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# Interceptive [4 + 1] Annulation of in Situ Generated 1,2-Diaza-1,3-dienes with Diazo Esters: Direct Access to Substituted Mono-, Bi-, and Tricyclic 4,5-Dihydropyrazoles

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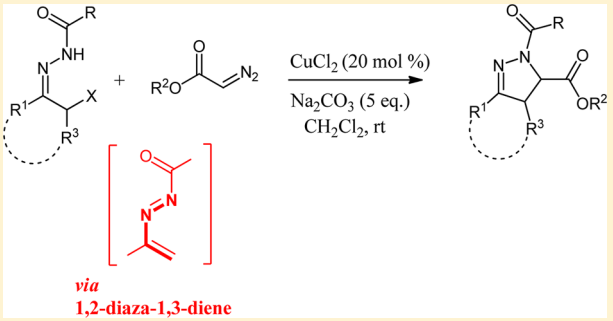
Supporting Information

**ABSTRACT:** In situ derived acyclic and cyclic 1,2-diaza-1,3-dienes (DDs) were engaged in interceptive [4 + 1] annulation strategy with diazo esters (DEs). The catalytic activity of inexpensive copper(II) chloride allows the direct synthesis of mono-, bi-, and tricyclic 4,5-dihydropyrazole-5-carboxylic acid derivatives in a process that circumvents the use of an anhydrous and inert atmosphere.



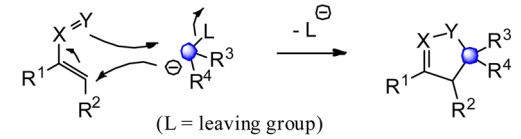

## INTRODUCTION

Irreversible trapping of highly reactive species, particularly those including dipole-type intermediates, has great potential in the elaboration of new high-step-economy reactions.[1]

Among the various types of reactions reported in the literature, the [4 + 1] annulation reactions between four-atom 1,3-conjugated systems and 1,1-dipolar C1 synthons represent an appealing and powerful method for the assembly of synthetically and biologically active carbo- and heterocyclopenten(on)es.[2−6] For this purpose, in addition to carbon monoxide,[2] isocyanides,[3] and nucleophilic carbenes,[4] used as typical one-carbon units, ylides[5] and diazo compounds[6] have also been extensively studied and used as functional reagents for many years in reactions with various electron-deficient conjugated components (Scheme 1).

For example, several groups independently reported that α-ylidene-β-diketones and α,β-unsaturated imines could react with either a nitrogen ylide or a sulfur ylide, giving 2,3-dihydrofurans and 2,3-dihydropyrroles.[5,6a] Recently, Bolm's group has reported the first example of asymmetric synthesis of dihydropyrazoles by formal [4 + 1] cycloaddition of in situ derived azoalkenes and sulfur ylides.[7]

**Scheme 1. [4 + 1] Annulation Strategy for the Synthesis of Carbo- and Heterocyclopenten(on)es Involving "Carbenoid" Reagents**




X = CR, N
Y = CO, O, NR

In this field, we are interested in the design and implementation of novel [4 + 1] annulation involving in situ generated highly reactive $C_1$ and $C_2N_2$ partners that provide new and attractive routes to pyrazoline structures. Dihydropyrazoles belong to an important class of heterocyclic compounds having multiple pharmacological applications such as antimicrobial, antifungal, anticonvulsant, hypotensive, antidepressant, immunosuppressive, analgesic, anti-inflammatory, antiamoebic, antibacterial, and antitumor activities.[8−10]

Several examples of transformations of DDs have demonstrated the potential of this class of 1,3-conjugated compounds in the context of heterocyclic chemistry.[2a,7,13] Exhibiting both diene and dienophile roles in Diels−Alder reaction and acting as Michael acceptors, they are employed as flexible partners for diverse [2 + 2], [3 + 2], [4 + 1], [4 + 2], and [5 + 2] annulations where two, three, or four ring atoms (C−C, C−C−N, or C−C−N−N) of the azoene component are incorporated in the cycloaddition products. On the basis of these results, we imagined that electron-deficient DDs which are easily generated from the corresponding α-halo *N*-EWG hydrazones could be successfully used as 1,4-dipoles and intercepted by α-diazocarbonyl compounds[11,12] in a [4 + 1] annulation strategy. Following this approach, diazo compounds would react with DDs through the carbon as a soft nucleophilic center and act as

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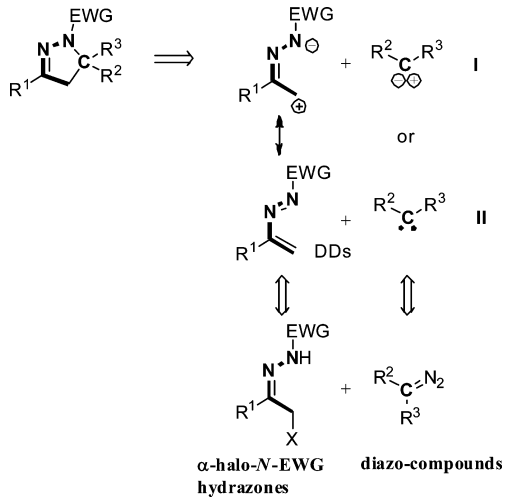
a synthetic equivalent of a 1,1-dipole one-carbon synthon (**I**) or a carbene (**II**) (Scheme 2).

**Scheme 2. Retrosynthetic Approach to the Dihydropyrazole Ring**




## RESULTS AND DISCUSSION

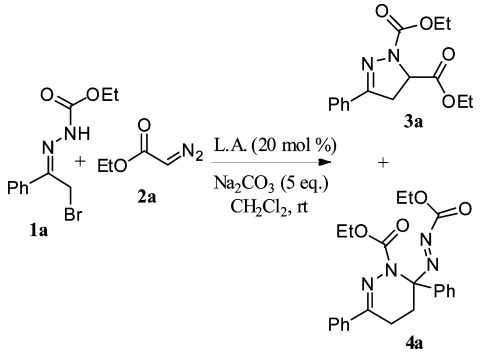
We started using the reaction between *N*-ethoxycarbonyl hydrazone **1a** and commercially available ethyl diazoacetate **2a**,[12] as a representative model system (Table 1). We initially tested the conditions previously used by Pinho e Melo[14] and others which comprised the use of $Na_2CO_3$ as base in dichloromethane at room temperature (benchmark reaction). After 24 h, total conversion of the starting ethoxycarbonyl hydrazone **1a** was observed and the expected [4 + 1] annulation product (dihydropyrazole) **3a** was obtained in 17% yield together with the major product **4a** in 62% yield (Table 1, entry 1). The cyclodimerization (regioselective intermolecular [4 + 2] cycloaddition) of the transient azoene intermediates to give pyridazine **4a** is a known process when no suitable partners for the annulation reaction are present.[15]

This initial result inspired us to examine the optimal conditions for the reaction in order to improve the competition toward the [4 + 1] annulation over the cyclodimerization of the designed transformation. Thus, the catalytic activities of the different metal catalysts were screened in the reaction. **4a** was afforded as the major product using $ZnCl_2$, $Bi(OTf)_3$, $InCl_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$ (Table 1, entries 2−6), while employing copper sources such as $Cu(OAc)_2$, $Cu(OTf)_2$, $CuCl_2$, CuCl, and $Cu_2O$ led to **3a** predominantly (Table 1, entries 7−11). Among these latter catalysts, the relatively common and inexpensive $CuCl_2$ showed the best catalytic performance (entry 9) and resulted in the exclusive **3a** in a 92% yield (no competitive pyridazine **4a** was observed!).

Notably, the reaction catalyzed by $CuCl_2$ was also accompanied by the visible evolution of $N_2$ gas, and a check on the reaction medium showed complete formation of **3a** in almost 4.0 h. The superior catalytic activity achieved by $CuCl_2$[16] might have resulted from the high coordination of the azoene intermediate that secured a fast trapping of diazo ester carbenoid species, thus preventing the dimerization of the 1,2-diaza-1,3-diene.

