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Reactivity of 4-*tert*-Butyldimethylsiloxy-1,2,3,6-tetrahydro-pyridines with Hydrazines

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Abstract: The reactivity of 6-(nitrophenyl or trimethoxyphenyl)-4-*tert*-butyldimethyl-siloxy-1,2,3,6-tetrahydropyridine derivatives with hydrazines under acid conditions is described. The structure of the products isolated − hydrazones, pyrazolines or pyridazinones − depended on the conditions used. In addition, a systematic study of the reaction outcomes was carried out by introducing variations on the substituents of the tetrahydropyridine ring.

Keywords: Siloxy-1,2,3,6-tetrahydropyridines, hydrazones, pyrazolines, pyridazinones.

Introduction

The Fischer reaction of piperidones with phenylhydrazines has been described for the preparation of compounds with the carboline structure. The (α, β or γ) carboline derivatives represent a large number of naturally and synthetic indole alkaloids with interesting biological and pharmaceutical activities [1]. β-Carboline-type alkaloids are the best known, owing to their antiviral, antitumor and antimicrobial activities [2, 3]. γ-Carbolines have also shown antipsychotic, antibiotic or antitumor activities [4, 5]. This Fischer reaction has been described to give the carbolines in good to moderate yields under a variety of acidic conditions. For instance, the reaction between *N*-methyl-4-piperidone and tolylhydrazine in glacial acetic acid gives the corresponding carboline in 60% yield; if the reaction is carried out with trifluoroacetic acid, the yield increases up to 87% [6]. The reaction also depends on

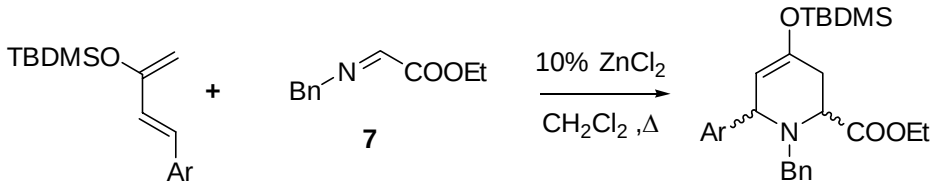
the substituents of the phenylhydrazine. In some cases, the formation of the phenylhydrazone (an enehydrazone tautomer) occurs, but no cyclization to the carboline is detected [7].

In previous work we used the hetero Diels-Alder reaction to synthesize 1-benzyl-4-(*tert*-butyl-dimethylsiloxy)-6-(nitro or methoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylates, which are interesting starting materials for the synthesis of differently substituted carbolines. Here we describe the reactivity of those compounds towards hydrazine and phenylhydrazine; the reaction was expected to produce different substituted-γ-carbolines of particular interest due to the coexistence of an ester and different aromatic groups. The different conditions used for this reaction in no case allowed us to obtain carbolines, although different pyrazoline and pyridazinone derivatives were isolated. Representative pyrazoline and pyridazinone derivatives are included in pharmacologically important compounds due to their anti-inflammatory, analgesic, antihypertensive, antibacterial, anticancer activity as well as inhibitors of the kinesin spindle protein (KSP) [8,9,10,11].

Results and Discussion

As starting materials we used ethyl 1-benzyl-4-(*tert*-butyldimethylsiloxy)-6-(nitro or methoxyphenyl)-1,2,3,6-tetrahydropyridine-2-carboxylates **1-3**, obtained by a hetero Diels-Alder reaction between the siloxydienes **4-6** and the imine **7** (Scheme 1).

Scheme 1.



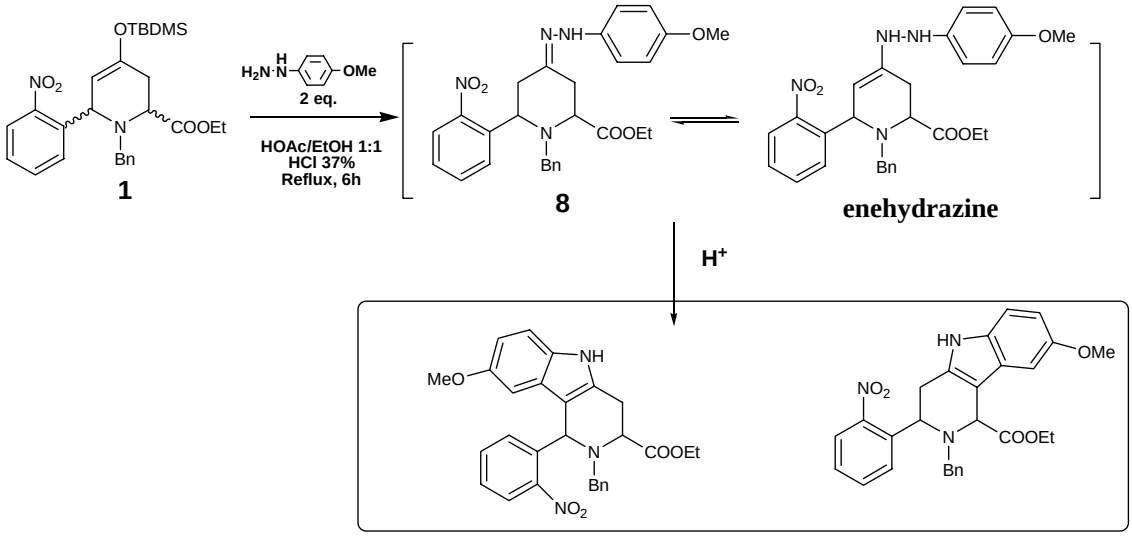
4 Ar = 2-NO_2Ph
5 Ar = 3-NO_2Ph
6 Ar = 3,4,5-OMe

