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Silver(I)-Catalyzed Tandem Sigamatropic Rearrangement/1,3-H Shift/6π Aza-electrocyclization of *N*-Propargylic Hydrazones: A Mild Synthetic Route to 1,6-Dihydropyridazines

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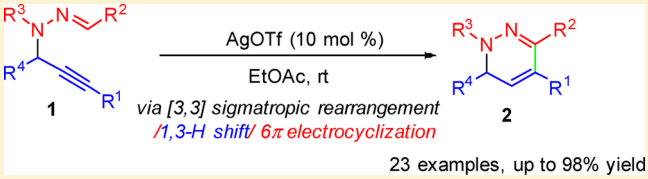
Supporting Information

ABSTRACT: A highly efficient AgOTf catalyzed [3,3] sigmatropic rearrangement/1,3-H shift/6π aza-electrocyclization cascade reaction of *N*-propargylic hydrazones has been developed. This method provides a new mild synthetic route to various polysubstituted 1,6-dihydropyridazines including the 3-CF_3-substituted ones with high selectivity.



The pyridazine-derived structures form the core of many commercial drugs and drug candidates.[1] Among those pyridazine derivatives, pyridazinone and dihydropyridazine (including 1,4-dihydropyridazine and 1,6-dihydropyridazine) derivatives show versatile pharmacological activities. The former have been used as antagonists for various targets to treat inflammation and diabetes and as antifungal or antibiotic reagents.[2] The latter has been used as antihypertensive, coronary insufficiency therapeutic, and spasmolytic agents.[3] For these reasons, a variety of strategies have been developed for the synthesis of 1,4-dihydropyridazines.[4] Nevertheless, methods for the preparation of 1,6-dihydropyridazines remain rare and usually rely on the cycloaddition of aromatic diazonium salts with dienes[5] or [4 + 2] cycloaddition of α-halogenated hydrazones with alkenes.[6] Despite these pioneering methodologies, the further development of a general and efficient process for the synthesis of 1,6-dihydropyridazines is a highly desirable and yet challenging task.

Transition-metal catalyzed skeletal rearrangements involving cleavage and formation of several covalent bonds have proven to be efficient and attractive transformations in the construction of nitrogen- and oxygen-containing heterocyclic pounds.[7] Particularly, the [3,3] rearrangements of propargylic systems have been well studied.[8] We have explored the [3,3] rearrangements of *N*-propargylic hydrazones and expanded the scope of these reactions.[9] Interestingly, we have found that the transformations can be channelled to form different types of products by the proper choice of substituents of a common substrate. As shown in Scheme 1, we have reported that the *N*-propargylic sulfonylhydrazones undergoes a novel [3,3] rearrangement to give (1*E*,3*E*)-2-sulfonyl-1,3-dienes in the presence of $[CuPPh_3I]_4$ (Scheme 1a).[9a] However, changing the *N*-sulfonyl group to a *N*-aryl or *N*-alkyl group leads to the formation of pyrazoles by a $PtCl_4$-catalyzed [3,3] rearrangement/cyclization sequence (Scheme 1b).[9b] As part of our ongoing efforts in expanding the synthetic utility of *N*-propargylic hydrazones, we have screened a host of catalysts for promoting the formation of pyridazine derivatives from the same *N*-propargylhydrazones. Fortunately, we have discovered that switching from $PtCl_4$ to the cheaper AgOTf as the catalyst results in the highly selective formation of 1,6-dihydropyridazine as the sole product (Scheme 1c). Herein, we report the synthesis of 1,6-dihydropyridazines from easily available *N*-propargyl hydrazones through a AgOTf-catalyzed [3,3] sigmatropic rearrangement/1,3-H shift/6π aza-electrocyclization cascade with high efficiency under mild conditions.

We began our investigation by reacting **1a** with a catalytic amount of $PtCl_4$ (10 mol %), the catalyst we previously employed to convert *N*-propargyl hydrazones to pyrazoles.[9b] Pleasingly, the desired 1,6-dihydropyridazine **2a** was obtained in 43% yield, albeit accompanied by the formation of **3a** (Table 1, entry 1). The yield of pyrazole **3a** was improved to 62% with the use of $Rh_2(Oct)_4$ as the catalyst in reflux toluene (Table 1, entry 3). Other transition-metal catalysts, such as $Cu(OTf)_2$, $Pd(PPh_3)_2Cl_2$, $Zn(OTf)_2$, $AuPPh_3Cl$, and AgOAc failed (Table 1, entries 4−8). Several Ag(I) salts were evaluated as the catalyst, and we were delighted to find that the use of AgOTf dramatically improved the yield of **2a** to 86% (Table 1, entries 9−11). Among the solvents tested, ethyl acetate provided the best results although other solvents such as chloroform, dichloroethane, tetrahydrofuran, toluene, and 1,4-dioxane also afforded acceptable yields except acetonitrile (Table 1, entries 12−18). No reaction could occur in the absence of catalyst (Table 1, entry 19). Hence, the optimal reaction conditions were determined to be performing the reaction in ethyl acetate at room temperature with AgOTf (10 mol %) as the catalyst (Table 1, entry 18).

