Pergamon

Tetrahedron Letters 39 (1998) 5135–5138

TETRAHEDRON LETTERS

Solid Phase Synthesis of 1-Aminohydantoin Libraries

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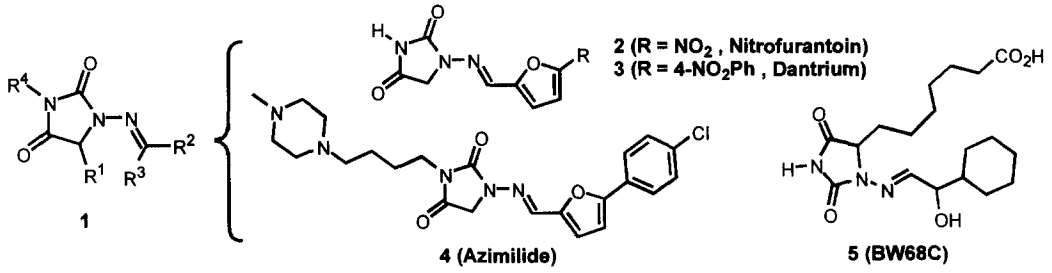
Received 6 March 1998; accepted 12 May 1998

Abstract: *The solid support synthesis of a series of 1-aminohydantoins based on a diverse set of hydrazino amino acids, aldehydes, and amines is described. The method involves the construction of resin attached hydrazino acid precursors, followed by subsequent derivatization, and then cyclizative cleavage off the resin. Overall yields vary per example between 15 and 60%, and the samples are suitable for biological evaluations without further purification.*

Resin based combinatorial chemistry methods have blossomed over this decade, and prove to be highly useful for multi-step synthetic protocols.[1] As part of our on-going effort to create molecular scaffolds which contain significant pharmacophores, we focused on the construction of the 1-amino variant of the hydantoin nucleus (**1**). Interest in this novel set of compounds stems from their demonstrated (**2** - anti-infective, **3** - skeletal muscle relaxant[2a]) and potential commercial significance (**4** - class III anti-arrhythmic[2b]), as well as other intriguing pharmacological diversity (**5** - Prostaglandin D receptor agonist).[2c] Furthermore, they contain the aza surrogate of amino acids (*i.e.* hydrazino acids), which has pharmacological significance in many therapeutic areas.[3] This aza replacement adds significantly different chemical and physical properties to the hydantoin ring system allowing stable imine formation at the 1-amino position.[3d]



We chose to develop a method that would construct the ring system utilizing a traceless cyclization-cleavage step since we targeted a scheme that would provide a diverse set of compounds for screening, require no further purification, and lend itself to synthesis automation.[4] Our first goal was to explore the synthesis of hydrazino-esters on the resin (Scheme 1, **9**). First, we investigated direct displacement on the resin,[5] and coupling of hydroxymethyl polystyrene (**6**) with bromoacetic acid (**7**, R^1=H), followed by reaction with t-butylcarbazate (DMF, room temp.) resulted in an excellent yield of the resin hydrazino ester (**9**, R^1=H, Table 1, >95%). This resin was then of suitable form to be carried through the remainder of the steps. However, when trying to incorporate other groups at the R^1 position through this method, a sharp decrease in the loading of the desired ester (**9**) was observed even upon heating the displacement step (with the exception of 2-bromopropionic and α-bromophenylacetic acids, **7** - R^1=Me and Ph). This followed a distinct S_N2 type steric effect, as evidenced by the resin loading observed (Table 1: H to Et to i-Pr - 97% to 56% to <5%). Although this procedure was acceptable and could utilize most of the resin intermediates (R^1=H, Me, Et, *n*-Hex & Ph), we sought to investigate another more direct method via coupling of the requisite BOC protected hydrazino acid building blocks (**8**). These were synthesized from alpha hydroxy acids via triflate

