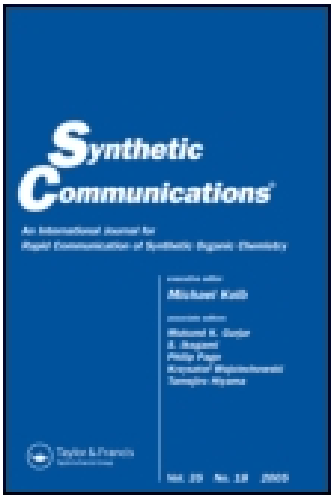

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Solvent-Free Synthesis of Arylamides and Arylimides, Analogues of Acetylcholine

J. Trujillo-Ferrara [a], José Correa-Basurto [a], Judith Espinosa [a], Jazmín García [a], Francisco Martínez [b] & René Miranda [c]

[a] Escuela Superior de Medicina, Instituto Politécnico Nacional, Sección de Estudios del Posgrado e investigación y Departamento de Bioquímica, Plan de San Luis y Díaz Mirón , México

[b] Unidad Profesional Interdisciplinaria de Biotecnología, Instituto Politécnico Nacional, Departamento de Química , Barrio Ticomán, México

[c] Facultad de Estudios Superiores Cuautitlán, Departamento de Química , Universidad Nacional Autónoma de México , Col. Santa Maria de las Torres, Cuautitlán Izcalli, México

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J. Trujillo-Ferrara, José Correa-Basurto, Judith Espinosa, and Jazmín García
Escuela Superior de Medicina, Instituto Politécnico Nacional, Sección de Estudios del Posgrado e investigación y Departamento de Bioquímica, Plan de San Luis y Díaz Mirón, México

Francisco Martínez
Unidad Profesional Interdisciplinaria de Biotecnología, Instituto Politécnico Nacional, Departamento de Química, Barrio Ticomán, México

René Miranda
Facultad de Estudios Superiores Cuautitlán, Departamento de Química, Universidad Nacional Autónoma de México, Col. Santa Maria de las Torres, Cuautitlán Izcalli, México

Abstract: Several arylamides and arylimides, novel inhibitors of acetylcholinesterase, were obtained under solventless conditions; the target molecules were produced with a good overall yield and short reaction times.

Keywords: Solvent-free, anilines, imides, acetylcholinesterase, Alzheimer's disease

INTRODUCTION

Several clinical trials have shown that acetylcholinesterase inhibitors (ACHEIs) are promising drugs in the treatment of Alzheimer's disease

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Address correspondence to J. Trujillo-Ferrara, Escuela Superior de Medicina, Instituto Politécnico Nacional, Sección de Estudios del Posgrado e investigación y Departamento de Bioquímica, Plan de San Luis y Díaz Mirón, México, D.F. 11340, México. Tel/Fax: +52 55 57296000 Ext. 62744; E-mail: jtrujillo@ipn.mx

(AD).[1,2] Tacrine, galantamine, rivastigmine, and donepezil are some ACHEIs currently used, but their clinical use is limited because of several undesirable side effects, such as hepatotoxicity.[3–5] Therefore, the synthesis and study of new compounds as ACHEIs is required[6] to improve their activity and reduce adverse side effects.[7–9]

The chemistry of amides and imides has received great attention because of the interesting pharmacological and industrial uses of this class of molecules.[10,11] Among other methods,[12,13] these kinds of compounds can be synthesized from the corresponding nitriles in various steps, using the respective diamides by the action of $SOCl_2$ in dioxane, or more generally from the corresponding dicarboxilic acid.[14–16] However, many of these methods require the employment of hazardous reagents and solvents.[17]

The classical method for obtaining amides is the pyrolysis of the salt of the respective carboxylic acid in the presence of primary or secondary amines, requiring around 1 h of heating at a high temperature; although it is of preparative value, it is very tedious[18] as well as enviromentally toxic. Therefore, in this study the maleic acid derivatives (**1a–e**, **2a–e**) were synthesized under simple eco-friendly (solventless) conditions. These compounds were physically (mp) and spectroscopically identified by EIMS and ^{1}H and ^{13}C NMR.

