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# Reaction between isocyanides and chalcones: an efficient solvent-free synthesis of 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones

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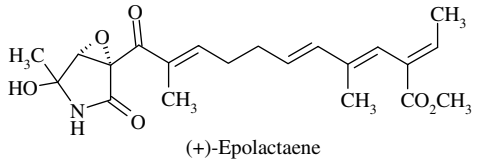
**Abstract**—A simple and efficient synthesis of 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones is described. Heating a mixture of an isocyanide and a 1,3-diaryl-2-propen-1-one under solvent-free conditions produces the title compounds in good to excellent yields.


A 5-hydroxy-pyrrolidin-2-one (γ-hydroxy γ-lactam) unit is found in a number of biologically active compounds and natural products. Epolactaene, one such compound, is a microbial metabolite isolated from the fungal strain *Penicillium* sp. BM 1689-P,[1] and was originally shown to be effective in promoting neural outgrowth and arresting the cell cycle at the $G_0/G_1$ phase in a human neuroblastoma cell line, SH-SY5Y.[2] It has also shown DNA polymerase inhibitory activity,[3] chaperone inhibitory activity[4] and apoptosis-inducing effects on BALL-1 cells.[5] Some 5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones have been shown to be useful in the treatment of patients suffering from intellectual or nervous asthenias, memory failures, senescence or mental strain.[6]



(+)-Epolactaene

Some recent 5-hydroxy-pyrrolidin-2-one skeleton syntheses involved treatment of a γ-keto-α-pentafluoroethyl thioester with diisopropylamine followed by addition of primary amines,[7] reaction of an enamine derived from addition of a secondary amine to dibenzoylacetylene with an arylsulfonyl isocyanate,[8] Pd(0)-catalyzed coupling-cyclization of 2,3-allenamides with organic iodides,[9] acetylene insertion into chromium aminocarbene complexes followed by addition of thiophenol to the nitrogen ylide intermediate and then air oxidation in the presence of $Cr(CO)_6$/pyridine,[10] photooxidation of *N*-methylpyrroles[11] and treatment of 5-methoxy-3-furan-2-one with ammonia.[11]

In 1997, it was reported[12] that the reaction between isocyanides and 3-benzylidene-2,4-pentanedione was a convenient route for the preparation of highly substituted 2-aminofurans. However, Quai et al.[13] proved that 5-hydroxy-2*H*-pyrrol-2-ones and not 2-aminofurans were the cycloaddition products between alkyl isocyanides and highly electron-deficient benzylidene-1,3-diketones.

As far as we know, there is no report concerning the reaction between less-electrophilic 1,3-diaryl-2-propen-1-ones (chalcones) and isocyanides. As part of our continuing efforts on the development of efficient routes for the preparation of biologically active heterocyclic compounds,[14] herein we report that the solvent-free

*Keywords*: 5-Hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones; γ-Hydroxy-α,β-unsaturated γ-lactams; 1,3-Diaryl-2-propen-1-ones; Isocyanides; Solvent-free synthesis.
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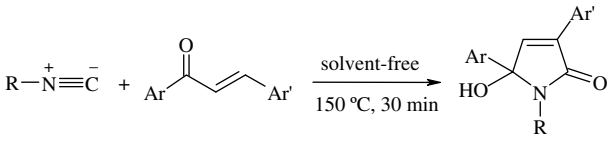
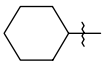
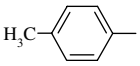
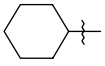
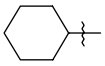
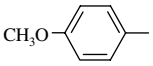
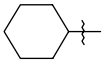
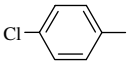
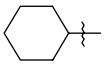
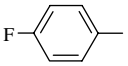
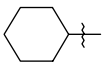
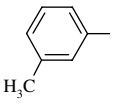
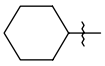
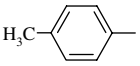
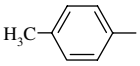
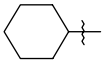
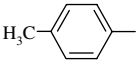
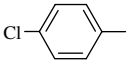
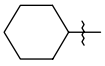
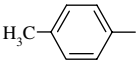
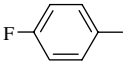
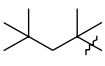
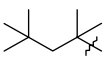
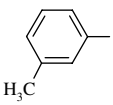
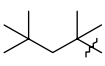
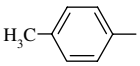
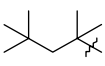
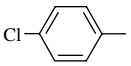
reaction between chalcones and isocyanides results in the formation of substituted pyrrolones. Thus, a range of 5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones **3a**–**m** were synthesized in 85–97% yields by heating a mixture of isocyanide **1** and chalcone **2** at 150 °C for 30 min under solvent-free conditions. $^{1}$H NMR analysis of the reaction mixtures clearly indicated formation of the γ-hydroxy-α,β-unsaturated γ-lactams **3** in good to excellent yields. Any product other than **3** could not be detected by NMR spectroscopy. The results are given in Table 1.

