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[4+2] Annulation Reaction of *in situ* Generated Azoalkenes with Azlactones: Access to 4,5-Dihydropyridazin-3(2*H*)-ones

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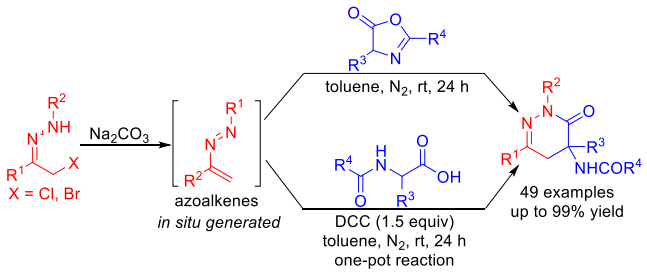


Abstract

An unprecedented [4+2] annulation reaction between *in situ* formed azoalkenes and azlactones has been developed. This reaction provides a facile access to an array of 4,5-dihydropyridazin-3(2*H*)-one derivatives, which are very promising in medicinal application as potential biologically active candidates. Notably, these dihydropyridazinones also could be synthesized via a one-pot reaction protocol by using the *in situ* formed azlactones from *N*-acyl amino acids and *in situ* generated azoalkenes from *α*-halogeno hydrazones. The potential applications of the methodology were also demonstrated by the gram scale experiments and the versatile conversions of the products into other nitrogen-containing compounds.

INTRODUCTION

Pyridazinones have becoming the privileged scaffolds for drug discovery.[1] Due to the easy functionalization to result in structurally novel compounds with rich biological activities, extensive effort has been devoted to the development of various methods for the synthesis of pyridazinone derivatives.[2] In particular, 4,5-dihydropyridazin-3(*2H*)-ones, as one type of pyridazinone derivatives, are ubiquitous core structure unit found in many pharmaceuticals and biologically active molecules (Figure 1). For examples, clinical trials showed that Indolidan and Bemoradan have effective antihypertensive activity,[3] and Levosimendan and Pimobendan exhibit certain anti-congestive heart failure activities.[4] Although several elegant synthetic strategies to obtain diverse 4,5-dihydropyridazin-3(2*H*)-one compounds have been reported,[5] given their great potential value in organic and medicinal chemistry for drug research and development, exploiting creative methods to construct diversified 4,5-dihydropyridazin-3(2*H*)-one derivatives is an important goal in the area of organic synthesis.

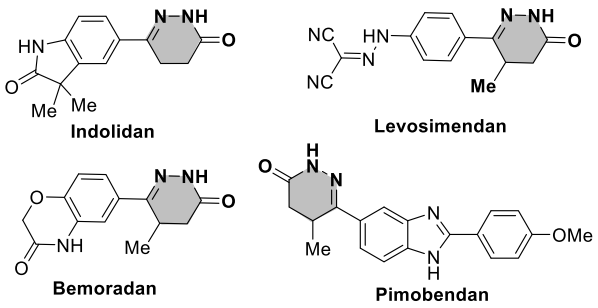
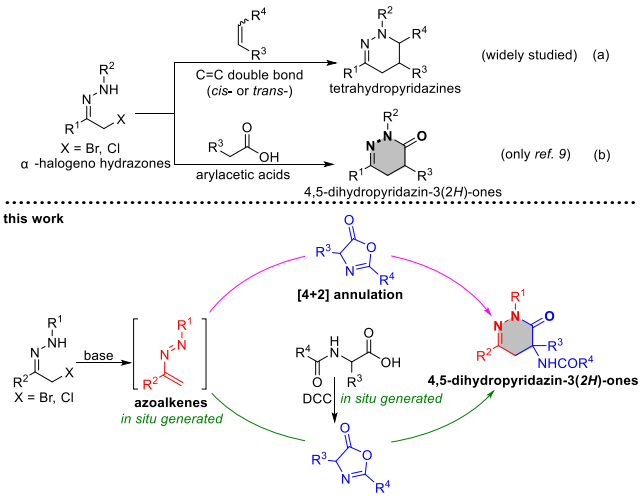


Figure 1. Pharmaceutical molecules containing 4,5-dihydropyridazin-3(2*H*)-one unit.

Azoalkenes (1,2-diaza-1,3-dienes), which are *in situ* generated from *α*-halogeno hydrazones with a base, have been widely employed as powerful four-atom building units in the [4+1],[6] [4+2],[7] or [4+3][8] annulation to access various valuable nitrogen-containing heterocyclic compounds. Actually, the involvement of azoalkenes in [4+2] annulation belongs to one of the direct and convenient strategies for the construction of nitrogen-containing six-membered

heterocycles. However, the most [4+2] annulation reactions developed to date are based on the reaction of α-halogeno hydrazones with various reactants containing carbon-carbon double bonds to access diversified tetrahydropyridazine compounds (Scheme 1a).[7] Surprisingly, there exists only one report by Yao and co-workers, who realized the formal [4+2] cycloaddition of azoalkenes with arylacetic acids under the catalysis of isothiourea to access 4,5-dihydropyridazin-3(*2H*)-ones (Scheme 1b).[9] On the other hand, azlactones have been proved to be a robust and versatile two-carbon synthetic building block and found wide application in the construction of lactam compounds.[10-11] By this token, azlactone serving as two-carbon synthon can firstly react with a wide variety of electrophiles from its α-position. Subsequently, ring opening the azlactone via a possible intramolecular aminolysis will assemble cyclic lactam system. In this context, we envisioned that the *in situ* formed azoalkenes could react with azlactones via [4+2] annulation reaction (Scheme 1), giving structurally important 4,5-dihydropyridazin-3(2*H*)-one compounds containing an α-quaternary α-acylamino moiety, which may have promising application as potential biologically active candidates in the research and development of drug discovery.

Scheme 1. Outline of This Work



As a continuation of our research program on the development of new methodology for the

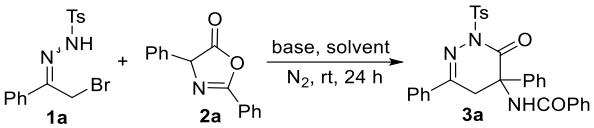
construction of heterocyclic compounds,[12] herein, we wish to report our success in the [4+2] annulation reaction of *α*-halogeno hydrazones and azlactones for the synthesis of 4,5-dihydropyridazin-3(2*H*)-one compounds with catalyst-free under basic conditions. Moreover, in order to avoid the elaborate preparation of azlactones, we also demonstrate that these dihydropyridazinones could also be synthesized via a one-pot reaction process by using *in situ* formed azlactones from *N*-acyl amino acids and *in situ* generated azoalkenes from *α*-halogeno hydrazones (Scheme 1).

