Pergamon

Tetrahedron, Vol. 53, No. 19, pp. 6653-6679, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00223-8

Exploitation of the Ugi 4CC Reaction: Preparation of Small Molecule Combinatorial Libraries *via* Solid Phase

Kevin M. Short, Brett W. Ching and Adnan M.M. Mjalli*

Ontogen Corporation, 2325 Camino Vida Roble, Carlsbad CA 92009

***Abstract**: The potential of the Ugi 4CC reaction has been explored with regard to the preparation of large combinatorial libraries of small organic molecules of varying structures. These include small-ring lactams, α-(dialkylamino)amides, hydantoin 4-imides, 2-thiohydantoin 4-imides and 5-(1'-aminoalkyl)tetrazoles.* © 1997 Published by Elsevier Science Ltd.

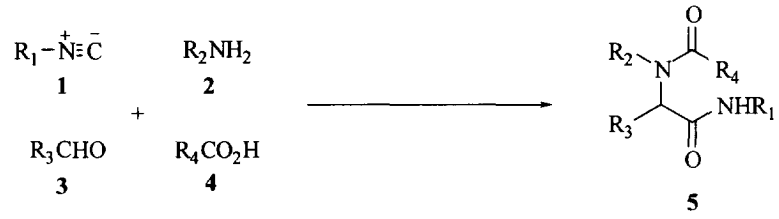
INTRODUCTION

The field of solid-phase chemistry has witnessed an explosion of interest in recent years.[1] Merrifield's early work[2] led to efficient methods for amide and ester coupling techniques, crucial methodologies in the preparation of polypeptides.[3] Only in recent years, however, has the chemistry community explored other reactions on solid phase. The list of these is rapidly expanding; it has now become commonplace to see reactions reported in major journals.[4]

The wide choice of reactions on solid-phase has obvious implications for automation.[5] Recent advances in this area have now led to the burgeoning field of combinatorial chemistry.[6] Large libraries of non-peptidyl, small organic molecules have been prepared using this approach and the combination of this with high-throughput screening techniques has provided lead compounds against many biological targets.

It is recognized that in order to maximize the potential for generating 'hits' in biological screens, one should include as much diversity as possible.[7] An ideal way of doing this is to design the solid-phase reaction (or sequence of reactions) to include a 'multi-component condensation'.[8] Provided that the reagent inputs are readily available, the potential for generating a very large array of products in one step then becomes very attractive.

Thus, the Ugi four component condensation (4CC) reaction, amongst others, is a candidate for the installation of maximum diversity. The reaction of isocyanide **1**, amine **2**, aldehyde **3** (or ketone) and carboxylic acid **4** leads to the α-(acylamino)amide **5** (Scheme 1).[9] The scope of this reaction has been comprehensively explored. In conjunction with a genetic algorithm, Weber and co-workers reported a relatively active thrombin inhibitor[10] based upon the solution phase Ugi 4CC reaction.



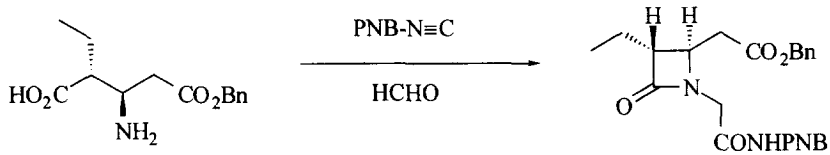
Scheme 1

The Ugi 4CC reaction has also been carried out on solid support[11] by attachment to one of the functional group inputs. Although the utility of the Ugi 4CC reaction is important by itself, further chemical manipulation of the Ugi 4CC product makes the reaction even more attractive. This has been illustrated in the solid-phase preparation of pyrroles[11d,f] and imidazoles,[11c] attractive pharmacophoric moieties in their own right. In this manuscript, however, we wish to report on the solid-phase preparation of small-ring lactams,[12] α-(dialkylamino)amides, hydantoin 4-imides,[13] 2-thiohydantoin 4-imides and 5-(1'-aminoalkyl)tetrazoles. Each example is a result of a variation on the 'classical' Ugi 4CC reaction.[9]

DISCUSSION

Small-Ring Lactams: Solution Phase

An adaptation of the Ugi 4CC reaction involves connection of two of the functional groups **1** → **4** in the starting material, thereby forming a cyclic species. This has been exploited, to good effect, by several groups in the synthesis of pharmaceutically interesting β-lactams (Scheme 2). Here, the amine component **2** and carboxylic acid component **4** are intramolecularly disposed within the starting material (β-alanine and derivatives thereof).[14,15]

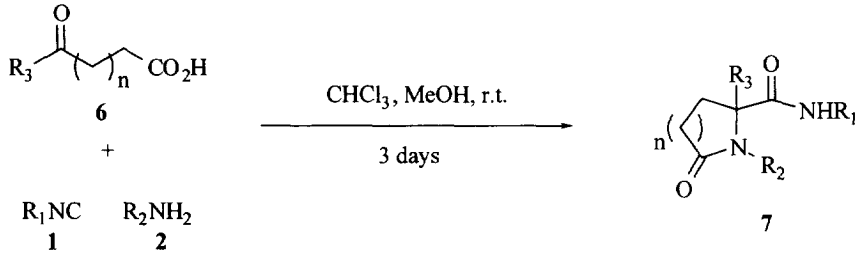


Scheme 2

To our knowledge, a case in which the aldehyde component **3** and carboxylic acid **4** are intramolecularly disposed has not been reported.[16] This is unsurprising given the commercial limitations of the necessary

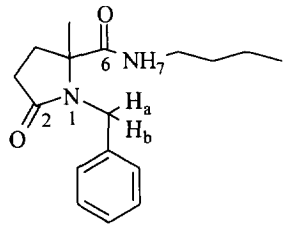
starting materials.[17] On the other hand, a wide array of compounds in which the aldehyde component **3** is replaced by a *ketone* component **6** (ω-ketoacids) are available.

In a model study, levulinic acid **6a** was exposed to benzylamine **2a** and *n*-butyl isocyanide **1a** under the Ugi 4CC reaction conditions (chloroform:methanol; 3:1, 0.2 M, 3 days, r.t.)(Scheme 3).



Scheme 3

After a simple aqueous work-up, the only product isolated was the expected γ-lactam **7a**. This was confirmed by examination of ^{1}H and ^{13}C NMR data, in addition to analysis by electrospray mass spectrometry (ESMS). Thus, the presence of an AB quartet centered at δ4.35 was consistent with installation of diastereotopic benzylic protons $\mathbf{H_{a,b}}$. Also, a triplet at δ6.27 was observed in $CDCl_3$ and was absent in CD_3OD. This observation supports the existence of an exchangeable amide proton $\mathbf{H_7}$. Signals at δ173.3 and δ176.5 in the ^{13}C NMR spectrum were strongly indicative of amide carbonyls $\mathbf{C_{2,6}}$; a signal at δ68.0 corresponded to a carbon α- to both the lactam nitrogen and acyclic amide carbonyl *i.e.* $\mathbf{C_5}$. Finally, observation of a positive ion mode ESMS signal corresponding to 289 confirmed the structure as lactam **7a**.



7a

This study was extended to include other primary amines **2** and ω-ketoacids **6** (Table 1). Examination of the data reveals that the reaction is limited to the formation of 5- and 6-membered ring lactams: in entry **f**,

starting ketoacid **6** (R_3 = Me, n = 3) was recovered unchanged. In addition, ω-aroylacids (entries **b** and **e**) appeared to hinder the course of the reaction as, in these cases, the product lactams were produced in only low yields.

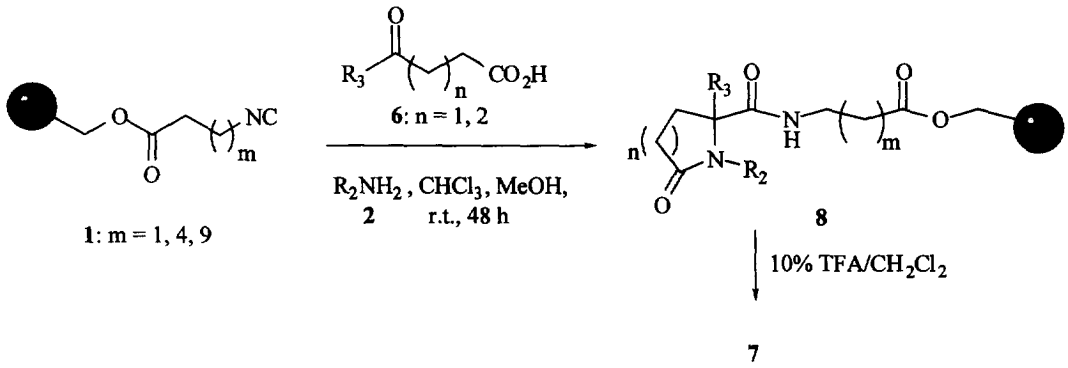
Table 1. Yields for Lactams **7** Formed from Solution Phase Four-Component Condensation Reaction

entry	n	R_1	R_2	R_3	% Yield
7a	1	*n*-Bu	Bn	Me	98
7b	1	*n*-Bu	Bn	*p*-BrPh	33
7c	1	*n*-Bu	*n*-Bu	Me	83
7d	2	*n*-Bu	Bn	Me	70
7e	2	*n*-Bu	*n*-Bu	Ph	20
7f	3	*n*-Bu	Bn	Me	0[a]

[a] The ω-ketoacid was recovered unchanged from the reaction mixture.

Small-Ring Lactams: Solid-Phase

That this novel reaction could possibly be carried out in a combinatorial manner led us to consider polymer support of one of the inputs. Support of the isocyanide component **1** was considered to be best suited for this purpose. Thus, resin-bound isocyanides **1**[11c] (derived from Wang[18] resin) were reacted with a series of ω-ketoacids **6** and primary amines **2** in a methanol-chloroform (1:3) mixture (Scheme 4). After stirring at room temperature for 3 days, the resins **8** were washed (chloroform (3x), methanol (3x), followed by chloroform (3x)); the solvent and reagent-free resins **8** were then cleaved with 10% trifluoroacetic acid-dichloromethane (2 x 20 minutes). Solvent was then removed, leaving an oily residue. ^{1}H, ^{13}C NMR and TLC analyses of many of the examples showed the expected lactams **7** to be practically homogeneous.



