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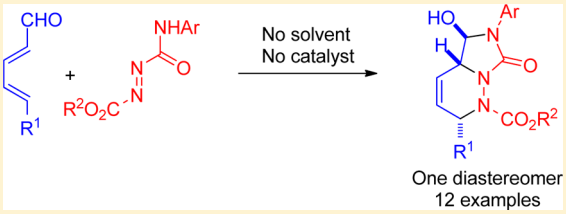
Solvent- and Catalyst-Free Synthesis of Nitrogen-Containing Bicycles through Hemiaminal Formation/Diastereoselective Hetero-Diels–Alder Reaction with Diazenes

Laurence Crouillebois, Loïc Pantaine, Jérôme Marrot, Vincent Coeffard,* Xavier Moreau,* and Christine Greck

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles-St-Quentin-en-Yvelines, 45 Avenue des États-Unis, 78035 Versailles cedex France

Supporting Information

ABSTRACT: A solvent- and catalyst-free synthesis of nitrogen-containing bicyclic derivatives through a three-bond forming process is reported. Starting from dienals and readily available diazenes, the strategy involving the hemiaminal formation/hetero-Diels–Alder reaction affords the bicyclic products in a highly diastereoselective manner. This simple and green procedure has been applied to a selection of substrates, giving rise to 12 examples of nitrogen-containing bicyclic architectures. These products underwent various synthetic transformations. A sequence involving the cleavage of the hydrazine allowed the preparation of a hydantoin motif bearing an aminopropyl side chain, which is a structure found in natural products. A mechanism has also been suggested to explain the observed selectivities.

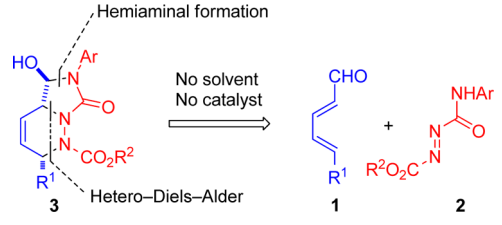


Nitrogen-containing heterocycles are found in a myriad of natural products, marketed drugs, and functionalized materials. The quest for new synthetic methodologies toward sp^3-rich nitrogen-containing heterocycles stands as a formidable challenge facing the chemist community in light of the importance of these structures in drug discovery programs.[1] Besides the general parameters describing a chemical reaction (e.g., yield, selectivity, cost), the rise of industrial and academic awareness about environmental issues has prompted the scientific community to design more sustainable synthetic routes.[2] In a chemical reaction, the solvent is potentially the major source of waste, and therefore, replacing toxic solvent is a crucial point in designing environmentally improved routes toward functionalized heterocycles. From an economic and chemical standpoint, the implementation of methodologies in a solvent-free environment represents an appealing strategy to address waste issues.[3] Within this framework, solvent- and catalyst-free synthetic processes have recently gained widespread currency owing to the advantages offered by these strategies: (i) minimization of waste, (ii) operational simplicity, and (iii) reduced cost.[4] In addition to these advantages, striking examples have shown that some reactions proceeded in higher yields under solvent- and catalyst-free conditions. For instance, the group of Yus reported a regioselective hydrophosphanation of alkenes that proceeded in high yields in the absence of solvent and catalyst, whereas low conversions were observed under solvent conditions.[5] Similarly, Ranu et al. described the synthesis of dihydropyrimidinones without any solvent or catalyst.[6] A dramatic decrease in reactivity was noticed by performing the reaction in various solvents. The group of Zou and Zhang achieved the synthesis of α-amino phosphonates through a microwave-assisted solvent- and catalyst-free Kabachnik–Fields reaction.[7] Under similar reaction conditions, the addition of solvents prevented the formation of the desired target, whereas high yields were obtained under solvent-free conditions.

As part of a program devoted to the preparation of nitrogen-containing heterocycles,[8] we anticipated that the reaction of dienals **1** with azo compounds **2** could afford the heterocyclic derivatives **3** through a synthetic sequence combining hemiaminal formation and diastereoselective hetero-Diels–Alder reaction (Scheme 1).[9,10]

Hetero-Diels–Alder reactions with diazene compounds have received much attention,[9] in particular for the implementation of asymmetric transformations.[11] Despite such achievements, the pursuit of synthetic chemistry toward new heterocyclic architectures continues to grow in parallel to the demand for greener and more sustainable methodologies. To the best of

Scheme 1. Solvent- and Catalyst-Free Synthetic Strategy



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our knowledge, hetero-Diels–Alder reactions with diazene compounds as dienophiles in the absence of solvent and catalyst have never been reported. Therefore, the preparation of nitrogen-containing heterocycles **3** under solvent- and catalyst-free conditions was deemed worthy of investigation given the salient features of the heterocyclic architecture. For example, the cleavage of the hydrazine bond could afford interesting hydantoin precursors toward biorelevant compounds[12] and natural products such as the family of agesamide,[13] parazoanthine,[14] and midpacamide[15] (Figure 1).

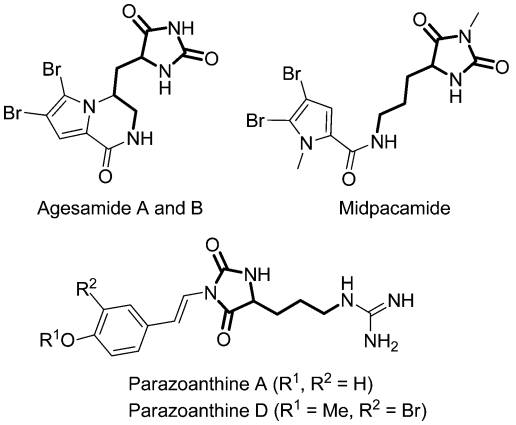


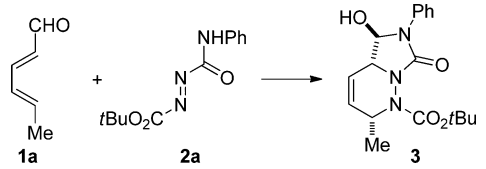
Figure 1. Selected examples of hydantoin natural products.

