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[1+4] Cycloaddition of Vinyl Isocyanates with Isocyanides. Construction of Functionally Elaborate Pyrrolinone Derivatives

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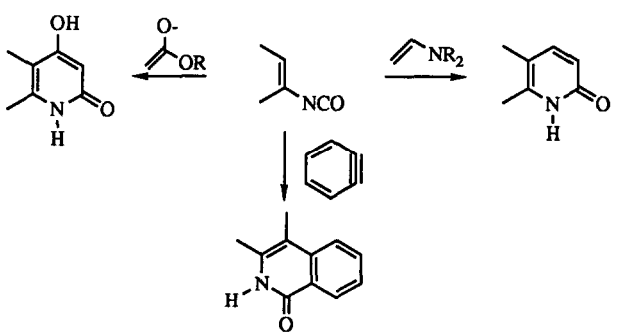
Abstract: Reaction of alkyl isocyanides with vinyl isocyanates affords highly functionalized pyrrolinone and hydroindolone products via a novel [1+4] cyclization process.

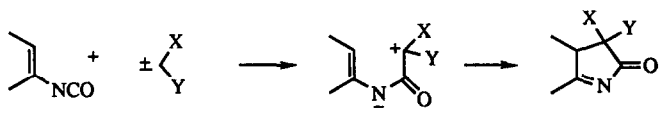
Current interest in the synthesis of pharmacologically significant members of a number of alkaloid families has stimulated the continuing development of progressively more efficient methods for the construction of five- and six-membered nitrogen heterocycles.[1] Vinyl isocyanates are versatile participants in a range of cyclization processes that afford highly substituted pyridine derivatives.[2] Exploitation of the electrophilic nature of the isocyanate carbonyl carbon by reaction with 1,2-dipole equivalents forms the basis of this methodology. The ease of preparing vinyl isocyanates from the corresponding, readily available α,β-unsaturated carboxylic acids via Curtius rearrangement is an important aspect of these transformations as well. Generic examples of typical "4+2" type cyclization reactions of vinyl isocyanates are depicted in Scheme I.

Scheme I

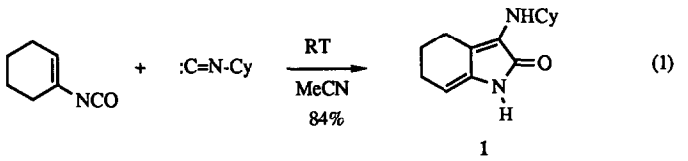


In analogy with the above combinations, the interaction of a vinyl isocyanate function with an appropriate 1,1-dipole equivalent should afford substituted pyrrolinone products via a formal [1+4] cycloaddition process (Scheme II).[3]

Scheme II



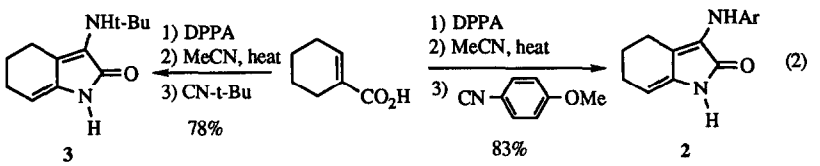
Viable 1,1-dipole equivalents are relatively rare species; however, the unique reactivity profile displayed by alkyl and aryl isocyanides suggested these species as possible reaction partners in our projected cyclization process.[4] Although these intriguing compounds have been employed for some time as key components in the well-known Passerini and Ugi reactions,[5] there has been a recent flurry of activity exploiting the unique character of isocyanide chemistry in novel approaches to a variety of alkaloid targets.[6]



(1)

1

We wish to report that a wide variety of vinyl isocyanates have been found to undergo smooth [1+4] cycloaddition with readily available cyclohexyl isocyanide (CyNC) and related species to afford highly functionalized pyrrolinone products. The reaction in equation (1) typifies the process.[7] The isocyanate partner is efficiently generated from the corresponding α,β-unsaturated carboxylic acid by treatment with diphenyl phosphorazidate (DPPA)[8] followed by heating, typically in refluxing acetonitrile. The resultant solution is then exposed to a slight excess of cyclohexyl isocyanide[9] at ambient temperature. In most cases the product precipitates from the reaction mixture and is isolated by filtration. The [1+4] cyclization proceeds smoothly with other isocyanide partners as well (Eq. (2)).

