Three-Component, One-Pot Sequential Synthesis of 1,3-Disubstituted 5-Arylhydantoins

Francesca Olimpieri,[a] Alessandro Volonterio,*[a,b] Matteo Zanda*[b]

[a] Dipartimento di Chimica, Materiali e Ingegneria Chimica 'Giulio Natta', Politecnico di Milano, Via Mancinelli 7, 20131 Milano, Italy
Fax +39(02)23993080; E-mail: alessandro.volonterio@polimi.it

[b] C.N.R., Istituto di Chimica del Riconoscimento Molecolare, Sezione 'A. Quilico', Via Mancinelli 7, 20131 Milano, Italy

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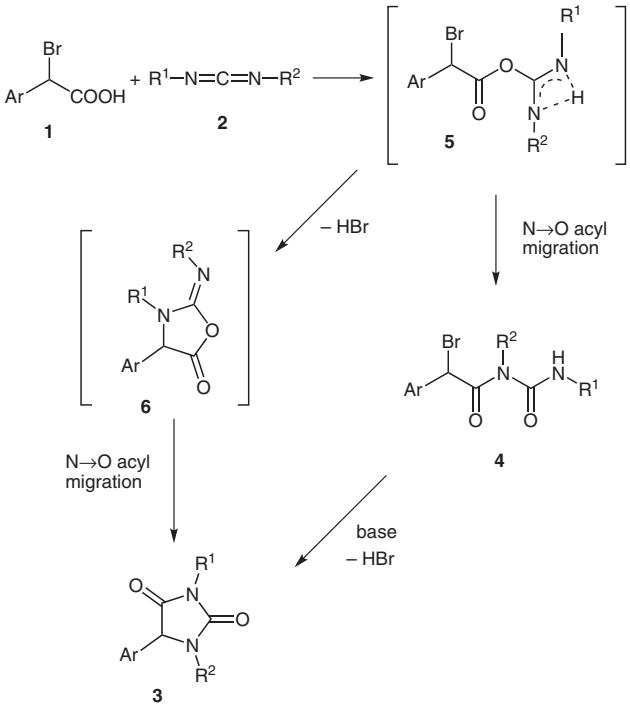
Abstract: Reaction of carbodiimides with α-Br(Cl)-aryl acetic acids produces N,N′-substituted 5-arylhydantoins under very mild conditions and high yields. When the carbodiimides are generated in situ by Staudinger reaction, the process becomes a one-pot, three-component sequential synthesis of libraries of differently substituted 5-arylhydantoins.

Key words: heterocycles, multicomponent reactions, combinatorial chemistry, carbodiimides, sequential synthesis

While the past 50 years have witnessed extraordinary progress in the discovery of new reagents, reactions, and synthetic strategies,[1] the tools of synthetic organic chemistry are often found inadequate when confronted with the challenge of preparing even modestly elaborate molecules in a practical fashion. One powerful approach toward this goal is to combine two or more distinct reactions into a single transformation, thereby producing a sequential reaction process.[2] Efficiency is also being pursued, when possible, by implementation of classical multicomponent (MC) reactions,[3] as well as by the invention of new ones. In this context 'one-pot' MC sequential syntheses feature a high degree of reaction mass efficiency[4] and are especially suitable in combinatorial chemistry and diversity-oriented synthesis programs. Traditionally, methods based on MC reactions have proved quite efficient for the construction of many different types of heterocycles.[5]

5-Arylhydantoins have shown versatile therapeutic applications and some of them have been approved by the FDA as therapeutics.[6] Moreover, 5-arylhydantoins are important building blocks for the synthesis of enantiomerically pure phenylglycine derivatives by dynamic kinetic resolution of the racemate. The feasibility of this method was demonstrated on an industrial scale by Ajinomoto and Kanegafuchi for the production of D-*p*-hydroxyphenylglycine.[7] Since 1,3,5-substituted hydantoins were previously prepared by multistep synthesis starting from the appropriate amino acids,[8] or by palladium-catalyzed carbonylation reaction,[9] we decided to develop a new synthesis of libraries of 1,3-disubstituted 5-arylhydantoins that was practical, experimentally simple, and suitable for the one-pot generation of several new chemical bonds.