At the outset of the studies, we carried out a reactivity screen across a series of experiments using 2,4-hexadienal **1a** and the readily available azo compounds **2a** as starting materials (Table 1).[11c,16]

The reaction of dienal **1a** (3 equiv) with **2a** (1 equiv) at 0 °C for 16 h under neat conditions did not produce the desired product, while increasing the reaction time to 64 h allowed the isolation of **3** in 27% yield as the only regio- and diastereomer (entries 1 and 2).[17] A further screening of the temperature was performed, and the best results were obtained by running the reaction at 50 °C (entries 3–5). NMR studies showed that higher temperatures lead to a faster decomposing of the azo reagent **2a** into byproducts. Although accelerated by additional heat, the aforementioned reagent degradation does still occur over time and could explain the moderate yields obtained. The product **3** was obtained in a 29% yield by heating the mixture for 1 h at 100 °C under microwave irradiation, while performing the reaction at 100 °C for 16 h under conventional heating led to similar results (entries 5 and 6). To study the influence of the ratio of **1a**/**2a** on the reaction outcome, 1 equiv of dienal **1a** was reacted with 2 equiv of azo compound **2a** for 16 h at room temperature. Under these conditions, a lower yield of 23% of **3** was obtained compared to the results with a **1a**/**2a** ratio of 3/1 (entries 3 and 7). By increasing the temperature and optimizing the reaction time, there was a substantial increase in yield and **3** was produced in 60% yield after 2 h of reaction at 65 °C (entries 8–10). A lower excess of dienal **2a** (1.2 equiv) led to a decrease in yield (entry 11). In order to study the influence of the solvent-free conditions, we screened the substrates **1a** and **2a** across a series of four solvents (toluene, DMF, $CHCl_3$, and MeCN). The data collected from these results showed the dramatic impact of the solvent on the reaction (entries 12–15). The compound **3** was obtained in low-to-moderate yields under solvent conditions (<29% yield), while the reaction proceeded efficiently by stirring the neat starting materials for 2 h at 65 °C (60% yield, entry 10).

With the optimized conditions in hand, we sought to investigate the reaction scope by exploring diverse dienals **1** and azo compounds **2** (Table 2).

Table 1. Optimization of Reaction Conditions[a]



entry	**1a** (equiv)	**2a** (equiv)	solvent	conditions	yield **3** (%)[b]
1	3	1	none	16 h, 0 °C	n.r.[c]
2	3	1	none	64 h, 0 °C	27
3	3	1	none	16 h, rt	41
4	3	1	none	16 h, 50 °C	50
5	3	1	none	16 h, 100 °C	27
6	3	1	none	1 h, MW, 100 °C	29
7	1	2	none	16 h, rt	23
8	1	2	none	16 h, 50 °C	46
9	1	2	none	1 h 65 °C	45
10	1	2	none	2 h, 65 °C	60
11	1	1.2	none	2 h, 65 °C	36
12	1	2	toluene	2 h, 65 °C	29
13	1	2	DMF	2 h, 65 °C	<10
14	1	2	$CHCl_3$	2 h, 65 °C	28
15	1	2	MeCN	2 h, 65 °C	16

[a]For entries 1–6: dienal **1a** (1.2 mmol) and azo compound **2a** (0.4 mmol); for entries 7–10: dienal **1a** (0.4 mmol) and azo compound **2a** (0.8 mmol); for entry 11: dienal **1a** (0.4 mmol) and azo compound **2a** (0.48 mmol); for entries 12–15: dienal **1a** (0.4 mmol), azo compound **2a** (0.8 mmol) in solvent (0.8 mL). [b]Isolated yields and only one diastereomer was detected by ^{1}H NMR of the crude. [c]No reaction.

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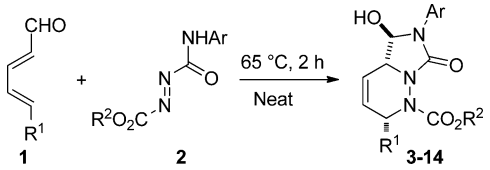
Table 2. Substrate Scope[a]



entry	R^1	R^2	Ar	bicyclic product	yield (%)[b]
1	Me	*t*Bu	Ph	**3**	60
2	Et	*t*Bu	Ph	**4**	38
3	Pr	*t*Bu	Ph	**5**	40
4	Pent	*t*Bu	Ph	**6**	<10
5	Me	Bn	Ph	**7**	67
6	Et	Bn	Ph	**8**	56
7	Pr	Bn	Ph	**9**	52
8	Pent	Bn	Ph	**10**	44
9	Ph	Bn	Ph	**11**	33
10	Me	Bn	4-ClC_6H_4	**12**	38
11	Me	Bn	4-FC_6H_4	**13**	46
12	Me	Bn	4-$MeOC_6H_4$	**14**	47

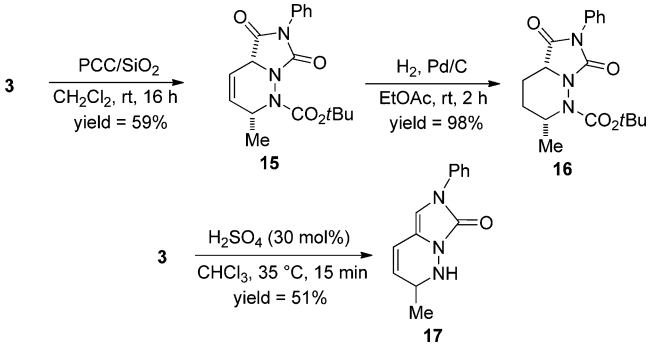
[a]**1** (0.4 mmol) and azo compound **2** (0.8 mmol) were stirred for 2 h at 65 °C. [b]Isolated yields and only one diastereomer was detected by ^1H NMR of the crude.

