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Synthesis of Highly Substituted Imidazolidine-2,4-dione (Hydantoin) through Tf_2O-Mediated Dual Activation of Boc-Protected Dipeptidyl Compounds

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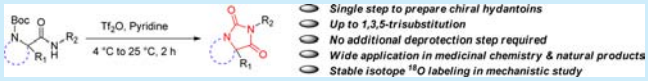
Supporting Information

ABSTRACT: Highly substituted chiral hydantoins were readily synthesized from simple dipeptides in a single step under mild conditions. This reaction proceeded through the dual activation of an amide and a *tert*-butyloxycarbonyl (Boc) protecting group by Tf_2O-pyridine. This method was successfully applied in the preparation of a variety of biologically active compounds, including drug analogs and natural products.



Hydantoin (imidazolidine-2,4-dione) is a privileged scaffold of azaheterocycle found in a variety of biologically active compounds, such as drugs and natural products (Figure 1).[1] For example, phenytoin sodium and ethotoin are marketed as anticonvulsant drugs;[2] nilutamide[3] is an androgen receptor antagonist for the treatment of advanced prostate cancer; BMS-564929 is an orally active and selective androgen receptor modulator;[4] and parazoanthines (A and D)[5] are chiral hydantoin alkaloids isolated from the Mediterranean Sea anemone *Parazoanthus axinellae*.

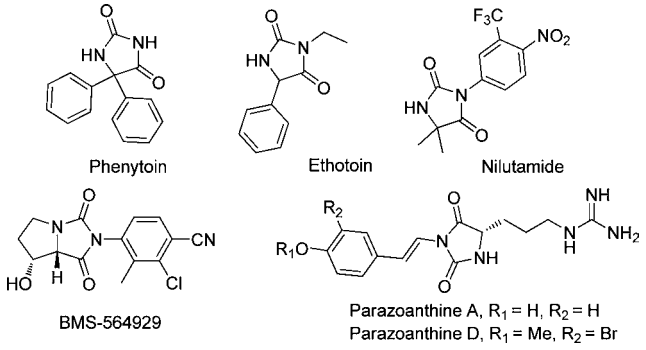


Figure 1. Substituted hydantoins with various biological activities.

Substituted hydantoins are also valuable intermediates for the synthesis of enantiomerically pure amino acids[6] through dynamic kinetic resolution. Moreover, chiral hydantoins are of considerable interest in organic synthesis because of their synthetic utility as intermediates, chiral auxiliaries,[7] and metal ligands[8] in asymmetric catalysts.

Many methods have been reported in the literature[1] for the synthesis of substituted hydantoins. The classical approaches[9] include the Urech method involving amino acid derivatives, the Bucherer–Bergs multicomponent reaction,[9a] and the condensation of urea with dicarbonyl compounds.[9b,c] These reactions generally involve harsh conditions and/or toxic reagents. Recent developments for the synthesis of substituted nonchiral hydantoins include transition-metal catalyzed reactions,[10] the Ugi condensation,[11] reactions of activated carboxylic acids,[12] and an aminobarbituric acid–hydantoin rearrangement.[13] The synthesis of enantiopure hydantoins can be performed both in the solid[14] and solution[15] phases from enantiopure α-amino amides or α-amino esters with phosgene (or CDI) and isocyanates, respectively. The use of isocyanates as a preactivated reactant limited its applicability because they are not always commercially available, especially chiral isocyanates, whose preparation and handling can be problematic. Moreover, these strategies are multistep procedures that require an additional deprotection step.

Inspired by elegant studies on the electrophilic activation of amides for synthesizing diverse heterocycles,[16] we reasoned that amide activation in peptides, coupled with an intramolecular reaction involving neighboring groups, could provide rapid access to azaheterocycles bearing stereogenic center(s). Herein, we demonstrate a single-step synthesis of highly substituted chiral hydantoins from simple and unactivated substrates under mild conditions. This reaction proceeded through the dual activation of an amide and a *tert*-butyloxycarbonyl (Boc) protecting group by trifluoromethanesulfonic anhydride[17] (Tf_2O) and pyridine without the additional step of Boc deprotection.

