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Microwave-enhanced rhodium-catalyzed conjugate-addition of aryl boronic acids to unprotected maleimides

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Abstract—Various boronic acids were treated with a rhodium(I) catalyst enabling their 1,4-conjugate addition to unprotected maleimide. The scope of the reaction was explored to include both electron-rich and electron poor boronic acids. These reactions were also performed in the microwave resulting in reduced reaction times and improved efficiencies. Additionally, substrates that were recalcitrant under conventional conditions were successfully reacted under microwave conditions. The reaction worked satisfactorily with boronic acids having a free OH or NH group.

1. Introduction

Rhodium-catalyzed conjugate carbon–carbon bond forming reactions are garnering widespread attention due to their broad applicability.[1–3] Miyaura and co-workers used rhodium catalysts to promote conjugate addition reactions to α,β-unsaturated amides and lactams.[4–6] Hayashi and co-workers have extended the conjugate addition reaction scope to include maleimides (Scheme 1), pioneered the enantioselective conjugate-addition of aryl boronic acids to N-protected maleimides[7] and proposed a mechanism for the rhodium catalysis in a recent paper.[8]

In the course of a total synthesis project, we sought to use the rhodium-catalyzed conjugate-addition reaction of an aryl boronic acid to an N-protected maleimide. While the reaction itself was successful, we faced challenges in choosing a suitable protecting group for maleimide that was both facile to introduce and remove. Nitrogen protection of maleimide was inconsistent and the yields were usually low. In order to circumvent these problems, we decided to explore the direct rhodium-catalyzed conjugate additions to unprotected maleimide. A survey of the literature revealed that such additions to unprotected maleimides are, to the best of our knowledge, novel and heretofore unexplored.

2. Results and discussion

Our initial test reaction, the addition of 4-methoxyphenyl boronic acid **5** to maleimide **4** proceeded cleanly and in a 70% yield (Scheme 2). Encouraged by this result, we sought to investigate the scope and limitations of this reaction by testing a range of boronic acids.

As expected, we found that electron-rich boronic acids were very reactive and worked in good yields, usually within 3 h at 50 °C in an oil bath. In an effort to further broaden the applicability of this reaction, we investigated electron-deficient boronic acids. They reacted slowly (4–6 h) and in poor yields. Analysis confirmed that the boronic acids were undergoing competitive hydrolysis resulting in cleavage of boron from the aryl ring.[9] A higher proportion of the decomposed boronic acids were found in the slower or incomplete reactions. To circumvent this problem, we sought to increase the rate of the reaction and thereby minimize the time available for hydrolysis to occur.

In our efforts to speed up the reaction, we turned to microwave chemistry.[10] Optimization efforts allowed us to shorten the reaction time to 5 min from 3 to 6 h while increasing the temperature from 50 °C to 100 °C. We observed no decomposition of the maleimide or the rhodium catalyst at these elevated temperatures. Test reactions were run to directly compare microwave heating to conventional heating at 100 °C keeping all other parameters (including heating time) identical.

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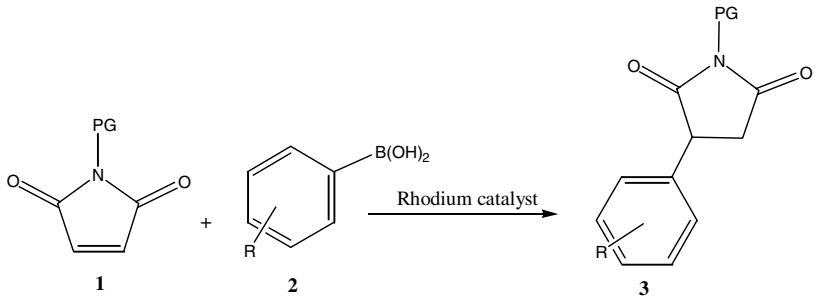
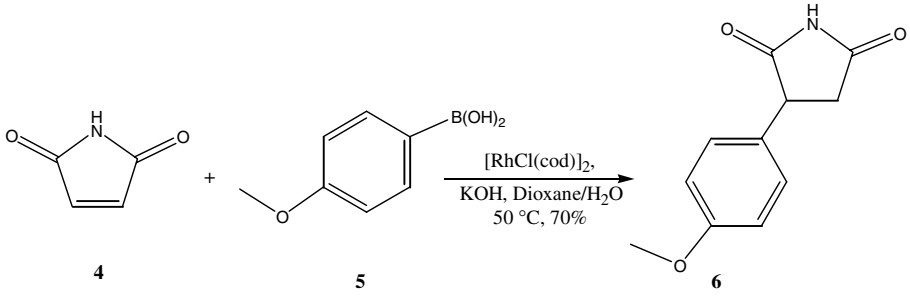