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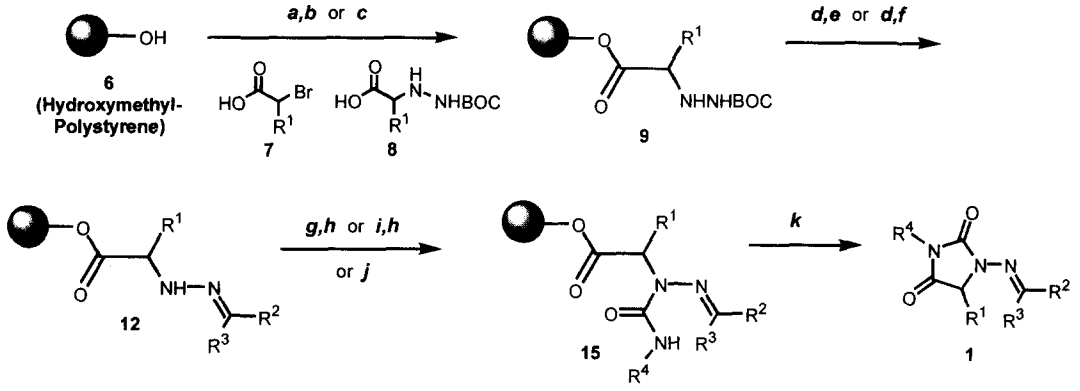
≈ Dedicated to the memory of our friend and colleague Hoang Do.

0040-4039/98/$19.00
PII: S0040-4039(98)01009-0

displacement on the corresponding methyl esters with t-butyl carbazate.[6] Resin attachment of these intermediates was then achieved by careful selection of the coupling conditions favoring utilization of a Mitsunobu esterification protocol.[7] This coupling method proved more than satisfactory after only 1 cycle, and the corresponding loadings of **9** were in excess of 90% for every example studied (see Table 1).

Scheme 1: Synthetic scheme for the solid phase synthesis of 1-aminohydantoins (**1**).



Reagents: (each reaction sequence is repeated once, except (c)) - (a) **7**, DIC, DMAP, 1,2-DCE, rt; (b) $BOCNHNH_2$, DMF, TBAI, rt or Δ; (c) **8**, PPh_3, DEAD, DCM/THF (1:1), 0° to rt; (d) TFA, 1,2-DCE, rt; (e) R^2CHO (**10**), DMF, DIPEA, rt; (f) R^2R^3CO (**11**), EtOH, AcOH, Reflux; (g) p-$NO_2PhO(CO)Cl$, DIPEA, THF-1,2-DCE (1:1), rt; (h) R^4NH_2 (**13**), DMF, DIPEA, rt; (i) Triphosgene, DIPEA, 1,2-DCE, rt; (j) R^4NCO (**14**), DMAP, DMF, rt; (k) BSTFA (10%), 1,2-DCE, 70-80°C, 8-24 hrs.

Table 1: Loading of Hydrazino-ester resins (**9**) from both 2-bromoacids (**7**) and hydrazino acids (**8**). Reported as percentages of N elemental composition compared to theoretical (as determined by combustion analysis).

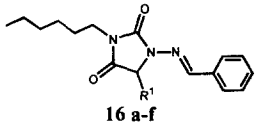
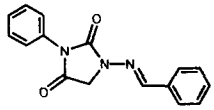
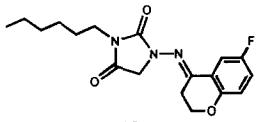
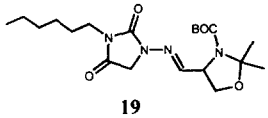
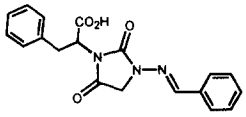
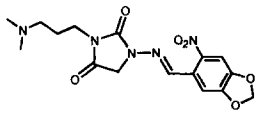
R^1 of **9**	H	Me	Et	i-Bu	n-Hex	CH_2Ph	i-Pr	Ph
% N of **9** From **7**	>95%	95%	57%	-	56%	-	<5%	95%
% N of **9** From **8**	-	>95%	92%	>95%	-	>95%	95%	-