RESULTS AND DISCUSSION

Table 1 summarizes the results of the preparation of products **1a–e** and **2a–e**, which were obtained in good yields, with low reaction times and an easy-to-use method, and under environmentally friendly (solventless) conditions. The products were readily isolated and purified by means of several washings with water. Of particular interest was the production of **2b**, directly obtained by the action of sodium acetate **2a**. In conclusion, an efficient and green chemical

Table 1. Amides and imides synthesized under solventless conditions

Products	R	Mp (°C) found (reported)	Yield (%)	EIMS $M^{+\cdot}$ m/z (% ra)
1a	H	210 (220–221)[19]	99	191 (31)
1b	OH	224 (220–223)[19]	97	207 (6)
1c	CO_2H	224 (214–217)[20]	97	235 (4)
1d	NH_2	206 (163–165)[21]	98	206 (6)
1e	OCH_3	198 (213–214)[19]	96	221 (54)
2a	H	89 (88–89.5)[22]	85	173 (7)
2b	OAc	185 (186)[23]	80	233 (9)
2c	CO_2H	238 (235–237)[20]	82	217 (11)
2d	NH_2	153 (172–173)[21]	75	188 (14)
2e	OCH_3	146 (145–148)[22]	78	203 (10)

alternative was developed that could be used for synthesizing many other related compounds.

For the structural attributions of the target compounds, first we verified by the mass-spectrometric method that the molecular ions (Table 1) were in agreement with the corresponding molecular weights, and that the common fragments $[M\text{-}18]^{+\cdot}$, $[M\text{-}45]^{+\cdot}$ and $[aniline]^{+\cdot}$ were present in all compounds synthesized. The corresponding structures of the products became evident from the respective nuclear-magnetic-resonance data (Tables 2 and 3) of the compounds obtained, because the chemical shifts (^1H, ^{13}C) and the respective coupling patterns on ^1H are in agreement with previous reports.[7]

Finally, it is worth mentioning that these molecules continue to be excellent acetylcholinesterase inhibitors; consequently, they could be interesting drugs in the treatment of Alzheimer's disease.

EXPERIMENTAL

The starting materials, maleic anhydride and the anilines, are commercially available (Aldrich Chemical Co.) and were used without further purification. The reactions were monotired by TLC using Watman precoated plates (silica gel 60 F_{254}, 0.25 mm). The product visualization was done using a 254-nm UV lamp. The molecules obtained were identified by ^1H and ^{13}C NMR spectra recorded on a Jeol GSX-270 spectrometer using DMSO-d_6 as a solvent and TMS as an internal reference. EIMS (70 ev) experiments were determined on a Hewlett Packard 5989A mass spectrometer under the electron-impact ionization mode and by direct insertion. Uncorrected melting points were obtained in open-ended capillary tubes with an Electrothermal 9300 digital apparatus.

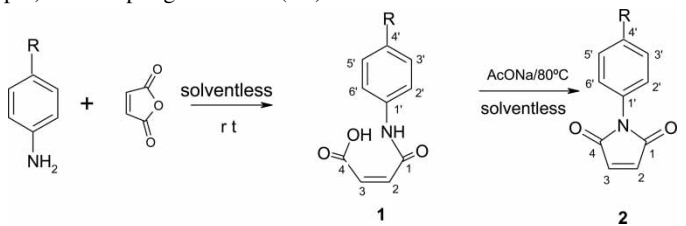
General Procedures for the Preparation of 1a–e

1a–e. Equimolar quantities (10 mmol) of maleic anhydride and the corresponding aniline were mixed at room temperature. The mixture was stirred for 2 h and the reaction was monitored by TLC (acetone/ethanol 1:1; SiO_2). The products obtained (yellow solids) were suspended and washed with H_2O (3×30 mL) until reaching pH $\cong$ 4. The resulting suspension was filtered and then the corresponding amides were dried at 40°C, yielding 96–99% of the desired products **1a–e**.

