ORGANIC LETTERS

2003
Vol. 5, No. 20
3599−3602

Versatile Access to Benzhydryl-Phenylureas through an Unexpected Rearrangement during Microwave-Enhanced Synthesis of Hydantoins

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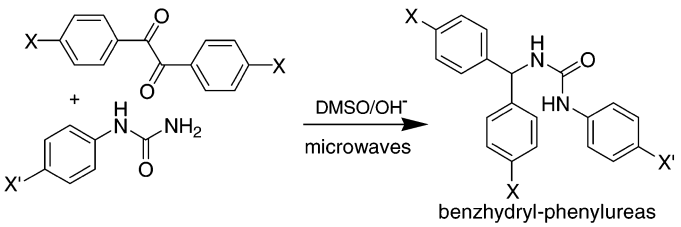
Received July 11, 2003

ABSTRACT



A new access to benzhydryl-phenylureas is described. These new interesting urea derivatives were obtained by reaction of substituted benzils with substituted phenylureas under microwave irradiation. Phenylthiourea, when reacted with benzil, gave 3-phenyl-thiohydantoin. Moreover, benzylurea, as phenethylurea, gave the corresponding 3-substituted hydantoin derivatives, demonstrating that only phenylurea derivatives can result in benzhydryl-phenylureas under the applied conditions. This new reaction proved to be an easy access to substituted 1-benzhydryl-3-phenyl-ureas.

In the course of the investigation of Biltz's synthesis of phenytoin, we have developed a microwave-enhanced synthesis in order to obtain phenytoin and N-3 alkyl phenytoin-related compounds in high yields and short reaction times starting from benzil and alkylurea by using an unmodified domestic microwave oven.[1] The use of microwaves in chemical synthesis, which was first reported by Gedye[2] and Giguere[3] in 1986, has become a widely used method.[4]

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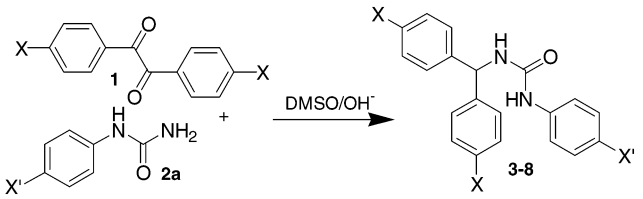
10.1021/ol035282x CCC: $25.00
Published on Web 09/09/2003

Scheme 1. Reaction of Benzil Derivatives (**1**) with Phenylurea Derivatives (**2a**)



Moreover, a growing number of papers report the use of household microwave ovens to speed-up chemical reactions.[5] In the early 1990s, Bose and co-workers described the microwave-induced organic reactions enhancement (MORE) method, where reactions are carried out in unsealed vessels in unmodified domestic microwave ovens using selected solvents.[6]

Herein, we wish to report that an unexpected reaction yielding 1-benzhydryl-3-phenylurea (**3**, X = H), instead of 3,5,5′-triphenylhydantoin,[7] has been obtained from benzil (**1**, X = H) and phenylurea (**2a**, X = H) in DMSO−aqueous KOH under microwave irradiation. Although unexpected, this reaction turned out to be an excellent method for obtaining benzhydryl-phenylurea derivatives (**3**−**8**) (Scheme 1), which may represent a new template for medicinal chemistry applications. To the best of our knowledge, only two authors have reported the synthesis of such derivatives. Their procedures are hampered either by a long reaction time (over 18 h)[8] or by poor flexibility with respect to the substitution of the phenyl rings.[9]

Thus, we report an easy, rapid, and original pathway to this type of compounds.

Several para-halogenated benzils (**1**, X = F, Cl, or Br) have been reacted[10] with phenylurea as examples of this reaction to assess whether the deactivating effect of the halogens has an influence on the resulting compounds. Apart from a slightly reduced yield, the halogens had no effect on the reaction (Table 1).

To assess whether these products were obtained as a result of any "microwave effect", the reactions were carried out under classical reflux conditions (thermal heating).[11] Even under these conditions, the resulting products were the 1-benzhydryl-3-phenylurea derivatives, proving that the microwaves are not responsible for obtaining these compounds. Nevertheless, it is noteworthy that the yields were slightly lower under the reflux conditions compared to the microwave-assisted conditions (data not shown).

