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Microwave-assisted Suzuki-Miyaura couplings on α-iodoenaminones

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Abstract

A systematic study of α-iodination and subsequent Suzuki-Miyaura couplings between non-attenuated enaminones and a wide range of aromatic boronic acids is reported. The microwave-assisted variant of this transformation furnished the α-arylenaminones in significantly shorter reaction times and slightly improved yields as compared to conventional heating.

Recently we reported a new method for the preparation of mono and bicyclic enaminones.[1] This procedure allows direct access to a variety of substituted, six membered vinylogous amides. Although compounds such as these have been studied, it is our view that they remain underutilized in natural product and chemical library synthesis.[2,3] To increase their synthetic value we became interested in employing them as coupling partners in the Suzuki-Miyaura reaction (Figure 1).[4,5]

Our strategy relied upon the unique ambident nature of the enaminone to first function as a nucleophile (α-iodination) and then as an electrophile (oxidative insertion). While the α-iodination of unprotected *E*-enaminones is well known,[6] the same transformation with unprotected *Z*-enaminones has only been recently reported.[4,7] Conditions for the α-iodination of enones first developed by Johnson,[8] as well as modifications thereof,[6a,b] were investigated on a series of vinylogous amides, which were prepared according to our previously reported procedure (Table 1).[1] Gratifyingly, installation of iodine was achieved in near quantitative yield under the standard Johnson conditions (Table 1, conditions A).[9] Furthermore, the modified Johnson conditions reported by Kim *et al.* (Method B) proceeded smoothly on both bicyclic (**1**–**3**) and monocyclic (**4**–**6**) systems.[10] It is notable that tertiary *Z*-enaminones (**1**–**4** and **6**) posed no problems despite a report that this reaction does not proceed on *tertiary E*-enaminones.[6a] In addition, the use of I_2 and DMAP also provided the desired iodinated enaminones in excellent yields (Method C).[6b,11] Furthermore, a tolerance for substitution adjacent to the ring fused nitrogen (**3a**) as well as a secondary vinylogous amide nitrogen (**5a**) was demonstrated.

With the α-iodoenaminones in hand, we next turned to their coupling with boronic acids. A survey of the literature reveals that coupling reactions have been achieved on α-halo vinylogous amides with success.[13] However, in most cases, the resonance contribution of the enaminone nitrogen is attenuated via an electron withdrawing protecting group.[12] Without this protecting group the resonance contribution of the nitrogen is greatly enhanced. In turn, this electron rich system is less willing to undergo oxidative insertion, often the rate limiting step in this coupling

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process, leading to poor conversion and low yields.[4a] This limits the use of Suzuki coupling reactions in these systems to those that do not contain tertiary aliphatic substitution. This is unfortunate, given the common occurrence of this structural feature in alkaloid natural products.[13]

A variety of conditions were explored with enaminone **1a** and 4-methoxyphenylboronic acid to determine optimal conditions for coupling (Table 2). In all cases $Pd(PPh_3)_4$ was employed as the palladium source and heating was required for conversion. In addition, it was critical that the solvent mixtures be carefully deoxygenated. The best conditions were obtained when a mixture of dioxane and water was used as solvent and $Ba(OH)_2$ employed as base (Table 2, entry 6).[14] Although pleased with the results of our optimization, the reaction times were less than ideal. Microwave irradiation has been used to decrease reaction times and in some cases increase reaction yields.[5] Thus microwave conditions were applied to this system and a dramatic rate enhancement was noted (Table 2, entry 7, 14–20 h reduced to 15 min) along with a modest increase in yield.[15]

The scope of the reaction was next investigated under the optimized microwave conditions using the enaminones and boronic acid coupling partners shown in Table 3. In general, electron rich boronic acids participated well in the coupling reaction while electron poor coupling partners delivered moderate yields (**1b**–**1h** and **4b**–**4h**). Employing an unprotected phenolic boronic acid resulted in a poor yield of enaminones **1g** and **4g**. Both the 5/6 (**1a**) and 6/6 (**2a** and **3a**) enaminone systems couple effectively as do monocyclic enaminones (**4a**–**6a**). It should be pointed out that even the sterically encumbered substrate **3a** underwent coupling under these conditions. In addition it should be noted that a free NH was tolerated (**5a**).

