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Article

Microwave-mediated and Customery Synthesis of *N*-benzoyl- or *N*-Substituted Benzoyl-*N*,*N*′-Dialkylureas from Arylcarboxylic Acids and *N*,*N*′-Disubstituted Carbodiimides under Solvent-free Conditions

Ricardo A. W. Neves Filho, Ronaldo N. de Oliveira and Rajendra M. Srivastava*

Departamento de Química Fundamental, Universidade Federal de Pernambuco, Cidade Universitária, 50740-540 Recife-PE, Brazil

Uma síntese fácil, eficiente e rápida de *N*-benzoil-(e benzoil *N*-substituída)-*N*,*N*′-dialquil-uréias foi realizada com bons rendimentos em condições livre de solvente. Primeiramente, a reação entre um ácido carboxílico e uma carbodiimida dissubstituída foi feita empregando radiação de microondas, e depois a mesma reação foi realizada sob aquecimento convencional. Os rendimentos são comparáveis em ambos os casos.

An easy, efficient and quick synthesis of *N*-benzoyl-(and *N*-substituted benzoyl)-*N*,*N*′-dialkylureas, in good yields, under solvent-free conditions is described. First, the reaction between a carboxylic acid and a disubstituted carbodiimide was carried out employing microwave radiation, and later on the same reaction was performed separately under dry heating without any radiation. The yields are comparable in both cases.

Keywords: microwave irradiation, *N*,*N*′-dialkylureas, carbodiimides, solvent-free conditions

Introduction

N-Acylureas exhibit a wide range of biological activities, and a number of them possesses analgesic, antiinflammatory, anthelmintic, antifungal, and larvicidal properties.[1] Another unusual *N*-acylurea, cabergoline, acts as an agonist mainly at dopamine (D1)-D2 receptors, and is used as monotherapy in early untreated Parkinson's disease (PD) and as adjunctive therapy to L-dopa in PD.[2] The efficacy of cabergoline has been evaluated in many clinical trials.[3-5] The synthesis of cabergoline, an *N*-acylurea and a potent prolactin inhibitor, has been reported by Ashford *et al*. in 2002,[6] and in the same year, its effectiveness in treating acromegaly has also been announced.[7] Furthermore, some acylureas have found application in agriculture because they hamper the growth and reproduction of the fall armyworm and house fly.[8] In fact, these ureas also serve as intermediates for their transformation into amides and esters.[9] Because of these properties, *N*-acylureas are of interest as potential drugs, and also as starting intermediates for the preparation of amides and esters, hence our interest in synthesizing such compounds.

*e-mail: rms_indu@yahoo.com

Discovering new high-yielding, selective reactions is vital for the advancement of synthetic organic chemistry. Reactions that generate products with a minimum of operations are not only noteworthy but are fundamental for synthesizing new compounds in a shorter time. For achieving this goal, microwave-mediated reaction has great advantage, and during the last decade this technique experienced tremendous growth and development.[10] Because of its cleanliness and reduced work-up, we decided to examine the reaction of benzoic acid and substituted benzoic acids with *N*,*N*′-dicyclohexyl- and *N*,*N*′-diisopropylcarbodiimides employing microwave radiation.

A literature pursuit revealed the existence of a sole example involving the preparation of 1-benzoyl-1,3-diisopropylurea employing benzoic acid and *N*,*N*′-diisopropylcarbodiimide in a mixture of CH_2Cl_2 / DMF (9:1), containg DMAP as a catalyst, under microwave radiation for 60 min.[11] This reaction was performed in a sealed tube having a pressure of 3.0 bar and at 90 °C. The usual method for synthesizing *N*-acylureas involves: *i*) reactions between *N*-substituted amides and isocyanates in refluxing toluene for 24h;[12] *ii*) benzoyl peroxide and dicyclohexylcarbodiimide in methanol again at reflux

temperature for 12h,[13] and *iii*) carboxylic acids and *N*,*N*′-disubstituted carbodiimides in solution.[14] In 1991, Corriu *et al*.[15] reported that *N*-acylureas can also be obtained from pentacoordinated silicon hydride and *N*, *N*′-dialkyl-carbodiimides in two steps. In this article, we wish to describe two methods, one by microwave irradiation and the other by dry heating, both without the use of any solvent. None of these procedures have been found in the literature. These protocols are speedy, eco-friendly and involve simple purification of the products. Therefore, this type of reaction can be considered as a part of green chemistry.