Regardless of the substrates, the bicyclic derivatives were obtained as a single regio- and diastereomer after 2 h at 65 °C. The influence of the chain length (R^1) of the dienal was investigated in the *tert*-butoxycarbonyl series, and the experimental data showed an alteration of the yields by increasing the alkyl chain length. For instance, the pentyl derivative **6** was obtained in less than 10% yield, while the methyl analogue **3** was produced in 60% yield (entries 1 and 4). By starting from the azo compound **2b** bearing a carboxybenzyl group, a similar tendency was noticed even if higher yields for **7**−**10** (44−67%, entries 5−8) were obtained compared to **3**−**6** (<10−60%, entries 1−4). The reaction of 5-phenylpent-2,4-dienal with the azo compound **2b** bearing a carboxybenzyl group gave rise to **11** in 33% yield (entry 9). The influence of the aromatic substituent borne by **2** was studied, and the results showed a slight influence on the reaction outcome. Compounds **12**−**14** were synthesized in yields ranging from 38% to 47% yields (entries 10−12).

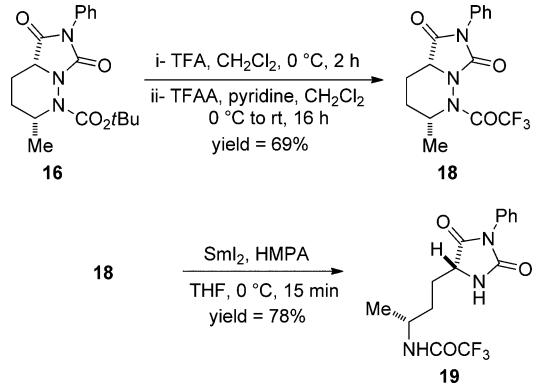
The bicyclic structures **3**−**14** formed by our solvent- and catalyst-free strategy should hold great promise in organic synthesis. To illustrate this point, the bicyclic compound **3** was transformed into the corresponding hydantoin **15** in 59% yield by oxidation with pyridinium chlorochromate immobilized onto silica gel to facilitate the removal of chromium byproducts (Scheme 2).[18] The compound **15** underwent a selective reduction of the double bond in the presence of Pd/C to afford the compound **16** in 98% yield. The reaction of **3** with a catalytic amount of sulfuric acid gave rise to **17** in 51% yield through both cleavage of the carbamate and dehydration.

The cleavage of the hydrazine was deemed particularly worthy of investigation in order to form natural product motifs (Figure 1). The sequence started with the cleavage of the carbamate in the presence of trifluoroacetic acid, followed by acylation of the hydrazine (Scheme 3). Under these conditions, the desired product **18** was isolated in 69% yield over two steps. The hydrazine bond cleavage was performed with a mixture of SmI_2 and HMPA in THF, and under these conditions, the hydantoin **19** was isolated in 78% yield.

Scheme 2. Synthetic Applications of 3

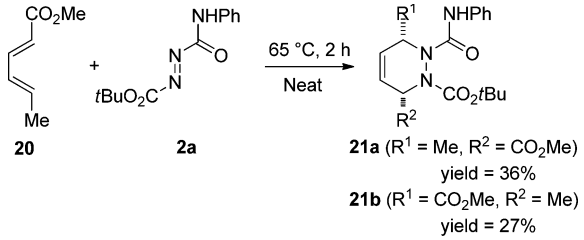


Scheme 3. Hydrazine Bond Cleavage



Regarding the mechanism of the transformation, it is suggested that the first step is the formation of the hemiaminal, followed by a diastereoselective intramolecular hetero-Diels−Alder reaction. To lend further credence to this hypothesis, the ester **20** was prepared and engaged in the reaction with **2a** (Scheme 4).

Scheme 4. Control Experiment



Under solvent- and catalyst-free conditions, a mixture of two regioisomers **21a**/**21b** was obtained in 63% yield, while only one regioisomer was obtained starting from the dienals **1**. These results indicate that the formation of the hemiaminal is the first reaction occurring in the synthesis of bicyclic compounds **3**−**14**. Based on literature data and the above results, a plausible mechanism is depicted in Scheme 5.[19,20]

The dienal **1** would react with the azo compound **2** to give the corresponding hemiaminal **A**. The diastereoselectivity of the intramolecular Diels−Alder reaction would be dictated by allylic 1,3-strain.[19] The hemiaminal **A** would adopt a conformation such that the hydrogen of C(1) is eclipsed with the hydrogen of C(3) in order to minimize the allylic 1,3-strain.[20] From the intermediate **A**, the intramolecular hetero-

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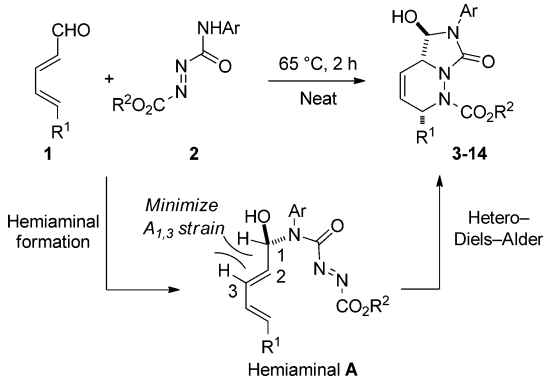
Scheme 5. Proposed Reaction Mechanism



Diels–Alder reaction would lead to the bicyclic system in a highly diastereoselective manner.

