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The Synthesis of Hydantoin 4-Imides on Solid Support

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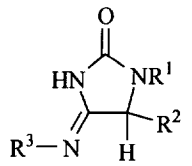
Abstract: Solid phase synthesis of hydantoin 4-imides via the 'Ugi' 4-component condensation reaction is reported. This process is then shown to proceed well in a combinatorial fashion, by immobilization of the isocyanide component on Wang resin. The desired product is then released from the support upon treatment with 20% trifluoroacetic acid-CH_2Cl_2. Copyright © 1996 Elsevier Science Ltd

The field of drug discovery has seen ample demonstrations of the utility of combinatorial chemistry. A prerequisite for efficient construction of compound 'libraries' is that sufficient diversity is included. The use of multi-component condensation (MCC) chemistry as purveyor of such diversity has been described.[1,2] We have previously described novel 'post' Ugi 4CC chemistry in the preparation of imidazoles,[3] pyrroles[4] and lactams.[5] In this Letter we discuss the synthesis of hydantoin 4-imides **1** on solid support, based upon the Ugi 4CC reaction.

Hydantoin 4-imides **1** have found application within key therapeutic areas. Namely, imide **2** has shown activity as an antineoplastic,[6] and imide **3** (Imexon) has shown promising utility as an immunomodulator.[7]



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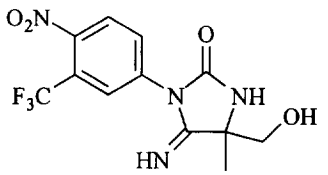

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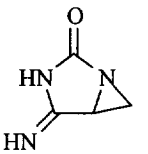
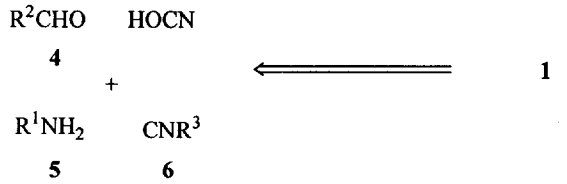


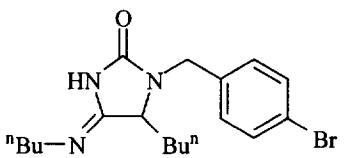
3

Early on in Ugi's work, it was shown that the reaction of aldehydes **4**, amines **5** and isocyanides **6** in the presence of HOCN led to heterocycles **1** *via* incorporation of the acid counterion (Scheme 1).[8] In the course of studies utilizing solid-phase chemistry and the OntoBLOCK system,[9] it was recognized that the preparation of hydantoin 4-imides **1** could be accessed *via* polymer support.



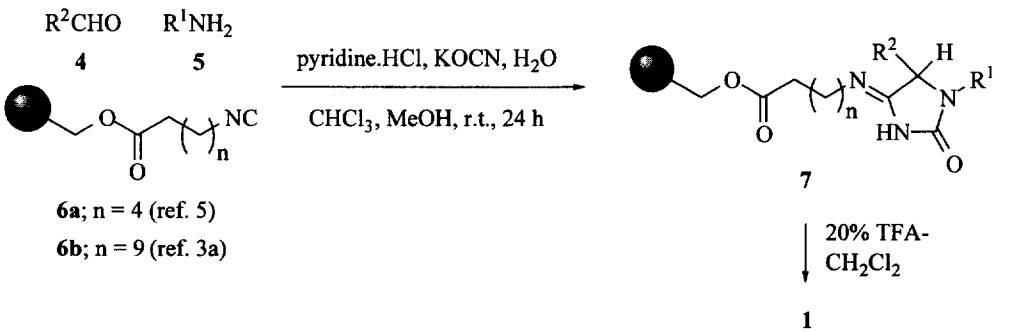
Scheme 1

Since a key step involves trifluoroacetic acid (TFA)-assisted cleavage of the product from the resin, the stability of compounds **1** to TFA exposure was tested. Thus, **1a** was prepared *via* standard solution-phase protocols,[8] then stirred overnight with varying concentrations of TFA in CH_2Cl_2 (2, 5, 10, 20%). Solvent was removed, and the characteristics of the residue then compared with those of the starting material. In each case, the products were identical to the starting hydantoin 4-imide **1a**. Therefore, it was expected that solid-phase construction of compounds **1** would not be followed by deleterious acid-induced decomposition reactions.



1a

With the isocyanide component chosen to be immobilized on solid support, the Wang resin[10]-supported isocyano compounds **6**[3a,8] were prepared as previously described. Thus, resins **6a**, **6b** were stirred with aldehydes **4**, amines **5**, and *in situ*-generated HOCN[11] in a 5:5:1 MeOH-$CHCl_3$-H_2O mixture (Scheme 2). After stirring for 24 h, the resins **7** were filtered, then washed (MeOH (3x), DMF (3x), CH_2Cl_2 (3x)) and treated with 20% TFA-CH_2Cl_2 to provide the desired hydantoin 4-imides **1** in 36 - 81% yields (Table 1).