RESULTS AND DISCUSSION

Our initial investigation began with the reaction of *α*-bromo-*N*-Ts hydrazone **1a** and 2,4-diphenyloxazol-5(4*H*)-one **2a** by using $KHCO_3$ as the base in CH_2Cl_2 under nitrogen atmosphere. To our delight, the expected [4+2] annulation reaction occurred well and furnished adduct **3a** in 68% yield (Table 1, entry 1). Afterwards, various bases including Na_2CO_3, K_2CO_3, Cs_2CO_3, Et_3N and *N*,*N*-diisopropylethylamine (DIPEA) were examined with the model reaction, and it was found that Na_2CO_3 was the best choice in light of yield of product **3a** (Table 1, entry 2 vs entries 3-6). Having identified Na_2CO_3 as the best base, a series of solvents were screened (Table 1, entries 7-11), and it was observed that different solvents had significant effect on the reactions. For instances, in the application of chlorinated solvents such as CH_2Cl_2 and 1,2-dichloroethane (DCE), the reaction gave **3a** in good yield (Table 1, entries 7 and 8). When the reaction was carried out in ethyl acetate (EtOAc) or THF, **3a** was obtained in 52% and 61% yield, respectively (Table 1, entries 9 and 10). Excitingly, running the reaction in toluene led to an obviously increased yield to give **3a** in 96% yield (Table 1, entry 11). Ultimately, reducing the loading of Na_2CO_3 from 2.0 equivalents to 1.0 equivalent, the reaction also afforded **3a** in 98%

yield (Table 1, entry 12).

Table 1. Optimization of Reaction Conditions[a]



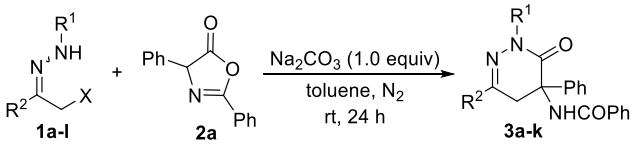
Entry	base	solvent	yield (%)[b]
1	$KHCO_3$	CH_2Cl_2	68
2	Na_2CO_3	CH_2Cl_2	69
3	K_2CO_3	CH_2Cl_2	54
4	Cs_2CO_3	CH_2Cl_2	35
5	Et_3N	CH_2Cl_2	48
6	DIPEA	CH_2Cl_2	50
7	Na_2CO_3	$CHCl_3$	71
8	Na_2CO_3	DCE	61
9	Na_2CO_3	EtOAc	52
10	Na_2CO_3	THF	61
11	Na_2CO_3	toluene	96
12[c]	Na_2CO_3	toluene	98

[a]Unless specified, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol) and base (0.2 mmol, 2.0 equiv) in 2.0 mL of solvent under nitrogen atmosphere at room temperature for 24 h. [b]isolated yield. [c]1.0 equivalent of Na_2CO_3 was used.

With the optimal reaction conditions in hand, we next explored the reaction scope and generality. Various α-halo hydrazone substrates were firstly examined by reacting with α-phenyl azlactone **2a**, and the results are summarized in Table 2. Diverse sulfonyl substitutents of the *N*-protecting group of α-halo hydrazones, such as Ts-, Ms-, and Bs- were found to be suitable for the current reaction system, affording corresponding products **3a-c** in high yields (Table 2, entries 1-4). However, as for *N*-acyl protected α-halo hydrazones such as *N*-Boc, N-Cbz and *N*-Bz substituents, the reactions did not proceed, probably due to the lower reactivity (not shown in Table 2). In addition, different electron-donating substituents at different positions on the phenyl ring of α-halo hydrazones were also tolerated well, giving the desired

4,5-dihydropyridazin-3(2*H*)-one derivatives **3d-f** in 85-94% yields (Table 2, entries 5-7). Meanwhile, the substrates **1h-k**, with an electron-withdrawing group (F-, Cl-, F_3C-, and NO_2-) at the *para*- or *meta*-position on the phenyl ring, also showed good reactivities and provided products **3g-j** in yields ranging from 85% to 99% (Table 2, entries 8-11). The reaction with substrate **1l** bearing sterically hindered 2-naphthyl group also proceeded well and afforded product **3k** in 91% yield (Table 2, entry 12). Disappointingly, when R^2 is alkyl group, such as Me-, the reaction became messy monitored by TLC and no main product could be obtained (not shown in Table 2).

Table 2. Substrate Scope of *α*-Halo Hydrazones 1[a]



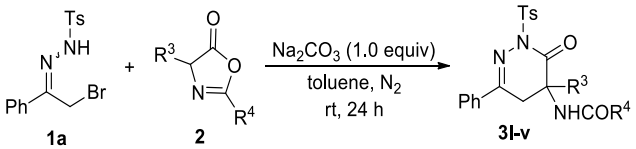
entry	1				3	yield (%)[b]
1	R^1 = Ts	R^2 = Ph	X = Br	**1a**	**3a**	98
2	R^1 = Ts		X = Cl	**1b**	**3a**	78
3	R^1 = Ms		X = Cl	**1c**	**3b**	84
4	R^1 = Bs		X = Br	**1d**	**3c**	81
5	R^1 = Ts	R^2 = 4-MeC_6H_4	X = Br	**1e**	**3d**	88
6		R^2 = 4-$MeOC_6H_4$		**1f**	**3e**	85
7		R^2 = 3-$MeOC_6H_4$		**1g**	**3f**	94
8		R^2 = 4-FC_6H_4		**1h**	**3g**	85
9		R^2 = 4-ClC_6H_4		**1i**	**3h**	93
10		R^2 = 4-$CF_3C_6H_4$		**1j**	**3i**	99
11		R^2 = 3-$NO_2C_6H_4$		**1k**	**3j**	99
12		R^2 = 2-naphthyl		**1l**	**3k**	91

[a]Unless specified, the reactions were carried out with **1** (0.2 mmol), **2a** (0.3 mmol) and Na_2CO_3 (0.2 mmol) in toluene (4.0 mL) under N_2 at room temperature for 24 h. [b]isolated yield. Ts = Toluenesulfonyl; Ms = Methanesulfonyl; Bs = Benzenesulfonyl.

Next, a variety of azlactones were examined by reacting with *α*-bromo-*N*-Ts hydrazone **1a** to

further explore the generality of the reaction (Table 3). We first investigated the effects of the substituent (R^3) at the C2-position of azlactones, and found that *ortho*-substitution on the phenyl ring led to a significantly reduced chemical yield, presumably due to the steric hindrance effect (Table 3, entry 1). Substrates bearing different electron-withdrawing groups, such as Cl- and F- at the *meta*- or *para*-position were compatible well with the conditions, providing the products **3m-o** in 83-98% yields (Table 3, entries 2-4). As for electron-donating group on the phenyl ring such as substrate **2f**, the reaction gave product **3p** only in 38% yield (Table 3, entry 5), which is probably due to the instable and decomposed easily property of azlactone **2f** in the basic mixture. However, with alkyl substituent at the C2-position of azlactone (such as 4-benzyl-2-phenyloxazol-5(4*H*)-one and 4-methyl-2-phenyloxazol-5(4*H*)-one), the desired [4+2] annulation reaction did not take place under the standard conditions (not shown in Table 3). Furthermore, as for R^4 group, we found the substituent on the aromatic ring did not influence the reactivity, regardless of electric nature or steric hindrance of the substituent, the reactions gave the products **3q-t** in yields ranging from 80% to 96% (Table 3, entries 6-9). Ultimately, the heteroaromatic ring substituted substrates also prove to be amenable to this [4+2] annulation protocol, providing the corresponding products **3u** and **3v** in 52% and 79% yields, respectively (Table 3, entries 10-11).