In summary, we have reported a novel solvent- and catalyst-free transformation toward nitrogen-containing bicyclic systems. The strategy is based on the combination of hemiaminal formation and diastereoselective hetero-Diels–Alder reaction to create three carbon–nitrogen bonds in one process. The high diastereoselectivity is thought to originate from minimization of allylic 1,3-strain in the hemiaminal structure. The salient features lie in a highly regio- and diastereoselective process without any additive and the operational simplicity of the protocol. This new methodology was harnessed to achieve various synthetic transformations, such as hydrazine cleavage, which produced natural product motifs.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (200 or 300 MHz) and ^{13}C (50 or 75 MHz) spectra were recorded with 200 or 300 MHz spectrometers in chloroform-*d* with the residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million, and coupling constants are given as absolute values expressed in hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument. Samples (solubilized in ACN at 1 mg/mL and then diluted by 1000) were introduced into the MS via an UHPLC system while a Leucine Enkephalin solution was coinjected via a micro pump. Infrared spectra were recorded with an FT spectrometer. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040–0.060 mm). Solvents were dried immediately before use by distillation from standard drying agents. Dienals **1** are commercially available or were prepared according to the literature procedure.[21]

General Procedure to Prepare Azo Compounds 2a–e through a Two-Step Sequence.[11c,16] To a solution of *tert*-butyl or benzyl carbazate (4 mmol) in toluene (0.5 M) was added the corresponding isocyanate (4.8 mmol). The mixture was stirred at 80 °C for 4 h and then filtered. The crude residue was directly diluted in dichloromethane (0.33 M), and pyridine (647 μL, 8 mmol) was added dropwise. Finally, NBS (712 mg, 4 mmol) was slowly added at room temperature and the mixture was stirred for 1 h. The reaction mixture was washed with 1 N HCl, a saturated solution of $Na_2S_2O_3$, and a saturated solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to dryness. The azo derivatives **2a–e** were used for the next sequence without further purification.

*tert-Butyl (E)-(Phenylcarbamoyl)diazenecarboxylate (**2a**).* According to the general procedure, 4 mmol of *tert*-butyl carbazate (529 mg) and 4.8 mmol of phenyl isocyanate (572 mg) afforded the azo compound **2a** (808 mg) as an orange solid in 81% yield over the two steps. mp 82–84 °C (Lit. 89 °C);[22] ^{1}H NMR (300 MHz, DMSO-d6) δ 1.61 ppm (s, 9H), 7.21 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.74 (d, J = 7.5 Hz, 2H), 11.56 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d6) δ 27.4 ppm (3C), 87.2, 119.7 (2C), 125.2, 129.2 (2C), 137.3, 157.0, 160.4; HRMS (ESI) Calcd for $C_{12}H_{15}N_3O_3Na$ [M + Na]$^+$: 272.1011, Found: 272.1015.

*Benzyl (E)-(Phenylcarbamoyl)diazenecarboxylate (**2b**).* According to the general procedure, 4 mmol of benzyl carbazate (665 mg) and 4.8 mmol of phenyl isocyanate (572 mg) afforded the azo compound **2b** (850 mg) as an orange solid in 75% yield over the two steps. mp 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 ppm (s, 2H), 7.22–7.27 (m, 1H), 7.36–7.47 (m, 7H), 7.66 (d, J = 7.8 Hz, 2H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.9 ppm, 119.8 (2C), 126.2, 129.0 (4C), 129.4, 129.6 (2C), 133.7, 136.0, 154.9, 161.6; HRMS (ESI) Calcd for $C_{15}H_{14}N_3O_3$ [M + H]$^+$: 284.1047, Found: 284.1035.

*Benzyl (E)-(4-Chlorophenylcarbamoyl)diazenecarboxylate (**2c**).* According to the general procedure, 4 mmol of benzyl carbazate (665 mg) and 4.8 mmol of 4-chlorophenyl isocyanate (737 mg) afforded the azo compound **2c** (1.070 g) as an orange solid in 84% yield over the two steps. mp 112–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 ppm (s, 2H), 7.37–7.46 (m, 7H), 7.60–7.64 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.0 ppm, 121.0 (2C), 129.0 (4C), 129.5, 129.7 (2C), 131.5, 133.7, 134.5, 154.8, 161.4; HRMS (ESI) Calcd for $C_{15}H_{12}ClN_3O_3Na$ [M + Na]$^+$: 340.0465, Found: 340.0455.

*Benzyl (E)-(4-Fluorophenylcarbamoyl)diazenecarboxylate (**2d**).* According to the general procedure, 4 mmol of benzyl carbazate (665 mg) and 4.8 mmol of 4-fluorophenyl isocyanate (658 mg) afforded the azo compound **2d** (964 mg) as a yellow solid in 80% yield over the two steps. mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 ppm (s, 2H), 7.09–7.15 (m, 2H), 7.40–7.47 (m, 5H), 7.63–7.67 (m, 2H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.8 ppm, 116.5 (d, $J_{C\text{-}F}$ = 22.8 Hz, 2C), 121.6 (d, $J_{C\text{-}F}$ = 8.2 Hz, 2C), 129.0 (4C), 129.4, 132.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 133.7, 155.0, 160.6 (d, $J_{C\text{-}F}$ = 244.8 Hz), 161.5; HRMS (ESI) Calcd for $C_{15}H_{12}FN_3O_3Na$ [M + Na]$^+$: 324.0760, Found: 324.0757.

*Benzyl (E)-(4-Methoxyphenylcarbamoyl)diazenecarboxylate (**2e**).* According to the general procedure, 4 mmol of benzyl carbazate (665 mg) and 4.8 mmol of 4-methoxyphenyl isocyanate (716 mg) afforded the azo compound **2e** (1.35 g) as a deep red oil in 90% yield over the two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 ppm (s, 3H), 5.43 (s, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.38–7.43 (m, 5H), 7.59 (d, J = 8.8 Hz, 2H), 8.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6 ppm, 70.8, 114.6 (2C), 121.4 (2C), 128.9 (4C), 129.2, 129.3, 133.8, 155.1, 157.7, 161.7; HRMS (ESI) Calcd for $C_{16}H_{16}N_3O_4$ [M + H]$^+$: 314.1141, Found: 314.1138.

