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Tin powder-promoted allylation and cyclization of 2-(benzylideneamino)isoindoline-1,3-diones

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Abstract: α -Methylene- γ -lactams were synthesized from readily available *N*-acylhydrazones by a tin-mediated Barbier-type reaction. The method avoids the use of toxic allylstannanes and the reaction proceeds smoothly under mild conditions.

Keywords: allylation; homoallylic *N*-aminophthalimide; lactam; tin powder.

Introduction

The addition of allylic organometallic compounds to imines is one of the most important methods for the preparation of homoallylic amines [1–5]. Many allylic organometallics such as allylic magnesium, zinc, boron, silane and stannane reagents have been used in such reactions [6–13]. In particular, allylstannanes are stable toward heat, hydrolysis, oxygen, and are compatible with many functional groups [3, 4, 8, 9]. However, the application of allylstannanes in organic synthesis is restricted due to their toxicity and the formation of undesirable trialkyltin-containing by-products [14, 15]. Besides, Lewis acids or transition-metal catalysts are often needed in allylstannane-mediated allylation reactions [3, 4, 8, 9]. In 1981, Mukaiyama and Harada [16] reported for the first time the allylation reaction of carbonyl compounds with allylic halide in the presence of tin powder to give the corresponding homoallylic alcohols. Additional reactions of this type with imines have been investigated [17–21]. In this report, we describe a practical procedure for the preparation of homoallylic *N*-aminophthalimides and α -methylene- γ -lactams by the reactions of aromatic aldehydes and *N*-acylhydrazones derived from *N*-aminophthalimide in

the presence of tin powder. The combination of tin powder and allylic bromide as an allylation system avoids the use of toxic allylstannane.

Results and discussion

Initially, a mixture of 1 equivalent of 2-(benzylideneamino)-isoindoline-1,3-dione (**1a**, generated from benzaldehyde and *N*-aminophthalimide), 1.5 equivalents of 2-(bromomethyl)acrylate (**2**) and 2 equivalents of tin powder in ethanol was heated under reflux. After 2 h, product **3a** was obtained in 32% yield, and a trace amount of cyclized derivative **4a** was also detected (Scheme 1). Under optimized conditions, the use of 1 equivalent of **1a**, 3 equivalents of **2** and 3.5 equivalents of tin powder in ethanol furnished the desired product **3a** in 57% yield. The use of dichloromethane, tetrahydrofuran, methanol, toluene and 1,4-dioxane have been examined. The product **3a** was obtained in a 36% yield after 2 h of heating in methanol under reflux. In the remaining solvents under similar conditions, the allylation reaction of **1a** did not occur. These results show that ethanol is the optimized solvent for the allylation reaction of **1a**. Then, the allylation reaction was examined using various substrates **1** (Scheme 1). It was found that substituted acylhydrazones **1** are allylated smoothly with reagent **2** in the presence of tin powder. The position of the substituent on the phenyl ring has little effect on the yield of the corresponding product **3**. However, an attempted reaction of substrate **1** bearing an amino or nitro group on the phenyl ring did not afford the desired product **3**, and a complex mixture was obtained.

The cyclized by-products **4a** were observed in these allylation reactions (Scheme 1). Related α -methylene- γ -lactam units are important scaffolds found in some biologically active synthetic molecules and natural products [22–26]. It was found that prolonging the reaction time resulted in the formation of compounds **4** as the major products. For example, heating of the mixture of the substrates for 2 h furnished **3a** in a 57% yield, and the subsequent heating for an additional 2 h furnished product **4a** in an 83% yield. Afterwards, different substituted 2-(benzylideneamino)isoindoline-1,3-diones **1** were examined for the synthesis of α -methylene- γ -lactams **4** (Scheme 1). The results show

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Scheme 1

Scheme 2

that acylhydrazones **1** with an electron-donating or electron-withdrawing group on phenyl ring undergo the cyclization reactions smoothly to give the corresponding products **4** in good to excellent yields. Again, the attempted cyclization of acylhydrazones **1** bearing an amino or nitro group on the phenyl ring did not afford the corresponding products **4**.