Table 3. Substrate Scope of Azlactones 2[a]



entry	2			3	yield (%)[b]
1	R^3 = 2-ClC_6H_4		**2b**	**3l**	25
2	R^3 = 3-ClC_6H_4		**2c**	**3m**	83
3	R^3 = 4-ClC_6H_4	R^4 = Ph	**2d**	**3n**	84
4	R^3 = 4-FC_6H_4		**2e**	**3o**	98
5	R^3 = 4-MeC_6H_4		**2f**	**3p**	38

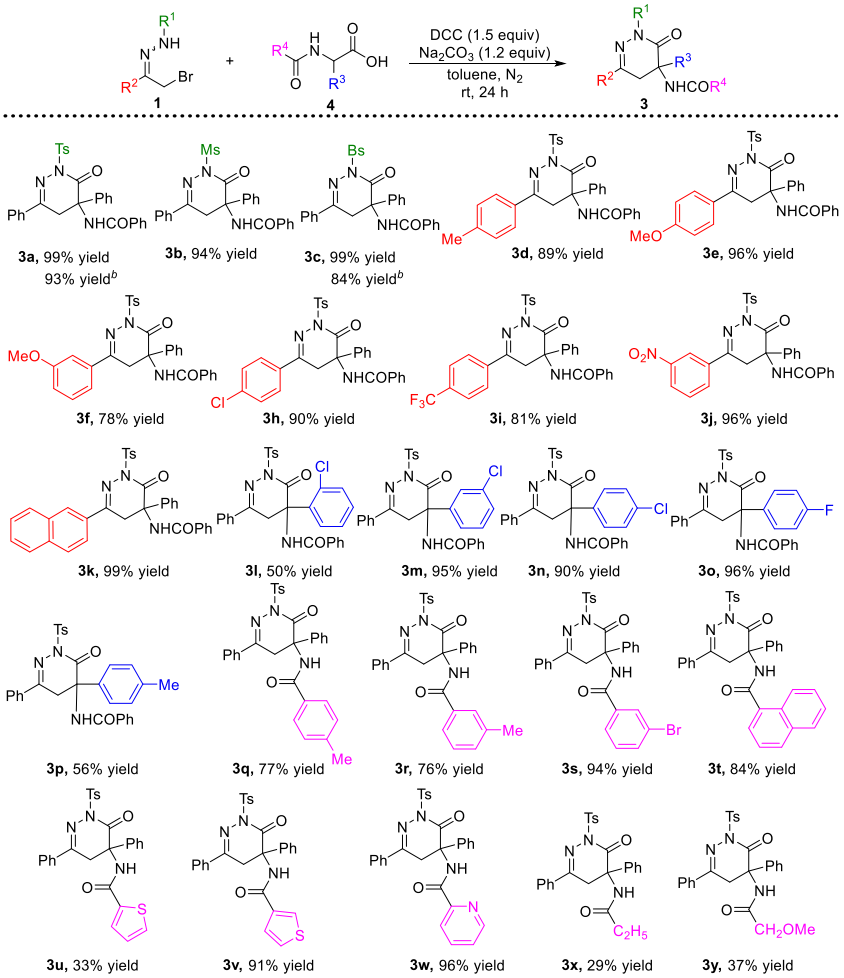
6	R^3 = Ph	R^4 = 4-MeC_6H_4	**2g**	**3q**	88
7		3-MeC_6H_4	**2h**	**3r**	80
8		3-BrC_6H_4	**2i**	**3s**	87
9		1-naphthyl	**2j**	**3t**	96
10		2-thiophenyl	**2k**	**3u**	52
11		3-thiophenyl	**2l**	**3v**	79

[a]Unless specified, the reactions were carried out with **1a** (0.2 mmol), **2** (0.3 mmol) and Na_2CO_3 (0.2 mmol) in toluene (4.0 mL) under N_2 at room temperature for 24 h. [b]isolated yield.

In fact, the separation and purification of azlactone substrates is a relatively tedious operation during the preparation of them.[13] In order to avoid this tedious operation and conveniently use this kind of compounds in organic synthesis, we attempted to develop a one-pot protocol to synthesize the 4,5-dihydropyridazin-3(2*H*)-ones by using the *in situ* formed azlactones and the *in situ* generated azoalkenes. As shown in Scheme 2, when we added 1.5 equivalents of dicyclohexylcarbodiimide (DCC) into the reaction mixture to promote the cyclodehydration of 2-benzamido-2-phenylacetic acid **4a** for the formation of azlactone, to our delight, the desired **3a** was able to be obtained in almost quantitative yield in the reaction of **1a** and **4a** in the presence of DCC and Na_2CO_3 in toluene under nitrogen atmosphere after 24 h.[14] Nevertheless, under the same conditions, the reaction of α-chloro-*N*-Ts hydrazone **1b** and **4a** also proceeded smoothly and afforded **3a** in 93% yield. And then, we further investigated the scope of the reactions of **4a** and different α-halo-hydrazones with the developed one-pot protocol. It was found that the expected 4,5-dihydropyridazin-3(2*H*)-one products **3b-j** could be obtained in good to excellent chemical yields, regardless of the pattern of sulfonyl substituents in the *N*-protecting group and the substituent's electronic nature and position on the phenyl ring for the α-halo-hydrazone substrates. The bulker naphthyl group also tolerated well in the one-pot protocol, and the corresponding cycloadduct **3k** was obtained in 99% yield. On the other hand, diverse substituted amino acids **4**,

possessing electron-withdrawing or electron-donating groups at *ortho*-, *meta*- or *para*-position of the phenyl ring (R^3), reacted well with α-bromo-*N*-Ts hydrazone **1a**, delivering their corresponding products **3l-p** in moderate to high yields. Meanwhile, different aryl substituents of the *N*-protecting group (R^4) of the amino acids, regardless of electronic property and steric hindrance of the substituents, as well as the heteroaromatic ring as substituent group, were tolerated in this one-pot reaction to give the products **3q-w** in yields ranging from 33% to 96%. It's worth noting that the substrates bearing aliphatic substituent as the *N*-protecting group of the amino acids were able to participate in the [4+2] annulation transformation, affording the corresponding products **3x** and **3y** in 29% and 37% yields, respectively.

Scheme 2. One-pot [4+2] Annulation Reaction of *in situ* Generation of Two Substrates for the Synthesis of 4,5-Dihydropyridazin-3(2*H*)-ones[a]

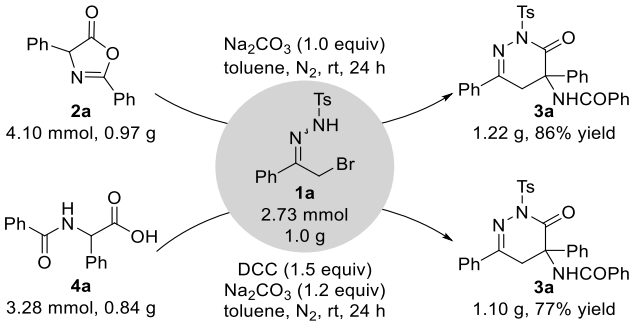


[a]Reaction conditions: The reactions were carried out with **1** (0.2 mmol), **4** (0.24 mmol), DCC (0.3 mmol) and Na_2CO_3 (0.24 mmol) in toluene (4.0 mL) under N_2 at room temperature for 24 h. The reported yields of **3** refer to the isolated yield. [b]Replacing *α*-bromo-*N*-Ts hydrazone **1a** with *α*-chloro-*N*-Ts hydrazone **1b** for the reaction.