The use of $CuCl_2$ as the optimal catalyst prompted us to investigate the scope of this transformation, oriented to develop

**Table 1. Screening Activity of Various Metal Catalysts for the Reaction of *N*-Ethoxycarbonyl Hydrazone 1a with Ethyl Diazoacetate 2a**




| entry[a] | catalyst | *t* (h) | product yield (%)[b] 3a | 4a |
|---|---|---|---|---|
| 1 | | 24.0 | 17 | 62 |
| 2 | $ZnCl_2$ | 24.0 | trace | 33 |
| 3 | $Bi(OTf)_3$ | 40.0 | 21 | 45 |
| 4 | $InCl_3$ | 24.0 | 15 | 65 |
| 5 | $Yb(OTf)_3$ | 40.0 | 18 | 50 |
| 6 | $Sc(OTf)_3$ | 24.0 | 22 | 31 |
| 7[c] | $Cu(OAc)_2$ | 50.0 | 37 | 19 |
| 8 | $Cu(OTf)_2$ | 3.0 | 39 | |
| **9** | **$CuCl_2$** | **4.0** | **92** | |
| 10 | CuCl | 6.0 | 76 | |
| 11 | $Cu_2O$ | 60.0 | 38 | 25 |

[a]All of the reactions were carried out in $CH_2Cl_2$ (4 mL) at room temperature by using *N*-ethoxycarbonyl hydrazone **1a** (0.5 mmol), ethyl diazoacetate **2a** (1.5 mmol), $Na_2CO_3$ (2.5 mmol), and catalyst (20 mol %). [b]Isolated yield after chromatographic purification. [c]α-Acetoxyhydrazone (18%) derived from the Michael addition of acetate residue on the azoene was also isolated.

a novel, efficient, and direct method for the preparation of substituted dihydropyrazoles which are not easily available from other methodologies. Thus, the substrate generality with respect to the α-halo *N*-EWG hydrazones was investigated. As described in Table 2, variously substituted hydrazones **1a−n** were used as precursors to a number of 4,5-dihydropyrazole-5-carboxylic acid derivatives **3a−s**.

First, the protective group of the N atom was investigated. It was found that alkyl- or aryl-acyl, aminocarbonyl, and alkoxycarbonyl groups (−COR) were compatible with the reaction.

Regarding the structure of the *N*-acyl hydrazones, the process takes place efficiently with hydrazones derived from 2-bromoacetophenones, ethyl 3-bromo-2-oxopropanoate, and chloroacetone. Both electron-withdrawing (Table 2, entries 7 and 8) and electron-donating (Table 1, entry 9) substituents on the phenyl ring were well tolerated in the cycloaddition reaction. Thus, hydrazones derived from 2-bromo-4-nitro-acetophenones **1g,h** and 2-bromo-3-methoxyacetophenone **1i** led to relative 4,5-dihydropyrazoles **3** with excellent yields. Notably, the reaction with chloroacetone-derived hydrazones **1j,k** provided the desired dihydropyrazoles **3** in lower yields (Table 1, entries 10, 11, and 18).

In addition, benzyl diazoacetate **2b**[12] was successfully employed in this transformation, providing the corresponding cyclic products **3o−s** with good yields (Table 2, entries 15−19).[17]


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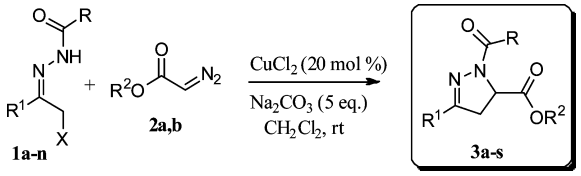
**Table 2. Formal [4 + 1] Cycloaddition of α-Halo *N*-Acyl Hydrazones 1a−n with Diazo Esters 2a,b: Synthesis of 4,5-Dihydropyrazoles 3a−s**




| entry | *N*-Acyl hydrazone **1** | | | | Diazoester **2** | | Dihydro pyrazole **3** | t (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | R | $R^1$ | X | | $R^2$ | | | |
| 1 | **1a** | OEt | Ph | Br | **2a** | Et | **3a** | 4.0 | 92 |
| 2 | **1b** | OMe | Ph | Br | **2a** | Et | **3b** | 3.0 | quant. |
| 3 | **1c** | Ph | Ph | Br | **2a** | Et | **3c** | 2.0 | 87 |
| 4 | **1d** | Bn | Ph | Br | **2a** | Et | **3d** | 22.0 | 87 |
| 5 | **1e** | NHPh | Ph | Br | **2a** | Et | **3e** | 22.0 | 85 |
| 6 | **1f** |  | Ph | Br | **2a** | Et | **3f** | 2.0 | 84 |
| 7 | **1g** | *n*-Bu | 4-$NO_2$-Ph | Br | **2a** | Et | **3g** | 19.0 | 92 |
| 8 | **1h** | Ph | 4-$NO_2$-Ph | Br | **2a** | Et | **3h** | 0.5 | 77 |
| 9 | **1i** | OEt | 3-MeO-Ph | Br | **2a** | Et | **3i** | 4.0 | 98 |
| 10 | **1j** | OEt | Me | Cl | **2a** | Et | **3j** | 5.0 | 64 |
| 11 | **1k** | NHPh | Me | Cl | **2a** | Et | **3k** | 6.0 | 64 |
| 12 | **1l** | OMe | $CO_2Et$ | Br | **2a** | Et | **3l** | 3.0 | 81 |
| 13 | **1m** | Bn | $CO_2Et$ | Br | **2a** | Et | **3m** | 4.0 | 91 |
| 14 | **1n** | NHPh | $CO_2Et$ | Br | **2a** | Et | **3n** | 18.0 | quant. |
| 15 | **1a** | OEt | Ph | Br | **2b** | Bn | **3o** | 1.0 | 82 |
| 16 | **1c** | Ph | Ph | Br | **2b** | Bn | **3p** | 4.5 | 84 |
| 17 | **1e** | NHPh | Ph | Br | **2b** | Bn | **3q** | 4.0 | 83 |
| 18 | **1j** | OEt | Me | Cl | **2b** | Bn | **3r** | 23.0 | 63 |
| 19 | **1l** | OMe | $CO_2Et$ | Br | **2b** | Bn | **3s** | 5.0 | 88 |

[a]Yield of the isolated purified compounds **3a−s** based on the starting hydrazones **1a−n**.

Finally, we examined the effect of cyclic rings on the α-halo *N*-acyl hydrazones on the reaction, leading to biologically interesting bi- and tricyclic 4,5-dihydropyrazoles[18] **3t−x**. A range of cyclic hydrazones **1o−r**, including five-, six-, and seven-membered rings worked well, producing substituted 2,3,3a,4,5,6-hexahydrocyclopenta[*c*]pyrazole **3t**, 3,3a,4,5,6,7-hexahydro-2*H*-indazoles **3u,v**, 2,3,3a,4,5,6,7,8-octahydrocycloheptа[*c*]pyrazole **3w**, and 3,3a,4,5-tetrahydro-2*H*-benz[*g*]indazole **3x** (Table 3, entries 1−5). Notably, the use of these hydrazones derived from secondary halides furnished a mixture of *cis* and *trans* diastereoisomers **3**,[19] which have been separated through column chromatography.

A plausible mechanism for this formal [4 + 1] annulation is proposed as shown in Scheme 3.

α-Halo *N*-acyl hydrazone **1** reacts with base ($Na_2CO_3$) to generate the short-lived azoene species **A**. 1,4-Conjugated addition of diazo ester ylide **2** to DD **A** produces hydrazone intermediate **B**. Subsequent intramolecular cyclization with displacement of $N_2$ may occur to form dihydropyrazole **3**. In this context, the *N*-acyl azoene skeleton provides a suitable template for the chelation of $CuCl_2$, which should activate the 1,3-conjugated system over the diazo ester for the [4 + 1] cycloaddition reaction.

## CONCLUSION

In conclusion, we have developed a copper-catalyzed interceptive [4 + 1] annulation of DDs generated in situ from acyclic and cyclic α-halo *N*-acyl hydrazones with DEs leading to substituted mono-, bi-, and tricyclic 4,5-dihydropyrazole. Likely, the diazo ester acts a synthetic equivalent of a 1,1-dipole C1 synthon or a carbene in this approach. Despite the variety of synthetic approaches which are available for the construction of the pyrazoline ring, 4,5-dihydropyrazole-5-carboxylic acid derivatives such as **3a−x** are unknown in the literature. The ready availability of the starting materials, the experimental simplicity of the reactions, and the potential utilities of products dramatically increase the synthetic usefulness of this novel procedure.