Scheme 4

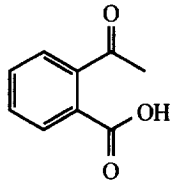
Examination of Table 2 reveals that the Ugi 4CC lactamization reaction is general for a wide range of primary amines **2**, alkyl isocyanides **1**, alkyl- and carboxy-substituted ω-ketoacids **6**. ^1H and ^{13}C NMR analyses of lactams **7g-n** showed attributes similar to that of **7a** (*vide supra*). In addition, characteristic signals corresponding to carboxy-substituted methylene groups (-$C\underline{H}_2CO_2H$, triplet at ~δ2.3) were observed in each case. Finally, all lactams **7g-n** showed correct electrospray mass spectral characteristics, as measured in the negative mode expected for carboxylic acids.

Table 2. Yields for Lactams **7** Formed from Solid Phase Four-Component Condensation Reaction[a]

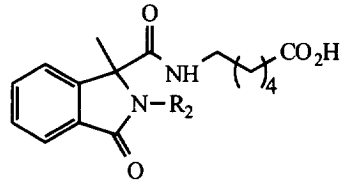
entry	n	R_2	R_1	R_3	% Yield
7g	1	Bn	$(CH_2)_{10}CO_2H$	Me	93
7h	1	*n*-$C_{11}H_{23}$	$(CH_2)_5CO_2H$	Me	98
7i	1	$CH_2C{\equiv}CH$	$(CH_2)_5CO_2H$	Me	47
7j	1	Ph	$(CH_2)_{10}CO_2H$	CO_2H	84
7k	1	Bn	$(CH_2)_2CO_2H$	Me	91
7l	2	Bn	$(CH_2)_2CO_2H$	Me	60
7m	2	Bn	$(CH_2)_{10}CO_2H$	Me	96
7n	1	*n*-Bu	$(CH_2)_{10}CO_2H$	Me	94

[a] All yields correspond to column chromatography-purified material and are relative to the initial loadings of the isocyanides **1**.

The Ugi 4CC lactamization reaction was additionally probed in benzo-fused examples, whereby *o*-acetylbenzoic acid was exploited as the ketoacid input. Thus, isocyanide **1c** was reacted with *o*-acetylbenzoic acid **9** and two primary amines, in a manner identical with the preparation of lactams **7g-n**. After evaporation of the trifluoroacetic acid-dichloromethane solvent, TLC analysis unveiled one major component present in each case. Flash column chromatography conducted on the residue revealed the expected benzo-fused lactams **10a** and **10b**. Similar spectral characteristics were observed for **10a** and **10b** as with lactams **7g-n**.



9



10a: R_2 = n-C_8H_{17}
10b: R_2 = allyl

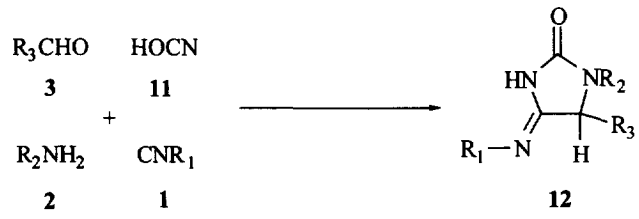
In summary, it has been shown that the Ugi 4CC-type condensation of ω-ketoacids **6** with isocyanides **1** and amines **2** provides for novel, multisubstituted 5- and 6-membered lactams **7** and **10**. Additionally, attachment of the isocyanide component to Wang resin via an ester linkage provides a means for preparation of a combinatorial array.

Alternative 4CC Pathways

Early in the development of the Ugi 4CC reaction (Scheme 1), it was found that the carboxylic acid component **4** could be replaced by inorganic acids.[9] Whilst in the 'classical' reaction the ultimate product is the α-(acylamino)amide **5**, incorporation of an acid counterion (*i.e.* HOCN, H_2O, HN_3, HSCN) leads to an alternative product. It was thought that these reactions would be amenable to reaction on the solid phase.

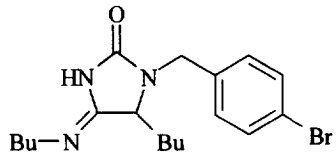
Hydantoin 4-Imides and 2-Hydantoin 4-Imides

The reaction of isocyanides **1**, amines **2** and aldehydes **3** in the presence of HOCN **11** leads to hydantoin 4-imides **12** *via* incorporation of the acid counterion (NCO^-, **11a**, Scheme 5).



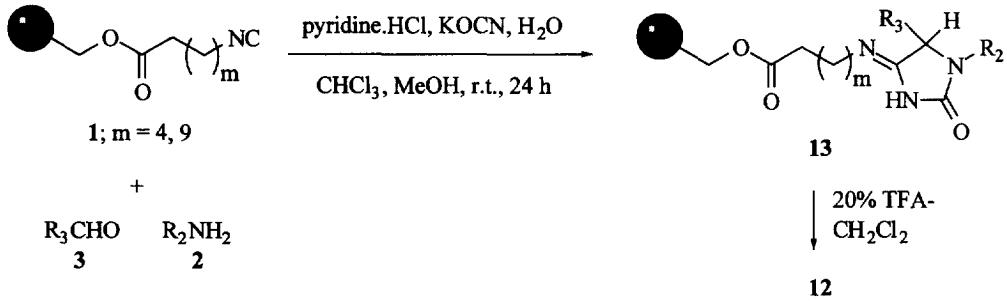
Scheme 5

Although this reaction is well-precedented in solution phase, for combinatorial purposes, the feasibility of carrying out the reaction on solid phase required testing. Since use of the OntoBLOCK system[5] typically involves exposure of the final product to trifluoroacetic acid mixtures, the stability of solution phase-prepared **12** to trifluoroacetic acid was tested. Thus, **12a** was prepared *via* standard solution-phase protocols,[9] then stirred overnight with varying concentrations of trifluoroacetic acid in dichloromethane (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 **12a**. Therefore, it was expected that solid-phase construction of compounds **12a** would not be followed by deleterious acid-induced decomposition reactions.



12a

As with the syntheses of γ- and δ-lactams (*vide supra*), the isocyanide component was chosen to be immobilized on solid support. Thus, isocyanides **1** (m = 4, 9) were stirred with aldehydes **3**, amines **2** and cyanic acid **11** in a 5:5:1 methanol-chloroform-H_2O mixture. After stirring for 24 h, the resins **13** were filtered, then washed (methanol (3x), dimethylformamide (3x), dichloromethane (3x)) and treated with 20% trifluoroacetic acid- dichloromethane (2 x 20 min)(Scheme 6). The resultant residues were column chromatographed, to yield the expected hydantoin imides **12**, in 36 - 81% yields (Table 3).



Scheme 6

Table 3. Yields for Hydantoin 4-imides **12** Formed from Solid Phase Four-Component Condensation Reaction.[a]

entry	R_1	R_2	R_3	% Yield
12b	$(CH_2)_{10}CO_2H$	*n*-C_8H_{17}	*n*-C_3H_7	77
12c	$(CH_2)_{10}CO_2H$	*sec*-C_4H_9	*trans*-$(CH_2)_2CH{=}CH(CH_2)_4CH_3$	75
12d	$(CH_2)_{10}CO_2H$	*i*-C_3H_7	*n*-C_3H_7	41
12e	$(CH_2)_{10}CO_2H$	*p*-$BrPhCH_2$	*n*-C_7H_{15}	62
12f	$(CH_2)_{10}CO_2H$	*n*-C_4H_9	*sec*-C_4H_9	81
12g	$(CH_2)_{10}CO_2H$	*p*-$BrPhCH_2$	*n*-C_3H_7	55
12h	$(CH_2)_{10}CO_2H$	*p*-$ClPhCH_2$	*n*-C_3H_7	59
12i	$(CH_2)_{10}CO_2H$	*n*-C_4H_9	*n*-C_3H_7	63
12j	$(CH_2)_5CO_2H$	*m*-F-*o*-MePh	$-CH_2CH(CH_3)CH_2C(CH_3)_3$	61
12k	$(CH_2)_5CO_2H$	*i*-C_5H_{11}	$-CH(CH_2CH_3)(CH_2)_3CH_3$	36

[a] All yields correspond to preparative TLC-purified material, and are relative to the initial loadings of the isocyanides **1**.

The reagent cocktail was arrived at *via* Ugi's original finding that reaction yields were directly proportional to solvent polarity.[9] Unfortunately, the increase of methanol content on solid phase invariably leads to shrinkage of polystyrene resins, and concomitant lowering of yield. In addition, one method reported in the original work[19] required use of pre-made cyanic acid **11**, an undesirable situation for our purposes. Mineral acid-catalysed decomposition of potassium cyanate **11b** was chosen to form **11** *in situ*. This provides

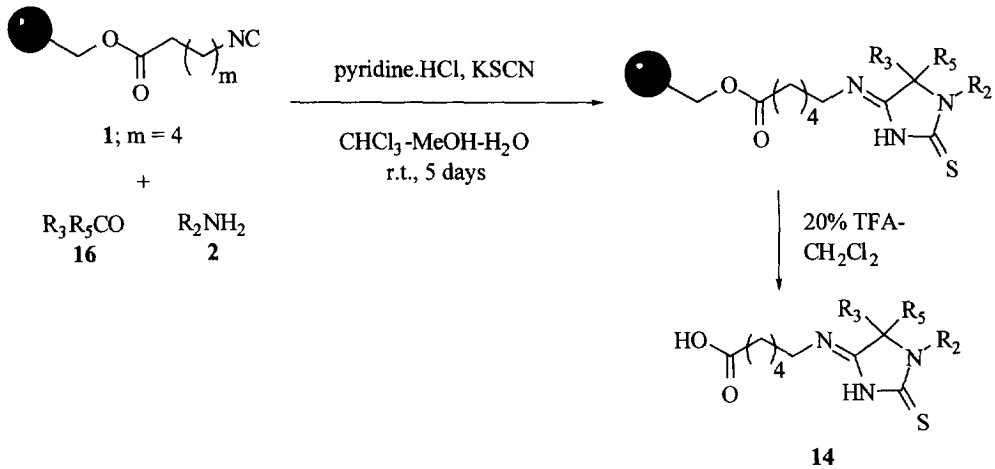
a convenient procedure for automated synthesis allowing the delivery of aqueous potassium cyanate solutions, and methanolic solutions of pyridine hydrochloride, a convenient source of mineral acid.