Results and Discussion

In the present work, *N*,*N*′-dicyclohexyl- and *N*,*N*′-diisopropylcarbodiimides have been allowed to react with aromatic carboxylic acids under the influence of microwave irradiation using a domestic oven (Scheme 1).[16] In general, it took from 5-12 min. for completion of the reaction and the temperature varied between 100-114 °C. In each case the reaction between the reagents cited above furnished mainly the desired *N*-aroylureas, acid anhydrides and *N*,*N*′-disubstituted ureas.

The formation of such products by the reaction of an acid and a carbodiimide employing usual methods has been known since 1962.[17] We observed the reaction rate enhancement when the phenyl ring of the acid carried an electron-withdrawing group. Increased reaction rate has also been reported earlier by Šlebioda.[18] He studied the substituent effect in the reaction of dicyclohexyl-carbodiimide with substituted benzoic acids in buffered solution and found the velocity increment of the reaction containing electron-withdrawing substituent in the phenyl ring.

In order to compare the results described above, the reactants were mixed and heated in a glass tube in solventless condition without microwaves. The reaction took place at 110 °C, but required a little longer time for its completion (see Table 1). With this, it is concluded that *N*-benzoyl- or substituted aroylureas can easily be obtained either from benzoic acid and substituted benzoic acids and a diimide. There is no report in the literature regarding the dry conventional heating for obtaining *N*-acylureas. Table 1 contains, besides other details, the yields of our two methods and their comparison with the literature values.

Separation of compounds **3a-i** and **4a-g** was achieved by liquid chromatography over silica gel. The yields of the chromatographically pure products are provided in the experimental section. The infrared and NMR spectra of the isolated substances agreed with the structure.

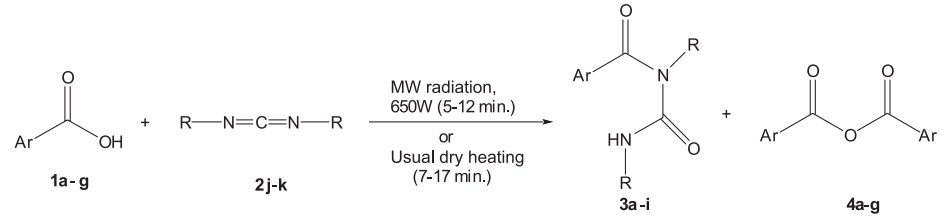
Conclusions

In summary, this study has highlighted the ready generation of *N*-aroyl-*N*,*N*′-disubstituted ureas from benzoic and substituted benzoic acids and *N*,*N*′-disubstituted carbodiimides under solvent-free conditions in a domestic microwave oven. This opens up the scope for synthesizing a variety of acylureas using such radiation technique. Also, the classical method for the above-cited preparation by dry heating is an achievement.

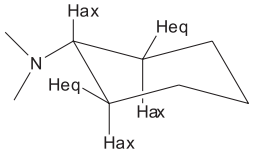
Experimental

General experimental procedures

Melting points were determined on an Electrothermal (Mel-Temp) apparatus (Model No. 1002D) and are



Ar		Ar		R	
a: Ph	R= C_6H_{11}	f: 4-FPh	R= C_6H_{11}	j:	C_6H_{11}
b: 3-NO_2Ph	R= C_6H_{11}	g: 4-CH_3OPh	R= C_6H_{11}	k:	C_3H_7
c: 4-NO_2Ph	R= C_6H_{11}	h: Ph	R= C_3H_7		
d: 3,5-$(NO_2)_2$Ph	R= C_6H_{11}	i: 4-NO_2Ph	R= C_3H_7		
e: 3-CH_3,4-NO_2Ph	R= C_6H_{11}				



Representation of the cyclohexyl ring linked to nitrogen atom in compounds **3a-i**

Scheme 1.