Next, the substrate scope was probed under the optimized conditions (Scheme 2). The reaction was compatible with various R^1 substituents. Hence, phenyl substituted with

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Scheme 1. Transition-Metal-Catalyzed [3,3]-Rearrangement of *N*-Propargyl Hydrazones and Possibilities for Forming Different Products

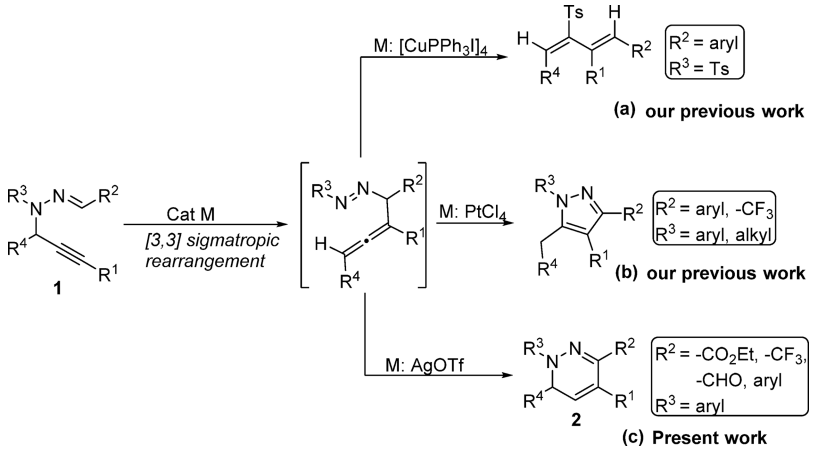
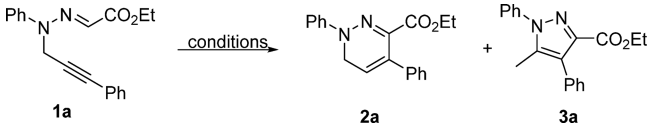


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	yield (**2a**/**3a**)[b]
1	$PtCl_4$	DCM	43%/28%
2	$Rh_2(Oct)_4$	DCM	NR[c]
3[d]	$Rh_2(Oct)_4$	toluene	0%/62%
4	$Cu(OTf)_2$	DCM	NR
5	$Pd(PPh_3)_2Cl_2$	DCM	NR
6	$Zn(OTf)_2$	DCM	NR
7	$AuPPh_3Cl$	DCM	NR
8	AgOAc	DCM	NR
9	$AgSbF_6$	DCM	64%/0%
10	AgOTf	DCM	86%/0%
11	$AgBF_4$	DCM	82%/0%
12	AgOTf	$CHCl_3$	88%/0%
13	AgOTf	DCE	89%/0%
14	AgOTf	THF	93%/0%
15	AgOTf	MeCN	trace/0%
16	AgOTf	toluene	74%/0%
17	AgOTf	1,4-dioxane	80%/0%
18	AgOTf	EtOAc	98%/0%
19	none	EtOAc	NR

[a]Reaction conditions: The reaction was carried out using **1a** (0.3 mmol) and catalyst (10 mol %) in the solvent (3 mL) for 12 h at room temperature unless otherwise noted. [b]Determined by NMR. [c]NR = no reaction. [d]Reacted at 120 °C.

electron-donating groups (−Me, −OMe) or electron-withdrawing groups (−COOMe) or halogens (−Br, −F) at different positions were all tolerated (Scheme 2, products **2a**−**2h**, 91−98% yields). Moreover, a heteroaryl group (2-thienyl) and the bulky 1-naphthyl or alkyl groups, including cyclohexenyl and *n*-propyl, were found to be suitable (Scheme 2, products **2i**−**2l**, 31−90% yields). However, a terminal alkyne led to no reaction (Scheme 2, product **2m**, 0% yield). Branching at the propargyl position (R^4 = methyl or ethyl) did not affect the efficiency, and the polysubstituted 1,6-dihydropyridazines **2n** and **2o** were obtained in 93% and 94% yields respectively (Scheme 2, products **2n**−**2o**, 93−94% yields). A survey of various R^3 substituents was also performed. Both electron-rich (−OMe) and electron-deficient ($-NO_2$, −Br) phenyl groups were well-tolerated with the latter affording higher yields (Scheme 2, products **2p**−**2r**, 85−98% yields). The structure of **2r** was further confirmed by single-crystal X-ray diffraction analysis (Figure 1; see Supporting Information). Replacing the R^3 phenyl group with an electron-withdrawing *tert*-butyloxy carbonyl group completely shut down the reaction even in reflux ethyl acetate (Scheme 2, product **2s**, 0% yield). Incorporation of a trifluoromethyl group to a heterocycle has attracted increasing attention in recent years due to the ubiquity of this motif in pharmaceuticals and agrochemicals.[10] As expected, the current method had the ability to furnish the 3-CF_3-1,6-dihydropyridazine **2t** in 82% yield (Scheme 2, product **2t**, 82% yield). Furthermore, the dihydropyridazine ring bearing a formyl group was also successfully synthesized (Scheme 2, product **2u**, 91% yield). Unfortunately, when R^2 was changed into an electron-donating group such as a pentyl, a complex result occurred (Scheme 2, product **2v**). Interestingly, this method was also compatible with the use of aromatic aldehyde hydrazone as the substrate albeit with moderate efficiency (Scheme 2, product **2w**, 45% yield).

Note that when **1x** (R^3 = H) was tested as the substrate, the 1,3-dienes **4x** and **4x′** were isolated in 62% combined yield (*Z*/*E* = 4:9), which clearly indicated a AgOTf catalyzed [3,3] sigmatropic rearrangement and N_2 extrusion had occurred (Scheme 3).

Pyridazinone derivatives have been demonstrated as building blocks in many pharmaceuticals and pesticides.[2a] To demonstrate the synthetic utility of this method, the oxidations of 1,6-dihydropyridazines **2r**, **2t**, and **2u** were performed with SeO_2 as the oxidant leading to efficient access to pyridazinones bearing a useful trifluoromethyl (**5b**) or an aldehyde group (**5c**) (Scheme 4).