General Procedure to Prepare the Bicyclic Derivatives 3–14. To the azo derivative **2** (0.8 mmol) was added the dienal **1** (0.4 mmol), and the mixture was stirred at 65 °C for 2 h. The crude product was directly purified by flash chromatography (eluent pentane/ethyl acetate) to afford the expected bicyclic compounds **3–14**.

*tert-Butyl 5-Hydroxy-2-methyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**3**).* According to the general procedure, 0.8 mmol of **2a** (200 mg) and 0.4 mmol of (2*E*,4*E*)-hexa-2,4-dienal (38 mg) afforded the bicyclic compound **3** (83 mg) as an oil in 60% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 ppm (d, J = 8.0 Hz, 3H), 1.52 (s, 9H), 4.06 (br d, J = 4.0 Hz, 1H), 4.47 (br s, 1H), 5.28 (br s, 1H), 5.72–5.85 (m, 2H), 7.10 (t, J = 8.0 Hz, 1H), 7.26–7.34 (m, 2H), 7.62–7.68 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1 ppm, 28.4 (3C), 51.4, 58.8, 81.6, 82.5, 120.5 (2C), 123.0, 124.5, 129.0 (2C), 131.7, 138.0, 155.2, 156.5; FTIR (neat) cm^{-1} 3327, 2978, 2931, 1695; HRMS (ESI) Calcd for $C_{18}H_{23}N_3O_4Na$ [M + Na]$^+$: 368.1586, Found: 368.1582.

*tert-Butyl 5-Hydroxy-2-ethyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**4**).* According to the general procedure, 0.8 mmol of **2a** (200 mg) and 0.4 mmol of (2*E*,4*E*)-hepta-2,4-dienal (44 mg) afforded the bicyclic compound **4** (55 mg) as an oil in 38% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 ppm (br t, J = 8.0 Hz, 3H), 1.47–1.61 (m, 1H), 1.53 (s, 9H), 1.68–1.78 (m, 1H), 2.68 (s, 1H), 4.15 (s, 1H), 4.33 (br s, 1H), 5.34 (br s, 1H), 5.80–5.94 (m, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.2 Hz,

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2H), 7.67 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3 ppm, 28.3 (3C), 30.4, 57.0, 58.7, 81.8, 82.8, 120.8 (2C), 122.9, 124.6, 129.0 (2C), 130.4, 137.9, 155.9, 156.4; FTIR (neat) cm^{-1} 3342, 2960, 2932, 1695; HRMS (ESI) Calcd for $C_{19}H_{25}N_3O_4Na$ $[M + Na]^+$: 382.1743, Found: 382.1748.

*tert-Butyl 5-Hydroxy-2-propyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**5**).* According to the general procedure, 0.8 mmol of **2a** (200 mg) and 0.4 mmol of (2*E*,4*E*)-octa-2,4-dienal (50 mg) afforded the bicyclic compound **5** (60 mg) as an oil in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 ppm (br t, J = 7.2 Hz, 3H), 1.44−1.73 (m, 13H), 3.02 (s, 1H), 4.08 (s, 1H), 4.38 (br s, 1H), 5.29 (br s, 1H), 5.50−5.89 (m, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 ppm, 19.6, 28.3 (3C), 37.0, 55.2, 58.6, 81.7, 82.7, 120.6 (2C), 122.8, 124.5, 128.9 (2C), 130.3, 137.9, 156.7, 156.3; FTIR (neat) cm^{-1} 3308, 2961, 1698; HRMS (ESI) Calcd for $C_{20}H_{27}N_3O_4Na$ $[M + Na]^+$: 396.1899, Found: 396.1903.

*Benzyl 5-Hydroxy-2-methyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**7**).* According to the general procedure, 0.8 mmol of **2b** (227 mg) and 0.4 mmol of (2*E*,4*E*)-hexa-2,4-dienal (38 mg) afforded the bicyclic compound **7** (102 mg) as an oil in 67% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 ppm (d, J = 6.8 Hz, 3H), 2.84 (s, 1H), 4.10 (br s, 1H), 4.50−4.64 (m, 1H), 5.20 (s, 2H), 5.30 (br s, 1H) 5.72−5.86 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.28−7.31 (m, 2H), 7.36 (br s, 5H), 7.62 (d, J = 8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3 ppm, 51.4, 58.9, 68.6, 81.9, 120.8 (2C), 123.0, 124.8, 128.2 (3C), 128.7 (2C), 129.1 (2C), 131.2, 135.8, 137.8, 156.0, 156.6; FTIR (neat) cm^{-1} 3354, 3032, 2931, 1700; HRMS (ESI) Calcd for $C_{21}H_{22}N_3O_4$ $[M + H]^+$: 380.1610, Found: 380.1602.

*Benzyl 5-Hydroxy-2-ethyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**8**).* According to the general procedure, 0.8 mmol of **2b** (227 mg) and 0.4 mmol of (2*E*,4*E*)-hepta-2,4-dienal (44 mg) afforded the bicyclic compound **8** (88 mg) as an oil in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 ppm (br t, J = 8.0 Hz, 3H), 1.50−1.64 (m, 1H), 1.67−1.82 (m, 1H), 2.87 (br s, 1H), 4.10 (br s, 1H) ; 4.34−4.50 (m, 1H), 5.19 (s, 2H), 5.24−5.38 (m, 1H), 5.76−5.88 (m, 2H), 7.12 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.2 Hz, 2H), 7.36 (br s, 5H), 7.61 (br d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1 ppm, 28.3, 57.0, 58.8, 68.8, 81.9, 121.0 (2C), 122.9, 124.9, 128.3 (2C), 128.5, 128.7 (2C), 129.1 (2C), 129.9, 135.5, 137.7, 156.4, 157.0; FTIR (neat) cm^{-1} 3362, 3064, 3031, 2917, 1705; HRMS (ESI) Calcd for $C_{22}H_{24}N_3O_4$ $[M + H]^+$: 394.1767, Found: 394.1765.