## EXPERIMENTAL SECTION

**General Methods.** All of the commercially available reagents and solvents were used without further purification. *N*-acyl hydrazones **1a−r** were prepared through condensation of hydrazides with α-halo ketone according to the literature procedure.[1] Chromatographic purification of compounds was carried out on silica gel (60−200 μm). TLC analysis was performed on preloaded (0.25 mm) glass-supported silica gel plates (Kieselgel 60); compounds were visualized


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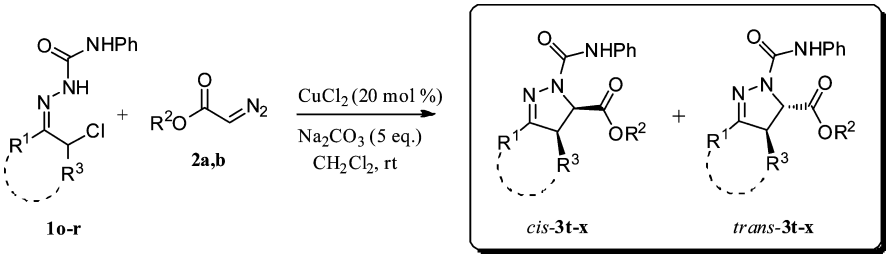
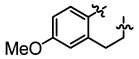
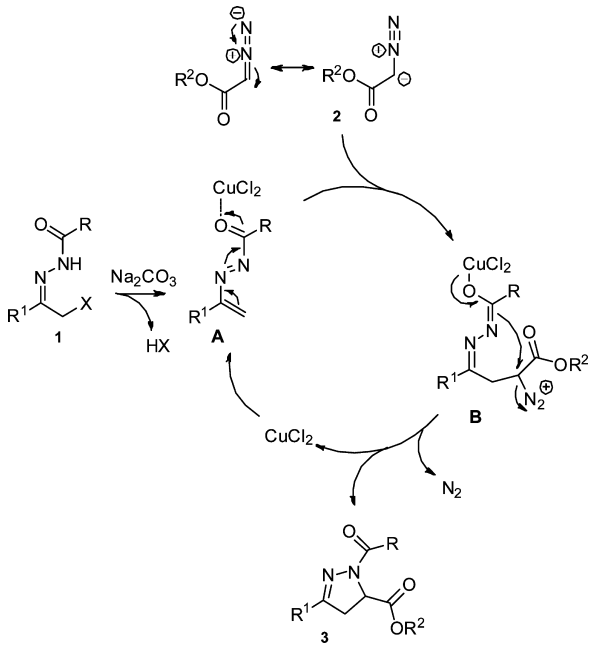
**Table 3. Formal [4 + 1] Cycloaddition of Cyclic *N*-Anilinocarbonyl Hydrazones 1o−r with Diazo Esters 2a,b: Synthesis of Bi- and Tricyclic 4,5-Dihydropyrazoles 3t−x**




| entry | | Cyclic hydrazone **1** | Diazoester **2** | | Dihydro pyrazole **3** | t (h) | Yield (%)[a] | Cis/Trans ratio[b] |
|---|---|---|---|---|---|---|---|---|
| | | $R^1$ $R^3$ | | $R^2$ | | | | |
| 1 | **1o** | $-(CH_2)_3-$ | **2a** | Et | **3t** | 4.0 | 46 | 60/40 |
| 2 | **1p** | $-(CH_2)_4-$ | **2a** | Et | **3u** | 2.0 | 41 | 70/30 |
| 3 | **1p** | $-(CH_2)_4-$ | **2b** | Bn | **3v** | 1.5 | 55 | 69/31 |
| 4 | **1q** | $-(CH_2)_5-$ | **2b** | Bn | **3w** | 5.0 | 56 | 61/39 |
| 5 | **1r** |  | **2b** | Bn | **3x** | 8.0 | 67 | 69/31 |

[a]Yield of the isolated purified compounds **3t−x** (*cis* and *trans*) based on the starting hydrazones **1o−r**. [b]*cis*/*trans* ratio was calculated by $^1$H NMR on the crude reaction mixture.

**Scheme 3. Proposed Mechanism of the Formal [4 + 1] Annulation Reaction**




by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$ and 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of $\delta$ 7.26 ppm for proton (middle peak) and $\delta$ 77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, sex = sextet, m = multiplet, and br s = broad signal. All coupling constants (*J*) are given in Hz. FT-IR spectra were obtained as Nujol mulls. Only molecular ions (M + 1) are given for the ESI-MS analysis. Melting points were determined in open capillary tubes and are uncorrected. Elemental analyses were within ±0.4 of the theoretical values (C, H, N).

**General Procedure for the Synthesis of Dihydropyrazoles by Copper-Catalyzed [4 + 1] Cycloaddition of in Situ Generated 1,2-Diaza-1,3-dienes (DDs) and Diazo Esters (DEs).** $CuCl_2$ (20 mol %) was added to a solution of *N*-acyl hydrazone **1** (0.5 mmol), diazo ester **2** (1.5 mmol), and $Na_2CO_3$ (2.5 mmol) in $CH_2Cl_2$ (4 mL), and the reaction mixture was stirred at room temperature for the time indicated (see Tables 2 and 3, monitored by TLC). The mixture was then filtered through a Celite pad, which was washed with $CH_2Cl_2$. After removal of the solvent, the residue was purified directly by flash column chromatography on silica gel (elution mixture: ethyl acetate/cyclohexane) to give the corresponding cyclized product **3**.

*Diethyl 3-phenyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3a**):* yield 133.6 mg (92%); white solid, mp 89−90 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.28 (t, *J* = 6.8 Hz, 6H), 3.31 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.21−4.25 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.91 (dd, *J* = 12.8 Hz, *J* = 6.0 Hz, 1H), 7.38−7.41 (m, 3H), 7.72−7.74 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 14.6 (q), 37.7 (t), 59.1 (d), 61.8 (t), 62.5 (t), 126.8 (d), 128.6 (d), 130.3 (d), 130.7 (s), 152.8 (s), 170.3 (s) ppm; IR (Nujol) $\nu_{max}$ 3257, 1754, 1734 cm$^{-1}$; EI-MS *m*/*z* (%) 290 ($M^+$) (29), 217 (78), 173 (47), 145 (100), 118 (33). Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.31): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.13; H, 6.32; N, 9.72.

*5-Ethyl 1-methyl 3-phenyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3b**):* yield 137.4 mg (100%); white solid, mp 100−102 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.29 (t, *J* = 7.2 Hz, 3H), 3.32 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.63 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 3.90 (s, 3H), 4.22−4.28 (m, 4H), 4.93 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 7.38−7.42 (m, 3H), 7.42−7.74 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 37.7 (t), 53.5 (q), 59.1 (d), 61.9 (t), 126.8 (d), 128.6 (d), 130.4 (d), 130.6 (s), 153.1 (s), 170.2 (s) ppm; IR (Nujol) $\nu_{max}$ 1741, 1695 cm$^{-1}$; EI-MS *m*/*z* (%) 276 ($M^+$) (19), 203 (100), 159 (33), 144 (5), 132 (9), 115 (19). Anal. Calcd for $C_{14}H_{16}N_2O_4$ (276.28): C, 60.86; H, 5.84; N, 10.14. Found: C, 60.98; H, 5.78; N, 10.19.

*Ethyl 1-benzoyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3c**):* yield 140.6 mg (87%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.30 (t, *J* = 7.2 Hz, 3H), 3.31 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.60 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.27 (dq, *J* = 7.2 Hz, *J* = 2.4 Hz, 2H), 5.20 (dd, *J* = 12.4 Hz, *J* = 6.4 Hz, 1H), 7.39−7.51 (m,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6H), 7.66−7.68 (m, 2H), 8.03−8.06 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.0 (q), 36.4 (t), 59.1 (d), 61.8 (t), 126.6 (d), 127.6 (d), 128.7 (d), 130.0 (d), 130.5 (d), 130.8 (s), 131.1 (d), 133.4 (s), 154.1 (s), 166.5 (s), 170.0 (s) ppm; IR (Nujol) $\nu_{max}$ 1756, 1657 cm$^{-1}$; EI-MS *m*/*z* (%) 322 (M$^+$) (50), 249 (100), 115 (24). Anal. Calcd for $C_{19}H_{18}N_2O_3$ (322.35): C, 70.79; H, 5.63; N, 8.96. Found: C, 70.89; H, 5.55; N, 9.02.

*Ethyl 1-phenyl-1-(phenylacetyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (**3d**):* yield 146.2 mg (87%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.23 (t, *J* = 7.2 Hz, 3H), 3.27 (dd, *J* = 18.0 Hz, *J* = 6.0 Hz, 1H), 3.54 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.15 (s, 2H), 4.16−4.22 (m, 2H), 4.96 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.42−7.45 (m, 5H), 7.72−7.74 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.8 (q), 37.1 (t), 40.4 (t), 57.8 (d), 61.6 (t), 126.4 (d), 126.5 (d), 128.2 (d), 128.6 (d), 129.4 (d), 130.4 (d), 130.7 (s), 135.0 (s), 153.4 (s), 169.2 (s), 169.7 (s) ppm; IR (Nujol) $\nu_{max}$ 1752, 1666 cm$^{-1}$; EI-MS *m*/*z* (%) 336 (M$^+$) (20), 218 (59), 145 (100), 118 (18). Anal. Calcd for $C_{20}H_{20}N_2O_3$ (336.38): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.54; H, 6.09; N, 8.27.