Recently, we demonstrated that carbodiimides, when treated with suitable carboxylic acids in the absence of a nucleophile, are useful reagents for the multicomponent synthesis of small heterocycles.[10] Herein we show that differently substituted carbodiimides **2** smoothly react with easily accessible α-halo-arylacetic acids **1** leading to the formation of N,N′-disubstituted 5-arylhydantoins **3** under very mild conditions (Scheme 1). The reaction sequence involves initial addition of **1** to **2** to form the reactive *O*-acyl isourea **5** which readily cyclizes to the intermediate **6** through an intramolecular nucleophilic displacement of the halide. The following O→N acyl migration gives rise to the formation of the hydantoin **3**. In some cases, the O→N acyl migration is competitive with the cyclization, leading to the formation of the *N*-acyl ureas **4** as a byproduct or even as the main product. However, *N*-acyl ureas **4** can be convergently transformed into the target hydantoins **3** by in situ treatment with a suitable base. When the carbodiimides **2** are prepared in situ from the corresponding azides and isocyanates through the Staudinger (aza-Wittig) reaction, the process becomes a



Scheme 1 Synthesis of 5-arylhydantoins **3**

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three-component, one-pot sequential synthesis of libraries of structurally diverse 5-arylhydantoins.

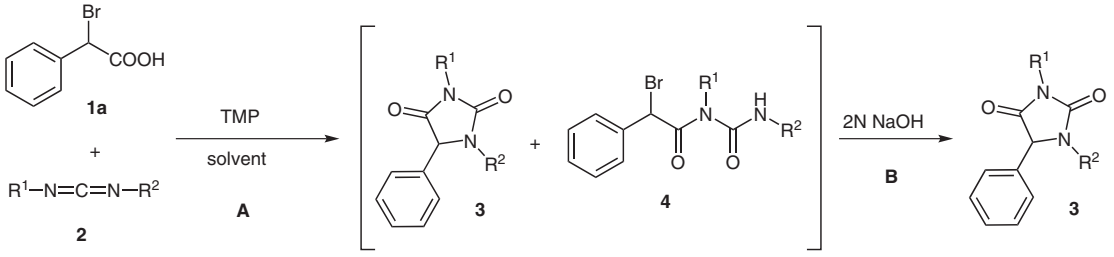
To determine the best conditions for the reaction, we first examined the condensation of α-bromo-phenylacetic acid (**1a**) with different carbodiimides **2**, namely *N*,*N*′-dialkylcarbodiimides **2a**–**d**, *N*-alkyl- *N*′-arylcarbodiimide **2e**, and *N*,*N*′-diarylcarbodiimide **2f** (Scheme 1, Table 1).

Hydantoins **3a**–**d** were readily obtained, as the only products, upon treatment of **1a** with **2a**–**d** in the presence of 1 equivalent of TMP at room temperature. The yields were dependent on the solvent: the best results were obtained with less polar CH_2Cl_2 (entries 3 and 5, Table 1); whereas more polar solvents such as dioxane (entries 2 and 4) and MeCN (entry 1) gave lower yields. As expected,[10a] when the two carbodiimide alkyl substituents R^1 and R^2 were sterically very different – such as in **2d** where R^1 = *tert*-butyl and R^2 = *p*-methoxybenzyl – the reaction was regiospecific leading to the exclusive formation of the regioisomer **3d** (entry 7). In contrast, carbodiimide **2c**, where R^1 and R^2 have similar steric bulk, afforded **3c** as an equimolecular mixture of the two regioisomers (entry 6). Carbodiimide **2e** afforded a 2:1 mixture of hydantoin **3e** and *N*-acyl urea **4e**, as single regioisomers, upon treatment with **1a** (entry 8). However, in situ addition of a 2 M aqueous NaOH solution promoted the cyclization of **4e** under Schotten–Bauman conditions, leading to the exclusive formation of the hydantoin **3e** in excellent yield (entry 9). Finally, **2f** reacted with **1a** leading to the exclusive formation of the *N*-acyl urea **4f** (entry 10).[11]

Also in this case, in situ addition of a 2 M aqueous NaOH solution to **4f** led to the formation of the hydantoin **3f** in very good yield (entry 11).