Table 1. Reaction temperature, time and ratio of the products **3** and **4** obtained from **1a-g** and **2j-k**

Entry	Reactants	Microwave Irradiation (MW)			Dry Heating[d]			Literature Yields (%)[e]
		Temp. (°C)[a]	time (min)	Products' 3:4 Ratio (%)[b]	Temp. (°C)[c]	time (min)	Products' 3:4 Ratio (%)[b]	
1	**1a** + **2j**	111	9	77:23	~110	15	76:24	92[13]
2	**1b** + **2j**	107	5	85:15	~110	8	87:13	56[24]
3	**1c** + **2j**	106	10	83:17	~110	12	84:16	86[24]
4	**1d** + **2j**	108	5	85:15	~110	7	86:14	N.A.
5	**1e** + **2j**	114	10	82:18	~110	14	83:17	41[24]
6	**1f** + **2j**	114	6	85:15	~110	12	84:16	48[24]
7	**1g** + **2j**	112	11	71:29	~110	15	75:25	71[15]
8	**1h** + **2k**	108	12	78:22	~110	17	79:21	58[11]
9	**1i** + **2k**	100	7	84:16	~110	13	87:13	71[15]

[a] Temperature recorded by an infrared thermometer, model Minipa 350. [b] Obtained after thick layer chromatography. [c] Oil bath temperature. [d] This work. [e] All reactions reported in the literature used solvent and heated the contents for an extended period of time.

uncorrected. All reactions were monitored by TLC analysis (TLC plates contained GF_{254}, Merck). IR spectra were measured with a IFS66 Bruker spectrometer employing either a KBr disc or a nujol mull. ^{1}H NMR spectra were recorded with a Varian unity plus 300 MHz spectrometer using $CDCl_3$ as solvent and $SiMe_4$ as an internal standard. All reactions were conducted in a domestic microwave oven Model Sanyo EM-300B, 220/650W/2450 MHz.

Synthesis of N-benzoyl- or N-substituded benzoyl-N,N′-dialkylureas

A suitable aromatic carboxylic acid **1a-g** (1.0 mmol) and an appropriate carbodiimide (1.1 mmol of DCC and 2.0 mmol of DIC. [23] were well triturated and placed in a small glass test tube. Two separate experiments were carried out. (*i*) microwave irradiation: the mixture was irradiated between 5-12 min. in an unmodified domestic microwave oven (100% potency, 650W), cooled and the components were purified by chromatography. (*ii*) Conventional heating experiments: the mixture was heated in a preheated oil bath maintained at 110 °C for a certain length of time and cooled. In both cases the crude product was treated with chloroform and filtered to remove the insoluble urea. Chloroform: ethyl acetate (8.0:2.0) for entries **1-7** and chloroform: ethyl acetate (9.0:1.0) for entries **8** and **9** were used to develope the tlc plates followed by their revelation under ultraviolet light. Two spots were observed – one due symmetrical anhydrides with R_f values ≈ 0.60 and *N*-acyl ureas having R_f values ≈ 0.43. The chloroform solution of the products was applied to a thick-layer chromatographic plate and developed using the above-mentioned solvent system. Work-up furnished chromatographically pure *N*-acyl ureas **3a-i** and symmetrical anhydrides **4a-g**.