*Ethyl 1-(anilinocarbonyl)-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3e**):* yield 143.7 mg (85%); white solid, mp 121−123 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.30 (t, *J* = 6.8 Hz, 3H), 3.35 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.66 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.26 (dq, *J* = 7.2 Hz, *J* = 1.2 Hz, 2H), 5.03 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.43−7.46 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.71−7.73 (m, 2H), 8.05 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 38.0 (t), 58.0 (d), 61.9 (t), 119.2 (d), 123.2 (d), 126.5 (d), 128.8 (d), 128.9 (d), 130.4 (d), 130.6 (s), 138.2 (s), 151.4 (s), 170.5 (s) ppm; IR (Nujol) $\nu_{max}$ 3345, 3312, 1741, 1674 cm$^{-1}$; EI-MS *m*/*z* (%) 337 (M$^+$) (21), 218 (47), 145 (100), 118 (25). Anal. Calcd for $C_{19}H_{19}N_3O_3$ (337.37): C, 67.70; H, 5.59; N, 12.41. Found: C, 67.63; H, 5.71; N, 12.49.

*5-Ethyl 1-(2-furyl)-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3f**):* yield 131.3 mg (84%); white solid, mp 136−138 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.30 (t, *J* = 6.8 Hz, 3H), 3.32 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.61 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.23−4.28 (m, 2H), 5.17 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 6.57 (d, *J* = 3.2 Hz, 1H), 7.44−7.47 (m, 3H), 7.64−7.65 (m, 2H), 7.68 (d, *J* = 3.2 Hz, 1H), 7.74−7.76 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 36.3 (t), 58.8 (d), 62.0 (t), 111.6 (d), 119.5 (d), 126.7 (d), 128.8 (d), 130.7 (d), 145.7 (d), 154.7 (s), 156.1 (s), 169.8 (s) ppm; IR (Nujol) $\nu_{max}$ 1745, 1632 cm$^{-1}$; EI-MS *m*/*z* (%) 312 (M$^+$) (41), 239 (100), 115 (18). Anal. Calcd for $C_{17}H_{16}N_2O_4$ (312.32): C, 65.38; H, 5.16; N, 8.97. Found: C, 65.50; H, 5.22; N, 9.03.

*Ethyl 3-(4-nitrophenyl)-1-pentanoyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3g**):* yield 159.8 mg (92%); white solid, mp 97−99 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 0.95 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.42 (sex, *J* = 7.6 Hz, 2H), 1.68−1.74 (m, 2H), 2.75−2.86 (m, 2H), 3.29 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.60 (dd, *J* = 17.6 Hz, *J* = 12.8 Hz, 1H), 4.24 (q, *J* = 6.8 Hz, 2H), 5.03 (dd, *J* = 12.8 Hz, *J* = 6.4 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 8.26 (d, *J* = 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.8 (q), 14.0 (q), 22.3 (t), 26.9 (t), 33.4 (t), 36.8 (t), 52.2 (d), 62.0 (t), 124.0 (d), 127.1 (d), 136.9 (s), 148.5 (s), 150.6 (s), 169.6 (s), 172.3 (s) ppm; IR (Nujol) $\nu_{max}$ 1751, 1656 cm$^{-1}$; EI-MS *m*/*z* (%) 347 (M$^+$) (4), 263 (51), 264 (7), 191 (20), 190 (100), 144 (28), 115 (6). Anal. Calcd for $C_{17}H_{21}N_3O_5$ (347.36): C, 58.78; H, 6.09; N, 12.10. Found: C, 58.86; H, 6.18; N, 12.03.

*Ethyl 1-benzoyl-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-5-carboxylate (**3h**):* yield 141 mg (77%); white solid, mp 130−132 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.32 (t, *J* = 7.2 Hz, 3H), 3.36 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.66 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 5.27 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 7.45−7.55 (m, 3H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.89−8.01 (m, 2H), 8.25 (d, *J* = 9.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 36.2 (t), 59.5 (d), 62.1 (t), 124.0 (d), 127.4 (d), 127.8 (d), 130.0 (d), 131.6 (d), 133.0 (s), 136.8 (s),148.6 (s), 151.7 (s), 167.0 (s), 170.0 (s) ppm; IR (Nujol) $\nu_{max}$ 1739, 1646 cm$^{-1}$; EI-MS *m*/*z* (%) 367 (M$^+$) (89), 294 (100), 144 (4), 115 (24). Anal. Calcd for $C_{19}H_{17}N_3O_5$ (367.35): C, 62.12; H, 4.66; N, 11.44. Found: C, 62.04; H, 4.75; N, 11.50.

*Diethyl 3-(3-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3i**):* yield 156 mg (98%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.25 (t, *J* = 6.8 Hz, 3H), 1.28−1.38 (m, 3H), 3.26 (dd, *J* = 17.6 Hz, *J* = 5.6 Hz, 1H), 3.57 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 3.80 (s, 3H), 4.16−4.30 (m, 4H), 4.87 (dd, *J* = 12.4 Hz, *J* = 5.6 Hz, 1H), 6.90−6.93 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.30 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.3 (q), 14.8 (q), 38.0 (t), 55.6 (d), 59.3 (d), 62.0 (t), 62.7 (t), 111.5 (d), 117.0 (d), 119.6 (d), 129.8 (d), 132.2 (s), 153.0 (s), 153.1 (s), 159.9 (s), 170.4 (s) ppm; IR (Nujol) $\nu_{max}$ 1746, 1699, 1604 cm$^{-1}$; EI-MS *m*/*z* (%) 320 (M$^+$) (24), 247 (42), 203 (29), 188 (4), 175 (100), 160 (25), 145 (5), 131 (4), 115 (3). Anal. Calcd for $C_{16}H_{20}N_2O_5$ (320.34): C, 59.99; H, 6.29; N, 8.74. Found: C, 60.04; H, 6.20; N, 8.81.

*Diethyl 3-methyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3j**):* yield 73 mg (64%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.24 (t, *J* = 6.8 Hz, 6H), 2.01 (s, 3H), 2.83 (dd, *J* = 17.6 Hz, *J* = 5.0 Hz, 1H), 3.17 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 4.18 (q, *J* = 6.8 Hz, 2H), 4.22−4.27 (m, 2H), 4.70 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.0 (q), 14.5 (q), 15.5 (q), 41.3 (t), 58.6 (d), 61.6 (t), 154.0 (s), 170.3 (s) ppm; IR (Nujol) $\nu_{max}$ 2991, 1755, 1698 cm$^{-1}$; EI-MS *m*/*z* (%) 228 (M$^+$) (15), 155 (100), 111 (30). Anal. Calcd for $C_{10}H_{16}N_2O_4$ (228.24): C, 52.62; H, 7.07; N, 12.27. Found: C, 52.50; H, 7.01; N, 12.19.

*Ethyl 1-(anilinocarbonyl)-3-methyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3k**):* yield 88 mg (64%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.27 (t, *J* = 7.2 Hz, 3H), 2.02 (s, 3H), 2.88 (dd, *J* = 18.0 Hz, *J* = 6.0 Hz, 1H), 3.20 (dd, *J* = 18.0 Hz, *J* = 12.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.82 (dd, *J* = 12.4 Hz, *J* = 6.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.88 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.0 (q), 15.5 (q), 41.7 (t), 57.6 (d), 61.6 (t), 118.9 (s), 122.8 (d), 128.8 (d), 138.4 (s), 151.6 (s), 152.5 (s), 170.7 (s) ppm; IR (Nujol) $\nu_{max}$ 3178, 1713, 1687 cm$^{-1}$; EI-MS *m*/*z* (%) 275 (M$^+$) (100), 156 (85), 119 (73). Anal. Calcd for $C_{14}H_{17}N_3O_3$ (275.30): C, 61.08; H, 6.22; N, 15.26. Found: C, 61.16; H, 6.14; N, 15.21.

*3,5-Diethyl 1-methyl 4,5-dihydro-1H-pyrazole-1,3,5-tricarboxylate (**3l**):* yield 110 mg (81%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.23 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 3.16 (dd, *J* = 18.8 Hz, *J* = 6.4 Hz, 1H), 3.42 (dd, *J* = 18.8 Hz, *J* = 13.2 Hz, 1H), 3.82 (s, 3H), 4.18 (dq, *J* = 6.8 Hz, *J* = 3.2 Hz, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.84 (dd, *J* = 13.2 Hz, *J* = 6.4 Hz, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.9 (q), 14.0 (q), 36.9 (t), 53.7 (q), 59.6 (d), 61.9 (t), 145.8 (s), 152.6 (s), 161.0 (s), 169.1 (s) ppm; IR (Nujol) $\nu_{max}$ 2996, 1754, 1714 cm$^{-1}$; EI-MS *m*/*z* (%) 272 (M$^+$) (9), 227 (7), 199 (100), 171 (18), 153 (98), 127 (13), 110 (2). Anal. Calcd for $C_{11}H_{16}N_2O_6$ (272.25): C, 48.53; H, 5.92; N, 10.29. Found: C, 48.66; H, 5.83; N, 10.18.