The isolated 5-hydroxy-2*H*-pyrrol-2-ones **3a**–**m** were characterized on the basis of IR, $^{1}$H and $^{13}$C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **3a** displayed the molecular ion ($M^{+}$) peak at *m*/*z* 347, which is 16 mass units higher than the 1:1 adduct of cyclohexyl isocyanide and 3-(4-

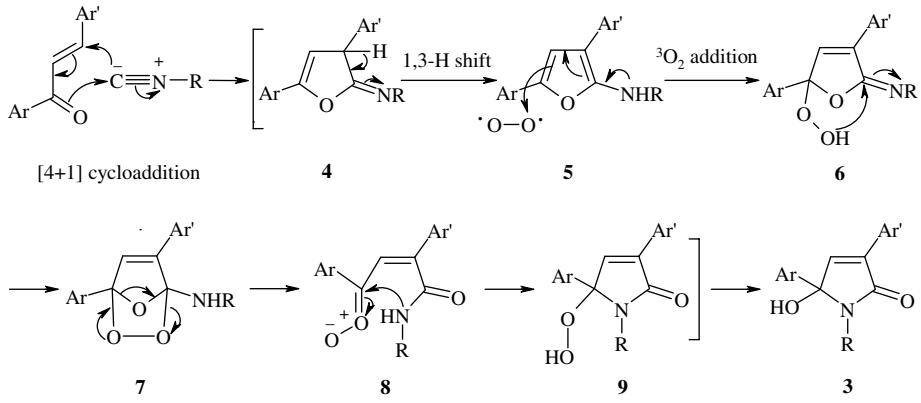
**Table 1.** Solvent-free synthesis of 5-hydroxy-2*H*-pyrrol-2-ones




**1** **2** **3**

| Entry | R | Ar | Ar′ | % yield of **3**[a] |
|---|---|---|---|---|
| **a** |  |  |  | 92 |
| **b** |  |  |  | 94 |
| **c** |  |  |  | 97 |
| **d** |  |  |  | 91 |
| **e** |  |  |  | 90 |
| **f** |  |  |  | 92 |
| **g** |  |  |  | 93 |
| **h** |  |  |  | 96 |
| **i** |  |  |  | 90 |
| **j** |  |  |  | 87 |
| **k** |  |  |  | 85 |
| **l** |  |  |  | 90 |
| **m** |  |  |  | 85 |

[a] Isolated yields.