Examination of Table 3 reveals that the reaction is quite tolerant to the nature of the amine **2**. Aliphatic aldehydes (branched and unbranched) are also tolerated, but product from aromatic aldehydes was not evident. The reasons for this observation are unclear and further studies underway.

As with the lactam work described heretofore, products **12** were confirmed by analysis of ESMS, ^{1}H and ^{13}C NMR spectra. For example, the sole ring methine proton appears as a signal at ~ δ4.1 in the ^{1}H NMR spectra. Also, a signal at ~ δ8.0 with $CDCl_3$ as the NMR solvent, absent with CD_3OD, suggested the presence of the ring amidine NH proton.

In addition to the preparation of hydantoin 4-imides **12**, the synthesis of 2-thiohydantoin 4-imides **14** was also examined briefly.[9] A protocol similar to that for the preparation of compounds **12** was followed for the chemistry leading to **14**, except that potassium thiocyanate **15** was substituted for potassium cyanate **11b**, and ketones **16** were substituted for aldehydes **3**. This is due to the observation that reactions to prepare 2-thiohydantoin 4-imides **14** convert only ketones **16**.[20]

Thus, exposure of isocyanides **1** to ketones **16**, amines **2** and KSCN **15** in a chloroform-methanol-water mixture containing pyridine hydrochloride led to the required 2-thiohydantoin 4-imides **14**, but only in very low yields (Scheme 7, Table 4). This may be related to the very long reaction times necessary for this reaction (5 days), as well as the requirement for high solvent polarity.[9]



14

Scheme 7

Table 4. Yields for 2-Thiohydantoin 4-imides **14** Formed from Solid Phase Four-Component Condensation Reaction.[a]

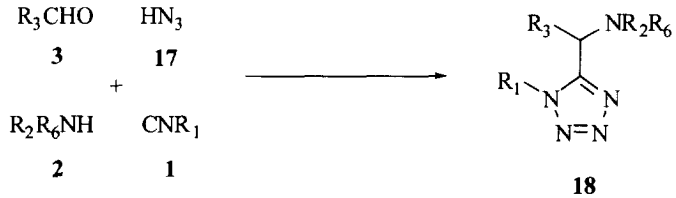
entry	R_2	R_3	R_5	% Yield
14a	*p*-BrPhCH$_2$	CH_3	CH_3	5
14b	*p*-BrPhCH$_2$	-$(CH_2)_5$-		11

[a] Both yields correspond to preparative TLC-purified material, and are relative to the initial loading of the isocyanide **1** (m = 4).

As before, the compounds were confirmed by electrospray mass spectra. Characteristic bromine isotopic doublets also confirmed the compounds' presence. Finally, although the absence of a ring proton supported the structure as in the hydantoin 4-imides **12**, other features in the ^{1}H NMR confirmed **14**. For example, for entry **14a**, a sharp singlet at δ1.25, integrating to 6 protons, is indicative of the presence of 2 magnetically isolated CH_3 groups. Also in entry **14a**, two doublets at δ7.31 and δ7.41 are indicative of a *para*-substituted aryl group.

5-(1'-Aminoalkyl)tetrazoles

Encouraged by our successes in solid-phase Ugi-type 4CC reactions, the 4CC reaction wherein HN_3 **17** replaces the carboxylic acid component was examined (Scheme 8). Here, the products formed are tetrazoles **18**.[9]

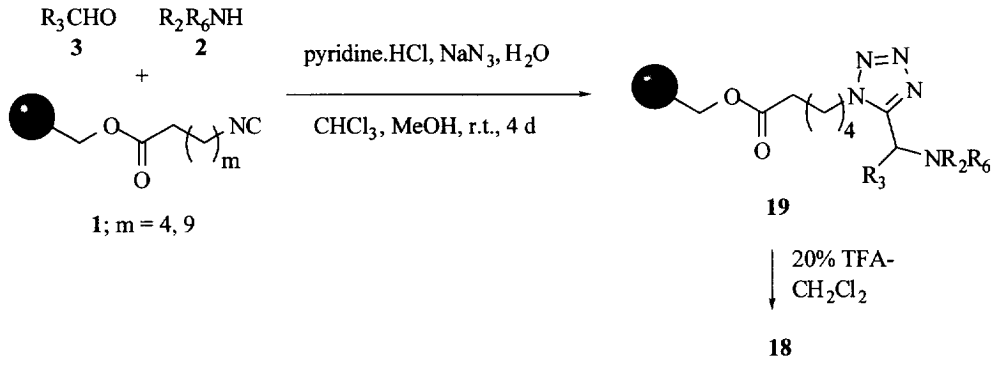


18

Scheme 8

Again, the original preparative method was not used in this reaction *i.e.* use of a 'stock' solution of HN_3. Instead, the reaction on solid phase was attempted by direct use of NaN_3. Thus, exposure of isocyanides **1** to a range of amines **2**, aldehydes **3** and NaN_3 with pyridine hydrochloride in a mixture of methanol-dichloromethane-water (1:1:0.3) for 4 days led to the resins **19**. These were washed alternately with methanol

(3x) and dichloromethane (3x), then agitated with 20% trifluoroacetic acid in dichloromethane (2 x 20 minutes). The solvent was then removed under reduced pressure, revealing residues that were largely pure by TLC analysis. Preparative TLC of the residues led to pure compounds that were consistent with the expected 5-(1'-aminoalkyl)tetrazoles **18** (Scheme 9). A small range of compounds were prepared in moderate yields by this method (Table 5).



Scheme 9

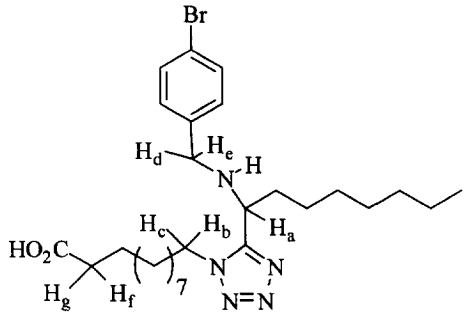
Table 5. Yields for 5-(1'-Aminoalkyl)tetrazoles **18** Formed from Solid Phase Four-Component Condensation Reactions.[a]

entry	R_1	R_2	R_6	R_3	% Yield
18a	$(CH_2)_5CO_2H$	*p*-$BrPhCH_2$	H	*n*-C_7H_{15}	43
18b	$(CH_2)_{10}CO_2H$	Ph	C_2H_5	*trans*-$(CH_2)_2CH{=}CH(CH_2)_4CH_3$	34
18c	$(CH_2)_{10}CO_2H$	$-(CH_2)_5-$		Ph	52
18d	$(CH_2)_{10}CO_2H$	*p*-$BrPhCH_2$	H	*c*-C_6H_{11}	33

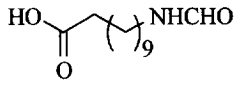
[a] All yields correspond to preparative TLC-purified material, and are relative to the initial loadings of the isocyanides **1**.

Inspection of Table 5 shows that the 4CC reaction to prepare 5-(1'-aminoalkyl)tetrazoles **18** is quite general. Both primary and secondary amines lead to the required product, as does the aniline derivative **18b**. In addition, aromatic aldehydes would appear to be tolerated (**18c**), in contrast to the results reported for the hydantoin 4-imides. Although the four results only represent a small selection, the reaction seems to be quite promising.

Once again, electrospray mass spectrometry in the negative mode showed that all compounds exhibited the expected molecular ions. Examination of ^{1}H NMR spectra for tetrazoles **18** was also illuminative. For example, **18a** shows a triplet at δ4.11 integrating to one proton $\mathbf{H_a}$, indicative of a proton benzylic to the tetrazole moiety. A tight multiplet centered at δ4.35 is also characteristic of benzylic protons, and can be attributed to protons $\mathbf{H_{b,c}}$ α- to the tetrazole nitrogen. An AB quartet centered at δ3.55 can be associated with the benzylic protons $\mathbf{H_{d,e}}$ and the familiar triplet at δ2.17 with the carboxy-substituted methylene protons $H_{f,g}$.

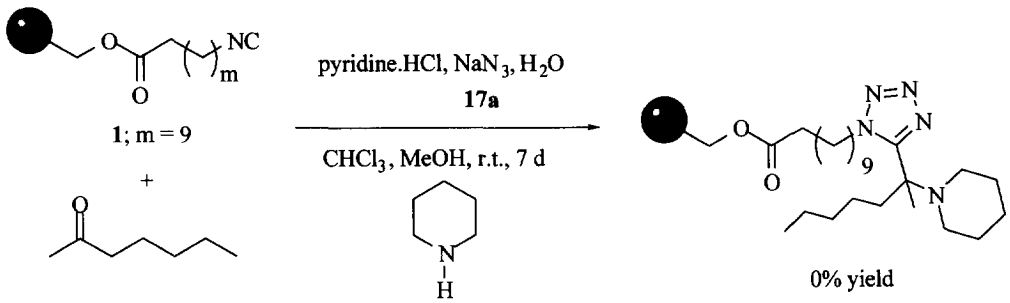


18a



20

On a side note, an additional reaction was attempted using isocyanide **1** (m = 9), piperidine, HN_3 and 2-heptanone (Scheme 10), under conditions used for the preparation of tetrazoles **18**. After stirring for 7 days, the usual filtration and cleavage protocol gave only the formamide **20**. This presumably reflects the sluggish reactivity of the ketone in this reaction, a phenomenon already noticed by Ugi in early solution-phase work.[9, 20]



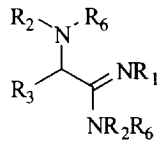
Scheme 10

α-(Dialkylamino)amides

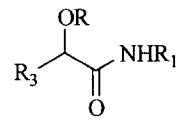
In addition to the heterocycles furnished by incorporation of inorganic acids in the Ugi 4CC reaction, the reaction of isocyanides **1** with aldehydes **3** and secondary amines was briefly investigated. It had previously been reported that such a combination yielded α-(dialkylamino)amides (Scheme 11), wherein the carboxylic

Scheme 11

acid component in the familiar 4CC reaction is not included.[9, 20] An effort to perform this reaction on solid phase was undertaken. Early work in this area had delineated ideal conditions to promote condensation.[21] That is, it had been noticed that simple admixture of components **1**→**3** gave no product. Recognition that acid catalysis was necessary to promote the reaction led to the optimal situation where addition of acetic acid gave only **21**. Other variations of catalyst (*e.g.* mineral acids), or equivalents of acetic acid, led to mixtures containing **21**, amidines **22** and Passerini-type adducts **23a**,**b**. Thus, the solid-phase work was designed to include the addition of acetic acid as a catalyst.