1 Ar = 2-NO_2Ph
2 Ar = 3-NO_2Ph
3 Ar = 3,4,5-OMe

As previously mentioned, carbolines can be obtained by the reaction of 4-piperidones with phenylhydrazines under acid conditions. We have used the tetrahydropyridine 4-sylilenolether directly instead of the corresponding ketone, because the reaction conditions should lead to the hydrolysis of the silylenolether to the corresponding ketone. In fact, in previous work we had carried out the Fischer indolization of other related silylenolethers with good results [12]. Encouraged by those findings, compound **1** was reacted at reflux with *p*-methoxyphenylhydrazine, 1:1 glacial acetic acid/EtOH and a few drops of 37% HCl, producing the hydrazone **8** (Scheme 2). The structure of **8** was established by ^{1}H- and ^{13}C-NMR spectroscopy, which revealed the presence of the two isomeric hydrazones (*Z*/*E*).

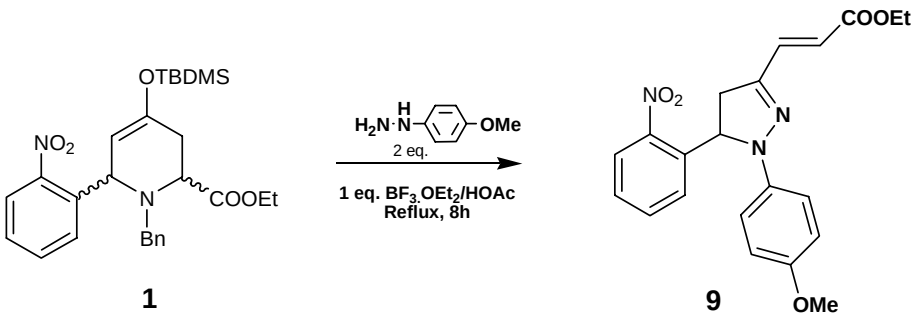
Different conditions to facilitate tautomerization to the enehydrazine and diaza-Cope breakdown of the N-N bond have been examined [13]. We used H_2SO_4/HOAc at 75ºC, but only degradation of the starting material was detected.

Scheme 2.



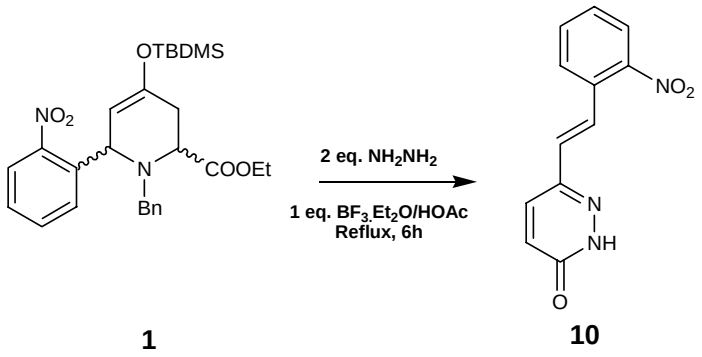
By reacting compound **1** with *p*-methoxyphenylhydrazine in the presence of $BF_3 \cdot Et_2O$/HOAc at reflux pyrazoline **9** was obtained in 65% yield (Scheme 3). This compound was characterized by HRMS, ^{1}H- and ^{13}C-NMR data. In the ^{1}H-NMR spectra we observed three double doublets at 2.91, 3.85 and 5.88 ppm, corresponding to the pyrazoline ring. The olefinic protons resonate at 7.66 and 5.82 ppm as doublets with *J*=15.8Hz, indicating an *E* stereochemistry. The regiochemistry of compound **9** was established by HMBC connectivities: the olefinic proton at 5.82 ppm with the quaternary carbon (C=N) at 145 ppm; the olefinic proton at 7.66 ppm with the CH_2 carbon at 41.5 ppm; and the aromatic CH at 7.29 ppm (dd *J*=8.0, 1.2Hz) with the CH at 61.4 ppm.

