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Catalyst- and steric-controlled alkenylation via chemoselective C–H activation and C–Br activation in Heck reaction of methyl 1-(2-bromoaryl)-3-(2-furyl/thienyl)-5-oxopyrrolidine-2-carboxylates and diethyl 1-(2-bromoaryl)-3-(2-furyl/thienyl)-5-oxopyrrolidine-2,2-dicarboxylate derivatives

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ABSTRACT

Pd(II)-catalyzed alkenylation of methyl 1-(2-bromoaryl)-3-(2-furyl/thienyl)-5-oxopyrrolidine-2-carboxylate derivatives **1(a–d)** resulted in the formation of **3(a–d)** exclusively via C–H activation in the heteroaryl moiety. Similar observations were observed for the corresponding diester analogues **4(a–d)** to form **5(a–d)**. Normal Heck reaction, however, was observed in the case of **1(a–f)** to furnish **2(a–f)** when the reaction was carried out with Pd(0) catalyst generated in situ. Pd(0)-catalyzed vinylation of **4(a–f)** via C–Br oxidation, however, failed due to steric reason.

The synthetic studies toward novel γ-lactam antibacterial agents as non-β-lactam mimics of β-lactam antibiotics[1] is a growing field since four decades and it has been further stimulated by the isolation of many naturally occurring γ-lactam derivatives with potential biological activities.[2] Synthetic monocyclic γ-lactam derivatives like 1-aryl-3-heteroaryl-5-oxopyrrolidine-2-carboxylic acids have been found to display significant antibacterial activities.[3] The activity in turn depends on the nature of 1- and 3-aryl moiety and the C_2–COOH group present in the γ-lactam framework. In our ongoing project in search of novel antibacterial agents with enhanced antibacterial activity, we were studying the Pd-catalyzed Heck reaction[4] of γ-lactam derivatives **1(a–f)** and **4(a–f)**, respectively, with methyl acrylate. We have observed some interesting catalyst-dependent chemoselective C–H oxidation in the heteroaryl part over the expected C–Br bond in the *N*-aryl part of γ-lactam dicarboxylic ester derivatives **4**(**a**–**d**) (Scheme 2) and the corresponding monoester derivatives **1**(**a**–**f**) (Scheme 1). When $Pd(OAc)_2$ was used as catalyst, vinylation took place by replacement of C_5–H in the heteroaryl moiety. However, normal results were obtained in the Pd(0) (generated in situ from $Pd(OAc)_2$ and PPh_3)-catalyzed alkenylation of the γ-lactam monocarboxylic ester derivatives **1**(**a**–**f**) to furnish **2(a–f)** in moderate yields. Attempted vinylation of the corresponding diester derivatives **4(a–f)**, under identical condition, however, met with failure. Herein, we report our results.

Thus when methyl 1-(2-bromophenyl)-3-(2-furyl)-5-oxopyrrolidine-2-carboxylate (**1a**) was subjected to Heck reaction with methyl acrylate in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3, NaOAc, Bu_4NCl (cat.) at 110–120 °C, in DMF, under argon atmosphere afforded compound **2a** in 35% yield. Similar results were obtained in the case of **1b** to produce **2b** as the only isolable product. When the 2-furyl group was replaced with a 2-thienyl group (**1c** and **1d**) or a phenyl group (**1e** and **2f**), the vinylation occurred in the *N*-aryl part only to furnish **2**(**c**–**d**) (35–36%) and **2(e–f)** (36–40%) via activation of C–Br bond (Scheme 1). The compounds have been characterized by usual spectroscopic and analytical data.[5]

Under identical conditions, attempted vinylation of diethyl 1-(2-bromoaryl)-3-(2-furyl/thienyl)-5-oxopyrrolidine-2,2-dicarboxylate derivatives **4(a–f)** afforded no product (**6**) with *N*-aryl–vinyl bond formation. Instead heteroaryl–vinyl bond formation via C–H oxidation was noticed in the reaction of **4**(**a**–**d**) with methyl acrylate and **5**(**a**–**d**) formed in 35–55% yield (Scheme 2). Thus when compound **4a** or **4b** was subjected to Heck reaction with methyl