**Scheme 1.**

methylphenyl)-1-phenyl-2-propen-1-one confirming addition of an oxygen atom to the 1:1 adduct. The IR spectrum of **3a** shows absorptions at 3391 and 1676 $cm^{-1}$ indicating the presence of alcohol and amide functionalities. The $^1H$ NMR spectrum of **3a** exhibited two sharp singlets due to a methyl group ($\delta$ 2.36 ppm) and a vinylic hydrogen ($\delta$ 6.76 ppm) along with characteristic signals with appropriate chemical shifts and coupling constants for the eleven protons of the cyclohexyl ring and the nine protons of the two aryl substituents. A broad signal ($\delta$ 7.95 ppm) was observed for the OH group. In the $^{13}C$ NMR spectrum of **3a**, the amide carbonyl resonated at $\delta$ 168.88 ppm and the signal for COH was evident at $\delta$ 90.48 ppm, in agreement with the proposed structure. The presence of a chiral centre in the structure of the isolated products was confirmed by NMR spectroscopy. For example, the two diastereotopic methylene H atoms of the *N*-tetramethylbutyl substituent in **3k** appeared as an *AB* quartet ($\delta$ 2.06 and 2.27 ppm, $^2J = 14.2$ Hz).[15]

The formation of the pyrrolone scaffold probably involves a complex multistep sequence of events. On the basis of the chemistry of isocyanides,[16] mechanistically, it is reasonable to assume that initial [4+1] cycloaddition of the α,β-unsaturated ketone and the isocyanide gives an iminolactone intermediate **4**, which tautomerizes to 2-aminofuran **5**. The readily oxidizable 2-aminofuran may combine with triplet oxygen to form hydroperoxide **6**, which is cyclized to ozonide intermediate **7**. The ozonide fragments to an open form **8**, which cyclizes rapidly to hydroperoxide **9**. The hydroperoxide disproportionates under the reaction conditions to afford the stable hydroxyamide **3** (Scheme 1). A similar mechanism has previously been proposed.[13,17]

In conclusion, we have developed an efficient solvent-free synthesis of 1-alkyl-5-hydroxy-3,5-diaryl-1,5-dihydro-2*H*-pyrrol-2-ones (γ-hydroxy-α,β-unsaturated γ-lactams) of potential synthetic and pharmacological interest. To the best of our knowledge, this is the first report on the solvent-free synthesis of this structure. The use of simple starting materials, the solvent-free conditions, good yields of the products and short reaction times are the main advantages of this method. This procedure appears to have broad scope with respect to variation in the pyrrolone three- and five-positions.