A possible mechanism that includes the literature data [27, 28] and our previous research results [18–21] is shown in Scheme 2. Thus, substrate **1** undergoes a reaction with the intermediate product **5**, to generate the intermediate product **6**. Hydrolysis of compound **6** gives the observed product **3**. On the other hand, cyclization of **6** generates compound **7**, which is the precursor to the observed product **4**.

reactions, a mixture of allylic bromide and tin powder is used to replace toxic allylic stannane.

Experimental

All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar. Silica gel column chromatography was carried out using silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was done using silica gel GF₂₅₄. Compounds were visualized by exposure to ultraviolet light, phosphomolybdic acid solution, potassium permanganate solution or iodine vapor. Proton nuclear magnetic resonance (¹H NMR) (600 MHz) and carbon-13 nuclear magnetic resonance (¹³C NMR) (150 MHz) spectra were recorded in deuterated chloroform (CDCl₃). Melting points are uncorrected. Infrared (IR) spectra were recorded using KBr pellets. Substituted 2-(benzylideneamino)isoindoline-1,3-diones **1** were prepared as previously described [29, 30].

Conclusion

Efficient methods for the synthesis of homoallylic amines and α -methylene- γ -lactams are described. In these

General procedure for the synthesis of compounds **3** and **4**

A mixture of **1** (0.4 mmol, 1 equiv.), **2** (1.2 mmol, 3 equiv.) and Sn powder (1.4 mmol, 3.5 equiv.) in anhydrous ethanol (4 mL) protected

from atmospheric moisture was stirred and heated under reflux for a period of time indicated below. After the formation of compound **3** or **4**, as monitored by TLC, the mixture was cooled to room temperature. The solvent was removed under reduced pressure, the residue was treated with a saturated solution of ammonium chloride (4 mL), and the mixture was stirred for 15 min. The mixture was extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic phases were dried (MgSO₄) and concentrated. Purification of the residue by silica gel column chromatography using petroleum ether and ethyl acetate (5:1) as an eluent furnished pure product **3** or **4**.

Ethyl 4-((1,3-dioxoisindolin-2-yl)amino)-2-methylene-4-phenylbutanoate (3a) Reaction time 2 h; white solid; yield 80 mg (57%); mp 81–82°C; ¹H NMR: δ 7.76 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.68 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.44 (d, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 6.19 (s, 1H), 5.57 (s, 1H), 4.66 (t, J = 7.2 Hz, 1H), 4.21 (qd, J = 7.2 Hz and 2.4 Hz, 2H), 2.83 (m, 2H), 1.28 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.8, 166.6, 139.6, 136.8, 134.1, 130.1, 128.3, 128.1, 128.00, 128.0, 123.3, 62.3, 60.9, 38.6, 14.1; IR: ν 3430, 3289, 2974, 2920, 1798, 1721, 1628, 1461, 1380, 1192, 1079, 706 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₂₀N₂O₄Na, [M + Na]⁺: m/z 387.1315. Found: m/z 387.1312.

Ethyl 4-((1,3-dioxoisindolin-2-yl)amino)-4-(2-fluorophenyl)-2-methylenebutanoate (3b) Reaction time 2.1 h; white solid; yield 46 mg (30%); mp 111–112°C; ¹H NMR: δ 7.77 (dd, J = 9.0 Hz and 3.6 Hz, 2H), 7.69 (m, 3H), 7.21 (m, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.94 (m, 1H), 6.24 (s, 1H), 5.62 (s, 1H), 4.99 (t, J = 6.6 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 2.87 (m, 2H), 1.57 (s, 1H), 1.31 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.6, 166.5, 135.9 (d, J = 241.5 Hz), 134.1, 130.1, 129.4 (d, J = 9.0 Hz), 129.3 (d, J = 4.5 Hz), 128.1, 124.2 (d, J = 3.0 Hz), 123.4, 120.0, 115.2 (d, J = 22.5 Hz), 61.0, 56.0, 37.3, 14.1; IR: ν 3430, 3289, 2978, 2937, 1781, 1724, 1627, 1377, 1284, 1192, 1081, 882, 710 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₁₉FN₂O₄Na, [M + Na]⁺: m/z 405.1221. Found: m/z 405.1217.