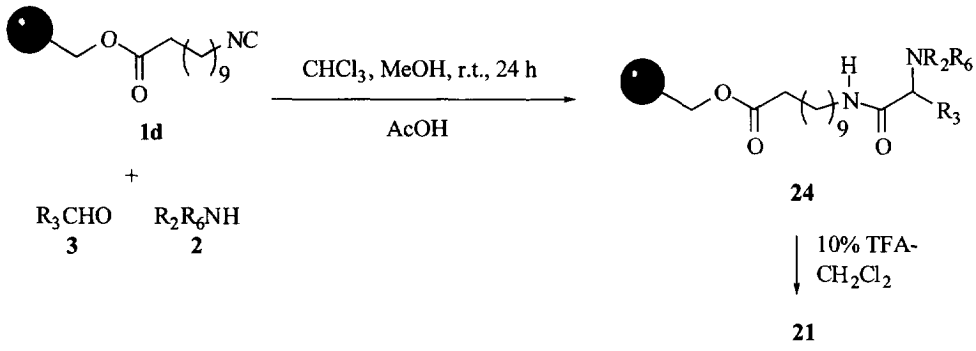


22



23a; R = H
23b; R = Ac

Admixture of isocyanide **1** (m = 9) with amines **2** and aldehydes **3** in chloroform-methanol (4.5:1), containing 1 mol eq acetic acid per amine **2** for 72 h gave resins **24**. Washing and cleavage of the resin followed that described previously; after evaporation of solvents the residue was purified by preparative TLC, yielding the expected α-(dialkylamino)amides **21** in moderate yields (Scheme 12, Table 6).



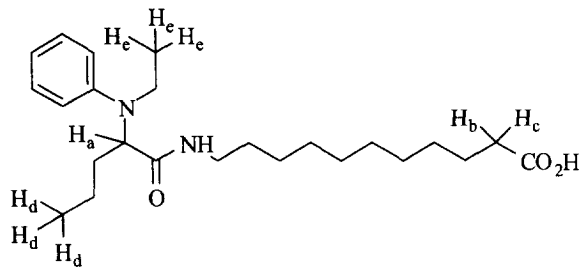
Scheme 12

Table 6. Yields for α-(Dialkylamino)amides **21** Formed from Solid Phase Four-Component Condensation Reaction.[a]

entry	R_3	R_2	R_6	% Yield
21a	Ph	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	52
21b	*n*-C_3H_7	Ph	C_2H_5	57

[a] Both yields correspond to preparative TLC-purified material, and are relative to the initial loading of the isocyanide 1 (m = 9).

Examination of the ^{1}H NMR spectrum revealed presence of required products **21**. For example, **21b** exhibits a triplet signal at δ5.04 ($\mathbf{H_a}$). Other signals at δ2.15 (triplet, $\mathbf{H_{b,c}}$), and overlapping triplets at high field (δ0.84-0.94, $\mathbf{H_{d,e}}$) further confirmed the structures.



21b

CONCLUSION

In summary, the potential offered by Ugi-type 4CC chemistry has been exploited on solid phase. A novel application of the Ugi 4CC reaction was discovered, wherein ω-ketoacids served as two-component, one input reagents. The diversity created by this and the other reactions described heretofore demanded their presence in combinatorial chemistry. Through polymer support of one of the inputs in each reaction class, it was discovered that the reactions could indeed be achieved on solid phase. This now allows for the automated synthesis of large libraries.

ACKNOWLEDGEMENTS

The authors thank Ms. Sonja Krane for her assistance in conducting the mass spectral analyses. Thanks also to Tom Baiga and Farid Bakir for their aid in the production of chemical libraries resulting from this chemistry. Finally, we thank Drs. Edmund Moran and Barry Toyonaga for their invaluable assistance in proof-reading this manuscript.

EXPERIMENTAL SECTION

General procedures

All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade. Anhydrous ether, tetrahydrofuran (THF), and toluene were distilled from sodium and/or benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). *N*, *N*, Dimethylformamide (DMF) was distilled from phosphorous pentoxide and calcium hydride. Methanol was distilled from magnesium and iodine. Organic acids and bases were reagent grade. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F-254) plates (0.25 mm). Visualization was effected using standard procedures unless otherwise stated. Flash column chromatography was carried out on Merck silica gel 60 particle size (0.040-0.063 mm, 230-400 Mesh). Proton and carbon magnetic resonance spectra (^{1}H-NMR, ^{13}C-NMR) were recorded on a Varian Unity plus Fourier transform spectrometer at 400 and 100 MHz. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm), MeOH (3.30 ppm for ^{1}H and 49.0 ppm for ^{13}C) or $CHCl_3$ (7.24 ppm for ^{1}H

and 77.0 ppm for ^{13}C) as internal reference. Electrospray mass spectrometry was carried out on a Finnegan SSQ 7000 machine.

General Procedure for the Preparation of Lactams 7; Solution Phase

To a solution of ω-ketoacid **6** in a methanol-dichloromethane mixture (1:3, 0.13 M) was added sequentially the amine **2** (1.2 mol eq) and isocyanide **1a** (1.2 mol eq). The mixture was stirred for 3 days; the contents were then pipetted into 1% HCl/H_2O and ether. The ethereal phase was washed with 1% HCl, followed by brine. This was then dried ($MgSO_4$), filtered and evaporated to an oily residue. Flash column chromatography of this residue yielded the lactams **7**.

Physical Data for Lactams (7)

7a. ^1H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.06-1.21 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 1.29 (s, 3H, $C\underline{H}_3$), 1.83 (ddd, J = 13.2, 9.6, 9.4 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.22 (ddd, J = 13.2, 9.6, 4.0 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.31-2.46 (m, 2H, $C\underline{H}_2C(O)$), 2.87 (ddd, J = 13.2, 13.2, 6.0 Hz, 1H, $C(O)NHC\underline{H}_2$), 3.02 (ddd, J = 13.2, 13.2, 6.8 Hz, 1H, $C(O)NHC\underline{H}_2$), 4.13, 4.56 (2d, AB quartet, J = 15.2 Hz, 2H, NCH_2Ph), 6.27 (br t, 1H, $C(O)N\underline{H}$), 7.12-7.22 (m, 5H, aromatics) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 ($\underline{C}H_3$), 20.2, 23.4, 29.8, 31.4, 33.6, 39.7, 44.9, 68.0 (ring C), 127.7, 128.1, 128.9, 138.1, 173.3, 176.5 ppm; ESIMS, m/z for $C_{17}H_{25}N_2O_2$ $[M+H]^+$: 289.

7b. ^1H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.99-1.10 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 2.28-2.54 (m, 3H), 2.80-2.89 (m, 3H), 3.81, 4.64 (2d, AB quartet, J = 15.2 Hz, 2H, $NC\underline{H}_2Ph$), 5.67 (t, J = 5.2 Hz, 1H, $C(O)N\underline{H}$), 7.0-7.03 (m, 2H, aromatics), 7.08 (d, J = 8.4 Hz, 2H, aromatics), 7.15-7.18 (m, 3H, aromatics), 7.40 (d, J = 8.4 Hz, 2H, aromatics) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 ($\underline{C}H_3$), 20.2, 29.6, 31.1, 35.2, 39.9, 45.7, 74.7 (ring C), 122.9, 127.9, 128.4, 129.0, 130.0, 132.1, 137.4, 137.8, 170.8, 176.6 ppm; ESIMS, m/z for $C_{22}H_{26}{}^{81}BrN_2O_2$ $[M+H]^+$: 431.

7c. ^1H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J = 7.2 Hz, 6H, $CH_2C\underline{H}_3$), 1.16-1.25 (m, 4H), 1.31-1.41 (m, 3H), 1.43 (s, 3H, $C\underline{H}_3$), 1.50-1.61 (m, 1H), 1.81 (ddd, J = 13.2, 9.6, 9.6 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.18 (ddd, J = 13.2, 9.2, 3.6 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.23-2.36 (m, 2H, $C\underline{H}_2C(O)$), 2.80 (ddd, J = 13.2, 11.2, 5.2 Hz, 1H, $NC\underline{H}_2$), 3.10-3.20 (m, 2H, $NC\underline{H}_2$), 3.28 (ddd, J = 13.2, 10.8, 5.2 Hz, 1H, $NC\underline{H}_2$), 6.48 (br t, 1H, $C(O)N\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.87, 13.88 (2 x CH_3), 20.3, 20.7, 23.4, 29.9, 31.2, 31.7, 33.3, 39.7, 41.8, 67.8 (ring C), 173.7, 175.8 ppm; ESIMS, m/z for $C_{14}H_{25}N_2O_2$ $[M-H]^-$: 253.4.

7d. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.08-1.18 (m, 2H), 1.23-1.32 (m, 2H), 1.28 (s, 3H, $C\underline{H}_3$), 1.66-1.73 (m, 3H), 2.12-2.20 (m, 1H), 2.42-2.49 (m, 2H), 2.99 (ddd, J = 13.2, 13.2, 6.8 Hz, 1H, $NC\underline{H}_2$), 3.12 (ddd, J = 13.2, 13.2, 6.8 Hz, 1H, $NC\underline{H}_2$), 3.81, 5.20 (2d, AB quartet, J = 15.6 Hz, 2H, $NC\underline{H}_2Ph$), 6.99 (br t, 1H, C(O)N$\underline{H}$), 7.06-7.21 (m, 5H. aromatics) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 17.7, 20.3, 25.6, 31.7, 32.8, 36.6, 40.0, 48.4, 67.1 (ring C), 126.8, 127.0, 128.7, 138.8, 172.0, 173.4 ppm. ESIMS, m/z for $C_{18}H_{25}N_2O_2$ $[M-H]^-$: 301.4.