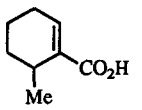
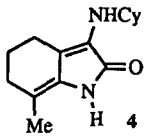
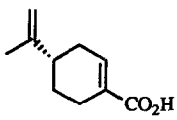
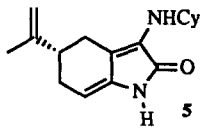
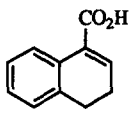
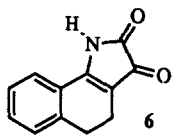
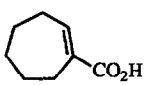
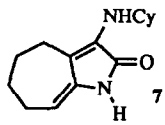
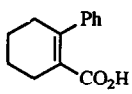
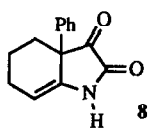


(2)

3 2

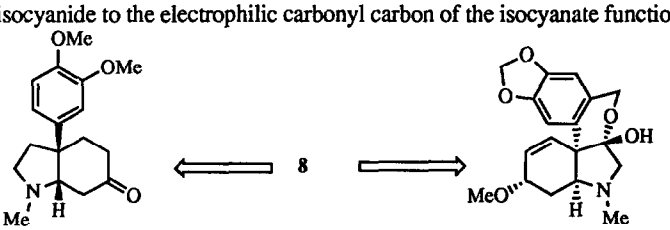
Table I displays several substituted hydroindolone products that can be readily prepared from the corresponding carboxylic acids using this sequence. In each case yields are reported from the α,β-unsaturated acid. In most cases the intermediate acyl azide is not characterized, but is immediately subjected to the Curtius thermolysis conditions. Entry 1 illustrates that the regiochemistry of the α,β-unsaturated acid with respect to the methyl group is translated with complete integrity in the final bicyclic product. A noteworthy result is shown in entry 5 in which the unsaturated acid is substituted with a β-aryl group. While the cyclization is slowed somewhat in this case, requiring elevated temperatures, a useful yield of the hydroindolone product **8** is obtained. Related intermediates could be useful for accessing alkaloids such as mesembrine[10] and tazettine.[11]

Table I. Preparation of Substituted Hydroindolones and Related Species.

Entry	Acid	Product	Yield (%)
1		 **4**	75
2		 **5**	68
3		 **6**	82[a]
4		 **7**	75
5		 **8**	51[a,b]

[a] Hydrolyzed by adventitious water in reaction mixture. [b] Cyclization performed by heating a mixture of CyNC and the corresponding isocyanate in refluxing xylene.

The success of the cyclization described above wherein bond formation occurs at a particularly hindered center illustrates a key feature of the [1+4] cyclization protocol. It is presumed that the reaction proceeds via an initial addition of the isocyanide to the electrophilic carbonyl carbon of the isocyanate function to produce dipolar

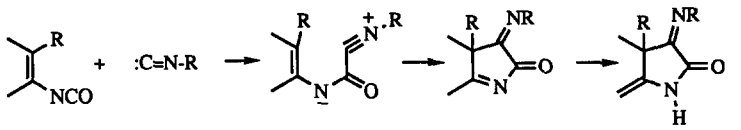


mesembrine tazettine

intermediate **A**, which then closes to afford the observed product after double bond tautomerism (Scheme III). An important consequence of this putative pathway is that the second, and presumably irreversible bond

formation benefits from being *intra*molecular in nature. This aspect of the reaction probably permits successful ring formation at hindered centers such as in entry 5, Table I.