Ethyl 4-(2-chlorophenyl)-4-((1,3-dioxoisindolin-2-yl)amino)-2-methylenebutanoate (3c) Reaction time 2.2 h; white solid; yield 92 mg (57%); mp 116–117°C; ¹H NMR: δ 7.94 (d, J = 7.8 Hz, 1H), 7.76 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.68 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.32 (t, J = 7.2 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 6.28 (s, 1H), 5.67 (s, 1H), 5.24 (t, J = 6.6 Hz, 1H), 4.26 (q, J = 6.6 Hz, 2H), 2.81 (m, 2H), 1.54 (br, 1H), 1.32 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.8, 166.7, 136.6, 134.1, 130.1, 129.2, 128.9, 128.4, 127.0, 123.4, 61.07, 40.9, 37.6, 14.2; IR: ν 3429, 3289, 2978, 2928, 1789, 1720, 1628, 1464, 1377, 1192, 1074, 883, 705 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₁₉ClN₂O₄Na, [M + Na]⁺: m/z 421.0926. Found: m/z 421.0923.

Ethyl 4-(3-chlorophenyl)-4-((1,3-dioxoisindolin-2-yl)amino)-2-methylenebutanoate (3d) Reaction time 2.2 h; white solid; yield 60 mg (42%); mp 142–144°C; ¹H NMR: δ 7.78 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.69 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.46 (s, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.23 (m, 2H), 6.23 (s, 1H), 5.60 (s, 1H), 4.79 (s, 1H), 4.64 (t, J = 6.6 Hz, 1H), 4.22 (q, J = 6.6 Hz, 2H), 2.81 (dd, J = 13.8 Hz and 7.2 Hz, 1H), 2.76 (dd, J = 13.8 Hz and 7.2 Hz, 1H), 1.30 (t, J = 6.6 Hz, 3H); ¹³C NMR: δ 166.7, 166.5, 141.9, 136.5, 134.2, 134.1, 130.0, 129.6, 128.3, 128.2, 128.1, 126.1, 123.4, 61.9, 61.0, 38.8, 14.1; IR: ν 3445, 3203, 2923, 2852, 1774, 1747, 1650, 1463, 1385, 1139, 1052, 914, 716 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₁₉ClN₂O₄Na, [M + Na]⁺: m/z 421.0926. Found: 421.0924.

Ethyl 4-(4-chlorophenyl)-4-((1,3-dioxoisindolin-2-yl)amino)-2-methylenebutanoate (3e) Reaction time 2 h; white solid; yield 96 mg (60%); mp 108–109°C; ¹H NMR: δ 7.77 (dd, J = 8.4 Hz and 4.8 Hz, 2H), 7.69 (dd, J = 8.4 Hz and 4.8 Hz, 2H), 7.39 (m, 2H), 7.25 (m, 2H),

6.21 (d, J = 1.8 Hz, 1H), 5.57 (d, J = 1.2 Hz, 1H), 4.66 (t, J = 10.2 Hz, 1H), 4.22 (qd, J = 10.8 Hz and 1.8 Hz, 2H), 2.78 (m, 2H), 1.55 (br, 1H), 1.30 (t, J = 10.2 Hz, 3H); ¹³C NMR: δ 166.7, 166.5, 138.2, 136.6, 134.2, 133.7, 130.0, 129.4, 128.5, 128.2, 123.4, 61.6, 61.0, 38.8, 14.2; IR: ν 3441, 2924, 2854, 1797, 1224, 1666, 1458, 1373, 1115, 1080, 887 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₁₉ClN₂O₄Na, [M + Na]⁺: m/z 421.0926. Found: m/z 421.0923.