General Procedure for the Preparation of Lactams 7; Solid Phase

To a dry, pre-silylated scintillation vial (initial rinse with 1% Me_3SiCl/PhMe, followed by regular rinse with water, acetone, ether) was added resin-supported isocyanide **1b-d**, followed by ω-ketoacid **6** (5 mol eq), amine **2** (5 mol eq) and finally chloroform-methanol (2:1, 0.3 M with respect to amine **2**). The heterogeneous mixture was stirred for 48 hours; the contents were then transferred to a filter funnel, and the residue flushed with dichloromethane (3x), methanol (3x), followed finally by dichloromethane (3x). The resin was then agitated with 10% trifluoroacetic acid-dichloromethane, and then drained. This process was repeated once more, then the resultant solution was evaporated at reduced pressure, yielding a lightly colored residue. Flash column chromatography yielded the required lactams **7**, as clear oils.

Physical Data for Lactams (7)

7g. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08-1.29 (m, 14H), 1.35 (s, 3H, $C\underline{H}_3$), 1.50-1.58 (m, 2H), 1.88 (ddd, J = 13.2, 9.6, 9.6 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.26 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 2.24-2.31 (m, 1H), 2.42-2.49 (m, 2H), 2.88 (ddd, J = 13.0, 13.0, 6.8 Hz, 1H, $NC\underline{H}_2$), 3.05 (ddd, J = 13.0, 13.0, 6.8 Hz, 1H, $NC\underline{H}_2$), 4.19, 4.59 (2d, AB quartet, J = 15.6 Hz, 2H, $NC\underline{H}_2Ph$), 6.24 (t, J = 5.6 Hz, 1H, C(O)N$\underline{H}$), 7.16-7.26 (m, 5H, aromatics) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 24.8, 26.9, 29.0, 29.1 (2 degenerate CH_2's, doublet), 29.2, 29.3 (2 degenerate CH_2's, doublet), 29.9, 33.6, 34.2, 40.1, 45.0, 68.4 (ring C), 127.9, 128.2, 129.0, 137.7, 163.8, 173.3, (177.5, 178.3 rotameric doublet, $C(CH_3)\underline{C}(O)NH$) ppm. ESIMS, m/z for $C_{24}H_{35}N_2O_4$ $[M-H]^-$: 415.6.

7h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 1.14-1.65 (m, 27H), 1.87 (ddd, J = 13.2, 9.6, 9.6 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.2-2.4 (m, 5H), 2.77-2.84 (m, 1H), 3.15-3.21 (m, 2H), 3.31-3.41 (m, 1H), 6.78 (t, J = 4.8 Hz, 1H, C(O)N$\underline{H}$), 9.88 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 23.4, 24.2, 26.4, 27.4, 28.9, 29.0, 29.4, 29.5, 29.7, 29.71, 29.74, 30.0, 32.0, 33.1, 33.8, 39.9, 42.4, 68.6 (ring C), 164.2, 173.8, (177.9, 178.1 rotameric doublet, $C(CH_3)\underline{C}(O)NH$) ppm. ESIMS, m/z for $C_{23}H_{41}N_2O_4$ $[M\text{-}H]^-$: 409.5.

7i. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25-1.32 (m, 2H), 1.43-1.59 (m, 4H), 1.56 (s, 3H, $C\underline{H}_3$), 1.91 (ddd, J = 13.2, 9.6, 9.6 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.20-2.46 (m, 6H), 3.15-3.25 (m, 2H), 3.94, 4.00 (2dd, AB quartet, J = 17.6, 1.6 Hz, 2H, $NC\underline{H}_2C{\equiv}CH$), 6.83 (t, J = 5.2 Hz, 1H, C(O)N$\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.5, 24.3, 26.4, 28.9, 29.6, 30.3, 33.5, 33.9, 39.9, 67.8 (ring C), 72.8 ($C{\equiv}\underline{C}H$), 78.4 ($\underline{C}{\equiv}CH$), 164.0, 173.4, (176.8, 178.1 rotameric doublet, $C(CH_3)\underline{C}(O)NH$) ppm. ESIMS, m/z for $C_{15}H_{21}N_2O_4$ $[M\text{-}H]^-$: 293.2.

7j. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92-0.99 (m, 2H), 1.06-1.28 (m, 12H), 1.51-1.59 (m, 2H), 2.28 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 2.33-2.52 (m, 2H), 2.55-2.65 (m, 1H), 2.68-2.79 (m, 1H), 3.05 (ddd, J = 13.2, 11.2, 5.2 Hz, 1H, $NC\underline{H}_2$), 3.10-3.20 (m, 2H, $NC\underline{H}_2$), 3.28 (ddd, J = 13.2, 13.2, 6.4 Hz, 1H, $NC\underline{H}_2$), 3.18 (ddd, J = 13.2, 13.2, 6.4 Hz, 1H, $NC\underline{H}_2$), 7.12-7.27 (m, 5H, aromatics), 7.89 (br t, 1H, C(O)N$\underline{H}$), 9.60 (br s, 2H, 2 x CO_2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 26.6, 28.8, 29.0, 29.1, 29.2, 29.2 (2 degenerate CH_2's), 30.4, 32.1, 34.2, 40.5, 70.9 (ring C), 123.3, 127.0, 129.4, 136.6, 164.9, (171.8, 172.2 rotameric doublet, $C(CO_2H)\underline{C}(O)NH$), 177.1, 179.7 ppm. ESIMS, m/z for $C_{23}H_{31}N_2O_6$ $[M\text{-}H]^-$: 431.5.

7k. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, $C\underline{H}_3$), 1.88 (ddd, J = 13.2, 10.4, 10.4 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.27 (ddd, J = 13.2, 8.4, 4.0 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.34-2.56 (m, 4H), 3.26 (ddd, J = 12.8, 12.8, 5.6 Hz, 1H, $NC\underline{H}_2$), 3.38 (ddd, J = 12.8, 12.8, 5.6 Hz, 1H, $NC\underline{H}_2$), 4.07, 4.72 (2d, AB quartet, J = 15.6 Hz, 2H, $NC\underline{H}_2Ph$), 7.06 (t, J = 5.6 Hz, 1H, C(O)N$\underline{H}$), 7.16-7.24 (m, 5H, aromatics), 7.75 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 29.8, 33.3, 33.5, 35.9, 45.2, 68.6 (ring C), 127.9, 128.0, 128.9, 137.1, 164.4, 173.8, 176.0, 178.4 (including rotameric doublet, $C(CH_3)\underline{C}(O)NH$) ppm. ESIMS, m/z for $C_{16}H_{19}N_2O_4$ $[M\text{-}H]^-$: 303.3.

7l. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, $C\underline{H}_3$), 1.68-1.80 (m, 3H), 2.19-2.25 (m, 1H), 2.49-2.60 (m, 4H), 3.52 (dt, *J* = 5.6 Hz, 2H, C(O)NHC$\underline{H}_2$), 3.84, 5.27 (2d, *J* = 16.8 Hz, 2H, NC$\underline{H}_2$Ph), 7.04-7.23 (m, 5H, aromatics), 7.64 (t, *J* = 5.6 Hz, 1H, C(O)N$\underline{H}$), 9.20 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 25.3, 32.5, 33.7, 36.1, 36.5, 49.1, 67.4 (ring C), 126.6, 127.2, 128.7, 137.6, 164.5, 173.7, 175.0, 176.3 (including 2 rotameric carbonyls) ppm. ESIMS, m/z for $C_{17}H_{21}N_2O_4$ $[M-H]^-$: 317.3.

7m. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19-1.30 (m, 12H), 1.36 (s, 3H, $C\underline{H}_3$), 1.38-1.47 (m, 2H), 1.52-1.61 (m, 2H), 1.66-1.80 (m, 3H), 2.20-2.31 (m, 3H), 2.54-2.58 (m, 2H), 3.13 (ddd, *J* = 13.2, 13.2, 6.0 Hz, 1H, C(O)NHC$\underline{H}_2$), 3.22 (ddd, *J* = 13.2, 13.2, 6.0 Hz, 1H, C(O)NHC$\underline{H}_2$), 3.95, 5.22 (2d, *J* = 15.2 Hz, 2H, NC$\underline{H}_2$Ph), 6.83 (t, *J* = 6.0 Hz, 1H, C(O)N$\underline{H}$), 7.09-7.26 (m, 5H, aromatics), 9.6 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 24.8, 25.3, 26.9, 29.0, 29.1, 29.3 (3 degenerate CH_2's), 32.4, 34.2, 36.2, 40.6, 48.9, 67.4 (ring C), 126.8, 127.3, 128.8, 137.8, 164.6, 173.6, 174.6, 179.4 (including 2 rotameric signals) ppm. ESIMS, m/z for $C_{25}H_{37}N_2O_4$ $[M-H]^-$: 429.4.

7n. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.14-1.26 (m, 14H), 1.30-1.64 (m, 6H), 1.47 (s, 3H, $C\underline{H}_3$), 1.85 (ddd, *J* = 13.2, 9.8, 9.8 Hz, 1H, $C\underline{H}_2CH_2C(O)$), 2.18-2.27 (m, 3H), 2.34-2.41 (m, 2H), 2.83 (ddd, *J* = 14.0, 10.8, 5.2 Hz, 1H, NC$\underline{H}_2$), 3.10-3.20 (m, 2H), 3.29-3.37 (m, 1H), 6.62 (t, *J* = 5.2 Hz, 1H, C(O)N$\underline{H}$), 10.04 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.6, 23.3, 24.8, 26.9, 29.0, 29.11, 29.17, 29.25 (2 degenerate CH_2's), 29.31, 30.0, 31.0, 33.1, 34.1, 40.2, 42.1, 68.4 (ring C), 163.9, 173.7, (177.6, 178.3 rotameric doublet, $C(CH_3)\underline{C}(O)NH$) ppm. ESIMS, m/z for $C_{21}H_{37}N_2O_4$ $[M-H]^-$: 381.6.