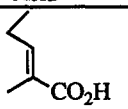
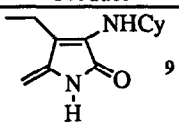
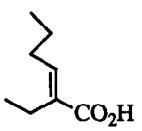
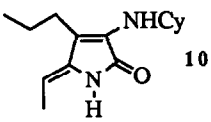
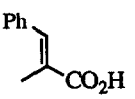
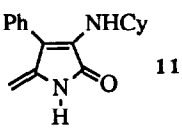
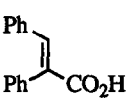
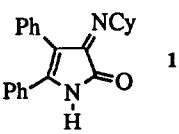
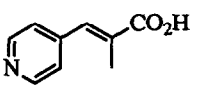
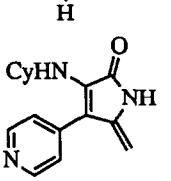
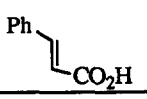
Scheme III



A

The [1+4] cyclization methodology can also be used to prepare functionally elaborate monocyclic pyrrolinone products. Examples of this type of transformation are compiled in Table II. It is noteworthy that

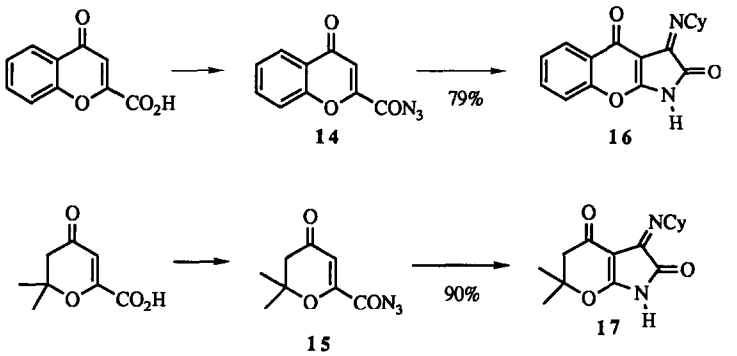
Table II. [1+4] Cycloaddition of Acyclic Vinyl Isocyanates.

Entry	Acid	Product	Yield (%)
1		 9	41
2		 10	67[a]
3		 11	77
4		 12	92
5		 13	81
6		———	–

[a] Produced as a single isomer with geometry assigned based on pertinent NOE experiments.

while this process is fairly general, it appears that a non-hydrogen substituent is required on the α-carbon of the vinyl isocyanate partner for the reaction to proceed effectively to product. This point is dramatically illustrated by comparing entries 1-5 with entry 6. Furthermore, the result in entry 4 reveals that the α-substituent need not possess hydrogen substitution to exert its influence on the cyclization event. It is possible that the α-substituent affects the course of these transformations by modifying rotamer populations either in the initial isocyanate species or at the enamide anion stage, although no independent data is currently available to support this contention.

Functionally elaborate vinyl isocyanates are also effective participants in the [1+4] cycloaddition reaction. The readily available acyl azides **14** and **15** can be converted into the corresponding isocyanates, which undergo smooth cyclization with cyclohexyl isocyanide (CyNC). A unique feature of these particular transformations is that the isocyanide partner is present in the reaction mixture during the thermal conversion of the acyl azide to the reactive isocyanate function. Yields were inferior in these cases when the cycloadditions were performed in the conventional fashion. The success of this modification suggests that this methodology will be suitable for use with highly labile vinyl isocyanate partners as well.



Work is currently underway to exploit for synthetic advantage the unique collection of functionalization present in the products of the isocyanate-isocyanide cycloaddition process.

Experimental Section

General. All reactions were conducted under a nitrogen atmosphere unless otherwise indicated. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. A General Electric QE-300 NMR spectrometer was used for obtaining the 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectra. A Varian Unity--500 spectrometer was used to obtain 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra. IR spectra were recorded on a Nicolet 30 DX spectrophotometer. Combustion analyses were performed by Midwest Microanalytical Laboratories, Indianapolis, IN and Galbraith Laboratories, Knoxville, TN. Tetrahydrofuran was distilled from sodium-benzophenone ketyl under a nitrogen atmosphere. Hexane (technical grade) was distilled at atmospheric pressure. Acetonitrile was freshly distilled from CaH_2 prior to use.