Based on the experimental results presented above and previous reports,[9,11] a proposed reaction mechanism is depicted in Scheme 5. Coordination of the transition metal catalyst with the alkyne activates the triple bond of **1**, which allows a 6-*endo*-*dig* addition of hydrazone onto the metal−alkyne complex **I** leading to the intermediate **II**. The allenic intermediate **III** is formed by the decomposition of **II** with concomitant regeneration of the metal catalyst. $Rh_2(Oct)_4$-catalyzed 5-*exo*-*dig* cyclization of intermediate **III** affords pyrrole derivative **3** (path a). In contrast, AgOTf promotes the formation of 1,6-

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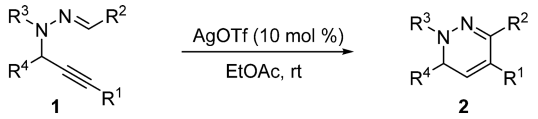
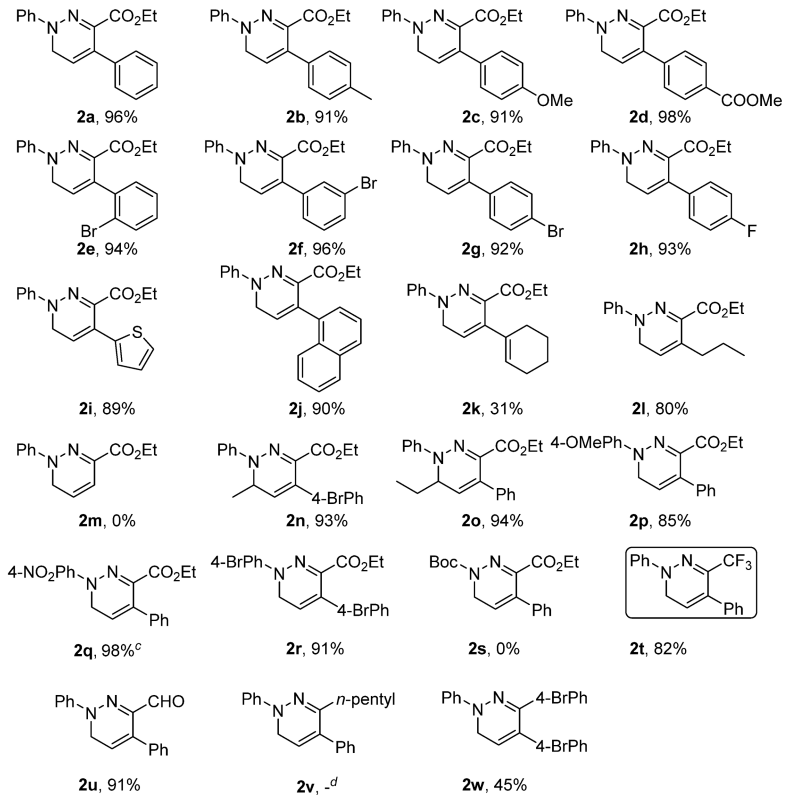
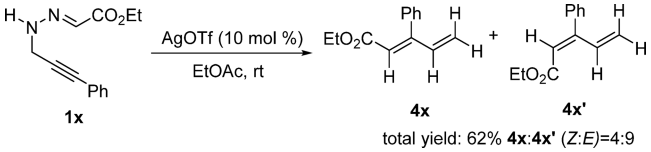
Scheme 2. AgOTf Catalyzed Synthesis of 1,6-Dihydropyridazines[a,b]



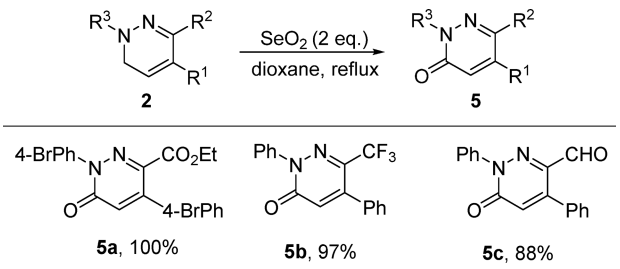


[a]Reaction conditions: The reaction was carried out using 1 (0.3 mmol) and AgOTf (10 mol %) in EtOAc (3 mL) at rt for 12 h. [b]Isolated yields. [c]Reacted at 60 °C for 24 h. [d]Complex result.

Scheme 3. AgOTf (I) Catalyzed Formation of 1,3-Dienes

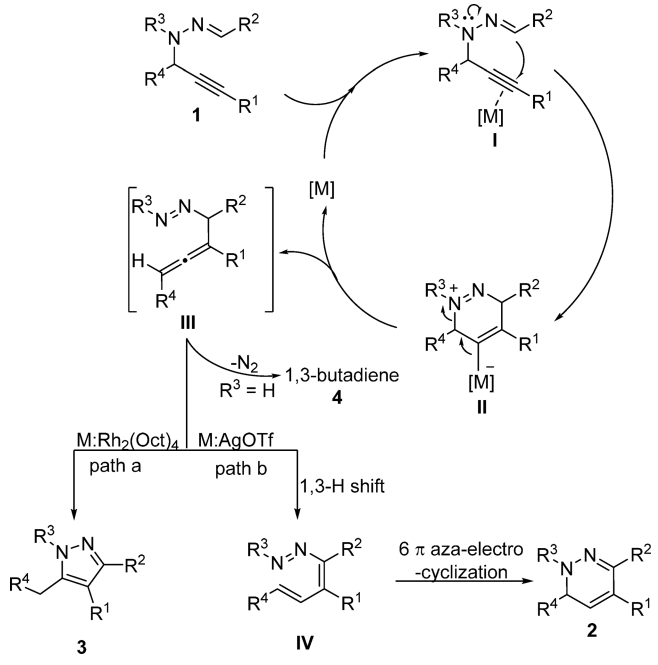


Scheme 4. Synthesis of Pyridazinone by Oxidation of 1,6-Dihydropyridazine



dihydropyridazine **2** by a 1,3-H shift and subsequent 6π-aza-electrocyclization of **IV** (path b, R^3 = aryl). In this process, we propose the ability to catalyze the [3,3] rearrangement of the metals ranks Ag > Pt > Rh (Table 1), and the intermediate **III**