## Acknowledgement

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15. The procedure for the preparation of 1-cyclohexyl-5-hydroxy-3-(4-methylphenyl)–5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one**3a** is described as an example: A mixture of 3-(4-methylphenyl)-1-phenyl-2-propen-1-one (0.444 g, 2 mmol) and cyclohexyl isocyanide (0.218 g, 2 mmol) was stirred at 150 °C for 30 min. Then the reaction mixture was cooled to room temperature and the residue was purified by column chromatography using 1:2 *n*-hexane–EtOAc as eluent. The solvent was removed and the solid residue was recrystallized from 1:1 *n*-hexane–EtOAc to afford **3a** as colourless crystals, mp 160–162 °C, yield 0.64 g, 92%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3391 (OH), 1676 (C=O), 1632, 1514, 1450, 1420, 1369, 1269, 1169, 1105, 1061, 941, 822, 758. EI-MS, *m*/*z* (%): 347 ($M^+$, 100), 325 (14), 265 (72), 249 (40), 242 (30), 215 (20), 187 (24), 105 (86), 92 (22), 77 (26). Anal. Calcd for $C_{23}H_{25}NO_2$ (347.46): C, 79.51; H, 7.25; N, 4.03. Found: C, 79.3; H, 7.3; N, 3.9. $^1$H NMR (500.1 MHz, $CDCl_3$): $\delta$ 0.90–2.20 [10H, m, CH(C$H_2$)$_5$], 2.36 (3H, s, $CH_3$), 3.22 (1H, tt, $J = 12.2$ Hz and $J = 3.7$ Hz, CH), 6.76 (1H, s, CH), 7.17 (2H, d, $J = 7.9$ Hz, 2CH), 7.30–7.37 (3H, m, 3CH), 7.52 (2H, dd, $J = 7.2$ Hz and $J = 1.3$ Hz, 2CH), 7.77 (2H, d, $J = 7.9$ Hz, 2CH), 7.95 (1H, br s, OH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ 21.37 ($CH_3$), 25.30, 26.26, 26.27, 29.48 and 30.73 (5 $CH_2$), 53.08 [NCH(CH$_2$)$_5$], 90.48 (COH), 126.28, 127.50, 127.94 and 128.40 (4CH), 129.10 (C), 129.16 (CH), 134.83, 137.53 and 139.08 (3C), 141.12 (CH), 168.88 (C=O). Compound **3d**: mp 142–144 °C, yield 0.67 g, 91%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3306 (OH), 1672 (C=O), 1637, 1622, 1493, 1452, 1425, 1367, 1194, 1166, 1090, 943, 829, 698. EI-MS, *m*/*z* (%): 367 ($M^+$, 79), 285 (75), 269 (55), 256 (14), 207 (27), 178 (17), 149 (13), 105 (100), 77 (37). Anal. Calcd for $C_{22}H_{22}ClNO_2$ (367.87): C, 71.83; H, 6.03; N, 3.81. Found: C, 71.8; H, 6.0; N, 3.7. $^1$H NMR (500.1 MHz, $CDCl_3$): $\delta$ 0.89–2.26 [10H, m, CH(C$H_2$)$_5$], 3.23 [1H, tt, $J = 12.1$ Hz and $J = 3.7$ Hz, NC$H$(CH$_2$)$_5$], 6.92 (1H, s, CH), 7.30–7.41 (6H, m, 5 CH and OH), 7.53 (2H, d, $J = 7.1$ Hz, 2CH), 7.86 (2H, d, $J = 8.4$ Hz, 2CH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ 25.26, 26.22, 26.23, 29.51 and 30.75 (5$CH_2$), 53.19 [N$C$H(CH$_2$)$_5$], 90.52 (COH), 126.20, 128.50, 128.57, 128.66 and 128.88 (5 CH),129.20, 133.95, 135.09 and 137.14 (4C), 142.23 (CH), 168.37 (C=O). Compound **3k**: mp 155–157 °C, yield 0.64 g, 85%. IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3238 (OH), 1664 (C=O), 1639, 1601, 1447, 1377, 1299, 1260, 1161, 1069, 875, 800, 766, 699. EI-MS, *m*/*z* (%): 377 ($M^+$, 5), 322 (11), 306 (11), 249 (100), 228 (60), 162 (9), 119 (26), 105 (66), 91 (14), 77 (22). Anal. Calcd for $C_{25}H_{31}NO_2$ (377.53): C, 79.54; H, 8.28; N, 3.71. Found: C, 79.3; H, 8.4; N, 3.6. $^1$H NMR (500.1 MHz, $CDCl_3$): $\delta$ 1.01 [9H, s, C($CH_3$)$_3$], 1.45 and 1.53 [6H, 2 s, C($CH_3$)$_2$], 2.06 and 2.27 (2H, 2d, AB system, $^2J = 14.2$ Hz, $CH_AH_B$), 2.36 (3H, s, $CH_3$), 6.74 (1H, s, CH), 7.15 (1H, d, $J = 7.5$ Hz, CH), 7.25 (1 H, dd, $J = 8.2$ Hz and $J = 7.6$ Hz, CH), 7.34–7.46 (5H, m, 5 CH), 7.61 (1H, d, $J = 7.6$ Hz, CH), 7.69 (1H, s, CH), 8.52 (1H, br s, OH). $^{13}$C NMR (125.8 MHz, $CDCl_3$): $\delta$ 21.40 ($CH_3$), 27.32 and 27.38 (C($C$H$_3$)$_2$), 31.58 ($C$(CH$_3$)$_3$), 31.77 (C($C$H$_3$)$_3$), 51.74 ($CH_2$), 61.91 [$C$(CH$_3$)$_2$], 100.44 (COH), 124.87, 125.75, 128.26, 128.33, 128.39, 128.59 and 129.67 (7 CH), 130.63, 135.30, 137.38 and 137.96 (4C), 140.55 (CH), 170.97 (C=O).
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