Our initial studies were performed on a simple dipeptide *N*-Boc-L-Ala-L-Phe-OMe (**1a**). As probed by the reaction conditions depicted in Table 1, the choice of base was found to be crucial for obtaining the desired hydantoins. The previously reported Tf_2O/2-chloropyridine system in the electrophilic activation of amides[16,18] was not suitable for this reaction. Although this system proceeded surprisingly fast (**1a** was fully consumed within 30 min, even at −78 °C, as indicated by TLC

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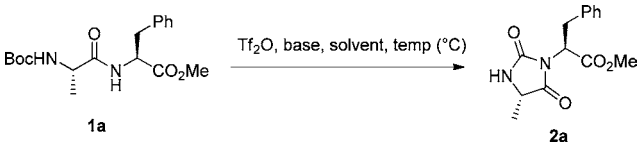
Table 1. Optimization of the Reaction Conditions[a]



entry	Tf_2O	base	equiv	solvent	t (h)	yield[b] (%)[c]
1[d]	1.2	2-Cl-pyridine	1.3	DCM	0.5	13
2	1.2	2-Cl-pyridine	4.0	DCM	2	42
3	1.2	pyridine	1.4	CH_3CN	4	59
4	1.2	pyridine	2.5	CH_3CN	10	20 (71)
5	1.2	pyridine	2.5	DCM	10	51 (30)
6[d]	1.5	pyridine	3.0	DCM	2	85
7	1.5	pyridine	3.0	DCM	2	86
8	1.5	2,6-lutidine	3.0	DCM	2	46 (44)

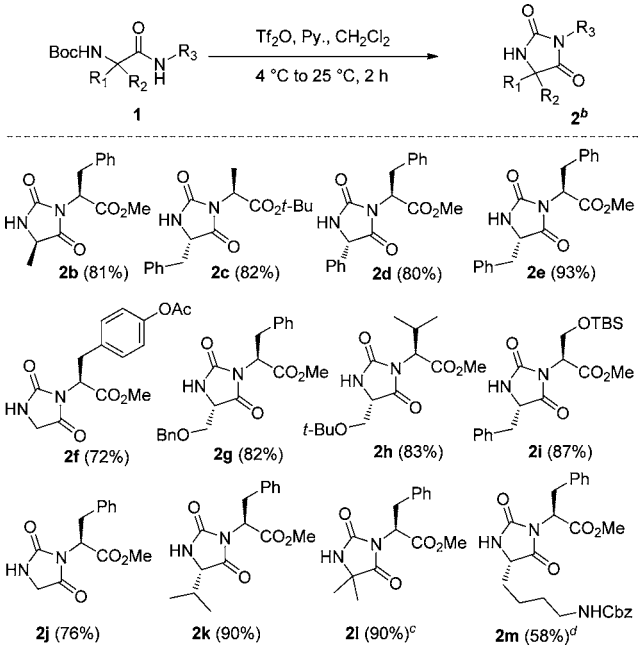
[a]Conditions: **1** (0.25 mmol) in solvent (2.5 mL), base, then Tf_2O, 4 °C, 5 min, then 25 °C. [b]Isolated yield. [c]Yields of recovered starting material are in parentheses. [d]Reaction temperature from −78 to 25 °C.

analysis), it only gave a 13% yield (entry 1). The major side product was a Boc-deprotected free amine, which was easily transformed to its diketopiperidine (DKP) counterpart through intramolecular acyl transfer. This side reaction could be partially mitigated by using excess 2-chloropyridine to obtain a higher yield of the desired product (42%, entry 2).

Using pyridine as the base in acetonitrile resulted in an even higher yield (59%, entry 3). However, increasing the equivalent of pyridine appeared to impede the reaction, affording the desired product in just a 20% yield with 71% recovered starting material, even by extending the reaction time to 10 h (entry 4). It is interesting to note that the aforementioned side reaction was virtually completely prevented and no DKP product was isolated. Dichloromethane (DCM) was determined to be a better solvent than CH_3CN (51% yields, entries 4−5). Additionally, it was found that a lower reaction temperature gave nearly an identical yield (85%, entry 6), despite the appearance of a significant amount of precipitants in the process of this reaction. The best reaction conditions were achieved in entry 7 (1.5 equiv of Tf_2O, 3.0 equiv of pyridine, CH_2Cl_2), where complete conversion was reached within 2 h with an 86% isolated yield. Notably, warming the reaction mixture to 25 °C after the addition of Tf_2O at 4 °C is necessary for complete consumption of the starting material. Otherwise, a significant amount of **1a** could be recovered when the reaction temperature was kept below 20 °C. Finally, in contrast to pyridine, neither 2,6-lutidine nor triethylamine was effective in facilitating this reaction, leading to incomplete conversion under otherwise identical reaction conditions.[19]

With the optimized reaction conditions in hand, we investigated a variety of dipeptides, and the results are listed in Scheme 1. The sequence and stereochemistry of peptides (**2b**, **2c**) appear to have little influence on this process; several substituted chiral hydantoins were isolated in good to excellent yields. In all cases with at least two stereogenic centers, hydantoins were formed as a single diastereomer, as determined by ^1H NMR, indicating that no racemization had occurred during this process. Indeed, even using the highly epimerization-prone L-phenylglycine derivative, satisfactory results were obtained with a diastereomeric ratio >19:1 and an 80% yield (**2d**). The literature known compound **2e** could be efficiently prepared in excellent yield (93%) with the specific rotation value $[\alpha]_D^{27.7}$ −206.2 (*c* 0.5, acetone) that is in good agreement with the literature reported value ($[\alpha]_D^{21.4}$ −207.8 (*c* 1.0, acetone)).[15b]