Scheme 5. Plausible Reaction Mechanism



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undergoes a Ag-catalyzed 1,3-H shift at room temperature and obtain the highly selective 1,6-dihydropyridazine. In contrast, the [3,3] rearrangement could not be carried out catalyzed by $Rh_2(Oct)_4$ at room temperature (Table 1, entry 2), and reflux toluene leads to the formation of intermediate **III** but shut down the 1,3-H shift thus producing the sole pyrazole (Table 1, entry 3). In the case of **1x** (R^3 = H), the intermediate **III** may be unstable and undergo N_2 extrusion to afford the 1,3-butadiene **4**. If R^3 is Boc, we proposed intermediate **II** could not be formed due to its carbon atom of the imine to exhibit weak nucleophilicity caused by the strong electron-withdrawing ability of Boc, which would lead to the no reaction result here. In addition, the product **2m** could not be obtained which may be due to the terminal alkyne **1m** (R^1 = H) failing to become activated by Ag catalysis under the standard conditions to undergo the [3,3] rearrangement leading to the recovery of the starting material.

In conclusion, we have reported a general and efficient method for the synthesis of 1,6-dihydropyridazines from easily available *N*-propargylhydrazones. The reactions proceed through a [3,3] rearrangement/1,3-H shift/6π aza-electrocyclization process and are high-yielding with a broad substrate scope under extremely mild conditions. The Ag(I) catalyst promotes highly selective 1,6-dihydropyridazine formation, in sharp contrast to our previous synthesis of pyrazoles catalyzed by $PtCl_4$. In addition, we have also developed a new synthetic route to functionalized pyridazinones. We anticipate that the strategy of this Ag-catalyzed cascade process will find its applications in medicinal chemistry.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. All reaction mixtures were stirred with a magnetic bar in a flame-dried tube. ^{1}H and ^{13}C spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts were reported in ppm. ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm), and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). All ^{13}C NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet; and *J*, coupling constant in Hz. IR spectra were recorded on an FTIR spectrometer as thin film. Absorptions were given in wavenumbers (cm^{-1}). HRMS spectra were recorded with a Quadrupole/Time-of-Flight Tandem mass spectrometer using electron spray ionization.

General Experimental Procedures for Preparation of Propargyl Hydrazones 1. To a solution of ethyl 2-oxoacetate or glyoxal (5 mmol) in MeOH (10 mL) was added the corresponding hydrazine (5 mmol), and the reaction mixture was refluxed for about 1 h and then cooled to room temperature. The mixture was filtered through a sintered disc, and the corresponding hydrazone was obtained as a white or yellow solid in high yield. The corresponding hydrazone (4 mmol) and K_2CO_3 (4.4 mmol) were added to an oven-dried round-bottomed flask, and then DMF (15 mL) was added. Finally, the corresponding propargyl bromine (4.8 mmol) was added under the protection of N_2, and the reaction mixture was stirred at room temperature. Upon completion (monitored by TLC), the mixture was diluted by 20 mL of water and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed by vacuum, and the crude residue was purified by silica gel column chromatography to afford the corresponding propargyl hydrazones in 62%−95% yields (eluent: petroleum ether/EtOAc = 30/1−5/1). The substrate **1t** was prepared according to our previous work.[9b] In particular, **1x** was prepared from **1s** by heating the mixture of **1s** and silica gel in toluene which was then purified by silica gel column chromatography.

General Experimental Procedures for Ag(I)-Catalyzed Synthesis of 1,6-Dihydropyridazine 2. The corresponding propargyl hydrazone **1** (0.3 mmol) and AgOTf (10 mol %) were added to 10 mL Schlenk tube followed by the addition of EtOAc (3 mL), and the reaction mixture was stirred at room temperature for about 12 h. Upon completion (monitored by TLC), the solvent was removed by vacuum and the crude residue was purified by silica gel column chromatography to afford the corresponding 1,6-dihydropyridazine **2** (eluent: petroleum ether/EtOAc = 30/1).

General Experimental Procedures for Oxidation of 1,6-Dihydropyridazine. The corresponding 1,6-dihydropyridazine (**2r**, **2t**, or **2u**) (0.5 mmol) and SeO_2(1.0 mmol) were added to a 10 mL Schlenk tube followed by the addition of Dioxane (5 mL), and the reaction mixture was stirred at 105 °C for about 4 h. Upon completion (monitored by TLC), the solvent was removed by vacuum and the crude residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 10/1) to afford the corresponding pyridazinones **5** as a white solid.

Ethyl 1,4-Diphenyl-1,6-dihydropyridazine-3-carboxylate (2a). A yellow oil (88.2 mg, 96% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.07 (t, 3H, *J* = 7.2 Hz), 4.11 (q, 2H, *J* = 7.2 Hz), 4.51 (d, 2H, *J* = 4.6 Hz), 5.81 (t, 1H, *J* = 4.6 Hz), 7.10−7.14 (m, 1H), 7.21−7.24 (m, 2H), 7.30−7.37 (m, 3H), 7.39−7.42 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.7, 44.4, 60.6, 115.9, 119.4, 123.2, 126.9, 127.5, 128.0, 129.0, 132.2, 135.5, 138.3, 145.2, 163.6; **IR** (film): 2980, 1718, 1597, 1492, 1371 cm^{-1}; **HRMS** (ESI) *m*/*z* calculated for $C_{19}H_{18}N_2O_2Na^+$ $[M + Na]^+$ 329.1260, found 329.1263.