General Procedure for the [1+4] Cycloaddition of Vinyl Isocyanates with Alkyl Isocyanides. To the α,β-unsaturated carboxylic acid (1 equiv.) in toluene was added triethylamine (1 equiv.), followed after 20 min by diphenyl phosphorazidate (DPPA)[8] (1 equiv.). After stirring at rt for 30 min, the resultant solution was passed through a plug of silica gel. The solvent was removed *in vacuo* to provide the crude acyl azide, which was immediately dissolved in acetonitrile and heated at reflux for 30-40 min to effect rearrangement to the isocyanate. The solution was cooled to rt and cyclohexyl isocyanide[9] (1.2 equiv.) was added and the resulting solution allowed to stir at rt for 15 h. The precipitate that formed was isolated by filtration and washed with acetonitrile. Recrystallization from acetonitrile afforded purified product.

3-(Cyclohexylamino)-1,4,5,6-tetrahydro-2*H*-indol-2-one (1). Prepared from cyclohexene-1-carboxylic acid (10.0 g, 80.0 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (7.3 g, 67.0 mmol) in acetonitrile (50 mL) by stirring at rt for 15 h. This afforded 11.9 g (84%) of product: mp = 145-146 °C (MeCN); IR (KBr) ν 3372, 3182, 1685, 1665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09-1.33 (m, 5H), 1.61 (m, 1H), 1.72-1.81 (m, 4H), 1.95 (m, 2H), 2.24 (q, J=5.4 Hz, 2H), 2.60 (dd, J=6.0, 6.0 Hz, 2H), 3.29 (m, 1H), 3.94 (d, J=9.3 Hz, 1H, exchangeable), 5.32 (t, J=4.5 Hz, 1H), 7.73 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.7, 23.8, 24.7, 25.7, 34.3, 52.1, 104.5, 106.5, 130.4, 136.6, 168.4; mass spectrum: m/e (rel. int.) 232 (100), 189 (64), 150 (98). Anal. calcd. for $C_{14}H_{20}N_2O$: C, 72.39, H, 8.67, N, 12.06, found: C, 72.38, H, 8.61, N, 12.09.

3-(4'-Methoxyphenylamino)-1,4,5,6-tetrahydro-2*H*-indol-2-one (2). Prepared from cyclohexene-1-carboxylic acid (0.51 g, 4.1 mmol), using the general procedure for isocyanate synthesis, and 4-methoxyphenyl isocyanide[12] (0.55 g, 4.1 mmol) in acetonitrile (3 mL) by stirring at rt for 15h. The product was isolated by filtration, washed with cold ethyl ether and recrystallized from the same solvent to afford 0.72 g (85%) of product **2**: mp = 129-131 °C (ethyl ether); IR (NaCl) ν 3323, 2936, 2837, 1682, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61-1.65 (m, 2H), 2.14-2.21 (m, 4H), 3.72 (s, 3H), 5.43 (t, J=4.3 Hz, 1H), 5.90 (s, 1H, exchangeable), 6.76 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 8.27 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 24.0, 24.1, 55.6, 107.3, 112.5, 114.3, 122.3, 128.2, 134.6, 136.6, 155.6, 168.8; mass spectrum: m/e (rel. int.) 256 (100), 242 (22), 198 (3); HRMS: calcd. for $C_{15}H_{16}N_2O_2$, 256.1211, found: 256.1208. Anal. calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29, H, 6.29, N, 10.93; found: C, 69.81, H, 6.37, N, 10.81.

3-(t-Butylamino)-1,4,5,6-tetrahydro-2*H*-indol-2-one (3). Prepared from cyclohexene-1-carboxylic acid (0.51 g, 4.1 mmol), using the general procedure for isocyanate synthesis, and t-butyl isocyanide[9] (0.40 g, 4.8 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. The product was isolated by filtration, washed with cold acetonitrile and recrystallized from the same solvent to yield 0.53 g (78%) of **3**: mp 122-124 °C (MeCN): IR (NaCl) ν 3365, 3217, 2929, 1689, 1632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.73 (quint., J=6.0 Hz, 2H), 1.91 (q, J=5.4 Hz, 2H), 2.60 (t, J=6.3 Hz, 2H), 4.06 (s, 1H, exchangeable), 5.32 (t, J=4.5 Hz, 1H), 7.96 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.2, 25.4, 30.9, 51.3, 105.6, 109.8, 130.5, 137.1, 169.5; mass spectrum: m/e (rel. int.) 206 (38), 191 (16), 150 (100); HRMS: calcd. for $C_{12}H_{18}N_2O$: 206.1419, found: 206.1421.