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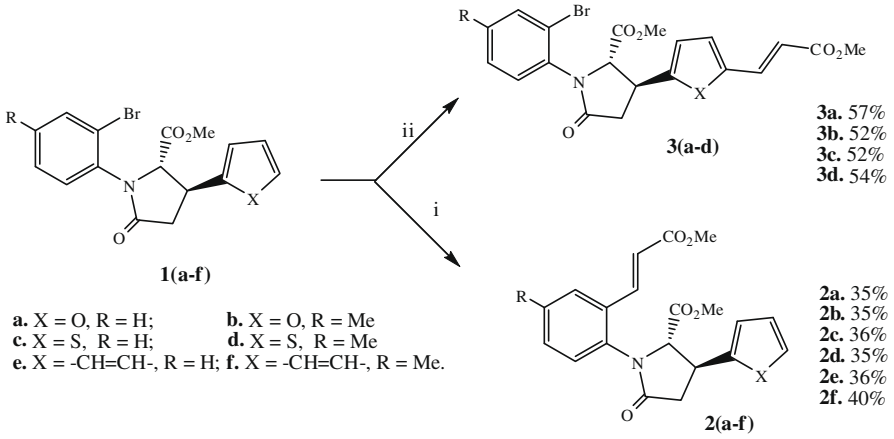
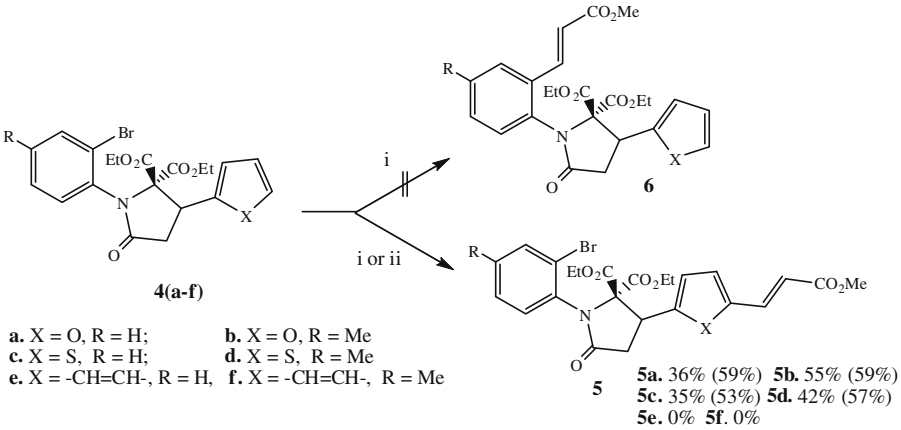


Scheme 1. Reagents and conditions: (i) methyl acrylate, $Pd(OAc)_2$ (5 mol %), PPh_3, *n*-Bu_4NCl (cat.), NaOAc, DMF, 110–120 °C, 8–10 h under argon atmosphere; (ii) methyl acrylate $Pd(OAc)_2$ (5 mol %), $Cu(OAC)_2$, DMF 90–100 °C, 8–9 h.



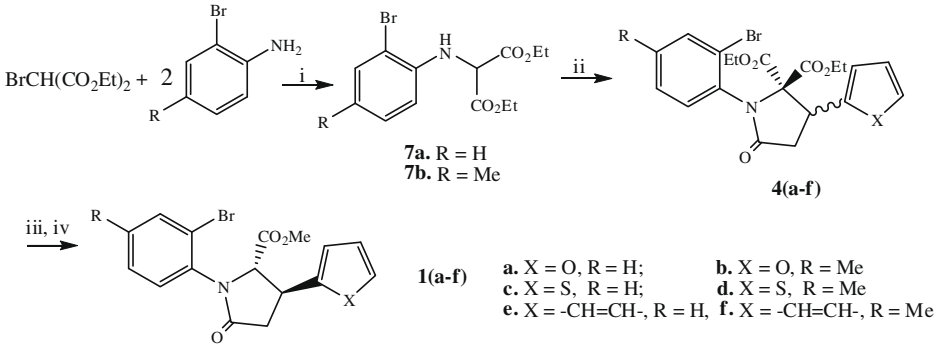
Scheme 2. Reagents and conditions: (i) methyl acrylate, $Pd(OAc)_2$ (5 mol %), PPh_3, *n*-Bu_4NCl (cat.), NaOAc, DMF, 110–120 °C, 8–12 h under argon atmosphere (yields 0–55%); (ii) methyl acrylate, $Pd(OAc)_2$ (5 mol %), $Cu(OAC)_2$, DMF 90–100 °C, 8–9 h (yields 53–57%) (within parenthesis).