*1-Benzoyl-1,3-dicyclohexylurea (**3a**)*

Colorless crystals from chloroform, m.p. 165-166 °C (51% from MW method and 56% from conventional method); Lit.[13] m.p. 160-161 °C, crystals from methanol-water (79%); Lit.[13] m.p. 164-165.5 °C, crystals from ethanol (92%); Lit.[9] m.p. 175-175.5 °C (76%). IR and ^{1}H NMR spectra gave the same absorptions as reported earlier.[9]

*1,3-Dicyclohexyl-1-(3-nitrobenzoyl)-urea (**3b**)*

Yellow crystals from chloroform, m.p. 175-176 °C (66% from MW method and 65% from conventional method); Lit.[24] m.p. 175 °C (56%). IR: 3315, 2922, 2853, 1700, 1646, 1532, 1346, 1235 cm^{-1}. ^{1}H NMR: δ 0.81-1.96 (m, 20H, 10 CH_2), 3.42-3.51 (m, 1H, CH), 4.07-4.19 (m, 1H, CH′), 6.09 (bd, 1H, NH, J = 7.5 Hz), 7.59 (t, 1H, J 8.1 Hz, arom.), 7.89 (dd, 1H, J 8.1 and J 0.9 Hz, arom.), 8.30 (dd, 1H, J 8.1 and 2.1 Hz, arom.), 8.40 (t, 1H, J 2.1 Hz, arom.).

*1,3-Dicyclohexyl-1-(4-nitrobenzoyl)-urea (**3c**)*

Yellow crystals from ethyl acetate, m.p. 203-204 °C (70% from MW method and 72% from conventional method); Lit.[24] m.p. 204 °C (86%). IR: 3295, 2928, 2855, 1699, 1646, 1519, 1343, 1237 cm^{-1}. ^{1}H NMR: δ 0.83-2.04 (m, 20H, 10CH_2), 3.42-3.56 (m, 1H, CH), 4.03 (dddd, 1H, CH′, $J_{1ax,2ax\ (1ax,6ax)}$ 12.0 Hz and $J_{1ax,2eq\ (1ax,6eq)}$ 3.6 Hz), 6.11 (bd, 1H, NH, J 6.6 Hz), 7.07 (d, 2H, J 8.9 Hz, arom.), 8.27 (d, 2H, J 8.9 Hz, arom.).

*1,3-Dicyclohexyl-1-(3,5-dinitrobenzoyl)-urea (**3d**)*

Yellow crystals from chloroform, m.p. 177-179 °C (73% from MW method and 76% from conventional method); Lit.[25] m.p. 177-179 °C. IR: 3290, 2935, 2857, 1675, 1543, 1343 cm^{-1}. ^{1}H NMR: δ 0.97-1.97 (m, 20H, 10 CH_2), 3.39-3.57 (m, 1H, CH), 4.24 (dddd, 1H, CH′, $J_{1ax,2ax\ (1ax,6ax)}$ 12.3 Hz and $J_{1ax,2eq\ (1ax,6eq)}$ 3.6 Hz), 5.88 (bd, 1H, NH,

J 8.1 Hz), 7.26 (t, 1H, *J* 1.0 Hz, arom.), 8.73 (t, 1H, *J* 1.0 Hz, arom.), 9.10 (t, 1H, *J* 1.8 Hz, arom.).

1,3-Dicyclohexyl-1-(3-methyl,4-nitrobenzoyl)-urea ***(3e)***

Colorless crystals from chloroform, m.p. 133-134 °C (63% from MW method and 60% from conventional method); Lit.[24] m.p. 133 °C (41%). IR: 3311, 2923, 2850, 1701, 1651, 1593 cm^{-1}. ^1H NMR: δ 0.84-2.11 (m, 20H, 10 CH_2), 2.61 (s, 3H, CH_3), 3.45-3.51 (m, 1H, CH), 4.06 (dddd, 1H, CH′, $J_{1ax,2ax}$ $_{(1ax,6ax)}$ 11.7 Hz and $J_{1ax,2eq\ (1ax,6eq)}$ 3.6 Hz), 6.25 (bs, 1H, NH), 7.50 (m, 2H, arom.), 7.69 (d, 1H, *J* 8.4 Hz, arom.).