3-(Cyclohexylamino)-7-methyl-1,4,5,6-tetrahydro-2*H*-indol-2-one (4). Prepared from 6-methyl-1-cyclohexene-1-carboxylic acid[13] (0.60 g, 4.2 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (0.39 g, 3.6 mmol) in acetonitrile (3 mL) at rt for 15 h. The product was isolated by

filtration, washed with cold MeCN and recrystallized from the same solvent to afford 0.56 g (75%) of **4**: mp = 152-154 °C (MeCN); IR (NaCl) ν 3309, 3224, 2929, 1678, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11-1.33 (m, 6H), 1.72-1.81 (m, 4H), 1.84 (s, 3H), 1.96 (m, 2H), 2.15 (m, 2H), 2.56 (t, J=6.3 Hz, 2H), 3.28 (m, 1H), 3.81 (s, 1H, exchangeable), 8.37 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 22.5, 23.6, 24.9, 25.9, 30.2, 34.4, 52.4, 108.9, 114.5, 129.9, 131.7, 168.6; mass spectrum: m/e (rel. int.) 246 (100), 203 (44), 164 (66); HRMS: calcd. for $C_{15}H_{22}N_2O$: 246.1732, found: 246.1732.

(+)-3-(Cyclohexylamino)-5(S)-isopropenyl)-1,4,5,6-tetrahydro-2*H*-indol-2-one (5). Prepared from (S)-perillic acid (2.0 g, 12.0 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (1.13 g, 10.5 mmol) in MeCN (10 mL) at rt for 15 h. The product was isolated by removing the acetonitrile and chromatographing the residue (silica gel, EtOAc/hexane, 1:5). This afforded 2.1 g (68%) of **5**: mp = 120-2 °C dec (Et_2O); $[\alpha]_D^{25}$ = +38 ° (c 0.52, EtOH); IR (CCl_4) ν 3472, 3377, 3031, 1694, 1669, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11-1.39 (m, 6H), 1.62 (m, 1H), 1.71 (m, 1H), 1.79 (s, 3H), 1.96 (m, 2H), 2.17-2.40 (m, 3H), 2.43 (m, 1H), 2.80 (q, J=11.0 Hz, 1H), 3.31 (m, 1H), 3.98 (brs, 1H, exchangeable), 4.80 (s, 2H), 5.32 (dd, J=6.0, 3.0 Hz, 1H), 7.82 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 24.6, 24.7, 25.6, 27.6, 29.1, 34.0, 34.3, 42.9, 52.1, 103.5, 106.5, 109.9, 130.7, 136.5, 148.6, 168.7; mass spectrum: m/e (rel. int.) 272 (100), 231 (78), 189 (15); HRMS: calcd. for $C_{17}H_{24}N_2O$: 272.1888, found: 272.1893.

4,5-Dihydro-1*H*-benz[g]indole-2,3-dione (6). Prepared from 3,4-dihydro-1-naphthoic acid[14] (0.70 g, 4.0 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (0.41 g, 3.7 mmol) in acetonitrile (3 mL) at rt for 15 h. The product was isolated by filtration and recrystallization from diethyl ether which afforded 0.71 g (82%) of **6**: mp = 210-212 °C dec (Et_2O); IR (Nujol) ν 3244, 1744, 1699, 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (t, J=8.0 Hz, 2H), 3.01 (t, J=8.0 Hz, 2H), 7.34-7.44 (m, 2H), 7.51-7.61 (m, 2H), 9.38 (s, 1H, exchangeable); ^{13}C NMR ($CDCl_3$) δ 16.2, 27.8, 107.5, 123.6, 124.3, 127.5, 129.2, 133.8, 141.1, 162.2, 162.7, 181.3; mass spectrum: m/e (rel. int.) 199 (100), 171 (84), 143 (56); HRMS: calcd. for $C_{12}H_9NO_2$: 199.0633, found: 199.0629.

