A Facile Synthesis of 1,3,5-Trisubstituted Hydantoins via Ugi Four-Component Condensation

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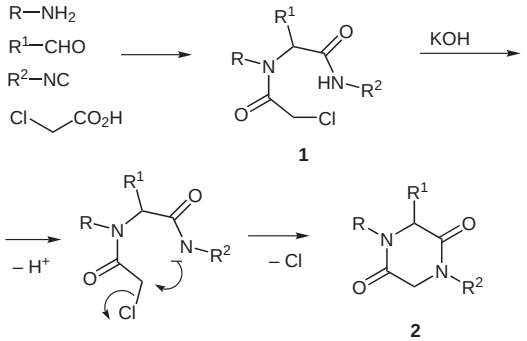
Abstract: A facile access to 1,3,5-trisubstituted hydantoins is achieved by combining an Ugi four-component condensation with a base-induced cyclization. This two-step sequence, which differs from any other method, is experimentally simple and allows a wide variety in the substitution pattern. In this synthesis the acid component, namely trichloroacetic acid, acts as a carbonic acid equivalent.

Key words: Ugi four-component condensation (U-4CC), isocyanides, heterocycles, cyclizations, multicomponent reactions

The synthesis of iminohydantoins[2] and iminothiohydantoins[3] is one of the earlier achievements of the Ugi four-component condensation.[4] The preparation of these heterocyclic systems, apart from the synthetic interest, is a remarkable example of the versatility of the Ugi reaction with respect to the variation of the components: iminohydantoins and iminothiohydantoins are obtained by employing cyanic and thiocyanic acid as the acid component, respectively.

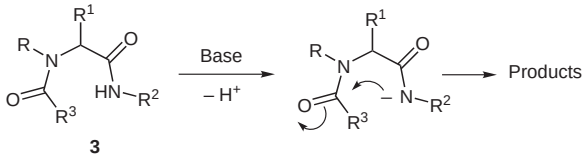
Although a wide variety of heterocyclic systems is obtainable by means of the Ugi reaction, either directly[5] or by post-condensation modifications,[6] only one report dealing with the synthesis of hydantoins via isocyanide-based multicomponent reactions has appeared in the literature.[7] In this paper a very elegant route to the desired products via a Ugi five-component condensation followed by a BOC-deprotection and cyclization is described.



Scheme 1 Formation of 2,5-diketopiperazines **2** from Ugi-4CC adducts **1**

In a previous paper[8] we reported that the Ugi-4CC adducts **1** arising from primary amines, aldehydes, isocyanides, and chloroacetic acid underwent a ring-closure reaction to 2,5-diketopiperazines **2** upon treatment with potassium hydroxide. The key step is the formation of the internal nucleophile by deprotonation of the amide nitrogen (Scheme 1).

In principle, an Ugi-4CC adduct **3** arising from primary amines, aldehydes, isocyanides, and carboxylic acids may undergo an intramolecular nucleophilic attack in basic medium, but the low electrophilic strength of the α-acylamino group prevents it (Scheme 2).



Scheme 2 Hypothetical reactivity of Ugi 4-CC adducts **3**

Keeping in mind the above results we decided to prepare a number of Ugi-4CC in which the electrophilic strength of the α-acylamino group is enhanced. In order to achieve this goal we reacted primary amines **4**, aldehydes **5**, trichloroacetic acid (**6**), and isocyanides **7**. The reaction took place smoothly in methanol at room temperature to afford the expected adducts **8** in low to good yields.[9] A strong yield improvement for compounds **8c**,**d** was achieved by performing the Ugi reaction with the preformed imine in Et_2O (Table 1, entries 3, 4).[10] With the exception of compounds **8g**,**i** the Ugi adducts precipitated from the reaction mixture in a pure form. The structure of compounds **8** was confirmed by analytical and spectral data. In the IR spectra the amide NH and the CCl_3 absorptions were detected at 3256–3368 cm^{-1} and 697–846 cm^{-1}, respectively. In most of the spectra the trichloroacetamide and the amide carbonyl groups gave two well-separated peaks at 1654–1694 cm^{-1} and 1651 cm^{-1}, respectively. Furthermore, when *n*-hexyl- and cyclohexyl isocyanide were employed as the starting isocyanide, a strong absorption at about 2920 cm^{-1}, due to the $C–H_{aliph}$ stretching was detected. In the ^1H NMR spectra of **8**, the proton in the position α to the amide group was detected at δ = 5.70–6.17.

