Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 2671–2674

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Microwave Assisted Synthesis of *N*-Arylphthalamic Acids with Hyperlipidemic Activity

Vera L. M. Sena,[a] Rajendra M. Srivastava,[a,*] Shalom P. Oliveira[b] and Vera L. M. Lima[b]

[a]*Departamento de Química Fundamental, Universidade Federal de Pernambuco (UFPE), Av. Luis Freire, S/N, CEP 50.740-540, Recife, PE, Brazil*

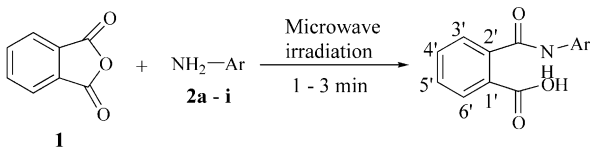
[b]*Departamento de Bioquímica, Universidade Federal de Pernambuco (UFPE), Av. Prof. Moraes Rego, S/N, Cidade Universitária, CEP 50.670-420, Recife, PE, Brazil*

Received 12 March 2001; accepted 19 July 2001

Abstract—A series of substituted *N*-arylphthalamic acids **3a–i** has been synthesized by the reaction of phthalic anhydride **1** and aryl- or heterocyclic amines **2a–i**, in the absence of solvents, in a domestic microwave oven. The formation of nine *N*-arylphthalamic acids was accomplished in 1–3 min giving excellent yields for compounds **3a–g**, but moderate yield of compounds **3h** and **3i**, respectively. Compounds **3h** and **3i** are new. Interestingly, *N*-arylphthalamic acids **3a–i** induced hyperlipidemia in Swiss white mice and also increased animals' body weight.

Phthalamic acids are an interesting class of compounds due to their application and biological activities. For example, some phthalamic acids have negative geotropic effect in germinating roots.[1] The phytotropin, *N*-(1-naphthyl)phthalamic acid, inhibits rooting if applied during the first three days after the cutting is made, but does not affect auxin concentration or metabolism at the rooting site.[2] It has also been shown that intravenous administration of *N*-benzylimidazole phthalamic acid decreases the blood pressure,[3] and other phthalamic acids possess diuretic properties in rats.[4] Phthalamic acids may be obtained by the ring-opening reaction of phthalic anhydride with amines by using conventional heating,[1,5,6] which takes longer time and requires more laboratory work than by using the method described in this study. The use of microwaves has been reported for organic synthesis, in oxidation reactions,[7] aromatic substitutions,[8] *N*-alkylations,[9,10] pericyclic reactions,[11,12] and others,[13–15] but very little work appeared about microwave-mediated synthesis of phthalamic acids. The literature cites two works where the anhydride rings were opened by such radiation. First, a review[16] describes the application of microwave dielectric heating effects to synthetic problems in chemistry. In this report, a small section deals with the reaction of benzophenone tetracarboxylic acid dianhydride (BTDA) with 3,3′-diaminodiphenylsulfone (DDS). Second, the synthesis of phthalimides by microwave irradiation of alkylamines with phthalic anhydride gave excellent yields, but in some cases, the yields were low because of the formation of phthalamic acids,[17] although the major products were phthalimides. In this communication, we report a clean and practical synthesis of amic acids **3a–i** (Scheme 1), without any contamination of phthalimides. Besides this, we found an interesting pharmacological property of these acids **3a–i**, because they cause hyperlipidemia and an increase in animals' body weight.

The reaction for obtaining *N*-arylphthalamic acids is based on the principle that two solid reagents with low



Ar

a: Ph d: *p*-ClPh g: *p*-FPh
b: *o*-ClPh e: *o*-FPh h: *N*-[1H-(1,2,4)Triazol-3-yl)
c: *m*-ClPh f: *m*-FPh i: *N*-[1,2,4]Triazol-4-yl

Scheme 1.

