as eluent; yellow solid; mp 178.1 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.73 (s, 3H), 5.21 (s, 2H), 6.98-7.50 (m, 12H), 8.69 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.5, 71.0, 111.9, 116.1, 116.3, 122.1, 122.3, 122.5, 122.8, 127.4 (2C), 127.9, 128.4 (2C), 132.4, 136.4, 138.3, 139.5, 144.3, 152.2, 169.0. Anal. Calc. for $C_{21}H_{18}N_2O_5$: C 63.96; H 4.60; N 7.10. Found: C 64.32; H 4.95; N 7.49.

*2-(4-Benzyloxy-3-methoxy-phenylamino)-3-methoxybenzoic acid (**3k**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; yellowish solid; mp 187.6 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.67 (s, 3H), 3.68 (s, 3H), 4.95 (s, 2H), 6.15 (dd, *J* 8.0, 2.0 Hz, 1H), 6.43 (d, *J* 2.0 Hz, 1H), 6.80 (d, *J* 8.0 Hz, 1H), 7.01 (t, *J* 8.0 Hz, 1H), 7.19-7.46 (m, 8H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.4 (2C), 70.8, 103.1, 108.6, 114.8, 116.0, 120.6, 121.0, 122.7, 127.6 (2C), 127.6, 128.2 (2C), 134.5, 137.5, 138.8, 141.8, 149.4, 151.8, 169.4. Anal. Calc. for $C_{22}H_{21}NO_5$: C 69.64; H 5.58; N 3.69. Found: C 69.26; H 6.09; N 3.85.

*2-(4-Benzyloxy-3-nitro-phenylamino)-3,4,5-trimethoxybenzoic acid (**3l**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (70:30:0.3) as eluent; yellow solid; mp 187.7 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.57 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 5.21 (s, 2H), 7.04-7.44 (m, 10H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.9, 59.2, 60.7, 70.9, 109.3, 111.7, 116.5, 117.2, 122.1, 127.3 (2C), 127.9, 128.4 (2C), 131.5, 136.4, 138.9, 139.6, 144.3, 146.5, 146.9,

148.2, 168.3. Anal. Calc. for $C_{23}H_{22}N_2O_8$: C 60.79; H 4.88; N 6.16. Found: C 61.14; H 5.13; N 6.46.

*2-(4-Benzyloxy-3-methoxy-phenylamino)-4,5-difluorobenzoic acid (**3m**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; white solid; mp 192.7 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 3.76 (s, 3H), 5.06 (s, 2H), 6.75-7.05 (m, 5H), 7.29-7.48 (m, 5H), 7.78 (dd, *J* 11.0, 8.0 Hz, 1H), 9.45 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 55.6, 70.2, 101.2 (d, *J* 21.5 Hz), 107.1 (dd, *J* 4.7, 2.5 Hz), 108.7 (d, *J* 0.5 Hz), 114.5, 115.3, 119.5 (d, *J* 17.5 Hz), 127.7 (2C), 127.7, 128.3 (2C), 133.0, 137.1, 140.5 (dd, *J* 234.0, *J* 13.5 Hz), 145.1, 146.7 (dd, *J* 10.0, 1.0 Hz), 150.0, 153.3 (dd, *J* 249.2, 13.5 Hz), 168.3 (dd, *J* 2.2, 0.5 Hz). Anal. Calc. for $C_{21}H_{17}F_2NO_4$: C 65.45; H 4.45; N 3.63. Found: C 65.63; H 5.55; N 3.72.

*2-(4-Benzyloxy-3-nitro-phenylamino)-4,5-difluorobenzoic acid (**3n**)*

Purified by flash chromatography employing hexanes: ethyl acetate:acetic acid (80:20:0.3) as eluent; yellow solid; mp 216.8 °C; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.06 (s, 2H), 6.97 (dd, *J* 14.0, 6.0 Hz, 1H), 7.30-7.59 (m, 8H), 7.76-7.86 (m, 2H), 9.55 (s, 1H). ^{13}C NMR (50 MHz, DMSO-d_6): δ 70.2, 102.1 (d, *J* 20.0 Hz), 108.8 (dd, *J* 4.5, 2.5 Hz), 119.8, 119.1, 119.7 (d, *J* 15.5 Hz), 127.7 (2C), 128.0, 128.4 (2C), 128.7, 133.0, 136.0, 139.9, 141.3 (dd, *J* 235.7, 13.5 Hz), 145.2 (dd, *J* 9.5, 1.0 Hz), 147.4, 153.3 (dd, *J* 262.0, 13.5 Hz), 168.1 (d, *J* 1.5 Hz). Anal. Calc. for $C_{20}H_{14}F_2N_2O_5$: C 60.00; H 3.52; N 9.49; found: C 59.66; H 3.87; N 7.16.

Acknowledgments

We acknowledge FAPESP and CNPq for financial support.