Scheme 1. Synthesis of 3,5-Disubstituted or 3,5,5′-Trisubstituted Chiral Hydantoins from Dipeptides[a]



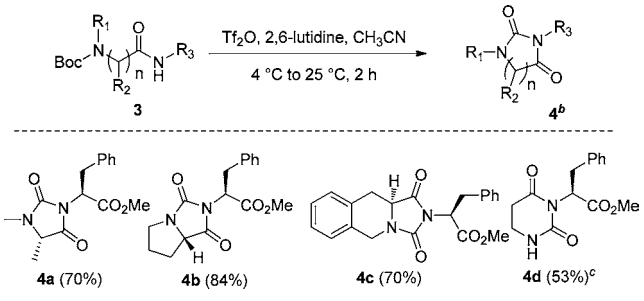
[a]Conditions: **1** (1 equiv), Tf_2O (1.5 equiv), Py. (3.0 equiv), CH_2Cl_2 (0.1 M), 4 to 25 °C. [b]Isolated yields are in parentheses. [c]Tf_2O (2.0 equiv), Py. (4.0 equiv), 4 h. [d]69% yield based on recovered starting material.

This procedure is compatible with a range of common protecting groups, such as methyl esters, acetyl (**2f**), and benzyl (**2g**) protecting groups. The acid-sensitive *tert*-butyl ester (**2c**), *tert*-butyl ether (**2h**), and silyl protecting groups (**2i**) could also remain intact.

While glycine-derived dipeptides without α-substitution gave lower yields (72−76%, **2f**, **2j**), a sterically congested substrate could also undergo cyclization efficiently when a more activating reagent and a longer reaction time were employed (**2l**). The chemoselectivity can be achieved in the presence of a carboxybenzyl (Cbz) protecting group, which survived under these conditions (58% yield, 69% based on recovered starting material, **2m**).

The synthesis of 1,3,5-trisubstituted hydantoins proved to be challenging, and the above conditions only afforded products in

Scheme 2. Synthesis of 1,3,5-Trisubstituted Hydantoins from Peptides[a]



[a]Conditions: **3** (1 equiv), Tf_2O (3.0 equiv), 2,6-lutidine (6.0 equiv), CH_3CN, 4 to 25 °C. [b]Isolated yields are in parentheses. [c]Tf_2O (1.5 equiv), Py. (3.0 equiv), CH_2Cl_2, 4 to 25 °C.

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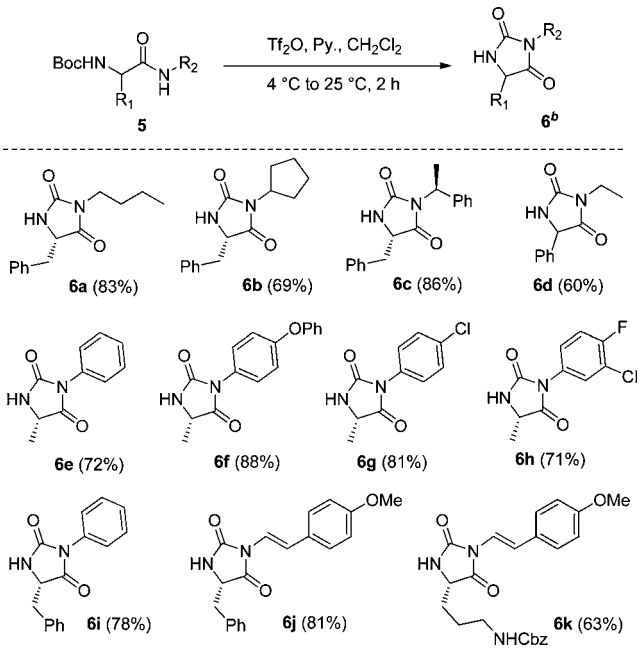
low yields. Reinvestigation of the reaction conditions revealed that using CH_3CN as the solvent was superior to CH_2Cl_2 for these types of substrates. Using this approach, highly substituted hydantoins were synthesized in good to high yields (**4a**–**4c**, 70–84% yields, Scheme 2). These fused bicyclic (**4b**) and tricyclic (**4c**) compounds with rigid scaffolds are important structural motifs in many biologically active compounds.[20] Notably, a six-membered ring analog (5,6-dihydrouracil) could also be formed from a β-amino acid derived dipeptide in a relatively lower yield (**4d**, 53%).

