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A Hydrazine- and Phosgene-Free Synthesis of Tetrazinanones, Precursors to 1,5-Dialkyl-6-Oxoverdazyl Radicals

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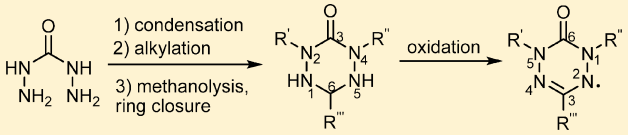
Supporting Information

ABSTRACT: A complementary approach to published synthetic methods for tetrazinanones, precursors to verdazyl radicals, is described herein. This approach uses carbohydrazide, a commercially available reagent, as a common starting material. Unlike previous methods described in the literature, this synthetic scheme does not rely on phosgene, phosgene substitutes, or the limited pool of commercially available monosubstituted hydrazines for its execution. A large variety of alkyl substitution patterns at the N-1 and N-5 positions of verdazyl radicals are possible, including both symmetrically and unsymmetrically substituted products. An initial condensation reaction of carbohydrazide with a specific aldehyde introduces the desired C-3 substituent in the final verdazyl radical product and protects the NH_2 groups during the subsequent N-1 and N-5 alkylation reactions. A succeeding methanolysis and concomitant ring-closing reaction gives the tetrazinanone. A number of known oxidation methods can then be employed to form the final verdazyl radical product.



INTRODUCTION

Verdazyl radicals, a class of resonance stabilized hydrazyl radicals, were first reported by Kuhn and Trischmann in 1963.[1] They are characterized by a six-membered heterocyclic ring with four nitrogen atoms and, for the most part, are stable enough to be isolated and stored at ambient temperature in air for extended periods of time.[2] This remarkable property has been attributed to the spin delocalization of the single electron across all four nitrogens. Verdazyl radicals' innate stability, without having to rely on sterically bulky substituent groups, has made them popular spin bearing molecules in the study of molecular magnets.[3] In addition, they have been used as spin labels in ESR,[4] as polymerization inhibitors,[5] and as mediators in living radical polymerizations.[6] Only recently have verdazyl radicals emerged as substrates for organic synthesis,[7] an interesting omission considering the preponderance of heteroatoms in their structures and, therefore, their potential as substrates for the synthesis of many new and varied heterocyclic compounds.

Verdazyl radicals containing a carbon at the 6-position can be readily categorized into two classes depending on the hybridization of that carbon. In one class, the carbon is sp^3-hybridized, either CH_2 or CHR. In the other class, the carbon is sp^2-hybridized with a carbonyl or thiocarbonyl group, and the resulting compounds are, respectively, referred to as oxoverdazyl and thioverdazyl radicals. The C-6 sp^3 class of verdazyl molecules has been synthesized exclusively with aryl substituents at the N-1 and N-5 positions, whereas the oxoverdazyl radicals have been made with aryl and alkyl groups at these same nitrogen positions.

Oxoverdazyl radicals were first reported in 1980 by Neugebauer and Umminger[8] and have been our group's focus for making several classes of heterocycles, including oxadiazolones,[9] pyrazolotriazinones, dihydropyrazolotetrazinones, and tetrahydropyrazolotetrazinones.[10] The scope of this work, to date, has been limited to the 1,5-dimethyl-3-aryl-6-oxoverdazyl radicals since they were the easiest to make using previously reported syntheses. The synthetic procedure reported herein allows the expansion of the substitution patterns available in these heterocycles by enabling the alkyl groups at N-1 and N-5 to be varied with relative ease.

The most common procedure used in the preparation of oxoverdazyl radicals uses either phosgene or the safer alternative reagent triphosgene, which generates phosgene in situ, with alkyl or aryl hydrazines, sometimes requiring protection of the NH_2 groups, to provide 1,1′-disubstituted-carbonic dihydrazides. The dihydrazides are condensed with an aldehyde to yield tetrazinanones, which are subsequently oxidized using any one of a number of oxidants, such as $NaIO_4$, $K_3Fe(CN)_6$, PbO_2, or Dess–Martin reagent, to afford the verdazyl radicals.[11] This approach is greatly limited by the choice of commercially available monosubstituted hydrazines and, in our particular case, is further limited by our inability to purchase methyl hydrazine because of its restricted sale in Canada. The method also only provides symmetrically substituted N-1 and N-5 verdazyl radicals, and even then, there is a restriction to the steric bulk of the alkyl group that can be accommodated. When the alkyl group in the alkyl hydrazine is bulky, phosgene reacts with the NH_2 rather than the desired NH group. As a consequence, the N-1, N-5-diisopropyl derivative is made using a protecting group

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Scheme 1. Synthetic Pathway

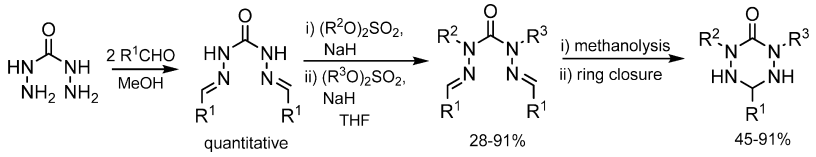
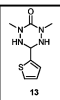
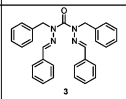
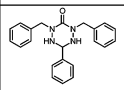
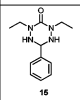
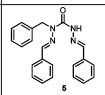
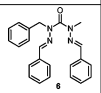
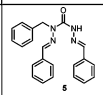
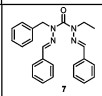
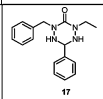
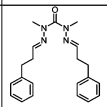
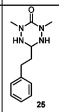
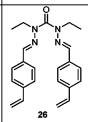
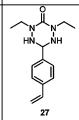


