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Unprecedented One-Pot Chemocontrolled Entry to Thioxoimidazolidinones and Aminoimidazolones: Synthesis of Kinase Inhibitor Leucettamine B

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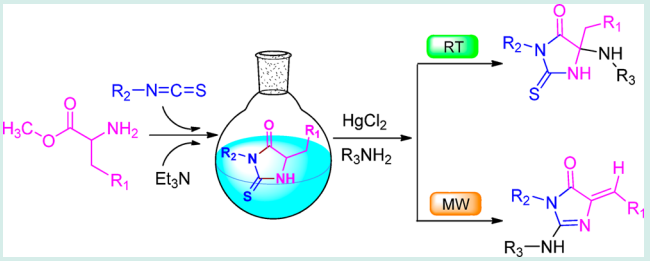
Supporting Information

ABSTRACT: A novel and highly chemoselective protocol for the construction of thioxoimidazolidinone and aminoimidazolone frameworks was explored, and the influence of the reaction conditions on product formation was studied to establish two distinct approaches for their selective formation. In this one-pot reaction, ambient temperature generally resulted in the formation of thioxoimidazolidinones, whereas microwave irradiation provided aminoimidazolones exclusively. An attempt to elucidate the observed chemoselectivity is described, and the products were confirmed by X-ray studies. One-pot synthesis toward Leucettamine B, a marine alkaloid, was achieved on the basis of this protocol.



KEYWORDS: *chemoselectivity, one-pot protocol, domino reactions, microwave chemistry, total synthesis*

INTRODUCTION

Diversity-oriented synthesis is recognized as being a powerful synthetic strategy owing to its great potential to produce chemically and skeletally diversified molecular scaffolds from the same or commonly used precursors; this strategy is continuously aimed at developing high levels of efficiency in organic synthesis.[1] A challenging task encountered with diversified synthesis from a common intermediate is the precise control of chemo-, regio-, and stereoselectivities through fine tuning the reaction conditions. In recent years, many groups have reported the control of chemoselectivity with metal catalysts and solvents, whereas reaction conditions (temperature, microwave, and reflux) dependent selectivity has been relatively less explored.[2,3] Consequently, the development of reaction conditions-based chemoselective transformation is a worthy and challenging goal.[4] In this context, we disclose a novel domino reaction leading to the selective synthesis of thioxoimidazolidinones at room temperature and aminoimidazolones under microwave irradiation in a straightforward manner, which is normally difficult to achieve in a single operation.

A conformationally strained small molecule, aminoimidazolone, represents an attractive motif in the quest for new drug development.[5] It is envisioned as a combination of two important pharmacophores, guanidine and imidazole, which appear in many bioactive molecular scaffolds and therapeutic agents (Figure 1).[6,7] Among these, aplysinopsin (I), a marine natural product, was identified as an anticancer agent against the HT 29 cell line.[8,9] Leucettines (II), a family of kinase inhibitors derived from the marine sponge Leucettamine B, were investigated as potential therapeutics for Alzheimer's disease and in diseases involving abnormal pre-mRNA splicing.[10] Aminoimidazolones constitute an attractive template to exploit the chemical diversity of a broad drug-like library. A structure−activity relationship study on a diversified small molecule library of aminoheterocycle (III) provided a novel series of γ-secretase modulators.[11,12]

Normally, 4-benzylidene-substituted aminoimidazolones are synthesized by the condensation of 2-thioxoimidazolidinone (or 2-alkylthio-imidazolones) with aldehydes followed by reaction with alkylamines.[13] Ding et al. assembled an aminoimidazolone ring system by the reaction of aliphatic primary amines with carbodiimides, which were generated from aza-Wittig reactions of vinylimino-phosphorane with isocyanates.[14] Similarly, Houghten reported the solid-phase synthesis of 5-substituted aminoimidazolones through guanidine derivatives.[15,16] All of these reports involved the reaction of primary amines with thiourea in the presence of guanylating agents to furnish aminoimidazolones. There are two possible pathways that can be postulated for this reaction, as depicted in Scheme 1. Nucleophilic attack of amines in the presence of mercuric chloride leads to the generation of a guanidine intermediate that subsequently undergoes intramolecular amidation (Scheme 1, route 1). In view of the equal spatial proximity and

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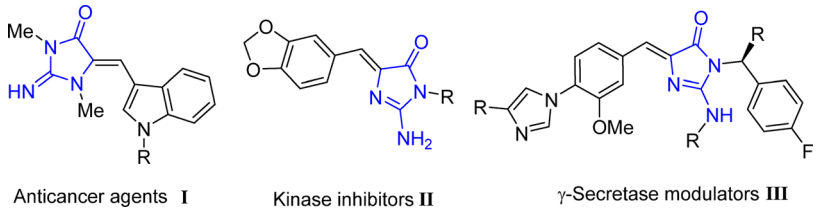
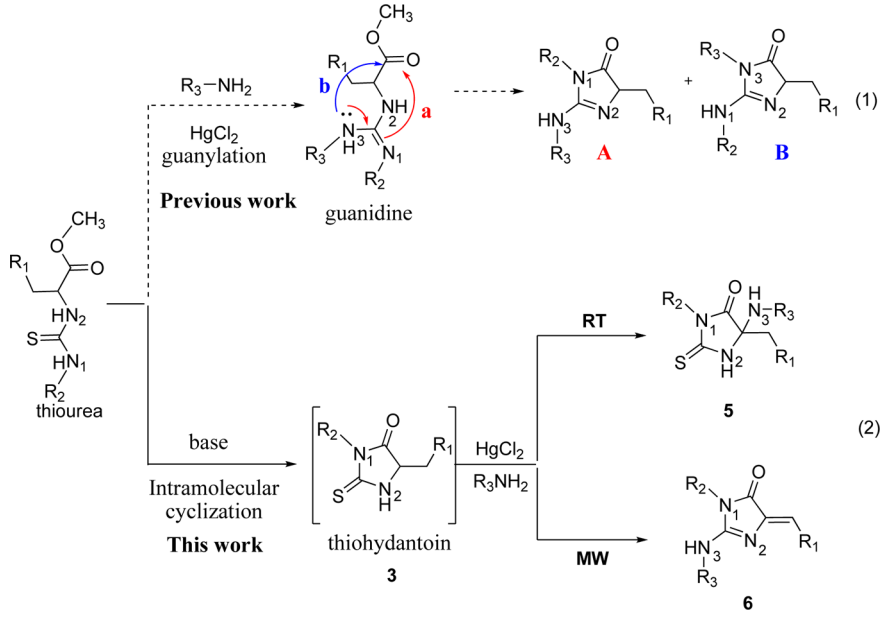


Figure 1. Bioactive heterocycles containing an aminoimidazolone framework.

