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SYNTHESIS OF 5-CHLOROMETHYLENE HYDANTOINS AND THIOHYDANTOINS

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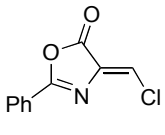
Abstract – 5-Chloromethylene hydantoins were prepared by condensation of ureas with chloropyruvic acid. 5-Chloromethylene thiohydantoins were prepared by chlorination of dehydroalanines followed by condensation with thiophosgene. Convenient methods for formation of aminomethylene hydantoins and thiohydantoins using *N*,*N*,*N*',*N*'-tetramethylformamidinium chloride are also reported.

INTRODUCTION

In the course of a total synthesis effort towards the oroidin dimers, we became interested in the dienophilic capacity of β-chlorodehydroalanine derivatives. One example of such a dienophile, 4-(chloromethylene)-2-phenyl-5-[4*H*]oxazolone (**1**) was known,[1] but it was found to be poorly diastereoselective in Diels-Alder reactions. We thus sought a broader variety of β-chlorodehydroalanine derivatives to examine in the Diels-Alder context. While 5-(alkylidene)hydantoins and thiohydantoins are easily prepared by condensation of the parent heterocycle with the appropriate aldehyde under acidic or basic conditions, extension of these conditions to the direct introduction of the =CHCl group is not feasible. Confronted with a paucity of methods for the introduction of such functionality, we initiated synthetic studies of 5-(chloromethylene)hydantoins (**2**) and thiohydantoins (**3**) and disclose the results of those studies herein.



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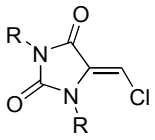

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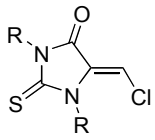

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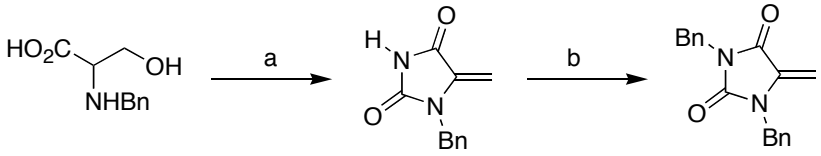
RESULTS AND DISCUSSION

The synthesis of the desired β-chloromethylenehydantoins and thiohydantoins was initially envisaged to result from chlorination of a 5-(methylene)hydantoin or thiohydantoin. Ravindranathan has synthesized

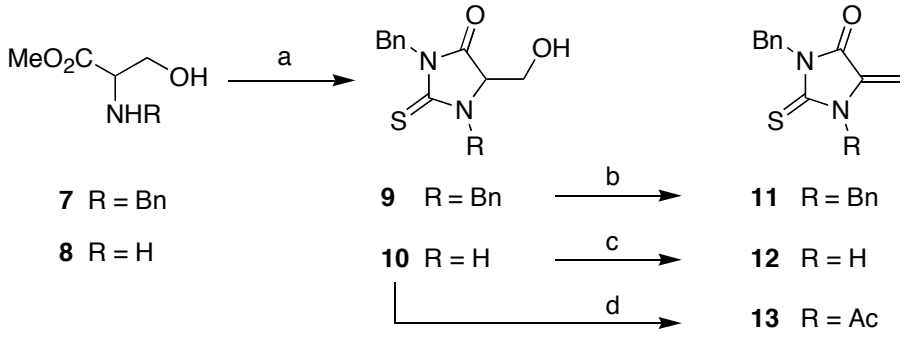
1,3-dibenzyl-5-(methylene)hydantoin (**6**) from cystine[2] and Pyne and coworkers recently prepared similar substrates by elimination of serine derived hydantoins.[3] Furthermore, Murahashi reported the preparation of 5-(methylene)hydantoin by condensation of urea with pyruvic acid. In the present context, condensation of *N*,*N*'-dibenzylurea with pyruvic acid did generate **6** but a multistep protocol, involving condensation of *N*-benzylserine (**4**) with potassium cyanate followed by acid catalyzed dehydration and N_3-benzylation, was more reliable (Scheme 1).



4 **5** **6**

Scheme 1. Reaction conditions: (a) i) KOCN, H_2O, reflux, 45 min. ii) HCl (aq), pH 2, reflux, 2 h, 32%. (b) BnCl, NaH, DMF, 23 °C, 20 h, 88%.

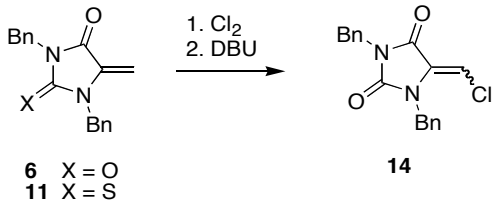
5-(Methylene)thiohydantoins were accessed from serine by routes similar to those described above (Scheme 2). Thus, reaction of either serine methyl ester or *N*-benzylserine methyl ester with benzyl isothiocyanate followed by elimination with methanesulfonyl chloride (for **9** → **11**) or trifluoroacetic anhydride (for **10** → **12**) generated the desired 5-(methylene)thiohydantoins. An N_1-acylated thiohydantoin (**13**) was prepared by a slightly longer route, involving TBS protection of **10**, DMAP catalyzed acetylation, removal of the TBS group and elimination of the resulting alcohol with methanesulfonyl anhydride and triethylamine.



Scheme 2. Reaction conditions: (a) benzylisothiocyanate, NEt_3, CH_2Cl_2, reflux, 5 h, **9**: 83%; **10**: 55%. (b) MsCl, NEt_3, CH_2Cl_2, 0 °C, 45 min, 99%. (c) TFAA, NEt_3, CH_2Cl_2, 0 °C, 1 h, 66%. (d) i) TBSCl, imidazole, THF, 23 °C, 2.5 h, 92%. ii) Ac_2O, NEt_3, DMAP, THF, 23 °C, 3.5 h, 93%. iii) HF (aq), MeCN, 23 °C, 5 h, 87%. iv) Ms_2O, NEt_3, CH_2Cl_2, 0 °C, 30 min, 95%.

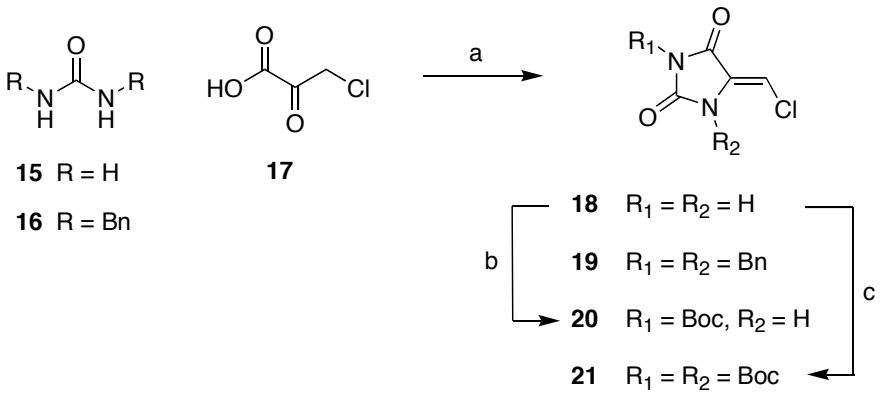
Chlorination of 1,3-dibenzyl-5-(methylene)hydantoin (**6**) followed by treatment with DBU successfully generated **14** (Equation 1) but formation of a significant amount of an inseparable dichlorinated byproduct (not shown) forced recourse to a different strategy. Chlorination of thiohydantoin (**11**) was

even less successful. In 1911, Johnson reported that chlorination of a 5-(benzylidene)thiohydantoin gave the desired 5-(chlorobenzylidene)thiohydantoin. However, it was found that while chlorination of **11** does indeed introduce the chloromethylene functionality, as a mixture of *E*/*Z*-isomers, it is accompanied by oxidative extrusion of sulfur, thus generating hydantoin (**14**) instead of the desired 5-(chloromethylene)thiohydantoin (Equation 1).