10a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J* = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 0.99-1.10 (m, 2H), 1.19-1.35 (m, 12 H), 1.38-1.46 (m, 2H), 1.48-1.58 (m, 1H), 1.73 (s, 3H, $C\underline{H}_3$), 1.73-1.82 (m, 1H), 2.17 (t, *J* = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 3.02-3.10 (m, 2H), 3.16 (ddd, *J* = 13.6, 11.2, 5.2 Hz, 1H, NC$\underline{H}_2$), 3.62 (ddd, *J* = 13.6, 11.2, 5.2 Hz, 1H, NC$\underline{H}_2$), 6.48 (t, *J* = 5.2 Hz, 1H, C(O)N$\underline{H}$), 7.40-7.54 (m, 3H, aromatics), 7.71 (d, *J* = 7.2 Hz, 1H, aromatics) 8.00 (br s, 1H, $CO_2\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 21.2, 22.8, 23.9, 26.0, 27.5, 28.6, 28.8, 29.4 (2 degenerate C's), 31.9, 33.8, 39.8, 42.2, 70.6 ($\underline{C}(CH_3)C(O)NH$), 121.8, 123.9, 129.3, 130.1, 133.0,

147.4, 164.6, (170.0, 171.0 rotameric doublet, $C(CH_3)\underline{C}(O)NH$), 178.4 ppm; ESIMS, m/z for $C_{24}H_{35}N_2O_4$ $[M-H]^-$: 415.6.

10b. ^1H NMR (400 MHz, $CDCl_3$): δ 1.02-1.14 (m, 2H), 1.30-1.64 (m, 4H), 1.70 (s, 3H, $C\underline{H}_3$), 2.14-2.21 (m, 2H, $C\underline{H}_2CO_2H$), 3.01 (ddd, J = 13.2, 6.8, 6.8, 1H, $NC\underline{H}_2$), 3.10 (ddd, J = 13.2, 6.8, 6.8, 1H, $NC\underline{H}_2$), 3.87 (dd, J_{gem} = 15.4, J_{vic} = 6.4 Hz, 1H, $NC\underline{H}_2CH=CH_2$), 4.30 (dd, J_{gem} = 15.4, J_{vic} = 6.0 Hz, 1H, $NC\underline{H}_2CH=CH_2$), 5.13-5.25 (m, 2H, $NCH_2CH=C\underline{H}_2$), 5.82-5.92 (m, 1H, $NCH_2C\underline{H}=CH_2$), 6.54 (t, J = 5.2 Hz, 1H, $C(O)N\underline{H}$), 7.38-7.70 (m, 4H, aromatics), 5.1-8.0 (v br s, 1H, $CH_2CO_2\underline{H}$) ppm. ESIMS, m/z for $C_{19}H_{24}N_2O_4$ $[M-H]^-$: 343.2.

Physical Data for Hydantoin 4-Imide (12a)

^1H NMR (400 MHz, $CDCl_3$): δ 0.72 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.79 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.92-1.02 (m, 2H), 1.17-1.26 (m, 2H), 1.41-1.50 (m, 2H), 1.51-1.62 (m, 1H), 1.74-1.85 (m, 1H), 3.18-3.30 (m, 2H), 3.87, 4.69 (2d, J = 15.2 Hz, 2H, $C\underline{H}_2Ar$), 4.06 (br s, 1H, ring $C\underline{H}$), 6.98, 7.31 (2d, J = 8.0 Hz, 4H, aromatics), 8.00 (t, J = 6.0 Hz, 1H, $C(O)N\underline{H}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.28 ($\underline{C}H_3$), 13.32 ($\underline{C}H_3$), 15.5, 20.0, 30.8, 31.0, 42.4, 43.7, 60.6 (ring $\underline{C}H$), 121.3, 129.9, 131.7, 137.1, 169.5, 177.7 ppm.

General Procedure for the Preparation of Hydantoin 4-Imides 12; Solid Phase

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, resin-supported isocyanide **1b-d**, followed by aldehyde **3** (5 mol eq), amine **2** (5 mol eq), potassium cyanate **11b** (10 mol eq) and a chloroform-methanol-water mixture (5:5:1, 0.35 M with respect to amine **2**. Following this cocktail, pyridine hydrochloride (10 mol eq) was added. The heterogeneous mixture was stirred for 24 hours; the contents were then transferred to a filter funnel, and the residue flushed alternately with methanol (3x), dimethylformamide (3x), methanol (3x), followed finally by dichloromethane (3x). The resin was then agitated with 20% trifluoroacetic acid-dichloromethane, and then drained. This process was repeated once more, then the resultant solution was evaporated at reduced pressure, yielding a lightly colored residue. Flash column chromatography yielded the required hydantoin 4-imides **12**, as clear oils.

Physical Data for Hydantoin 4-Imides (12)

12b. ^{1}H NMR (400 MHz, CD_3OD): δ 0.85 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.88 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.92-1.13 (m, 2H), 1.22-1.35 (m, 22H), 1.42-1.60 (m, 6H), 1.70-1.91 (m, 2H), 2.14 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 2.95 (ddd, J = 14.2, 8.6, 5.6 Hz, 1H, C(O)NC$\underline{H}_2$), 3.22-3.37 (m, 2H, C=NC$\underline{H}_2$), 3.51 (ddd, J = 14.2, 7.6, 7.6 Hz, 1H, C(O)NC$\underline{H}_2$), 4.31 (br s, 1H, ring C$\underline{H}$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 13.0, 13.3, 15.2, 22.5, 26.1, 26.7 (2 degenerate $\underline{C}H_2$'s), 28.1, 28.6, 29.17, 29.18, 29.38, 29.41, 29.46, 29.48, 30.9, 31.8, 37.0, 40.0, 42.4, 48.7, 60.5 (ring $\underline{C}H$), 169.3, 177.6, 180.5 ($\underline{C}O_2H$) ppm. ESIMS, m/z for $C_{25}H_{46}N_3O_3$ $[M-H]^-$: 436.

12c. ^{1}H NMR (400 MHz, CD_3OD): δ 0.81 (d, J = 6.8 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 0.85 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 0.90 (d, J = 6.8 Hz, 3H, CH(C$\underline{H}_3$)$_2$), 1.21-1.36 (m, 18H), 1.51-1.62 (m, 4H), 1.63-1.75 (m, 2H), 1.78-1.88 (m, 2H), 1.89-1.98 (m, 3H), 2.19 (t, J = 7.6 Hz, 2H, $C\underline{H}_2CO_2H$), 2.78 (dd, J = 13.6, 6.0 Hz, 1H, NC$\underline{H}_2$C(CH$_3$)$_2$), 3.21-3.41 (m, 3H, NC$\underline{H}_2$C(CH$_3$)$_2$, C=NC$\underline{H}_2$), 4.34 (br s, 1H, ring C$\underline{H}$), 5.28-5.42 (m, 2H, $CH_2C\underline{H}$=C$\underline{H}CH_2$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 13.3, 19.1, 19.5, 22.4, 25.3, 25.6, 26.8, 27.5, 28.6, 29.1, 29.26, 29.30 (2 degenerate CH_2's), 29.35, 29.4, 29.5, 31.4, 32.4, 35.4, 42.5, 48.7, 60.4 (ring C$\underline{H}$), 128.2, 131.7, 169.5, 177.4 ($\underline{C}O_2H$ missing) ppm. ESIMS, m/z for $C_{27}H_{48}N_3O_3$ $[M-H]^-$: 462.

12d. ^{1}H NMR (400 MHz, CD_3OD): δ 0.89 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 0.93-1.04 (m, 2H), 1.22 (d, J = 7.2 Hz, 3H, NCH(C$\underline{H}_3$)$_2$), 1.24 (d, J = 7.2 Hz, 3H, NCH(C$\underline{H}_3$)$_2$), 1.25-1.33 (m, 12 H), 1.51-1.59 (m, 4H), 1.72-1.88 (m, 2H), 2.15 (t, J = 7.6 Hz, 2H, $C\underline{H}_2CO_2H$), 3.20-3.35 (m, 2H, C=NC$\underline{H}_2$), 3.96 (dq, J = 7.2 Hz, 1H, NC$\underline{H}$(CH$_3$)$_2$), 4.35 (t, J = 3.2 Hz, 1H, ring C$\underline{H}$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.9, 14.8, 19.1, 20.6, 25.9, 26.7, 28.6, 29.16, 29.32, 29.36, 29.39, 29.42, 32.8, 36.5, 42.4, 44.7, 60.1 (ring C$\underline{H}$), 169.2, 177.5 (missing $\underline{C}O_2H$) ppm. ESIMS, m/z for $C_{20}H_{36}N_3O_3$ $[M-H]^-$: 366.

12e. ^{1}H NMR (400 MHz, CD_3OD): δ 0.84 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.85-0.94 (m, 2H), 1.0-1.18 (m, 5H), 1.20-1.34 (m, 15H), 1.50-1.60 (m, 4H), 1.67-1.75 (m, 2H), 2.14 (t, J = 7.6 Hz, 2H, $C\underline{H}_2CO_2H$), 3.19-3.40 (m, 2H, C=NC$\underline{H}_2$), 4.17 (t, J = 3.2 Hz, 1H, ring C$\underline{H}$), 4.26, 4.56 (2d, J = 15.2 Hz, 2H, NC$\underline{H}_2$Ar), 7.20, 7.44 (2d, J = 8.0 Hz, 4H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 13.3, 21.7, 22.4, 22.5, 26.1, 26.8, 28.6,

28.8, 29.1, 29.2, 29.38, 29.42, 29.48, 31.7, 36.9, 42.5, 43.8, 48.7, 61.0 (ring CH), 121.2, 129.9, 131.6, 137.2, 169.5, 177.6, 178.3 ($\underline{C}O_2H$) ppm. ESIMS, m/z for $C_{28}H_{43}{}^{81}BrN_3O_3$ $[M-H]^-$: 550.

12f. ^{1}H NMR (400 MHz, CD_3OD): δ 0.84 (d, J = 6.4 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.87 (d, J = 6.4 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.90 (t, J = 6.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.24-1.35 (m, 14H), 1.41-1.60 (m, 7H), 1.70 (dd, J = 15.2, 6.4 Hz, 1H), 1.80 (dd, J = 14.6, 6.4 Hz, 1H), 2.16 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 2.94 (ddd, J = 14.0, 8.0, 5.2 Hz, 1H, $C(O)NC\underline{H}_2$), 3.23-3.34 (m, 2H, $C{=}NC\underline{H}_2$), 3.58 (ddd, J = 14.8, 7.6, 7.6 Hz, 1H, $C(O)NC\underline{H}_2$), 4.31 (br s, 1H, ring C<u>H</u>) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.9, 19.8, 22.4, 22.7, 23.9, 25.9, 26.8, 28.5, 29.14, 29.18, 29.31, 29.37, 29.42, 30.0, 36.3, 37.6, 40.0, 42.6, 59.8, 169.2, 178.2, 179.9 ppm. ESIMS, m/z for $C_{22}H_{40}N_3O_3$ $[M-H]^-$: 394.

