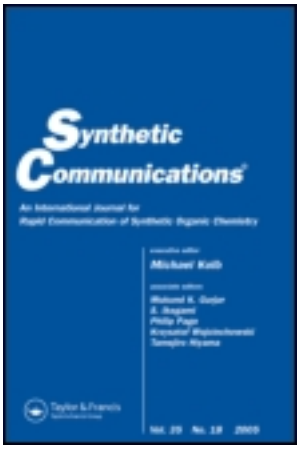

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 29 May 2012.Version of record first published: 06 Mar 2013.

To cite this article: Alajos Grün , Mátyás Milen , Tamás Földesi , Péter Ábrányi-Balogh , László Drahos & György Keglevich (2013): Microwave-Assisted Amidation of Arylacetic Acids by Reaction with 2-Aryl-ethylamines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:11, 1491-1498

To link to this article: http://dx.doi.org/10.1080/00397911.2011.642925

Synthetic Communications®, 43: 1491–1498, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.642925

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MICROWAVE-ASSISTED AMIDATION OF ARYLACETIC ACIDS BY REACTION WITH 2-ARYL-ETHYLAMINES

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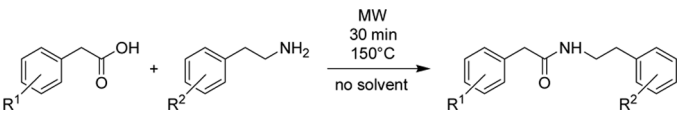
GRAPHICAL ABSTRACT



Abstract *Twenty-five amides were synthesized in almost quantitative yields by microwave-assisted condensation of arylacetic acids and 2-aryl-ethylamines under solventless conditions. The N-arylethyl-arylacetylamides are intermediates of the corresponding isoquinoline derivates.*

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Keywords Amidation; arylacetic acid; arylethylamine; microwave; solventless

INTRODUCTION

The amide function plays an important role in bioorganic chemistry and is present in numerous natural products (proteins and peptides), plastics, drugs, and pesticides.[1–4] Therefore, the synthesis of amides is significant and well-known in organic chemistry.[5,6] The carboxylic amides may be prepared by the acylation of amines by carboxylic acids directly above 100 °C or in the presence of well-known condensing agents, such as carbodiimides[7–9] or benztriazole derivatives[10–13] under

Received November 14, 2011.
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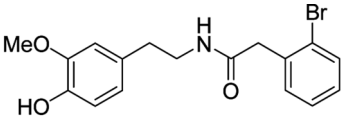
milder conditions. Additional coupling reagents are bis(2,2,2-trifluoroethoxy)-triphenylphosphorane,[14] diethyl phosphorobromidate,[15] 2-oxo-3-oxazolinylphosphonate,[16] which can be used under mild conditions and are efficient and cheap. The activation of carboxylic acids for the preparation of carboxamides can be achieved by other reagents, such as $TiCl_4$,[17] Lawesson's reagent,[18] $Sn[N(TMS)_2]_2$,[19] *N*-halosuccinimide/Ph_3P,[20] Cl_3CCN/Ph_3P,[21] SO_2ClF,[22] $ArB(OH)_2$,[23] $(R_2N)_2Mg$,[24] and chlorosulfonyl isocyanate.[25] Amidations were also described in the presence of trimethylamine-borane in boiling xylene.[26] Last but not least, the easily available Fe^{3+}-K-10 montmorillonite clay is mentioned as an efficient catalyst for amidation.[27] The only disadvantage is that the condensation is carried out in boiling chloroform for prolonged (7.5–9 h) reaction times.

Microwave (MW) irradiation is a useful tool to conduct reactions efficiently in short reaction times.[28] Condensation is a typical reaction that may be well accomplished under MW conditions.[29] Not only thermally well-established esterifications and amidations of carboxylic acids but also the otherwise thermally impossible esterifications of phosphinic acids could be performed under MW irradiation.[30,31] The use of the MW technique is often associated with solventless conditions offering an additional advantage. Recently, the preparation of amides under solvent-free conditions has been reported.[32–35]

It was a challenge for us to study the condensation of arylacetic acids with 2-aryl-ethylamines under MW and solventless conditions. The resulting amides would be valuable intermediates of the Bischler–Napieralski ring-closure reactions. Beside this, these amides may be the starting materials for a variety of alkaloids or their synthetic derivatives. For example, amide **A** was converted to racemic lirinidine belonging to the family of aporphine alkaloids or to racemic nuciferine, in seven or eight steps, respectively.[36] Tilacorine belonging to bisbenzylizoquinolines with more complicated structure, that is, among others, the alkaloid of Tilacora racemosa,[37] was synthesized from amide **B** by Pachaly et al.[38–40] The simple preparation of racemic dihydrothebainone, dihydrocodeinone, and nordihydrocodeinone was described using amide **C**.[41]



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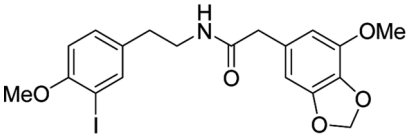

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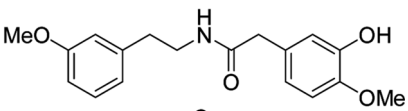

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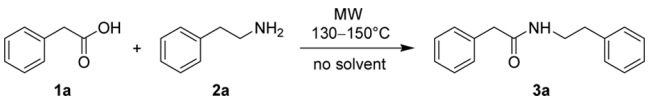


Scheme 1. Amidation of phenylacetic acid with phenylethylamine.