Next, we investigated the use of the Staudinger reaction in order to develop a three-component, one-pot sequential process starting from easily accessible azides **7**, isocyanates **8**, and α-halo-arylacetic acids **1**, without isolation of the intermediate carbodiimides **2** (Table 2). Symmetrical *N*,*N*′-dibenzylcarbodiimide, generated from benzyl azide **7a** and isocyanate **8a** in CH_2Cl_2 at room temperature, reacted in situ with the acid **1a** and α-bromodiphenylacetic acid (**1c**) affording the hydantoins **3aa** (entry 1, Table 2) and **3ah** (entry 8), respectively, in good yields. As expected, when **1a** and α-bromo-*p*-fluorophenylacetic acid (**1b**) were treated with the asymmetric dialkylcarbodiimide generated from **7a** and *tert*-butylisocyanate **8b**, hydantoins **3ab** (entry 2) and **3ae** (entry 5) were, respectively, formed as the only regioisomers.[12] The carbodiimide prepared in situ from **7b** and **8a** reacted with **1a** and **1b** affording mixtures of the corresponding hydantoins and *N*-acyl ureas, which were converted to the regioisomers **3ac** (entry 3) and **3af** (entry 6), respectively, upon treatment with a 2 M aqueous NaOH solution. The three-component process worked well even with aryl azide **7c** and aryl isocyanate **8c** when reacted with acids **1a**–**c**, leading to the *N*,*N*′-diarylhydantoins **3ad** (entry 4), **3ag** (entry 7) and **3ai**

Table 1 Reaction between Acid **1a** and Differently Substituted Carbodiimides

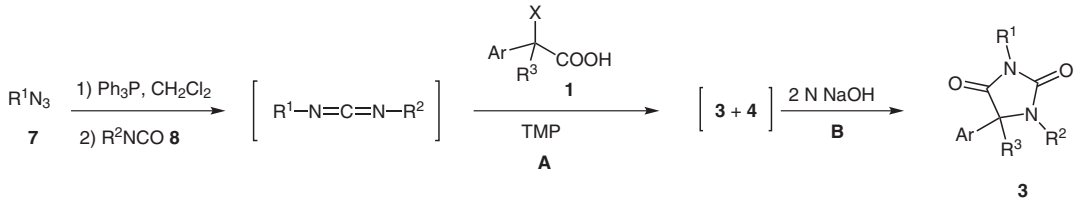


Entry	Carbodiimide	R^1	R^2	Solvent	Procedure	Hydantoin, yield (%)	*N*-Acylurea, yield (%)
1	**2a**	*c*-Hex	*c*-Hex	MeCN	**A**	**3a** (33)	–
2	**2a**	*c*-Hex	*c*-Hex	dioxane	**A**	**3a** (57)	–
3	**2a**	*c*-Hex	*c*-Hex	CH_2Cl_2	**A**	**3a** (100)	–
4	**2b**	*i*-Pr	*i*-Pr	dioxane	**A**	**3b** (45)	–
5	**2b**	*i*-Pr	*i*-Pr	CH_2Cl_2	**A**	**3b** (100)	–
6	**2c**	Me	PMB	CH_2Cl_2	**A**	**3c** (93)[a]	–
7	**2d**	*t*-Bu	PMB	CH_2Cl_2	**A**	**3d** (85)	–
8	**2e**	PMP	PMB	CH_2Cl_2	**A**	**3e** (62)	**4e** (31)
9	**2e**	PMP	PMB	CH_2Cl_2	**A + B**	**3e** (87)	–
10	**2f**	*p*-Tol	*p*-Tol	dioxane	**A**	–	**4f** (85)
11	**2f**	*p*-Tol	*p*-Tol	dioxane	**A + B**	**3f** (81)	–

[a] Equimolar ratio of the two regioisomers **3c** and **3c′**.

(entry 9), respectively, after cyclization promoted by the NaOH solution. Highly electrophilic α-chloro-2,2-diphenylacetic acid (**1d**) reacted smoothly when submitted to the three-component process with *N*-alkyl, *N*′-aryl, and *N*,*N*′-diarylcarbodiimides, directly affording the hydantoins **3aj** (entry 10) and **3ak** (entry 11), respectively, in good yields. Finally, quite surprisingly, even the less electrophilic acid **1e** reacted with in situ generated *N*-alkyl, *N*′-aryl, and *N*,*N*′-diarylcarbodiimides affording the corresponding hydantoins **3al** (entry 12) and **3am** (entry 13), respectively, in acceptable yields.