Scheme 3.



Based on these results, we carried out the reaction between **1** and hydrazine monohydrate under the same reaction conditions. The resulting reaction mixture afforded **10** in 63% yield after purification by crystallization from ether/hexane (Scheme 4). The ^{1}H and ^{13}C-NMR data of **10** showed signals representative of a monosubstituted pyridazinone.

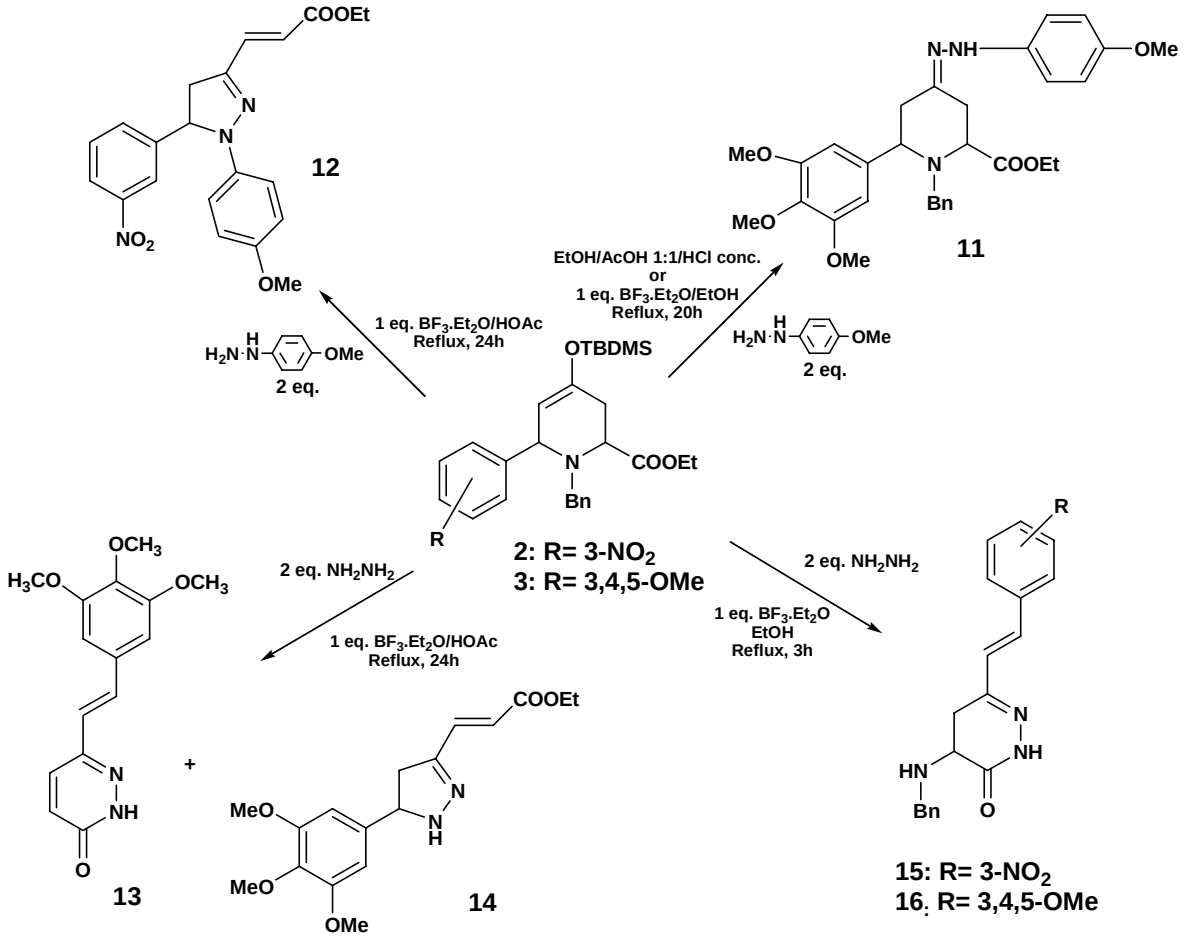
Scheme 4.



1 **10**

To investigate whether the substituents on the aryl group of the cycloadduct might have some influence in the observed reactivity, we studied the reactions of **2** and **3** with hydrazines. When *p*-methoxyphenylhydrazine was added to **3**, under the same conditions described above for **8**, the formation of hydrazone **11** was observed. The same results were detected upon replacing the acetic acid by the Lewis acid $BF_3 \cdot Et_2O$. However, when the acid medium was generated by one equivalent of $BF_3 \cdot Et_2O$ in acetic acid, the major reaction product was the pyrazoline **12** (77%) (Scheme 5).