3-(Cyclohexylamino)-4,5,6,7-tetrahydrocyclohepta[b]pyrrol-2(1*H*)-one (7). Prepared from cycloheptene-1-carboxylic acid (2.0 g, 12.0 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (1.18 g, 12.2 mmol) in acetonitrile (10 mL) at rt for 15 h. The product was isolated by filtration and recrystallization from MeCN, which afforded 2.24 g (75%) of **7**: mp = 112-114 °C (MeCN); IR (CCl_4) ν 3465, 3367, 2929, 1691, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08-1.33 (m, 6H), 1.61 (m, 1H), 1.71-1.76 (m, 5H), 1.96 (m, 2H), 2.39 (m, 2H), 2.64 (m, 2H), 3.47 (m, 1H), 3.82 (brs, 1H, exchangeable), 5.32 (t, J=5.1 Hz, 1H), 8.13 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8, 25.7, 26.4, 27.7, 28.0, 29.5, 34.6, 52.3, 111.0, 111.9, 135.2, 136.9, 167.4; mass spectrum: m/e (rel. int.) 246 (100), 203 (37); Anal. calcd. for $C_{15}H_{22}N_2O$: C, 73.13, H, 9.00, N, 11.37, found: C, 73.11, H, 9.04, N, 11.42.

3a-Phenyl-3a,4,5,6-tetrahydro-1*H*-indole-2,3-dione (8). Prepared from 2-phenylcyclohexene-1-carboxylic acid (0.4 g, 2.0 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (0.65 g, 6 mmol) in xylene (1 mL) at reflux for 6 h. The product was isolated by solvent removal and chromatography (silica gel, EtOAc/hexane 1:5). This afforded 0.17 g (51%) of compound **8**: mp = 186-188 °C (Et_2O); IR (KBr) ν 3164, 2949, 1764, 1737, 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19-1.33 (m,

1H), 1.67-1.79 (m, 1H), 1.87 (dt, J=12.9, 3.0 Hz, 1H), 2.11-2.30 (m, 2H), 2.39 (dt, J=12.9, 3.0 Hz, 1H), 5.50 (t, J=3.6 Hz, 1H), 7.33 (m, 3H), 7.44 (m, 2H), 10.46 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 22.8, 29.7, 54.5, 106.5, 127.9, 128.2, 129.0, 133.2, 135.5, 160.9, 197.3; mass spectrum: m/e (rel. int.) 227 (28), 199 (73), 198 (87), 184 (15); HRMS: calcd. for $C_{14}H_{13}NO_2$: 227.0946, found: 227.0950; Anal. calcd. for $C_{14}H_{13}NO_2 \cdot 0.5\ H_2O$: C, 71.17, H, 5.97, N, 5.92; found: C, 71.58, H, 6.24, N, 5.79.

3-(Cyclohexylamino)-1,5-dihydro-4-ethyl-5-methylene-2*H*-pyrrol-2-one (9). Prepared from the carboxylic acid (1.0 g, 8.7 mmol), using the general procedure for the isocyanate synthesis, and cyclohexyl isocyanide (0.94 g, 8.6 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. Chromatography (silica gel, EtOAc/hexanes, 1:9) afforded 0.65 g (41%) of the product as a yellow oil: IR (NaCl) ν 3379, 2929, 1700, 1683 cm^{-1}: ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.31 (m, 9H), 1.68-1.73 (m, 2H), 1.92-1.95 (m, 2H), 2.34 (q, J=7.5 Hz, 2H), 3.30-3.33 (m, 1H), 4.05 (d, J=9.0 Hz, 1H), 4.51 (s, 1H), 4.57 (s, 1H), 8.91 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 16.7, 24.6, 25.5, 34.1, 51.7, 88.3, 110.3, 133.5, 143.7, 168.9; mass spectrum: m/e (rel. int.) 220 (100), 177 (57), 138 (79); HRMS calcd for $C_{13}H_{20}N_2O$ 220.1575, found: 220.1573.