In order to demonstrate the potential utility of the [4+2] annulation reaction, we performed the reactions **1a** with **2a** and **1a** with **4a** on a gram scale, respectively. As shown in Scheme 3, under the standard conditions, both reactions proceeded well and afforded **3a** in good yield. Notably, when the gram scale reactions were complete, product **3a** could be obtained conveniently by filtration and no silica gel column chromatography isolation required, which is generally deemed to be a more reliable and industrially convenient operation for large-scale production.

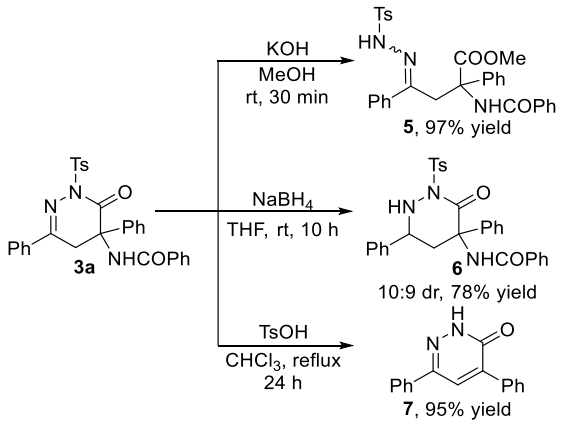
Certainly, the gram-scale experiments suggest that the developed protocol has good scalability and the potential value in organic synthesis.

Scheme 3 Gram-scale Experiments



To further illustrate the synthetic potential value and versatility of this methodology, we explored several transformations of the product **3a** into other nitrogen-containing compounds (Scheme 4). Treating **3a** with potassium hydroxide in MeOH at room temperature for 30 mins, ring-opening alcoholysis product **5** was obtained in 97% yield. The C=N double bond in **3a** could be reduced by using $NaBH_4$ in THF to give tetrahydropyridazinone **6** in 78% yield with 10:9 diastereoselectivity. In addition, treating **3a** with *p*-toluenesulfonic acid in $CHCl_3$ under refluxing for 24 h, pyridazinone derivative **7** could be obtained in 95% yield.

Scheme 4. Different Transformations of Compound 3a

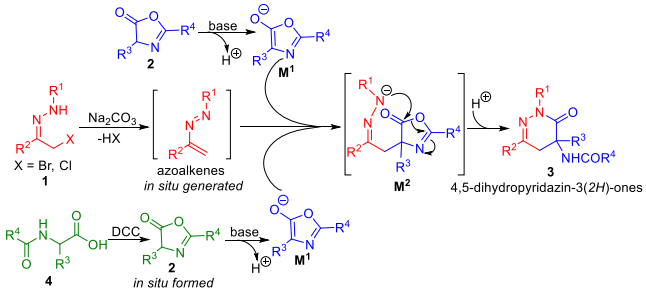


The structure of product **3a** was unambiguously determined via X-ray crystallographic study of single crystal (see Supporting Information).[15] All the dihydropyridazinone compounds in this

work were characterized by nuclear magnetic resonance spectroscopy and high resolution mass spectrometry.

A plausible reaction mechanism was proposed for this [4+2] annulation reaction (Scheme 5). In the presence of Na_2CO_3, *α*-halogeno hydrazones **1** *in situ* produce reactive azoalkenes. At the same time, azlactones **2** can give the reactive azlactone enolate $\mathbf{M^1}$ under the basic conditions. And then, the enolates $\mathbf{M^1}$ attack the electrophilic azoalkenes for the C-C bond formation to give intermediate $\mathbf{M^2}$. Subsequently, opening the azlactone ring via an intramolecular aminolysis results in the 4,5-dihydropyridazin-3(2*H*)-one products **3**. On the other hand, the readily available *N*-acyl amino acids **4** are able to be *in situ* converted into azlactones **2** with DCC. Thus under the basic conditions, the *in situ* formed azlactones **2** can react with the in situ generated azoalkenes via one-pot [4+2] annulation reaction to afford 4,5-dihydropyridazin-3(2*H*)-one products **3**.

Scheme 5. Reaction Mechanism Proposal



CONCLUSION

In summary, we have developed an unprecedented [4+2] annulation reaction between *in situ* formed azoalkenes and azlactones. With the developed protocol, a wide range of structurally important dihydropyridazinone compounds, which are very promising in medicinal application as potential biologically active candidates, could be smoothly obtained in up to 99% yield under mild conditions. Notably, these dihydropyridazinones also could be synthesized via a one-pot reaction

protocol by using the *in situ* formed azlactones from *N*-acyl amino acids and *in situ* generated azoalkenes from *α*-halogeno hydrazones. The potential applications of the methodology were also demonstrated by the gram scale experiments and the versatile conversions of the products into other nitrogen-containing compounds.

Experimental Section

General Methods

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Solvents were dried and purified according to the standard procedures before use. Reactions were monitored by TLC. Flash column hromatography was performed on silica gels (200-300 mesh). ^{1}H NMR and ^{13}C{^{1}H} NMR (300 and 75 MHz, respectively) spectra were recorded on a Bruker 300 MHz NMR spectrometer in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ 7.26 ppm, DMSO-d_6 δ 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, td = triplet of doublets, q = quartet, m = multiplet), coupling constants (Hz) and integration. ^{13}C{^{1}H} chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm, DMSO-d_6 at 39.51 ppm). HRMS data were obtained on a Bruker Daltonics. Inc mass instrument (ESI). Melting points were recorded on a Buchi Melting Point B-545. The *α*-halo hydrazone substrates **1**[6,7,8], azlactones **2**[13] and *N*-acyl amino acids[13] used in this work, are known compounds and prepared according to the reported literature procedures.

Representative procedure for preparing 3 via the reaction of azlactones and *α*-halo hydrazones. To a flame dried reaction tube were added *α*-halo hydrazone **1** (0.2 mmol), azlactone

2 (0.3 mmol) and anhydrous Na_2CO_3 (21.2 mg, 0.2 mmol), followed by adding anhydrous toluene (4 mL). The atmosphere in tube was replaced by N_2, and the reaction was carried out at room temperature under N_2 for 24 h. After completion, water (10 mL) was added to the reaction system, and the mixture was extract with CH_2Cl_2 (10 mL × 3). The organic layers were combined, dried over by Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether : ethyl acetate = 5:1~4:1 as eluent) to give **3** as white solid.