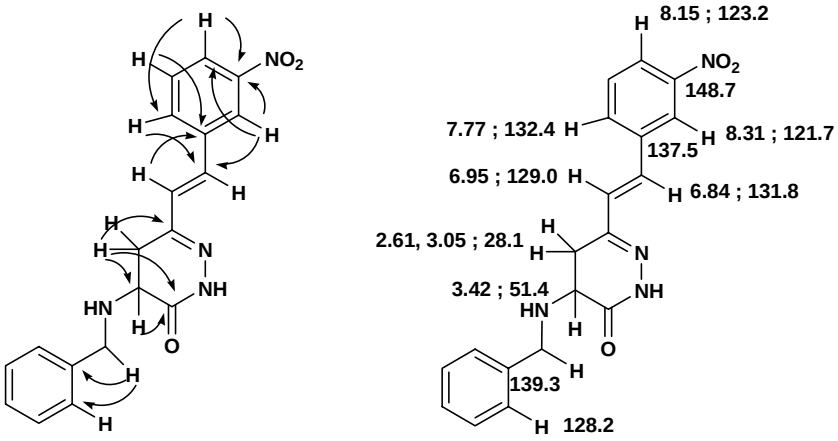
Scheme 5.



When hydrazine monohydrate and **3** were used under these conditions, compound **13** was isolated (41%) by crystallization (from ether/hexane), and hence the reaction outcome was similar to the case of **1.** ^{1}H-NMR of the mother liquor revealed signals corresponding to a minor pyrazoline **14**, which could not be purified, and this structure was proposed by comparison with related compounds.

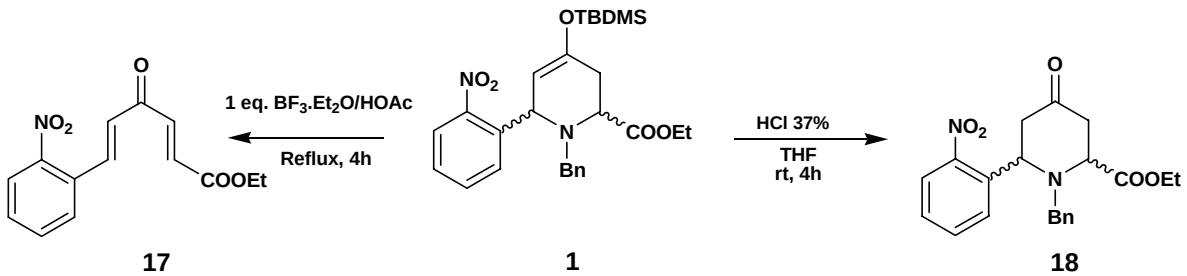
When **2** and **3** were treated with hydrazine and $BF_3 \cdot OEt_2$/EtOH in the absence of other inorganic acids at reflux, **15** (54%) and **16** (60%) were isolated. The structure of these pyridazinones was confirmed through NMR experiments (Scheme 6).

Scheme 6. Important connectivities found in the HMBC spectra of **15**, and ^{1}H- and ^{13}C-NMR assignments.



In order to understand these transformations we checked the reactivity of **1** in the different acid media used in the previous transformations, without added hydrazines (Scheme 7). The reaction of **1** with $BF_3 \cdot Et_2O$/HOAc yielded the enone **17**, produced by hydrolysis of the enol-ether, ring opening and the elimination of $BnNH_2$. Treatment of **1** with HCl led to the hydrolysis of the enol to the ketone **18**, with conservation of the piperidine structure.

Scheme 7.