Scheme 1. Synthetic Strategy for Aminoimidazolones and Thioxoimidazolidinones



comparable nucleophilicities of nitrogens N_1 and N_3 of the guanidine intermediate, two regioisomeric imidazolones (**A** and **B**) through pathway **a** or **b** are possible, in principle, and their formation has been reported in the literature.[17] In both pathways, thioureas may undergo guanylation by an *in situ* formation of carbodimides followed by a nucleophilic addition with amines.

The present synthetic strategy makes use of the tunable reactivity of thiohydantoin generated from disubstituted thioureas (Scheme 1, route 2). In our novel approach, the initial formation of a thiohydantoin by a base-induced intramolecular amidation affords a suitable intermediate for a subsequent regioselective guanylation with primary amines promoted by mercuric chloride. The formation of thioxoimidazolidinones **5** involves the initial *in situ* oxidation of the thiohydantoin to a cyclic imine followed by a nucleophilic attack of a primary amine at room temperature to the imine. In contrast, under microwave irradiation, thiohydantoin **3** delivers a cyclic enamine intermediate that subsequently undergoes guanylation to furnish aminoimidazolones **6**. The *in situ* generation of thiohydantoin effectively prevents the formation of regioisomeric products from the acyclic guanidine intermediate.[18] Hence, the need to specifically functionalize substrates and the regioisomeric issues associated with carbodimide intermediates were setbacks encountered in earlier reports. The synthesis and biological evolution of 4-amino-substituted thioxoimidazolidinone have been little-explored. Previously, amino-substituted thioxoimidazolidinone **5** was accomplished only intramolecularly by using DDQ as an oxidant.[19] In light of the above observations, it would be of interest to develop a robust method for the effective synthesis of 2-aminoimidazolone and 4-amino thioxoimidazolidinone from the common intermediate by tuning the reaction conditions. Hence, the reaction conditions play a crucial role in the product outcome, and the application of microwave irradiation not only increases the reaction rate but also switches the selectivity of the product distribution.

RESULTS AND DISCUSSIONS

At the outset of our studies, we intended to probe the reactivity and chemoselectivity of thiohydantoins under guanylation conditions to generate the first ever guanidine derivative of thiohydantoin. Initial reaction of phenyl alanine methyl ester with butyl isothiocyanate in the presence of triethylamine in dichloromethane furnished thiohydantoin **3**{*1,1*}. The obtained intermediate was treated with isobutylamine **4**{*1*}, mercuric chloride, and triethylamine in DMF at room temperature (Table 1). To our surprise, the anticipated guanidine product was not observed, and an unexpected 4-amino thioxoimidazolidinone **5**{*1,1,1*} possessing a quaternary carbon was isolated instead. Careful scrutinization of the analytical data revealed the participation of all of the starting materials in the obtained product, and the exact structure was confirmed by single-crystal X-ray analysis (Figure 2). We reasoned that, in the presence of base and $HgCl_2$, **3**{*1,1*} underwent oxidation followed by nucleophilic addition of the amine to deliver the product, **5**{*1,1,1*}. Although the envisioned product was not obtained by the reaction of thiohydantoin, this unexpected formation of **5**{*1,1,1*} might be more rewarding, as there are no earlier

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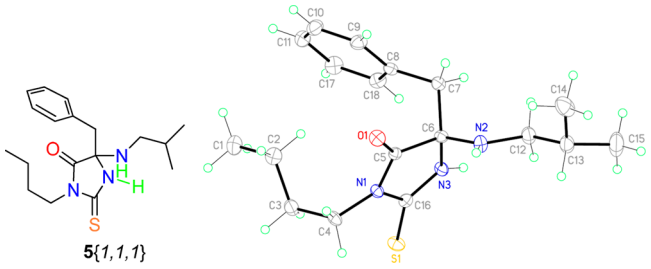


Figure 2. ORTEP representation of 4-amino thioxoimidazolidinone 5{*1,1,1*}.

reports on such a convenient one-pot synthesis from these readily available reagents.

In order to study the formation of 5{*1,1,1*}, the reaction conditions were fine-tuned with various solvents at different temperatures (Table 1). Switching the solvent to dichloromethane leads to complete conversion to compound 5{*1,1,1*} with a yield of 85% (entry 4). The reaction did not afford complete conversion in DMF, THF, acetone, acetonitrile, or toluene under the same conditions (entries 1−3 & 5−6). As part of our interest in developing microwave-assisted reactions,[20] the same reaction was powered by microwave irradiation at 60 °C for 10 min in dichloromethane. A serendipitous outcome was discovered here when compound 5{*1,1,1*} was obtained in only 20% yield while the major product was identified as compound 6{*1,1,1*} with 65% yield (entry 9). The use of microwave irradiation altered the reactivity of hydantoin 3{*1,1*} by the predominant formation of enamine rather than imine to deliver compound 6{*1,1,1*}.

Finally, the optimized conditions to deliver compound 6{*1,1,1*} exclusively were identified as Et_3N (1.5 equiv) and $HgCl_2$ (1.5 equiv) in dichloromethane at 80 °C for 10 min (entry 10). With the same stoichiometry, increasing the temperature to 100 °C did not improve the reaction yield. In the absence of either the base or $HgCl_2$, the final products were not produced. However, compound 5{*1,1,1*} was obtained in the absence of $HgCl_2$ at room temperature with 30% yield (entry 8), whereas the addition of $HgCl_2$ furnished product 5{*1,1,1*} in 2 h with 85% yield.