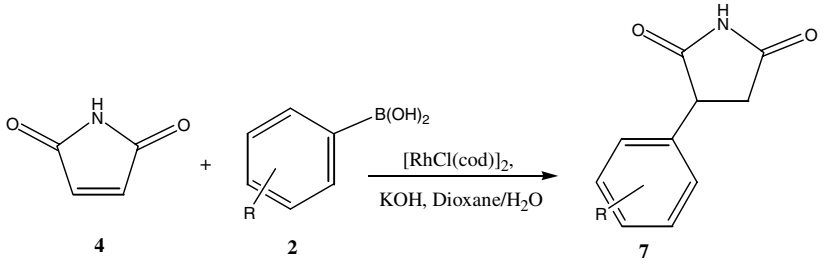
Scheme 1.



Scheme 2.

Conventional heating at 100 °C resulted in significantly lower yields.[11] Table 1 shows a comparison between conventional heating and microwave heating. Electron-deficient systems like the *p*-fluorophenyl and the *p*-trifluorophenyl boronic acids (entries 6, 7) that had given poor yields or failed under conventional conditions now proceeded in acceptable yields in the microwave. Electron-rich boronic acids (entries 1–5) gave consistently high yields both conventionally and in the microwave. Good yields were also obtained using bulky boronic acids (entries 10, 11), such as naphthyl and biphenyl. To our delight, additions using boronic acids

Table 1.



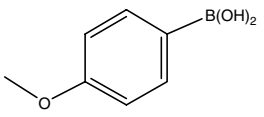
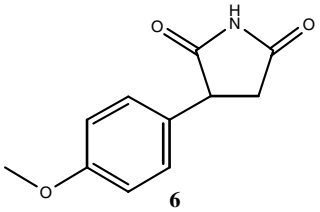
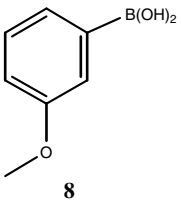
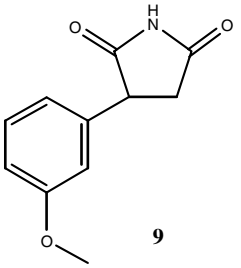
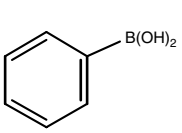
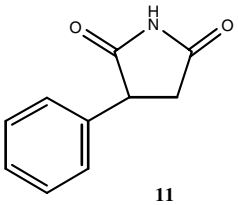
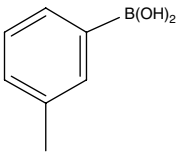
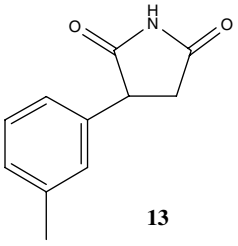
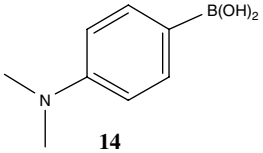
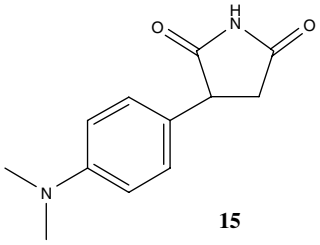
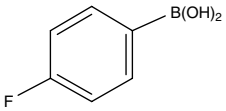
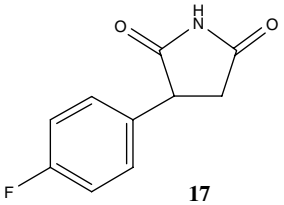
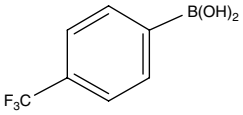
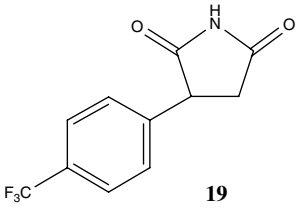
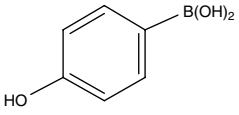
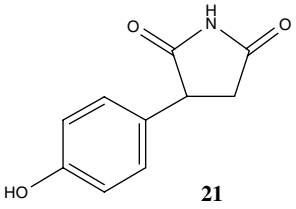
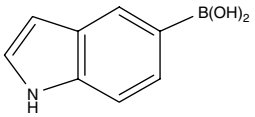
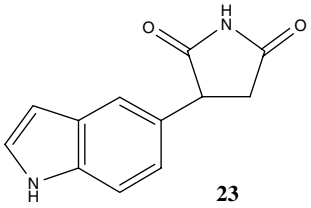
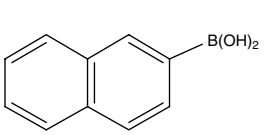
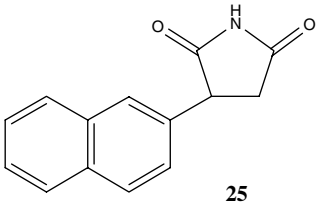
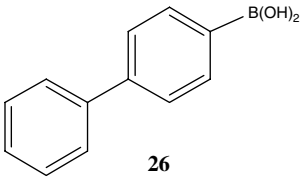
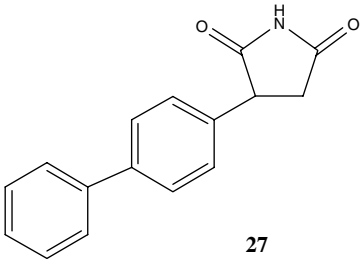
Rxn #	Boronic acid	Product	Method A		Method B	
			Yield (%)	Time (min)	Yield (%)	Time (min)
1	 **5**	 **6**	70	180	69	5
2	 **8**	 **9**	45	360	58	15