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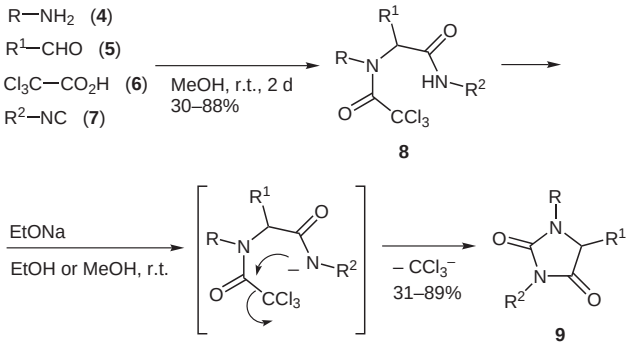
Upon treatment with sodium ethoxide in ethanol or methanol, compounds **8** underwent a ring-closure reaction to give hydantoins **9** in good yields. A possible mechanism is reported in Scheme 3.



4	R
a	C_6H_5
b	4-ClC_6H_4
c	4-$CH_3C_6H_4$
d	$C_6H_4CH_2$

5	R^1
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-ClC_6H_4
d	2-Pyridyl

7	R^2
a	*c*-C_6H_{11}
b	*n*-C_6H_{13}
c	4-(Phenylazo)phenyl
d	4-$CH_3C_6H_4$

8,9	R	R^1	R^2
a	C_6H_5	C_6H_5	*c*-C_6H_{11}
b	4-ClC_6H_4	4-$CH_3C_6H_4$	*c*-C_6H_{11}
c	4-ClC_6H_4	C_6H_5	*c*-C_6H_{11}
d	4-ClC_6H_4	C_6H_5	*n*-C_6H_{13}
e	C_6H_5	C_6H_5	4-(Phenylazo)phenyl
f	4-$CH_3C_6H_4$	4-ClC_6H_4	*n*-C_6H_{13}
g	$C_6H_4CH_2$	4-$CH_3C_6H_4$	*n*-C_6H_{13}
h	C_6H_5	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$
i	C_6H_5	2-Pyridyl	*c*-C_6H_{11}
j	4-ClC_6H_4	2-Pyridyl	*n*-C_6H_{13}

Scheme 3 Two-step route towards 1,3,5-trisubstituted hydantoins **9**

The presence of chloroform, arising from the reaction of the CCl_3^- anion with a proton source, was confirmed in earlier experiments by GCMS of the crude reaction mixture. With regard to the cyclization step, it was essential to add the sodium ethoxide solution to a suspension of **8** in a relatively quick manner, until a clear solution resulted. In this case hydantoins **9** precipitated from the mother liquors in an almost pure form, otherwise, mixtures of hydantoins and the starting Ugi products were always obtained (Table 2).

Again, the IR spectra gave useful information about the structure of compounds **9**. In fact, the absorptions due to the amide NH and to the CCl_3 group were not detected. Furthermore, a CO peak at 1766–1781 cm^{-1} was found, in agreement with the presence of a cyclic urea moiety. The CO absorptions due to the γ-lactam and the amide moieties were overlapped and a unique peak at 1699–1722 cm^{-1} was observed. As expected, neither the NH proton signal in the ^1H NMR spectra nor the CCl_3 carbon signal in the ^{13}C NMR was detected. Furthermore, in the ^1H NMR spectra of compounds arising from *n*-hexyl and cyclohexyl isocyanide, a lower multiplicity of the signals attributable to the proton(s) linked to the carbon adjacent to the nitrogen was seen.