acrylate with $Pd(OAc)_2$ (cat.), PPh_3, NaOAc, Bu_4NCl (cat.), DMF, 110–120 °C, under argon atmosphere compound **5a** or **5b**[5] was produced in 36% and 55% yields, respectively, with exclusive vinylation by activation of C_5–H in 2-furyl ring. When the 2-furyl group was replaced with a 2-thienyl group (**4c** and **4d**), under similar reaction conditions, vinylation occurred (in 35% and 42% yields, respectively) in the C_5-position of the thiophene ring also but no alkenylation in *N*-aryl ring was observed. In the case of 3-phenyl derivative (**4e** or **4f**), however, there was no reaction at all and the starting material was recovered unchanged showing the inert nature of the *N*-(2-bromoaryl) group toward Pd(0)-catalyzed Heck reaction.

The reason for this may be the steric effect due to two CO_2Et groups at C_2 of the γ-lactam ring which restricts the oxidative addition of Pd(0) to C–Br bond. Vinylation in the heteroaryl moiety possibly takes place by electrophilic palladation[6a] at C-5 position with $Pd(OAc)_2$ present in the reaction medium, followed by alkenylation with methyl acrylate. This is further proved by the fact that when the reaction was carried out using only $Pd(PPh_3)_4$ as catalyst instead of palladium acetate and triphenyl phosphine mixture there was no reaction at all. However, when the γ-lactam monocarboxylic ester derivatives **1**(**a**–**f**) or the diester derivatives **4**(**a**–**d**) were allowed to react with $Pd(OAc)_2$ (used in stoichiometric ratio or in catalytic amount in combination with $Cu(OAc)_2$ which converts Pd(0) back to Pd(II) species) in the absence of PPh_3 and inert atmosphere, they afforded **3**(**a**–**d**) or **5**(**a**–**d**), respectively (Schemes 1 and 2). Under this condition compound **1**(**a**–**d**) produced only **3**(**a**–**d**) by heteroaryl–vinyl bond formation but no formation of compounds like **2**(**a**–**d**) was noticed. For example, when a mixture of **1d** and methyl acrylate in DMF was heated with palladium acetate (~5 mol %), $Cu(OAc)_2$ (2–3 equiv), and NaOAc at 90–100 °C (no argon atmosphere was used) compound **3d** was formed in 54% yield as indicated from spectral data.[5]

Here the heteroaryl moiety first undergoes electrophilic palladation with Pd(II) species which is followed by addition–elimination[6a] with methyl acrylate to show vinylation in heteroaryl moiety. The trans stereochemistry around the alkene functionality was established from the coupling constant of the vinylic protons (J = 15–16 Hz). In the case of vinylation of **4**(**a**–**d**) with Pd–acetate/$Cu(OAc)_2$ much better yields (53–59%) were obtained. Thus reaction of diethyl 1-(2-bromoaryl)-3-(2-furyl)-5-oxopyrrolidine-2,2-dicarboxylate **4a** with $Pd(OAc)_2$ (cat.), NaOAc, and $Cu(OAc)_2$ in DMF at 90–100 °C produced **5a** in 59% yield. Other compounds **4**(**b**–**d**) also behaved in a similar fashion to yield **5**(**b**–**d**) (53–59%). Pd-catalyzed C_2–H oxidation of furan in the reaction with acrylic esters though known is not common.[6] But prior to this report, we have not come across any C–H oxidation in aryl/heteroaryl ring despite the presence of an aryl bromide moiety in the molecule.