*Diethyl 1-(phenylacetyl)-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate (**3m**):* yield 151 mg (91%); pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.18 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 6.8 Hz, 3H), 3.11 (dd, *J* = 18.8 Hz, *J* = 6.4 Hz, 1H), 3.38 (dd, *J* = 18.8 Hz, *J* = 12.8 Hz, 1H), 4.07 (s, 2H), 4.11−4.16 (m, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.89 (dd, *J* = 13.2 Hz, *J* = 6.4 Hz, 1H), 7.20−7.32 (m, 5H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.7 (q), 14.0 (q), 36.7 (t), 40.0 (t), 58.6 (d), 61.8 (t), 61.9 (t), 126.7 (d), 128.2 (d), 129.4 (d), 134.0 (s), 146.2 (s), 160.8 (s), 168.8 (s), 170.1 (s) ppm; IR (Nujol) $\nu_{max}$ 1747, 1721, 1687 cm$^{-1}$; EI-MS *m*/*z* (%) 332 (M$^+$) (24), 141 (70), 118 (100). Anal. Calcd for $C_{17}H_{20}N_2O_5$ (332.35): C, 61.44; H, 6.07; N, 8.43. Found: C, 61.32; H, 6.15; N, 8.34.

*Diethyl 1-(anilinocarbonyl)-4,5-dihydro-1H-pyrazole-3,5-dicarboxylate (**3n**):* yield 166 mg (100%); white solid, mp 96−98 °C; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.28 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 6.8 Hz, 3H), 3.21 (dd, *J* = 18.8 Hz, *J* = 6.4 Hz, 1H), 3.48 (dd, *J* = 18.4 Hz, *J* = 13.2 Hz, 1H), 4.25 (dq, *J* = 7.2 Hz, *J* = 2.4 Hz, 2H), 4.35 (q, *J* = 6.8 Hz, 2H), 5.01 (dd, *J* = 12.8 Hz, *J* = 6.4 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.99 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.0 (q), 14.1 (q),


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37.1 (t), 59.0 (d), 62.1 (t), 119.4 (d), 123.7 (d), 128.9 (d), 137.5 (s), 143.7 (s), 150.5 (s), 160.9 (s), 169.6 (s) ppm; IR (Nujol) $\nu_{max}$ 3340, 1750, 1700 $cm^{-1}$; EI-MS *m/z* (%) 333 ($M^+$) (14), 141 (100), 119 (33), 111 (28). Anal. Calcd for $C_{16}H_{19}N_3O_5$ (333.33): C, 57.65; H, 5.75; N, 12.61. Found: C, 57.76; H, 5.79; N, 12.54.

*5-Benzyl 1-ethyl 3-phenyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3o**):* yield 144 mg (82%); pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.29 (t, *J* = 7.2 Hz, 3H), 3.27 (dd, *J* = 17.2 Hz, *J* = 5.2 Hz, 1H), 3.56 (dd, *J* = 17.6 Hz, *J* = 13.2 Hz, 1H), 4.27 (m, 2H), 4.94 (dd, *J* = 12.0 Hz, *J* = 5.2 Hz, 1H), 5.20 (dd, *J* = 12.4 Hz, 2H), 7.34−7.39 (m, 8H), 7.70−7.71 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.3 (q), 37.4 (t), 58.9 (d), 62.3 (t), 67.2 (t), 126.6 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 130.1 (d), 130.5 (s), 135.0 (s), 152.7 (s), 169.9 (s) ppm; IR (Nujol) $\nu_{max}$ 1754, 1695 $cm^{-1}$; EI-MS *m/z* (%) 352 ($M^+$) (18), 217 (32), 173 (23), 145 (100), 118 (15). Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.38): C, 68.17; H, 5.72; N, 7.95. Found: C, 68.08; H, 5.67; N, 7.90.

*Benzyl 1-benzoyl-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3p**):* yield 161 mg (84%); white solid, mp 120−122 °C; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 3.31 (dd, *J* = 18.0 Hz, *J* = 6.4 Hz, 1H), 3.62 (dd, *J* = 17.6 Hz, *J* = 12.4 Hz, 1H), 5.27 (dd, *J* = 12.4 Hz, 2H), 5.29 (dd, *J* = 12.4 Hz, *J* = 6.4 Hz, 1H), 7.35−7.53 (m, 11H), 7.66−7.68 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 36.4 (t), 50.1 (d), 67.5 (t), 126.7 (d), 127.7 (d), 128.2 (d), 128.4 (d), 128.6 (d), 128.7 (d), 130.1 (d), 130.5 (d), 130.7 (s), 131.2 (d), 133.4 (s), 135.2 (s), 154.1 (s), 166.7 (s), 169.8 (s) ppm; IR (Nujol) $\nu_{max}$ 1751, 1639, 1598 $cm^{-1}$; EI-MS *m/z* (%) 384 ($M^+$) (100), 339 (10). Anal. Calcd for $C_{24}H_{20}N_2O_3$ (384.42): C, 74.98; H, 5.24; N, 7.29. Found: C, 75.09; H, 5.29; N, 7.36.

*Benzyl 1-(anilinocarbonyl)-3-phenyl-4,5-dihydro-1H-pyrazole-5-carboxylate (**3q**):* yield 165 mg (83%); white solid, mp 143−144 °C; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 3.33 (dd, *J* = 17.6 Hz, *J* = 6.0 Hz, 1H), 3.63 (dd, *J* = 17.6 Hz, *J* = 12.8 Hz, 1H), 5.10 (dd, *J* = 12.4 Hz, *J* = 6.0 Hz, 1H), 5.24 (dd, *J* = 12.4 Hz, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.31−7.38 (m, 7H), 7.42−7.45 (m, 3H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.68−7.71 (m, 2H), 8.07 (s, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 37.8 (t), 57.9 (d), 67.4 (t), 119.2 (d), 123.1 (d), 126.4 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.7 (d), 128.9 (d), 130.4 (d), 130.5 (s), 135.2 (s), 138.2 (s), 151.4 (s), 170.2 (s) ppm; IR (Nujol) $\nu_{max}$ 3333, 1744, 1683, 1598 $cm^{-1}$; EI-MS *m/z* (%) 399 ($M^+$) (43), 280 (100), 264 (2). Anal. Calcd for $C_{24}H_{21}N_3O_3$ (399.44): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.24; H, 5.22; N, 10.45.

*5-Benzyl 1-ethyl 3-methyl-4,5-dihydro-1H-pyrazole-1,5-dicarboxylate (**3r**):* yield 91 mg (63%); pale yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.24 (t, *J* = 7.2 Hz, 3H), 1.98 (m, 3H), 2.79 (dd, *J* = 18.0 Hz, *J* = 5.6 Hz, 1H), 3.14 (dd, *J* = 18.0 Hz, *J* = 12.8 Hz, 1H), 4.21 (m, 2H), 4.75 (dd, *J* = 12.0 Hz, *J* = 5.2 Hz, 1H), 5.15 (dd, *J* = 12.4 Hz, 2H), 7.26−7.34 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.4 (q), 15.4 (q), 41.1 (t), 58.5 (d), 62.1 (t), 67.0 (t), 128.0 (d), 128.2 (d), 128.4 (d), 135.0 (s), 153.8 (s), 170.0 (s) ppm; IR (Nujol) $\nu_{max}$ 1751, 1696 $cm^{-1}$; EI-MS *m/z* (%) 290 ($M^+$) (4), 257 (7), 155 (100), 125 (30), 111 (90). Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.31): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.15; H, 6.31; N, 9.72.

*5-Benzyl 3-ethyl 1-methyl 4,5-dihydro-1H-pyrazole-1,3,5-tricarboxylate (**3s**):* yield 147 mg (88%); white solid, mp 135−137 °C; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.29 (t, *J* = 7.2 Hz, 3H), 3.13 (dd, *J* = 18.8 Hz, *J* = 6.0 Hz, 1H), 3.41 (dd, *J* = 18.8 Hz, *J* = 13.2 Hz, 1H), 3.78 (m, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.90 (dd, *J* = 13.2 Hz, *J* = 6.0 Hz, 1H), 5.16 (dd, *J* = 12.0 Hz, 2H), 7.28−7.34 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.0 (q), 36.9 (t), 53.7 (q), 59.6(d), 62.0 (t), 67.5 (t), 128.2 (d), 128.4 (d), 128.5 (d), 134.7 (s), 145.8 (s), 160.9 (s), 168.9 (s) ppm; IR (Nujol) $\nu_{max}$ 1756, 1745, 1713 $cm^{-1}$; EI-MS *m/z* (%) 334 ($M^+$) (6), 289 (8), 199 (70), 153 (100), 127 (17), 109 (42). Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.32): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.57; H, 5.50; N, 8.36.