Representative procedure for preparing 3 via one-pot process of *in situ* azlactones formation from the corresponding *N*-acyl amino acids with *α*-halo hydrazones. To a flame dried reaction tube were added *α*-halo hydrazone **1** (0.2 mmol), *N*-acyl amino acid **4** (0.24 mmol), dicyclohexylcarbodiimide (DCC, 61.8 mg, 0.3 mmol) and anhydrous Na_2CO_3 (25.4 mg, 0.24 mmol), followed by adding anhydrous toluene (4 mL). The atmosphere in tube was replaced by N_2, and reaction was carried out at room temperature under N_2 for 24 h. After completion, water (10 mL) was added to the reaction system, and the mixture was extract with CH_2Cl_2 (10 mL × 3). The organic phases were combined, dried over by Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether : ethyl acetate = 5:1~4:1 as eluent) to give **3** as white solid.

*N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide (**3a**)*. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 102.4 mg, 98% yield; m.p.: 225.1-226.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.75-7.73 (m, 3H), 7.52-7.38 (m, 6H), 7.27-7.18 (m, 3H), 7.14-7.07 (m, 4H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.42 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 165.9, 152.6, 145.5, 134.6, 134.3, 134.0, 133.6, 132.1, 131.0, 129.5 (2C), 129.0, 128.9

(2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.1 (2C), 58.7, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{25}N_3NaO_4S$: 546.1458; found: 546.1454.

N-(2-(methylsulfonyl)-3-oxo-4,6-diphenyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3b)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 75.0 mg, 84% yield; m.p.: 189.0-191.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.80-7.77 (m, 2H), 7.56-7.42 (m, 9H), 7.34-7.32 (m, 3H), 4.70 (d, *J* = 17.4 Hz, 1H), 3.79 (d, *J* = 17.5 Hz, 1H), 3.39 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.6, 166.5, 153.1, 134.9, 134.2, 133.5, 132.2, 131.1, 129.6, 129.4 (2C), 128.9 (2C), 128.7 (2C), 127.0 (2C), 126.5 (2C), 126.2 (2C), 59.2, 41.3, 32.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{24}H_{21}N_3NaO_4S$: 470.1145; found: 470.1131.

N-(3-oxo-4,6-diphenyl-2-(phenylsulfonyl)-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3c)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 82.2 mg, 81% yield; m.p.: 221.8-222.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 2H), 7.88 (d, *J* = 6.5 Hz, 2H), 7.75-7.71 (m, 3H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.53-7.38 (m, 8H), 7.22-7.18 (m, 1H), 7.11-7.09 (m, 4H), 4.94 (d, *J* = 17.5 Hz, 1H), 3.47 (d, *J* = 17.4 Hz, 1H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 166.0, 152.8, 136.9, 134.5, 134.2 (2C), 133.5, 132.1, 131.1, 129.1, 128.9 (2C), 128.87 (2C), 128.65 (2C), 128.64 (2C), 127.0 (2C), 126.6 (2C), 126.0 (2C), 58.8, 32.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{29}H_{23}N_3NaO_4S$: 532.1301; found: 532.1319.

N-(3-oxo-4-phenyl-6-(p-tolyl)-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3d)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent);

White solid; 95.0 mg, 88% yield; m.p.: 159.4-161.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83-7.73 (m, 7H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43-7.38 (m, 2H), 7.28-7.17 (m, 5H), 7.14-7.06 (m, 4H), 4.97 (t, *J* = 17.6 Hz, 1H), 3.36 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 166.0, 152.6, 145.4, 141.5, 134.7, 134.0, 133.6, 132.0, 131.5, 129.6 (2C), 129.4 (2C), 128.9, 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.1 (2C), 58.7, 32.1, 21.7, 21.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_4S$: 560.1614; found: 560.1611.

N-(6-(4-methoxyphenyl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3e)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 4:1 as eluent); White solid; 94.0 mg, 85% yield; m.p.: 208.0-209.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.80 (m, 5H), 7.74 (t, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43-7.38 (m, 2H), 7.26-7.18 (m, 3H), 7.14-7.06 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.97 (d, *J* = 17.4 Hz, 1H), 3.87 (s, 3H), 3.33 (d, *J* = 17.5 Hz, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 166.0, 161.9, 152.3, 145.4, 134.7, 134.1, 133.6, 132.2, 129.4 (2C), 128.9, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.3 (2C), 127.0 (2C), 126.7, 126.1 (2C), 114.2 (2C), 58.7, 55.4, 31.9, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_5S$: 576.1564; found: 576.1560.

N-(6-(3-methoxyphenyl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3f)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 4:1 as eluent); White solid; 104.0 mg, 94% yield; m.p.: 179.1-180.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.75-7.72 (m, 3H), 7.52-7.34 (m, 6H), 7.26-7.17 (m, 3H), 7.15-7.08 (m, 4H), 7.02 (dd, *J* = 8.1, 1.7 Hz, 1H), 4.89 (d, *J* = 17.6 Hz, 1H), 3.84 (s, 3H), 3.44 (d, *J* = 17.6 Hz, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 165.9, 159.9, 152.3, 145.4, 135.6, 134.6, 133.9, 133.5, 132.0, 129.8, 129.4 (2C), 129.0, 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.1 (2C), 119.1,

116.8, 111.7, 58.7, 55.4, 32.3, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_5S$: 576.1564; found: 576.1569.

N-(6-(4-fluorophenyl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3g)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 92.0 mg, 85% yield; m.p.: 212.1-213.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.74-7.72 (m, 3H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.43-7.38 (m, 2H), 7.27-7.09 (m, 9H), 4.91 (d, *J* = 17.5 Hz, 1H), 3.42 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 164.3 (d, *J* = 224.3 Hz, 1C), 151.6, 145.5, 134.6, 133.9, 133.5, 132.1, 130.5 (d, *J* = 3.0 Hz, 2C), 129.5 (2C), 129.0, 128.8 (2C), 128.73 (2C), 128.71 (2C), 128.6 (2C), 127.0 (2C), 126.0 (2C), 116.0 (d, *J* = 21.8 Hz, 2C), 58.7, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}FN_3NaO_4S$: 564.1364; found: 564.1370.

N-(6-(4-chlorophenyl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3h)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 104.0 mg, 93% yield; m.p.: 228.3-229.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 4H), 7.74-7.71 (m, 3H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.44-7.38 (m, 4H), 7.27-7.19 (m, 3H), 7.13-7.07 (m, 4H), 4.90 (t, *J* = 17.6 Hz, 1H), 3.42 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.2, 165.7, 151.4, 145.6, 137.2, 134.5, 133.9, 133.5, 132.7, 132.1, 129.5 (2C), 129.1 (2C), 129.0, 128.9 (2C), 128.7 (2C), 128.6 (2C), 127.9 (2C), 127.0 (2C), 126.0 (2C), 58.7, 32.1, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}ClN_3NaO_4S$: 580.1068; found: 580.1054.

N-(3-oxo-4-phenyl-2-tosyl-6-(4-(trifluoromethyl)phenyl)-2,3,4,5-tetrahydropyridazin-4-yl)be

*nzamide (**3i**).* Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 117.0 mg, 99% yield; m.p.: 180.0-181.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.75-7.68 (m, 5H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.43-7.38 (m, 2H), 7.28-7.21 (m, 3H), 7.14-7.07 (m, 4H), 4.91 (d, *J* = 17.6 Hz, 1H), 3.52 (d, *J* = 17.6 Hz, 1H), 2.45 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.3, 165.6, 151.0, 145.7, 137.6, 134.5, 133.9, 133.5, 132.6 (q, *J* = 33.0 Hz, 1C), 132.1, 129.6 (2C), 129.2, 129.0 (2C), 128.8 (2C), 128.7 (2C), 127.0 (2C), 126.9 (2C), 126.0 (2C), 125.9 (q, *J* = 3.8 Hz, 2C), 123.8 (q, *J* = 270.0 Hz, 1C), 58.8, 32.3, 21.7. HRMS (ESI-TOF) m/z: [M + Na]$^{+}$ Calcd. for $C_{31}H_{24}F_3N_3NaO_4S$: 614.1332; found: 614.1333.