Ethyl 1-Phenyl-4-(*p*-tolyl)-1,6-dihydropyridazine-3-carboxylate (2b). A yellow solid (87.5 mg, 91% yield, mp: 123−125 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, *J* = 7.1 Hz), 2.36 (s, 3H), 4.13 (q, 2H, *J* = 7.1 Hz), 4.49 (d, 2H, *J* = 4.6 Hz), 5.79 (t, 1H, *J* = 4.6 Hz),7.09−7.16 (m, 5H), 7.38−7.42 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 21.2, 44.5, 60.7, 116.0, 119.1, 123.2, 126.9, 128.8, 129.0, 132.2, 135.3, 135.8, 137.3, 145.4, 163.8; **IR** (film): 2979, 1717, 1597, 1496, 1372 cm^{-1}; **HRMS** (ESI) *m*/*z* calculated for $C_{20}H_{20}N_2O_2Na^+$ $[M + Na]^+$ 343.1417, found 343.1421.

Ethyl 4-(4-Methoxyphenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2c). A yellow oil (91.7 mg, 91% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, *J* = 7.1 Hz), 3.81 (s, 3H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.48 (d, 2H, *J* = 4.7 Hz), 5.76 (t, 1H, *J* = 4.7 Hz), 6.86−6.88 (m, 2H), 7.13−7.15 (m, 2H), 7.38−7.41 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.4, 55.2, 60.7, 113.5, 115.9, 118.6, 123.1, 128.1, 129.0, 130.6, 131.7, 135.8, 145.3, 159.1, 163.8; **IR** (film): 2979, 1719, 1598, 1512, 1496, 1369 cm^{-1}; **HRMS** (ESI) *m*/*z* calculated for $C_{20}H_{20}N_2O_3Na^+$ $[M + Na]^+$ 359.1366, found 359.1367.

Ethyl 4-(4-(Methoxycarbonyl)phenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2d). A yellow solid (107.1 mg, 98% yield, mp: 137−139 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.08 (t, 3H, *J* = 7.1 Hz), 3.91 (s, 3H), 4.11 (q, 2H, *J* = 7.1 Hz), 4.53 (d, 2H, *J* = 4.4 Hz), 5.83 (t, 1H, *J* = 4.4 Hz), 7.11−7.13 (m, 1H), 7.26−7.28 (m, 2H), 7.38−7.41 (m, 4H), 8.00−8.02 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.8, 44.4, 52.0, 60.7, 116.0, 120.3, 123.5, 127.0, 129.0, 129.1, 129.3, 131.6, 134.5, 143.1, 145.0, 163.3, 166.7; **IR** (film): 2919, 1717, 1558, 1457, 1374 cm^{-1}; **HRMS** (ESI) *m*/*z* calculated for $C_{21}H_{20}N_2O_4Na^+$ $[M + Na]^+$ 387.1315, found 387.1317.

Ethyl 4-(2-Bromophenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2e). An orange solid (108.5 mg, 94% yield, mp: 98−100 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.08 (t, 3H, *J* = 7.1 Hz), 4.10 (q, 2H, *J* = 7.1 Hz), 4.48 (s, 1H), 4.71 (s, 1H), 5.76 (t, 1H, *J* = 4.3 Hz), 7.10−7.14 (m, 1H), 7.16−7.20 (m, 1H), 7.23−7.26 (m, 1H), 7.30−7.33 (m, 1H), 7.37−7.42 (m, 4H), 7.53−7.55 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.8, 44.5, 60.6, 115.8, 121.8, 122.8, 123.3, 127.2, 128.9, 129.0, 129.9, 131.8, 132.0, 132.9, 140.2, 145.3, 163.2; **IR** (film): 2979, 1712, 1593, 1497, 1372 cm^{-1}; **HRMS** (ESI) *m*/*z* calculated for $C_{19}H_{17}BrN_2O_2Na^+$ $[M + Na]^+$ 407.0366 and 409.0345, found 407.0368 and 409.0347.

Ethyl 4-(3-Bromophenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2f). An orange solid (110.8 mg, 96% yield, mp: 105−107 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, *J* = 7.1 Hz), 4.14 (q, 2H, *J* = 7.1 Hz), 4.52 (d, 2H, *J* = 4.6 Hz), 5.79 (t, 1H, *J* = 4.6 Hz), 7.11−7.15 (m, 2H), 7.18−7.22 (m, 1H), 7.36−7.42 (m, 5H), 7.43−

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7.46 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.5, 60.8, 116.1, 120.0, 122.1, 123.5, 125.8, 129.1, 129.5, 130.2, 130.5, 131.2, 134.6, 140.5, 145.1, 163.4; **IR** (film): 2979, 1712, 1593, 1497, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{17}BrN_2O_2Na^+$ $[M + Na]^+$ 407.0366 and 409.0345, found 407.0368 and 409.0347.