Ethyl 4-(4-bromophenyl)-((1,3-dioxoisindolin-2-yl)amino)-2-methylenebutanoate (3f) Reaction time 2.1 h; white solid; yield 123 mg (69%); mp 106–107°C; ¹H NMR: δ 7.76 (dd, J = 5.4 Hz and 3.6 Hz, 2H), 7.68 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.33 (d, J = 5.4 Hz, 2H), 6.21 (s, 1H), 5.57 (s, 1H), 4.65 (t, J = 6.6 Hz, 1H), 4.22 (qd, J = 7.2 Hz and 3.0 Hz, 2H), 2.77 (m, 2H), 1.54 (br, 1H), 1.30 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.7, 166.5, 138.8, 134.2, 131.5, 130.0, 129.7, 128.7, 128.2, 123.4, 61.7, 61.0, 38.8, 14.2; IR: ν 3478, 3281, 2933, 2874, 1764, 1610, 1625, 1441, 1328, 1251, 1045, 945, 776 cm⁻¹. ESI-HRMS. Calcd for C₂₁H₁₉BrN₂O₄Na, [M + Na]⁺: m/z 465.0420. Found: m/z 465.0416.

Ethyl 4-((1,3-dioxoisindolinyl)amino)-2-methylene-4-(4-(trifluoromethyl)phenyl)butanoate (3g) Reaction time 2.2 h; white solid; yield 92 mg (53%); mp 103–104°C; ¹H NMR: δ 7.77 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.69 (dd, J = 5.4 Hz and 3.0 Hz, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 6.24 (s, 1H), 5.60 (s, 1H), 4.76 (t, J = 6.6 Hz, 1H), 4.23 (m, 2H), 2.79 (m, 2H), 1.31 (t, J = 7.2 Hz, 3H), 1.25 (s, 1H); ¹³C NMR: δ 166.7, 166.5, 144.0, 136.5, 134.3, 129.9, 128.4, 128.3, 125.3 (q, J = 4.5 Hz), 123.4, 61.9, 61.1, 39.1, 14.2; IR: ν 3446, 3281, 2921, 2830, 1805, 1683, 1621, 1465, 1382, 1123, 1067, 879, 709 cm⁻¹. ESI-HRMS. Calcd for C₂₂H₁₉F₃N₂O₄Na, [M + Na]⁺: m/z 455.1189. Found: m/z 455.1187.

Ethyl 4-((1,3-dioxoisindolin-2-yl)amino)-2-methylene-4-(*o*-tolyl)-butanoate (3h) Reaction time 2.2 h; colorless crystals; yield 61 mg (40%); mp 86–87°C; ¹H NMR: δ 7.78 (m, 3H), 7.68 (m, 2H), 7.23 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.17 (s, 1H), 5.57 (s, 1H), 5.03 (t, J = 7.2 Hz, 1H), 4.71 (s, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.78 (d, J = 6.6 Hz, 2H), 2.32 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.9, 166.6, 137.8, 136.8, 136.5, 134.1, 130.2, 130.1, 128.1, 127.5, 126.2, 123.3, 110.0, 60.9, 57.4, 38.5, 19.2, 14.1; IR: ν 3435, 3285, 2982, 2932, 1784, 1729, 1629, 1464, 1383, 1192, 1026, 887, 711 cm⁻¹. ESI-HRMS. Calcd for C₂₂H₂₂N₂O₄Na, [M + Na]⁺: m/z 401.1472. Found: m/z 401.1471.

Ethyl 4-((1,3-dioxoisindolin-2-yl)amino)-2-methylene-4-(*m*-tolyl)-butanoate (3i) Reaction time 2.3 h; colorless crystals; yield 61 mg (40%); mp 77–78°C; ¹H NMR: δ 7.77 (dd, J = 8.4 Hz and 4.8 Hz, 2H), 7.68 (dd, J = 8.4 Hz and 5.4 Hz, 2H), 7.26 (d, J = 4.8 Hz, 1H), 7.22 (d, J = 5.4 Hz, 1H), 7.17 (dd, J = 13.2 Hz and 7.8 Hz, 1H), 7.04 (m, 1H), 6.18 (d, J = 4.8 Hz, 1H), 5.56 (d, J = 4.8 Hz, 1H), 4.61 (dd, J = 12.6 Hz and 6.6 Hz, 1H), 4.18 (m, 2H), 2.80 (m, 2H), 2.31 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.8, 166.7, 139.5, 137.9, 136.9, 134.1, 130.1, 128.8, 128.6, 128.2, 127.9, 125.0, 123.3, 62.2, 60.9, 38.6, 21.4, 14.1; IR: ν 3468, 3289, 2974, 2928, 1781, 1720, 1624, 1464, 1377, 1192, 1076, 879, 705 cm⁻¹. ESI-HRMS. Calcd for C₂₂H₂₂N₂O₄Na, [M + Na]⁺: m/z 401.1472. Found: m/z 401.1470.