Table 2 The Three-Component One-Pot Sequential Synthesis of 5-Arylhydantoin **3**



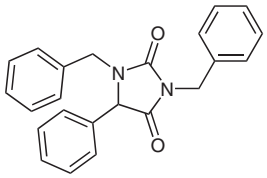
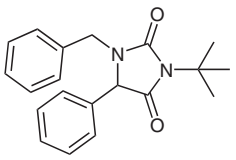
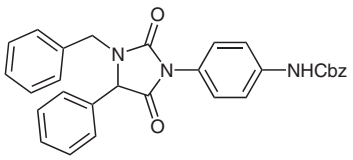
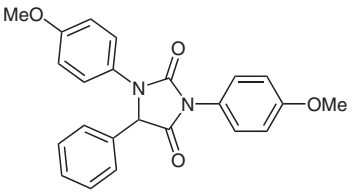
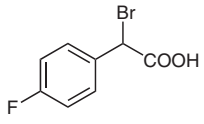
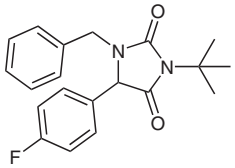
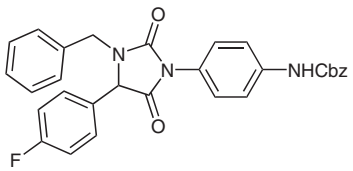
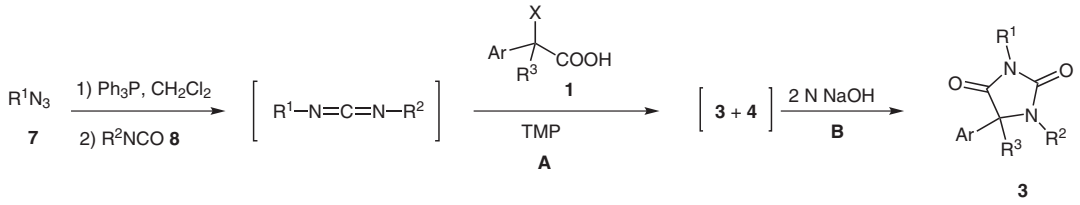
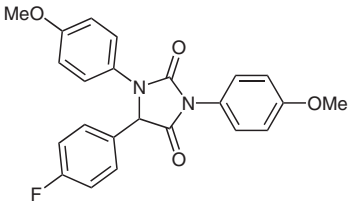
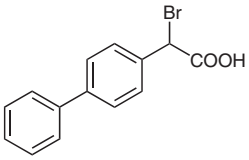
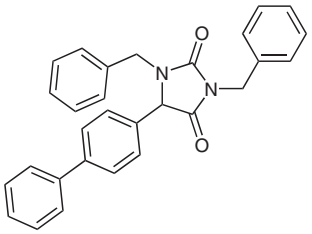
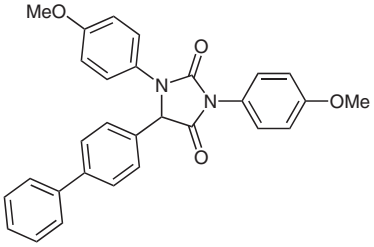
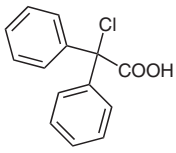
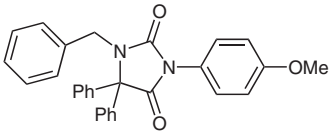
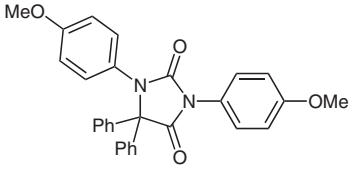
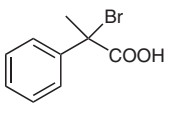
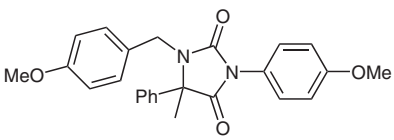
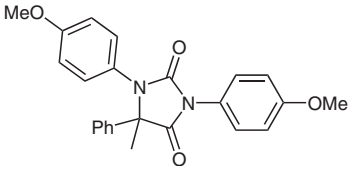
Entry	Azide, R^1	Isocyanate, R^2	Acid	Method	Hydantoin	Product, yield (%)
1	**7a**, Bn	**8a**, Bn	**1a**	**A**		**3aa**, 61
2	**7a**, Bn	**8b**, *t*-Bu	**1a**	**A**		**3ab**, 55
3	**7b**, 4-CbzNHC$_6$H$_4$	**8a**, Bn	**1a**	**A + B**		**3ac**, 83
4	**7c**, 4-MeOC$_6$H$_4$	**8c**, 4-MeOC$_6$H$_4$	**1a**	**A + B**		**3ad**, 69
5	**7a**, Bn	**8b**, *t*-Bu	 **1b**	**A**		**3ae**, 51
6	**7b**, 4-CbzNHC$_6$H$_4$	**8a**, Bn	**1b**	**A + B**		**3af**, 90