RESULTS AND DISCUSSION

First we studied if the use of the MW technique offers an advantage in the condensation reaction of phenylacetic acid (**1a**) and 2-phenylethylamine (**2a**). Equimolar mixtures of the reactants were irradiated at 130 °C, 140 °C, and 150 °C to afford the corresponding amide (**3a**) in practically quantitative yields after reaction times of 120 min, 60 min, and 22 min, respectively (Scheme 1, Table 1). In the comparative thermal experiment carried out at 150 °C, the reaction time was 100 min (Table 1). It can be seen that on MW irradiation the amidation became much faster.

Then the optimum temperature of 150 °C was adapted to the condensation of other model compounds. To be sure, a reaction time of 30 min was applied to all cases. On measuring together the acid (**1**) and the amine (**2**), the exothermic formation of the corresponding salt could be observed. For this, the vial was put into the MW reactor only after cooling it back to 25 °C.

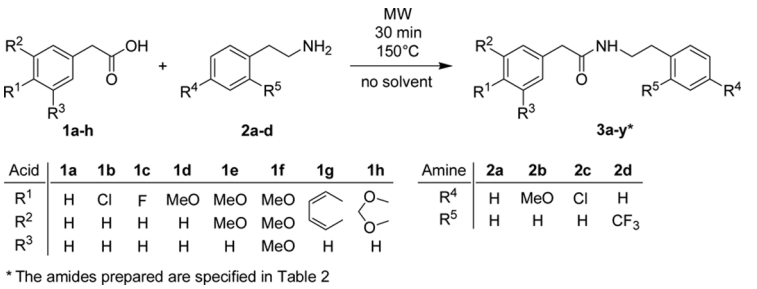
In the first set of experiments, a series of substituted arylacetic acids (**1a–c, f–h**) including 2-naphthyl-acetic acid and 3,4-methylenedioxy-acetic acid were reacted with 2-phenylethylamine (**2a**). Next, the arylacetic acids (**1a–h**) were reacted with 4-methoxyphenylethylamine (**2b**) and then with 4-chlorophenylethylamine (**2c**). In the final stage, the arylacetic acids (**1a–h**) were condensed with 3-trifluoromethylphenylethylamine (**2d**) (Scheme 2, Table 2). With 4-nitro substituent in the arylacetic acid, there was no reaction with any of the arylethylamines.

In all cases, the amides (**3a–z**) were obtained in almost quantitative yields after flash column chromatography. Amides **3a–c, 3e, 3i, 3n, 3p**, and **3r** were described in the literature but were not characterized. All of the amides (**3a–z**) (Table 2) prepared by us have been characterized by ^{1}H and ^{13}C NMR, as well as high-resolution mass spectrometric (HR-MS) spectral data.

To evaluate the effect of substituents on the reactivity, the amide formation was carried out, in three different combinations at 140 °C for 30 min. First, the unsubstituted model compounds **1a** and **2a** were reacted to give amide **3a** in 63% conversion. Then, 4-MeO-phenylacetic acid (**1d**) was reacted with 4-Cl-phenylethylamine (**2c**) to afford amide **2g** in a conversion of 69%. Finally, the reaction of 4-Cl-phenylacetic

Table 1. Amidation of $PhCH_2CO_2H$ with $Ph(CH_2)_2NH_2$ under MW and thermal conditions

Mode of heating	Temperature (°C)	Reaction time (min)	Yield of **3a** (%)	Entry
MW	130	120	95	1
MW	140	60	95	2
MW	150	22	~99	3
Δ	150	100	~97	4



Scheme 2. Amidation of arylacetic acids with arylethylamine.

acid (**1b**) with 4-MeO-phenylamine (**2b**) was carried out providing the amide (**3o**) in 57% conversion (Table 3). It can be seen that the most advantageous combination is when the arylacetic acid has an electron-donating substituent (i.e., a MeO group) in position 4 and the arylethylamine contains an electron-withdrawing substituent (i.e., a chlorine atom) in the *para* position. An explanation may be that in this case the reactants are more reactive. In case of the 4-MeO substituent, the arylacetic acid (**1**) is deprotonated to a smaller extent, and hence the C=O moiety remains more

Table 2. Products (**3**) from the amidation of arylacetic acids (**1**) and arylethylamines (**2**) along with the yields