(1)

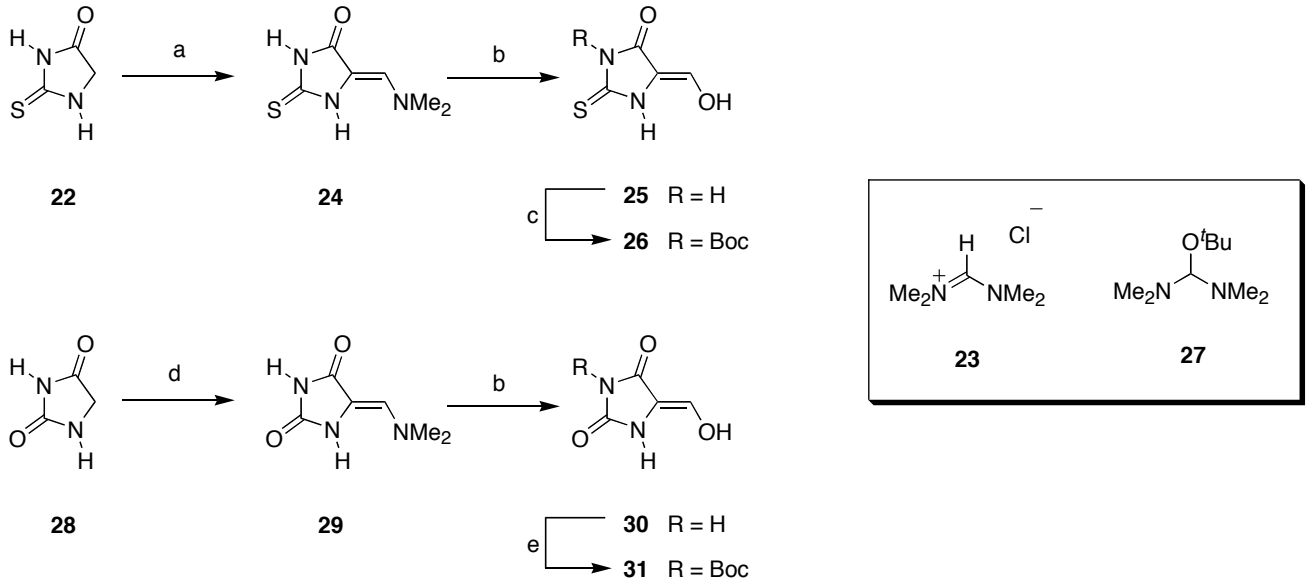
Schechter recently reported that reaction of bromopyruvic acid with ureas in the presence of BF_3•Et_2O leads to 5-(bromomethylene)hydantoins.[4,5,6] These conditions were likewise applicable to the preparation of 5-(chloromethylene)hydantoins (Scheme 3). Thus, treatment of urea (**15**) or *N*,*N*'-dibenzylurea (**16**)[7] with freshly distilled chloropyruvic acid (**17**)[8] and BF_3•Et_2O (0.4 equiv) generated **18** and **19** in 42% and 60% yields, respectively. Hydantoin (**18**) could be N_3- or N_1,N_3-Boc protected using catalytic DMAP and Boc_2O. In general, it was found that the β-chloromethylenes are more stable than their unchlorinated analogues. For example, **19** is bench stable for more than a year whereas **6** readily decomposes in the course of several weeks under ambient conditions.



Scheme 3. Reaction conditions: (a) BF_3•Et_2O (0.4 equiv), MeCN, reflux, 24-30 h, **18**: 42%, **19**: 60%. (b) Boc_2O (1 equiv), NEt_3, DMAP, THF, 23 °C, 12 h, 70%. (c) Boc_2O (2 equiv), NEt_3, DMAP, THF, 23 °C, 2 h, 90%.

Preparation of a 5-(chloromethylene)thiohydantoin was considerably more challenging. Approaches such as treatment of 5-(chloromethylene)hydantoins (**18**-**20**) with Lawesson's reagent or treatment of oxazolone (**1**) with ammonium thiocyanate[9] failed to deliver 5-(chloromethylene)thiohydantoins. Not surprisingly, reaction of thiourea with chloropyruvic acid under BF_3•Et_2O catalysis, as described above, gave 2-amino-4-carboxythiazole hydrochloride in 89% yield via the Hantzsch-Traumann reaction.[10]

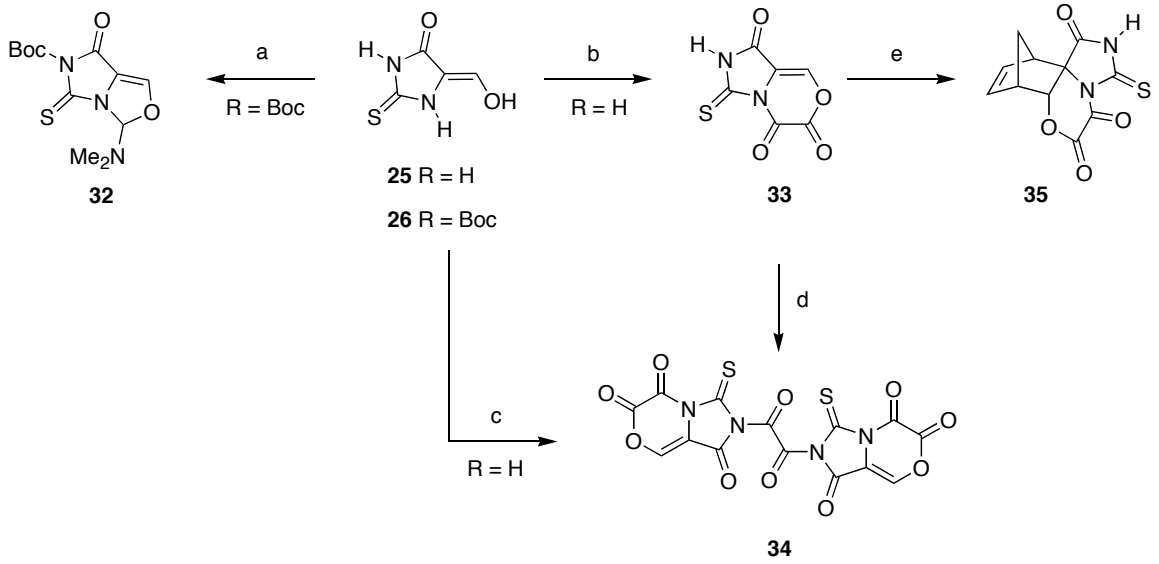
The desired 5-(chloromethylene)hydantoins (**2**) and thiohydantoins (**3**) can be viewed as vinylogous carbamyl chlorides which could seemingly arise from dehydrative chlorination of the corresponding hydoxymethylenes. Towards this goal, thiohydantoin (**22**, Scheme 4) was aminoformylated in 74% yield upon reaction with *N*,*N*,*N*',*N*'-tetramethylformamidinium chloride (**23**)[11] and triethylamine. The aminoformylation of **22** was also achieved in 68% yield with commercially available *t*-butoxy bis(dimethylamino)methane (Bredereck's reagent, **27**). However, **23**, an easily prepared bench-stable solid, was found to be much more economical than **27** for large-scale applications. Additionally, while **27** inherently generates *t*-butoxide as base, **23** offers the ability to vary the base according to the requirements of the substrate. For instance, while triethylamine is sufficiently basic to effect reaction of **22**, no reaction occurs between hydantoin (**28**) and **23** under these conditions. In contrast, addition of sodium *t*-butoxide as base effects rapid aminoformylation of **28**, presumably via *in situ* formation of **27**. To complete the introduction of hydroxymethylene functionality, **24** and **29** were hydrolyzed with aqueous trifluoroacetic to afford **25** and **30** which were N_3-acylated to give **26** and **31**, respectively.



Scheme 4. Reaction conditions: (a) **23**, NEt_3, MeCN, reflux, 40 min, 74%. (b) TFA, H_2O, reflux, 15 min, **25**: 73%; **30**: 56% (c) Boc_2O, NEt_3, DMAP, THF, 23 °C, 3.5 h, 63%. (d) **23**, NaO*t*Bu, MeCN, reflux, 1.5 h, 65%. (e) Boc_2O, NEt_3, DMAP, THF, 23 °C, 14 h, 81%.