1,3-Dicyclohexyl-1-(4-fluorobenzoyl)-urea ***(3f)***

Colorless crystals from chloroform, m.p. 177-178 °C (67% from MW method and 64% from conventional method); Lit.[24] m.p. 178 °C (48%). IR: 3277, 2935, 2857, 1709, 1620, 1541 cm^{-1}. ^1H NMR: δ 0.83-2.05 (m, 20H, 10 CH_2), 3.42-3.58 (m, 1H, CH), 4.10 (dddd, 1H, CH', $J_{1ax,2ax}$ $_{(1ax,6ax)}$ 12.0 Hz and $J_{1ax,2eq\ (1ax,6eq)}$ 3.6 Hz), 5.92 (bd, 1H, NH, *J* 6.3 Hz), 7.08 (dd, 2H, $^3J_{H,F}$ 8.6 Hz and $^3J_{H,H}$ 8.6 Hz, arom.), 7.57 (dd, 2H, $^3J_{H,H}$ 8.7 Hz and $^4J_{H,F}$ 5.1 Hz, arom.).

1,3-Dicyclohexyl-1-(4-methoxybenzoyl)-urea ***(3g)***

Colorless crystals from chloroform, m.p. 149-150 °C (55% from MW method and 53% from conventional method); Lit.[15] m.p. 151 °C (71%). IR and ^1H NMR spectra gave the same absorptions as reported earlier.

1-Benzoyl-1,3-diisopropylurea ***(3h)***

Colorless crystals from chloroform, m.p. 111-112 °C (61% from MW method and 54% from conventional method); Lit.[11] m.p. 114 °C (58%). IR and ^1H NMR spectra gave the same absorptions as reported earlier.

1,3-Diisopropyl-1-(4-nitrobenzoyl)-urea ***(3i)***

Yellow crystals from chloroform, m.p. 129-130 °C (72% from MW method and 76% from conventional method); Lit.[15] m.p. 130 °C (71%). IR and ^1H NMR spectra gave the same absorptions as reported earlier.

Benzoic anhydride ***(4a)***

Colorless crystals from chloroform, m.p. 42-43 °C (49% from MW method and 44% from conventional method); Lit.[26] m.p. 42-44 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

3-Nitrobenzoic anhydride ***(4b)***

Yellow crystals from chloroform, m.p. 160-162 °C (34% from MW method and 35% from conventional method); Lit.[27] m.p. 162-163 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

4-Nitrobenzoic Anhydride ***(4c)***

Yellow crystals from chloroform, m.p. 172-173 °C (30 from MW method and 28% from conventional method); Lit.[26] m.p. 172-176 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

3,5-Dinitrobenzoic anhydride ***(4d)***

Yellow crystals from chloroform, m.p. 107-108 °C (27% from MW method and 24% from conventional method); Lit.[28] m.p. 108-109 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

4-Methylbenzoic anhydride ***(4e)***

Colorless crystals from chloroform, m.p. 77-78 °C (37% from MW method and 40% from conventional method); Lit.[26] m.p. 78-80 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

4-Fluorobenzoic anhydride ***(4f)***

Colorless crystals from chloroform, m.p. 107-108 °C (33% from MW method and 36% from conventional method); Lit.[29] m.p. 108-110 °C (21%). ^1H NMR: δ 7.15 (ddd, 2H, ^3J 8.7 Hz and ^3J 8.7, and ^4J 2.1 Hz), 8.13 (dd, 2H, ^3J 8.7 Hz and ^4J 2.1 Hz).

4-Methoxybenzoic anhydride ***(4g)***

Colorless crystals from chloroform, m.p. 84-88 °C (45% from MW method and 47% from conventional method); Lit.[24] m.p. 88-93 °C. IR and ^1H NMR spectra gave the same absorptions as reported earlier.

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