*Benzyl 5-Hydroxy-2-propyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**9**).* According to the general procedure, 0.8 mmol of **2b** (227 mg) and 0.4 mmol of (2*E*,4*E*)-octa-2,4-dienal (50 mg) afforded the bicyclic compound **8** (85 mg) as an oil in 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 ppm (br s, 3H), 1.45−1.58 (m, 3H), 1.69−1.80 (m, 1H), 2.70 (s, 1H), 4.10−4.17 (m, 1H), 4.42−4.60 (m, 1H), 5.20 (s, 2H), 5.27−5.42 (m, 1H), 5.70−5.90 (m, 2H), 7.14 (t, J = 7.2 Hz, 1H), 7.33 (t, J = 7.2 Hz, 2H), 7.37 (br s, 5H), 7.63 (br d, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 ppm, 19.6, 37.1, 55.3, 58.8, 68.9, 81.9, 120.9 (2C), 122.9, 124.9, 128.5 (2C), 128.7 (2C), 128.9, 129.1 (2C), 130.1, 135.4, 137.8, 156.3, 156.9.7.0; FTIR (neat) cm^{-1} 3245, 3015, 2961, 1733, 1700; HRMS (ESI) Calcd for $C_{23}H_{26}N_3O_4$ $[M + H]^+$: 408.1923, Found: 408.1929.

*Benzyl 5-Hydroxy-2-pentyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**10**).* According to the general procedure, 0.8 mmol of **2b** (227 mg) and 0.4 mmol of (2*E*,4*E*)-deca-2,4-dienal (61 mg) afforded the bicyclic compound **10** (77 mg) as an oil in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 ppm (br s, 3H), 1.26−1.53 (m, 7H), 1.71−1.80 (m, 1H), 2.67 (br s, 1H), 4.11 (s, 1H), 4.40−4.56 (m, 1H), 5.14−5.20 (m, 2H), 5.30−5.36 (m, 1H), 5.74−5.78 (m, 1H), 5.87 (br s, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.29−7.36 (m, 7H), 7.63 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 ppm, 22.6, 26.2, 31.6, 35.0, 55.6, 58.9, 68.9, 82.0, 120.9 (2C), 122.8, 124.8, 128.4, 128.6 (2C), 128.7 (2C), 129.1 (2C), 130.1, 135.5, 137.8, 156.3, 157.0; FTIR (neat) cm^{-1} 3014, 2956, 1700; HRMS (ESI) Calcd for $C_{25}H_{30}N_3O_4$ $[M + H]^+$: 436.2236, Found: 436.2233.

*Benzyl 5-Hydroxy-2-phenyl-7-oxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**11**).* According to the general procedure, 0.8 mmol of **2b** (227 mg) and 0.4 mmol of (2*E*,4*E*)-5-phenylpenta-2,4-dienal (63 mg) afforded the bicyclic compound **11** (58 mg) as an oil in 33% yield. Mixture of rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 1H), 4.24 ppm (br s, 1H), 5.22 (s, 2H), 5.35−5.40 (m, 1H), 5.57−5.81 (m, 1H), 6.04 (br s, 2H), 7.09−7.17 (m, 1H), 7.31−7.36 (m, 12H), 7.55 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.2 ppm, 57.5, 58.9, 68.2, 69.2, 82.0, 120.7120.7, 124.4, 124.7, 127.9, 128.5, 128.7, 129.0, 135.3, 136.1, 137.9, 155.1, 156.4; FTIR (neat) cm^{-1} 3354, 3031, 2958, 1701; HRMS (ESI) Calcd for $C_{26}H_{24}N_3O_4$ $[M + H]^+$: 442.1767, Found: 442.1767.

*Benzyl 5-Hydroxy-2-(4-chlorophenyl)-7-oxo-6-methyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**12**).* According to the general procedure, 0.8 mmol of **2c** (254 mg) and 0.4 mmol of (2*E*,4*E*)-hexa-2,4-dienal (38 mg) afforded the bicyclic compound **12** (63 mg) as an oil in 38% yield. Mixture of rotamers ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 ppm (d, J = 6.9 Hz, 3H), 2.76 (s, 1H), 4.10 (s, 1H), 4.51−4.66 (m, 1H), 5.20 (bs, 3H), 5.78−5.87 (m, 2H), 7.24−7.36 (m, 7H), 7.57 (br d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 ppm, 20.4, 50.5, 51.4, 58.9, 68.0, 68.8, 81.7, 121.8, 122.9, 127.9, 128.2, 128.7, 129.1, 130.1, 131.4, 132.1, 135.5, 136.4, 155.4, 156.4; FTIR (neat) cm^{-1} 3307, 3016, 2958, 1700; HRMS (ESI) Calcd for $C_{21}H_{21}ClN_3O_4$ $[M + H]^+$: 414.1221, Found: 414.1217.

*Benzyl 5-Hydroxy-2-(4-fluorophenyl)-7-oxo-6-methyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**13**).* According to the general procedure, 0.8 mmol of **2d** (241 mg) and 0.4 mmol of (2*E*,4*E*)-hexa-2,4-dienal (38 mg) afforded the bicyclic compound **13** (73 mg) as an oil in 46% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.37 ppm (d, J = 7.0 Hz, 3H), 2.65 (s, 1H), 4.13 (s, 1H), 4.52−4.67 (m, 1H), 5.17−5.26 (m, 3H), 5.76−5.94 (m, 2H), 7.00 (t, J = 8.4 Hz, 2H), 7.37 (br s, 5H), 7.56 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 ppm, 51.4, 59.1, 68.7, 82.3, 115.8 (d, J = 21.8 Hz, 2C), 122.7, 123.1 (d, J = 8.2 Hz, 2C), 128.1 (2C), 128.6, 128.7 (2C), 131.3, 133.7, 135.6, 156.3, 156.7, 160.0 (d, J = 242.2 Hz); FTIR (neat) cm^{-1} 3318, 2975, 1700; HRMS (ESI) Calcd for $C_{21}H_{21}FN_3O_4$ $[M + H]^+$: 398.1516, Found: 398.1511.