*N-(6-(3-nitrophenyl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide (**3j**).* Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 112.4 mg, 99% yield; m.p.: 198.8-199.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 7.3 Hz, 2H), 7.69-7.63 (m, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.44-7.39 (m, 2H), 7.32-7.23 (m, 3H), 7.17-7.09 (m, 4H), 4.84 (d, *J* = 17.6 Hz, 1H), 3.65 (d, *J* = 17.6 Hz, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.3, 165.4, 150.1, 148.6, 145.9, 136.1, 134.4, 133.6, 133.3, 132.2 (2C), 130.0, 129.6 (2C), 129.3, 129.0 (2C), 128.8 (2C), 128.6 (2C), 127.0 (2C), 125.9 (2C), 125.3, 121.2, 58.8, 32.4, 21.7. HRMS (ESI-TOF) m/z: [M + Na]$^{+}$ Calcd. for $C_{30}H_{24}N_4NaO_6S$: 591.1309; found: 591.1315.

*N-(6-(naphthalen-2-yl)-3-oxo-4-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide (**3k**).* Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 104.0 mg, 91% yield; m.p.: 175.9-176.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ

8.34 (s, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.97-7.94 (m, 1H), 7.90-7.84 (m, 5H), 7.77 (d, *J* = 7.1 Hz, 2H), 7.61-7.49 (m, 3H), 7.45-7.40 (m, 2H), 7.28-7.25 (m, 2H), 7.22-7.16 (m, 3H), 7.11-7.06 (m, 2H), 5.21 (d, *J* = 17.6 Hz, 1H), 3.46 (d, *J* = 17.5 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 166.2, 166.0, 152.1, 145.5, 134.5, 134.5, 134.0, 133.6, 132.9, 132.1, 131.6, 129.5 (2C), 129.0, 128.9, 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.8 (2C), 127.7, 127.1, 127.0 (2C), 126.9, 126.1 (2C), 123.2, 58.7, 31.9, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{34}H_{27}N_3NaO_4S$: 596.1614; found: 596.1616.

N-(4-(2-chlorophenyl)-3-oxo-6-phenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3l)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 28.0 mg, 25% yield; m.p.: 214.4-216.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.80-7.75 (m, 4H), 7.53-7.33 (m, 10H), 7.20 (td, *J* = 8.3, 1.3 Hz, 1H), 6.93 (td, *J* = 8.0, 1.1 Hz, 1H), 6.80 (dd, *J* = 7.9, 1.1 Hz, 1H), 4.76 (d, *J* = 17.5 Hz, 1H), 3.84 (d, *J* = 17.5 Hz, 1H), 2.46 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 166.4, 165.8, 153.3, 145.5, 134.3, 134.2, 133.5, 132.6, 132.4, 132.1, 132.0, 130.9, 130.6, 129.6 (2C), 129.2, 129.0 (2C), 128.8 (2C), 128.6 (2C), 127.1 (2C), 126.9, 126.6 (2C), 60.1, 33.3, 21.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}ClN_3NaO_4S$: 580.1068; found: 580.1064.

N-(4-(3-chlorophenyl)-3-oxo-6-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3m)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 92.0 mg, 83% yield; m.p.: 192.0-193.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) 7.93-7.90 (m, 2H), 7.83-7.80 (m, 3H),7.75-7.72 (m, 2H), 7.54-7.40 (m, 6H), 7.29-7.26 (m, 2H), 7.18-7.02 (m, 3H), 6.93 (t, *J* = 1.7 Hz, 1H), 5.03 (d, *J* = 17.6 Hz, 1H), 3.32 (d, *J* = 17.7 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 166.1, 165.4, 152.7, 145.9, 136.3, 134.8, 134.0, 133.5,

133.3, 132.2, 131.2, 129.8, 129.6 (2C),129.2, 129.0 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.4, 124.6, 58.2, 31.8, 21.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}ClN_3NaO_4S$ $[M+Na]^+$: 580.1068; found: 580.1072.

N-(4-(4-chlorophenyl)-3-oxo-6-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3n)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 94.0 mg, 84% yield; m.p.: 215.0-216.0 ^oC. ^1H NMR (300 MHz, $CDCl_3$) 7.92-7.89 (m, 2H), 7.85 (s, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.75-7.72 (m, 2H), 7.54-7.39 (m, 6H), 7.27-7.24 (m, 2H), 7.03-7,04 (m, 4H), 5.00 (d, *J* = 17.7 Hz, 1H), 3.31 (d, *J* = 17.7 Hz, 1H), 2.46 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 166.0, 165.5, 152.2, 145.7, 135.0, 134.0, 133.6, 133.3, 132.9, 132.2, 131.2, 129.5 (2C), 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.6 (2C), 127.6 (2C), 126.9 (2C), 126.6 (2C), 58.0, 31.9, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}ClN_3NaO_4S$: 580.1068; found: 580.1075.

N-(4-(4-fluorophenyl)-3-oxo-6-phenyl-2-tosyl-2,3,4,5-tetrahydro-pyridazin-4-yl)benzamide ***(3o)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 106.0 mg, 98% yield; m.p.: 216.5-217.2 ^oC. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92-7.89 (m, 2H), 7.84-7.81 (m, 3H), 7.75-7.69 (m, 2H), 7.54-7.39 (m, 6H), 7.28-7.26 (m, 2H), 7.13-7.08 (m, 2H), 6.79-6.74 (m, 2H), 5.01 (d, *J* = 17.6 Hz, 1H), 3.32 (d, *J* = 17.7 Hz, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 166.1, 165.8, 162.7 (d, *J* = 248.3 Hz, 1C), 152.4, 145.7, 134.1, 133.8, 133.4, 132.2, 131.2, 130.3 (d, *J* = 3.8 Hz, 1C), 129.5 (2C), 129.0 (2C), 128.70 (2C), 128.68 (2C), 128.2 (d, *J* = 8.3 Hz, 2C), 127.0 (2C), 126.6 (2C), 115.7 (d, *J* = 21.8 Hz, 2C), 58.0, 32.1, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{30}H_{24}FN_3NaO_4S$: 564.1364; found: 564.1363.

N-(3-oxo-6-phenyl-4-(p-tolyl)-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3p)***.

Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 41.0 mg, 38% yield; m.p.: 221.8-222.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.75-7.72 (m, 3H), 7.52-7.38 (m, 6H), 7.27-7.24 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.92 (d, *J* = 17.6 Hz, 1H), 3.41 (d, *J* = 17.6 Hz, 1H), 2.45 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.1, 166.0, 152.5, 145.4, 138.9, 134.3, 134.0, 133.6, 132.0, 131.6, 131.0, 129.5 (2C), 129.4 (2C), 128.8 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.0 (2C), 58.5, 32.2, 21.7, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_4S$: 560.1614; found: 560.1633.