Table 1 (*continued*)

Rxn #	Boronic acid	Product	Method A		Method B	
			Yield (%)	Time (min)	Yield (%)	Time (min)
3	 **10**	 **11**	62	360	82	5
4	 **12**	 **13**	68	360	78	5
5	 **14**	 **15**	80	360	85	5
6	 **16**	 **17**	34	360	62	5
7	 **18**	 **19**	0	360	64	15
8	 **20**	 **21**	40	360	55	15
9	 **22**	 **23**	63	360	65	5

(*continued on next page*)

Table 1 (*continued*)

Rxn #	Boronic acid	Product	Method A		Method B	
			Yield (%)	Time (min)	Yield (%)	Time (min)
10	 **24**	 **25**	59	360	60	5
11	 **26**	 **27**	78	360	80	5

Method A: Conventional heating (50 °C, 3–6 h).
Method B: Microwave heating (100 °C, 5–15 min).

with potentially labile functionalities (entries 8, 9) such as a free OH or a free NH (4-hydroxyphenyl boronic acid and 5-indoleboronic acid) were also successful. While this reaction methodology has broad scope, one limitation is the use of highly hindered boronic acids. *ortho*-Substituted boronic acids faired poorly under both conventional and microwave conditions (data not shown).

In summary, the novel reaction of boronic acids with unprotected maleimide is a robust reaction and a useful contribution to organic synthesis. We have demonstrated the microwave-adaptability of this reaction and developed conditions to improve the rates and yields of these reactions. The methodology described herein allows rapid access to the pyrrolidine-2,5-dione (maleimide) core that is found in several natural products and marketed drug molecules.[12]

3. Experimental

3.1. General procedure

All reactions were performed in sealed tubes. Solvents were purchased from commercial sources and used without further purification. Microwave reactions were performed using a Personal Chemistry Emrys™ Optimizer EXP. All ^{1}H and ^{13}C NMR spectra were obtained using a Bruker Avance 300 MHz and all chemical shifts are reported in ppm relative to tetramethylsilane. Mass spectra were obtained using a Waters Micromass spectrometer.