Table 1. Products and Reaction Yields of Mono- and Dialkylation and Methanolysis and Ring-Closure Reactions

Entry	Product of first alkylation	% Yield of first alkylation	Product of second alkylation	% Yield of second alkylation	Product of methanolysis and ring closure	% Yield of methanolysis and ring closure
1		85	N/A	N/A		88
2		56	N/A	N/A		62
3		91	N/A	N/A		91
4		82	N/A	N/A		82
5		80		88		45
6		79		88		49
7		74		80		72

Entry	Product of first alkylation	% Yield of first alkylation	Product of second alkylation	% Yield of second alkylation	Product of methanolysis and ring closure	% Yield of methanolysis and ring closure
8		80		75		69
9		94	N/A	N/A	N/A	N/A
10		56		86		84
11		90	N/A	N/A		46
12		28	N/A	N/A		64

approach, specifically a Boc group, to limit the otherwise unsubstituted nitrogen's nucleophilicity, to form the symmetrical 1,1′-diisopropyl-carbonic dihydrazide.[12]

Unsymmetrical N-1-aryl-N-5-alkyl oxoverdazyl radicals have been prepared by Milcent and co-workers[13] with a procedure subsequently refined by Brook and co-workers.[14] A hydrazone, obtained from a condensation reaction between an aldehyde and an aryl hydrazine, is reacted with an equivalent of phosgene in the presence of triethylamine. The intermediate acyl ammonium ion formed in situ is then reacted with a Boc-protected alkyl hydrazine. The Boc group is removed by acid hydrolysis, and a subsequent ring-closing reaction produces the desired tetrazinanone. While effective, the method still relies on commercially available aryl hydrazines, as well as the toxic and expensive triphosgene reagent. To date, unsymmetrically substituted 1,5-dialkyl-oxoverdazyls have not been made.

RESULTS AND DISCUSSION

Herein, we report an alternative synthesis of symmetrical and unsymmetrical 2,4-dialkyl-1,2,4,5-tetrazinan-3-ones that avoids the use of phosgene and alkyl hydrazines. As illustrated in the examples provided, this synthetic strategy allows the realization of previously unreported verdazyl radicals specifically based on the tetrazinanones **15**−**19** and **23**. Scheme 1 illustrates the general synthetic approach.

The synthesis is initiated with commercially available carbohydrazide. Condensation with an aryl aldehyde protects the NH_2 groups from the subsequent alkylation reaction while introducing the desired C-3 aryl substituent in the target verdazyl radical. N-alkylation is typically accomplished in anhydrous tetrahydrofuran (THF) with the appropriate dialkylsulfate and sodium hydride. Although alkyl sulfates are typically used for consistency, alkyl iodides also work well,

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except in cases where their boiling point is inconveniently low. In the cases where the two alkyl groups differ, alkylation is performed stepwise with the first step requiring smaller equivalences of the alkylating agent and sodium hydride. Fortuitously, the monoalkylated carbohydrazide is less reactive than carbohydrazide itself, enabling the monoakylation to proceed in high yield and purity. The reaction to form the dialkylated product is then accomplished using additional alkylating agent and NaH. In cases where higher reaction temperatures are necessary for the second alkylating reaction to reach completion, anhydrous toluene can be substituted for THF. The last steps in the reaction sequence, methanolysis and ring closure, occur concomitantly to produce the tetrazinanone, which can then be oxidized to the verdazyl radical. Methanolysis and ring closure is achieved in methanol at room temperature in 1 h with *p*-toluenesulfonic acid as an acid catalyst. One hydrazone group on the starting material undergoes acid-catalyzed methanolysis and the newly formed free amine attacks the C=N bond of the remaining hydrazone, resulting in a 6-*endotrig* cyclization to form the product tetrazinanone. In our initial studies of this last reaction, it was observed by TLC and ^{1}H NMR that the starting dialkylated bishydrazone was in equilibrium with the tetrazinanone and the free aldehyde, preventing the reaction from going beyond ~50% conversion. Adding carbohydrazide to react with the free aldehyde to form the corresponding mono- and dihydrazones resulted in significant increases in the yield of the tetrazinanone. The hydrazones conveniently precipitated out of solution and were readily isolated by filtration. They were subsequently used as starting materials when the reaction scheme was repeated.

Table 1 shows a series of tetrazinanones prepared by this method as an illustration of the scope of the synthetic procedure. The alkylation reactions proceed well with primary alkyl groups; however, secondary groups (i.e., isopropyl, cyclohexyl) were problematic, which is where Milcent's synthesis[11] could be applied instead. Also, when thiocarbohydrazide was used as a starting material in an attempt to make a 6-thioverdazyl radical, alkylation was observed to occur selectively on only one nitrogen and on the sulfur, affording compound **20** in high yield (94%), rather than the desired di-N-alkylated product. Yields for the alkylation reactions range from 28 to 91%, and yields for the methanolysis and ring-closure reactions range from 45 to 91%.

CONCLUSION

To conclude, a synthesis complementary to existing methods to make tetrazinanones, without the use of phosgene or hydrazines, that can be oxidized to 1,5-dialkyl-6-oxoverdazyl radicals, is described. This method, via stepwise alkylation, can be readily used to generate unsymmetrical substitution patterns in 1,5-dialkyl-6-oxoverdazyl radicals that have not been previously reported in the literature. The scope of available alkyl substituents at these positions is greatly improved over current methods due to the wider commercial availability of alkylating agents relative to the monosubstituted hydrazines used in most of the other previously published procedures. Both aryl and alkyl groups can be introduced at the C-3 position of the verdazyl radical by using the appropriate substituted aldehyde during the initial condensation reaction.