Treatment of vinylogous acids (**25** or **26**) with a variety of dehydrative chlorination reagents did not generate the desired chloromethylene thiohydantoins. Activation of the hydroxymethylene was clearly observed in many cases, but nucleophillic attack on the activated intermediates by chloride ion did not take place. Collapse of the activated intermediates to generate novel heterocyclic products was occasionally observed. For instance, treatment of **26** with *N*,*N*-dimethylchloroformiminium chloride gave thioxoimidazooxazole (**32**) (Scheme 5) which was isolated in 25% yield after silica gel

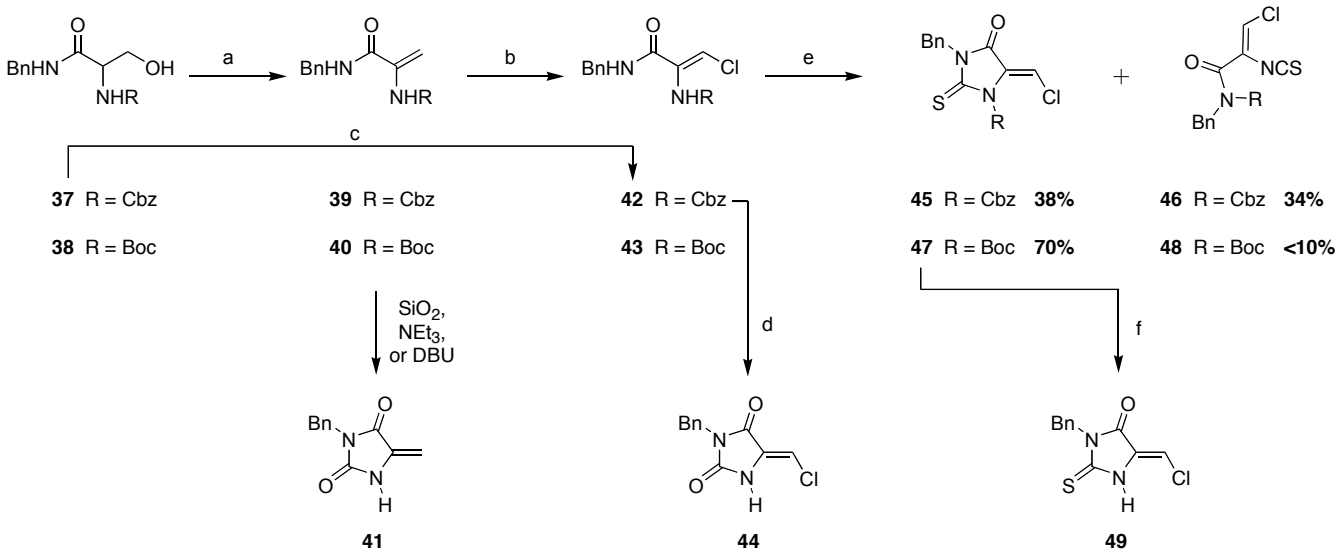
chromatography. Treatment of **25** with one or three equivalents of oxalyl chloride gave products which were spectrally consistent (^{1}H-NMR, ^{13}C-NMR) with thioxoimidazooxazine (**33**) and dimeric thioxoimidazooxazine (**34**), respectively, but whose identity could not be unambigously established by mass spectra or elemental analysis due to decomposition. The identity of **33** could be inferred by treatment with cyclopentadiene to form cycloadduct (**35**), which was unambiguously characterized.



Scheme 5. Reaction conditions: (a) $(COCl)_2$ (3 equiv), DMF (3 equiv), CH_2Cl_2/Et_2O, 23 °C, 2.5 h, 25%. (b) $(COCl)_2$ (1 equiv), MeCN, 23 °C, 2 h, >95% (NMR yield). (c) $(COCl)_2$ (3 equiv), MeCN, reflux, 11 h, >95% (NMR yield). (d) $(COCl)_2$ (1 equiv), MeCN, reflux, 4 h, >80% (NMR yield). (e) cyclopentadiene, CH_2Cl_2, reflux, 16 h, 46% (from **25**), 9:1 *dr* (major diastereomer shown).

The desired 5-(chloromethylene)thiohydantoins were successfully prepared by an alternate strategy which installed the chloromethylene functionality prior to heterocycle formation (Scheme 6). β-Chlorodehyroalanine amides (**42** and **43**) were prepared from *N*-Cbz-serine benzylamide (**37**) and *N*-Boc-serine benzylamide (**38**), respectively, by a dehydration-chlorination-elimination sequence. Mesylation and elimination of **37** or **38** using DBU as base afforded the desired dehydroalanines (**39**) and (**40**) but, particularly in the case of the *N*-Cbz substrate, the elimination was accompanied by cyclization to hydantoin (**41**).[12] An improved protocol, involving conversion of the mesylate to an iodide followed by elimination under mild conditions, minimized the formation of **41**. Crude dehydroalanine (**39**) prepared by this method was chlorinated and eliminated to afford **42** in good overall yield. Unlike **39** and **40**, the chlorinated substrates were significantly more stable and only cyclized to give **44** when treated with strong bases such as KHMDS at 0 °C. Deprotonation of **42** with LiHMDS at –78 °C and trapping with thiophosgene gave 5-(chloromethylene)thiohydantoin (**45**) along with a considerable amount of a separable isothiocyanate (**46**) which apparently results from acyl shift following addition of the carbamate nitrogen to thiophosgene. Treatment of **42** with thiocarbonyldiimidazole under the same

conditions led to exclusive formation of **44**. By employing Boc as protecting group, the formation of the isothiocyanate was minimized and the desired 5-(chloromethylene)thiohydantoin (**47**) was obtained in 70% yield. Deprotection of **47** with TFA gave thiohydantoin (**49**) in 90% yield.



Scheme 6. Reaction conditions: (a) i) MsCl, NEt_3, CH_2Cl_2, 0 → 23 °C, 1.5 h. ii) DBU, CH_2Cl_2, 23 °C, 1 h. **39**: 42%; **40**: 66% (b) i) Cl_2, CH_2Cl_2, -10 °C, 10 min. ii) DABCO, MeCN, -10 °C, 30 min. **42**: 84%; **43**: 63%. (c) i) MsCl, NEt_3, CH_2Cl_2, 0 → 23 °C, 1 h. ii) NaI, acetone, reflux, 3.5 h. iii) NEt_3, acetone, 23 °C, 3 h. iv) Cl_2, CH_2Cl_2, -10 °C, 10 min. v) DABCO, MeCN, -10 °C, 40 min, 48% (from **37**) (d) KHMDS, THF, 0 °C, 30 min, 72%. (e) LiHMDS, THF, -78 °C → -20 °C, 25 min. ii) thiophosgene, THF, -78 °C, 5 min. (f) TFA. CH_2Cl_2, 23 °C, 2 h, 90%.

CONCLUSION

We have developed routes to a variety of 5-methylene, 5-(hydroxymethylene), and 5-(chloromethylene)hydantoins and thiohydantoins. The Diels-Alder capacity of these compounds is currently under investigation in our labs.

EXPERIMENTAL

General Procedures: Reactions were performed in flame- or oven-dried glassware under an atmosphere of argon unless noted otherwise. Flash column chromatography was carried out on 230-400 mesh silica gel (Silicyle) using reagent grade solvents. Thin-layer chromatography (TLC) was carried out on glass plates, coated with 250 μm of 230-400 mesh silica gel impregnated with F-254 indicator, and visualized by UV (254 nm) or potassium permanganate indicator. Melting points (mp) were obtained in open capillaries on a Mel-Temp apparatus and are uncorrected. Tetrahydrofuran and diethyl ether were purified by distillation from sodium benzophenone ketyl radical under a nitrogen atmosphere. Toluene, acetonitrile, dichloromethane and triethylamine were purified by distillation from calcium hydride under a

dry air atmosphere. Deuterated chloroform was stored over activated 4 Å molecular sieves. Deuterated solvents were purchased in analytically pure form and stored in ampoules. All other reagents were used as obtained from commercial vendors.

1-Benzyl-5-methyleneimidazolidine-2,4-dione (5): DL-*N*-Benzylserine (**4**)[13] (23.1 g, 119 mmol, 1.0 equiv) and potassium cyanate (12.0 g, 148 mmol, 1.2 equiv) were stirred at reflux in deionized water (1 L) for 45 min. The solution was cooled to 23 °C and adjusted to pH 2 with 1 M hydrochloric acid then concentrated to ~400 mL by distillation. Allowing this solution to stand at 23 °C overnight resulted in precipitation of the product. The white solid was isolated by vacuum filtration and recrystallized from water to give a white solid (9.37 g, 32% yield): IR (KBr) 3198, 2715, 1762, 1732, 1717, 1660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.71 (d, *J* = 2.4 Hz, 1H), 4.78 (s, 2H), 5.36 (d, *J* = 2.4 Hz, 1H), 7.25-7.38 (m, 5H), 7.91 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.3, 96.5, 127.5, 128.2, 129.1, 135.0, 136.4, 154.3, 163.0; mp 141-145 °C; HRMS found 202.0745 +/- 0.0006 (calc. 202.0742).