In summary, we have demonstrated a significant improvement in the technology available for preparing α-iodoenaminones and coupling them with arylboronic acids. The use of microwave irradiation proved advantageous in the coupling process. The scope of both the enaminone and boronic acid partners demonstrated versatility. Ongoing studies in these labs are directed toward further method development upon these vinylogous amide scaffolds as well as applications in natural product and diversity-oriented synthesis (DOS).

Acknowledgements

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9. Table 1, method A: **6-Iodo-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (1a).** Enaminone **1** (760 mg, 5.54 mmol) was dissolved in CCl_4/pyridine (1:1, 10 mL) and cooled to 0 °C. To this mixture was added iodine (3.52 g, 13.9 mmol) in CCl_4/pyridine (1:1, 2 mL) dropwise. The reaction was then allowed to warm to rt. After 5 h this solution was concentrated into a brown oil under reduced pressure and purified via flash column chromatography (silica gel, 1% Et_3N in EtOAc) to provide 1.45 g of the title compound (99%) as a yellow solid (mp = 97–98 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62–1.72 (m, 1H) 1.90–2.10 (m, 1H), 2.07–2.17 (m, 1H), 2.22–2.23 (m, 1H), 2.43 (dd, *J* = 16.2 Hz, 16.2 Hz, 1H), 2.74 (dd, *J* = 15.9 Hz, 4.7 Hz, 1H), 3.59–3.66 (m, 2H), 3.81–3.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 32.4, 40.3, 49.8, 58.3, 59.9, 154.7, 185.3; IR (neat) 2970, 2872, 1620, 1559, 1296, 1223 cm^{-1}; HRMS (ES+) *m/e* calc'd for $[M+H]^+$ $C_8H_{11}INO$: 263.9885, found 263.9886.
10. Iodination Method B: **6-Iodo-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (1a).** To a stirred solution of enaminone **1** (137 mg, 1.0 mmol) and iodine (254 mg, 1.0 mmol) in CH_2Cl_2 (3 ml) was added Et_3N (140 μl, 1.0 mmol) at rt. After 5 min this solution was concentrated into a brown oil under reduced pressure then purified via flash chromatography (silica gel, 1% Et_3N in EtOAc) to provide the desired α-iodoenaminone **1a** (95%).
11. Iodination Method C: **3-Iodo-7,8,9a-tetrahydro-1*H*-quinolizin-2(*6H*)-one (2a)**. A solution of I_2 in CH_2Cl_2 (210 mg, 0.83 mmol, 0.05M) was added dropwise over 20 min to a solution of enaminone **2** (104 mg, 0.69 mmol) and DMAP (171 mg, 1.38 mmol) in CH_2Cl_2 (15 mL) at rt. After stirring overnight at the same temperature, the reaction mixture was quenched by the addition of water and extracted with CH_2Cl_2 (2×). The combined organic layers were washed with saturated aq. NH_4Cl, water, saturated aq. $Na_2S_2O_3$, water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, 50% EtOAc in hexanes) to afford iodide **2a** (186 mg, 97%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30–1.57 (m, 3H), 1.69–1.83 (m, 3H), 2.42 (dd, 1H, *J* = 13.2 Hz), 2.70 (dd, 1H, *J* = 5.4 Hz), 3.04 (td, 1H , *J* = 3 Hz, 3.36–3.43 (m, 2H), 7.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.91, 25.53, 31.55, 41.94, 53.17, 57,26, 62.71, 159.48, 186.03; IR (neat) 2924, 2853, 1630, 1564, 1461, 1318, 1136 cm^{-1}; HRMS (ES+) *m/e* calc'd for $[M+H]^+$ $C_9H_{13}INO$: 278.0036, found 278.0038.
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13. Cordell GA. The Alkaloids: Chemistry and Biology 2003;60
14. Conventional heating method: **6-(3,4-Dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (1h).** α-Iodoenaminone **1a** (240 mg, 0.91 mmol) was dissolved in degassed dioxane:water (3:1, 4 mL). The 3,4-dimethoxyphenylboronic acid (282 mg, 1.55 mmol), barium hydroxide (345 mg, 1.82 mmol), and $Pd(PPh_3)_4$ (210 mg, 0.182 mmol) were added sequentially. This mixture, equipped with reflux condenser, was heated to 110 °C for 18 h. The reaction was allowed to cool to rt, concentrated under reduced pressure, dissolved in CH_2Cl_2, filtered, dried over Na_2SO_4, and purified via flash column chromatography (silica gel, 1% Et_3N in EtOAc) to provide 161 mg of the title compound (65%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65–1.80 (m, 1H) 1.91–2.07 (m, 1H), 2.08–2.18 (m, 1H), 2.26–2.39 (m, 1H), 2.45–2.60 (m, 2H), 3.55–3.63 (m, 2H), 3.83–3.88 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.80–6.86 (m, 2H), 7.09 (s, 1H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.8, 33.4, 42.7, 50.2, 56.2, 56.3, 58.2, 110.0, 111.5, 112.0, 119.7, 129.0, 130.3, 147.4, 148.9, 149.3, 189.5; IR (neat) 3381, 2935, 2835, 1609, 1514, 1407, 1250 cm^{-1}; HRMS (ES+) *m/e* calc'd for $[M+H]^+$ $C_{16}H_{20}NO_3$: 274.1443, found 274.1441.