EXPERIMENTAL SECTION

General. Silica gel chromatography was performed with silica gel 60 (particle size 40–63 Å). Carbo-di-*N*-benzylhydrazides were previously synthesized by condensation of carbohydrazide with the appropriate aldehyde. NMR spectra were recorded at 23 °C, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectroscopy. Chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (δ = 0 ppm) for ^{1}H NMR spectra and $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants (J) are reported in hertz (Hz). Mass spectrometry was performed with an ESI source, MS/MS, and accurate mass capabilities, associated with a capillary LC system.

General Methanolysis and Ring-Closure Procedure. Carbo-di(*N*′-benzylidene-*N*-methylhydrazide) (**1**) (5.00 g, 17 mmol) was dissolved in 250 mL of methanol. *p*-Toluenesulfonic acid (4.85 g, 25.5 mmol) and carbohydrazide (2.30 g, 25.5 mmol) were added to the solution, and the reaction was allowed to stir for 1 h at room temperature. Once the reaction was complete, as indicated by disappearance of (**1**) on TLC, sodium methoxide was added incrementally until the solution was basic, pH ~ 10. Following this, the solvent was evaporated in vacuo and the crude product was filtered through a short silica gel column using 1:19 methanol in ethyl acetate as the eluent and recrystallized in 1:2 EtOAc in hexanes to yield white needle-like crystals (3.07 g, 88%): mp 103–105 °C; FT-IR (ν, cm^{-1}, KBr) 3254, 3218, 2967, 2938, 2877, 1598, 1506, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (d, J = 7.3 Hz, 2H), 7.42–7.34 (m, 3H), 5.09–5.02 (t, J = 9.9 Hz, 1H), 4.40–4.35 (d, J = 10.0 Hz, 2H), 3.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.2, 128.72, 128.67, 126.5, 69.4, 38.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_{15}N_4O$, 207.12459; found, 207.12373.

Carbo-di(*N*′-benzylidene-*N*-methylhydrazide) (1). Carbo-di-*N*-benzylhydrazide (5.10 g, 19.1 mmol) was added to a 500 mL round-bottom flask and dissolved in 200 mL of dry THF with stirring. Dimethylsulfate (2.2 equiv, 5.30 g, 3.9 mL, 42.0 mmol) was added, followed by a slow addition of 3 equiv of sodium hydride (1.38 g, 57 mmol). The solution was brought to reflux and allowed to react for 2 h. The reaction mixture was cooled to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol until no effervescence was observed with added methanol. The volume of the reaction mixture was reduced in vacuo and then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (3:2 EtOAc in hexanes as the eluent) and recrystallized in 1:19 EtOAc in hexanes to yield off-white crystals (4.73 g, 85%): mp 131–134 °C; FT-IR (ν, cm^{-1}, KBr) 3062, 3030, 2952, 2919, 1656, 1597, 1478; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.66–7.60 (m, 4H), 7.32–7.27 (m, 6H), 3.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 137.7, 135.3, 129.1, 128.6, 127.0, 32.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{19}N_4O$, 295.15589; found, 295.15631.

Carbo-di(*N*′-2-thienylidene-*N*-methylhydrazide) (2). Carbo-di-*N*-2-thienylhydrazide (1.00 g, 3.59 mmol) was added to a 100 mL round-bottom flask and dissolved in 50 mL of dry THF with stirring. Dimethylsulfate (2.2 equiv, 1.22 g, 0.9 mL, 7.90 mmol) was added, followed by a slow addition of 3 equiv of sodium hydride (259 mg, 10.8 mmol). The solution was heated at reflux for 2 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was carefully quenched with the slow addition of methanol. The solution volume was reduced in vacuo and then taken up in 50 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was isolated using silica gel column chromatography (2:3 EtOAc in hexanes as the eluent) and recrystallized in 1:4 EtOAc in hexanes to yield white crystals (613 mg, 56%): mp 160–163 °C; FT-IR (ν, cm^{-1}, KBr) 3086, 3072, 1645, 1587, 1420; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 2H), 7.24–7.19 (m, 4H), 7.02–6.99 (m, 2H), 3.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 140.6, 132.8, 127.9, 126.9, 126.7, 33.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{15}N_4OS_2$, 307.06873; found, 307.06962.

Carbo-di(*N*′-benzylidene-*N*-benzylhydrazide) (3). Carbo-di-*N*-benzylhydrazide (6.00 g, 22.5 mmol) was added to a 500 mL round-

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bottom flask and dissolved in 150 mL of anhydrous toluene with stirring. Benzylbromide (2.2 equiv, 8.40 g, 5.9 mL, 49.6 mmol) was added, followed by the slow addition of 3 equiv of sodium hydride (1.62 g, 67.6 mmol). The solution was heated at reflux for 24 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was carefully quenched by the slow addition of methanol. The solution was taken up in 100 mL of EtOAc and washed three times with 70 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The resulting product was filtered through a short silica gel column (DCM as the eluent) and recrystallized in methanol to yield colorless granular crystals (9.16 g, 91%): mp 117−120 °C; FT-IR (ν, cm^{-1}, KBr) 3052, 2972, 2927, 1669, 1602, 1495; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.43−7.38 (m, 8H), 7.37−7.32 (m, 4H), 7.29−7.22 (m, 3H), 7.21−7.14 (m, 5H), 5.36 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 139.1, 135.9, 134.9, 128.9, 128.7, 128.3, 127.0, 126.9, 126.3, 49.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{27}N_4O$, 447.21849; found, 447.21949.