Acid	Amine	Product	R^1	R^2	R^3	R^4	R^5	Yield (%)	Lit.	Entry
1a	**2a**	**3a**	H	H	H	H	H	99	[34]	1
1a	**2b**	**3b**	H	H	H	MeO	H	95	[42,43]	2
1a	**2c**	**3c**	H	H	H	Cl	H	98	[42,43]	3
1a	**2d**	**3d**	H	H	H	H	CF_3	99	—	4
1d	**2a**	**3e**	MeO	H	H	H	H	99	[44]	5
1d	**2b**	**3f**	MeO	H	H	MeO	H	99	—	6
1d	**2c**	**3g**	MeO	H	H	Cl	H	99	—	7
1d	**2d**	**3h**	MeO	H	H	H	CF_3	99	—	8
1e	**2b**	**3i**	MeO	MeO	H	MeO	H	99	[45]	9
1e	**2d**	**3j**	MeO	MeO	H	H	CF_3	99	—	10
1f	**2a**	**3k**	MeO	MeO	MeO	H	H	99	—	11
1f	**2b**	**3l**	MeO	MeO	MeO	MeO	H	99	—	12
1f	**2d**	**3m**	MeO	MeO	MeO	H	CF_3	99	—	13
1b	**2a**	**3n**	Cl	H	H	H	H	99	[43]	14
1b	**2b**	**3o**	Cl	H	H	MeO	H	99	—	15
1b	**2c**	**3p**	Cl	H	H	Cl	H	99	[46]	16
1b	**2d**	**3q**	Cl	H	H	H	CF_3	98	—	17
1c	**2a**	**3r**	F	H	H	H	H	99	[42]	18
1c	**2b**	**3s**	F	H	H	MeO	H	93	—	19
1c	**2d**	**3t**	F	H	H	H	CF_3	99	—	20
1g	**2a**	**3u**	–CH=CH–CH=CH–		H	H	H	96	—	21
1g	**2b**	**3v**	–CH=CH–CH=CH–		H	MeO	H	99	—	22
1g	**2d**	**3w**	–CH=CH–CH=CH–		H	H	CF_3	99	—	23
1h	**2a**	**3x**	–O–CH_2–O–		H	H	H	99	—	24
1h	**2b**	**3y**	–O–CH_2–O–		H	MeO	H	98	—	25
1h	**2d**	**3z**	–O–CH_2–O–		H	H	CF_3	99	—	26

Table 3. MW-assisted reactions of arylacetic acids (**1**) with arylethylamines (**2**) at 140 °C for 30 min

Acid	Amine	Amide	Conversion (%)	Entry
1a	**2a**	**3a**	63	1
1d	**2c**	**2g**	69	2
1b	**2b**	**3o**	57	3

electrophilic. At the same time, the 4-Cl substituent somewhat prevents the protonation of the amino function of the arylethylamine (**2**), thus enhancing its nucleophilicity.

In summary, a convenient and efficient synthesis of *N*-arylethyl-arylacetylamides has been elaborated by the MW-assisted and solventless condensation of a series of arylacetic acids and 2-arylethylamines.

EXPERIMENTAL

General Procedure for the Preparation of Amides 3a–z

The acid (1.0 mmol) and amine (1.0 mmol) were measured in vial. After 3 min, the vial was placed in the MW reactor and the mixture was heated to 150 °C in 3 min, applying 30–50 W. After a 30-min reaction time, the crude product was taken up in 5 ml methanol and purified by flash column chromatography (using a silica column of 10 cm and 3% methanol in dichloromethane as the eluent) to afford amides **3a–z**, mostly as crystalline products. Recrystallization from ethanol led to entirely pure samples.

N-Phenylethyl-phenylacetic Amide (3a)

Mp 92–94 °C (mp[34] 94–96 °C), ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.15 (m, 8H, Ar*H*), 7.02 (d, 2H, $J = 6.2$, ArH), 5.41 (bs, 1H, CON*H*), 3.52 (s, 2H, CH_2C=O), 3.45 (q, 2H, $J = 6.5$, NCH_2), 2.72 (t, 2H, $J = 6.8$, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1 (*C*=*O*), 138.8 (Ar), 135.0 (Ar), 129.6 (Ar), 129.2 (Ar), 128.9 (Ar), 128.7 (Ar), 127.5 (Ar), 126.6 (Ar), 44.0 (N*C*H$_2$), 40.9 (*C*H$_2$C=O), 35.6 (*C*H$_2$). HRMS $(M + H)^+$: 240.1393; $C_{16}H_{18}NO$ requires 240.1388.

The spectral characterization of products **3b–z** together with the ^{1}H and ^{13}C NMR spectra of all compounds (**3a–z)** can be found online in the Supplementary Information.

ACKNOWLEDGMENTS

This project was supported by the Hungarian Scientific and Research Fund (OTKA K83118). This work is connected to the scientific program of the ''Development of Quality-Oriented and Harmonized R+D+I Strategy and Functional Model at BME'' project. This project is supported by the New Hungary Széchenyi Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

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