Table 1. Yields after Recrystallization (Ethanol) of the 1-Benzhydryl-3-phenylureas (**3a**−**d**) Obtained from Substituted Benzil (**1**) and Phenylurea (**2a**) under Microwave-Assisted Conditions

compound	X	yield
3a	H	59%
3b	F	50%
3c	Cl	48%
3d	Br	50%

Since only 5.5 min of actual transfer energy (total pulse time) was necessary during the microwave procedure, compared to the 4 h requested for the thermal one, to obtain similar yields, we can assume that the reaction in the microwave procedure is 40 times faster than the thermal one. As an open system was used for the microwave procedure, this rate enhancement was not due to higher temperatures reached during this procedure. This acceleration effect on reactions conducted under microwave irradiation was already shown in the early 1990s.[12] X-ray analysis of compound **3c** was carried out in order to confirm that the obtained compounds were 1-benzhydryl-3-phenylurea derivatives (Figure 1). All compounds have NMR spectral data consistent with their proposed structure.

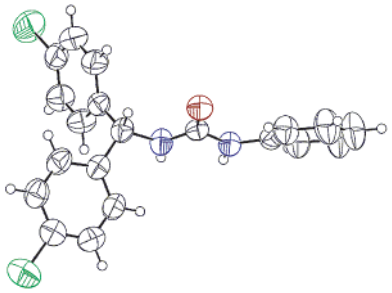


Figure 1. ORTEP diagram of compound **3c**.

Another part of the investigation was the possibility of substituting the phenyl ring of the phenylurea with halogens.

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(7) Also termed 3,5,5′-triphenylimidazolidine-2,4-dione.

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(10) **General Procedure for the Microwave-Assisted Method.** To a solution of 3 g of benzil (14.3 mmol) and 1.94 g of phenylurea (28.6 mmol) in 25 mL of DMSO was added 25 mL of 1.2 M aqueous KOH under stirring. Following an initial 90 s, 750W microwave irradiation, the mixture was stirred for 5 min. Additional 30 s pulses were applied at 6, 9, 12, 15, 18, 21, 24, 30 min. Between pulses the mixture was stirred. After the completion of the sequence, the mixture was poured onto cold water, the resulting precipitate was filtered, dried, and recrystallized from a suitable solvent. All microwave irradiations were carried out in an open system.

Table 2. Yields after Recrystallization of Some 1-Benzhydryl-3-phenylureas (**4**−**8**) Obtained from Benzil (**1**) and Substituted Phenylurea (**2a**, X = H) under Microwave Irradiation

compound	X	X′	yield
4	H	Cl	52%
5	H	I	45%
6	Cl	Br	47%
7	Br	Br	48%
8	Br	I	43%

This substitution did not affect the reaction as illustrated in Scheme 1 and Table 2.

To investigate how benzylurea and phenethylurea would react with benzil derivatives under these conditions, benzil (**1**, X = H), 4,4′-difluorobenzil (**1**, X = F), 4,4′-dibromobenzil (**1**, X = Br), and 4,4′-dimethoxybenzil (**1**, X = OMe) were reacted with the urea derivatives.

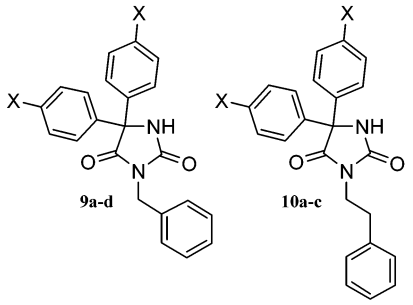


Figure 2. Structure of 3-benzyl-5,5′-diphenylhydantoins (**9a**−**d**) and 3-phenethyl-5,5′-diphenylhydantoins (**10a**−**c**).