15. Microwave irradiation method: **6-(3,4-Dimethoxyphenyl)-2,3,8,8a-tetrahydroindolizin-7(1*H*)-one (1h).** α-Iodo enaminone **1a** (240 mg, 0.91 mmol) was dissolved in degassed dioxane:water (3:1, 4 mL). The 3,4-dimethoxyphenylboronic acid (282 mg, 1.55 mmol), barium hydroxide (345 mg, 1.82 mmol), and $Pd(PPh_3)_4$ (210 mg, 0.182 mmol) were added sequentially. This mixture was heated under microwave irradiation at 150 °C for 1 h. The reaction was allowed to cool to rt, concentrated under reduced pressure, dissolved in CH_2Cl_2, filtered, dried over Na_2SO_4, and purified via flash column chromatography (silica gel, 1% Et_3N in EtOAc) to provide 187 mg of the title compound (75%).

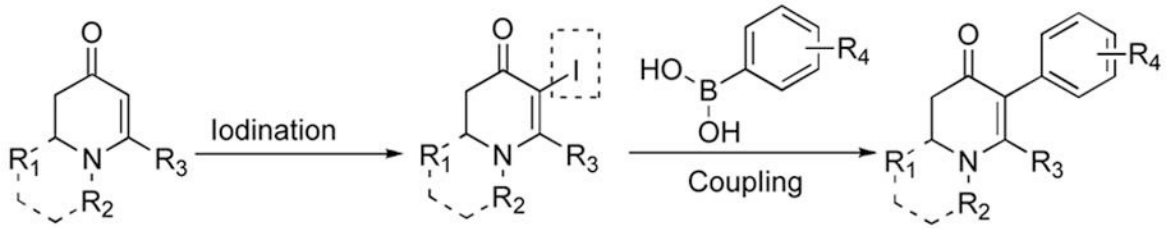
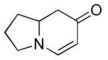
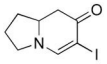
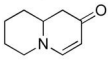
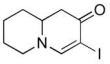
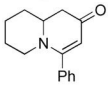
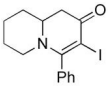
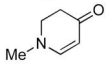
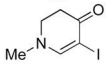
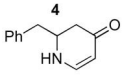
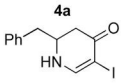
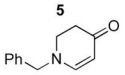
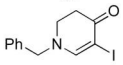


Figure 1.
Proposed route to α-aryl enaminones.