Carbo-di(*N*′-benzylidene-*N*-ethylhydrazide) (4). Carbo-di-*N*-benzylhydrazide (7.00 g, 26.3 mmol) was added to a 500 mL round-bottom flask and dissolved in 150 mL of anhydrous toluene with stirring. Diethylsulfate (2.2 equiv, 8.90 g, 7.4 mL, 57.9 mmol) was added, followed by a slow addition of 3 equiv of sodium hydride (1.89 g, 78.9 mmol). The solution was brought to reflux and allowed to react for 24 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:199 methanol in DCM as the eluent) and recrystallized from 1:19 EtOAc in hexanes to yield off-white crystals (6.95 g, 82%): mp 83−85 °C; FT-IR (ν, cm^{-1}, KBr) 3022, 2978, 2934, 2873, 1659, 1604, 1597, 1464; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 7.61−7.56 (m, 4H), 7.28−7.24 (m, 6H), 4.10−4.03 (q, J = 7.1 Hz, 4H), 1.34−1.28 (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 138.5, 135.2, 128.9, 128.4, 126.8, 39.8, 11.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{23}N_4O$, 323.18719; found, 323.18744.

Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-benzylhydrazide) (5). Carbo-di-*N*-benzylhydrazide (5.00 g, 18.8 mmol) was added to a 500 mL round-bottom flask and dissolved in 250 mL of dried THF with stirring. Benzylbromide (1.1 equiv, 3.53 g, 2.46 mL, 20.7 mmol) was added, followed by the slow addition of 2 equiv of sodium hydride (901 mg, 37.6 mmol). The solution was heated to reflux and allowed to react for 4 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 150 mL of EtOAc and washed three times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:49 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white crystals (5.35 g, 80%): mp 188−191 °C; FT-IR (ν, cm^{-1}, KBr) 3338, 3029, 1708, 1607, 1498, 1485; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.15 (s, 1H), 7.82−7.77 (m, 2H), 7.58−7.51 (m, 3H), 7.42−7.21 (m, 11H), 5.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 145.5, 138.8, 135.1, 133.9, 129.8, 129.7, 128.8, 128.6, 128.5, 127.33, 127.29, 126.8, 126.5, 45.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{21}N_4O$, 357.17154; found, 357.17284.

Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-methylhydrazide) (6). Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-benzylhydrazide) (**5**) (2.40 g, 6.73 mmol) was added to a 250 mL round-bottom flask and dissolved in 100 mL of anhydrous toluene with stirring. Dimethylsulfate (1.1 equiv, 934 mg, 0.70 mL, 7.40 mmol) was added, followed by slow a addition of 2 equiv of sodium hydride (323 mg, 13.5 mmol). The solution was heated to 85 °C and allowed to react for 2 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution volume was reduced in vacuo. This solution was then taken up in 75 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (DCM as the eluent) and recrystallized from methanol to yield off-white crystals (2.20 g, 88%): mp 97−99 °C; FT-IR (ν, cm^{-1}, KBr) 3061, 3024, 1708, 1667, 1604, 1423; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.62 (s, 1H), 7.54−7.46 (m, 4H), 7.39−7.30 (m, 4H), 7.28−7.17 (m, 7H), 5.30 (s, 2H), 3.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 139.1, 137.7, 135.9, 135.1, 134.9, 128.93, 128.90, 128.7, 128.4, 128.3, 127.0, 126.89, 126.86, 126.3, 49.3, 32.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{23}N_4O$, 371.18719; found, 371.18559.

Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-ethylhydrazide) (7). Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-benzylhydrazide) (**5**) (625 mg, 1.75 mmol) was added to a 100 mL round-bottom flask and dissolved in 20 mL of anhydrous toluene with stirring. Diethylsulfate (1.2 equiv, 324 mg, 0.27 mL, 2.10 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (84 mg, 3.51 mmol). The solution was heated to reflux and allowed to react for 10 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by a slow addition of methanol, and the solution volume was reduced in vacuo. This solution was then taken up in 50 mL of EtOAc and washed once with 100 mL of 1 M $NaOH_{(aq)}$ and two more times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (DCM as the eluent) to yield an orange oil (510 mg, 75%): FT-IR (ν, cm^{-1}, KBr) 3061, 3025, 2974, 2933, 1665, 1598, 1426; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.61 (s, 1H), 7.50−7.42 (m, 4H), 7.39−7.29 (m, 4H), 7.27−7.13 (m, 7H), 5.28 (s, 2H), 4.16−4.04 (q, J = 6.9 Hz, 2H), 1.36−1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 139.1, 138.6, 136.2, 135.2, 135.1, 129.0, 128.9, 128.8, 128.5, 128.3, 127.05, 126.94, 126.93, 126.4, 49.6, 39.7, 11.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{25}N_4O$, 385.20284; found, 385.20202.

Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-ethylhydrazide) (8). Carbo-di-*N*-benzylhydrazide (5.00 g, 18.8 mmol) was added to a 500 mL round-bottom flask and dissolved in 250 mL of dried THF with stirring. Diethylsulfate (1.1 equiv, 3.18 g, 2.6 mL, 20.7 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (902 mg, 37.6 mmol). The solution was heated to reflux and allowed to react for 4 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. The solution was then taken up in 150 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:99 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white crystals (4.38 g, 79%): mp 128−130 °C; FT-IR (ν, cm^{-1}, KBr) 3298, 3267, 3018, 2979, 1681, 1516, 1404; ^1H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.07 (s, 1H), 7.78−7.74 (m, 2H), 7.68−7.64 (m, 3H), 7.46−7.33 (m, 6H), 4.13−4.07 (q, J = 7.1 Hz, 2H), 1.24−1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 145.1, 137.0, 134.3, 134.0, 129.63, 129.61, 128.7, 128.4, 127.2, 126.7, 35.4, 11.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{21}N_4O$, 309.17154; found, 309.17177.