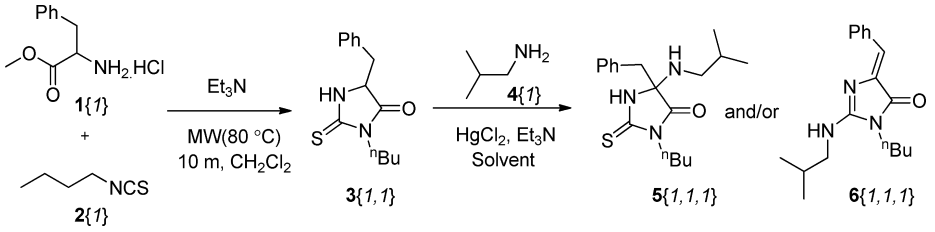
Still, the actual role of mercuric chloride was not ascertained; we assume that it may act as an oxidant as well as a desulfurizing agent for this transformation. In general, the oxidation of an amine to an imine is demonstrated with various metal catalysts in combination with oxygen.[21] However, the reported mercuric chloride-mediated oxidation of thiohydantoins to imines and enamines is a new addition to such a transformation. The diversity of amino esters, isothiocyanates, and various amines is depicted in Figure 3.

Having established two selective protocols for the formation of 5{*1,1,1*} and 6{*1,1,1*}, the scope of the reaction was investigated, as shown in Tables 2 and 3, respectively. All of the amino ester substituents as well as various isothiocyanates were well-tolerated under these reaction conditions, delivering the final products with satisfactory yields. Next, we focused on the wider utility of primary and secondary amines for the current transformations.

All of the primary amines **4** afforded satisfactory yields, whereas the secondary amines **4** (Table 3, entries 10 and 12) resulted in lower yields. During the course of the substrate scope studies, we explored the reactivity of thiohydantoin from phenyl glycine having no hydrogen on its beta carbon, which cannot undergo oxidation, to provide an enamine intermediate. As shown in Table 4, we observed the formation of iminoimidazolone **7** under the optimized conditions, and a possible explanation for this observation is illustrated in Scheme 3.

To gain insight into the reaction mechanism, we carried out a few control experiments (shown in Scheme 2). When the

Table 1. Influence of the Reaction Conditions on the Reactivity of 3{*1,1*} with Butyl Amine 4{*1*}[a]



				yields (%)[b]	
entry	catalyst	solvent	conditions temperature (° C)/time	5{*1,1,1*}	6{*1,1,1*}
1	$HgCl_2/Et_3N$	DMF	rt/16 h	60	0
2	$HgCl_2/Et_3N$	THF	rt/16 h	20	0
3	$HgCl_2/Et_3N$	acetone	rt/16 h	30	0
4	**$HgCl_2/Et_3N$**	**DCM**	**rt/2 h**	**85**	**0**
5	$HgCl_2/Et_3N$	acetonitrile	rt/16 h	15	0
6	$HgCl_2/Et_3N$	toluene	rt/16 h	35	0
7	none	DCM	rt/16 h	10	0
8	Et_3N	DCM	rt/24 h	30	0
9	$HgCl_2/Et_3N$	DCM	60(MW)/10 m	20	65
10[c]	**$HgCl_2/Et_3N$**	**DCM**	**80(MW)/10 m**	**0**	**85**
11[c]	$HgCl_2/Et_3N$	DCM	100(MW)/10 m	0	85
12[c]	$HgCl_2/Et_3N$	DCM	40/16 h	60	15

[a]Reaction conditions: 1{*1*} (1.0 equiv), 2{*1*} (1.2 equiv), 4{*1*} (1.5 equiv), $HgCl_2$ (1.0 equiv), Et_3N (1.0 equiv). [b]Isolated yields. [c]$HgCl_2$ (1.5 equiv) and Et_3N (1.5 equiv).

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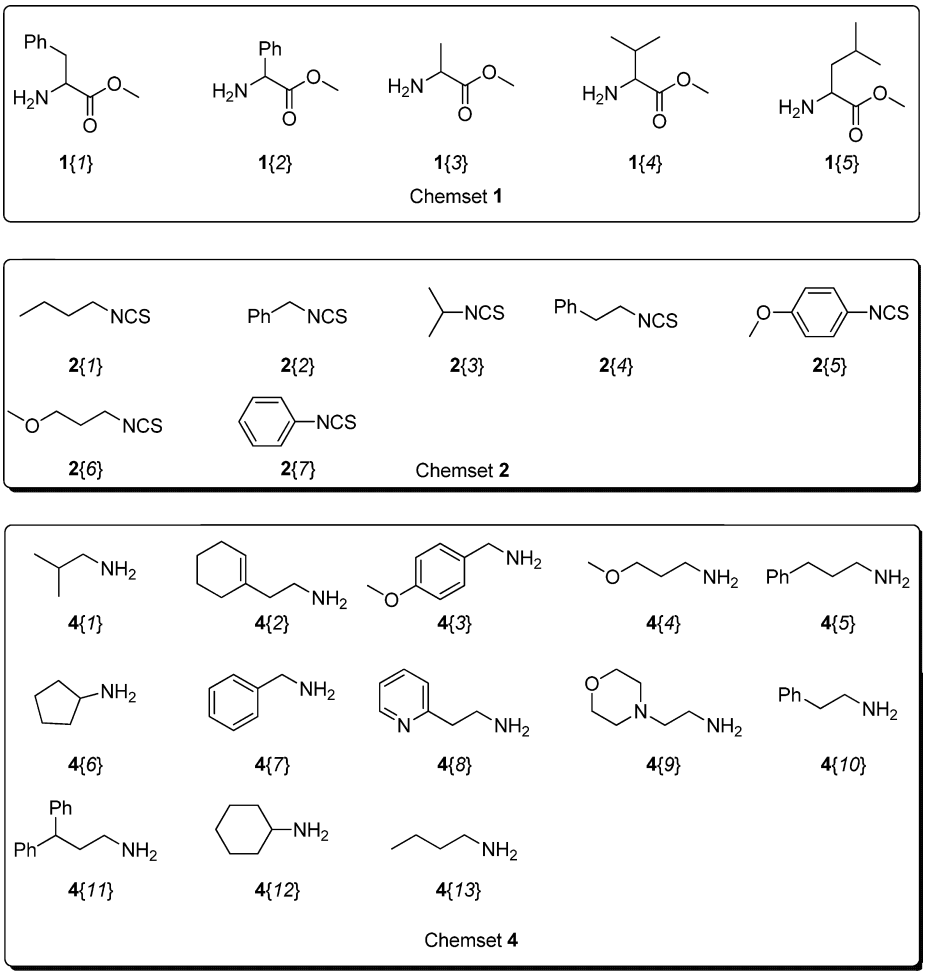
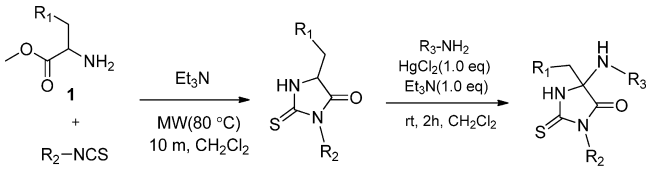