Required γ-lactam diester derivatives **4**(**a**–**f**) were prepared, in 55–65% yields, by intermolecular Michael addition followed by intramolecular amidification reaction[7] of 2-bromoarylamino malonate and β-aryl/heteroaryl-α,β-unsaturated acid chlorides in the



Scheme 3. Reagents and conditions: (i) 100–110 °C, 24 h; (ii) β-aryl/heteroaryl-α,β-unsaturated acid chloride, Et_3N, benzene, reflux, 8–10 h; (iii) KOH, EtOH, H_2O, reflux, 4 h; (iv) CH_2N_2, Et_2O, 10–15 °C.

presence of Et_3N/benzene under reflux (Scheme 3). Hydrolysis (KOH, EtOH–H_2O, and reflux) and in situ decarboxylation afforded the trans acid (70–78% yield) (very minor amount cis product formed was removed during recrystallization) which was esterified with diazomethane to obtain the γ-lactam monoester derivatives **1(a–f)** in very good to excellent yields. The compounds have been characterized by usual spectral and analytical data. The trans geometry of the C_4- and C_5-substituents in the γ-lactam ring was assigned from the coupling constant values of C_4–H and C_5–H (J = 3.2–4.7 Hz), respectively, as well as by analogy.[3,8]

Thus this Letter describes some Pd(II)-catalyzed chemoselective C–H oxidation in heteroaryl moiety in vinylation of the γ-lactam diester derivatives **1(a–d)** or **4**(**a**–**d**) with methyl acrylate even in the presence of aryl bromide functionality and Pd(0)-catalyzed C–Br oxidation in vinylation of γ-lactam diester derivatives **1(a–f)**. To the best of our knowledge such types of observations are unknown till date. Though the yields are not very high in some cases there are wide scopes to study the reaction by variation of Pd-catalysts, reagents, conditions, and/or solvents etc to improve the yield which will be our future course of work in this connection.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.005.