12g. ^{1}H NMR (400 MHz, CD_3OD): δ 0.78 (t, J = 7.2 Hz, 3H, $C\underline{H}_3$), 0.87-1.06 (m, 2H), 1.24-1.33 (m, 12H), 1.51-1.58 (m, 4H), 1.62-1.80 (m, 2H), 2.17 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 3.21-3.37 (m, 2H, $C{=}NC\underline{H}_2$), 4.12 (t, J = 3.2 Hz, 1H, ring C<u>H</u>), 4.16, 4.67 (2d, J = 15.2 Hz, 2H, $NC\underline{H}_2Ar$), 7.19, 7.44 (2d, J = 8.0 Hz, 4H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.8, 15.2, 25.7, 26.7, 28.5, 29.1, 29.29, 29.30, 29.33, 29.40, 30.8, 35.9, 42.5, 43.6, 60.6 (ring C<u>H</u>), 121.2, 129.8, 131.7, 137.0, 169.4, 177.6 ($\underline{C}O_2H$ missing). ESIMS, m/z for $C_{24}H_{35}{}^{81}BrN_3O_3$ $[M-H]^-$: 494.

12h. ^{1}H NMR (400 MHz, CD_3OD): δ 0.78 (t, J = 7.6 Hz, 3H, $C\underline{H}_3$), 0.89-1.07 (m, 2H), 1.22-1.34 (m, 12H), 1.51-1.59 (m, 4H), 1.64-1.81 (m, 2H), 2.14 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 3.21-3.37 (m, 2H, $C{=}NC\underline{H}_2$), 4.13 (t, J = 3.2 Hz, 1H, ring C<u>H</u>), 4.17, 4.68 (2d, J = 16.0 Hz, 2H, $NC\underline{H}_2Ar$), 7.24, 7.28 (2d, J = 8.0 Hz, 4H, 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, 29.50, 30.9, 37.1, 42.5, 43.5, 60.6, 128.6, 129.5, 133.2, 136.5, 169.5, 177.6, 180.6 ppm. ESIMS, m/z for $C_{24}H_{35}{}^{35}ClN_3O_3$ $[M-H]^-$: 448.

12i. ^{1}H NMR (400 MHz, CD_3OD): δ 0.89, 0.90 (2t, J = 7.2 Hz, 6H, $2CH_3$'s), 0.94-1.13 (m, 2H), 1.25-1.32 (m, 14H), 1.41-1.59 (m, 6H), 1,70-1.90 (m, 2H), 2.15 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 2.92-2.99 (m, 1H, $NC\underline{H}_2$), 3.22-3.37 (m, 2H), 3.53 (ddd, J = 14.0, 7.4, 7.4 Hz, 1H, $NC\underline{H}_2$), 4.31 (t, J = 3.2 Hz, 1H, ring C<u>H</u>) ppm.

^{13}C NMR (100 MHz, CD_3OD): δ 12.9, 15.2, 19.8, 25.9, 26.7, 29.16, 29.33, 29.37, 29.40, 29.43, 30.2, 30.8, 30.9, 36.5, 39.7, 42.4, 60.5 (ring C<u>H</u>), 169.3, 177.6, 179.9 (<u>C</u>O_2H) ppm. ESIMS, m/z for $C_{21}H_{38}N_3O_3$ $[M-H]^-$: 380.

12j. ^1H NMR (400 MHz, CD_3OD): δ 0.58, 0.66 (2s, 9H, $C(C\underline{H}_3)_3$), 0.75, 0.82 (2d, J = 6.4 Hz, 3H, diastereomeric $CH_2CH(C\underline{H}_3)CH_2$), 0.84-1.10 (m, 1H), 1.25-1.46 (m, 2H), 1.58-1.69 (m, 5H), 1.90 (s, 3H, $ArC\underline{H}_3$), 2.11-2.19 (m, 3H), 2.22 (t, J = 7.2 Hz, 2H, $C\underline{H}_2CO_2H$), 3.36-3.39 (m, 2H, $C{=}NC\underline{H}_2$), 3.60-3.65 (m ,1H, ring C<u>H</u>), 6.96-7.24 (m, 3H, aromatic protons) ppm. ESIMS, m/z for $C_{24}H_{35}FN_3O_3$ $[M-H]^-$: 432.

12k. ^1H NMR (400 MHz, CD_3OD): δ 0.85-1.1 (m, 9H, 3 x $CH_2C\underline{H}_3$'s), 1.18-1.88 (m, 22H), 2.16-2.21 (m, 2H, $C\underline{H}_2CO_2H$), 3.15-3.64 (m, 3H, $C{=}NC\underline{H}_2$, $NC\underline{H}(CH_3)$), 4.26-4.28 (br s, 1H, ring C<u>H</u>) ppm. ESIMS, m/z for $C_{21}H_{38}N_3O_3$ $[M-H]^-$: 380.

General Procedure for the Preparation of 2-Thiohydantoin 4-Imides 14

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, resin-supported isocyanide **1c**, followed by aldehyde **3** (5 mol eq), amine **2** (5 mol eq), potassium thiocyanate **15** (10 mol eq) and a chloroform-methanol-water mixture (5:5:1, 0.35 M with respect to amine **2**. Following this cocktail, pyridine hydrochloride (10 mol eq) was added. The heterogeneous mixture was stirred for 96 hours; the contents were then transferred to a filter funnel, and the residue flushed alternately with methanol (3x), dimethylformamide (3x), methanol (3x), followed finally by dichloromethane (3x). The resin was then agitated with 20% trifluoroacetic acid-dichloromethane, and then drained. This process was repeated once more, then the resultant solution was evaporated at reduced pressure, yielding a lightly colored residue. Flash column chromatography yielded the required hydantoin 4-imides **14**, as clear oils.

Physical Data for 2-Thiohydantoin 4-Imides (14)

14a. ^{1}H NMR (400 MHz, CD_3OD): δ 1.25 (s, 6H, 2 C$\underline{H}_3$'s), 1.30-1.40 (m, 2H), 1.55-1.65 (m, 4H), 2.12-2.19 (m, 2H, C$\underline{H}_2CO_2H$, 3.27 (br s, 2H, C=NC$\underline{H}_2$), 4.92 (s, 2H, NC$\underline{H}_2$Ar), 7.31, 7.41 (2d, J = 8.0 Hz, 4H, aromatic protons) ppm. ESIMS, m/z for $C_{18}H_{23}{}^{81}BrN_3O_2S$ $[M-H]^-$: 426.

14b. ^{1}H NMR (400 MHz, CD_3OD): δ 1.24-1.76 (m, 16H), 2.16 (t, J = 7.2 Hz, 2H, C$\underline{H}_2CO_2H$), 3.42 (t, J = 7.2 Hz, 2H, C=NC$\underline{H}_2$), 5.10 (br s, 2H, NC$\underline{H}_2$Ar), 7.20, 7.39 (2d, J = 8.0 Hz, 4H, aromatic protons) ppm. ESIMS, m/z for $C_{21}H_{27}{}^{81}BrN_3O_2S$ $[M-H]^-$: 466.

General Procedure for the Preparation of 5-(1'-Aminoalkyl)tetrazoles 18

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, resin-supported isocyanide **1d**, followed by aldehyde **3** (5 mol eq), amine **2** (5 mol eq), sodium azide **17a** (10 mol eq) and a chloroform-methanol-water mixture (5:5:2, 0.39 M with respect to amine **2**. Following this cocktail, pyridine hydrochloride (10 mol eq) was added. The heterogeneous mixture was stirred for 96 hours; the contents were then transferred to a filter funnel, and the residue flushed alternately with methanol (3x), dimethylformamide (3x), methanol (3x), followed finally by dichloromethane (3x). The resin was then agitated with 20% trifluoroacetic acid-dichloromethane for 10 minutes, and then drained. This process was repeated once more, then the resultant solution was evaporated at reduced pressure, yielding a lightly colored residue. Flash column chromatography yielded the required 5-(1'-aminoalkyl)tetrazoles **18**, as clear oils.

Physical Data for 5-(1'-Aminoalkyl)tetrazoles (18)

18a. ^{1}H NMR (400 MHz, CD_3OD): δ 0.84 (t, J = 6.4 Hz, 3H, C$\underline{H}_3$), 1.11-1.36 (m, 10H), 1.55-1.63 (m, 2H), 1.76-1.93 (m, 4H), 2.17 (t, J = 7.2 Hz, 2H, C$\underline{H}_2CO_2H$), 3.51, 3.60 (2d, AB quartet, J = 14.0 Hz, 2H, NHC$\underline{H}_2$Ar), 4.11 (t, J = 7.2 Hz, 1H, $ArCH_2N(H)C\underline{H}$), 4.30-4.40 (m, 2H, $HO_2C(CH_2)_4C\underline{H}_2N$), 7.16, 7.39 (2d, J = 8.8 Hz, 4H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 13.3, 22.5, 25.4, 25.8, 26.3, 29.0, 29.2, 29.4, 31.7, 34.0, 36.3, 47.4, 50.2, 52.0, 120.7, 130.1, 131.3, 138.9, 156.8 (tetrazole C), 179.6 ppm. ESIMS, m/z for $C_{22}H_{33}{}^{79}BrN_5O_2$ $[M-H]^-$: 478.