Ethyl 4-(4-Bromophenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2g). A yellow solid (106.4 mg, 92% yield, mp: 120−121 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.14 (t, 3H, J = 7.1 Hz), 4.14 (q, 2H, J = 7.1 Hz), 4.50 (d, 2H, J = 4.6 Hz), 5.77 (t, 1H, J = 4.6 Hz), 7.07−7.10 (m, 2H), 7.11−7.15 (m, 1H), 7.37−7.40 (m, 4H), 7.44−7.48 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.4, 60.8, 116.0, 119.7, 121.5, 123.4, 128.7, 129.0, 131.1, 131.4, 134.5, 137.3, 145.1, 163.4; **IR** (film): 2979, 1712, 1595, 1495, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{17}BrN_2O_2Na^+$ $[M + Na]^+$ 407.0366 and 409.0345, found 407.0368 and 409.0347.

Ethyl 4-(4-Fluorophenyl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2h). A yellow solid (90.5 mg, 93% yield, mp: 79−81 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.0 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.50 (d, 2H, J = 4.7 Hz), 5.77 (t, 1H, J = 4.7 Hz), 7.01−7.05 (m, 2H), 7.10−7.15 (m, 1H), 7.16−7.20 (m, 2H), 7.37−7.42 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.5, 60.8, 115.0 (d, $^2J_{CF}$ = 21.5 Hz), 116.1, 119.5, 123.4, 128.7 (d, $^3J_{CF}$ = 8.1 Hz), 129.1, 131.4, 134.4 (d, $^4J_{CF}$ = 3.5 Hz), 135.0, 145.2, 162.4 (d, $^1J_{CF}$ = 246.1 Hz), 163.6; **IR** (film): 2981, 1716, 1510, 1497, 1371 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{17}FN_2O_2Na^+$ $[M + Na]^+$ 347.1166, found 347.1170.

Ethyl 1-Phenyl-4-(thiophen-2-yl)-1,6-dihydropyridazine-3-carboxylate (2i). A yellow oil (83.4 mg, 89% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.18 (t, 3H, J = 7.1 Hz), 4.20 (q, 2H, J = 7.1 Hz), 4.46 (d, 2H, J = 4.8 Hz), 5.94 (t, 1H, J = 4.8 Hz), 6.92−6.93 (m, 1H), 6.98−7.00 (m, 1H), 7.10−7.13 (m, 1H), 7.23−7.25 (m, 1H), 7.35−7.37 (m, 3H), 7.38−7.40 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.2, 60.9, 116.1, 120.1, 123.4, 124.9, 125.5, 125.7, 127.0, 129.0, 135.4, 139.0, 145.2, 163.5; **IR** (film): 2979, 1717, 1597, 1496, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{16}N_2O_2SNa^+$ $[M + Na]^+$ 335.0825, found 335.0826.

Ethyl 4-(Naphthalen-1-yl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2j). A yellow solid (96.2 mg, 90% yield, mp: 89−91 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.66 (t, 3H, J = 7.1 Hz), 3.80 (q, 2H, J = 7.1 Hz), 4.54 (m, 1H), 4.76 (m, 1H), 5.90 (t, 1H, J = 4.3 Hz), 7.13−7.17 (m, 1H), 7.34−7.36 (m, 1H), 7.41−7.50 (m, 7H), 7.78−7.88 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.3, 44.7, 60.4, 115.9, 121.6, 123.3, 125.1, 125.3, 125.7, 125.8, 126.2, 127.9, 128.3, 129.1, 130.9, 131.9, 133.2, 134.9, 136.9, 145.4, 163.2; **IR** (film): 3058, 2979, 1716, 1597, 1494, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{23}H_{20}N_2O_2Na^+$ $[M + Na]^+$ 379.1417, found 379.1421.

Ethyl 4-(Cyclohex-1-en-1-yl)-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2k). A yellow oil (28.8 mg, 31% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.2 Hz), 1.58−1.64 (m, 2H), 1.65−1.70 (m, 2H), 2.00−2.04 (m, 2H), 2.08−2.13 (m, 2H), 4.28 (q, 2H, J = 7.2 Hz), 4.35 (d, 2H, J = 4.6 Hz), 5.60−5.66 (m, 1H), 5.65 (t, 1H, J = 4.6 Hz), 7.05−7.09 (m, 1H), 7.29−7.40 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 14.2, 21.9, 22.7, 25.3, 28.4, 44.3, 60.8, 115.8, 117.3, 122.9, 124.6, 128.9, 134.2, 135.5, 136.1, 145.5, 164.0; **IR** (film): 2978, 1712, 1597, 1495, 1457, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{22}N_2O_2Na^+$ $[M + Na]^+$ 333.1573, found 333.1578.

Ethyl 1-Phenyl-4-propyl-1,6-dihydropyridazine-3-carboxylate (2l). A yellow oil (65.3 mg, 80% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 7.3 Hz), 1.38 (t, 3H, J = 7.2 Hz), 1.41−1.49 (m, 2H), 2.43−2.47 (m, 2H), 4.30 (q, 2H, J = 7.3 Hz), 4.36−4.38(m, 2H), 5.57−5.60 (m, 1H), 7.05−7.09 (m, 1H), 7.28−7.31 (m, 2H), 7.32−7.38 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.6, 14.2, 21.9, 34.1, 44.4, 60.6, 115.4, 117.9, 122.7, 128.9, 130.6, 133.9, 145.3, 164.0; **IR** (film): 3044, 2960, 1708, 1598, 1496, 1463, 1375 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{16}H_{20}N_2O_2Na^+$ $[M + Na]^+$ 295.1417, found 295.1421.