*Corresponding author. Tel.: +55-81-3271-8440; fax: +55-81-3271-8442; e-mail: rms@npd.ufpe.br

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00540-6

Table 1. Reaction time, melting point and yield of compounds **3a–i**[a]

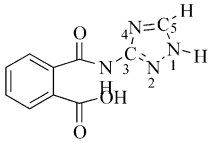
Compd	MW reaction time (min)	Observed mp (°C)	Yield (%)	Conventional reaction time (min)	Phthalimide, correspondent mp (°C)	Lit.
3a[a]	1	206–206.6	99	240	205–207	1
3b[b]	2	135.2–136.1	88	180	140–142	1
3c[b]	2	158–157.8	96	180	163–164	1
3d[b]	2	194–195.6	95	180	194–196	1
3e[b]	2	140–140.4	88	180	184–186	1
3f[b]	2	203–203.3	91	180	200–201	1
3g[b]	2	183–184	94	180	180–182	1
3h[c]	3	305–307	51	—	—	This work
3i[c]	3	269.7–270.4	55	—	—	This work

Solvent of crystallization: a = EtOH; b = CH_3COCH_3; c = MeOH.
[a]The melting points of phthalamic acids cannot be determined correctly because they cyclize on heating. Therefore, all melting points reported are close to their corresponding phthalimides.

melting points or a solid and a liquid reagent are able to melt rapidly, giving a polar liquid that is more prone to microwave absorption. In these conditions, the temperature can be around 135 °C and the reaction can occur when phthalic anhydride dissolves in amines.[17] The acids (**3a–i**) were obtained by mixing an equimolar quantity of phthalic anhydride (1.35 mmol) and an appropriate aromatic amine (**2a–g**) or heterocyclic amine **2h** or **2i** (1.35 mmol). The mixture was heated for 1–3 min in a domestic microwave oven operating at 1350 W and 2450 MHz. Each amic acid was crystallized from an appropriate solvent. The beauty of the reaction is that it does not require any catalyst.

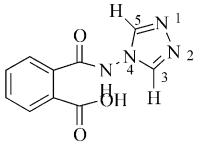
The ring opening occurs simply through the nucleophilic attack of the amine nitrogen atom on carbonyl carbon and the formation of arylphthalamic acids (Scheme 1). This way, nine *N*-arylphthalamic acids (**3a–i**) have been synthesized (Table 1),[1,6] seven of them (**3a–g**) gave excellent yields (88–99%) and two of them (**3h** and **3i**) gave moderate yields (51 and 55%, respectively).[18]

To our knowledge, the last two compounds, namely, **3h** and **3i** (Fig. 1), have not been reported in the literature. All compounds were characterized by their infrared, ^{1}H NMR spectra, and elemental analysis. The infrared spectra of compounds **3a–i** exhibit absorptions between 3326 and 3265 cm^{-1}, which are characteristic of the NH group; two strong absorptions between 1720 and 1679 are due to the stretching frequencies of carbonyl groups. The O–H stretching vibration appeared in the region 3000–2500 cm^{-1}. The ^{1}H NMR spectra of these compounds show interesting features, which allow the identification of the nature of the protons. The –OH protons of **3a–g** appeared between δ 10.5 and 9.3 ppm, but the OH protons of **3h** and **3i** absorbed between δ 14.65 and 12.00 ppm, respectively. A broad peak corresponding to NH proton showed up between δ 2.91 and 3.42 ppm for compounds **3a–g**. The amide proton of **3h** and **3i** presumably absorbed around δ 4.00 ppm, and NH of triazole ring appears to be in the aromatic region (δ 8.05 ppm) (Table 1). The aromatic protons of all compounds had correct integration. The H-5 of **3h** displayed a singlet at δ 8.74 ppm, whereas H-3 and H-5 of **3i** produced only one singlet at 8.66 ppm, respectively.