1,3-Dibenzyl-5-methyleneimidazolidine-2,4-dione (6): To a solution of **5** (897 mg, 3.72 mmol, 1.0 equiv) in dimethylformamide (20 mL) was added sodium hydride (60% dispersion in mineral oil, 179 mg, 4.47 mmol, 1.2 equiv). Benzyl bromide (642 μL, 5.58 mmol, 1.5 equiv) was added dropwise and the solution was stirred at 23 °C for 20 h. The solution was diluted with 100 mL of water and extracted with hexanes until the extracts showed no UV activity by TLC. The combined hexanes extracts were dried on anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was recrystallized from 2-propanol to yield white needles (956 mg, 88% yield). This product was prone to polymerization and extensive heating should be avoided. It was found beneficial to add preheated 2-propanol to the crude solid in the recrystallization step rather than heating the solution: IR (KBr) 2924, 1773, 1717, 1656, 1451; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, *J* = 2.4 Hz, 1H), 4.76 (s, 2H), 4.78 (s, 2H), 5.35 (d, *J* = 2.4 Hz, 1H), 7.21-7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.7, 44.3, 95.7, 127.3, 127.9, 128.0, 128.6, 128.7, 128.8, 134.9, 135.5, 135.7, 154.1, 162.0; mp 89.0-90.0 °C; HRMS found 292.1217 +/- 0.0008 (calc. 292.1212).

1,3-Dibenzyl-5-(hydroxymethyl)-2-thioxoimidazolidin-4-one (9): A suspension of *N*-benzylserine methyl ester, hydrochloride (**7**) (553 mg, 2.26 mmol, 1.0 equiv), benzyl isothiocyanate (300 μL, 2.26 mmol, 1.0 equiv), and triethylamine (315 μL, 2.26 mmol, 1.0 equiv) was refluxed in dichloromethane (7.5 mL) for 5 h then cooled to 23 °C. The solution was diluted with ethyl acetate and washed twice with saturated ammonium chloride, then brine, then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue taken up in a minimal amount of chloroform, loaded onto a plug of silica gel, washed with hexanes to remove residual benzyl isothiocyanate and then eluted with 50/50 ethyl acetate-hexanes affording a white solid (609 mg, 83% yield): IR (KBr) 3437, 2964, 1727, 1497, 1365, 1340, 1311, 1221; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.73 (bs, 1H), 3.84-3.94 (m, 3H), 4.74 (d, *J* = 15.0 Hz,

1H), 5.08 (s, 2H), 5.50 (d, *J* = 15.0 Hz, 1H), 7.27-7.47 (m, 10H); ^{13}C NMR (100 MHz, CD_3CN) δ 45.6, 49.0, 59.2, 63.2, 127.6, 127.9, 128.2, 128.3, 128.4, 129.0, 135.1, 135.6, 172.1, 183.6; mp 122-124 °C; HRMS found 326.1097 +/- 0.0010 (calc. 326.1089)

1,3-Dibenzyl-5-methylene-2-thioxoimidazolidin-4-one (11): A suspension of **9** (858 mg, 2.62 mmol, 1.0 equiv) in dichloromethane (15 mL) was cooled to 0 ºC, triethylamine (913 μL, 6.55 mmol, 2.5 equiv) added, then methanesulfonyl chloride (304 μL, 3.94 mmol, 1.5 equiv) was added slowly, dropwise. The solution was stirred at 0 ºC for 45 min, diluted with ether, washed with saturated ammonium chloride, then brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil (808 mg, 99% yield): IR (KBr) 3032, 1740, 1648, 1346, 1233, 879; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (d, *J* = 2.7 Hz, 1H), 5.13 (s, 2H), 5.24 (s, 2H), 5.44 (d, *J* = 2.7 Hz, 1H), 7.22-7.35 (m, 8H), 7.49 (dd, *J* = 7.7 Hz, 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.5, 47.6, 98.5, 127.1, 127.9, 128.0, 128.5, 128.8, 128.9, 134.6, 135.4, 135.6, 162.5, 179.1; HRMS found 308.0990 +/- 0.0009 (calc. 308.0983).

3-Benzyl-5-(hydroxymethyl)-2-thioxoimidazolidin-4-one (10): A suspension of serine methyl ester, hydrochloride (**8**) (1.17 g, 7.5 mmol, 1.0 equiv), benzyl isothiocyanate (1.0 mL, 7.5 mmol, 1.0 equiv), and triethylamine (1.05 mL, 7.5 mmol, 1.0 equiv) was refluxed in dichloromethane (25 mL) for 5 h then cooled to 23 ºC. The solution was diluted with ethyl acetate and washed twice with saturated ammonium chloride, then brine, then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was washed with some cold ether to remove residual benzyl isothiocyanate affording white spheres of analytical purity (2.61 g, 55% yield): IR (KBr) 3394, 3200, 1708, 1347, 1242; ^{1}H NMR (400 MHz, CD_3CN) δ 3.35 (t, *J* = 5.8 Hz, 1H), 3.82-3.87 (m, 2H), 4.19-4.21 (m, 1H), 4.95 (s, 2H), 7.24-7.33 (m, 5H), 8.12 (bs, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 44.8, 61.1, 62.7, 128.1, 128.2, 129.2, 137.3, 174.0, 185.3; mp 139-140 ºC; C,H,N Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C 55.91, H 5.12, N 11.86. Found: C 55.89, H 4.92, N 11.71.

3-Benzyl-5-methylene-2-thioxoimidazolidin-4-one (12): A suspension of **10** (424 mg, 1.79 mmol, 1.0 equiv) in dichloromethane (25 mL) was cooled to 0 ºC, triethylamine (1.25 mL, 8.95 mmol, 5.0 equiv) was added, then trifluoroacetic anhydride (760 μL, 5.38 mmol, 3.0 equiv) added slowly, dropwise. The solution was stirred at 0 ºC for 1 h, diluted with ether, washed with saturated sodium bicarbonate, then saturated ammonium chloride, then brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil which was purified by flash column chromatography on silica gel using gradient elution (hexanes → 20/80 ethyl acetate-hexanes) to give a shiny, pale-yellow solid (258 mg, 66% yield): IR (KBr) 3423, 2951, 1706, 1659, 1313, 1233; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H), 5.06 (d, *J* = 2.0 Hz, 1H), 5.46 (d, *J* = 2.0 Hz, 1H), 7.20-7.33 (m, 3H), 7.45-7.51 (m, 2H), 8.19 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.7, 98.2, 127.9, 128.5, 128.7, 133.9,

135.1, 162.4, 178.1; mp 210-225 ºC (dec.); HRMS found 218.0517 +/- 0.0003 (calc. 218.0514).

3-Benzyl-5-({[*t*-butyl(dimethyl)silyl]oxy}methyl)-2-thioxoimidazolidin-4-one (50): To a solution of **10** (1.00 g, 4.2 mmol, 1.0 equiv) in tetrahydrofuran (8.5 mL) was added chloro-*t*-butyldimethylsilane (702 mg, 4.7 mmol, 1.1 equiv) and imidazole (576 mg, 8.5 mmol, 2.0 equiv) and the resulting suspension stirred at 23 °C for 2.5 h. At this time, the reaction was diluted with ether, washed twice with saturated ammonium chloride, once with 10% sodium bicarbonate solution, and once with brine, then dried on sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in a minimal amount of ether onto which was floated approximately 10 volumes of hot hexanes. Slowly cooling to -4 ºC and leaving at this temperature overnight provided large, clear, colorless needles (1.37 g from two crops, 92% yield): IR (KBr) 3255, 2956, 1728, 1719, 1322, 1172; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.04 (s, 6H), 0.83 (s, 9H), 3.69 (dd, *J* = 10.7, 5.7 Hz, 1H), 3.96 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.18 (m, 1H), 4.94 (AB, *J* = 14.2 Hz, 1H), 5.02 (AB, *J* = 14.6 Hz, 1H), 6.99 (bs, 1H), 7.26-7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, -5.3, 18.2, 25.7, 44.6, 61.6, 62.1, 127.7, 128.3, 128.6, 135.4, 171.9, 184.3; mp 90.0-91.0 ºC; HRMS found 351.1566 +/- 0.0010 (MH^+ calc. 351.1562).