*Benzyl 5-Hydroxy-2-(4methoxyphenyl)-7-oxo-6-methyl-4a,5,6,7-tetrahydroimidazo[1,5-b]pyridazine-1(2H)-carboxylate (**14**).* According to the general procedure, 0.8 mmol of **2e** (251 mg) and 0.4 mmol of (2*E*,4*E*)-hexa-2,4-dienal (38 mg) afforded the bicyclic compound **14** (77 mg) as an oil in 47% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 ppm (d, J = 7.0 Hz, 3H), 2.99, (s, 1H), 3.73 (s, 3H), 4.10 (s, 1H), 4.50−4.64 (m, 1H), 5.18−5.23 (m, 3H), 5.73−5.82 (m, 2H), 6.82 (d, J = 8.9 Hz, 2H), 7.35 (br s, 5H), 7.44 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1 ppm, 51.1, 55.43, 58.9, 68.5, 82.3, 114.2 (2C), 122.9, 123.6 (2C), 128.0 (3C), 128.6 (2C), 130.4, 131.1, 135.7, 156.2, 156.9, 157.1; FTIR (neat) cm^{-1} 3336, 2959, 1701; HRMS (ESI) Calcd for $C_{22}H_{24}N_3O_5$ $[M + H]^+$: 410.1716, Found: 410.1722.

***tert*-Butyl 2-Methyl-5,7-dioxo-6-phenyl-4a,5,6,7-tetrahydroimidazo[1,5-*b*]pyridazine-1(2*H*)-carboxylate (15).** To a suspension of pyridinium chlorochromate (230 mg, 1.09 mmol) and silica gel (230 mg) in CH_2Cl_2 (6.5 mL) was added a solution of **3** (290 mg, 0.84 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred for 16 h at room temperature and filtered through a pad of Celite and silica gel. The solvent was evaporated to dryness, and the crude was purified by flash chromatography (pentane/EtOAc 3/1) to afford **15** as an oil (170 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 ppm (d, J = 6.8 Hz, 3H), 1.51 (s, 9H), 4.70−4.74 (m, 2H), 5.93−6.03 (m, 2H), 7.35−7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 ppm, 28.3 (3C), 51.3, 56.4, 82.6, 118.8, 125.9 (2C), 128.5, 129.2 (2C), 131.1, 132.4, 153.7, 155.4, 167.5; FTIR (neat) cm^{-1} 2974, 1793, 1729; HRMS (ESI) Calcd for $C_{18}H_{21}N_3O_4Na$ $[M + Na]^+$: 366.1430, Found: 366.1432.

***tert*-Butyl 2-Methyl-5,7-dioxo-6-phenylhexahydroimidazo-[1,5-*b*]pyridazine-1(2*H*)-carboxylate (16).** To a solution of **15** (150 mg, 0.44 mmol) in EtOAc (4.4 mL) was added Pd/C (15 mg).

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The reaction mixture was stirred for 2 h at room temperature under a hydrogen atmosphere and filtered through a pad of Celite. The solvent was evaporated to dryness to afford **16** as an oil (149 mg, 98%) without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 ppm (d, J = 6.9 Hz, 3H), 1.49 (s, 9H), 1.55−1.63 (m, 1H), 1.81−2.17 (m, 3H), 4.07−4.12 (m, 1H), 4.47 (br s, 1H), 7.33−7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 ppm, 21.5, 26.6, 28.2 (3C), 50.1, 55.4, 82.6, 126.1 (2C), 128.3, 129.1 (2C), 131.3, 153.9, 154.3, 170.3; FTIR (neat) cm^{-1} 2974, 2933, 1789, 1726; HRMS (ESI) Calcd for $C_{18}H_{23}N_3O_4Na$ [M + Na]$^+$: 368.1586, Found: 368.1588.

2-Methyl-6-phenyl-2,6-dihydroimidazo[1,5-*b*]pyridazin-7(1*H*)-one (17). To a solution of **3** (21 mg, 0.06 mmol) in $CHCl_3$ (0.6 mL) was added H_2SO_4 (1 μL, 0.02 mmol). The reaction mixture was stirred for 15 min at 35 °C, and the solvent was evaporated to dryness. The crude product was purified by preparative chromatography (EtOAc) to afford **17** as an oil (7 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 ppm (d, J = 6.9 Hz, 3H), 3.34 (br s, 1H), 3.91−3.93 (m, 1H), 5.90 (dd, J = 2.9 and 10.0 Hz, 1H), 6.36 (dd, J = 1.6 and 10.0 Hz, 1H), 6.46 (s, 1H), 7.21−7.26 (m, 1H), 7.41 (t, J = 7.9 Hz, 2H), 7.58 (d, J = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 ppm, 51.4, 103.7, 115.0, 118.5, 121.9 (2C), 126.0, 129.4 (2C), 130.2, 137.2, 149.7; FTIR (neat) cm^{-1} 3211, 3125, 2970, 2925, 2864, 1686; HRMS (ESI) Calcd for $C_{13}H_{14}N_3O$ [M + H]$^+$: 228.1137, Found: 228.1138.

