

# Copper Catalyzed Coupling of $\alpha$ -Bromocarboxylate with $\omega$ -Lactam

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**Abstract:** This paper especially deals with the problem associated with the reaction of  $\alpha$ -bromocarboxyl compound and 5-membered  $\omega$ -lactam ring. Specific heterogeneous copper catalyst was used to achieve the C–N nucleophilic coupling. Synthetic pathway of ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate as the key intermediate of new potential transdermal enhancers is described. All generated compounds were characterized by NMR and IR spectroscopy.

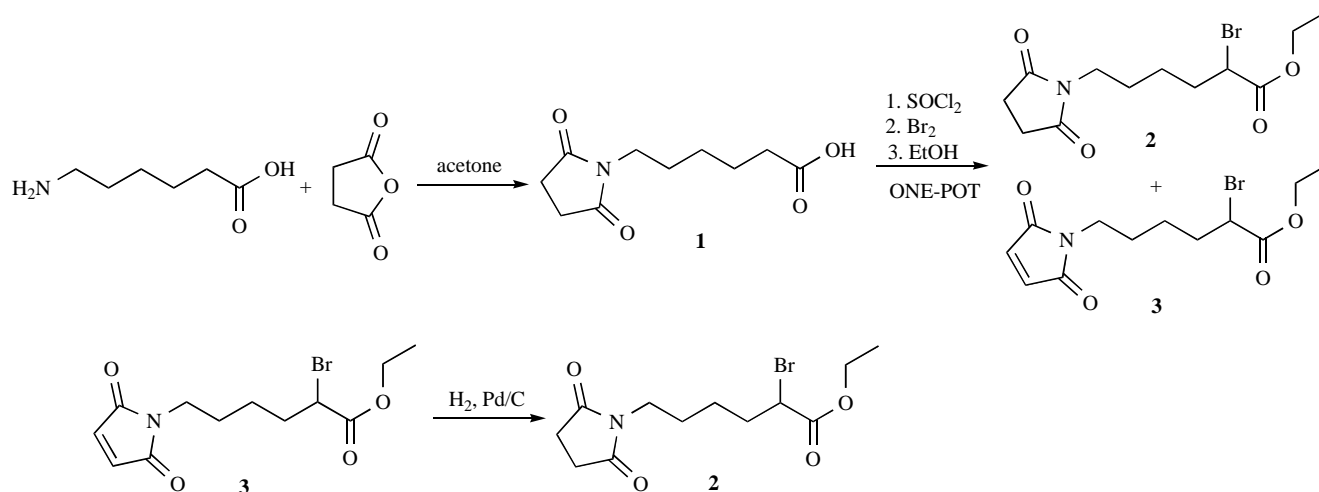
**Keywords:** Copper catalyst, C–N coupling,  $\omega$ -lactam derivatives, penetration enhancers.

Copper catalysts could be used in various types of carbon-carbon and carbon-heteroatom bond forming reactions. We investigated the synthesis of ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate as the key intermediate of potential transdermal enhancers. Skin penetration enhancers are used to allow formulation of transdermal delivery systems for drugs that are otherwise insufficiently skin-permeable [1, 2].

6-Aminohexanoic acid and succinic anhydride as starting materials for multistep synthesis were used, and by their reaction 6-(2,5-dioxopyrrolidin-1-yl)hexanoic acid (**1**) was obtained. Under optimised Schwenk and Papa procedure [3,

tion of compound **2**. Pyrroline derivative **3** was hydrogenated to pyrrolidine derivative **2** on heterogeneous Pd/C catalyst. The route of synthesis is shown in Scheme 1.

As the critical step of synthesis has been found out the C–N nucleophilic coupling of pyrrolidin-2-one and ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**). Several conventional methods under various conditions have been used, nevertheless the required product **6** was not obtained, see Scheme 2 methods a-e. These methods, reaction conditions and results are shown in Table 1. The starting compound **2** was isolated using methods a-c. The mixture of **2** and ethyl-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**4**) were



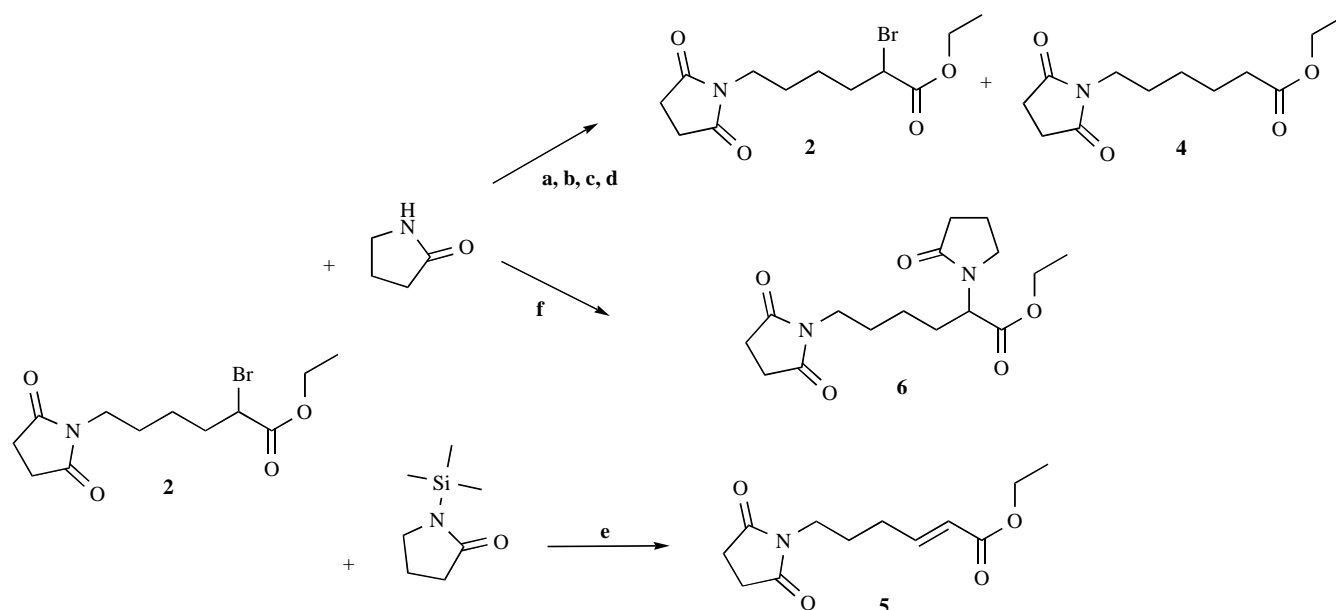
**Scheme 1.** Synthesis of ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**).