3.2. Method A: conventional synthesis

To a solution of chloro(1,5-cyclooctadiene)rhodium (I) dimer (0.025 g, 0.05 mmol, 5 mol % equiv) in 1,4-dioxane (2.6 mL) was added KOH (0.058 g, 1.03 mmol, 1.0 equiv) in water (0.5 mL) followed by the boronic acid (3.09 mmol, 3.0 equiv). After 3 min maleimide (0.100 g, 1.03 mmol, 1.0 equiv) in dioxane (2.6 mL) was added and the reaction mixture was heated in an oil bath at 50 °C for 3–6 h. The reaction mixture was cooled to room temperature, the solvents were removed in vacuo and the residue was purified by column chromatography.

3.3. Method B: microwave-assisted synthesis

To a solution of chloro(1,5-cyclooctadiene)rhodium (I) dimer (0.025 g, 0.05 mmol, 5 mol%) in 1,4-dioxane (0.9 mL) was added KOH (0.058 g, 1.03 mmol, 1.0 equiv) in water (0.18 mL) followed by the addition of boronic acid (3.09 mmol, 3.0 equiv). After 3 min maleimide (0.100 g, 1.03 mmol, 1.0 equiv) in dioxane (0.9 mL) was added and the reaction mixture was heated at 100 °C for 5–15 min in a microwave. The reaction mixture was cooled to room temperature, the solvents were removed in vacuo and the residue was purified by column chromatography.

3.4. 3-(4-Methoxyphenyl)pyrrolidine-2,5-dione (6)

Method A: The reaction mixture was heated for 3 h and yielded 70% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 69% of pure product. The material was purified by column chromatography using a gradient of 10–50% ethyl acetate/hexanes: Mp: 136.5–138.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.85 (dd, $J = 5.1$ Hz, 18.6 Hz, 1H), 3.23 (dd, $J = 9.6$ Hz, 18.6 Hz, 1H), 3.80 (s, 3H), 4.04 (dd, $J = 5.1$ Hz, 9.6 Hz, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 8.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.3, 46.6, 55.4, 114.7 (2C), 128.5 (2C), 128.6, 159.4, 176.1, 178.1; MS *m*/*z*

MH^+ 206; Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.70; H, 5.32; N, 6.93.

3.5. 3-(3-Methoxyphenyl)pyrrolidine-2,5-dione (9)

Method A: The reaction mixture was heated for 6 h and yielded 45% of pure product. Method B: The reaction mixture was heated for 15 min and yielded 58% of pure product. The material was purified by column chromatography using a gradient of 25–55% ethyl acetate/hexanes: Mp: 104.5–106.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.89 (dd, $J = 5.1$ Hz, 18.6 Hz, 1H), 3.24 (dd, $J = 9.7$ Hz, 18.6 Hz, 1H), 3.81 (s, 3H), 4.06 (dd, $J = 5.1$ Hz, 9.7 Hz, 1H), 6.78–6.88 (m, 3H), 7.30 (t, $J = 8.0$ Hz, 1H), 8.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.2, 47.3, 55.3, 113.3, 113.5, 119.5, 130.4, 138.1, 160.2, 175.7, 177.3; MS m/z MH^+ 206; Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.28; H, 5.25; N, 6.85.

3.6. 3-Phenylpyrrolidine-2,5-dione (11)

Method A: The reaction mixture was heated for 6 h and yielded 62% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 82% of pure product. The material was purified by column chromatography using a gradient of 25–60% ethyl acetate/hexanes: Mp: 80.5–83.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.88 (dd, $J = 5.1$ Hz, 18.6 Hz, 1H), 3.25 (dd, $J = 9.6$ Hz, 18.6 Hz, 1H), 4.09 (dd, $J = 5.1$ Hz, 9.6 Hz, 1H), 7.23–7.42 (m, 2H), 7.35 (m, 3H), 8.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.6, 47.7, 127.8 (2C), 128.5, 129.6 (2C), 137.0, 175.5, 176.3; MS m/z MH^+ 176; Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.83; H, 5.14; N, 8.12.