Ethyl 4-(4-Bromophenyl)-6-methyl-1-phenyl-1,6-dihydropyridazine-3-carboxylate (2n). A yellow oil (111.4 mg, 93% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.16 (t, 3H, J = 7.1 Hz), 1.28 (d, 3H, J = 6.4 Hz), 4.16 (m, 2H), 5.10 (m, 1H), 5.75 (d, 1H, J = 6.9 Hz), 7.07−7.13 (m, 3H), 7.36−7.40 (m, 2H), 7.44−7.50 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 16.5, 49.4, 60.8, 116.3, 121.5, 122.8, 123.4, 129.0, 129.2, 130.5, 131.0, 135.0, 137.5, 144.2, 163.4; **IR** (film): 2980, 1719, 1594, 1498, 1371 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{20}H_{19}BrN_2O_2Na^+$ $[M + Na]^+$ 421.0522 and 423.0502, found 421.0525 and 423.0505.

Ethyl 6-Ethyl-1,4-diphenyl-1,6-dihydropyridazine-3-carboxylate (2o). A yellow oil (94.3 mg, 94% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.6 Hz), 1.10 (t, 3H, J = 7.1 Hz), 1.61−1.72 (m, 1H), 1.80−1.92 (m, 1H), 4.14 (q, 2H, J = 7.1 Hz), 4.91−4.97 (m, 1H), 5.80 (d, 1H, J = 6.9 Hz), 7.08−7.12 (m, 1H), 7.21−7.24 (m, 2H), 7.31−7.40 (m, 5H), 7.49−7.51 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 8.2, 13.8, 23.9, 54.7, 60.6, 116.2, 121.0, 123.0, 127.3, 127.4, 127.9, 129.1, 131.9, 135.8, 138.5, 144.5, 163.6; **IR** (film): 2981, 1716, 1371 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{21}H_{22}N_2O_2Na^+$ $[M + Na]^+$ 357.1573, found 357.1577.

Ethyl 1-(4-Methoxyphenyl)-4-phenyl-1,6-dihydropyridazine-3-carboxylate (2p). A yellow oil (85.8 mg, 85% yield); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.2 Hz), 3.81 (s, 3H), 4.10 (q, 2H, J = 7.2 Hz), 4.46 (d, 2H, J = 4.7 Hz), 5.73 (t, 1H, J = 4.7 Hz), 6.92−6.95 (m, 2H), 7.20−7.22 (m, 2H), 7.30−7.35 (m, 5H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.8, 45.0, 55.6, 60.6, 114.3, 117.7, 118.2, 127.0, 127.4, 128.0, 132.4, 134.7, 138.5, 139.3, 156.2, 163.7; **IR** (film): 2979, 1718, 1509, 1464, 1371 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{20}H_{20}N_2O_3Na^+$ $[M + Na]^+$ 359.1366, found 359.1369.

Ethyl 1-(4-Nitrophenyl)-4-phenyl-1,6-dihydropyridazine-3-carboxylate (2q). A yellow solid (103.3 mg, 98% yield, mp: 146−148 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7.1 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.62 (d, 2H, J = 4.5 Hz), 6.01 (t, 1H, J = 4.5 Hz), 7.19−7.22 (m, 2H), 7.33−7.38 (m, 3H), 7.40−7.44 (m, 2H), 8.25−8.28 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.7, 44.5, 61.3, 114.6, 122.2, 125.2, 126.8, 128.0, 128.3, 131.7, 137.3, 138.5, 142.4, 149.9, 163.2; **IR** (film): 2919, 1724, 1594, 1496, 1341 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{17}N_3O_4Na^+$ $[M + Na]^+$ 374.1111, found 374.1113.

Ethyl 1,4-Bis(4-bromophenyl)-1,6-dihydropyridazine-3-carboxylate (2r). A yellow solid (126.7 mg, 91% yield, mp: 132−134 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.1 Hz), 4.12 (q, 2H, J = 7.1 Hz), 4.45 (d, 2H, J = 4.6 Hz), 5.80 (t, 1H, J = 4.6 Hz), 7.05−7.08 (m, 2H), 7.21−7.24 (m, 2H), 7.44−7.49 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 13.9, 44.4, 61.0, 116.2, 117.4, 120.4, 121.7, 128.7, 131.2, 131.3, 132.0, 135.1, 137.1, 144.2, 163.3; **IR** (film): 2979, 1720, 1558, 1487, 1370 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{16}Br_2N_2O_2Na^+$ $[M + Na]^+$ 486.9450 and 484.9471, found 486.9455 and 484.9476.

1,4-Diphenyl-3-(trifluoromethyl)-1,6-dihydropyridazine (2t). A yellow solid (74.3 mg, 82% yield, mp: 108−110 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.58 (d, 2H, J = 4.3 Hz), 5.80 (t, 1H, J = 4.3 Hz), 7.11−7.15 (m, 1H), 7.28−7.34 (m, 4H), 7.35−7.44 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 44.5, 115.2, 122.7, 122.9, 124.1 (q, $^1J_{CF}$ = 272 Hz), 128.0, 128.1, 128.4 (q, $^4J_{CF}$ = 1 Hz), 129.1, 130.3, 131.0 (q, $^2J_{CF}$ = 32 Hz), 136.4, 145.1; **IR** (film): 3062, 1597, 1378 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{13}F_3N_2Na^+$ $[M + Na]^+$ 325.0923, found 325.0925.

1,4-Diphenyl-1,6-dihydropyridazine-3-carbaldehyde (2u). A yellow solid (71.6 mg, 91% yield, mp: 122−124 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.65 (d, 2H, J = 4.2 Hz), 5.75 (td, 1H, J_1 = 4.2 and J_2 = 0.6 Hz), 7.21−7.25 (m, 3H), 7.34−7.38 (m, 3H), 7.46−7.48 (m, 4H), 9.47 (d, 1H, J = 0.6 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 45.7, 116.1, 120.0, 124.3, 127.6, 127.7, 127.8, 129.1, 131.0, 136.8, 139.8, 144.5, 187.7; **IR** (film): 3057, 2923, 1683, 1595 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{14}N_2ONa^+$ $[M + Na]^+$ 285.0998, found 285.1001.