3h

N-(1*H*-[1,2,4]Triazol-3-yl)-phthalamic acid



3i

N-[1,2,4]Triazol-4-yl-phthalamic acid

Figure 1.

N-Arylphthalamic acids, as discussed above, possess hypotensive[3] and diuretic[4] effects, but there are no reports about their effects on lipid levels. However, phthalimide itself and *N*-arylphthalimides, cyclic products resulting from dehydration of *N*-arylphthalamic acids, have been reported to influence lipid metabolism reducing the plasma cholesterol and triglyceride levels in rodents,[19] among other activities.[20,21] We thought to examine these acids to find whether they also possess such activity, but to our surprise amic acids produced the opposite effect. When we evaluated the pharmacological activity of *N*-arylphthalamic acids (**3a–i**) in normolipidemic Swiss white male mice, treated with 20 mg/kg/day for 14 days, interestingly these amic acids significantly increased cholesterol, triglycerides, and animals' body weight (Table 2).

Intraperitoneal administration of a 1% solution of carboxymethylcellulose (CMC) to the animals during 14 days produced no significant changes in mice plasma cholesterol and triglyceride levels or body weight (Table 2). *N*-Phenylphthalamic acid (**3a**) caused a significant increase in plasma cholesterol and triglyceride levels by 13 and 22%, respectively, after 14 days of treatment. Substitution of the phenyl ring showed mixed results. The substitution of chlorine atom at *ortho*, *meta*, and *para* positions exhibited a significant increase in plasma cholesterol and triglyceride levels, where the *ortho* compound (**3b**) showed better activity, increasing cholesterol and triglyceride levels by 15 and 25%, respectively. In

Table 2. Effect of *N*-arylphthalamic acid treatment on mice plasma cholesterol and triglyceride levels

Compd	Cholesterol (mmol/L)		Triglycerides (mmol/L)		Weight (g)	
	Before	After	Before	After	Before	After
a	2.71±0.26	3.06±0.23*	1.07±0.16	1.30±0.24*	28±5.7	29±5.7
b	2.11±0.30	2.43±0.32*	1.06±0.30	1.32±0.31*	26±4.2	29±4.4*
c	2.17±0.43	2.48±0.54*	1.04±0.29	1.28±0.33*	24±5.1	28±5.7*
d	2.30±0.25	2.51±0.22*	0.86±0.20	1.06±0.22*	25±4.1	28±3.5
e	3.06±0.54	3.40±0.53*	0.94±0.26	1.23±0.27*	26±4.1	30±5.0*
f	3.02±0.57	3.28±0.54*	1.01±0.08	1.35±0.08*	26±2.3	29±2.9*
g	2.66±0.35	3.17±0.22*	1.26±0.12	1.48±0.10*	20±3.5	25±6.1*
h	2.45±0.22	2.78±0.25***	1.14±0.23	1.58±0.32**	35±0.0	38±0.83***
i	2.46±0.33	2.95±0.32***	1.12±0.17	1.49±0.26**	35±2.7	39±2.82***
CMC	2.32±0.41	2.30±0.40	1.09±0.12	1.09±0.12	29±.1.7	30±1.0

Values represent the mean±SD for six animals in each group. Significant differences: *$p<0.05$, **$p<0.005$ and ***$p\pm0.001$.

the fluorophenyl series, *p*-fluorophenylphthalamic acid (**3g**) was found to be more active in increasing the cholesterol level; although *meta*-fluorophenylphthalamic acid (**3f**) has been less effective in terms of increasing cholesterol (9% elevation), it proved to be the most active in developing hypertriglyceridemia (34% increase). On the other hand, the new compound *N*-[1,2,4]triazol-4-yl-phthalamic acid (**3i**) afforded the best hypercholesterolemic activity (20% increase), whilst the best hypertriglyceridemic activity was found with compound *N*-(1*H*-[1,2,4]triazol-3-yl)phthalamic acid (**3h**) (39% increase). Except for the control group and compounds **3a** and **3d**, the mice body weight was significantly increased after 14 days of drugs' treatment (Table 2).