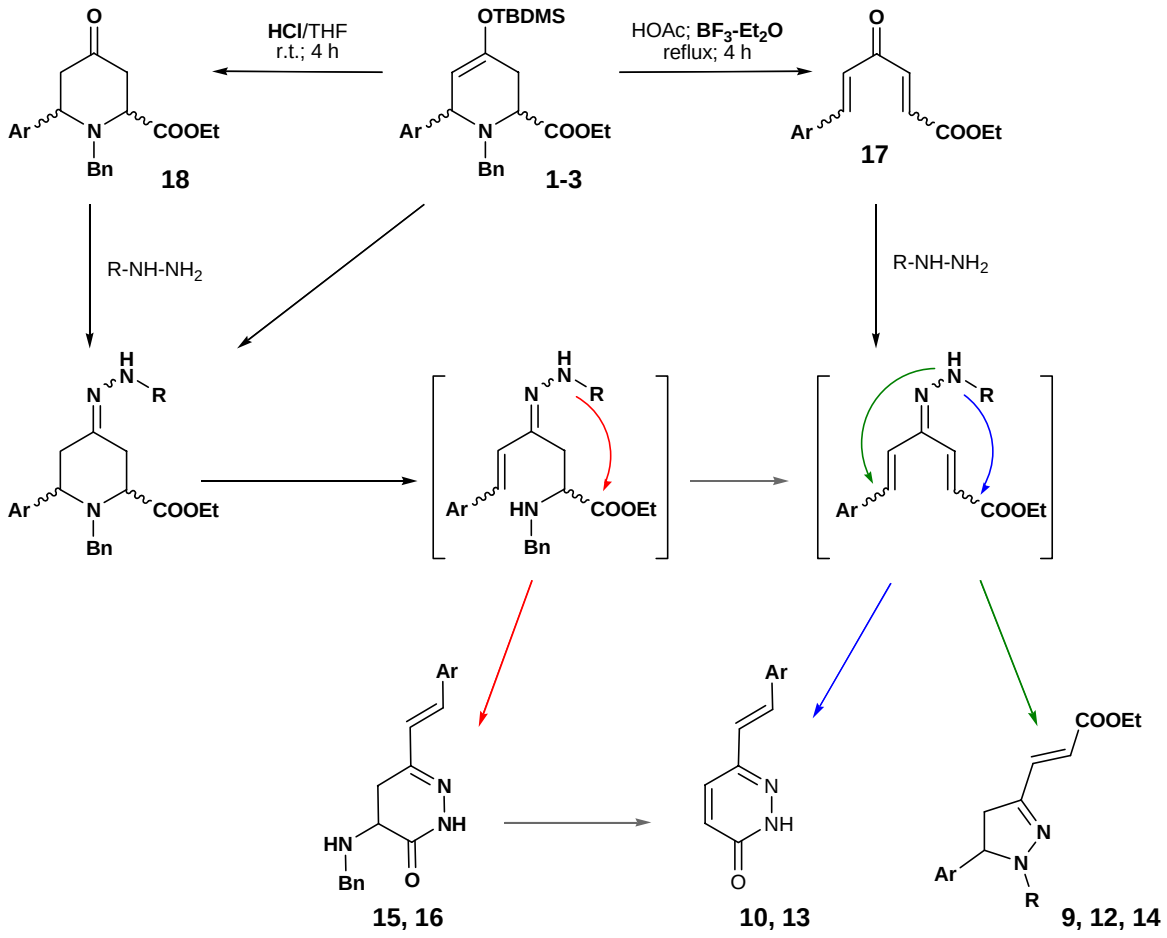


The results reported here are summarized in Scheme 8. The carbonyl derivatives can be postulated as the precursors of most of the isolated derivatives, for example, through the route from **18** to **8** and **11**, and then to other products, or a similar pathway through compound **17** or intermediate hydrazones. This mechanism is also supported by the described syntheses of these types of compound from conjugated ketones [14, 15, 16, 17].

The major differences are due to the presence of Lewis acid ($BF_3 \cdot Et_2O$), which facilitates the evolution to pyrazolines and pyridazinones, and to the use of hydrazine or phenylhydrazine as the

nucleophilic reagent. The stronger nucleophilic character of the unsubstituted nitrogen of the hydrazones from the hydrazine must be responsible for the formation of the final products **10**, **13**, **15** or **16**, whereas the lower reactive nitrogen of the hydrazones derived from the phenylhydrazine only reacts, with the double bond conjugated with the aromatic ring, after the double elimination of benzylamine. In this case, the absence of reaction with the carboxylate favours the formation of pyrazolines as the major reaction product.

Scheme 8. Proposal for the formation of pyrazolines and pyridazinones.



Conclusions

Adequate control of the reaction conditions allows the selection of final products from the reaction of the title compounds with hydrazines. These transformations are of interest for the synthesis of pyrazolines and pyridazinones, whose biological activity will be communicated in due course.

Acknowledgements

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Experimental

General

Melting points were determined on a Büchi 510 instrument and are uncorrected. NMR spectra were recorded on a Bruker ARX 400 and on a Bruker AC 200 spectrometer with TMS as internal standard. Mass spectra were obtained on a VGTS-250 mass spectrometer by using the electrospray ionization technique (ESI). Flash chromatography was performed with Merck 60 silica gel (0.063-0.2 or 0.040-0.063 mm).