Table 1

α-Iodination of enaminones.

Enaminone	Conditions	α-Iodo enaminone	Yield (%)[a]
	A. pyridine/CCl_4, I_2 B. CH_2Cl_2, I_2, then NEt_3		99 95
1		**1a**	
	B. CH_2Cl_2, I_2, then NEt_3 C. CH_2Cl_2, I_2, DMAP		87 97
2		**2a**	
	B. CH_2Cl_2, I_2, then NEt_3		85
3		**3a**	
	B. CH_2Cl_2, I_2, then NEt_3		88
4		**4a**	
	B. CH_2Cl_2, I_2, then NEt_3		85
5		**5a**	
	C. CH_2Cl_2, I_2, DMAP		94
6		**6a**	

[a] Isolated yield

Table 2

Optimization of coupling reaction between enaminone **1a** and 4-methoxyphenylboronic acid.[a]

Entry	Base	Solvent(s), Temperature	Reaction Time	Yield %[b]
1	$CaCO_3$	DMF/H_2O (3/1), 150 °C	20 h	0
2	Na_2CO_3	DME/H_2O (1/1), 100 °C	20 h	13
3	Na_2CO_3	toluene, 110 °C	20 h	23
4	Na_2CO_3	toluene/EtOH (1/1), 110 °C	20 h	25
5	CsF	MeCN/H_2O (1/1), 100 °C	14 h	27
6	$Ba(OH)_2$	dioxane/H_2O (3/1), 110 °C	14 h	65
7[c]	$Ba(OH)_2$	dioxane/H_2O (3/1), 150 °C MW[c]	15 min	70

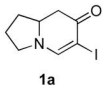
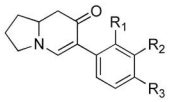
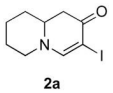
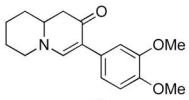
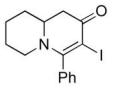
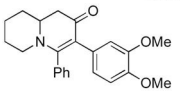
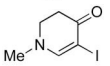
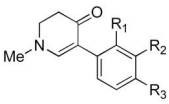
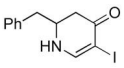
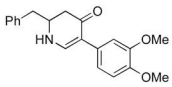
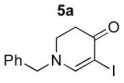
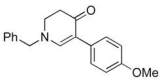
[a] Compound **1a** (0.10 mmol) was dissolved in degassed solvent mixture (0.25–0.5 M) under argon and 4-methoxyphenylboronic acid (0.17 mmol), base (0.20 mmol) and $Pd(PPh_3)_4$ (0.02 mmol) added.

[b] Isolated yield.

[c] Carried out employing microwave irradiation (150 °C, 15 min).

Table 3

Cross coupling of iodoenaminones and arylboronic acids.[a]

α-Iodo enaminone	Product	Substitution (R_1, R_2, R_3)	Yield (%)[b]
 1a		**1b** (H, H, OMe)	70
		1c (H, H, OBn)	71
		1d (H, NO_2, H)	57
		1e (Cl, Cl, H)	60
		1f (H, H, H)	65
		1g (H, H, OH)	45
		1h (H, OMe, OMe)	75[c]
 2a		**2b** (as shown)	72
 3a		**3b** (as shown)	60
 4a		**4b** (H, H, OMe)	60
		4c (H, H, OBn)	71
		4d (H, NO_2, H)	62
		4e (Cl, Cl, H)	50
		4f (H, H, H)	55
		4g (H, H, OH)	36
		4h (H, OMe, OMe)	68
 5a		**5b** (as shown)	70
 6a		**6b** (as shown)	69

[a] Coupling reactions were conducted as in Table 2, entry 7.

[b] Isolated yields.

[c] 1 h reaction time.