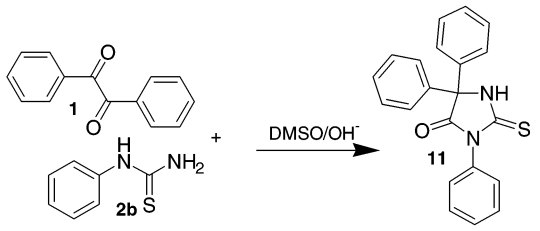
As shown in Figure 2, the reaction products were always the corresponding 3-benzyl-5,5′-diphenylhydantoins (**9a**−**d**) or 3-phenethyl-5,5′-diphenylhydantoins (**10a**−**c**). The 3-benzyl-5,5′-phenylhydantoins and 3-phenethyl-5,5-phenylhydantoins that have been synthesized are listed in Table 3.

A common bioisosteric replacement in medicinal chemistry is the substitution of an oxygen atom by a sulfur. Reaction under microwave irradiation of benzil (**1**) with

Table 3. 3-Benzyl- and 3-Phenethyl-hydantoins Synthesized from Benzil Derivative (**1**) and either Benzylurea or Phenethylurea under Microwave Irradiation

compound	X	yield
9a	H	60%
9b	F	54%
9c	Br	50%
9d	OMe	56%
10a	H	64%
10b	Cl	55%
10c	OMe	57%

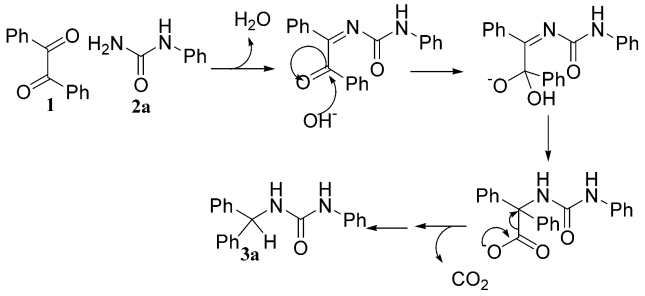
Scheme 2. Reaction of Benzil (**1**) with Phenylthiourea (**2b**) Leading to the 3,5,5′-Triphenyl-2-thioxo-imidazolidin-4-one



phenylthiourea (**2b**) resulted in 3,5,5′-triphenyl-2-thioxo-imidazolidin-2-one[13] (**11**) as shown in Scheme 2.

Summarizing the results, only phenylurea (**2a**), possibly substituted, when reacted with a benzil derivative will yield the 1-benzhydryl-3-phenylurea derivative (**3**−**8**). Neither benzylurea nor phenylthiourea will give a benzhydryl derivative. This could be interesting for an understanding of the reaction mechanism, which has not yet been elucidated. Nevertheless, on the basis of the present results, we propose a mechanism (Scheme 3) involving the condensation of

Scheme 3. Proposed Mechanism for the Synthesis of 1-Benzhydryl-3-phenylurea (**3a**) from Benzil (**1**) and Phenylurea (**2b**)[a]



[a] First condensation step is followed by a benzilic rearrangement and then by a decarboxylation leading to **3a**.

benzil (**1**) and phenylurea (**2a**), followed by a benzilic rearrangement. The subsequent decarboxylation step results in the final compound (**3a**).

The initial condensation step is identical with the first step in the synthesis of the 5,5′-diphenylhydantoin derivatives, but the intramolecular nucleophilic attack by the nitrogen bearing the phenyl, resulting in a five-membered ring and then the hydantoin,[14] is replaced by the nucleophilic attack by a hydroxide ion leading to a carboxylate. It is likely that the phenylthiourea gives the 2-thio-hydantoin compound (**11**) due to its more acidic proton, compared to the phenylurea one, which promotes the cyclization pathway.

(11) **General Procedure for the Classical Method.** As used for **9**, but the reacting mixture was refluxed over a period of 4 h instead of receiving the microwave pulse sequence.

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Acknowledgment. G.M. is very indebted to "Fonds pour la formation à la Recherche dans l'Industrie et l'Agriculture (FRIA)", Belgium, for the award of a research fellowship. This work was partially funded by a FRSM grant from the Belgian National Fund for Scientific Research and by a FSR grant from the Université catholique de Louvain.

Supporting Information Available: Procedures for the synthesis of benzil and urea derivatives and full characterization for synthesized compounds (IR, ^{1}H NMR, ^{13}C NMR, MS, elemental analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

OL035282X