Scheme 2

Examination of Table 1 reveals that the reaction is quite tolerant to the nature of the amine **5**. However, it was found to be highly dependent on the nature of the carbonyl component **4**. While aliphatic (branched and unbranched) aldehydes worked quite well, product from aromatic aldehydes under these reaction conditions was not evident. This is currently under investigation.[12]

Table 1. Yields for Hydantoin 4-imides **1** Formed from Four-Component Condensation.[a,b]

entry	R^1	R^2	R^3	**1** (% Yield)
a	*n*-C_8H_{17}	*n*-C_3H_7	-$(CH_2)_{10}CO_2H$	77
b	*sec*-C_4H_9	*trans*-$(CH_2)_2CH{=}CH(CH_2)_4CH_3$	-$(CH_2)_{10}CO_2H$	75
c	*i*-C_3H_7	*n*-C_3H_7	-$(CH_2)_{10}CO_2H$	41
d	*p*-$BrPhCH_2$	*n*-C_7H_{15}	-$(CH_2)_{10}CO_2H$	62
e	*n*-C_4H_9	*sec*-C_4H_9	-$(CH_2)_{10}CO_2H$	81
f	*p*-$BrPhCH_2$	*n*-C_3H_7	-$(CH_2)_{10}CO_2H$	55
g	*p*-$ClPhCH_2$	*n*-C_3H_7	-$(CH_2)_{10}CO_2H$	59
h	*n*-C_4H_9	*n*-C_3H_7	-$(CH_2)_{10}CO_2H$	63
i	*m*-F-*o*-MePh	-$CH_2CH(CH_3)CH_2C(CH_3)_3$	-$(CH_2)_5CO_2H$	61
j	*i*-C_5H_{11}	-$CH(CH_2CH_3)(CH_2)_3CH_3$	-$(CH_2)_5CO_2H$	36
k	-$CH(CH_3)CH_2CH(CH_3)_2$	*c*-C_6H_{11}	-$(CH_2)_5CO_2H$	75

[a] All compounds were synthesized in moderate to good purity. Analytical TLC of the cleavate revealed predominant presence of the required product, along with minor amounts of unidentified side-products. All yields correspond to preparative TLC-purified material, and are relative to the initial loadings of the isocyanides **6a,b**.

[b] We have subjected the crude residues to biological screening, without the need for further purification.

A representative experimental is as follows: To a dry, pre-silylated scintillation vial (initial rinse with 1% Me_3SiCl-PhMe, followed by regular rinse with water, acetone, ether) was added in a sequential fashion the following: resin **6b** (0.50 g, 0.4 mmol), chloroform (2.5 mL), butyraldehyde (0.18 mL, 2 mmol, 5 mol eq), potassium cyanate (0.324 g, 4 mmol, 10 mol eq), water (0.5 mL), methanol (2.5 mL), 4-chlorobenzylamine (0.24 mL, 2 mmol, 5 mol eq) and finally pyridine.HCl (0.462 g, 4 mmol, 10 mol eq). The heterogeneous mixture was stirred for 24 hours; the contents were then filtered, and the residue washed alternately with methanol (3x) and dimethylformamide (3x), followed by dichloromethane (3x) and methanol (3x). The resin was then agitated with 20% TFA-CH_2Cl_2 (10 mL, 20 minutes), drained, followed by further agitation with 20% TFA-CH_2Cl_2 (10 mL, 10 minutes). The resultant yellow solution was evaporated, yielding a light brown residue. Flash column chromatography furnished the required imide **1g** as a white powder (0.11 g, 59%). ^1H

NMR (400 MHz, CD_3OD) δ 0.78 (t, 3H, J = 7.2 Hz, $\underline{CH_3}$), 0.89-1.05 (m, 2H), 1.22-1.34 (br s, 12H), 1.50-1.59 (br s, 4H), 1.64-1.81 (m, 2H), 2.14 (t, 2H, J = 7.2 Hz, $HO_2CC\underline{H_2}$), 3.21-3.37 (m, 2H, $C\underline{H_2}N{=}C$), 4.13 (t, 1H, J = 3.2 Hz, $C\underline{H}$), 4.17, 4.68 (2d, 2H, J_{gem} = 16.0 Hz, AB quartet, $C\underline{H_2}Ar$), 7.24, 7.28 (2d, 4H, J_{vic} = 8.0 Hz, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ 12.9, 15.2, 26.2, 26.7, 28.5, 29.2, 29.36, 29.39, 29.44, 29.48, 30.9, 37.1, 42.5, 43.6, 60.6 ($\underline{C}H$) 128.6, 129.5, 133.2, 136.5 (aromatic C's), 169.45 ($\underline{C}O_2H$), 169.47, 177.6 (C=N, C=O) ppm; ESIMS, m/z for $C_{24}H_{35}ClN_3O_3$ $[M - H]^-$: 448.5.

In conclusion, we have successfully demonstrated that the condensation of aliphatic aldehydes **4**, amines **5**, Wang resin-supported isocyanides **6** and hydrazoic acid provides a combinatorial method for the synthesis of hydantoin 4-imides **1**. Based upon the commercial availability of amines, aldehydes and isocyanides, a large combinatorial library of structurally diverse hydantoin 4-imides may be produced.

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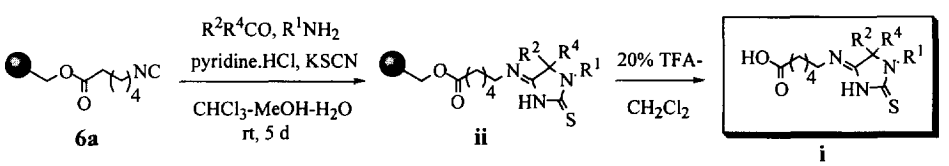
11. We found that HXCN could be conveniently generated *in situ*, by the addition of pyridine.HCl to KXCN (X=O,S).
12. In addition to the preparation of hydantoin 4-imides **1**, we briefly examined the preparation of 2-thiohydantoin 4-imides (**i**). Thus, exposure of resin **6a** to similar conditions as those described above, except for addition of KSCN[11] instead of KOCN, and addition of ketones instead of aldehydes, gave resins (**ii**). Treatment with 20% TFA-CH_2Cl_2 as before gave the required 2-thiohydantoin 4-imides (**i**) in low yields (6-11%).



6a **ii** **i**

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