*(3R,3aR)-rel-Ethyl 2-(phenylcarbamoyl)-2,3,3a,4,5,6-hexahydrocyclopenta[c]pyrazole-3-carboxylate (**cis-3t**):* yield 42 mg (28%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.26 (t, *J* = 7.2 Hz, 3H), 1.67−2.48 (m, 6H), 3.62−3.75 (m, 1H), 4.10−4.30 (m, 2H), 4.95 (d, *J* = 11.6 Hz, 1H), 6.99−7.05 (m, 1H), 7.25−7.31 (m, 2H), 7.45−7.50 (m, 2H), 7.91 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.2 (q), 22.2 (t), 25.5 (t), 26.9 (t), 54.2 (d), 61.4 (d), 61.8 (t), 119.0 (d), 122.8 (d), 128.8 (d), 138.5 (s), 152.4 (s), 168.0 (s) 168.4 (s) ppm; IR (Nujol) $\nu_{max}$ 3396, 1741, 1682 $cm^{-1}$; ESI-MS *m/z* (%) 302 (100) $[M + H]^+$. Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.34): C, 63.77; H, 6.36; N, 13.94. Found: C, 63.89; H, 6.28; N, 14.01.

*(3S,3aR)-rel-Ethyl 2-(phenylcarbamoyl)-2,3,3a,4,5,6-hexahydrocyclopenta[c]pyrazole-3-carboxylate (**trans-3t**):* yield 28 mg (18%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.31 (t, *J* = 7.2 Hz, 3H), 1.42−2.58 (m, 6H), 3.42−3.53 (m, 1H), 4.25−4.34 (m, 2H), 4.47 (d, *J* = 10.0 Hz, 1H), 6.99−7.05 (m, 1H), 7.25−7.31 (m, 2H), 7.44−7.50 (m, 2H), 7.83 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.2 (q), 21.9 (t), 25.8 (t), 28.4 (t), 57.0 (d), 61.7 (d), 65.8 (t), 119.1 (d), 123.0 (d), 128.9 (d), 138.3 (s), 152.8 (s), 167.3 (s) 170.9 (s) ppm; IR (Nujol) $\nu_{max}$ 3389, 1746, 1686 $cm^{-1}$; ESI-MS *m/z* (%) 302 (100) $[M + H]^+$. Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.34): C, 63.77; H, 6.36; N, 13.94. Found: C, 63.70; H, 6.25; N, 13.87.

*(3R,3aR)-rel-Ethyl 2-(phenylcarbamoyl)-3,3a,4,5,6,7-hexahydro-2H-indazole-3-carboxylate (**cis-3u**):* yield 46 mg (29%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.31 (t, *J* = 7.2 Hz, 3H), 1.27−2.22 (m, 7H), 2.69−2.76 (m, 1H), 3.25−3.35 (m, 1H), 4.15−4.28 (m, 2H), 4.91 (d, *J* = 12.0 Hz, 1H), 6.99−7.04 (m, 1H), 7.25−7.31 (m, 2H), 7.45−7.50 (m, 2H), 7.90 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.3 (q), 24.2 (t), 25.7 (t), 27.4 (t), 28.1 (t), 48.6 (d), 60.7 (d), 61.3 (t), 119.0 (d), 122.8 (d), 128.9 (d), 138.5 (s), 151.8 (s), 157.7 (s) 168.5 (s) ppm; IR (Nujol) $\nu_{max}$ 3394, 1749, 1678 $cm^{-1}$; ESI-MS *m/z* (%) 316 (100) $[M + H]^+$. Anal. Calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.74; H, 6.71; N, 13.32. Found: C, 64.87; H, 6.63; N, 13.39.

*(3S,3aR)-rel-Ethyl 2-(phenylcarbamoyl)-3,3a,4,5,6,7-hexahydro-2H-indazole-3-carboxylate (**trans-3u**):* yield 19 mg (12%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.28 (t, *J* = 7.2 Hz, 3H), 1.40−2.26 (m, 7H), 2.65−2.71 (m, 1H), 2.88−3.08 (m, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 7.6 Hz, 1H), 6.99−7.05 (m, 1H), 7.24−7.30 (m, 2H), 7.46−7.50 (m, 2H), 7.87 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 14.1 (q), 24.5 (t), 27.1 (t), 27.6 (t), 33.3 (t), 52.5 (d), 61.7 (d), 63.6 (t), 119.0 (d), 122.9 (d), 128.8 (d), 138.5 (s), 151.9 (s), 158.5 (s) 170.7 (s) ppm; IR (Nujol) $\nu_{max}$ 3394, 1744, 1683 $cm^{-1}$; ESI-MS *m/z* (%) 316 (100) $[M + H]^+$. Anal. Calcd for $C_{17}H_{21}N_3O_3$ (315.37): C, 64.74; H, 6.71; N, 13.32. Found: C, 64.61; H, 6.80; N, 13.41.

*(3R,3aR)-rel-Benzyl 2-(phenylcarbamoyl)-3,3a,4,5,6,7-hexahydro-2H-indazole-3-carboxylate (**cis-3v**):* yield 72 mg (38%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.23−2.21 (m, 7H), 2.65−2.73 (m, 1H), 3.24−3.32 (m, 1H), 4.97 (d, *J* = 11.6 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 7.00−7.05 (m, 1H), 7.24−7.39 (m, 7H), 7.46−7.51 (m, 2H), 7.91 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 24.1 (t), 25.6 (t), 27.3 (t), 28.0 (t), 48.7 (d), 60.7 (d), 67.1 (t), 119.0 (d), 122.8 (d), 128.4 (d), 128.5 (d), 128.6 (d), 128.8 (d), 135.2 (s), 138.4 (s), 151.8 (s), 157.7 (s) 168.4 (s) ppm; IR (Nujol) $\nu_{max}$ 3385, 1746, 1682 $cm^{-1}$; ESI-MS *m/z* (%) 378 (100) $[M + H]^+$. Anal. Calcd for $C_{22}H_{23}N_3O_3$ (377.44): C, 70.01; H, 6.14; N, 11.13. Found: C, 69.89; H, 6.05; N, 11.20.

*(3S,3aR)-rel-Benzyl 2-(phenylcarbamoyl)-3,3a,4,5,6,7-hexahydro-2H-indazole-3-carboxylate (**trans-3v**):* yield 32 mg (17%); brown oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.36−2.25 (m, 7H), 2.63−2.70 (m, 1H), 2.87−3.04 (m, 1H), 4.47 (d, *J* = 7.2 Hz, 1H), 5.18 (d, *J* = 12.4 Hz, 1H), 5.28 (d, *J* = 12.4 Hz, 1H), 7.00−7.06 (m, 1H), 7.24−7.39 (m, 7H), 7.35−7.51 (m, 2H), 7.89 (s, 1H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 24.4 (t), 27.0 (t), 27.5 (t), 33.2 (t), 52.3 (d), 63.5 (d), 67.2 (t), 119.0 (d), 122.9 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.8 (d), 135.4 (s), 138.4 (s), 151.9 (s), 158.5 (s) 170.4 (s) ppm; IR (Nujol) $\nu_{max}$ 3389, 1746, 1678 $cm^{-1}$; ESI-MS *m/z* (%) 378 (100) $[M + H]^+$. Anal. Calcd for $C_{22}H_{23}N_3O_3$ (377.44): C, 70.01; H, 6.14; N, 11.13. Found: C, 70.13; H, 6.22; N, 11.21.

*(3R,3aR)-rel-Benzyl 2-(phenylcarbamoyl)-2,3,3a,4,5,6,7,8-octahydrocyclohepta[c]pyrazole-3-carboxylate (**cis-3w**):* yield 66 mg (34%); yellow oil; $^1H$ NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.23−


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1.99 (m, 8H), 2.39−2.76 (m, 2H), 3.42−3.51 (m, 1H), 4.90 (d, $J$ = 11.6 Hz, 1H), 5.11 (d, $J$ = 12.4 Hz, 1H), 5.24 (d, $J$ = 12.4 Hz, 1H), 7.01−7.05 (m, 1H), 7.24−7.39 (m, 7H), 7.46−7.51 (m, 2H), 7.94 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 25.4 (t), 26.1 (t), 28.6 (t), 29.9 (t), 30.7 (t), 52.7 (d), 62.4 (d), 67.1 (t), 119.0 (d), 122.9 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.8 (d), 135.2 (s), 138.4 (s), 152.2 (s), 160.5 (s) 168.7 (s) ppm; IR (Nujol) $\nu_{max}$ 3392, 1745, 1684 cm$^{-1}$; ESI-MS $m/z$ (%) 392 (100) $[M + H]^+$. Anal. Calcd for $C_{23}H_{25}N_3O_3$ (391.46): C, 70.57; H, 6.44; N, 10.73. Found: C, 70.44; H, 6.35; N, 10.66.