3.7. 3-(3-Tolyl)pyrrolidine-2,5-dione (13)

Method A: The reaction mixture was heated for 6 h and yielded 68% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 78% of pure product. The material was purified by column chromatography using a gradient of 25–50% ethyl acetate/hexanes: Mp: 97.0–99.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.36 (s, 3H), 2.88 (dd, $J = 5.0$ Hz, 18.6 Hz, 1H), 3.24 (dd, $J = 9.6$ Hz, 18.6 Hz, 1H), 4.05 (dd, $J = 5.0$ Hz, 9.6 Hz, 1H), 7.04 (d, $J = 7.3$ Hz, 1H), 7.05 (s, 1H), 7.14 (d, $J = 7.3$ Hz, 2H), 7.24–7.30 (m, 1H), 8.20 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 21.4, 38.4, 47.3, 124.4, 128.1, 128.9, 129.2, 136.6, 139.1, 175.9, 177.8; MS m/z MH^+ 190; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.90; H, 5.83; N, 7.49.

3.8. 3-(4-Dimethylaminophenyl)pyrrolidine-2,5-dione (15)

Method A: The reaction mixture was heated for 6 h and yielded 80% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 85% of pure product. The material was purified by column chromatography using a gradient of 25–55% ethyl acetate/hexanes: Mp: 140.8–141.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.84 (dd, $J = 5.0$ Hz, 18.6 Hz, 1H), 2.94 (s, 6H), 3.19 (dd, $J = 9.6$ Hz, 18.6 Hz, 1H), 3.98 (dd, $J = 5.0$ Hz, 9.6 Hz, 1H), 6.71 (d, $J = 8.8$ Hz, 2H), 7.10 (d, $J = 8.8$ Hz, 2H), 8.42 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.3, 40.5 (2C), 46.6, 113.0 (2C), 124.0, 128.0 (2C), 150.3, 176.5, 178.7; MS m/z MH^+ 219; Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.01; H, 6.44; N, 12.72.

3.9. 3-(4-Fluorophenyl)pyrrolidine-2,5-dione (17)

Method A: The reaction mixture was heated for 6 h and yielded 34% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 62% of pure product. The material was purified by column chromatography using a gradient of 25–60% ethyl acetate/hexanes: Mp: 110.9–111.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.85 (dd, $J = 5.3$ Hz, 18.6 Hz, 1H), 3.25 (dd, $J = 9.7$ Hz, 18.6 Hz, 1H), 4.08 (dd, $J = 5.3$ Hz, 9.7 Hz, 1H), 7.04–7.11 (m, 2H), 7.20–7.27 (m, 2H), 8.43 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.2, 46.5, 116.3 (d, $J = 22$ Hz, 2C), 129.2 (d, $J = 8$ Hz, 2C), 132.3, 162.5 (d, $J = 248$ Hz, 1C), 175.7, 177.6; MS m/z MH^+ 194; Anal. Calcd for $C_{10}H_8FNO_2$: C, 62.17; H, 4.17; N, 7.25. Found: C, 62.58; H, 4.17; N, 7.26.

3.10. 3-(4-Trifluoromethylphenyl)pyrrolidine-2,5-dione (19)

Method A: The reaction mixture was heated for 6 h and yielded no product. Method B: The reaction mixture was heated for 15 min and yielded 64% of pure product. The material was purified by column chromatography using a gradient of 25–55% ethyl acetate/hexanes: Mp: 125.5–127.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.89 (dd, $J = 5.3$ Hz, 18.6 Hz, 1H), 3.29 (dd, $J = 9.7$ Hz, 18.6 Hz, 1H), 4.17 (dd, $J = 5.3$ Hz, 9.7 Hz, 1H), 7.40 (d, $J = 8.1$ Hz, 2H), 7.65 (d, $J = 8.1$ Hz, 2H), 8.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 37.8, 47.0, 125.0 (q, $J = 313$ Hz, 447 Hz, 1C), 126.2 (d, $J = 4$ Hz, 2C), 128.0 (3C), 140.3, 175.4, 176.9; MS m/z MH^+ 244; Anal. Calcd for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.14; H, 3.30; N, 5.76.