Carbo-*N*′-benzylidene-*N*-ethylhydrazide(*N*′-benzylidene-*N*-methylhydrazide) (9). Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-ethylhydrazide) (**8**) (4.37 g, 14.8 mmol) was added to a 500 mL round-bottom flask and dissolved in 200 mL of anhydrous toluene with stirring. Dimethylsulfate (1.2 equiv, 2.24 g, 1.7 mL, 17.8 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (710 mg, 29.6 mmol). The solution was heated to 85 °C and allowed to react for 2 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol, and the solution volume was reduced in vacuo. The solution was then taken up in 150 mL of EtOAc and washed three times with 100 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:199 methanol in DCM as the eluent) to yield off-white crystals

(4.02 g, 88%): mp 99−101 °C; FT-IR (ν, cm^{-1}, KBr) 3062, 3023, 2980, 2933, 2903, 1651, 1598, 1427; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73 (s, 1H), 7.64−7.58 (m, 4H), 7.31−7.25 (m, 6H), 4.12−4.04 (q, J = 7.1 Hz, 2H), 3.47 (s, 3H), 1.34−1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.5, 137.3, 135.2, 135.1, 129.0, 128.8, 128.41, 128.36, 126.9, 126.8, 39.6, 33.0, 11.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{21}N_4O$, 309.17154; found, 309.17245.

Carbo-*N*′-benzylidene-*N*-methylhydrazide(*N*′-benzylidene-*N*-propylhydrazide) (10). Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-propylhydrazide) (**11**) (2.00 g, 6.49 mmol) was added to a 250 mL round-bottom flask and dissolved in 40 mL of anhydrous toluene with stirring. Dimethylsulfate (1.4 equiv, 1.15 g, 0.86 mL, 9.08 mmol) was added, followed by a slow addition of 2.2 equiv of sodium hydride (340 mg, 14.3 mmol). The solution was heated to 85 °C and allowed to react for 2 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol, and the solution volume was reduced in vacuo. This solution was then taken up in 75 mL of EtOAc and washed three times with 50 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:99 methanol in DCM as the eluent) to yield a light yellow oil (1.67 g, 80%): FT-IR (ν, cm^{-1}, KBr) 3059, 3027, 2962, 2932, 2874, 1666, 1598, 1572, 1422; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.65 (s, 1H), 7.63−7.56 (m, 4H), 7.24−7.17 (m, 6H), 4.98−4.91 (t, J = 7.4 Hz, 2H), 3.37 (s, 3H), 1.79−1.68 (sextet, J = 7.4 Hz, 2H), 1.00−0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 138.3, 137.3, 135.3, 135.2, 129.0, 128.8, 128.42, 128.37, 126.89, 126.85, 46.3, 33.0, 19.2, 11.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{23}N_4O$, 323.1866; found, 323.1866.

Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-propylhydrazide) (11). Carbo-di-*N*-benzylhydrazide (2.50 g, 9.39 mmol) was added to a 500 mL round-bottom flask and dissolved in 100 mL of dried THF with stirring. Iodopropane (1.2 equiv, 1.92 g, 1.1 mL, 11.3 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (451 mg, 18.8 mmol). The solution was heated to reflux and allowed to react for 24 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (2:98 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield off-white crystals (2.14 g, 74%): mp 114−116 °C; FT-IR (ν, cm^{-1}, KBr) 3327, 2960, 2937, 2874, 1695, 1608, 1511, 1402; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.05 (s, 1H), 7.77−7.73 (m, 2H), 7.67−7.63 (m, 2H), 7.61 (s, 1H), 7.45−7.31 (m, 6H), 4.02−3.96 (t, J = 7.5 Hz, 2H), 1.70−1.59 (sextet, J = 7.5 Hz, 2H), 1.00−0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 145.1, 137.1, 134.2, 134.0, 129.6, 128.7, 128.4, 127.2, 126.7, 42.1, 18.9, 11.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{21}N_4O$, 309.17154; found, 309.17177.

2,4-Dimethyl-6-phenyl-1,2,4,5-tetrazinan-3-one (12). Carbo-di(*N*′-benzylidene-*N*-methylhydrazide) (**1**) (5.00 g) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (3.07 g, 88%): mp 103−105 °C; FT-IR (ν, cm^{-1}, KBr) 3254, 3218, 2967, 2938, 2877, 1598, 1506, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.51 (d, J = 7.3 Hz, 2H), 7.42−7.34 (m, 3H), 5.09−5.02 (t, J = 9.9 Hz, 1H), 4.40−4.35 (d, J = 10.0 Hz, 2H), 3.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.2, 128.72, 128.67, 126.5, 69.4, 38.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{10}H_{15}N_4O$, 207.12459; found, 207.12373.