2-Methyl-6-phenyl-1-(trifluoroacetyl)tetrahydroimidazo-[1,5-*b*]pyridazine-5,7(1*H*,6*H*)-dione (18). To a solution of **16** (149 mg, 0.43 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (1 mL). The reaction mixture was stirred for 1 h at this temperature, and the solvent was evaporated to dryness. The crude product was taken up in EtOAc and washed with a saturated solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to dryness. To a solution of the crude deprotected hydantoin derivative in CH_2Cl_2 (2 mL) at 0 °C was added pyridine (0.18 mL, 2.2 mmol) and TFAA (0.31 mL, 2.2 mmol). The reaction mixture was stirred for 16 h (from 0 °C to room temperature) and washed with a saturated solution of $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to dryness. The crude was purified by flash chromatography (pentane/EtOAc 3/1) to give **18** as an oil (105 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 ppm (d, J = 6.7 Hz, 3H), 1.43−1.60 (m, 1H), 1.97−2.27 (m, 3H), 4.33 (dd, J = 5.5 and 6.9 Hz, 1H), 4.54 (sex, J = 6.8 Hz, 1H), 7.38−7.54 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 ppm, 22.2, 25.7, 53.1, 58.2, 115.8 (q, J = 286.0 Hz), 125.9 (2C), 129.0, 129.4 (2C), 130.7, 156.7, 158.3 (q, J = 36.0 Hz), 169.8; FTIR (neat) cm^{-1} 2974, 2933, 1793, 1736; HRMS (ESI) Calcd for $C_{15}H_{15}F_3N_3O_3$ [M + H]$^+$: 342.1066, Found: 342.1066.

***N*-[3-(2,5-Dioxo-1-phenylimidazolidin-4-yl)-1-methylpropyl]-2,2,2-trifluoroacetamide (19).** To a solution of **18** (52 mg, 0.15 mmol) in THF (1.4 mL) at 0 °C was added a freshly prepared solution of SmI_2 and HMPA [to a solution of Sm (229 mg, 1.52 mmol), $C_2H_4I_2$ (216 mg, 0.77 mmol) in THF (7.3 mL) was added HMPA (0.08 mL, 0.46 mmol)]. The reaction mixture was stirred for 15 min at this temperature. The septum was removed, and the mixture was exposed to air. After the color changed from blue to yellow, the mixture was washed with water. The organic layer was extracted with EtOAc, dried over $MgSO_4$, and filtered through a plug of Celite, and the solvent was evaporated to dryness. The crude was purified by flash chromatography (pentane/EtOAc 1/2) to give **19** as an oil (41 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 ppm (d, J = 6.6 Hz, 3H), 1.54−1.63 (m, 1H), 1.67−1.79 (m, 1H), 1.83−1.96 (m, 2H), 3.96−4.05 (m, 1H), 4.16 (t, J = 5.5 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H) 6.90, (s, 1H), 7.34−7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 ppm, 28.4, 31.0, 46.1, 56.3, 115.9 (q, J = 285.7 Hz), 126.3 (2C), 128.6, 129.3 (2C), 131.4, 156.7, 157.1 (q, J = 36.7 Hz), 172.8; FTIR (neat) cm^{-1} 3297, 3096, 2929, 1773, 1707; HRMS (ESI) Calcd for $C_{15}H_{17}F_3N_3O_3$ [M + H]$^+$: 344.1222, Found: 344.1226.

Preparation of Methyl Sorbate Derivatives 21a and 21b. To the powdered azo compound **2a** (110 mg, 0.44 mmol) was added the methyl sorbate **20** (28 mg, 0.22 mmol), and the mixture was stirred at 65 °C for 2 h. The crude product was directly purified by flash chromatography (pentane/EtOAc, 4/1) to afford **21a** (30 mg, 36%) and **21b** (23 mg, 27%) as colorless oils. The structure assignment of **21a** and **21b** has been determined by NOESY NMR experiment. See the Supporting Information for further details.

*1-tert-Butyl 6-Methyl 3-methyl-2-(phenylcarbamoyl)-3,6-dihydropyridazine-1,6(2H)-dicarboxylate (**21a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 ppm (s, 9H), 1.53 (d, J = 6.3 Hz, 3H), 3.85 (s, 3H), 4.24 (br s, 1H), 5.40 (br s, 1H), 5.70 (d, J = 9.9 Hz, 1H), 5.97−6.03 (m, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.8 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 8.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5 ppm, 28.1 (3C), 50.2, 53.2, 57.2, 83.8, 118.6, 120.7, 122.5 (2C), 129.0 (2C), 133.6, 139.4, 155.2, 155.8, 170.9; FTIR (neat) cm^{-1} 3342, 2978, 2929, 1735, 1708; HRMS (ESI) Calcd for $C_{19}H_{26}N_3O_5$ [M + H]$^+$: 376.1872, Found: 376.1876.

*1-tert-Butyl 3-Methyl 6-methyl-2-(phenylcarbamoyl)-3,6-dihydropyridazine-1,3(2H)-dicarboxylate (**21b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 ppm (s, 9H), 1.56 (d, J = 7.0 Hz, 3H), 3.80 (s, 3H), 4.78−4.83 (m, 2H), 5.69 (dd, J = 1.8 and 10.6 Hz, 1H), 6.15−6.19 (m, 1H), 7.05 (t, J = 7.3 Hz, 1H), 7.26−7.32 (m, 2H), 7.41−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 ppm, 28.0 (3C), 52.1, 53.0, 56.8, 83.9, 119.3 (2C), 121.2, 123.4, 129.1 (2C), 133.5, 138.1, 155.0, 156.7, 169.6; FTIR (neat) cm^{-1} 3363, 2978, 2929, 1732, 1695; HRMS (ESI) Calcd for $C_{19}H_{26}N_3O_5$ [M + H]$^+$: 376.1872, Found: 376.1878.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H, ^{13}C NMR and relevant NOE spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: vincent.coeffard@uvsq.fr (V.C.).
*E-mail: xavier.moreau@uvsq.fr (X.M.).

Notes

The authors declare no competing financial interest.

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