Ethyl 4-((1,3-dioxoisindolin-2-yl)amino)-2-methylene-4-(*p*-tolyl)butanoate (3j) Reaction time 2.3 h; white solid; yield 152 mg (53%); mp 84–85°C; ¹H NMR: δ 7.79–7.73 (m, 2H), 7.68 (m, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.18 (s, 1H), 5.56 (s, 1H), 4.77 (br, 1H), 4.62 (t, J = 7.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 2.81 (dd, J = 14.4 Hz and 7.2 Hz, 1H), 2.78 (dd, J = 13.8 Hz and 6.6 Hz, 1H), 2.28 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ¹³C NMR: δ 166.7, 166.6, 137.6, 136.9, 136.5, 134.0, 130.0, 129.0, 127.8, 123.3, 62.0, 60.8, 38.5, 21.1, 14.1; IR: ν 3449, 3291, 2980,

2929, 1782, 1727, 1628, 1479, 1381, 1194, 1080, 885, 710 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4$, $[\text{M} + \text{H}]^+$: m/z 379.1652, Found: m/z 379.1648.

2-(3-Methylene-2-oxo-5-phenylpyrrolidin-1-yl)isoindoline-1,3-dione (4a) Reaction time 4 h; white solid; yield 106 mg (83%); mp 168–169°C; ^1H NMR: δ 7.83 (dd, $J=2.4$ Hz and 1.8 Hz, 1H), 7.77 (dd, $J=4.8$ Hz and 2.4 Hz, 1H), 7.72 (m, 2H), 7.47 (d, $J=7.2$ Hz, 2H), 7.33 (t, $J=7.2$ Hz, 2H), 7.29 (t, $J=7.2$ Hz, 1H), 6.28 (s, 1H), 5.58 (s, 1H), 5.17 (t, $J=7.2$ Hz, 1H), 3.40 (dd, $J=17.4$ Hz and 8.4 Hz, 1H), 2.92 (m, 1H); ^{13}C NMR: δ 166.0, 165.1, 163.7, 138.2, 135.1, 134.7, 134.5, 130.1, 129.8, 128.8, 128.8, 127.4, 124.1, 123.7, 119.6, 61.0, 35.0. IR: ν 3078, 3038, 2897, 1788, 1743, 1673, 1462, 1342, 1277, 1224, 1078 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_3$, $[\text{M} + \text{H}]^+$: m/z 319.1077. Found: m/z 319.1075.

2-(5-(2-Fluorophenyl)-3-methylene-2-oxopyrrolidin-1-yl)isoindoline-1,3-dione (4b) Reaction time 4 h; white solid; yield 117 mg (87%); mp 170–171°C; ^1H NMR: δ 7.86 (m, 1H), 7.80 (m, 1H), 7.74 (m, 2H), 7.69 (td, $J=7.8$ Hz and 1.8 Hz, 1H), 7.27 (m, 1H), 7.17 (td, $J=7.8$ Hz and 0.6 Hz, 1H), 7.01 (m, 1H), 6.30 (t, $J=2.4$ Hz, 1H), 5.60 (t, $J=2.4$ Hz, 1H), 5.54 (dd, $J=8.4$ Hz and 6.0 Hz, 1H), 3.47 (dd, $J=17.4$ Hz and 8.4 Hz, 1H), 2.93 (m, 1H); ^{13}C NMR: δ 166.1, 165.0, 163.9, 161.0 (d, $J=246.0$ Hz), 134.7, 134.6, 134.6, 130.0 (d, $J=7.5$ Hz), 130.1, 129.8, 128.5 (d, $J=3.0$ Hz), 125.6 (d, $J=12.0$ Hz), 124.7 (d, $J=4.5$ Hz), 124.1, 123.9, 120.0, 115.5 (d, $J=6.0$ Hz), 54.1, 33.3; IR: ν 3099, 3019, 2928, 1791, 1742, 1656, 1493, 1347, 1267, 1225, 1105 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{19}\text{H}_{13}\text{FN}_2\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 359.0802. Found: m/z 359.0804.