3-(Cyclohexylamino)-1,5-dihydro-5-ethylidene-4-(n-propyl)-2*H*-pyrrol-2-one (10). Prepared from the carboxylic acid (0.5 g, 3.5 mmol) using the general procedure for the isocyanate synthesis, and cyclohexyl isocyanide (0.23 g, 2.1 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. Chromatography (silica gel, hexanes/ethyl acetate, 9:1) provided 0.35 g (67%) of compound **10**: mp 116-118 °C (acetonitrile); IR (NaCl) ν 3330, 2929, 1703, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.2 Hz, 3H), 1.09-1.96 (m, 12H), 2.26 (t, J=7.5 Hz, 2H), 3.29-3.35 (m, 1H), 3.83 (s, 1H, exchangeable), 4.96 (q, J=7.5 Hz, 1H), 9.24 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 14.3, 23.7, 25.0, 25.8, 34.4, 52.2, 100.8, 112.1, 133.2, 138.2, 169.2; mass spectrum: m/e (rel. int.) 248 (6), 207 (100), 193 (25); HRMS: calcd. for $C_{15}H_{24}N_2O$: 248.1888, found: 248.1883.

3-(Cyclohexylamino)-1,5-dihydro-5-methylene-4-phenyl-2*H*-pyrrol-2-one (11). Prepared from the carboxylic acid (0.50 g, 3 mmol) using the general procedure for the isocyanate synthesis, and cyclohexyl isocyanide (0.33 g, 3 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. The precipitate was filtered (suction) and washed with cold acetonitrile (2 x 1 mL) to afford 0.55 g (77%) of **11**: mp 154-155 °C (acetonitrile); IR (NaCl) ν 2960, 2932, 1730, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76-1.09 (m, 6H), 1.38-1.70 (m, 4H), 2.93-3.03 (m, 1H), 4.31 (s, 1H, exchangeable), 4.35 (s, 1H), 4.62 (d, J=1.2 Hz, 1H), 7.30-7.36 (m, 5H), 8.45 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.4, 33.6, 51.2, 90.5, 108.9, 127.3, 127.7, 130.6, 133.1, 134.5, 144.0, 167.9; mass spectrum: m/e (rel. int.) 268 (100), 255 (53), 186 (60); HRMS: calcd. for $C_{17}H_{20}N_2O$ 268.15755, found: 268.1570. Anal. calcd. for $C_{17}H_{20}N_2O$: C, 76.08, H, 7.51, N, 10.43; found: C, 76.00, H, 7.68, N, 10.53

3-(Cyclohexylimino)-1,5-dihydro-4,5-diphenyl-2*H*-pyrrol-2-one (12). Prepared from the carboxylic acid (1 g, 4.4 mmol) using the general procedure for the isocyanate synthesis, and cyclohexyl isocyanide (0.44 g, 4 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. The precipitate was filtered (suction) and washed with cold acetonitrile (2 x 1.5 mL) to afford 1.21 g (92%) of **12**: mp (decomp.) 230-232 °C (acetonitrile); IR (NaCl) ν 3201, 2928, 2848, 1711; ^1H NMR (500 MHz, acetone-d_6) δ 1.26-1.80 (m, 10H), 5.12 (m, 1H), 7.21-7.29 (m, 5H), 7.38 (m, 5H), 9.46 (s, 1H, exchangeable); ^{13}C NMR (125 MHz, acetone-

d_6) δ 24.3, 25.6, 34.0, 58.5, 126.7, 127.8, 128.2, 128.5, 128.6, 130.0, 130.3, 130.6, 132.3, 145.9, 154.8, 159.0; mass spectrum: m/e (rel. int.) 330 (100), 301 (9), 249 (28); HRMS: calcd. for $C_{22}H_{22}N_2O$ 330.17320, found: 330.1728. Anal. calcd. for $C_{22}H_{22}N_2O$: C, 79.96, H, 6.71, N, 8.47; found: C, 79.58, H, 6.81, N, 8.44.