References

1. Thorarensen, A.; Li, J.; Wakefield, B. D.; Romero, D. L.; Marotti, K. R.; Sweeney, M, T.; Zurenko, G. E.; Sarver, R. W.; *Bioorg. Med. Chem. Lett*. **2007**, *17*, 3113.
2. Thorarensen, A.; Wakefield, B. D.; Romero, D. L.; Marotti, K. R.; Sweeney, M. T.; Zurenko, G. E.; Rohrer, D. C.; Han, F.; Bryant, G. L.; *Bioorg. Med. Chem. Lett*. **2007**, *17*, 2823.
3. Bajaj, S.; Sambi, S. S.; Madan, A. K.; *Bioorg. Med. Chem.* **2004**, *12*, 3695.
4. Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemiere, P.; Debreu, M.-A.; Davioud-Charvet, E.; Sergheraert, C.; *J. Med. Chem.* **2000**, *43*, 2646.
5. Demeunynck, M.; Charmantray, F.; Martelli, A.; *Curr. Pharm. Des.* **2001**, *7*, 1703.
6. Brana, M. F.; Cacho, M.; De Pascual-Teresa, B.; Ramos, A.; *Curr. Pharm. Des.* **2001**, *7*, 1745.
7. Boumendjel, A.; Macalou, S.; Ahmed-Belkacem, A.; Blanca, M.; Di Pietro, A.; *Bioorg. Med. Chem.* **2007**, *15*, 2892.
8. Winter, R. W.; Kelly, J. X.; Smilkstein, M. J.; Dodean, R.; Bagby, G. C.; Rathbun, R. K.; Levin, J. I.; Hinrichs, D.; Riscoe, M. K.; *Exp. Parasitol.* **2006**, *114*, 47.
9. Stefaska, B.; Bontemps-Gracz, M. M.; Antonini, I.; Martelli, S.; Arciemiuk, M.; Piwkowska, A.; Rogacka, D.; Borowski, E.; *Bioorg. Med. Chem.* **2005**, *13*, 1969.
10. Kamal, A.; Srinivas, O.; Ramulu, P.; Ramesh, G.; Kumar, P. P.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4107.
11. Mai, H. D. T.; Gaslonde, T.; Michel, S.; Tillequin, F.; Koch, M.; Bongui, J. B.; Elomri, A.; Seguin, E.; Pfeiffer, B.; Renard, P.; Cordonnier, M. H. C.; Laine, W.; Bailly, C.; Berthier, L. K.; Stéphane Léonce, S.; Hickman, J. A.; Pierre, A.; *J. Med. Chem.* **2003**, *46*, 3072.
12. Krishnegowda, G.; Thimmaiah, P.; Hegde, R.; Dass, C.; Houghtonb, P. J.; Thimmaiah, K. N.; *Bioorg. Med. Chem.* **2002**, *10*, 2367.
13. Bongui, J. B.; Elomri, A.; Seguin, E.; Tillequin, F.; Pfeiffer, B.; Renard, P.; Pierré, A.; Atassi G.; *Chem. Pharm. Bull.* **2001**, *49*, 1077.
14. Su, T. S.; Köhler, B.; Chou, T. C.; Moon Woo Chun, M. W.; Watanabet, K. A.; *J. Med. Chem.* **1992**, *35*, 2703.
15. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M.; *Chem. Rev*. **2002**, *102*, 1359.
16. Maradolla, M. B.; Amaravathi, M.; Kumar, V. N.; Mouli, G.V. P. C.; *J. Mol. Catal. A: Chem.* **2007**, *266*, 47.
17. Mei, X.; August, A. T.; Wolf, C.; *J. Org. Chem.* **2006**, *71*, 142.
18. Ozaki, K.; Yamada, Y.; Oine, T.; Ishizuka, T.; Iwasawa, Y.; *J. Med. Chem.* **1985**, *28*, 568.
19. Rewcastle, G. W.; Denny, W. A.; *Synth. Commun.* **1987**, *17*, 309.
20. Zhang, H.; Cai, Q.; Ma, D.; *J. Org. Chem.* **2005**, *70*, 5173.
21. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*. Oxford University Press: New York, 1998.
22. Pellon, R. F.; Docampo, M. L.; Fascio, M. L.; *Synth. Commun.* **2007**, *37*, 1853.
23. Hanoun, J. P.; Galy, J. P.; Tenaglia, A.; *Synth. Commun.* **1995**, *25,* 2443.
24. Hayes, B. L.; *Aldrichim. Acta* **2004**, *37*, 66.
25. Ferguson, J. D.; *Mol. Diversity* **2003**, *7*, 281.
26. Kappe, C. O.; *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
27. Whittaker, A. G.; Mingos, D. M. P.; *J. Chem. Soc., Dalton Trans.* **2002**, *21*, 3967.
28. Martín, A.; Pellón, R. F.; Mesa, M.; Docampo, M. L.; Gómes, V.; *J. Chem. Res.* **2005**, *9*, 561.

29. Baqi, Y; Müller, C. E.; *Org. Lett.* **2007**, *9*, 1271.
30. Pellón, R. F.; Martín, A. Pu. Y. M.; Ku, Y. Y.; Grieme, H. R.; Bhatia, A. V.; *Tetrahedron Lett.* **2006**, *47*, 149.
31. Pu, Y. M.; Ku, Y. Y.; Grieme, H. R.; Bhatia, A. V.; *Tetrahedron Lett.* **2006**, *47*, 149.
32. Deng, W.; Wang; Zhang, C.; Liu, L.; Guo, Q. Q. X.; *Chin. Chem. Lett.* **2006**, *17*, 313
33. Csuk, R.; Barthel, A.; Raschke, C.; *Tetrahedron* **2004**, *60*, 5737.
34. Yamada, Y.; Ozaki, K.; Oine, T.; Ishizuka, T.; Iwasawa, Y.; *J. Med. Chem.* **1985**, *28*, 568.
35. Hayes, B. L.; *Microwave Synthesis-Chemistry at the Speed of Light,* CEM Publishing: USA, 2002.
36. Lindley, J.; *Tetrahedron* **1984**, *40*, 1433.
37. Brailey, D. A.; *US Patent 4510139* **1985**. *(CA 103:71072)*

Received: March 13, 2008
Web Release Date: August 1, 2008

FAPESP helped in meeting the publication costs of this article.