2-(5-(3-Chlorophenyl)-3-methylene-2-oxopyrrolidin-1-yl)isoindoline-1,3-dione (4c) Reaction time 7 h; white solid; yield 71 mg (50%); mp 104–105°C; ^1H NMR: δ 7.85 (m, 1H), 7.82 (dd, $J=4.8$ Hz and 1.8 Hz, 1H), 7.74 (m, 2H), 7.45 (s, 1H), 7.41 (d, $J=7.2$ Hz, 1H), 7.29 (m, 2H), 6.29 (s, 1H), 5.60 (s, 1H), 5.12 (t, $J=7.8$ Hz, 1H), 3.41 (dd, $J=17.4$ Hz and 7.8 Hz, 1H), 2.87 (m, 1H); ^{13}C NMR: δ 165.9, 165.1, 163.7, 140.5, 134.8, 134.6, 134.5, 130.2, 130.1, 129.7, 129.0, 127.7, 125.4, 124.2, 123.8, 120.1, 119.8, 60.5, 34.9; IR: ν 3055, 2937, 2686, 1791, 1740, 1666, 1413, 1350, 1272, 1221, 1076 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 375.0507. Found: m/z 375.0510.

2-(5-(4-Chlorophenyl)-3-methylene-2-oxopyrrolidin-1-yl)isoindoline-1,3-dione (4d) Reaction time 4 h; white solid; yield 129 mg (91%); mp 191–192°C; ^1H NMR: δ 7.84 (dd, $J=6.6$ Hz and 3.0 Hz, 1H), 7.80 (dd, $J=5.4$ Hz and 2.4 Hz, 1H), 7.74 (dd, $J=5.4$ Hz and 3.6 Hz, 2H), 7.41 (d, $J=8.4$ Hz, 2H), 7.30 (d, $J=8.4$ Hz, 2H), 6.29 (s, 1H), 5.59 (s, 1H), 5.14 (t, $J=7.2$ Hz, 1H), 3.40 (dd, $J=16.8$ Hz and 7.8 Hz, 1H), 2.87 (m, 1H); ^{13}C NMR: δ 165.9, 165.1, 163.7, 136.8, 134.8, 134.7, 134.7, 134.6, 130.1, 129.7, 129.0, 128.8, 124.2, 123.8, 120.0, 60.3, 35.0; IR: ν 3092, 2964, 2932, 1792, 1742, 1656, 1493, 1345, 1260, 1224, 1091 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{19}\text{H}_{13}\text{ClN}_2\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 375.0507. Found: m/z 375.0503.

2-(3-Methylene-2-oxo-5-(*o*-tolyl)pyrrolidin-1-yl)isoindoline-1,3-dione (4e) Reaction time 8 h; white solid; yield 55 mg (41%); mp 125–126°C; ^1H NMR: δ 7.82 (dd, $J=6.0$ Hz and 3.0 Hz, 1H), 7.79 (dd, $J=5.4$ Hz and 2.4 Hz, 1H), 7.72 (dd, $J=5.4$ Hz and 3.0 Hz, 2H), 7.22 (t, $J=8.4$ Hz, 1H), 7.09 (s, 1H), 7.00 (d, $J=7.8$ Hz, 1H), 6.82 (dd, $J=8.4$ Hz and 2.4 Hz, 1H), 6.27 (s, 1H), 5.58 (s, 1H), 5.17 (t, $J=7.2$ Hz, 1H), 3.81 (s, 3H), 3.39 (dd, $J=16.8$ Hz and 7.8 Hz, 1H), 2.88 (m, 1H); ^{13}C NMR: δ 166.1, 165.1, 163.7, 159.9, 139.9, 135.0, 134.7, 134.5, 130.2, 129.7, 124.1, 123.7, 119.7, 119.6, 115.0, 111.7, 60.9, 55.3, 35.1; IR: ν 3060, 2931, 2641, 1795, 1739, 1660, 1403, 1361, 1282, 1220, 1081 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 355.1053. Found: m/z 355.1058.