*(3S,3aR)-rel-Benzyl 2-(phenylcarbamoyl)-2,3,3a,4,5,6,7,8-octahydrocyclohepta[c]pyrazole-3-carboxylate (**trans-3w**):* yield 43 mg (22%); yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.23−2.02 (m, 8H), 2.43−2.63 (m, 2H), 3.15−3.21 (m, 1H), 4.48 (d, $J$ = 6.8 Hz, 1H), 5.18 (d, $J$ = 12.4 Hz, 1H), 5.26 (d, $J$ = 12.4 Hz, 1H), 7.01−7.06 (m, 1H), 7.21−7.40 (m, 7H), 7.47−7.51 (m, 2H), 7.90 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 25.5 (t), 28.2 (t), 29.2 (t), 29.3 (t), 33.0 (t), 54.6 (d), 65.2 (d), 67.2 (t), 119.0 (d), 122.9 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.8 (d), 135.4 (s), 138.4 (s), 152.0 (s), 160.3 (s) 170.4 (s) ppm; IR (Nujol) $\nu_{max}$ 3322, 1741, 1678 cm$^{-1}$; ESI-MS $m/z$ (%) 392 (100) $[M + H]^+$. Anal. Calcd for $C_{23}H_{25}N_3O_3$ (391.46): C, 70.57; H, 6.44; N, 10.73. Found: C, 70.69; H, 6.38; N, 10.81.

*(3R,3aR)-rel-Benzyl 7-methoxy-2-(phenylcarbamoyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indazole-3-carboxylate (**cis-3x**):* yield 105 mg (46%); brown oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.45−1.62 (m, 1H), 2.14−2.22 (m, 1H), 2.78−2.98 (m, 2H), 3.56−3.67 (m, 1H), 3.83 (s, 3H), 5.08 (d, $J$ = 12.4 Hz, 1H), 5.14 (d, $J$ = 11.6 Hz, 1H), 5.26 (d, $J$ = 12.4 Hz, 1H), 6.66 (d, $J$ = 2.4 Hz, 1H), 6.84 (dd, $J$ = 8.4 Hz, $J$ = 2.4 Hz, 1H), 7.05 (t, $J$ = 7.2 Hz, 1H), 7.22−7.39 (m, 7H), 7.55 (d, $J$ = 8.0 Hz, 2H), 7.93 (d, $J$ = 8.4 Hz, 1H), 8.13 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 24.1 (t), 29.6 (t), 47.8 (d), 55.3 (q), 61.4 (d), 67.2 (t), 113.1 (d), 113.7 (d), 119.2 (d), 119.5 (s), 123.0 (d), 126.9 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.9 (d), 135.2 (s), 138.5 (s), 141.0 (s), 152.2 (s), 152.9 (s), 161.4 (s) 168.4 (s) ppm; IR (Nujol) $\nu_{max}$ 3392, 1749, 1684 cm$^{-1}$; ESI-MS $m/z$ (%) 456 (100) $[M + H]^+$. Anal. Calcd for $C_{27}H_{25}N_3O_4$ (455.51): C, 71.19; H, 5.53; N, 9.22. Found: C, 71.32; H, 5.61; N, 9.29.

*(3S,3aR)-rel-Benzyl 7-methoxy-2-(phenylcarbamoyl)-3,3a,4,5-tetrahydro-2H-benzo[g]indazole-3-carboxylate (**trans-3x**):* yield 47 mg (21%); brown oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.82−1.98 (m, 1H), 2.39−2.47 (m, 1H), 2.64−2.82 (m, 2H), 3.22−3.30 (m, 1H), 3.35−3.44 (m, 3H), 3.96 (s, 3H), 4.57 (d, $J$ = 10.8 Hz, 1H), 5.26 (d, $J$ = 12.4 Hz, 1H), 5.34 (d, $J$ = 12.4 Hz, 1H), 6.91 (d, $J$ = 8.4 Hz, 1H), 7.06 (t, $J$ = 7.2 Hz, 1H), 7.20−7.41 (m, 8H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.87 (d, $J$ = 8.8 Hz, 1H), 7.99 (s, 1H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 27.2 (t), 29.7 (t), 50.1 (d), 56.4 (q), 64.9 (d), 67.5 (t), 110.4 (d), 119.3 (d), 120.7 (s), 123.2 (d), 124.4 (d), 128.2 (d), 128.4 (d), 128.6 (d), 128.9 (d), 135.4 (s), 138.2 (s), 138.4 (s), 152.3 (s), 152.6 (s), 156.9 (s) 170.2 (s) ppm; IR (Nujol) $\nu_{max}$ 3405, 1749, 1688 cm$^{-1}$; ESI-MS $m/z$ (%) 456 (100) $[M + H]^+$. Anal. Calcd for $C_{27}H_{25}N_3O_4$ (455.51): C, 71.19; H, 5.53; N, 9.22. Found: C, 71.08; H, 5.64; N, 9.14.

**Characterization Data of Dimer 4a.** *Ethyl 6-((ethoxycarbonyl)-diazenyl)-3,6-diphenyl-5,6-dihydropyridazine-1(4H)-carboxylate (**4a**):* pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.05 (br s, 3H), 1.41 (t, $J$ = 7.2 Hz, 3H), 2.05−2.17 (m, 1H), 2.23−2.34 (m, 1H), 2.63−2.73 (m, 2H), 3.95−4.08 (m, 2H), 4.39−4.49 (m, 2H), 7.29−7.44 (m, 6H), 7.60−7.67 (m, 2H), 7.78−7.83 (m, 2H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 13.9 (q), 14.1 (q), 18.0 (t), 32.4 (t), 62.3 (t), 64.7 (t), 86.5 (s), 124.8 (d), 125.7 (d), 127.5 (d), 128.4 (d), 128.7 (d), 129.3 (d), 136.8 (s), 143.0 (s), 146.8 (s), 153.1 (s), 162.0 (s) ppm; IR (Nujol) $\nu_{max}$ 1736 cm$^{-1}$; EI-MS $m/z$ (%) 408 ($M^+$) (2), 307 (59), 263 (19), 235 (100). Anal. Calcd for $C_{22}H_{24}N_4O_4$ (408.18): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.57; H, 5.99; N, 13.61.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures giving $^1$H and $^{13}$C NMR spectra for the compounds prepared in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) For selected reviews on the cascade reactions that involve dipole-type intermediates to construct heterocycles, see: (a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278−1293. (b) Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846−1913. (c) Padwa, A. *Prog. Heterocycl. Chem.* **2009**, *20*, 20−46. (d) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341−5378.

(2) For selected examples with carbon monoxide as a one-carbon unit in [4 + 1] annulations, see: (a) Boeckman, R., Jr.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 5651−3653. (b) Sigman, M. S.; Eaton, B. E. *J. Am. Chem. Soc.* **1996**, *118*, 11783−11788. (c) Sigman, M. S.; Eaton, B. E.; Heise, J. D.; Kubiak, C. P. *Organometallics* **1996**, *15*, 2829−2832. (d) Sigman, M. S.; Eaton, B. E. *J. Org. Chem.* **1994**, *59*, 7488−7491. (e) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545−7546. (f) Mandai, T.; Tsuji, J.; Tsujiguchi, Y.; Saito, S. *J. Am. Chem. Soc.* **1993**, *115*, 5865−5866. (g) Eaton, B. E.; Rollman, B.; Kaduk, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 6245−6246.

(3) For selected examples with isocyanides as one-carbon units in [4 + 1] annulations, see: (a) Oshita, M.; Yamashita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761−766. (b) Atlan, V.; Buron, C.; El Kaïm, L. *Sylett* **2000**, 489−490. (c) Buron, C.; El Kaïm, L.; Uslu, A. *Tetrahedron Lett.* **1997**, *38*, 8027−8030. (d) Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639−3644.

(4) For selected examples with nucleophilic carbenes as one-carbon units in [4 + 1] annulations, see: (a) Osyanin, V. A.; Osipov, D. V.; Demidov, M. R.; Klimochkin, Y. N. *J. Org. Chem.* **2014**, *79*, 1192−1198. (b) Boisvert, L.; Beaumier, F.; Spino, C. *Org. Lett.* **2007**, *9*, 5361−5363. (c) Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Bélanger, F. *J. Am. Chem. Soc.* **2004**, *126*, 9926−9927. (d) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673−1675.