Table 2 The Three-Component One-Pot Sequential Synthesis of 5-Arylhydantoin **3** (continued)



Entry	Azide, R^1	Isocyanate, R^2	Acid	Method	Hydantoin	Product, yield (%)
7	**7c**, 4-$MeOC_6H_4$	**8c**, 4-$MeOC_6H_4$	**1b**	**A** + **B**		**3ag**, 72
8	**7a**, Bn	**8a**, Bn	 **1c**	**A**		**3ah**, 63
9	**7c**, 4-$MeOC_6H_4$	**8c**, 4-$MeOC_6H_4$	**1c**	**A** + **B**		**3ai**, 95
10	**7c**, 4-$MeOC_6H_4$	**8a**, Bn	 **1d**	**A**		**3aj**, 62[a]
11	**7c**, 4-$MeOC_6H_4$	**8c**, 4-$MeOC_6H_4$	**1d**	**A**		**3ak**, 69[a]
12	**7c**, 4-$MeOC_6H_4$	**8d**, 4-$MeOC_6H_3CH_2$	 **1e**	**A**		**3al**, 45
13	**7c**, 4-$MeOC_6H_4$	**8c**, 4-$MeOC_6H_4$	**1e**	**A**		**3am**, 40

[a] Yield calculated with respect to the azide.

In conclusion, we have developed a novel and efficient process for the synthesis of libraries of 1,3-disubstituted 5-arylhydantoins having a high degree of diversity through a three-component sequential reaction involving simple and readily accessible starting materials. The operational simplicity and the good chemical yields, combined with favorable atom-economy aspects and a small number of synthetic steps, render this new synthetic strategy attractive and promising for the preparation of hydantoins and useful derivatives such as unnatural α-amino acids.

General Procedure for the Synthesis of 5-Arylhydantoins 3 Starting from α-Bromo Arylacetic Acids 1 and Carbodiimides 2

To a stirred solution of **1** (1 equiv) in CH_2Cl_2 (0.1 M solution) carbodiimide **2** (1.5 equiv), followed by TMP (1 equiv), was added at r.t., and the mixture was stirred overnight. When needed, a 2 N NaOH aq solution (10% in volume) was added and the mixture stirred for 2 h. Afterwards, 1 N HCl aq solution was added, and the resulting mixture extracted with CH_2Cl_2. The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by flash chromatography.

General Procedure for the Synthesis of 5-Arylhydantoins 3 under the Three-Component, One-Pot Sequential Process

To a stirred solution of the azide **7** (1.5 equiv) in anhyd CH_2Cl_2 (0.1 M) a solution of Ph_3P in anhyd CH_2Cl_2 was added dropwise at r.t. After 4 h the isocyanate **8** (1.5 equiv) was added, and the reaction stirred for 3 h. Finally, TMP (1 equiv), followed by the acid **1** (1 equiv), was added and the solution stirred overnight. When needed, a 2 M NaOH aq solution (10% in volume) was added and the mixture stirred for 2 h. Afterwards, 1 M HCl aq solution was added and the resulting mixture extracted with CH_2Cl_2. The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The crude material was purified by flash chromatography.

1,3-Dicyclohexyl-5-phenylimidazolidine-2,4-dione (3a)

R_f = 0.43 (hexane–EtOAc, 90:10). FTIR (Nujol): ν = 1700, 1684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (m, 5 H), 5.43 (s, 1 H), 4.00 (m, 1 H), 3.66 (m, 1 H), 2.32 (m, 2 H), 1.76 (m, 8 H), 1.36 (m, 10 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.7, 145.8, 134.5, 129.2, 128.9, 126.1, 79.1, 53.7, 53.1, 34.4, 34.3, 28.5, 28.4, 25.9, 25.8, 25.7, 25.1, 24.7, 24.6. ESI-MS: *m/z* (%) = 363.1 (86) [M^+ + Na], 341.1 (100) [M^+ + 1].

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(11) The reaction was carried out in dioxane because carbodiimide **2f** was insoluble in CH_2Cl_2.

(12) The lower yields obtained with *N*,*N*′-dialkylcarbodiimides in the three-component process are probably due to lower yields in the Staudinger reaction.