1-Acetyl-3-benzyl-5-({[*t*-butyl(dimethyl)silyl]oxy}methyl)-2-thioxoimidazolidin-4-one (51): To a solution of **50** (816 mg, 2.3 mmol, 1.0 equiv) in THF (20 mL) was added acetic anhydride (614 μL, 6.5 mmol, 2.8 equiv), triethylamine (1.0 mL, 7.2 mmol, 3.1 equiv), and 4-(dimethylamino)pyridine (85 mg, 0.7 mmol, 0.3 equiv) and the solution stirred at 23 ºC for 3.5 h. The reaction mixture was diluted with ether, washed twice with 0.5 M hydrochloric acid, and once with brine then dried on anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using gradient elution (hexanes → 10/90 ethyl acetate-hexanes) to obtain a clear, colorless oil (856 mg, 93% yield): IR (thin film) 2954, 1761, 1701, 1323, 1256, 1220; ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.09 (s, 6H), -0.07 (s, 6H), 0.73 (s, 9H), 2.82 (s, 3H), 4.10 (d, *J* = 10.0 Hz, 1H), 4.29 (dd, *J* = 10.6, 1.9 Hz, 1H), 4.67 (m, 1H), 5.00 (AB, *J* = 14.5 Hz, 1H), 5.06 (AB, *J* = 15.0 Hz, 1H), 7.26-7.30 (m, 3H), 7.41-7.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.8, -5.7, 17.8, 25.5, 45.0, 60.7, 63.3, 127.9, 128.5, 128.8, 134.9, 170.4, 171.0, 181.5; HRMS found 392.1592 +/- 0.0011 (calc. 392.1590).

1-Acetyl-3-benzyl-5-(hydroxymethyl)-2-thioxoimidazolidin-4-one (52): A solution of hydrofluoric acid was prepared by diluting an aqueous stock solution (48%, 3.0 mL) with acetonitrile (8.0 mL, final concentration 13% w/v). This solution was poured onto **51** (390 mg, 0.99 mmol, 1.0 equiv) and the reaction stirred for 5 h. The solution was diluted with ethyl acetate, washed with brine, 0.5 M hydrochloric acid, 10% sodium bicarbonate solution, and brine, then dried on anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was dissolved in a minimal amount of ether onto which was floated approximately 10 volumes of hot hexanes. Slowly cooling to -4 ºC and leaving at this temperature overnight provided white needles (240 mg from two crops, 87% yield): IR (thin film) 3470,

2934, 1758, 1701, 1342, 1243; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.55 (br s, 1H), 2.86 (s, 3H), 4.14 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.30 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.74 (m, 1H), 5.05 (AB, *J* = 14.5 Hz, 1H), 5.11 (AB, *J* = 14.5 Hz, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 45.2, 60.7, 63.5, 127.8, 128.3, 128.4, 128.7, 134.5, 170.7, 170.8, 180.9; mp 102-104 °C; HRMS found 278.0727 +/- 0.0008 (calc. 278.0725).

1-Acetyl-3-benzyl-5-methylene-2-thioxoimidazolidin-4-one (13): To a cooled (0 ºC) solution of **52** (208 mg, 0.75 mmol, 1.0 equiv) and methanesulfonyl anhydride (143 mg, 0.82 mmol, 1.1 equiv) in dichloromethane (8 mL) was added triethylamine (260 μL, 1.87 mmol, 2.5 equiv). The solution was stirred at 0 ºC for 30 min, diluted with ethyl acetate, washed with saturated ammonium chloride, then brine, then dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford an off-white solid (185 mg, 95% yield). This product was susceptible to polymerization and was therefore used without further purification: IR (KBr) 1748, 1722, 1298, 1209; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (s, 3H), 5.13 (s, 2H), 5.98 (d, *J* = 0.8 Hz, 1H), 6.48 (d, *J* = 0.8 Hz, 1H), 7.29-7.31 (m, 3H), 7.42-7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 45.2, 109.1, 128.1, 128.5, 128.8, 132.7, 134.6, 161.4, 170.8, 177.1; HRMS data could not be obtained for this sensitive substrate – the correct mass was inferred from the HRMS of the subsequent Diels-Alder product with cyclopentadiene.

(5*Z*)-5-(Chloromethylene)imidazolidine-2,4-dione (18): According to the method of Shechter[6], urea (**15**) (3.42 g, 57 mmol, 1.0 equiv) was added to a solution of freshly distilled chloropyruvic acid (**17**)[8] (7.00 g, 57 mmol, 1.0 equiv) and boron trifluoride etherate (3.0 mL, 23 mmol, 0.4 equiv) in 110 mL of acetonitrile. The solution was brought to reflux and stirred for 24 h at which point it was cooled and concentrated *in vacuo* to afford a pale yellow solid that was recrystallized from ethanol to give a white powder (3.47 g, 42% yield): IR (KBr) ; 3200, 3085, 1735, 1688, 1655, 743; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.49 (s, 1H), 10.68 (bs, 1H), 11.25 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 102.1, 133.3, 155.1, 163.2; mp 236 ºC (dec.); HRMS found 145.9887 +/- 0.0004 (calc. 145.9883).

(5*Z*)-1,3-Dibenzyl-5-(chloromethylene)imidazolidine-2,4-dione (19): According to the method of Shechter[6], *N*,*N*'-dibenzylurea (**16**)[7] (7.0 g, 29 mmol, 1.0 equiv) was added to a solution of freshly distilled chloropyruvic acid (**17**)[8] (10.5 g, 86 mmol, 3.0 equiv) and boron trifluoride etherate (1.5 mL, 12 mmol, 0.4 equiv) in acetonitrile (200 mL). The solution was brought to reflux and stirred for 30 h at which point it was cooled and concentrated *in vacuo*. The residue was taken up in ethyl acetate and washed consecutively with a saturated solution of sodium bicarbonate then brine. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* then crystallized from ethanol/water to give an off-white powder (5.7 g, 60% yield). Further recrystallization from 2-propanol gave white needles of analytical purity: IR (KBr) 3117, 2924, 1773, 1717, 1656, 731; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 2H), 5.19 (s, 2H), 6.48 (s, 1H), 7.26-7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.1, 44.9, 104.7, 126.8,

127.7, 128.1, 128.5, 128.6, 128.7, 129.2, 135.3, 136.5, 154.4, 161.1; mp 78.0-78.5 ºC; C,H,N Anal. Calcd for $C_{18}H_{15}N_2O_2Cl$: C 66.16, H 4.63, N 8.57. Found: C 66.01, H 4.46, N 8.47.

(5*Z*)-3-(*t*-Butoxycarbonyl)-5-(chloromethylene)imidazolidine-2,4-dione (20): To a solution of **18** (1.00 g, 6.83 mmol, 1.0 equiv), di-*t*-butyl dicarbonate (1.49 g, 6.83 mmol, 1.0 equiv), and 4-(dimethylamino)pyridine (83 mg, 0.68 mmol, 0.1 equiv) in tetrahydrofuran (35 mL) was added triethylamine (1.40 mL, 10.2 mmol, 1.5 equiv) and the solution stirred under argon for 12 h at 23 ºC. Solvent was removed at reduced pressure and the residue was purified by flash chromatography on silica gel (20/80 ethyl acetate-hexanes) giving a white solid (1.18 g, 70% yield): IR (KBr) ; 3198, 2985, 1802, 1774, 1728, 1654, 747; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 9H), 6.54 (s, 1H), 7.75 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.9, 86.5, 106.0, 128.5, 145.2, 148.9, 156.9; mp 235 ºC (decomp.); HRMS found 246.0402 +/- 0.0007 (calc. 246.0407).

(5*Z*)-1,3-*bis*(*t*-Butoxycarbonyl)-5-(chloromethylene)imidazolidine-2,4-dione (21): To a solution of **18** (725 mg, 4.95 mmol, 1.0 equiv), di-*t*-butyl dicarbonate (2.80 g, 12.9 mmol, 2.6 equiv), and 4-(dimethylamino)pyridine (60 mg, 0.50 mmol, 0.1 equiv) in tetrahydrofuran (25 mL) was added triethylamine (1.70 mL, 12.5 mmol, 2.5 equiv) and the solution stirred under argon for 2 h at 23 ºC during which time precipitation occurred and the suspension was filtered. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography on silica gel (5/95 ethyl acetate-hexanes) to obtain a clear colorless oil (1.545 g, 90% yield): IR (KBr) 2945, 1820, 1775, 1759, 1747, 1657; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H), 1.58 (s, 9H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 27.7, 86.8, 86.9, 112.9, 126.1, 144.6, 144.9, 146.2, 156.6; mp 46-49 ˚C; HRMS found 364.1267 +/- 0.0011 (calc. for MNH_4^+ 364.1275).