2,4-Dimethyl-6-(thiophen-2-yl)-1,2,4,5-tetrazinan-3-one (13). Carbo-di(*N*′-2-thienylidene-*N*-methylhydrazide) (**2**) (193 mg) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (82 mg, 62%): mp 123−125 °C; FT-IR (ν, cm^{-1}, KBr) 3246, 2970, 2923, 2875, 1602, 1507, 1434; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.29 (d, J = 4.9 Hz, 1H), 7.16−7.13 (m, 1H), 7.04−7.00 (t, J = 4.5 Hz, 1H), 5.24−5.18 (t, J = 8.8 Hz, 1H), 4.58−4.53 (d, J = 8.8 Hz, 2H), 3.15 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 138.1, 127.1, 126.0, 125.8, 66.9, 38.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_8H_{13}N_4OS$, 213.08101; found, 213.08115.

2,4-Dibenzyl-6-phenyl-1,2,4,5-tetrazinan-3-one (14). Carbo-di(*N*′-benzylidene-*N*-benzylhydrazide) (**3**) (1.50 g) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (1.09 g, 91%): mp 147−150 °C; FT-IR (ν, cm^{-1}, KBr) 3256, 3249, 3227, 1594, 1501, 1449; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.24 (m, 15H), 4.82−4.67 (m, 5H), 4.23−4.17 (d, J = 10.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 137.6, 134.8, 128.6, 128.4, 128.3, 127.3, 126.1, 69.5, 53.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{23}N_4O$, 359.18719; found, 359.18893.

2,4-Diethyl-6-phenyl-1,2,4,5-tetrazinan-3-one (15). Carbo-di-(*N*′-benzylidene-*N*-ethylhydrazide) (**4**) (347 mg) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (252 mg, 82%): mp 70−72 °C; FT-IR (ν, cm^{-1}, KBr) 3231, 3063, 3034, 2972, 2930, 2868, 1600, 1496, 1452, 1421; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.52 (m, 2H), 7.43−7.34 (m, 3H), 4.94−4.86 (t, J = 11.2 Hz, 1H), 4.19−4.13 (d, J = 11.3 Hz, 2H), 3.73−3.63 (sextet, J = 7.0 Hz, 2H), 3.56−3.45 (sextet, J = 7.0 Hz, 2H), 1.23−1.18 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 135.4, 128.8, 128.7, 126.3, 70.4, 44.6, 12.4; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_{19}N_4O$, 235.15589; found, 235.15581.

2-Benzyl-4-methyl-6-phenyl-1,2,4,5-tetrazinan-3-one (16). Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-methylhydrazide) (**6**) (6.10 g) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (2.11 g, 45%): mp 98−100 °C; FT-IR (ν, cm^{-1}, KBr) 3238, 3030, 2909, 1687, 1597, 1514; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.27 (m, 10H), 4.99−4.92 (t, J = 10.4 Hz, 1H), 4.79−4.73 (d, J = 14.5 Hz, 1H), 4.69−4.63 (d, J = 14.5 Hz, 1H), 4.35−4.30 (d, J = 10.4 Hz, 1H), 4.24−4.19 (d, J = 10.3 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 137.7, 134.9, 128.62, 128.57, 128.5, 128.3, 127.2, 126.2, 69.4, 53.5, 37.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_4O$, 283.15589; found, 283.15616.

2-Benzyl-4-ethyl-6-phenyl-1,2,4,5-tetrazinan-3-one (17). Carbo-*N*′-benzylidene-*N*-benzylhydrazide(*N*′-benzylidene-*N*-ethylhydrazide) (**7**) (290 mg) was reacted according to the general methanolysis and ring-closure procedure to yield an orange oil (154 mg, 69%): FT-IR (ν, cm^{-1}, KBr) 3234, 3062, 3030, 2971, 2927, 1613, 1495, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.20 (m, 10H), 4.82−4.56 (m, 3H), 4.35−4.27 (m, 2H), 3.73−3.62 (sextet, J = 7.0 Hz, 1H), 3.46−3.36 (sextet, J = 7.0 Hz, 1H), 1.19−1.14 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 137.8, 135.1, 128.5, 128.4, 128.3, 127.2, 126.2, 69.8, 53.5, 44.6, 12.3; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{21}N_4O$, 297.17154; found, 297.17162.

2-Ethyl-4-methyl-6-phenyl-1,2,4,5-tetrazinan-3-one (18). Carbo-*N*′-benzylidene-*N*-ethylhydrazide(*N*′-benzylidene-*N*-methylhydrazide) (**9**) (200 mg) was reacted according to the general methanolysis and ring-closure procedure to yield white needle-like crystals (70 mg, 49%): mp 78−80 °C; FT-IR (ν, cm^{-1}, KBr) 3251, 3226, 2972, 2932, 2871, 1593, 1490, 1450, 1430; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.40−7.28 (m, 3H), 4.89−4.81 (t, J = 10.0 Hz, 1H), 4.78−4.72 (d, J = 10.0 Hz, 1H), 4.64−4.58 (d, J = 10.0 Hz, 1H), 3.75−3.55 (sextet, J = 7.0 Hz, 1H), 3.41−3.30 (sextet, J = 7.0 Hz, 1H), 3.10 (s, 3H), 1.18−1.10 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 135.3, 128.4, 126.4, 69.7, 44.5, 37.8, 12.4; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_{17}N_4O$, 221.14024; found, 221.13961.

2-Methyl-6-phenyl-4-propyl-1,2,4,5-tetrazinan-3-one (19). Carbo-*N*′-benzylidene-*N*-methylhydrazide(*N*′-benzylidene-*N*-propylhydrazide) (**10**) (500 mg) was reacted according to the general methanolysis and ring-closure procedure to yield a yellow-orange oil (262 mg, 72%): FT-IR (ν, cm^{-1}, KBr) 3235, 3061, 3032, 2961, 2930, 2873, 1690, 1616, 1451; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.40−7.28 (m, 3H), 4.92−4.84 (t, J = 9.9 Hz, 1H), 4.77−4.69 (d, J = 10.1 Hz, 1H), 4.62−4.54 (d, J = 9.9 Hz, 1H), 3.55−3.44 (m, 1H), 3.37−3.26 (m, 1H), 3.11 (s, 3H), 1.68−1.55 (sextet, J = 7.3 Hz, 2H), 0.93−0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

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δ 154.8, 135.5, 128.6, 126.5, 69.7, 51.6, 38.0, 20.7, 11.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{19}N_4O$, 235.1553; found, 235.1558.