General Procedures for the Preparation of 2a–e

2a–e. The starting materials **1a–e** were transformed to the corresponding *N*-arylimides (**2a–e**) by heating them for 4 h at 80–85°C in the presence of

Table 2. ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) of **1a–e** and **2a–e**



Compounds	H-2	H-3	H-2′	H-3′	H-4′	H-5′	H-6′	NH	CH_3
1a	6.50	6.32	7.65	7.32	7.08	7.32	7.65	10.45	—
1b	6.48 d, $J = 12.4$	6.29 d, $J = 12.4$	7.43 d, $J = 8.9$	6.75 d, $J = 8.9$	—	6.75 d, $J = 8.9$	7.43 d, $J = 8.9$	10.52 s	—
1c	6.51 d, $J = 11.9$	6.33 d, $J = 11.9$	7.75 d, $J = 8.9$	7.93 d, $J = 8.6$	—	7.93 d, $J = 8.6$	7.75 d, $J = 8.9$	10.61 s	—
1d	6.48	6.31	7.41	6.59	—	6.59	7.41	10.42	—
1e	6.47 d, $J = 12.1$	6.31 d, $J = 12.1$	7.55 d, $J = 9.0$	6.91 d, $J = 9.0$	—	6.91 d, $J = 9.0$	7.55 d, $J = 9.0$	10.41 s	3.72 s
2a	7.17 s	—	7.34 d	7.49 t	7.39 t	7.49 t	7.34 d	—	—
2b	6.80 s	—	7.35 d, $J = 8.8$	7.19 d, $J = 8.8$	—	7.19 d, $J = 8.8$	7.35 d, $J = 8.8$	—	2.29
2c	7.22 s	—	7.68 d, $J = 8.6$	8.01 d, $J = 8.6$	—	8.01 d, $J = 8.6$	7.68 d, $J = 8.6$	—	—
2d	7.02	6.6	7.10	6.74	—	6.74	7.10	10.42	—
2e	6.82 s	—	7.23 d, $J = 8.9$	6.98 d, $J = 8.9$	—	6.98 d, $J = 8.9$	7.23 d, $J = 8.9$	—	3.82 s

Table 3. ^{13}C NMR chemical shifts (ppm) of **1a–e** and **2a–e**

Compounds	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1	C-2	C-3	C-4	CH_3
1a	139.4	119.5	128.5	123.8	128.5	119.5	165.2	131.7	130.4	166.7	—
1b	130.2	122.2	115.8	154.8	115.8	122.2	163.4	132.4	131.9	167.1	—
1c	143.2	119.3	131.0	126.2	131.0	119.3	164.2	132.3	130.7	167.5	—
1d	144.5	120.2	114.5	144.4	114.5	120.2	—	—	—	—	—
1e	131.9	121.8	114.5	156.4	114.5	121.8	163.4	132.3	131.5	167.1	55.7
2a	131.5	126.8	128.9	127.7	128.9	126.8	169.9	134.6	—	—	—
2b	129.0	126.8	122.2	149.7	122.2	126.7	169.2	234.1	—	—	21.0
2c	131.6	126.9	128.9	127.8	129.0	126.9	170.0	134.9	—	—	—
2d	148.4	127.3	114.6	148.4	114.6	127.3	—	—	—	—	—
2e	123.8	127.6	114.5	159.2	114.5	127.6	169.8	134.2	—	—	55.5

sodium acetate. The reactions were monitored by TLC (acetone/ethanol 1:1, SiO_2). The resulting mixtures were cooled, and the imides washed with H_2O (3×30 mL) until reaching pH $\cong$ 3. The solids were dried at 40°C, yielding 70–80% of the corresponding products.

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