The fact that hydantoins **9g**,**i** were obtained without isolating the Ugi adducts **8g**,**i** shows that the synthesis of hydantoins **9** from primary amines **4**, aldehydes **5**, trichloroacetic acid (**6**), and isocyanides **7** can be performed by a simple one-pot, two-step procedure.[12]

Table 1 Prepared Ugi-4CC Products **8a**–**f**,**h**,**j**

Entry	Product	Mp (°C)[a]	Yield (%)[b]	Yield (%)[c]
1	**8a**	186–187	58	
2	**8b**	171–172	54	
3	**8c**	187–188	33	75
4	**8d**	119–120	30	70
5	**8e**	201–202	88	
6	**8f**	141–142	65	
7	**8h**	208–209	67	
8	**8j**	126–127	65	

[a] Solvent: *i*-PrOH.
[b] Reaction performed in MeOH.
[c] Reaction performed with the preformed imine in Et_2O.

Table 2 Prepared Hydantoins **9a**–**j**[11]

Entry	Product	Base (equiv)[a]	Mp (°C)[b]	Yield (%)
1	**9a**	1.21	130–131	77
2	**9b**	0.67	180–181	89
3	**9c**	1.18	191–192	85
4	**9d**	0.58	105–106	69
5	**9e**	2.00	222–223	52
6	**9f**	0.31	83–84	72
7	**9g**	1.42	144–145	33
8	**9h**	0.36	145–146	57
9	**9i**	0.52	131–132	31
10	**9j**	0.08	101–102	45

[a] Equivalents of EtONa employed for the cyclization of **8**.
[b] Solvent: *i*-PrOH.

The synthesis of 1,3,5-trisubstituted hydantoins is usually accomplished by reacting N-substituted α-amino acids or their esters with isocyanates, either in solution[13] or in solid phase.[14] A viable route consists of the N-alkylation of mono- and disubstituted hydantoins.[15] Methods based on the ring transformation of 5-bromobarbituric acid,[16] imidazo[3,4-*a*]quinazoline,[17] and benzoxazol-2-one derivatives[18] are less important. Other methods, such as the irradiation of 1,2-dihydropyrazol-3-one derivatives[19] and the hydrolysis of their 5-phenylimino derivatives[20] have occasionally been used.

Recently, a very elegant and straightforward three-component synthesis of 1,3,5-trisubstituted hydantoins based on the reaction of N,N′-disubstituted ureas with carbon monoxide and aldehydes in the presence of a palladium catalyst under high pressures has been reported.[21]

The synthesis described in the present note is advantageous with respect to the known methods since the starting products are commercially available or easily obtainable. Furthermore, neither expensive catalysts nor special apparatus are required. The simple experimental procedure, the possibility of employing reagents and solvents as supplied, and the facile isolation of the products from the reaction medium represent additional advantages of this new route to 1,3,5-trisubstituted hydantoins.

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(9) **Synthesis of Ugi Adducts 8a–f,h,j. General Procedure.**
A solution of the amine **4** (12 mmol) in MeOH (10 mL) was treated with aldehyde **5** (finely powdered if solid; 12 mmol), a solution of isocyanide **7** (12 mmol) in MeOH (5 mL), and trichloroacetic acid (**6**, 1.96 g, 12 mmol) in the order given. The reaction mixture was stirred for 2 d at r.t. and then cooled at 0 °C and filtered. The collected solid was washed with a little cold *i*-Pr_2O and then with pentane and dried to give almost pure **8**. Analytical samples were obtained from *i*-PrOH.
2-(*N*-Phenyl-*N*-trichloroacetyl)amino-2-phenylacetic Acid *N*-Cyclohexyl Amide (8a).
IR (KBr): ν = 3275, 3062, 2930, 1688, 1651, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25–7.10 (m, 10 H), 5.81 (s, 1 H), 5.41 (d, *J* = 8.00 Hz, 1 H), 3.94–3.77 (m, 1 H), 1.98–0.89 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.46, 160.66, 138.20, 133.28, 132.40, 130.46, 128.70, 128.44, 128.34, 127.53, 93.01, 69.87, 48.76, 32.60, 32.55, 25.28, 24.69, 24.57 ppm.