3-(Cyclohexylamino)-1,5-dihydro-5-methylene-4-(4-pyridinyl)-2*H*-pyrrol-2-one (13). Prepared from trans-2-methyl-3-(4-pyridyl)-propenoic acid (0.50 g, 3.1 mmol), using the general procedure for isocyanate synthesis, and cyclohexyl isocyanide (0.29g, 2.7 mmol) in acetonitrile (3 mL) by stirring at rt for 15 h. The product was isolated by filtration and recrystallization from methanol, affording 0.57 g (81%) of **13**: mp: 215-16 °C dec (MeOH); IR (KBr) ν 3296, 3156, 2930, 1709, 1629 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.63-0.75 (m, 2H), 0.86-1.11 (m, 3H), 1.33-1.54 (m, 5H), 2.94 (m, 1H), 4.08 (s, 1H), 4.45 (s, 1H), 5.46 (d, J=9.0 Hz, 1H, exchangeable), 7.27 (d, J=5.7 Hz, 2H), 8.54 (d, J=5.7 Hz, 2H), 10.23 (s, 1H, exchangeable), ^{13}C NMR (DMSO-d_6) δ 24.9, 25.4, 33.0, 51.7, 88.7, 104.0, 125.9, 136.2, 142.1, 144.2, 149.7, 166.6; mass spectrum: m/e (rel. int.) 269 (100), 226 (44), 187 (57); Anal. calcd. for $C_{16}H_{19}N_3O$: C, 71.35, H, 7.11, N, 15.60, found: C, 71.50, H, 7.12, N, 15.65.

3-(Cyclohexylimino)-4-oxo-2*H*-1-benzopyrano[2,3-b]-pyrrol-2-one (16). A solution of azide **14** (0.31 g, 1.44 mmol), prepared from 4-oxo-4H-1-benzopyran-2-carboxylic acid, and cyclohexyl isocyanide (0.63 g, 5.76 mmol) in acetonitrile (20 mL) was refluxed for 4 h at which time the reaction mixture was cooled to rt and stirred at that temperature for 15 h. The solvent was removed *in vacuo* and the residue chromatographed (silica gel, EtOAc) to afford 0.34 g (79%) of compound **16** as an orange solid: mp = 177 °C (MeCN); IR ($CDCl_3$) ν 3379, 2929, 1721, 1666, 1617 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-2.13 (m, 10H), 5.20 (m, 1H), 7.35-7.41 (m, 2H), 7.63 (m, 1H), 7.92 (s, 1H, exchangeable), 8.11 (dd, J=7.8, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.8, 33.4, 58.6, 94.0, 118.1, 123.1, 126.2, 126.9, 134.5, 154.2, 154.4, 170.3, 174.4, 195.4; mass spectrum: m/e (rel. int.) 296 (32), 239 (6), 215 (100); Anal. calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91, H, 5.44, N, 9.45; found: C, 68.74, H, 5.42, N, 9.50.

5-(Cyclohexylimino)-3,4-dihydro,2,2-dimethyl-4-oxo-2*H*-pyrano[2,3-b]pyrrol-6-one (17). A solution of acyl azide **15** (0.58 g, 2.95 mmol), prepared from 3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid, and cyclohexyl isocyanide (1.29 g, 12.0 mmol) in acetonitrile (20 mL) was refluxed for 4 h at which time the reaction mixture was cooled to rt and allowed to stir at that temperature for 15 h. The solvent was removed and the residue recrystallized from acetonitrile to provide 0.73 g (90%) of compound **17** as a yellow solid: mp = 169-70 °C (MeCN); IR ($CHCl_3$) ν 3298, 3239, 3209, 2938, 1731, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34-1.56 (m, 5H), 1.60 (s, 6H), 1.65-2.04 (m, 5H), 2.64 (s, 2H), 4.79 (m, 1H), 7.29 (s, 1H, exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.8, 27.8, 33.2, 49.2, 57.4, 85.6, 91.5, 151.5, 176.1, 182.2, 197.3; mass spectrum: m/e (rel. int.) 376 (47), 221 (19), 193 (39); Anal. calcd. for $C_{15}H_{20}N_2O_3$: C, 65.20, H, 7.29, N, 10.14, found: C, 65.26, H, 7.43, N, 10.11.

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