Methyl-*N*′-2-dibenzylidene-1-methylhydrazinecarbohydrazonothioate (20). Thiocarbo-di-*N*-benzylhydrazide (1.00 g, 3.54 mmol) was added to a 250 mL round-bottom flask and dissolved in 75 mL of dried THF with stirring. Dimethylsulfate (2.2 equiv, 0.98 g, 0.7 mL, 7.79 mmol) was added, followed by a slow addition of 3 equiv of sodium hydride (254 mg, 10.6 mmol). The solution was brought to reflux and allowed to react for 2 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol, and the solution volume was reduced in vacuo. This solution was then taken up in 50 mL of EtOAc and washed three times with 100 mL of water. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was recrystallized from 1:9 EtOAc in hexanes to yield bright yellow crystals (1.03 g, 94%): mp 64−65 °C; FT-IR (ν, cm^{-1}, KBr) 3055, 3020, 2925, 1593, 1567, 1510, 1406; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.79−7.73 (m, 2H), 7.70−7.65 (d, J = 7.3 Hz, 2H), 7.62 (s, 1H), 7.42−7.34 (m, 5H), 7.34−7.28 (t, J = 7.2 Hz, 1H), 3.55 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 155.7, 136.3, 135.3, 135.1, 129.9, 128.8, 128.6, 128.5, 127.7, 126.6, 33.4, 17.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{19}N_4S$, 311.13304; found, 311.13254.

Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-allylhydrazide) (21). Carbo-di-*N*-benzylhydrazide (2.80 g, 10.5 mmol) was added to a 250 mL round-bottom flask and dissolved in 100 mL of dried THF with stirring. Allylbromide (5 equiv, 6.36 g, 4.5 mL, 52.5 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (876 mg, 21.0 mmol). The solution was heated to reflux and allowed to react for 24 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by the slow addition of methanol. This solution was then taken up in 100 mL of EtOAc and washed three times with 200 mL of water. The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:49 methanol in DCM as the eluent) and recrystallized from 1:9 EtOAc in hexanes to yield yellow crystals (1.80 g, 56%): mp 43−45 °C; FT-IR (ν, cm^{-1}, KBr) 3347.1, 3060.6, 3024.6, 1678.5, 1510.4, 1486.3; ^1H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.08 (s, 1H), 7.78−7.73 (m, 2H), 7.66−7.62 (m, 2H), 7.58 (s, 1H), 7.44−7.32 (m, 6H), 5.84−5.73 (m, 1H), 5.22−5.12 (m, 2H), 4.69−4.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 145.4, 138.7, 134.1, 134.0, 130.5, 129.71, 129.69, 128.7, 128.4, 127.2, 126.8, 117.0, 43.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_4O$, 307.1553; found, 307.1558.

Carbo-*N*′-benzylidene-*N*-methylhydrazide(*N*′-benzylidene-*N*-allylhydrazide) (22). Carbo-*N*′-benzylidene(*N*′-benzylidene-*N*-allylhydrazide) (**11**) (1.30 g, 4.24 mmol) was added to a 100 mL round-bottom flask and dissolved in 50 mL of anhydrous THF with stirring. Dimethylsulfate (1.2 equiv, 643 mg, 0.48 mL, 5.10 mmol) was added, followed by a slow addition of 2 equiv of sodium hydride (204 mg, 8.48 mmol). The solution was heated to reflux and allowed to react for 3 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol, and the solution volume was reduced in vacuo. This solution was then taken up in 75 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:99 methanol in DCM eluent) to yield a light orange oil (1.17 g, 86%): FT-IR (ν, cm^{-1}, KBr) 3060.1, 3024.1, 1664.3, 1606.0, 1421.5, 1384.4; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.64 (s, 1H), 7.63−7.55 (m, 4H), 7.22−7.16 (m, 6H), 5.92−5.80 (m, 1H), 5.34−5.26 (d, J = 17.3 Hz, 1H), 5.22−5.16 (d, J = 10.6 Hz, 1H), 4.64−4.60 (m, 2H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 138.7, 137.5, 135.3, 135.1, 131.5, 129.0, 128.9, 128.4, 126.93, 126.89, 116.8, 47.2, 32.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}N_4O$, 321.1709; found, 321.1710.

2-Methyl-6-phenyl-4-allyl-1,2,4,5-tetrazinan-3-one (23). Carbo-*N*′-benzylidene-*N*-methylhydrazide(*N*′-benzylidene-*N*-allylhydrazide) (**22**) (1.04 g, 4.48 mmol) was reacted according to the general methanolysis and ring-closure procedure to yield white crystals (632 mg, 84%): mp 74−76 °C; FT-IR (ν, cm^{-1}, KBr) 3250.3, 3226.1, 3084.0, 3009.3, 2971.4, 2910.4, 1696.4, 1488.8; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.48 (m, 2H), 7.37−7.27 (m, 3H), 5.89−5.77 (m, 1H), 5.25−5.18 (dd, J = 17.1 Hz, 1.5 Hz, 1H), 5.16−5.11 (dd, J = 10.2 Hz, 1.3 Hz, 1H), 4.92−4.80 (m, 2H), 4.77−4.70 (d, J = 8.9 Hz, 1H), 4.14−4.06 (m, 1H), 4.01−3.93 (m, 1H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 135.3, 133.5, 128.4, 126.5, 117.1, 69.5, 52.6, 37.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{17}N_4O$, 233.1396; found, 233.1395.