4-Methyl-N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3q)***.

Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 4:1 as eluent); White solid; 95.0 mg, 88% yield; m.p.: 224.3-225.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.72 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.51-7.43 (m, 3H), 7.26-7.19 (m, 5H), 7.13-7.06 (m, 4H), 4.96 (d, *J* = 17.6 Hz, 1H), 3.41 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 166.0, 165.9, 152.6, 145.4, 142.6, 134.7, 134.2, 133.9, 131.0, 130.7, 129.5 (2C), 129.3 (2C), 128.9,128.8 (2C), 128.7 (2C), 128.6 (2C), 127.0 (2C), 126.6 (2C), 126.1 (2C), 58.6, 32.2, 21.7, 21.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_4S$: 560.1614; found: 560.1607.

3-Methyl-N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3r)***.

Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 4:1 as eluent); White solid; 86.0 mg, 80% yield; m.p.: 224.8-226.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.75 (s, 1H), 7.55-7.46 (m, 5H), 7.30-7.18 (m, 5H), 7.11-7.06

(m, 4H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.41 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 166.3, 166.0, 152.6, 145.5, 138.5, 134.6, 134.2, 134.0, 133.5, 132.8, 131.0, 129.5 (2C), 128.9, 128.8 (2C), 128.7 (2C), 128.6 (2C), 128.5, 127.6, 126.6 (2C), 126.1 (2C), 124.0, 58.7, 32.2, 21.7, 21.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{31}H_{27}N_3NaO_4S$: 560.1614; found: 560.1615.

3-Bromo-N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)benzamide ***(3s)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 105.0 mg, 87% yield; m.p.: 225.0-226.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.81 (m, 5H), 7.70 (s, 1H), 7.66-7.60 (m, 2H), 7.52-7.43 (m, 3H), 7.31-7.19 (m, 4H), 7.10-7.09 (m, 4H), 4.91 (d, *J* = 17.5 Hz, 1H), 3.41 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 165.7, 164.6, 152.5, 145.5, 135.5, 135.0, 134.2, 134.1, 133.9, 131.1, 130.2, 130.1, 129.5 (2C), 129.1, 128.90 (2C), 128.80 (2C), 128.7 (2C), 126.6 (2C), 126.1 (2C), 125.5, 122.8, 58.8, 32.0, 21.7. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{24}BrN_3NaO_4S$ 624.0563; found: 624.0573.

N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)-1-naphthamide ***(3t)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 110.0 mg, 96% yield; m.p.: 206.8-207.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15-8.12 (m, 1H), 7.93-7.82 (m, 6H), 7.59 (d, *J* = 7.1 Hz, 1H), 7.53-7.40 (m, 6H), 7.34 (s, 1H), 7.27-7.13 (m, 7H), 4.91 (d, *J* = 17.4 Hz, 1H), 3.74 (d, *J* = 17.5 Hz, 1H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 168.8, 165.5, 152.5, 145.4, 134.7, 134.3, 134.1, 133.6, 133.2, 131.2,131.0, 130.0, 129.5 (2C), 129.2, 129.0 (2C), 128.9 (2C), 128.7 (2C), 128.3, 127.3, 126.6 (2C), 126.5, 126.1 (2C), 125.2, 125.1, 124.5, 59.4, 32.4, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{34}H_{27}N_3NaO_4S$: 596.1614; found: 596.1619.

N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)thiophene-2-carboxamide ***(3u)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 55.0 mg, 52% yield; m.p.: 226.6-227.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.61 (s, 1H), 7.50-7.43 (m, 5H), 7.27-7.16 (m, 3H), 7.10-7.04 (m, 5H), 4.97 (d, *J* = 17.6 Hz, 1H), 3.36 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 165.8, 160.8, 152.5, 145.5, 138.3, 134.4, 134.2, 133.9, 131.1, 130.9, 129.5 (2C), 129.0, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.68, 127.8, 126.6 (2C), 126.1 (2C), 58.7, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{28}H_{23}N_3NaO_4S_2$: 552.1022; found: 552.1043.

N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)thiophene-3-carboxamide ***(3v)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 84.0 mg, 79% yield; m.p.: 224.5-225.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.80 (m, 5H), 7.55 (s, 1H), 7.52-7.42 (m, 3H), 7.35-7.16 (m, 5H), 7.10-7.08 (m, 4H), 4.95 (d, *J* = 17.6 Hz, 1H), 3.38 (d, *J* = 17.6 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 165.9, 161.7, 152.5, 145.5, 136.7, 134.5, 134.2, 133.9, 131.0, 129.5 (2C), 129.1, 129.0, 128.9 (2C), 128.8 (2C), 128.7 (2C), 126.8, 126.6 (2C), 126.1 (2C), 125.9, 58.6, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{28}H_{23}N_3NaO_4S_2$: 552.1022; found: 552.1021.

N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)picolinamide ***(3w)***. Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 101.0 mg, 96% yield; m.p.: 186.5-187.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.54-8.53 (m, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.89-7.85 (m, 4H), 7.80 (td, *J* = 7.7, 1.6 Hz, 1H), 7.49-7.39 (m, 4H), 7.27-7.19 (m, 3H), 7.14-7.07 (m, 4H), 4.76 (d, *J* = 17.4 Hz, 1H), 3.61 (d, *J* = 17.4 Hz, 1H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 165.5, 163.7, 152.4, 149.2, 148.2, 145.3, 137.3, 134.8,

134.4, 134.1, 130.9, 129.4 (2C), 129.0, 128.9 (2C), 128.8 (2C), 128.7 (2C), 126.6 (2C), 126.1 (2C), 121.9, 58.7, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{29}H_{24}N_4NaO_4S$: 547.1410; found: 547.1429.

*N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)propionamide (**3x**).* Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 28.0 mg, 29% yield; m.p.: 200.7-201.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 4H), 7.49-7.41 (m, 3H), 7.26-7.17 (m, 3H), 7.11-7.01 (m, 4H), 6.87 (s, 1H), 4.74 (d, *J* = 17.5 Hz, 1H), 3.37 (d, *J* = 17.5 Hz, 1H), 2.44 (s, 3H), 2.23-2.14 (m, 2H), 1.07 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 173.0, 165.9, 152.6, 145.4, 134.9, 134.3, 134.1, 130.9, 129.4 (2C), 128.9, 128.84 (2C), 128.74 (2C), 128.7 (2C), 126.6 (2C), 126.0 (2C), 58.5, 32.3, 29.8, 21.7, 9.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{26}H_{25}N_3NaO_4S$: 498.1458; found: 498.1468.