Figure 3. Diversity of amino esters **1**{*1*−*5*}, isothiocyanates **2**{*1*−*7*}, and amines **4**{*1*−*13*}.

Table 2. Oxidation/Addition Reaction of Thiohydantoins with Amines



1 + R_2–NCS **2** → **3** → **5**

entry	product	isolated yield (%)[a]
1	**5**{*1,1,1*}	85
2	**5**{*2,2,2*}	87
3	**5**{*5,2,2*}	89
4	**5**{*5,4,3*}	87
5	**5**{*5,3,3*}	88
6	**5**{*3,2,2*}	90
7	**5**{*4,2,3*}	85
8	**5**{*4,3,4*}	84
9	**5**{*4,3,5*}	86

[a]Isolated yields.

reaction of **3**{*4,7*} with methoxypropyl amine in DCM at 80 °C was heated only to the halfway point (5 min), the oxidized enamine **9**{*4,7*} together with the desired product **6**{*4,7,3*} was observed.

The isolated enamine **9**{*4,7*} was converted smoothly to product **6**{*4,7,3*} in 80% yield under the optimized reaction conditions. These results clearly demonstrate that oxidation occurred before guanylation and that the oxidized product **9**{*4,7*} is an intermediate in the cascade reaction. Furthermore, compound **6**{*1,7,9*} possesses a *cis* ring junction and Z configuration at the alkene (Figure 4), and its absolute structure was unequivocally confirmed by X-ray analysis.[22]

In a similar way, we tried to isolate the cyclic imine intermediate **8** for the formation of **5** (Scheme 3), but the efforts were not fruitful, suggesting that under basic conditions the oxidation and nucleophilic addition are rapid. Although mechanistic details are not clear at this point, on the basis of experimental observations and literature precedent,[23] we propose a possible mechanism for the exclusive formation of these products based on the reaction conditions (Scheme 3). At room temperature, thiohydantoin **3** underwent oxidation to cyclic imine **8**, which underwent subsequent nucleophilic attack by an amine on the α carbon to deliver 4-amino-substituted thioxoimidazolidinone **5**. Under microwave irradiation, however, formation of enamine **9** through H^+ elimination is favored over the addition of an amine on imine **8**. Subsequently, the activation of the thio-carbonyl group by mercury(II) chloride to furnish the thio-mercury conjugate and the nucleophilic displacement of mercury-coordinated sulfur by amines could deliver cyclic guanidine **6** by an addition−elimination pathway. The thiohydantoin derived from phenyl glycine may deliver

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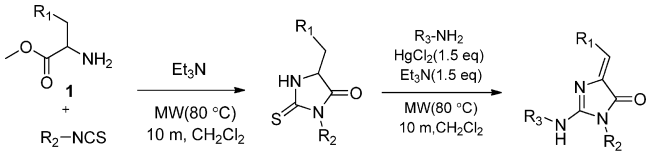
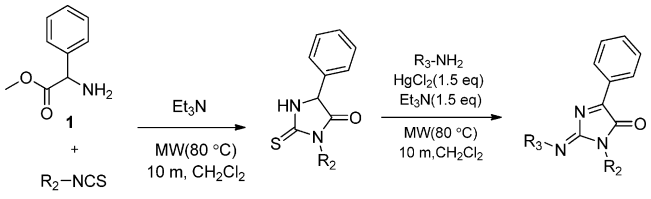
Table 3. Oxidation/Guanylation Reaction of Thiohydantoins with Amines



entry	product	isolated yield (%)[a]
1	**6**{*1,1,1*}	85
2	**6**{*1,1,13*}	83
3	**6**{*1,1,6*}	82
4	**6**{*1,1,7*}	80
5	**6**{*1,1,2*}	88
6	**6**{*1,1,8*}	79
7	**6**{*1,7,9*}	77
8	**6**{*1,5,10*}	85
9	**6**{*5,2,2*}	70
10	**6**{*5,2,9*}	61
11	**6**{*5,6,11*}	69
12	**6**{*5,6,12*}	65
13	**6**{*5,3,3*}	73
14	**6**{*5,4,3*}	69
15	**6**{*4,7,3*}	64
16	**6**{*4,2,3*}	68

[a]Isolated yields.