(5*Z*)-(Dimethylaminomethylene)-2-thioxoimidazolidin-4-one (24): *N*,*N*,*N'*,*N'*-Tetramethylformamidinium chloride (**23**) (10.6 g, 77.7 mmol, 1.0 equiv), prepared according to precedent[11] (mp 128-134 ˚C, lit., 130-139 ºC), and 2-thiohydantoin (**22**) (9.02 g, 77.7 mmol, 1.0 equiv) were taken up in acetonitrile (175 mL) and triethylamine (10.8 mL, 77.7 mmol, 1.0 equiv) was added. The suspension was heated to reflux and solution occurred. Reflux was continued for 40 min during which time the product precipitates. The reaction was cooled to 23 ºC, hexanes (50 mL) were added and the mixture was further cooled to 0 ºC to encourage complete precipitation of product. Isolation of product by filtration yields a bright pink solid (9.78 g, 74% yield): IR (KBr) 3116, 1701, 1628, 1517, 1290; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.07 (s, 6H), 6.62 (s, 1H), 11.11 (bs, 1H), 11.46 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 42.4, 103.7, 131.6, 165.0, 169.6; mp 215-225 ºC (decomp.). This compound has been previously described.[14] The corresponding hydantoin (**29**), which is also a known compound, was prepared according to this procedure but using sodium *t*-butoxide in place of triethylamine.

(5*Z*)-(Hydroxymethylene)-2-thioxoimidazolidin-4-one (25): Enamine (**24**) (1.79 g, 10.5 mmol, 1.0

equiv) was suspended in water (25 mL), trifluoroacetic acid (5 mL, 67.3 mmol, 6.4 equiv) was added and the suspension was brought to reflux. After 15 min, the product had precipitated and the solution was cooled to 0 ºC. Isolation of product by filtration yields a lustrous purple solid (1.09 g, 73% yield): IR (KBr) 3096, 1702, 1629, 1534, 1257, 1198; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (s, 1H), 11.43 (bs, 1H), 11.60 (bs, 1H), 11.63 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 113.6, 135.8, 165.6, 173.6; mp 200-210 ºC (dec.); HRMS found 143.9997 +/- 0.0004 (calc. 143.9993). The corresponding hydantoin (**30**), which is a known compound,[14] was prepared according to this procedure.

(5*Z*)-*t*-Butyl 4-(hydroxymethylene)-5-oxo-2-thioxoimidazolidine-1-carboxylate (26): Enol (**25**) (3.83 g, 26.6 mmol, 1.0 equiv) and di-*t*-butyl dicarbonate (5.80 g, 26.6 mmol, 1.0 equiv) were taken up in 150 mL of tetrahydofuran and cooled in an ice bath. Triethylamine (4.1 mL, 29 mmol, 1.1 equiv) then 4-(dimethylamino)pyridine (330 mg, 2.7 mmol, 0.1 equiv) were added and the ice bath was removed allowing the suspension to warm to 23 ºC. Stirring under argon was continued for 3.5 h, the reaction was poured onto a plug of silica gel and eluted (20/80 ethyl acetate-hexanes) rapidly to prevent product decomposition by silica. Removal of solvents afforded a pale yellow solid (4.09 g, 63%): IR (KBr) 3357, 3191, 1786, 1742, 1690; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.55 (s, 9H), 7.53 (s, 1H), 8.35 (bs, 1H), 8.42 (bs, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 27.7, 86.1, 119.1, 123.6, 165.3, 178.1, 178.2; mp 125-130 ˚C (dec.); HRMS found 245.0600 +/- 0.0007 (MH^+ calc. 245.0596).

(5*Z*)-*t*-Butyl 4-(hydroxymethylene)-2,5-dioxoimidazolidine-1-carboxylate (31): Prepared as **26** but with 14 h of stirring and product isolation by regular column chromatography on silica gel using gradient elution (20/80 ethyl acetate/hexanes → 50/50 ethyl acetate/hexanes) to obtain a white solid (81% yield): IR (thin film) 3228, 2983, 1766, 1738, 1700; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.53 (s, 9H), 7.26 (s, 1H), 9.40 (bs, 1H), 9.90 (bs, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 27.0, 85.0, 118.3, 121.8, 149.8, 153.4, 164.3; mp gas evolution at 156 ˚C, then 230-250 ºC (dec.); HRMS found 251.0638 +/- 0.0001 (MNa^+ calc. 251.0638).

Thioxoimidazooxazole (32): *N*,*N*-Dimethylchloroformiminium chloride was formed by treating a solution of DMF (51 μL, 0.663 mmol, 3.0 equiv) in dichloromethane (8 mL) with oxalyl chloride (58 μL, 0.663 mmol, 3.0 equiv) and stirring at 23 ºC for 10 min. A solution of enol (**26**) in dichloromethane-ether (1:1, 6 mL) was added via cannula and the reaction stirred at 23 ºC for 2.5 h. The solution was diluted with ethyl acetate and washed thrice with brine then dried on anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (25/75 ethyl acetate-hexanes) to obtain **32** as a clear, red oil (17 mg, 25% yield): ^{1}H NMR (500 MHz, acetone-d_6) δ 1.55 (s, 9H), 3.11 (s, 3H), 3.30 (s, 3H), 7.49 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9, 35.7, 41.7, 85.9, 132.1, 137.0, 150.9, 158.2, 167.2, 195.1; MS 322 $[M+Na]^+$, 300 $[M+H]^+$, 244 $[M+H]^+ - CHNMe_2$, 200 $[M+H]^+$ – Boc.

Thioxoimidazooxazine (33): Thiohydantion (**25**) (113 mg, 0.787 mmol, 1.0 equiv) was refluxed in acetonitrile (4 mL) with oxalyl chloride (74 μL, 0.787 mmol, 1.0 equiv) for 2 h then concentrated *in vacuo* to afford the title compound as a brown solid: IR (KBr) 3103, 1785 (shoulder), 1744, 1701, 1629, 1259; ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.61 (s, 1H), 10.58 (bs, 1H); ^{13}C NMR (125 MHz, acetonitrile-d_3) δ 116.0, 129.4, 146.2, 153.3, 159.4, 171.9; mp 120-140 ºC (decomp.); HRMS found 220.9627 +/- 0.0001 (MNa^+ calc. 220.9627) - NB: This peak was observed only as a minor peak in acquisitions taken immediately after injection.

Thioxoimidazooxazine dimer (34): To a suspension of enol (**25**) (75 mg, 0.520 mmol, 1.0 equiv) in acetonitrile (3 mL) was added oxalyl chloride (147 μL, 1.561 mmol, 3.0 equiv) and the mixture refluxed for 11 h. Concentration *in vacuo* gave **27** as a shiny black oil that readily decomposed: ^{1}H NMR (500 MHz, acetonitrile-d_3) δ 7.39 (s, 1H); ^{13}C NMR (125 MHz, acetonitrile-d_3) δ 126.9, 129.5, 140.7, 149.3, 157.0, 157.8, 179.6.

Diels-Alder Adduct (35): Dienophile (**33**) (147 mg, 0.742 mmol, 1.0 equiv) and cyclopentadiene (185 mL, 2.23 mmol, 3.0 equiv) were refluxed in dichloromethane (7.4 mL) for 16 h, then cooled, concentrated *in vacuo*, and purified by flash column chromatography on silica gel using gradient elution (20/80 ethyl-acetate-hexanes → 30/70 ethyl acetate-hexanes) to afford the title compound (95 mg, 46% yield over 2 steps) as an orange foam: IR (thin film) 3248, 1753, 1314, 1255; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (d, J = 10.8 Hz, 1H), 2.25 (d, J = 10.8 Hz, 1H), 3.35 (s, 1H), 3.60 (s, 1H), 5.42 (d, J = 3.6 Hz, 1H), 6.50-6.59 (m, 2H), 9.28 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.7, 49.2, 54.8, 68.7, 81.4, 138.8, 142.5, 148.5, 153.1, 171.0, 174.4; HRMS found 264.0213 +/- 0.0008 (calc. 264.0205).