18b. ^{1}H NMR (400 MHz, CD_3OD): δ 0.83-0.88 (m, 6H, 2 x $C\underline{H}_3$), 1.01-1.38 (m, 19H), 1.45-1.58 (m, 4H), 1.60-1.69 (m, 1H), 1.93-2.18 (m, 5H), 2.25-2.35 (m, 1H), 3.05-3.19 (m, 2H, N(Ph)$C\underline{H}_2CH_3$), 4.05 (t, J = 7.6 Hz, 2H, $HO_2C(CH_2)_9C\underline{H}_2N$), 5.25 (t, J = 6.4 Hz, 1H, PhN(Et)C$\underline{H}$), 5.32-5.46 (m, 2H, $CH_2C\underline{H}$=C$\underline{H}CH_2$), 6.75 (t, J = 7.2 Hz, 1H, N-*p*-Ph-H), 6.89 (d, J = 8.8 Hz, 2H, N-*o,o'*-Ph-H), 7.22 (dd, J = 8.8, 7.2 Hz, 2H, N-*m,m'*-Ph-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 12.5 ($\underline{C}H_3$), 13.3 ($\underline{C}H_3$), 22.4, 26.19, 26.26, 28.7, 28.9, 29.24, 29.25, 29.31 (2 degenerate CH_2's), 29.4, 29.5, 30.2, 31.4, 32.4, 37.0, 38.5, 52.1, 63.3 (PhN(Et)$\underline{C}$), 114.4 ($\underline{C}$H=CH), 118.5 (CH=$\underline{C}$H), 128.8, 129.5, 132.0, 147.4, 154.9 (tetrazole C), 180.6 (CO_2H) ppm. ESIMS, m/z for $C_{30}H_{48}N_5O_2$ $[M-H]^-$: 510.

18c. ^{1}H NMR (400 MHz, CD_3OD): δ 1.12-1.29 (m, 12H), 1.36-1.43 (m, 2H), 1.51-1.59 (m, 6H), 1.60-1.68 (m, 2H), 2.15 (t, J = 7.6 Hz, 2H, $HO_2C\,C\underline{H}_2$), 2.26-2.34 (m, 2H, PhC(H)NC$\underline{H}_2$), 2.43-2.50 (m, 2H, PhC(H)NC$\underline{H}_2$), 4.38 (t, J = 7.2 Hz, 2H, $HO_2C(CH_2)_9C\underline{H}_2N$), 4.99 (s, 1H, PhC($\underline{H}$)N), 7.27-7.42 (m, 5H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 24.1, 25.7, 25.9, 26.1, 28.8, 29.17 (2 degenerate $C\underline{H}_2$'s), 29.25, 29.27, 29.4, 36.4, 47.5, 52.1, 65.0 (PhC$\underline{H}$N), 128.56, 128.60, 129.1, 135.3, 155.2 (tetrazole C), 179.9 ($\underline{C}O_2H$) ppm. ESIMS, m/z for $C_{24}H_{36}N_5O_2$ $[M-H]^-$: 426.

18d. ^{1}H NMR (400 MHz, CD_3OD): δ 1.10-1.32 (m, 17H), 1.40-1.82 (m, 10H), 2.15 (t, J = 7.6 Hz, 2H, $HO_2CC\underline{H}_2$), 3.40, 3.59 (2d, J = 14.0 Hz, 2H, Ar$C\underline{H}_2$NH), 3.83 (d, J = 8.0 Hz, 1H, ArCH_2N(H)C$\underline{H}$), 4.27 (t, J= 7.2 Hz, 2H, $HO_2C(CH_2)_9C\underline{H}_2N$), 7.13, 7.38 (2d, J = 8.8 Hz, 4H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 22.4, 25.9, 26.08, 26.11, 26.3, 28.9, 29.31, 29.37, 29.48, 29.50, 29.68, 29.74, 36.8, 42.2, 50.3, 57.2120.6, 129.9, 131.3, 139.0, 156.4 (tetrazole C), ($\underline{C}O_2H$ missing) ppm. ESIMS, m/z for $C_{26}H_{39}{}^{81}BrN_5O_2$ $[M-H]^-$: 534.

General Procedure for the Preparation of α-(Dialkylamino)amides 21

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, resin-supported isocyanide **1d**, followed by amine **2** (5 mol eq), acetic acid (5 mol eq), aldehyde **3** (5 mol eq), and finally a chloroform-methanol mixture (4.5:1), 0.13 M with respect to amine **2** and aldehyde **3**. The heterogeneous mixture was stirred for 96 hours; the contents were then transferred to a filter funnel, and the residue flushed alternately with methanol (3x),

dimethylformamide (3x), methanol (3x), followed finally by dichloromethane (3x). The resin was then agitated with 10% trifluoroacetic acid-dichloromethane for 20 minutes, and then drained. This process was repeated once more, then the resultant solution was evaporated at reduced pressure, yielding a lightly colored residue. Flash column chromatography yielded the required α-(dialkylamino)amides **21**, as clear oils.

Physical Data for α-(Dialkylamino)amides 21

21a. ^{1}H NMR (400 MHz, CD_3OD): δ 1.12-1.58 (m, 16H), 2.15 (t, J = 7.6 Hz, 2H, $C\underline{H}_2CO_2H$), 3.00-3.60 (m, 2H, C(O)N(H)$C\underline{H}_2$), 5.03-5.13 (m, 4H, $N(C\underline{H}_2)_2$), 5.32 (s, 1H, PhC$\underline{H}$C(O)NH), 5.69-5.88 (m, 6H, $N(CH_2C\underline{H}{=}C\underline{H}_2)_2$, 7.22-7.38 (m, 5H, aromatic protons) ppm. ESIMS, m/z for $C_{25}H_{37}N_2O_3$ $[M\text{-}H]^-$: 413.

21b. ^{1}H NMR (400 MHz, CD_3OD): δ 0.93 (t, J = 6.8 Hz, 3H, CH_3), 1.05 (t, J = 6.8 Hz, 3H, CH_3), 1.12-1.41 (m, 20H), 1.51-1.59 (m, 2H), 1.61-1.71 (m, 1H), 1.86-1.95 (m, 1H), 2.15 (t, J = 7.6 Hz, 2H, $C\underline{H}_2CO_2H$), 3.21-3.38 (m, 2H, PhN$C\underline{H}_2CH_3$), 3.46 (t, J = 7.6 Hz, 2H, C(O)NHC$\underline{H}_2$), 5.04 (t, J = 7.6 Hz, 1H, PhN(Et)C$\underline{H}$), 6.66-7.17 (m, 5H, aromatic protons) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ 13.0 ($\underline{C}H_3$), 13.2 ($\underline{C}H_3$), 19.6, 24.9, 26.6, 29.01, 29.02, 29.12, 29.15, 29.21, 29.28, 31.5, 33.8, 39.4, 44.5, 61.7 (PhN(Et)$\underline{C}$H), 114.1, 117.7, 129.1, 147.8, 174.7, 176.1 ppm. ESIMS, m/z for $C_{24}H_{39}N_2O_3$ $[M\text{-}H]^-$: 403.

REFERENCES AND NOTES

1. (a); Gallop, M.A.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E.M. *J. Med. Chem.* **1994**, *37*, 1233. (b); Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A. *J. Med. Chem.* **1994**, *37*, 1385. (c); Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, *96*, 555.
2. Merrifield, R.B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
3. Barany, G.; Merrifield, R.B. in "The Peptides", Vol. 2 (Gross, E.; Meienhofer, J., eds.), p.1, New York, Academic Press, 1979.
4. Indeed, entire journal issues are now devoted to solid-phase chemistry. One recent example is the Symposium-in-Print entitled "Molecular Diversity, Creation and Application", *Biorg. & Med. Chem.* **1996**, *5*.

5. Cargill, J.F.; Maiefski, R.R.; Toyonaga, B.E. *International Symposium on Laboratory Automation and Robotics Proceedings (ISLAR '95)*, Boston, MA, Zymark Corporation, **1996**, 221.
6. Ellman, J.A. *Chemtracts-Organic Chemistry* **1995**, *8*, 1.
7. Dewitt, S.H.; Kiely, J.S.; Stankovic, C.J.; Schroeder, M.C.; Reynolds Cody, D.M.; Pavia, M.R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909, and references within.
8. Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115.
9. Ugi, I. *Angew. Chem. Int. Ed. Engl.* **1962,** *1*, 8.
10. Weber, L.; Wallbaum, S.; Broger, C.; Gubernator, K. *Angew. Chem. Int. Ed. Engl.* **1995,** *34*, 2280.
11. (a); Keating, T.A.; Armstrong, R.W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (b); Cao, X.; Moran, E.J.; Siev, D.; Lio, A.; Ohashi, C.; Mjalli, A.M.M. *Bio. Med. Chem. Lett.* **1995**, *5*, 2953. (c); Zhang, C.; Moran, E.J.; Woiwode, T.F.; Short, K.M.; Mjalli, A.M.M. *Tetrahedron Lett.* **1996**, *37*, 751. (d); Strocker, A.M.; Keating, T.A.; Tempest, P.A.; Armstrong, R.W. *Tetrahedron Lett.* **1996**, *37*, 1149. (e); Tempest, P.A.; Brown, S.D.; Armstrong, R.W. *Angew. Chem. Int. Ed. Engl.* **1996,** *35*, 640. (f); Mjalli, A.M.M.; Sarshar, S.; Baiga, T.J. *Tetrahedron Lett.* **1996**, *37*, 2943.
12. Short, K.M.; Mjalli, A.M.M. *Tetrahedron Lett.* **1996**, *37* accepted for publication.
13. Manuscript submitted for publication. Short, K.M.; Ching, B.W.; Mjalli, A.M.M. *Tetrahedron Lett.* **1996**, *37* submitted.
14. Isenring, H.R.; Hofheinz, W. *Synthesis*, **1981**, 385. Eckert, H.; Ugi, I. *Studies in Natural Product Chemistry* **1993**, *12*, 113.
15. Hatanaka, M.; Yamamoto, Y.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1981**, *22*, 3883. Hatanaka, M.; Nitta, H.; Ishimaru, T. *Tetrahedron Lett.* **1984**, *25*, 2387.
16. Indeed, Ugi discussed the possibility that lactams would be formed from ω-carboxyaldehydes. Ugi, I., Achatz, J.; Baumgartner-Rupnik, M.; Danzer, B.; Fleck, C.; Glahsl, G.; Herrmann, R.; Jacob, P.; Kambach, C. *et.al. Nat. Prod. Chem. 3* **1988**, 107.
17. A search of the ACD (Available Chemicals Directory, MDL information systems) showed that only one γ- or δ-carboxyaldehyde is commercially available (succinic semialdehyde).
18. Wang, S.S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.
19. Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734.
20. Ugi, I. "Isonitrile Chemistry", in "Organic Reactions", Academic Press, New York, 1971.
21. McFarland, J.W. *J. Org. Chem.* **1963**, *28*, 2179.

(*Received* 6 *September* 1996; *accepted* 8 *January* 1997)