The preliminary results suggest that these drugs are able to develop hyperlipidemia in mice, which may be of interest for experimental purposes, like inducing hypercholesterolemia and hypertriglyceridemia in animals followed by testing of new hypolipidemic drugs. This is based on the fact that hyperlipidemic animal models have been largely used to study coronary artery disease, and it would be advantageous to test the biological effect of antihyperlipidemic drugs. It is important to mention that in recent years attempts to induce hyperlipidemia in various animals species have been partially successful using a variety of exogenous compounds, for example: administration of polychlorinated biphenyls,[22] nicotine,[23] triton WR 1339 (a polyethylene ether of alkyl phenol),[24] among others;[25,26] amic acids may also be worth investigating.

The compounds tested (**3a**–**i**) were suspended in 1% CMC and administered intraperitoneally to Swiss white mice; the groups contained six animals weighing about 26 g each for 14 days, at a dose of 20 mg/kg/day. The dose was chosen based on the previous experiments with the animals treated with phthalimides resulting from dehydration of phthalamic acids.[27] The animals were kept on fasting about 16 h before puncturing the retro-orbital plexus for blood collection. Blood samples were withdrawn into tubes containing ethylenediaminetetraacetic acid (EDTA) disodium salt (1 mg/mL) before and after 14 days of treatment, and the plasma was separated by centrifugation at 2500*g*/min. The animals were weighed every day during the treatment. Samples of plasma were used in duplicate to determine the plasma cholesterol and triglyceride levels by using enzymatic assay CHOD-PAP[28] (by the action of cholesterol esterase, cholesterol oxidase and peroxidase contained in Merck test 1.14830.0001), Ecoline 25 reagents (diagnostica-Merck KGaA, Darmstadt, Germany) and GPO-PAP[29] (by the enzymes lipase, glycerokinase, glycerol phosphate oxidase and peroxidase present in Merck test 1.19706.0001 System Multi-Test) according to the manufacturer's instructions, respectively.

The results are expressed as the mean±standard error and they were evaluated statistically using the paired Student *t*-test and $p<0.05$ as the criterion of statistical significance.

Acknowledgements

We thank Brazilian National Research Council (CNPq) and Pernambuco State Foundation for Science and Technology (FACEPE) for financial support.

References and Notes

1. Pagani, G.; Baruffini, A.; Borgna, P.; Caccialanza, G. *Il Farmaco* **1968**, *23*, 448.
2. DiazSala, C.; Hutchison, K. W.; Goldfarb, B.; Greenwood, M. S. *Physiol. Plant*. **1996**, *97*, 481.
3. Wexler, R. R.; Carini, D. J.; Duncia, J. V.; Johnson, A. L.; Wells, G. J.; Chiu, A. T.; Wong, P. C.; Timmermans, P. B. M. W. M. *Am. J. Hypert*. **1992**, *5*, 209.
4. Braunlich, H.; Jordan, A.; Kersten, L.; Scheithauer, S.; Schiller, F.; Stolz, J.; Volkert, P. *Z. Klin. Med*. **1985**, *40*, 201.
5. Khajavi, M. S.; Nikpour, F.; Hajihadi, M. *J. Chem. Res. (S)* **1996**, 96.
6. Mochizuki, A.; Teranishi, T.; Ueda, M. *Polymer J*. **1994**, *26*, 315.
7. Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Roussell, J. *Tetrahedron Lett*. **1986**, *27*, 279.
8. Yuan, Y. C.; Gao, D. B.; Jiang, Y. L. *Synth. Commun*. **1992**, *22*, 2117.
9. Bogdall, D.; Pielichowski, J.; Borón, A. *Synlett* **1996**, 873.
10. Borah, H. N.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Res. (S)* **1998**, 272.