Synthesis of Ethyl 1-benzyl-4-(2-(4-methoxyphenyl)hydrazono)-6-(2-nitrophenyl)piperidine-2-carboxylate (**8**)

Compound **1** (100 mg, 0.20 mmol) was dissolved in EtOH/glacial AcOH (1:1 v/v, 16 mL) containing HCl (37%, 180 µL). Then, *p*-methoxyphenylhydrazine (2 equivalents) was added at reflux for 6 h. Ethanol was evaporated *in vacuo* and the residue was washed with a saturated solution of Na_2CO_3. The mixture was extracted with EtOAc and the organic layer was washed with a NaCl solution to pH 7, dried with Na_2SO_4, and evaporated *in vacuo*. The product was purified by flash chromatography (hexane/ether 1:1), affording 104 mg (54%) of **8** as a brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.10 (1H, m), 7.30-7.70 (8H, m), 6.72 (4H, s), 5.48 (1H, m), 4.20 (2H, c, *J*=7.0 Hz), 3.85 (1H, m), 3.70 (3H, s), 3.68 (2H, m), 3.52 (1H, s), 2.90-2.60 (2H, m), 2.60 (1H, m), 1.29 (3H, t, *J*=7.0 Hz); ^{13}C-NMR (100 MHz) δ (ppm): 174.1, 148.4, 147.5 x 2, 139.9, 139.5, 138.2, 134.4, 128.7 x 5, 127.3, 126.8, 125.2, 114.5 x 2, 114.3 x 2, 61.9, 61.1, 58.4, 55.7, 52.0, 46.1, 33.8, 14.4; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}N_4O_5$ [M+1] 503.2288, found 503.2279.

Synthesis of Ethyl 1-benzyl-4-(2-(4-methoxyphenyl)hydrazono)-6-(3,4,5-trimethoxyphenyl)piperidine-2-carboxylate (**11**)

Following the procedure described for **8**, 50 mg (40 % yield) of **11** were obtained as a brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.0-7.50 (5H, m), 6.88 (2H, d, *J*=8.8 Hz), 6.72 (2H, d, *J*=8.8 Hz), 6.55 (1H, s), 6.54 (1H, s), 4.70 (1H, m), 4.20 (2H, m), 4.10 (2H, m), 3.88 (3H, s), 3.82 (6H, s), 3.71 (3H, s), 3.60 (1H, m), 2.50-2.80 (4H, m), 1.23 (3H, m); ^{13}C-NMR (50.3 MHz) δ (ppm): 174.2, 153.7, 153.4, 148.5, 141.3, 139.6x2, 138.8, 137.0, 128.4x2, 127.5, 127.2 x 2, 115.2 x 2, 114.3 x 2, 102.8 x 2, 67.0, 61.1, 61.0, 58.5, 56.2 x 2, 55.6, 52.0, 46.9, 34.8, 14.4; HRMS (ESI) *m/z* calcd. for $C_{31}H_{37}N_3O_6$ [M^+] 547.2685, found 547.2678.

Synthesis of (E)-Ethyl 3-(1-(4-methoxyphenyl)-5-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)acrylate (**9**) *and (E)-Ethyl 3-(1-(4-methoxyphenyl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-3-yl)acrylate* (**12**)

p-Methoxyphenylhydrazine hydrate (2 equivalents) and $BF_3{\cdot}OEt_2$ (1 equivalent) were added to a solution of **1** or **2** (0.79 mmol) in glacial HOAc (60 mL) and the mixture was stirred at reflux for 8 h. The reaction was cooled and neutralized with a saturated Na_2CO_3 solution, extracted with EtOAc and

the organic layer was washed with a NaCl solution to pH 7, dried with Na_2SO_4, evaporated *in vacuo*, and purified by flash chromatography (hexane/ether 1:1) to give **9** and **12** respectively.

Compound **9**: Brown oil (65% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (1H, d, *J*= 8.0 Hz), 7.66 (1H, d, *J*=15.8 Hz), 7.55 (1H, t, *J*=8.0 Hz), 7.46 (1H, t, *J*=8.0 Hz), 7.29 (1H, d, *J*=8.0 Hz), 6.86 (2H, d, *J*=9.2 Hz), 6.75 (2H, d, *J*=9.2 Hz), 5.88 (1H, dd, *J*=12.7, 6.5 Hz), 5.82 (1H, d, *J*=15.8 Hz), 4.25 (2H, q, *J*=6.7 Hz), 3.85 (1H, dd, *J*=17.3, 12.7 Hz), 3.72 (3H, s), 2.91 (1H, dd, *J*=17.3, 6.5 Hz), 1.30 (3H, t, *J*=6.7 Hz); ^{13}C-NMR (100 MHz) δ (ppm): 166.5, 154.3, 147.2, 145.0, 136.5 x2, 136.3, 134.5, 128.8, 127.9, 125.5, 120.3, 114.7 x2, 114.6 x2, 61.4, 60.4, 55.5, 41.5, 14.2; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_3O_5$ [M+1] 396.1553, found 396.1538.