(5) For selected examples with ylides as one-carbon units in [4 + 1] annulations, see: (a) Yang, Q.-Q.; Wang, Q.; An, J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2013**, *19*, 8401−8404. (b) Lu, L.-Q.; Li, F.; An, J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. *Chem. Eur. J.* **2012**, *18*, 4073−4079. (c) Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; An, J.; Chen, J.-R.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495−4498. (d) Zheng, J.-C.; Zhu, C.-Y.; Sun, X.-L.; Tang, Y.; Dai, L. X. *J. Org. Chem.* **2008**, *73*, 6909−6912.

(6) For selected examples with diazo compounds as one-carbon units in [4 + 1] annulations, see: (a) Zhou, J.-L.; Liang, Y.; Deng, C.; Zhou, H.; Wang, Z.; Sun, X.-L.; Zheng, J.-C.; Yu, Z.-X.; Tang, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7874−7878. (b) Liu, C.-R.; Zhu, B.-H.; Zheng, J.-C.; Sun, X.-L.; Xieb, Z.; Tang, Y. *Chem. Commun.* **2011**, *47*, 1342−1344. (c) Guo, J.; Gaudette, J.; Cheng, J.-F. *Tetrahedron Lett.* **2009**, *50*, 933−935. (d) Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276−10278. (e) Son, S.; Fu, G. *J. Am. Chem. Soc.* **2007**, *129*, 1046−1047. (f) Dalton, A. M.;

Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465−2468. (g) Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4*, 2317−2320.

(7) Chen, J.-R.; Dong, W.-R.; Candy, M.; Pan, F.-F.; Jörres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924−6927.

(8) (a) Küchenthal, C. H.; Maison, W. *Synthesis* **2010**, 719−740. (b) Kissane, M.; Maguire, A. R. *Chem. Soc. Rev.* **2010**, *39*, 845−883. (c) Lévai, A. *J. Heterocycl. Chem.* **2002**, *39*, 1−13. (d) Behr, L. C.; Fusco, R.; Jarboe, C. H. *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings*; Interscience: New York, 1967; The Chemistry of Heterocyclic Compounds *22*.

(9) For selected examples of bioactive pyrazolines, see: (a) Sahoo, A.; Yabanoglu, S.; Sinha, B. N.; Ucar, G.; Basu, A.; Jayaprakash, V. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 132−136. (b) Isloor, A. M.; Kalluraya, B.; Shetty, P. *Eur. J. Med. Chem.* **2009**, *44*, 3784−3787. (c) Sunil, D.; Isloor, A. M.; Shetty, P. *Pharma Chem.* **2009**, *1*, 19−26. (d) Ali, M. A.; Shaharyar, M. *Bioorg. Med. Chem.* **2007**, *15*, 1896−1902.

(10) For recent syntheses of pyrazolines, see: (a) Wang, X.; Pan, Y.-m.; Huang, X.-c.; Mao, Z.-y.; Wang, H.-s. *Org. Biomol. Chem.* **2014**, *12*, 2028−2032. (b) Rueping, M.; Maji, M. S.; Küçük, H. B.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1−6. (c) Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371−376. (d) Safaei, S.; Mohammadpoor-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. *Adv. Synth. Catal.* **2012**, *354*, 3095−3104. (e) Mahe, O.; Dez, I.; Levacher, V.; Briere, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7072−7075. (f) Mahe, O.; Dez, I.; Levacher, V.; Briere, J.-F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7072−7075. (g) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276−8277.

(11) For reviews on diazo compounds, see: (a) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162−10173. (b) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45*, 1365−1377. (c) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577−6605. (d) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937−948. (e) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424. (f) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. (g) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(12) *Caution!* Diazo compounds are known to be toxic, unstable, and potentially explosive compounds. See: Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: London, 1986. Although we had no explosions while working with these compounds, suitable safety precautions were taken.

(13) For reviews on the chemistry of DDs, see: (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109−3127. (b) Lemos, A. In *Targets in Heterocyclic Systems-Chemistry and Properties*; Attanasi, O. A.; Spinelli, D., Eds.; Società Chimica Italiana: Rome, 2010; Vol. *14*, p 1. For some recent examples, see:. (c) Gao, S.; Chen, J.-R.; Hu, X.-Q.; Cheng, H.-G.; Lu, L.-Q.; Xiao, W.-J. *Adv. Synth. Catal.* **2013**, *355*, 3539−3544. (d) Hu, X.-Q.; Chen, J.-R.; Gao, S.; Feng, B.; Lu, L.-Q.; Xiao, W.-J. *Chem. Commun.* **2013**, *49*, 7905−7907. (e) Attanasi, O. A.; Favi, G.; Geronikaki, A.; Mantellini, F.; Moscatelli, G.; Paparisva, A. *Org. Lett.* **2013**, *15*, 2624−2627. (f) Attanasi, O. A.; Bianchi, L.; Campisi, L. A.; De Crescentini, L.; Favi, G.; Mantellini, F. *Org. Lett.* **2013**, *15*, 3646−3649. (g) Attanasi, O. A.; Bartoccini, S.; Favi, G.; Giorgi, G.; Perrulli, F. R.; Santeusanio, S. *J. Org. Chem.* **2012**, *77*, 1161−1167. (h) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546−4547. (i) Kanzian, T.; Nicolini, S.; De Crescentini, L.; Attanasi, O. A.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2010**, *16*, 12008−12016.

(14) Lopes, S. M. M.; Brigas, A. F.; Palacios, F.; Lemos, A.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, 2152−2160.

(15) (a) Banert, K.; Hagedorn, M. *Tetrahedron Lett.* **1992**, *33*, 7331−7334. (b) Gilchrist, T. L.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2511−2516. (c) Curtin, D. Y.; Tristram, E. W. *J. Am. Chem. Soc.* **1950**, *72*, 5238−5242.

(16) (a) Carbone, A.; Spanò, V.; Parrino, B.; Ciancimino, C.; Attanasi, O. A.; Favi, G. *Molecules* **2013**, *18*, 2518−2527. (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Serra-Zanetti, F. *J. Heterocycl. Chem.* **1986**, *23*, 25−28. (c) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S.; Serra-Zanetti, F. *Synthesis* **1985**, 157−158.

(17) Attempts to carry out the reaction of 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (diazo Meldrum's acid) were unsuccessful. Under the current reaction conditions the unreacted cyclic α-diazocarbonyl compound was recovered. Also, attempts to employ the reagent $Me_3SiCHN_2$ for the [4 + 1] cycloaddition were not fruitful.

(18) (a) Bishnoi, A.; Singh, S.; Tiwari, A. K.; Sethi, A.; Tripathi, C. M. *Med. Chem.* **2013**, *9*, 45−52. (b) Faidallah, H. M.; Khan, K. A.; Rostom, S. A. F.; Asiri, A. M. *J. Enzym. Inihib. Med. Ch.* **2013**, *28*, 495−508. (c) Choi, S.; Keys, H.; Staples, R. J.; Yuan, J.; Degterev, A.; Cuny, G. D. *Bioorgan. Med. Chem.* **2012**, *22*, 5685−5688. (d) Meyers, M. J.; Arhancet, G. B.; Hockerman, S. L.; Chen, X.; Long, S. A.; Mahoney, M. W.; Rico, J. R.; Garland, D. J.; Blinn, J. R.; Collins, J. T.; Yang, S.; Huang, H.-C.; McGee, K. F.; Wendling, J. M.; Dietz, J. D.; Payne, M. A.; Homer, B. L.; Heron, M. I.; Reitz, D. B.; Hu, X. *J. Med. Chem.* **2010**, *53*, 5979−6002. (e) Nesrin, G.-K.; Ozgun, S. O.; Ayse, E.; Kemal, Y.; Sibel, S. Z.; Samil, I.; Gulberk, U.; Altan, B. A. *Bioorg. Med. Chem.* **2009**, *17*, 6761−6772. (f) Jagtap, P. G.; Degterev, A.; Choi, S.; Keys, H.; Yuan, J.; Cuny, G. D. *J. Med. Chem.* **2007**, *50*, 1886−1895.

(19) The relative configuration of diastereoisomers **3t−x** was established by $^1$H NMR spectroscopic data and assigned by comparison to a known derivatives of this type of compounds: Lóránd, T.; Szabó, D.; Földesi, A.; Párkányi, L.; Kálmán, A.; Neszmélyi, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 481−486. For these compounds, the values of $^3J_{HH}$(*cis*) are greater than those of $^3J_{HH}$(*trans*) and are in the range reported by Hassner and Michelson (10−14 Hz for the *cis* and 3−10 Hz for the *trans* isomer).