***t*-Butyl 1-(benzylcarbamoyl)vinylcarbamate (40):** *N*-Boc-Serine benzylamide (**38**)[15] (314 mg, 1.07 mmol, 1.0 equiv) was taken up in dichloromethane (3 mL) and cooled in an ice bath. Triethylamine (447 μL, 3.21 mmol, 3.0 equiv) was added followed by methanesulfonyl chloride (165 μL, 2.14 mmol, 2.0 equiv). The reaction was stirred at 0 ºC for 40 min and then at 23 ºC for 20 min. The solution was diluted with ethyl acetate, washed thrice with a saturated solution of ammonium chloride, once with brine, then dried over anyhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the clean mesylate (398 mg, 100% yield) which was carried forward without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.97 (s, 3H), 4.36 (dd, J = 4.4, 10.0 Hz, 1H), 4.37-4.52 (m, 3H), 4.70 (dd, J = 3.6, 10.4 Hz, 1H), 5.30 (bs, 1H), 6.69 (bs, 1H), 7.29-7.46 (m, 10H). A portion of the mesylate (189 mg, 0.507 mmol, 1.0 equiv) was taken up in dichloromethane (3 mL) followed by addition of 1,8-diazabicylco[5.4.0]-undec-7-ene (80 μL, 0.533 mmol, 1.05 equiv) and stirring at 23 ºC for 1.5 h then poured onto silica gel and eluted (10/90 ethyl acetate-hexanes) to provide **41** (22 mg, 21% yield) and the title compound (93 mg, 66% yield): IR (thin film) 3388, 2973, 1728, 1656; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 4.50 (d, J = 6.0 Hz, 2H), 5.02 (s, 1H), 5.98 (s, 1H), 6.43 (bs, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$)

δ 28.2, 44.1, 80.6, 97.3, 127.7, 127.8, 128.8, 134.9, 137.5, 152.7, 164.0; mp 80.0-82.5 ºC; HRMS found 299.13661 +/- 0.00010 (MNa^+ calc. 299.13661). This compound has been previously reported but Yamada's data are not consistent with those presented here.[16]

Benzyl 1-(benzylcarbamoyl)vinylcarbamate (39): Prepared as above to afford a white solid in 42% yield: IR (KBr) 3371, 3032, 1735, 1731, 1659; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.51 (dd, *J* = 1.8, 5.4 Hz, 2H), 5.08 (s, 1H), 5.16 (s, 2H), 6.08 (s, 1H), 6.41 (bs, 1H), 7.25-7.38 (m, 10H), 7.61 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.1, 66.9, 98.3, 127.8, 127.9, 128.1, 128.3, 128.6, 128.8, 134.5, 135.9, 137.3, 153.3, 163.6; mp 102-104 ºC; HRMS found 311.1390 +/- 0.0005 (MH^+ calc. 311.1390).

Benzyl (*Z*)-1-(benzylcarbamoyl)-2-chlorovinylcarbamate (42): Enamine (**39**) (299 mg, 0.963 mmol, 1.0 equiv) was taken up in dichloromethane (25 mL) and cooled to -10 ºC with an ice-acetone bath. A dilute chlorine solution was prepared by brief exposure of dichloromethane to dry chlorine gas. The solution was cooled to -10 ºC and added to the enamine solution, open to air, slowly, dropwise until a very faint yellow color was obtained and TLC indicated complete consumption of starting material. With haste (total reaction time <10 min), the solvent was removed *in vacuo* to obtain a clear oil. This was taken up in acetonitrile (25 mL) and cooled to -10 ºC. A cold solution of 1,4-diazabicyclo-[2.2.2]octane (108 mg, 0.963 mmol, 1.0 equiv) in acetonitrile (3 mL) was added dropwise, open to air, with stirring resulting in the formation of a white precipitate that eventually dissolved. The solution was stirred for 30 min at -10 ºC, diluted with ethyl acetate, washed thrice with a saturated solution of ammonium chloride then once with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*, then purified by flash column chromatography on silica gel using gradient elution (20/80 ethyl acetate-hexanes → 30/70 ethyl acetate-hexanes) to afford the title compound as a colorless oil (278 mg, 84% yield): IR (thin film) 3276, 3022, 1724, 1659, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, *J* = 5.6 Hz, 2H), 5.13 (s, 2H), 6.43 (bs, 1H), 6.53 (bs, 1H), 6.68 (s, 1H), 7.25-7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.8, 68.0, 118.2 (broad), 127.6, 127.8, 128.3, 128.5, 128.6, 128.7, 132.9, 135.2, 137.4, 153.5, 162.2**;** HRMS found 345.1001 +/- 0.0001 (MH^+ calc. 345.1001).

***t*-Butyl (*Z*)-1-(benzylcarbamoyl)-2-chlorovinylcarbamate (43):** Prepared as above to give a white solid in 63% yield: IR (thin film) 3286, 2979, 1716, 1659, 1161, 775; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (s, 9H), 4.51 (d, *J* = 5.8 Hz, 2H), 6.09 (bs, 1H), 6.44 (bs, 1H), 6.66 (bs, 1H), 7.26-7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0, 43.9, 82.2, 110.7, 127.7, 128.7, 133.3, 137.5, 152.6, 162.4; mp 115-116 °C; HRMS found 311.1157 +/- 0.0001 (MH^+ calc. 311.1157).

Improved Protocol for Preparation of Benzyl (*Z*)-1-(benzylcarbamoyl)-2-chlorovinylcarbamate (42): *N*-Cbz Serine benzylamide (**37**)[15] (5.45 g, 16.58 mmol, 1.0 equiv) was taken up in dichloromethane (40 mL) and cooled in an ice bath. Triethylamine (3.5 mL, 24.87 mmol, 1.5 equiv) was added followed by methanesulfonyl chloride (1.41 mL, 18.24 mmol, 1.1 equiv). The reaction was

stirred at 0 ºC for 5 min and then at 23 ºC for 1 h. The solution was diluted with ethyl acetate, washed thrice with a saturated solution of ammonium chloride, once with brine, then dried over anyhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the crude mesylate (6.77 g) which was carried forward without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.97 (s, 3H), 4.36 (dd, J = 4.4, 10.0 Hz, 1H), 4.37-4.52 (m, 3H), 4.70 (dd, J = 3.6, 10.4 Hz, 1H), 5.30 (bs, 1H), 6.69 (bs, 1H), 7.29-7.46 (m, 10H). The aforementioned crude mesylate was taken up in acetone (40 mL), sodium iodide (4.97 g, 33.16 mmol, 2.0 equiv) was added, and the solution was gently refluxed for 3.5 h, cooled to rt, diluted with ether (120 mL), and filtered. The filtrate was further diluted with dichloromethane (100 mL) to prevent emulsification, and washed twice with 10% sodium bicarbonate, once with brine, then dried over anyhydrous sodium sulfate, filtered, and concentrated *in vacuo.* The residue was reconstituted in acetone (60 mL) and cooled in an ice bath. Triethylamine (2.5 mL, 18.05 mmol, 3.0 equiv) was then added, the ice bath removed after 5 min, and the solution stirred for 3 h at 23 ºC, then diluted with ethyl acetate, washed once with saturated sodium carbonate, twice with saturated sodium bicarbonate, thrice with saturated ammonium chloride, thrice with brine, then dried over anyhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give enamine (**39**) (4.43 g). The yellow residue was taken up in dichloromethane (50 mL) and cooled to -10 ºC with an ice-acetone bath. A dilute chlorine solution was prepared by brief exposure of dichloromethane to dry chlorine gas. The solution was cooled to -10 ºC and added to the enamine solution, open to air, slowly, until a very faint yellow color was obtained and TLC indicated complete consumption of starting material. With haste (total reaction time <10 min), the solvent was removed *in vacuo* to obtain a clear oil. This was taken up in acetonitrile (50 mL) and cooled to -10 ºC. A cold solution of 1,4-diazabicyclo[2.2.2]octane (1.59 mg, 14.18 mmol, 1.0 equiv. in 3 mL acetonitrile) was added dropwise, open to air, with stirring resulting in the formation of a white precipitate. The solution was stirred for 40 min at -10 ºC, diluted with ethyl acetate, washed thrice with a saturated solution of ammonium chloride then once with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*, then purified by flash column chromatography on silica gel using gradient elution (20/80 ethyl acetate-hexanes → 30/70 ethyl acetate-hexanes) to afford **42** as a colorless oil (2.73 g, 48% yield for 5 steps).