(10) **Improved Procedure for the Synthesis of Ugi Adducts 8c,d.**
A mixture of 4-chloroaniline (**4b**, 549 mg, 4.3 mmol), benzaldehyde (**5a**, 456 mg, 4.3 mmol), $CHCl_3$ (10 mL) and anhyd Na_2SO_4 (900 mg) was stirred for 4 h at r.t. and then filtered. The collected solid was washed with $CHCl_3$ (5 mL). The filtrate was evaporated to dryness and the residue dissolved in Et_2O (10 mL). The above solution was cooled at 10 °C and treated under stirring with a solution of isocyanide **7** (4.3 mmol) in Et_2O (5 mL) and then with trichloroacetic acid (**6**, 703 mg, 4.3 mmol). The solution turned violet and the precipitation of the reaction product began within 1 h. After 24 h stirring the reaction mixture was filtered to give almost pure **8**. Another crop was obtained by evaporating the filtrate and stirring the residue with *i*-PrOH (3–4 mL).
2-[*N*-(4-Chlorophenyl)-*N*-trichloroacetyl]amino-2-phenylacetic Acid *N*-Cyclohexyl Amide (8c).
IR (KBr): ν = 3268, 3064, 2927, 1691, 1651, 748 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–6.94 (m, 9 H), 5.88 (s, 1 H), 5.39 (d, *J* = 8.40 Hz, 1 H), 3.85–3.76 (m, 1 H), 1.97–0.96 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.29, 160.61, 136.38, 134.45, 134.06, 132.98, 130.51, 128.99, 128.52, 127.67, 92.84, 69.26, 48.87, 32.60, 25.28, 24.69 ppm.

(11) **Synthesis of Hydantoins 9a–f,h,i. General Procedure.**
A 1.0 M ethanolic solution of NaOEt was dropped into a well-stirred suspension of **8** (1.0 mmol) in EtOH (4–5 mL) until a clear solution was obtained. Within a few minutes the precipitation of a solid product commenced. The suspension was cooled at 0 °C and filtered to give almost pure **9**. Analytical samples were obtained from *i*-PrOH.
1-(4-Chlorophenyl)-3-cyclohexyl-5-phenylhydantoin (9a).
IR (KBr): ν = 3031, 2928, 1773, 1704 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.49–7.03 (m, 10 H), 5.36 (s, 1 H), 4.09–3.97 (m, 1 H), 2.26–1.17 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.85, 154.51, 136.51, 133.33, 129.14, 128.94, 128.90, 126.58, 124.45, 120.17, 63.52, 52.05, 29.26, 29.11, 25.75, 25.72, 24.92 ppm. Anal. Calcd for $C_{21}H_{22}N_2O_2$ (334.41): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.71; H, 6.81; N, 8.12.

(12) **Synthesis of Hydantoins 9g,i. General Procedure.**
Supporting Ugi reagents were allowed to react as described in ref. 11, general procedure. The clear reaction mixture was treated with 1.0 M ethanolic NaOEt and stirred for 15 min at r.t. The resulting suspension was cooled at 0 °C and filtered to give almost pure **9g,i**. Analytical samples were obtained from *i*-PrOH.
1-Benzyl-3-hexyl-5-(4-methylphenyl)hydantoin (9g).
IR (KBr): ν = 3033, 2929, 1766, 1698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.02 (m, 9 H), 5.11 (d, *J* = 14.7 Hz, 1 H), 4.53 (s, 1 H), 4.03–3.94 (m, 1 H), 3.68 (d, *J* = 14.7 Hz, 1 H), 2.37 (s, 3 H), 2.25–1.15 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.25, 156.33, 138.92, 135.50, 129.79, 128.65, 128.21, 127.77, 127.24, 62.02, 44.14, 29.32, 29.15, 25.72, 25.68, 24.82, 21.00 ppm. Anal. Calcd for $C_{23}H_{28}N_2O_2$ (364.48): C, 75.79; H, 7.74; N, 7.69. Found: C, 75.88; H, 7.41; N, 7.95.

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