Next, we turned our attention to nonpeptide substrates. Different types of hydantoins were prepared by variation of the R_2 substituent of **5** (Scheme 3). A variety of *N*-alkyl (chain and cyclic, **6a**–**6d**), *N*-aryl (**6e**–**6i**), and *N*-vinyl (**6j**, **6k**) amides served as substrates, which easily produced the corresponding hydantoin derivatives. The enantiomeric excess values of representative products (**6a**, **6e**, **6i**) were determined to be >98% by HPLC analysis with a chiral column.[19] It merits attention that ethotoin[21] can be produced efficiently in a 60% yield (**6d**) by using our method. When R_2 is an aryl group, the electron-donating group on the aromatic ring may facilitate this process to give a higher yield (88%, **6f**). It is also worth noting that the 3-vinyl hydantoin derivative **6k** could be considered an analog of the natural products parazoanthines[5] and may be useful in their total synthesis.

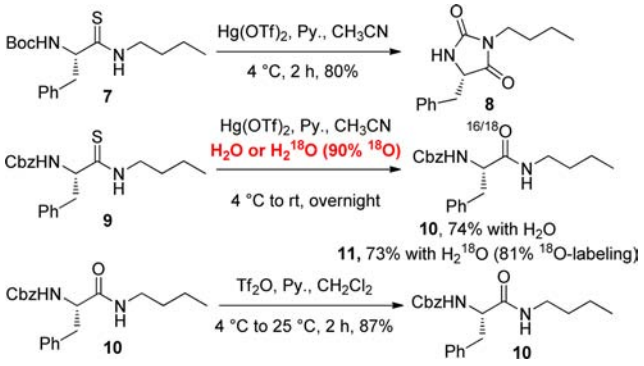
To investigate the reaction mechanism, we performed several control experiments, as indicated in Scheme 4. First, treatment of the thioamide surrogate **7** with Hg salt produced the corresponding hydantoin in an 80% yield. Mechanistically, the activation of thioamide by $Hg(OTf)_2$ is presumably the first step of this reaction because of the high affinity of mercury and sulfur. We note that no hydantoin was isolated when the Boc group was changed to Cbz (compound **9**) under identical reaction conditions.

Scheme 3. Synthesis of 3,5-Disubstituted Hydantoins from Nonpeptides[a]



[a]Conditions: **5** (1 equiv), Tf_2O (1.5 equiv), Py. (3.0 equiv), CH_2Cl_2 (0.1 M), 4 to 25 °C. [b]Isolated yields are in parentheses.

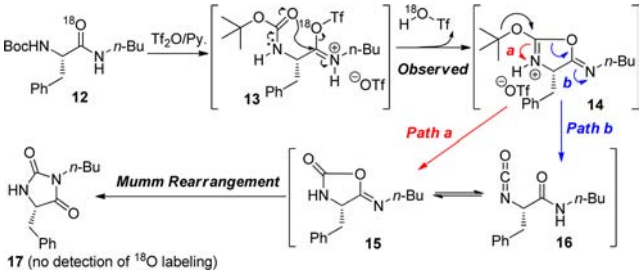
Scheme 4. Control Experiments



The thioamide **9** was hydrolyzed to its amide counterpart **10** when this reaction was performed under aqueous conditions or quenched by water. We envisioned that this reaction might offer an opportunity for stable-isotope ^{18}O-labeling when it was reacted with $H_2{}^{18}O$. To our delight, the desired ^{18}O-labeled compound **11** was smoothly formed in 73% yield with 81% ^{18}O-labeling (90% labeling based on the purity of $H_2{}^{18}O$).[19] As expected, the Cbz-protected amide compound **10** remained intact with the Tf_2O/pyridine system.[22]

A proposed reaction pathway that is consistent with the above observations is depicted in Scheme 5. The amide bond is activated by Tf_2O directly or by Tf_2O–pyridine adducts to afford intermediate **13**. Intramolecular cyclization of this intermediate, followed by expulsion of the *tert*-butyl cation, would generate the oxazolidinone[23] product **15** (the isocyanate intermediate **16** is also possible). The final step to give the hydantoin product **17** occurs possibly through a Mumm rearrangement.[24] Attempts to trap the reactive intermediate **15** or **16** by addition of an extra nucleophile (e.g., benzylamine) failed. When using an ^{18}O-labeled amide as the substrate, the ^{18}O-labeled HOTf was observed by HRMS;[19] thus, the possibility of single activation[25] of a Boc-protected amine producing intermediate **16** could be ruled out.

Scheme 5. Plausible Reaction Pathway



In summary, a new method of preparing highly substituted hydantoins has been developed. Using this single-step protocol, a variety of chiral hydantoins can be easily synthesized from readily available substrates in good to high yields. In addition, a selective procedure for stable-isotope ^{18}O-labeling was presented, which may have potential use in mechanistic studies of organic reactions and mass spectrometry based proteomics.[26]

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra data, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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