Compound **12**: Brown oil (77% yield); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 8.10 (1H, s), 8.11 (1H, m), 7.70 (1H, d, *J*=15.8 Hz), 7.50-7.60 (2H, m), 6.93 (2H, d, *J*=8.7 Hz), 6.75 (2H, d, *J*=8.7 Hz), 5.79 (1H, d, *J*= 15.8 Hz), 5.41 (1H, dd, *J*=12.7, 7.0 Hz), 4.23 (2H, q, *J*=7.4 Hz), 3.72 (3H, s), 3.67 (1H, dd, *J*=16.6, 12.7 Hz), 2.88 (1H, dd, *J*=16.6, 7.0 Hz), 1.30 (3H, t, *J*=7.4 Hz); ^{13}C-NMR (50.3 MHz) δ (ppm): 166.6, 154.6, 148.9, 144.6, 136.7x2, 136.3, 131.9, 130.6, 123.1, 121.2, 120.4, 115.4x2, 114.7x2, 64.7, 60.6, 55.5, 41.4, 14.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{21}N_3O_5$ [M^+] 395.1485, found 395.1470.

Synthesis of (E)-6-(2-nitrostyryl)pyridazin-3(2H)-one (**10**) *and (E)-6-(3,4,5-trimethoxystyryl)-pyridazin-3(2H)-one* (**13**)

Hydrazine monohydrate (2 equivalents) and BF_3.OEt_2 (1 equivalent) were added to a solution of **1** or **3** (0.13 mmol) in glacial HOAc (25 mL) and the resulting mixture was stirred at reflux for 8 h. The reaction was cooled and neutralized with a saturated Na_2CO_3 solution, then extracted with EtOAc and the organic layer was washed with NaCl solution to pH 7, dried with Na_2SO_4, evaporated *in vacuo*, and the product was purified by crystallization in ether.

Compound **10**: Brown solid (63% yield); ^{1}H-NMR (200 MHz, DMSO-d_6) δ (ppm): 8.01 (1H, d, *J*=8.0 Hz), 7.95 (1H, d, *J*=8.0 Hz), 7.87 (1H, d, *J*=8.0 Hz), 7.75 (1H, t, *J*=8.0 Hz), 7.59 (1H, t, *J*=8.0 Hz), 7.58 (1H, d, *J*=16.4 Hz), 7.10 (1H, d, *J*=16.4 Hz), 6.95 (1H, d, *J*=9.9 Hz); ^{13}C-NMR (50.3 MHz) δ (ppm): 162.9, 150.6, 145.7, 136.2, 133.7, 133.5, 132.4, 131.2, 131.9, 131.1, 129.2, 127.2; HRMS (ESI) *m/z* calcd. for $C_{12}H_9N_3O_3$ [M^+] 243.0650, found 243.0643.

Compound **13**: Brown solid purified by crystallization from ether (41% yield; ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 7.63 (1H, d, *J*=9.9 Hz), 7.08 (1H, d, *J*=16.4 Hz), 7.00 (1H, d, *J*=9.9 Hz), 6.89 (1H, d, *J*=16.4 Hz), 6.73 (2H, s), 3.90 (6H, s), 3.87 (3H, s); ^{13}C-NMR (50.3 MHz) δ (ppm): 161.1, 153.6 x 2, 145.0, 139.1, 133.2, 131.4, 130.6, 130.0, 123.0, 104.2 x 2, 61.0, 56.2 x 2; HRMS (ESI) *m/z* calcd. for $C_{15}H_{16}N_2O_4$ [M+Na] 311.1002, found 311.1018.

Synthesis of (E)-6-(3-nitrostyryl)-4-(benzylamino)-4,5-dihydropyridazin-3(2H)-one (**15**) *and (E)-6-(3,4,5-trimethoxystyryl)-4-(benzylamino)-4,5-dihydropyridazin-3(2H)-one* (**16**)

Hydrazine monohydrate (2 equivalents) and $BF_3.OEt_2$ (1 equivalent) were added to a solution of **2** or **3** (0.13 mmol) in EtOH (25 mL) and the mixture was stirred at reflux for 3 h. The reaction was cooled and neutralized with a saturated Na_2CO_3 solution. The solvent was evaporated *in vacuo* and the crude product was dissolved in EtOAc and washed with a solution of $NaHCO_3$.