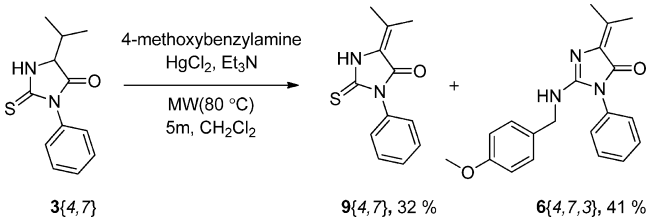
Table 4. Oxidation/Guanylation Reaction of Thiohydantoins with Amines



entry	product	isolated yield (%)[a]
1	**7**{*2,2,1*}	80
2	**7**{*2,2,13*}	79
3	**7**{*2,2,8*}	77

[a]Isolated yields.

Scheme 2. Control Experiments for the Formation of 6{*4,7,3*}



new intermediate **10**, which preferably undergoes an *in situ* auto-oxidation to provide iminoimidazolones **7**. It is believed that intermediate **10** is very unstable and undergoes dehydrogenation to the more stable conjugated iminoimidazolones **7**. A possible driving force could be the formation of the more stable product, which has a double bond in conjugation with the exocyclic carbonyl and the imine. All of the efforts to isolate compound **10** were unsuccessful, which demonstrated that conversion to final product **7** was very rapid. Thus, thiohydantoin can be treated as a suitable substrate for mercury-induced desulfurization without functionalizing the thione, facilitating nucleophilic attack of an amine at the C-2 and C-4 positions.

To further demonstrate the synthetic importance of our protocol, we applied this method to the synthesis of biologically active kinase inhibitor Leucettamine B. This marine alkaloid exerts selective inhibition toward protein kinases that are potential targets for the treatment of Alzheimer's disease. Although several methods were reported earlier, we disclosed herein a telescoped, rapid synthesis of Leucettamine B.[13b,24] Reaction of **11** with methyl isothiocyante in the presence of base provided the corresponding thiohydantoin, which was treated with ammonia(aq) under our unique reaction strategy to provide Leucettamine B, **12**, in 76% yield (Scheme 4).

Hence, the interesting results obtained from our synthetic approach indicate that the reaction conditions play a crucial role in controlling the reaction pathways, allowing the same starting materials to generate different types of products selectively.

CONCLUSIONS

In summary, the unique reactivity of thiohydantoins, which can be switched by the reaction conditions, was explored for the one-pot formation of thioxoimidazolidinones and amino-imidazolones. At room temperature, oxidation is followed by nucleophilic addition of amines to furnish 4-amino thioxoimi-dazolidinones, whereas under microwave irradiation, the sequential oxidation followed by guanylation delivers amino-imidazolones. The developed method was successfully applied to a concise synthesis of a kinase inhibitor, Leucettamine B. These results provide new insights into the divergent functionalization of thiohydantoins. Further studies on the detailed reaction mechanisms and their utility on other heterocycles for biological applications are underway by our group.

EXPERIMENTAL PROCEDURES

General Procedure for the Synthesis of 5-Benzyl-3-butyl-5-(isobutylamino)-2-thioxoimidazolidin-4-one (5{*1,1,1*}). To phenylalanine methyl ester hydrochloride **1**{*1*} (0.1 g, 0.46 mmol) in dichloromethane was added triethyl-amine (0.093 g, 0.92 mmol) followed by butyl isothiocyante **2**{*1*} (0.063 g, 0.55 mmol), and the resulting reaction mixture was subjected to microwave irradiation at 80 °C for 10 min to furnish thiohydantoin **3**{*1,1*}. To the same reaction mixture were added mercuric chloride (0.125 g, 0.46 mmol) and triethylamine (0.047 g, 0.46 mmol) followed by isobutyl amine **4**{*1*} (0.04 g, 0.55 mmol), and the mixture was allowed to stir at room temperature for 2 h. After completion of the reaction, the reaction mixture was filtered through a Celite pad and washed with dichloromethane (10 mL). The filtrate was concentrated, and the residue was purified by silica-gel column chromatography (20% ethyl acetate/hexane) to afford the desired product **5**{*1,1,1*} in 85% yield.

5-Benzyl-3-butyl-5-(isobutylamino)-2-thioxoimidazo-lidin-4-one, 5{*1,1,1*}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.34−7.24 (m, 3H), 7.21−7.19 (m, 3H), 3.72−3.49 (m, 2H), 3.12 (s, 2H), 2.23 (d, J = 6.4 Hz, 2H), 1.92 (s, 1H), 1.76−1.59 (m, 1H), 1.36−1.22 (m, 2H), 1.21−1.07 (m, 2H), 0.90 (d,