With efficient and diverse approaches to the hydrazino resin esters in hand, we next turned our attention to the remainder of the chemistry to complete the synthesis (Scheme 1). This is best exemplified by the synthesis of the class III anti-arrythmic Azimilide (**4**) via this route. Deprotection of the BOC group under standard conditions (40% TFA in 1,2-DCE) was followed by condensation with 5-(4-chlorophenyl)-furfural (**10**, 0.35 M solution in DMF, iPr_2NEt, 12 hrs, rt) to give **12**. After imine formation (**12**), we formed the urea by a two step process: (a) reaction with p-nitrophenyl chloroformate (p-$NO_2PhO(CO)Cl$, iPr_2NEt, 0.5 M each in THF/1,2-DCE (1:1)); followed by (b) urea formation via reaction with 1-(4-aminobutyl)-4-methyl-piperazine (**13**, 0.35 M solution in DMF, iPr_2NEt, 12 hrs, rt).[8] The final step, the "traceless" cyclizative cleavage demanded mild neutral conditions that would fulfill three requirements to prevent against: (i) the potential instabiltiy of the imine bond of **15** towards hydrolysis (*e.g.* HCl & heating)[4a]; (ii) the likelihood of ring opening of the final product (**1**) under mild nucleophilic conditions (*e.g.* MeOH, NEt_3)[4b]; and (iii) retro-isocyanate addition (**15** to **12**), which we observed under strongly basic conditions (*e.g.* NaH, THF or KOH, MeOH). Careful optimization of experimental conditions showed that silylation provided the best results, and the optimal conditions were treatment with bis(trimethylsilyl)trifluoroacetamide (BSTFA, 10% solution) in 1,2-dichloroethane at or near reflux (step k, Scheme 1).[9] Under these conditions, the cyclization proceeded smoothly, providing Azimilide (**4**) in 55% yield (Table 2, entry 1, 92% yield per step from **6**).[10] We further bench marked our procedure with the synthesis of the commercial product Dantrium (**3**, Table 2, entry 2, 36% from **6**), which utilized 5-(4-nitrophenyl)-furfural (for **10**) and ammonia (for **13**) as building blocks.

Based on these results, we expanded this method to incorporate other building blocks and bond forming conditions (Table 2).[10] Our observations were that both aliphatic and aromatic aldehydes worked well. The condensation (**9** to **12**) proceeded smoothly at room temperature for every aldehyde (**10**) we selected as evidenced by

ninhydrin testing (entries 3,10,12,14). Alternatively, we could introduce a ketone (**11**) at this stage by heating the ketone and resin in either ethanol or 1,4-dioxane (entry 11). Amine variations included the incorporation of basic groups (entries 1 and 14), aliphatic side chains (entries 1, 3-8, 14), anilines (entries 9 and 10), and acidic groups (entry 13).[4b,11] We also examined two alternative routes for urea formation (**12** to **15**): (a) treatment with triphosgene, followed by amine displacement (steps i & h); and (b) treatment with an isocyanate (step j).[4] We observed that triphosgene gave the best results for this bond construction (especially for anilines - entry 9), followed by p-nitrophenylchloroformate, and then isocyanate addition (see entries 3, 9, and 10). Overall, most of the final compounds were produced in greater than 90% purity.[10] In some cases, we observed samples that gave analytically pure material directly from the resin upon filtration and evaporation (*e.g.* entries 3 and 14).

Table 2: Yields of selected 1-aminohydantoins (**1**) synthesized by the route shown in Scheme 1 listed according to the methods utilized.[10]

Entry	1-Aminohydantoin (**1**)	Route/Methods to **15** from **9**	Yield from **6** (%)[10]
1	**4** (Azimilide)	d,e,g,h	92 (55)
2	**3** (Dantrium)	d,e,g,h	86 (36)
	 **16 a-f**		
3	**16a** , R^1 = H	d,e,g,h	89 (45)
4	**16b** , R^1 = Me	d,e,g,h	87 (44)
5	**16c** , R^1 = i-Bu	d,e,g,h	78 (23)
6	**16d** , R^1 = i-Pr	d,e,g,h	76 (20)
7	**16e** , R^1 = n-Hex	d,e,g,h	76 (15)
8	**16f** , R^1 = Ph	d,e,g,h	76 (15)
9	 **17**	d,e,i,h	92 (58)
10		d,e,j	73 (15)
11	 **18**	d,f,g,h	80 (20)
12	 **19**	d,e,g,h	89 (44)
13	 **20**	d,e,g,h	91 (53)
14	 **21**	d,e,g,h	86 (33)