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5. Physical and spectral data of representative compounds:
   Compound **1b**: Colorless solid, mp 124–125 °C (EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.83 (dd, 1H, J = 4.8 and 17.0 Hz), 3.06 (dd, 1H, J = 8.8 and 17.0 Hz), 3.70 (s, 3H), 3.79–3.87 (m, 1H), 4.83 (d, 1H, J = 3.6 Hz), 6.29 (d, 1H, J = 3.2 Hz), 6.35 (dd, 1H, J = 1.8 and 3.7 Hz), 7.14 (dd, 1H, J = 1.2 and 8.0 Hz), 7.29 (d, 1H, J = 8.0 Hz), 7.42–7.43 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.34, 34.79, 36.37, 53.06, 66.61, 107.19, 110.90, 122.20, 129.59, 131.29, 133.21, 134.35, 140.93, 142.82, 153.49, 171.46, 173.92 ppm; IR (KBr) ν_{max}: 1703.8, 1732.7 cm^{-1}.
   Compound **2b**: Colorless solid, mp 118–120 °C (Et_2O/−15 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.36 (s, 3H), 2.80 (dd, 1H, J = 4.2 and 17.2 Hz), 3.15 (dd, 1H, J = 9.2 and 17.2 Hz), 3.70 (s, 3H), 3.74–3.84 (m, 1H), 3.77 (s, 3H), 4.59 (d, 1H, J = 3.2 Hz), 6.30 (d, 1H, J = 3.4 Hz), 6.38 (dd, 1H, J = 1.8 and 3.2 Hz), 6.39 (d, 1H, J = 15.8 Hz), 7.13 (d, 1H, J = 8.2 Hz), 7.21 (dd, 1H, J = 1.8 and 8.0), 7.46 (br s, 1H), 7.49 (br d, 1H, J = 1.2 Hz), 7.75 (d, 1H, J = 15.8 Hz ppm; IR (KBr) ν_{max}: 1704.0–1734.6 (br strong), 1753.9 cm^{-1}; HRMS (ESI, 70 eV): m/z = 406.1318 (M$^+$+Na) [calculated mass for $C_{21}H_{21}NO_6Na$: 406.1267 (M$^+$+Na)].
   Compound **3d**: Colorless solid, mp 117–119 °C (Et_2O/−15 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.75 (dd, 1H, J = 6.0 and 17.0 Hz), 3.11 (dd, 1H, J = 9.5 and 17.0 Hz), 3.63 (s, 3H), 3.72 (s, 3H), 3.93 (m, 1H), 4.69 (d, 1H, J = 4.5 Hz), 6.12 (d, 1H, J = 16.0 Hz), 6.93 (d, 1H, J = 4.0 Hz), 7.07 (d, 1H, J = 4.0 Hz), 7.08 (br d, 1H, J∼8.0 Hz), 7.21 (d, 1H, J = 8.0 Hz), 7.36 (br s, 1H), 7.65 (d, 1H, J = 16.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.99, 37.92, 38.13, 51.87, 52.88, 68.91, 116.99, 122.09, 128.28, 129.41, 131.09, 131.35, 132.85, 134.15, 137.10, 139.07, 140.87, 147.39, 167.25, 170.78, 173.02 ppm IR (KBr) ν_{max}: 1618.0, 1714.4 (br strong), 1749.1 cm^{-1}.
   Compound **4a**: Colorless white, mp 156–157 °C (EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.82 (t, 3H, J = 7.2 Hz), 0.99 (t, 3H, J = 7.2 Hz), 2.85 (dd, 1H, J = 8.8 and 16.8 Hz), 3.13 (dd, 1H, J = 12.2 and 16.8 Hz), 3.78 (m, 1H), 3.93–4.12 (m, 3H), 4.74 (dd, 1H, J = 8.8 and 12.2 Hz), 6.31–6.37 (m, 2H), 7.19–7.36 (m, 3H), 7.54–7.61 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.09, 13.54, 32.89, 39.55, 62.37, 62.68, 76.96, 109.66, 110.67, 125.38, 128.40, 130.01, 130.69, 132.65, 136.41, 142.40, 149.17, 164.97, 167.61, 172.92 ppm; IR (KBr) ν_{max}: 1718.3, 1733.7, 1753.0 cm^{-1}.
   Compound **5a**: Colorless white, mp 118–120 °C (Et_2O/−15 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.85 (t, 3H, J = 7.2 Hz), 0.98 (t, 3H, J = 7.2 Hz), 2.89 (dd, 1H, J = 8.8 and 16.6 Hz), 3.18 (dd, 1H, J = 12.2 and 16.6 Hz), 3.74–3.82 (m, 1H), 3.79 (s, 3H), 3.96–4.14 (m, 3H), 4.76 ((dd, 1H, J = 8.8 and 12.2 Hz), 6.27 (d, 1H, J = 15.6 Hz), 6.50 (d, 1H, J = 3.4 Hz), 6.57 (d, 1H, J = 3.4 Hz), 7.22–7.40 (m, 2H), 7.37 (d, 1H, J = 15.5), 7.58–7.64 (m, 2H) ppm; IR (KBr) ν_{max}: 1638.2, 1702.8, 1730.8, 1752.0 cm^{-1}; HRMS (ESI, 70 eV): m/z = 534.4321 (M$^+$+H), 536.4301 (M$^+$+2+H) [calculated mass for $C_{24}H_{25}NO_8Br$: 534.0764 (M$^+$+H) and 536.0743 (M$^+$+2+H)].
   Compound **5b**: Colorless white, mp 132–133 °C (Et_2O/−15 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (t, 3H, J = 7.2 Hz), 1.01 (t, 3H, J = 7.2 Hz), 2.37 (s, 3H), 2.92 (dd, 1H, J = 8.6 and 16.7 Hz), 3.19 (dd, 1H, J = 12.3 and 16.7 Hz), 3.82 (m, 1H), 3.83 (s, 3H), 4.04–4.08 (m, 1H), 4.08–4.12 (m, 2H), 4.79 ((dd, 1H, J = 8.8 and 12.2 Hz), 6.30 (d, 1H, J = 15.7 Hz), 6.53 (d, 1H, J = 3.2 Hz), 6.60 (d, 1H, J = 3.1 Hz), 7.17 (br d, 1H, J = 8.2 Hz), 7.41 (d, 1H, J = 15.7), 7.47 (br s, 1H), 7.49 (d, 1H, J = 8.1 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.20, 13.56, 20.84, 32.77, 39.83, 51.69, 58.34, 62.57, 62.70, 112.70, 115.58, 115.85, 124.95, 129.26, 130.27, 130.62, 133.11, 133.41, 140.63, 150.63, 151.93, 164.87, 167.30, 167.41, 172.67 ppm; IR (KBr) ν_{max}: 1636.3, 1710.0–1730.0 (br, strong), 1735.0–1752.0 (br, strong) cm^{-1};
   HRMS (ESI, 70 eV): m/z = 570.0859(M$^+$+Na) and 572.0838 (M$^+$+2+Na) [calculated mass for $C_{25}H_{26}NO_8BrNa$: 570.0739 (M$^+$+Na) and 572.0719 (M$^+$+2+Na)].
   (Supplementary physical and spectral data enclosed for other compounds.)
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