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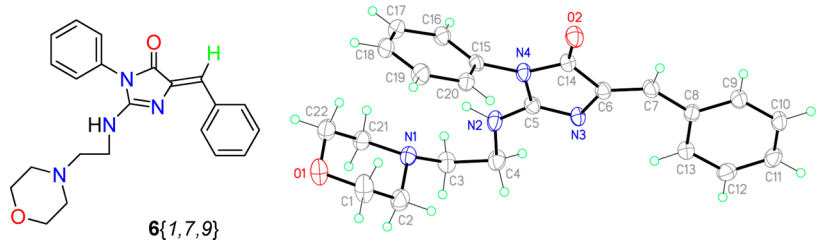
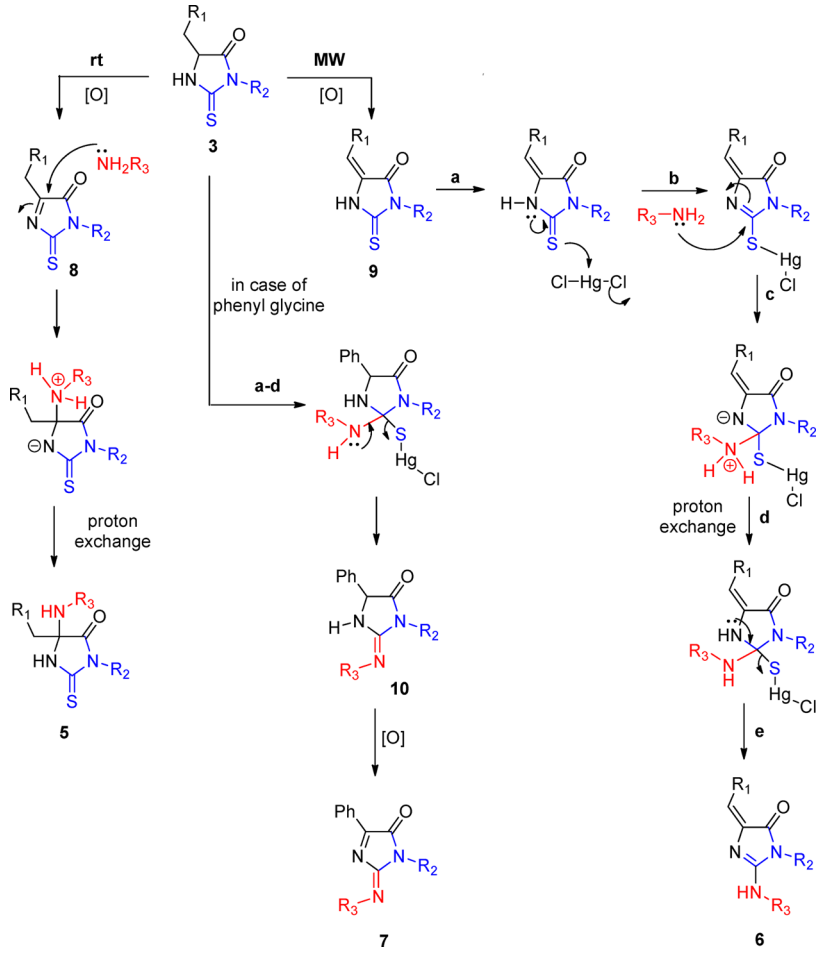
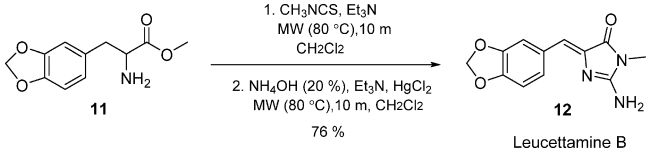


Figure 4. ORTEP representation of compound **6**{*1,7,9*}.

Scheme 3. Possible Mechanism for the Formation of 5−7



Scheme 4. Telescoped Synthesis of Leucettamine B



J = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 174.2, 132.5, 130.3, 128.5, 127.7, 79.4, 50.3, 43.3, 40.1, 29.4, 28.6, 20.4, 19.8, 13.6; MS (ESI) *m*/*z*: 334 (MH^+); HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{27}N_3OS$ [MH^+], 334.1948; found, 334.1955 (M+H).

General Procedure for the Synthesis of (*Z*)-4-Benzylidene-1-butyl-2-(isobutylamino)-1*H*-imidazol-5(4*H*)-one (6{*1,1,1*}). To phenylalanine methyl ester hydrochloride **1**{*1*} (0.1 g, 0.46 mmol) in dichloromethane was added triethylamine (0.093 g, 0.92 mmol) followed by butyl isothiocyante **2**{*1*} (0.063 g, 0.55 mmol), and the resulting reaction mixture was subjected to microwave irradiation at 80 °C for 10 min to furnish thiohydantoin **3**{*1,1*}. To the same reaction mixture were added mercuric chloride (0.188 g, 0.69 mmol) and triethylamine (0.070 g, 0.69 mmol) followed by isobutyl amine **4**{*1*} (0.06 g, 0.69 mmol), and the mixture was subjected to microwave irradiation at 80 °C for 10 min. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and washed with dichloromethane (10 mL). The filtrate was concentrated, and the residue was purified by silica-gel column chromatography (35% ethyl acetate/hexane) to afford the desired product **6**{*1,1,1*} in 85% yield.

(*Z*)-4-Benzylidene-1-butyl-2-(isobutylamino)-1*H*-imidazol-5(4*H*)-one, 6{*1,1,1*}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.26−7.23 (m, 1H), 6.7 (s, 1H), 4.57 (s, 1H), 3.58 (t, *J* = 7.2 Hz, 2H),

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3.43 (d, J = 6.3 Hz, 2H), 2.04 (sep, J = 6.6 Hz, 1H), 1.62 (quint, J = 6.6 Hz, 2H), 1.38 (sext, J = 7.2 Hz, 2H), 1.04 (d, J = 6.6 Hz, 6H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 157.4, 139.3, 135.7, 130.8, 128.4, 128.0, 116.7, 49.4, 39.0, 31.0, 28.5, 20.2, 20.1, 13.7; MS (FB+): m/z 300; HRMS (EI): calcd for $C_{18}H_{25}N_3O$, 299.1998; found, 299.2021.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data (^{1}H and ^{13}C NMR, LRMS, HRMS) of compounds **5**−**7** and X-ray data of compounds **5**{*1,1,1*} and **6**{*1,7,9*}. 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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■ REFERENCES

(1) (a) Burke, M. D.; Schreiber, S. L. A planning strategy for diversity-oriented synthesis. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (b) Brazeau, J. F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. Enantioselective cyclizations of silyloxyenynes catalyzed by cationic metal phosphine complexes. *J. Am. Chem. Soc.* **2012**, *134*, 2742. (c) Kotha, S.; Goyal, D.; Chavan, A. S. Diversity-oriented approaches to unusual α-amino acids and peptides: step economy, atom economy, redox economy, and beyond. *J. Org. Chem.* **2013**, *78*, 12288. (d) Brett, M. I.; Luca, L.; Esther, A.; Cornelius, O. J.; Sing, T. Y.; Huw, D. M. L.; Grahame, M.; Ashok, A. R.; David, S. R. Diversity-oriented synthesis as a tool for identifying new modulators of mitosis. *Nat. Commun.* **2014**, *5*, 4155.