2-(3-Methylene-2-oxo-5-(*m*-tolyl)pyrrolidin-1-yl)isoindoline-1,3-dione (4f) Reaction time 8 h; white solid; yield 85 mg (64%); mp 152–153°C; ^1H NMR: δ 7.83 (m, 1H), 7.79 (dd, $J=4.8$ Hz and 1.2 Hz, 1H), 7.72 (m, 2H), 7.26 (d, $J=4.2$ Hz, 2H), 7.16 (m, 1H), 7.10 (d, $J=7.2$ Hz, 1H), 6.27 (s, 1H), 5.57 (s, 1H), 5.14 (t, $J=7.2$ Hz, 1H), 3.38 (dd, $J=17.4$ Hz and 7.8 Hz, 1H), 2.89 (m, 1H), 2.32 (s, 3H); ^{13}C NMR: δ 166.1, 165.2, 163.7, 138.5, 138.2, 135.2, 134.6, 134.4, 130.2, 129.8, 129.5, 128.7, 128.1, 124.4, 124.1, 123.7, 119.5, 60.9, 35.1, 21.3; IR: ν 3040, 2925, 2691, 1878, 1733, 1605, 1418, 1349, 1279, 1221, 1080 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_3\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 355.1053. Found: 355.1049.

2-(3-Methylene-2-oxo-5-(*p*-tolyl)pyrrolidin-1-yl)isoindoline-1,3-dione (4g) Reaction time 8 h; white solid; yield 54 mg (40%); mp 183–184°C; ^1H NMR: δ 7.83 (dd, $J=7.2$ Hz and 3.0 Hz, 1H), 7.78 (dd, $J=8.4$ Hz and 4.8 Hz, 1H), 7.72 (m, 2H), 7.34 (d, $J=7.8$ Hz, 2H), 7.13 (d, $J=7.8$ Hz, 2H), 6.27 (s, 1H), 5.57 (s, 1H), 5.13 (t, $J=6.6$ Hz, 1H), 3.37 (dd, $J=16.8$ Hz and 7.8 Hz, 1H), 2.90 (m, 1H), 2.30 (s, 3H); ^{13}C NMR: δ 166.0, 165.1, 163.7, 138.7, 135.3, 135.1, 134.6, 134.4, 130.2, 129.8, 129.4, 127.4, 124.1, 123.7, 119.5, 60.8, 35.1, 21.1; IR: ν 3038, 3006, 2922, 1802, 1743, 1658, 1423, 1350, 1279, 1222, 1078 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_3$, $[\text{M} + \text{H}]^+$: m/z 333.1239. Found: m/z 333.1230.

2-(5-(4-Methoxyphenyl)-2-methylene-3-oxopyrrolidin-1-yl)-isoindoline-1,3-dione (4h) Reaction time 10 h; white solid; yield 93 mg (66%); mp 146–147°C; ^1H NMR: δ 7.83 (dd, $J=7.2$ Hz and 2.4 Hz, 1H), 7.78 (dd, $J=6.0$ Hz and 1.8 Hz, 1H), 7.72 (m, 2H), 7.37 (d, $J=8.4$ Hz, 2H), 6.84 (d, $J=9.0$ Hz, 2H), 6.27 (s, 1H), 5.57 (s, 1H), 5.12 (t, $J=7.2$ Hz, 1H), 3.76 (s, 3H), 3.36 (dd, $J=16.8$ Hz and 7.8 Hz, 1H), 2.90 (m, 1H); ^{13}C NMR: δ 165.9, 165.1, 163.7, 159.9, 135.3, 134.6, 134.4, 130.1, 129.9, 129.8, 128.8, 124.1, 123.7, 119.4, 114.1, 60.5, 55.2, 35.1; IR: ν 3100, 2965, 2931, 1796, 1737, 1610, 1515, 1338, 1252, 1222, 1076 cm^{-1} . ESI-HRMS. Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_4\text{Na}$, $[\text{M} + \text{Na}]^+$: m/z 371.1002. Found: m/z 371.0999.

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