3-Benzyl-5-methyleneimidazolidine-2,4-dione (41): DL-*N*-(*t*-Butoxycarbonyl)serine benzylamide (**38**)[15] (126 mg, 0.43 mmol, 1.0 equiv) was taken up in dichloromethane (1.5 mL) and cooled in an ice bath. Triethylamine (179 μL, 1.28 mmol, 3.0 equiv) was added followed by methanesulfonyl chloride (66 μL, 0.86 mmol, 2.0 equiv). The reaction was stirred for 40 min at 0 ºC, then the ice bath was removed, and the reaction stirred a further 10 min at 23 ºC. The solution was diluted with ethyl acetate and washed thrice with a saturated aqueous solution of ammonium chloride, once with brine, and the combined aqueous phase back-extracted once with ethyl acetate. The combined organic phase was dried

over anhydrous sodium sulfate and concentrated *in vacuo* to give 159 mg of pale yellow oil. This residue was reconstituted in dichloromethane (1.0 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (192 μL, 1.28 mmol, 3.0 equiv) was added dropwise to effect elimination of the mesylate. The reaction was stirred at rt for 1 h then diluted with ethyl acetate and washed with a saturated aqueous solution of ammonium chloride. The aqueous phase was separated and the organic phase dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10/90 ethyl acetate-hexanes) to give *t*-butyl 1-(benzylcarbamoyl)vinylcarbamate[16] (24 mg, 20% yield) and the title compound (37 mg, 43% yield): IR (thin film) 3272, 1773, 1720, 1670, 1441; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (s, 2H), 4.92 (d, J = 1.7 Hz, 1H), 5.43 (d, J = 1.7 Hz, 1H), 7.27-7.39 (m, 5H), 8.25 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.2, 96.7, 128.0, 128.7, 134.0, 135.6, 154.8, 162.6; HRMS found 203.0815 +/- 0.0007 (MH^+ calc. 203.0815). Cyclization onto the –Boc carbonyl also occurred cleanly but slowly (7 days, 23 ºC) with triethylamine (5 equiv) in chloroform.

(*Z*)-3-Benzyl-5-(chloromethylene)imidazolidine-2,4-dione (44): β-Chloroenamine (**42**) (95 mg, 0.276 mmol, 1.0 equiv) was taken up in THF (3 mL) and cooled to 0 ºC. Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.10 mL, 0.551 mmol, 2.0 equiv) was added dropwise over 2 min and the solution stirred for a further 30 min. The reaction was quenched by addition of 1 mL of 10% (w/w) potassium bisulfate, then warmed to rt, diluted with ethyl acetate, washed twice with a saturated solution of ammonium chloride, once with brine, then dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10/90 ethyl acetate-hexanes) to give the title compound (47 mg, 72% yield) as a white solid: IR (thin film) 3237, 1789, 1716, 1678, 701; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 (s, 2H), 6.52 (s, 1H), 7.21 (bs, 1H), 7.26-7.46 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.5, 104.9, 128.2, 128.7, 128.8, 130.2, 135.3, 153.4, 160.5; mp 157-160 °C; HRMS found 259.0245 +/- 0.0012 (MNa^+ calc. 259.0245).

(*Z*)-Benzyl 3-benzyl-5-(chloromethylene)-4-oxo-2-thioxoimidazolidine-1-carboxylate (45): Freshly distilled bis(trimethylsilyl)amine (347 μL, 1.664 mmol, 2.0 equiv) was taken up in THF (5 mL) and cooled to –78 °C at which point *n*-butyllithium (2.25 M in hexanes, 708 μL, 1.581 mmol, 1.9 equiv) was added and the solution stirred for 15 min then a cooled solution of enamine (**42**) (287 mg, 0.832 mmol, 1.0 equiv) in THF (5 mL) was added via cannula (2 mL of THF were used to wash the sides of the flask). The solution was warmed to 0 ºC and a colour change, from pale orange to maroon, was noted. After 5 min, the solution was cooled to –78 ºC and thiophosgene (*CAUTION!* 190 μL, 2.50 mmol, 3.0 equiv) was added rapidly (total addition time <1 s). After 5 min, a 10% (w/w) aqueous solution of potassium bisulfate (250 μL) was added and the solution warmed to 23 ºC. The solution was diluted with ethyl acetate, washed with dilute sodium bicarbonate solution, twice with a saturated aqueous solution of ammonium chloride, and once with brine, then dried over anhydrous sodium sulfate, concentrated *in*

vacuo, and purified by flash column chromatography on silica gel using gradient elution (2/98 ethyl acetate-hexanes → 5/95 ethyl acetate-hexanes) affording the title compound as a yellow oil (125 mg, 38% yield): IR (thin film) 3069, 1775, 1746, 1389, 1256, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (s, 2H), 5.42 (s, 2H), 6.64 (s, 1H), 7.29-7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 71.5, 109.6, 128.3, 128.6, 128.7, 129.1, 129.2, 133.2, 134.5, 148.6, 160.4, 175.3; HRMS found 387.0565 +/- 0.0006 (MH^+ calc. 387.0565) and *Z*-*N*-benzyl-*N*-carboxybenzyl-3-chloro-2-isothiocyanatoacrylamide (**46**) (109 mg, 34%) resulting from acyl-shift: IR (thin film) 3034, 2026, 1743, 1687, 1202, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 2H), 5.24 (s, 2H), 6.84 (s, 1H), 7.26-7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.4, 69.9, 126.3, 127.9, 128.1, 128.6, 128.7, 128.8, 128.9, 129.7, 133.9, 136.2, 153.3, 164.2; HRMS found 387.0565 +/- 0.0006 (MH^+ calc. 387.0565).

(*Z*)-*t*-Butyl 3-benzyl-5-(chloromethylene)-4-oxo-2-thioxoimidazolidine-1-carboxylate (47): Freshly distilled bis(trimethylsilyl)amine (110 μL, 0.528 mmol, 2.0 equiv) was taken up in THF (3 mL) and cooled to –78 ºC at which point *n*-butyllithium (2.25 M in hexanes, 222 μL, 0.501 mmol, 1.9 equiv) was added and the solution stirred for 15 min then a cooled solution of enamine (**43**) (82 mg, 0.264 mmol, 1.0 equiv) in THF (1 mL) was added via cannula (1 mL of THF was used to wash the sides of the flask). The solution was warmed to -20 ºC over 20 min then cooled to –78 ºC and thiophosgene (*CAUTION!* 60 μL, 0.792 mmol, 3.0 equiv) was added rapidly (total addition time <1 s). After 5 min, a 10% (w/w) aqueous solution of potassium bisulfate (100 μL) was added and the solution warmed to 23 ºC. The solution was diluted with ethyl acetate, washed with dilute sodium bicarbonate solution, twice with a saturated aqueous solution of ammonium chloride, and once with brine, then dried over anhydrous sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (2/98 ethyl acetate-hexanes) affording the title compound as a yellow oil (65 mg, 70% yield): IR (thin film) 2982, 1771, 1746, 1386, 1252, 839; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 5.04 (s, 2H), 6.62 (s, 1H), 7.29-7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.5, 45.2, 87.7, 108.9, 128.2, 128.4, 128.6, 129.0, 134.7, 146.6, 160.7, 175.8; HRMS found 375.0541 +/- 0.0010 (MNa^+ calc. 375.0541); the following data for the minor compound *Z*-*N*-benzyl-*N*-carboxybenzyl-3-chloro-2-isothiocyanatoacrylamide (**48**) were obtained from analysis of the crude reaction mixture: IR (thin film) 2026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (s, 2H), 6.86 (s, 1H).

(*Z*) 3-Benzyl-5-(chloromethylene)-2-thioxoimidazolidin-4-one (49): Thiohydantoin (**47**) (33 mg, 0.0944 mmol) was taken up in a (1:5) trifluoroacetic acid-dichloromethane solution (0.5 mL) and stirred at 23 ºC for 2 h. Solvent was removed *in vacuo* and the product was purified by flash column chromatography on silica gel (5/95 ethyl acetate-hexanes) to give the title compound as a yellow solid. On larger scales, purification was performed by recrystallization from acetonitrile-toluene: IR (KBr) 3239, 3041, 1721, 1665, 1473, 1342, 1211, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.04 (s, 2H), 6.49 (s, 1H),

7.26-7.46 (m, 5H), 8.54 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.8, 105.6, 128.2, 128.6, 128.9, 130.3, 135.0, 160.7, 177.3; mp 165-175 ºC (decomp.); HRMS found 275.0016 +/- 0.0004 (MNa^+ calc. 275.0016).

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