Carbo-di-(*N*′-3-phenylpropionyl-*N*-methylhydrazide) (24). Carbo-di-*N*-3-phenylpropionylhydrazide (815 mg, 2.52 mmol) was added to a 100 mL round-bottom flask and dissolved in 50 mL of dried THF with stirring. Dimethylsulfate (2.2 equiv, 732 mg, 0.55 mL, 5.79 mmol) was added, followed by a slow addition of 3 equiv of sodium hydride (0.182 g, 7.58 mmol). The solution was brought to reflux and allowed to react for 2 h. The reaction mixture was allowed to cool to 0 °C, the unreacted sodium hydride was quenched by the slow addition of methanol, and the solution volume was reduced in vacuo. This solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:1 EtOAc in hexanes as the eluent) to yield a yellow oil (0.797 g, 90%): FT-IR (ν, cm^{-1}, KBr) 3060, 3025, 2926, 1623, 1479, 1453, 1385, 1334; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 4H), 7.22−7.17 (m, 6H), 7.03 (t, 2H), 3.18 (s, 6H), 2.86 (t, 4H), 2.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 141.1, 140.9, 128.5, 128.4, 126.1, 34.5, 33.4, 33.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{27}N_4O$, 351.21849; found, 351.21844.

2,4-Dimethyl-6-(3-phenyl)propionyl-1,2,4,5-tetrazinan-3-one (25). Carbo-di(*N*′-3-phenylpropionyl-*N*-methylhydrazide) (**24**) (0.424 g) was reacted according to the general methanolysis and ring-closure procedure to yield an off-white solid (130 g, 46%): mp 82−84 °C; FT-IR (ν, cm^{-1}, KBr) 3232, 3205, 2956, 2919, 2869, 1597, 1495, 1439, 1392; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2H), 7.23−7.17 (m, 3H), 4.21−4.12 (d, J = 9.9 Hz, 2H), 3.82−3.69 (m, 1H), 3.07 (s, 6H), 2.81−2.74 (m, 2H), 1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 140.7, 128.36, 128.31, 126.0, 67.0, 37.9, 31.7, 31.6.1; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{15}N_4O$, 207.12459; found, 207.12373.

Carbo-di(*N*′-paravinylicbenzylidene-*N*-ethylhydrazide) (26). Carbo-di-*N*-paravinylicbenzylhydrazide (1.21 g, 4.53 mmol) was added to a 100 mL round-bottom flask and dissolved in 50 mL of anhydrous toluene with stirring. Diethylsulfate (4.0 equiv, 2.79 g, 2.3 mL, 18.1 mmol) was added, followed by a slow addition of 6 equiv of sodium hydride (0.651 g, 27.1 mmol). The solution was brought to reflux and allowed to react for 39 h. The reaction mixture was allowed to cool to 0 °C, and the unreacted sodium hydride was quenched by a slow addition of methanol. The solution was then taken up in 100 mL of EtOAc and washed three times with 75 mL of water. The crude extract was dried over anhydrous sodium sulfate, and the solvent was evaporated in vacuo. The crude product was filtered through a short silica gel column (1:1 EtOAc in hexanes as the eluent) and recrystallized from 1:19 EtOAc in hexanes to yield off-yellow solids (396 mg, 28%): mp 78−81 °C; FT-IR (ν, cm^{-1}, KBr) 3025, 2933, 1666, 1624, 1453, 1385, 1086, 752, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 2H), 7.58−7.28 (m, 8H), 6.72−6.61 (dd, J = 10.9 Hz, 6.9 Hz, 2H), 5.76−5.67 (d, J = 17.8 Hz, 2H), 5.27−5.20 (d, J = 11.8 Hz, 2H), 4.09−4.01 (q, J = 6.9 Hz, 4H), 1.34−1.27 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 138.3, 138.2, 136.4, 134.9, 127.1, 126.4, 114.3, 39.9, 11.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{27}N_4O$, 375.21849; found, 375.21848.

2,4-Diethyl-6-paravinylphenyl-1,2,4,5-tetrazinan-3-one (27). Carbo-di(*N*′-paravinylicbenzylidene-*N*-ethylhydrazide) (**26**) (108 mg) was reacted according to the general methanolysis and ring-closure procedure to yield a yellow oil (48 mg, 64%): FT-IR (ν, cm^{-1}, KBr) 3233, 2968, 2930, 1609, 1428, 1261, 1126, 1080, 1016; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53−7.48 (m, 2H), 7.45−7.40 (m, 2H), 6.77−6.67 (dd, J = 6.8 Hz, 10.9 Hz, 1H), 5.82−5.74 (d, J = 17.8 Hz, 1H), 5.33−5.26 (d, J = 10.9 Hz, 1H), 4.94−4.85 (t, J = 11.2 Hz, 1H), 4.20−4.11

(d, J = 11.3 Hz, 2H), 3.74−3.62 (sextet, J = 7.0 Hz, 2H), 3.56−3.44 (sextet, J = 7.0 Hz, 2H), 1.24−1.16 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 138.2, 136.1, 134.6, 126.4, 114.8, 70.1, 44.6, 12.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{21}N_4O$, 261.17154; found, 261.17221.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. 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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