In summary, we have provided a general route to this unique class of hydantoin molecules which involves a simultaneous cyclization - purification step. We have synthesized thousands of discrete compounds with this route via automation, and are currently expanding the chemistry. Future studies in this area will be reported in due course.

Acknowledgments: We wish to thank the following for providing feed stocks of the BOC protected hydrazino esters (**8**) for our studies: Paul Dybas, Ramonna Quintinella, Xin Ma, Dan Prohotsky, and Hoang Do. Also we wish to thank our analytical group, Tom Burt and Kenny Morand for MS and HPLC analysis on our samples.

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6. We prepared five BOC protected hydrazino acids in this fashion (**8**, R^1=Me, Et, i-Bu, i-Pr, Bn) using the method according to Hoffman, R.V.; Kim, H.-O. *Tetrahedron Lett.* **1990**, *31*, 2953-2956. This gives the option of introducing chirality at the alpha carbon, however racemic starting materials were utilized in each case.
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9. Davies, J.S.; Merritt, R.K.; Treadgold, R.C. *J. Chem. Soc. Perkin Trans. 1* **1982**, 2939-2947.
10. All new compounds (**16-21**) gave satisfactory ^{1}H NMR, ^{13}C NMR, and MS spectra, and a few examples gave satisfactory elemental analysis without further efforts (**16a** and **21**). Imine geometries are assigned as the E configuration according to X-ray structures of analogous compounds (see reference 3d). Average yield per step for seven steps from hydroxymethyl polystyrene (**6**), except entries 4-6 and 10 (average yield per step for six steps); yield in parenthesis refers to isolated yield of final compounds (**1**). Compounds **3** and **4** (Dantrium and Azimilide) were identical with authentic samples (TLC, MS, ^{1}H NMR). Selected Physical data - **16a**: White powder (45%) - mp 140-143°C; ^{1}H NMR (300 MHz, $CDCl_3$) d 7.86 (s, 1H), 7.77-7.74 (m, 2H), 7.41 (t, 3H, J = 4.5 Hz), 4.23 (s, 2H), 3.62 (t, 2H, J = 6.0 Hz), 1.67 (m, 2H), 1.32 (s, 6H), 0.89 (t, 3H, J = 6.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) d 167.1, 144.9, 142.0, 133.7, 130.7, 128.9, 127.7, 48.3, 39.5, 31.5, 28.2, 26.6, 22.7, 14.2; MS *m/e* 288 (M+1, 100); Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.85; H, 7.18; N, 14.75; **21**: Orange powder (45%) - mp 142-144°C; ^{1}H NMR (300 MHz, $CDCl_3$) d 8.19 (s, 1H), 7.48 (s, 1H), 7.11 (s, 1H), 6.01 (s, 2H), 4.10 (s, 2H), 3.55 (t, 2H, J = 7.2 Hz), 2.18 (t, 2H, J = 6.9 Hz), 2.05 (s, 6H), 1.68 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) d 152.1, 140.0, 126.1, 107.2, 105.6, 103.7, 57.2, 48.1, 45.7, 38.0, 26.1; MS *m/e* 378 (M+1, 100); Anal. Calcd. for $C_{16}H_{19}N_5O_6 \cdot 0.1$ CF_3CONH_2: C, 50.6; H, 4.98; N, 18.38. Found: C, 50.1; H, 4.73; N, 17.9.
11. For entry 13, phenyl alanine was utilized as the silylated (TMS) ester by first heating the acid in bis(trimethylsilyl)acetamide (BSA, 3 equiv., DMF, 80°C), followed by cooling to room temperature, and then addition of the solution directly to the resin (step h, Scheme 1). Also, DMAP was used in place of DIPEA.