Compound **15**: White solid (54% yield); mp 139-140 ºC (ether/hexane); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (1H, br s), 8.31 (1H, s), 8.15 (1H, d, *J*=7.0 Hz), 7.77 (1H, d, *J*=7.0 Hz), 7.55 (1H, t, *J*=7.0 Hz), 7.35-7.37 (5H, m), 6.95 (1H, d, *J*=16.5 Hz), 6.84 (1H, d, *J*=16.5 Hz), 3.96 (2H, s), 3.42 (1H, dd, *J*=12.0, 6.7 Hz), 3.05 (1H, dd, *J*=16.6, 6.8 Hz), 2.61 (1H, dd, *J*=16.6, 11.6 Hz); ^{13}C-NMR (100 MHz) δ (ppm): 168.1, 150.9, 148.7, 139.3, 137.5, 132.4, 131.8, 129.8, 129.0, 128.6 x 2, 128.2 x 2, 127.3, 123.2, 121.7, 51.6, 51.4, 28.1; HRMS (ESI) *m/z* calcd. for $C_{19}H_{18}N_4O_3$ [M+Na] 373.1271, found 373.1254.

Compound **16**: Brown solid (60% yield); mp 126-127 ºC (ether/hexane); ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 8.55 (1H, br s), 7.30-7.38 (5H, m), 6.77 (2H, s), 6.70 (2H, s), 3.86 (6H, s), 3.84 (3H, s), 3.80 (2H, s) 3.41 (1H, dd, *J*=12.4, 6.6 Hz), 3.08 (1H, dd, *J*=16.4, 6.9 Hz), 2.59 (1H, dd, *J*=16.4, 12.2 Hz); ^{13}C-NMR (50.3 MHz) δ (ppm): 168.4, 153.5, 153.4, 152.1, 139.5, 139.1, 135.0, 131.3, 128.6 x 2, 128.2 x 2, 127.3, 125.4, 104.3 x 2, 61.0, 56.2 x 2, 51.6, 51.5, 28.1; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}N_3O_4$ [M^+] 395.1853, found 395.1848.

Synthesis of (2E,5E)-ethyl 6-(2-nitrophenyl)-4-oxohexa-2,5-dienoate (**17**)

To a solution of **1** (120 mg, 0.24 mmol) in glacial HOAc (30 mL), $BF_3.OEt_2$ (1 equivalent) was added; the mixture was stirred at reflux for 3 h. The reaction was cooled and neutralized with a saturated Na_2CO_3 solution, extracted with EtOAc and the organic layer was washed with an NaCl solution to pH 7, dried with Na_2SO_4, evaporated *in vacuo* and purified by flash chromatography (hexane/ether 1:1) to give 45 mg (69 %) of **17** as a brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ (ppm): 8.13 (1H, d, *J*=15.8 Hz), 8.08 (1H, d, *J*=7.5 Hz), 7.5-7.7 (3H, m), 7.46 (1H, d, *J*=15.8 Hz), 6.83 (2H, d *J*=15.8 Hz), 4.28 (2H, q, *J*=7.0 Hz), 1.33 (3H, t, *J*=7.0 Hz); ^{13}C-NMR (50.3 MHz) δ (ppm): 188.2, 165.4, 148.5, 141.0, 137.6, 133.8, 132.0, 130.9, 130.5, 129.5, 129.2, 125.2, 61.5, 14.2.

Synthesis of Ethyl 1-benzyl-6-(2-nitrophenyl)-4-oxopiperidine-2-carboxylate **(18)**

Compound **1** (105 mg, 0.21 mmol) dissolved in THF (5 mL) was treated with 37% HCl (20 μL) and then stirred for 4 h. The reaction mixture was washed with saturated $NaHCO_3$, dried and evaporated. The residue was chromatographed (hexane/EtOAc 7:3) to afford **18** (60 mg, 75 %) as an orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.03 (1H, d, *J*=8.0 Hz), 7.78 (1H, d, *J*=8.1 Hz), 7.67 (1H, t, *J*=8.0 Hz), 7.43 (1H, t, *J*=8.1 Hz), 7.30-7.24 (5H, m), 4.99 (1H, dd, *J*=8.0, 5.6 Hz), 4.26 (2H, q, *J*=7.2 Hz), 3.88 (1H, dd, *J*=6.4, 2.0 Hz), 3.61 (1H, d, *J*=13.6 Hz), 3.46 (1H, d, *J*=13.6 Hz), 2.99 (1H,

dd, *J*=15.6, 5.6 Hz), 2.75 (1H, dd, *J*=14.8, 6.4 Hz), 2.60 (1H, dd, *J*=14.8, 2.0 Hz), 2.58 (1H, dd, *J*=15.6, 8.0 Hz), 1.33 (3H, t, *J*=7.2 Hz); ^{13}C-NMR (100 MHz) δ (ppm): 204.7, 171.2, 149.9, 137.5, 137.4, 133.2, 128.8, 128.6 x5, 127.5, 124.1, 61.1, 58.2, 56.8, 55.0, 47.3, 42.7, 14.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}N_2O_5$ [M^+] 382.1529, found 382.1536.

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