11. Srikrishna, A.; Nagaraju, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 311.
12. Diaz-Ortiz, A.; Diez-Barra, E.; de la Hoz, A.; Moreno, A.; Gòmez-Escalonilla, M. J.; Loupy, A. *Heterocycles* **1996**, *45*, 1021.
13. Caddick, S. *Tetrahedron* **1995**, *51*, 10403.
14. Danks, T. N. *Tetrahedron Lett*. **1999**, *40*, 3957.
15. Laurent, R.; Laporteri, A.; Dubac, J.; Berlan, J. *Organometallics* **1994**, *13*, 2493.
16. Mingos, M. P.; Baghurst, D. R. *Chem. Soc. Rev*. **1991**, *20*, 1.
17. Vidal, T.; Petit, A.; Loupy, A.; Gedye, R. N. *Tetrahedron* **2000**, *56*, 5473.
18. Compound **3h** *N*-[1,2,4]triazol-3-yl)phthalamic acid: ^{1}H NMR (DMSO-d_6) δ 14.65 (1H, b, OH), 8.74 (1H, s, H-5), 8.05–7.96 (5H, m, H-6′, H-5′, H-4′, H-3′ and H-1); IR (KBr), 3265, 3136, 3006, 2652, 2526, 1698, 1586 cm^{-1}. Elemental analysis: calcd for $C_{10}H_8O_3N_4$ (232,197): C, 51.72; H, 3.47; N, 24.13; found: C, 51.60; H, 3.06; N, 25.08. Compound **3i** *N*-[1,2,4-triazol-4-yl]phthalamic acid: ^{1}H NMR (DMSO-d_6) δ 12.00 (1H, b, OH), 8.66 (2H, s, H-3 and H-5 Het), 8.01 (1H, d, H-6′, J = 7.5 Hz), 7.71–7.59 (3H, m, H-5′, H-4′, H-3′); IR (KBr), 3326, 3105, 3079, 2668, 2512, 1720, 1679, 1598, 1268, 1243, 1127, 1111, 1081 cm^{-1}; calcd for $C_{10}H_8O_3N_4$ (232.197): C, 51.72; H, 3.47; N, 24.13; found: C, 51.37; H, 3.32; N, 24.17.
19. Chapman, J. M.; Voorstad, P. J.; Cocolas, G. H.; Hall, I. H. *J. Med. Chem*. **1983**, *26*, 243.
20. Antunes, R.; Batista, H.; Srivastava, R. M.; Thomas, G.; Araújo, C. C. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 3071.
21. Illey, J.; Calheiros, T.; Moreira, R. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 955.
22. Matsushita, O. H. N.; Hirabayashil, A.; Yoshida, A. *J. Nutr. Sci. Vitaminol*. **1990**, *36*, 117.
23. Frase, R.; Clark, S.; Day, W.; Murry, F. *Br. J. Exper. Pathol*. **1988**, *69*, 345.
24. Palmer, W. K.; Emerson, E. E.; Johnston, T. P. *Med. Sci. Sports Exercise* **1997**, *29*, 1416.
25. Gustafson, S.; Vahlquist, C.; Sjörloni, L.; Ekund, A.; Vahlquist, A. *J. Lip. Res*. **1990**, *31*, 183.
26. Cho, B.; Smith, T.; Park, J.; Kummerow, F. *Lipids* **1998**, *23*, 853.
27. Srivastava, R. M.; Oliveira, F. J. S.; Silva, L. P.; Freitas Filho, J. R.; Oliveira, S. P.; Lima, V. L. M. *Carbohydr. Res*. **2001**, *332*, 335.
28. Allain, C. C.; Poon, S. L.; Chan, C. S.; Richmond, W.; Fu, C. P. *Clin. Chem*. **1974**, *20*, 470.
29. McGrowan, M. W.; Artiss, J. D.; Strandberg, D. R.; Zac, B. *Clin. Chem*. **1983**, *29*, 538.