*2-Methoxy-N-(3-oxo-4,6-diphenyl-2-tosyl-2,3,4,5-tetrahydropyridazin-4-yl)acetamide (**3y**).* Purified by silica gel column chromatography (petroleum ether : ethyl acetate = 5:1 as eluent); White solid; 36.0 mg, 37% yield; m.p.: 138.7-139.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.81 (m, 5H), 7.45-7.43 (m, 3H), 7.27-7.19 (m, 3H), 7.12-7.02 (m, 4H), 4.63 (d, *J* = 17.3 Hz, 1H), 3.87-3.73 (m, 2H), 3.50 (d, *J* = 17.3 Hz, 1H), 3.38 (s, 3H), 2.44 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 169.0, 165.4, 152.4, 145.4, 134.6, 134.3, 134.1, 130.9, 129.4 (2C), 128.9 (2C), 128.8 (2C), 128.7 (2C), 126.5 (2C), 126.0 (2C), 71.9, 59.2, 58.4, 32.2, 21.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd. for $C_{26}H_{25}N_3NaO_5S$: 514.1407; found: 514.1418.

Scale-up experiments

(a) The reaction of *α*-bromo-*N*-Ts hydrazone **1a** and azlactone **2a**. *α*-bromo-*N*-Ts hydrazone

1a (1.0 g, 2.73 mmol), azlactone **2a** (0.97 g, 4.10 mmol) and anhydrous Na_2CO_3 (289 mg, 2.73 mmol) was added into a dry tube, followed by adding anhydrous toluene (27.3 mL). The atmosphere in tube was replaced by N_2, and reaction was carried out at room temperature under N_2 for 24 h. After completion, the solvent was removed. The residue was suspended in CH_2Cl_2 (50 mL), and kept stirring for 30 mins, then filtered. The filtrate was dried in vacuo by rotary evaporator, the residue was suspended in MeOH (10 mL), and kept stirring at room temperature for 30 mins, then filtered to collect the white solid that was dried in vacuo to give product **3a** (1.22 g, 86% yield) as white solid.

(b) One-pot process of *in situ* azlactone formation from *N*-benzoyl phenylglycine with *α*-bromo-*N*-Ts hydrazone **1a**. *α*-bromo-*N*-Ts hydrazone **1a** (1.0 g, 2.73 mmol), *N*-benzoyl phenylglycine **4a** (0.84 g, 3.28 mmol), DCC (0.84 g, 4.10 mmol) and anhydrous Na_2CO_3 (348 mg, 3.28 mmol) was added into a dry tube, followed by adding anhydrous toluene (27.3 mL). The atmosphere in tube was replaced by N_2, and reaction was carried out at room temperature under N_2 for 24 h. After completion, the solvent was removed. The residue was suspended in CH_2Cl_2 (50 mL), and kept stirring for 30 mins, then filtered. The filtrate was dried in vacuo by rotary evaporator, the residue was suspended in MeOH (10 mL), and kept stirring at room temperature for 30 mins, then filtered to collect the white solid that was dried in vacuo to give product **3a** (1.10 g, 77% yield) as white solid.

Synthesis of compound 5. To a solution of **3a** (52.3 mg, 0.1 mmol) in anhydrous MeOH (2 mL) was added dry KOH (22.4 mg, 0.4 mmol), and the reaction mixture was stirred at room temperature for 30 mins. When reaction completed, the mixture was poured into *aq.* citric acid and extracted with EtOAc. The combined organic layers were dried over by Na_2SO_4 and concentrated

in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 20:1 ~ 3:1) to give **5**.

*Methyl 2-benzamido-2,4-diphenyl-4-(2-tosylhydrazono)butanoate (**5**).* White solid; 54.0 mg, 97% yield; m.p.: 88.1-89.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.66-7.54 (m, 4H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.41-7.29 (m, 10H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 4.40 (d, *J* = 14.7 Hz, 1H), 4.22 (d, *J* = 14.7 Hz, 1H), 3.43 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$) δ 171.9, 167.9, 154.6, 143.0, 138.9, 137.3, 135.0, 133.2, 132.1, 129.7, 128.9 (2C), 128.8 (2C), 128.6 (2C), 128.5, 128.2 (2C), 128.0 (2C), 127.4 (2C), 126.9 (2C), 125.2 (2C), 63.3, 53.7, 35.2, 21.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{30}N_3O_5S$: 556.1901; Found: 556.1895.

Synthesis of compound 6. To a solution of **3a** (52.3 mg, 0.1 mmol) in anhydrous THF (2 mL) was added $NaBH_4$ (7.6 mg, 0.2 mmol), and the reaction mixture was stirred at room temperature for 10 h. When reaction completed, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/ethyl acetate = 10:1 ~ 2:1) to give **6**.

*N-(3-oxo-4,6-diphenyl-2-tosylhexahydropyridazin-4-yl)benzamide (**6**).* White solid; 41.0 mg, 78% yield; m.p.: 165.1-166.7 °C. 1:0.9 dr. ^{1}H NMR (300 MHz, DMSO-d_6) 8.71 (s, 0.9H, minor), δ 8.53 (s, 1H, major), 7.91-7.86 (m, 3.8H, major + minor), 7.76-7.70 (m, 5.70H, major + minor), 7.55-7.53 (m, 1.9H, major + minor), 7.48-7.35 (m, 17.1H, major + minor), 7.28-7.25 (m, 8.5H, major + minor), 7.14-7.12 (m, 1H, major), 6.71 (d, *J* = 6.7 Hz, 1H, major), 6.43 (d, *J* = 6.6 Hz, 0.9H, minor), 4.10 (d, *J* = 18.4 Hz, 0.9H, minor), 3.88 (d, *J* = 17.7 Hz, 1H, major), 3.10-3.03 (m, 1.9H, major + minor), 2.33 (s, 2.7H, minor), 2.30 (s, 3H, major). ^{13}C{^{1}H} (75 MHz, DMSO-d_6) δ (major + minor) 166.4, 165.6, 147.5, 147.0, 143.6, 143.4, 142.4, 141.9, 136.7, 135.7, 135.6, 135.0, 134.6, 131.4, 131.0, 129.7, 129.2, 129.1, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6,

127.4, 127.3, 127.0, 126.9, 125.4, 125.3, 76.7, 75.5, 57.8, 57.7, 29.8, 28.5, 21.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{27}N_3NaO_4S$: 548.1614; Found: 548.1617.

Synthesis of compound 7. To a solution of **3a** (52.3 mg, 0.1 mmol) in $CHCl_3$ (2 mL) was added $TsOH·H_2O$ (114 mg, 0.6 mmol), and the reaction mixture was kept stirring at reflux in oil bath for 24 h. When reaction completed, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether : ethyl acetate = 8:1 as eluent) to give **7**.

4,6-diphenylpyridazin-3(2H)-one (7). White solid; 24.0 mg, 95% yield; m.p.: 183.6-184.1 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 12.09 (s, 1H), 7.92-7.83 (m, 5H), 7.54-7.42 (m, 6H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$) δ 161.1, 146.3, 140.3, 134.9, 133.6, 129.9, 129.5, 129.0 (2C), 128.7 (2C), 128.5 (2C), 127.9, 126.0 (2C). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}N_2O$: 249.1022; Found: 249.1025.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website http://pubs.acs.org.

Copies of ^1H, ^{13}C NMR spectra data for all compounds; single crystal X-ray crystallography data for **3a** (PDF).

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Notes

The authors declare no competing financial interest.

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14. The reaction of **1a** and **4a** did not occur only in the presence of Na_2CO_3 without DCC.

15. CCDC-2012663 (**3a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.