(2) (a) Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. Controlling chemoselectivity in vinyl and allylic C−X bond activation with palladium catalysis: a pK_a-based electronic switch. *J. Am. Chem. Soc.* **2002**, *124*, 1288. (b) Lebel, H.; Paquet, V. Highly chemoselective rhodium-catalyzed methylenation of fluorine-containing ketones. *Org. Lett.* **2002**, *4*, 1671. (c) Zeng, Q.; Zhang, L.; Yang, J.; Xu, B.; Xiao, Y.; Zhang, J. Pyrroles versus cyclic nitrones: catalyst-controlled divergent cyclization of *N*-(2-perfluoroalkyl-3-alkynyl) hydroxylamines. *Chem. Commun.* **2014**, *50*, 4203.

(3) (a) Wang, J.; Mason, R.; Derveer, D. V.; Feng, K.; Bu, X. R. Convenient preparation of a novel class of imidazo[1,5-*a*]pyridines: decisive role by ammonium acetate in chemoselectivity. *J. Org. Chem.* **2003**, *68*, 5415. (b) Lin, M. L.; Maddirala, S. J.; Liu, R. S. Solvent-dependent chemoselectivity in ruthenium-catalyzed cyclization of iodoalkyne−epoxide functionalities. *Org. Lett.* **2005**, *7*, 1745. (c) Srinivas, S.; Rajesh, A. K.; Ruchir, K.; Bijoy, K. Diversity-oriented synthesis of ketoindoloquinoxalines and indolotriazoloquinoxalines from 1-(2-nitroaryl)-2-alkynylindoles. *J. Org. Chem.* **2014**, *79*, 2491.

(4) (a) Hoz, A. D. L.; Ortiz, A. D.; Moreno, A. Selectivity in organic synthesis under microwave irradiation. *Curr. Org. Chem.* **2004**, *8*, 903. (b) Hoz, A. D. L.; Ortiz, A. D.; Moreno, A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. *Chem. Soc. Rev.* **2005**, *34*, 164. (c) Chebanov, V. A.; Muravyova, E. A.; Desenko, S. M.; Musatov, V. I.; Knyazeva, I. V.; Shishkina, S. V.; Shishkin, O. V.; Kappe, C. O. Microwave-assisted three-component synthesis of 7-aryl-2-alkylthio-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamides and their selective reduction. *J. Comb. Chem.* **2006**, *8*, 427. (d) Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chernenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. Tuning of chemo- and regioselectivities in multicomponent condensations of 5-aminopyrazoles, dimedone, and aldehydes. *J. Org. Chem.* **2008**, *73*, 5110.

(5) Scala, F.; Fattorusso, E.; Menna, M.; Scafati, O. T.; Tierney, M.; Kaiser, M.; Tasdemir, D. Bromopyrrole alkaloids as lead compounds against protozoan parasites. *Mar. Drugs* **2010**, *8*, 2162.

(6) (a) Rodriguez, F.; Rozas, I.; Ortega, J. E.; Erdozain, A. M.; Meana, J. J.; Callado, L. F. Guanidine and 2-aminoimidazoline aromatic derivatives as alpha2-adrenoceptor ligands: searching for structure-activity relationships. *J. Med. Chem.* **2009**, *52*, 601. (b) Keller, K.; Pop, N.; Hutzler, C.; Sickinger, A. G. B.; Bernhardt, G.; Buschauer, A. Guanidine-acylguanidine bioisosteric approach in the design of radioligands: synthesis of a tritium-labeled N(G)-propionylarginina-mide ([^{3}H]-UR-MK114) as a highly potent and selective neuropeptide Y Y1 receptor antagonist. *J. Med. Chem.* **2008**, *51*, 8168.

(7) (a) Seo, H. J.; Park, E. J.; Kim, M. J.; Kang, S. Y.; Lee, S. H.; Kim, H. J.; Lee, K. N.; Jung, M. E.; Lee, M. W.; Kim, M. S.; Son, E. J.; Park, W. K.; Kim, J.; Lee, J. Design and synthesis of novel arylpiperazine derivatives containing the imidazole core targeting 5-HT$_{2A}$ receptor and 5-HT transporter. *J. Med. Chem.* **2011**, *54*, 6305. (b) Gomaa, M. S.; Bridgens, C. E.; Aboraia, A. S.; Veal, G. J.; Redfern, C. P. F.; Brancale, A.; Armstrong, J. L.; Simons, C. Small molecule inhibitors of retinoic acid 4-hydroxylase (CYP26): synthesis and biological evaluation of imidazole methyl 3-(4-(aryl-2-ylamino) phenyl)-propanoates. *J. Med. Chem.* **2011**, *54*, 2778.

(8) Metzger, A.; Lynch, V. M.; Anslyn, E. V. A synthetic receptor selective for citrate. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 862.

(9) Reddy, Y. T.; Reddy, P. N.; Koduru, S.; Damodaran, C.; Crooks, P. A. Synthesis and *in vitro* evaluation of *N*-alkyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one analogs as potential anticancer agents. *Bioorg. Med. Chem.* **2010**, *18*, 3570.

(10) Zhu, Z.; Sun, Z. Y.; Ye, Y.; Voigt, J.; Strickland, C.; Smith, E. M.; Cumming, J.; Wang, L.; Wong, J.; Wang, Y. S.; Wyss, D. F.; Chen, X.; Kuvelkar, R.; Kennedy, M. E.; Favreau, L.; Parker, E.; McKittrick, B. A.; Stamford, A.; Czarniecki, M.; Greenlee, W.; Hunter, J. C. Discovery of cyclic acylguanidines as highly potent and selective β-site amyloid cleaving enzyme (BACE) inhibitors: Part I—inhibitor design and validation. *J. Med. Chem.* **2010**, *53*, 951.

(11) Renault, S.; Bertrand, S.; Carreaux, F.; Bazureau, J. P. Parallel solution-phase synthesis of 2-alkylthio-5-arylidene-3,5-dihydro-4*H*-imidazol-4-one by one-pot three-component domino reaction. *J. Comb. Chem.* **2007**, *9*, 935.