3.11. 3-(4-Hydroxyphenyl)pyrrolidine-2,5-dione (21)

Method A: The reaction mixture was heated for 6 h and yielded 40% of pure product. Method B: The reaction mixture was heated for 15 min and yielded 55% of pure product. The material was purified by column chromatography using a gradient of 35–65% ethyl acetate/hexanes: Mp: 196.3–198.4 °C; ^{1}H NMR (300 MHz, acetone-d_6, δ, ppm) δ 2.72 (dd, $J = 5.3$ Hz, 18.1 Hz, 1H), 3.21 (dd, $J = 9.6$ Hz, 18.1 Hz, 1H), 4.10 (dd, $J = 5.3$ Hz, 9.6 Hz, 1H), 6.82–6.87 (m, 2H), 7.15–7.20 (m, 2H), 8.33 (br s, 1H), 10.00 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6, δ, ppm) δ 39.6, 47.9, 116.8 (2C), 130.1 (2C), 130.5, 158.0, 177.8, 179.9; MS m/z MH^+ 192; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.42; H, 4.67; N, 7.19.

3.12. 3-(1*H*-Indol-5-yl)pyrrolidine-2,5-dione (23)

Method A: The reaction mixture was heated for 3 h and yielded 63% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 65% of pure product. The material was purified by column chromatography using a gradient of 30–60% ethyl acetate/hexanes: Mp: 188.5–190.0 °C; ^{1}H NMR (300 MHz, acetone-d_6, δ, ppm) δ 2.65 (dd, $J = 5.0$ Hz, 18.2 Hz, 1H), 3.14 (dd, $J = 9.6$ Hz, 18.2 Hz, 1H), 4.08 (dd, $J = 5.0$ Hz, 9.6 Hz, 1H), 6.32 (d, $J = 3.1$ Hz, 1H), 6.91 (dd, $J = 1.8$ Hz, 8.4 Hz, 1H), 7.19–7.21 (m, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 1.3$ Hz, 1H), 10.10 (br s, 1H); ^{13}C NMR (100 MHz, acetone-d_6, δ, ppm) δ 40.3, 48.9, 102.8, 113.0, 120.6, 122.1, 126.7, 129.8, 130.6, 136.9, 178.1, 180.3; MS m/z MH^+ 215; Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.22; H, 4.75; N, 12.88.

3.13. 3-Naphthalen-2-ylpyrrolidine-2,5-dione (25)

Method A: The reaction mixture was heated for 6 h and yielded 59% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 60% of pure product. The material was purified by column chromatography using a gradient of 25–55% ethyl acetate/hexanes: Mp: 154.0–154.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.98 (dd, $J = 5.1$ Hz, 18.6 Hz, 1H), 3.31 (dd, $J = 9.6$ Hz, 18.6 Hz, 1H), 4.24 (dd, $J = 5.1$ Hz, 9.6 Hz, 1H), 7.32 (dd, $J = 1.9$ Hz, 8.5 Hz, 1H), 7.45–7.53 (m, 2H), 7.72 (s, 1H), 7.80–7.88 (m, 3H), 8.45 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 38.2, 47.5, 124.7, 126.5, 126.68, 126.72, 126.73, 127.8, 129.4, 132.8, 133.4, 133.8, 176.0, 177.8; MS m/z MH^+ 226; Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.91; H, 4.91; N, 6.34.

3.14. 3-Biphenyl-4-ylpyrrolidine-2,5-dione (27)

Method A: The reaction mixture was heated for 6 h and yielded 78% of pure product. Method B: The reaction mixture was heated for 5 min and yielded 80% of pure product. The material was purified by column chromatography using a gradient of 25–50% ethyl acetate/hexanes: Mp: 179.0–180.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm) δ 2.86 (dd, $J = 5.4$ Hz, 18.1 Hz, 1H), 3.30 (dd, $J = 9.6$ Hz, 18.1 Hz, 1H), 4.28 (dd, $J = 5.4$ Hz, 9.6 Hz, 1H), 6.92–7.38 (m, 2H), 7.39–7.51 (m, 4H), 7.65–7.70 (m, 3H), 10.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm) δ 39.2, 48.3, 128.1 (2C), 128.5 (2C), 128.7, 129.6 (2C), 130.1 (2C), 138.9, 141.4, 141.7, 177.7, 179.5; MS m/z MH^+ 252; Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 77.02; H, 5.15; N, 5.66.

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References and notes

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11. Entry 7 gave a 38% yield of desired addition product, compared to 0% (conventional 50 °C) and 64% (microwave, 100 °C). Entry 9 gave a 39% yield of the desired addition product, compared to 63% (conventional, 50 °C heating) and 65% (microwave heating, 100 °C).
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