3,4-Bis(4-bromophenyl)-1-phenyl-1,6-dihydropyridazine (2w). A yellow solid (63.2 mg, 45% yield, mp: 242−244 °C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.40 (d, 2H, J = 5.1 Hz), 6.11 (t, 1H, J = 5.1 Hz), 6.92−6.95 (m, 2H), 7.03−7.07 (m, 1H), 7.20−7.23 (m, 2H), 7.32−7.40 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 43.3, 115.2,

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121.6, 121.7, 121.9, 122.7, 129.0, 129.5, 129.7, 131.0, 131.4, 131.9, 135.4, 137.0, 143.5, 146.2; **IR** (film): 3063, 1597, 1498 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{16}Br_2N_2Na^+$ $[M + Na]^+$ 490.9552 and 488.9572, found 490.9556 and 488.9576.

Ethyl 5-Methyl-1,4-diphenyl-1*H*-pyrazole-3-carboxylate (3a). A yellow solid (57.0 mg, 62% yield); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 2.2 (s, 3H), 4.3 (q, 2H, J = 7.2 Hz), 7.36−7.40 (m, 3H), 7.42−7.47 (m, 3H), 7.50−7.55 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.3, 14.1, 60.7, 124.3, 125.6, 127.2, 127.9, 128.6, 129.2, 130.3, 132.5, 138.5, 139.3, 141.0, 162.5; **HRMS** (ESI) m/z calculated for $C_{19}H_{19}N_2O_2^+$ $[M + H]^+$ 307.1441, found 307.1445.

Ethyl (*Z*)-3-Phenylpenta-2,4-dienoate (4x). A yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J = 7.2 Hz), 3.99 (q, 2H, J = 7.2 Hz), 5.07−5.12 (m, 1H), 5.43−5.47 (m, 1H), 5.98 (s,1H), 6.64 (ddd, 1H, J_1 = 17.2, J_2 = 10.4, and J_3 = 0.4 Hz), 7.12−7.15 (m, 2H), 7.32−7.40 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 59.9, 120.4, 123.6, 127.5, 127.7, 128.3, 136.4, 139.5, 154.6, 165.9; **IR** (film): 2926, 1724, 1623, 1594, 1446, 1375 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{13}H_{15}O_2^+$ $[M + H]^+$ 203.1067, found 203.1070.

Ethyl (*E*)-3-Phenylpenta-2,4-dienoate (4x′). A yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 4.22 (q, 2H, J = 7.2 Hz), 5.29−5.33 (m, 1H), 5.58−5.61 (m, 1H), 5.81−5.82 (m,1H), 7.30−7.38 (m, 5H), 7.93 (ddd, 1H, J_1 = 17.4, J_2 = 10.8, and J_3 = 0.6 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 14.3, 60.0, 118.4, 124.9, 128.1, 128.5, 128.9, 133.8, 139.4, 155.5, 166.0; **IR** (film): 2922, 1724, 1625, 1595, 1443, 1378 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{13}H_{15}O_2^+$ $[M + H]^+$ 203.1067, found 203.1070.

Ethyl 1,4-Bis(4-bromophenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylate (5a). A white solid (239.0 mg, 100% yield, mp: 184−186 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.2 Hz), 4.21 (q, 2H, J = 7.2 Hz), 6.96 (s, 1H), 7.21−7.25 (m, 2H), 7.57−7.64 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.7, 62.4, 122.6, 124.2, 126.8, 128.9, 129.6, 132.0, 133.5, 138.7, 139.5, 143.9, 158.9, 162.9; **IR** (film): 2918, 1727, 1670, 1469, 1376 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{19}H_{15}Br_2N_2O_3^+$ $[M + H]^+$ 478.9423 and 476.9444, found 478.9428 and 476.9449.

2,5-Diphenyl-6-(trifluoromethyl)pyridazin-3(2*H*)-one (5b). A white solid (153.4 mg, 97% yield, mp: 131−132 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 7.37−7.40 (m, 2H), 7.43−7.55 (m, 6H), 7.69−7.73 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 123.3 (q, $^1J_{CF}$ = 272 Hz), 125.0, 127.9 (q, $^4J_{CF}$ = 1 Hz), 128.5, 128.93, 128.98, 129.6, 131.8, 133.3, 135.0 (q, $^2J_{CF}$ = 32 Hz), 140.4, 144.3, 158.9; **IR** (film): 2919, 1683, 1490 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{12}F_3N_2O^+$ $[M + H]^+$ 317.0896, found 317.0900.

6-Oxo-1,4-diphenyl-1,6-dihydropyridazine-3-carbaldehyde (5c). A white solid (121.6 mg, 88% yield, mp: 199−201 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.94 (s, 1H), 7.35−7.39 (m, 2H), 7.45−7.51 (m, 4H), 7.52−7.58 (m, 2H), 7.70−7.73 (m, 2H), 9.83 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 125.2, 128.1, 128.4, 129.0, 129.1, 129.6, 130.0, 133.4, 140.6, 140.7, 145.2, 159.3, 187.5; **IR** (film): 2919, 1705, 1663, 1470 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{17}H_{13}N_2O_2^+$ $[M + H]^+$ 277.0972, found 277.0975.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00428.

^{1}H and ^{13}C NMR spectra of all products (PDF)

Crystallographic data for **2r** (CIF)

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Notes

The authors declare no competing financial interest.

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