(12) Caldwell, J. P.; Bennett, C. E.; McCracken, T. M.; Mazzola, R. D.; Bara, T.; Buevich, A.; Burnett, D. A.; Chu, I.; Williams, C. M.; Josein, H.; Hyde, L.; Lee, J.; McKittrick, B.; Song, L.; Terracina, G.; Voigt, J.; Zhang, L.; Zhu, Z. Iminoheterocycles as γ-secretase modulators. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5380.

(13) (a) Debdab, M.; Renault, S.; Lozach, O.; Meijer, L.; Paquin, L.; Carreaux, F.; Bazureau, J. P. Synthesis and preliminary biological evaluation of new derivatives of the marine alkaloidLeucettamine B as kinase inhibitors. *Eur. J. Med. Chem.* **2010**, *45*, 805. (b) Cherouvrier, J. R.; Carreaux, F.; Bazureau, J. P. Microwave-mediated solventless synthesis of new derivatives of marine alkaloid Leucettamine B. *Tetrahedron Lett.* **2002**, *43*, 3581.

(14) Ding, M. W.; Xu, Z. F.; Liu, Z. J.; Wu, T. J. A facile and selective synthesis of 2-alkylamino-4*H*-imidazolin-4-ones. *Synth. Commun.* **2001**, *31*, 1053.

(15) (a) Fu, M.; Fernandez, M.; Smith, M. L.; Flygare, J. A. Solid-phase synthesis of 2-aminoimidazolones. *Org. Lett.* **1999**, *1*, 1351. (b) Li, M.; Wilson, L. J. A facile and practical solid-phase synthesis of trisubstituted 2-aminoimidazolones. *Tetrahedron Lett.* **2001**, *42*, 1455.

(16) Yu, Y.; Ostresh, J. M.; Houghten, R. A. Solid-phase synthesis of 2,3,5-trisubstituted 4*H*-imidazolones. *J. Comb. Chem.* **2001**, *3*, 521.

(17) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. Reaction of α-iminomethylene amino esters with mono- and bidentate

DOI: 10.1021/co500152s
ACS Comb. Sci. 2015, 17, 182−189

nucleophiles: a straightforward route to 2-amino-1*H*-5-imidazolones. *Tetrahedron* **2001**, *57*, 4371.
(18) (a) Kaila, J. C.; Baraiya, A. B.; Vasu, K. K.; Sudarsanam, V. A facile synthesis of structurally novel 1-aryl-2-arylamino-4-alkyl/phenyl-5-aroyl-1*H*-imidazoles from amidinothioureas. *Tetrahedron Lett.* **2008**, *49*, 7220. (b) Evindar, G.; Batey, R. A. Peptide heterocycle conjugates: a diverted edman degradation protocol for the synthesis of N-terminal 2-iminohydantoins. *Org. Lett.* **2003**, *5*, 1201.
(19) Fresneda, P. M.; Castañeda, M.; Sanz, M. A.; Bautistab, D.; Molina, P. An iminophosphorane-based approach for the synthesis of spiropyrrolidine−imidazole derivatives. *Tetrahedron* **2007**, *63*, 1849.
(20) (a) Swamy, K. M. K.; Yeh, W.-B.; Lin, M.-J.; Sun, C.-M. Microwave-assisted polymer-supported combinatorial synthesis of heterocyclic libraries. *Curr. Med.Chem.* **2003**, *10*, 2403. (b) Lai, J. J.; Salunke, D. B.; Sun, C. M. Multistep microwave-assisted divergent synthesis of indolo-fused pyrazino-/diazepinoquinoxalinones on PEG support. *Org. Lett.* **2010**, *12*, 2174. (c) Yellol, G. S.; Chou, C. T.; Chang, W. J.; Maiti, B.; Sun, C. M. Microwave-enhanced efficient regioselective synthesis of 1,3,4-trisubstituted 2-mercaptoimidazoles on a soluble support. *Adv. Syn. Catal.* **2012**, *354*, 187. (d) Maiti, B.; Chanda, K.; Selvaraju, M.; Tseng, C. C.; Sun, C. M. Multicomponent solvent-free synthesis of benzimidazolyl imidazo[1,2-*a*]-pyridine under microwave irradiation. *ACS. Comb. Sci.* **2013**, *15*, 291.
(21) (a) Kim, J.; Stahl, S. S. Cu/nitroxyl-catalyzed aerobic oxidation of primary amines into nitriles at room temperature. *ACS Catal.* **2013**, *3*, 1652. (b) Suzuki, K.; Watanabe, T.; Murahashi, S. I. Oxidation of primary amines to oximes with molecular oxygen using 1,1-diphenyl-2-picrylhydrazyl and WO_3/Al_2O_3 as catalysts. *J. Org. Chem.* **2013**, *78*, 2301.
(22) CCDC 992982 and CCDC 992926 contain the supplementary crystallographic data for compounds **5**{*1,1,1*} and **6**{*1,7,9*} respectively. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(23) Pepino, A. J.; Peláez, W. J.; Moyano, E. L.; Argüello, G. A. Highly efficient dehydrogenation of 5-benzyl-3-phenyl-2-thioxoimidazolidin-4-one: microwave versus flash vacuum pyrolysis conditions. *Eur. J. Org. Chem.* **2012**, *18*, 3424.
(24) Earlier methods for the synthesis of Leucettamine B. (a) Chérouvrier, J. R.; Boissel, J.; Carreaux, F.; Bazureau, J. P. A stereoselective route to 3-methyl-2-methylsulfanyl-5- ylidene-3,5-dihydroimidazol-4-one derivatives and precursor of Leucettamine B. *Green Chem.* **2001**, *3*, 165. (b) Debdab, M.; Renault, S.; Eid, S.; Lozach, O.; Meijer, L.; Carreaux, F.; Bazureau, J. P. An efficient method for the preparation of new analogs of Leucettamine B under solvent-free microwave irradiation. *Heterocycles* **2009**, *78*, 1191.

DOI: 10.1021/co500152s
ACS Comb. Sci. 2015, 17, 182−189