4] acid **1** in one-pot synthesis gave the mixture of ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**) and ethyl-2-bromo-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoate (**3**) as a by-product, which was formed during the prepara-

tion of compound **2**. Pyrroline derivative **3** was hydrogenated to pyrrolidine derivative **2** on heterogeneous Pd/C catalyst. The route of synthesis is shown in Scheme 1.

As the critical step of synthesis has been found out the C–N nucleophilic coupling of pyrrolidin-2-one and ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**). Several conventional methods under various conditions have been used, nevertheless the required product **6** was not obtained, see Scheme 2 methods a-e. These methods, reaction conditions and results are shown in Table 1. The starting compound **2** was isolated using methods a-c. The mixture of **2** and ethyl-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**4**) were

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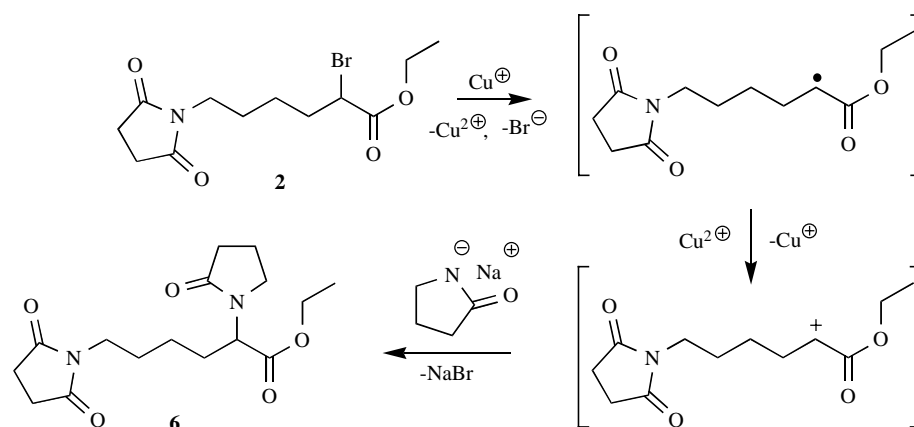
**Scheme 2.** Generated compounds by means of nucleophilic coupling. Conditions a-f – see Table 1.

**Table 1.** Summarization of Reaction Conditions and Results of Methods a-f

Method	Reaction Conditions	Isolated Materials	Yield (%)
a	2, pyrrolidin-2-one (1.0 equiv), Na (1.0 equiv), toluene, reflux, 60 h	2	95
b	2, pyrrolidin-2-one (2.0 equiv), Na (2.0 equiv), tetrabutylammonium bromide (0.1 equiv), toluene, reflux, 40 h	2	86
c	2, pyrrolidin-2-one (4.0 equiv), Na (4.0 equiv), DMSO, 25 °C, 70 h	2	64
d	2, pyrrolidin-2-one (2.0 equiv), Na (2.0 equiv), KI (0.1 equiv), xylene, reflux, 150 h	mixture of 2 and 4 [12]	45 and 40
e	2, 1-(trimethylsilyl)pyrrolidin-2-one [13] (1.0 equiv), tetrabutylammonium fluoride (1.0 equiv), DMF, 25 °C, 20 h, then reflux, 70 h	5 [14]	67
f	2, pyrrolidin-2-one (1.5 equiv), NaH (2.0 equiv), Cu <sub>2</sub> O (0.25 equiv), DMF, reflux, 9 h	6	66

per(I) oxide and copper(I) sulphide [5-8] or other Cu(I) derivatives were used [9-11, and refs. cited therein]. Contrary to the above mentioned articles, which deal with coupling of substituted aromatic rings, coupling of the aliphatic compounds is described in this paper. Heterogeneous copper(I) oxide was chosen for this reaction.

Ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (**2**) was coupled with pyrrolidin-2-one under catalysis by powdered copper(I) oxide and ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (**6**) was obtained. The proposed mechanism of nucleophilic coupling of compound **2** with 5-membered  $\omega$ -lactam ring allowed through heteroge-



**Scheme 3.** Proposed radical-ionic mechanism of nucleophilic coupling allowed through heterogeneous copper catalyst in polar aprotic solvent.

neous copper catalyst in polar aprotic solvent, radical anion and the changes in the oxidation numbers of copper catalyst are shown in Scheme 3. This mechanism is probably the same as recently described [6, 7].

## EXPERIMENTAL

### 6-(2,5-Dioxopyrrolidin-1-yl)hexanoic Acid (1)

To a suspension of 6-aminohexanoic acid (34.4 g, 262.0 mmol) in acetone (140 mL) was added dropwise a solution of succinic anhydride (45.0 g, 450.0 mmol) in acetone (230 mL). The reaction mixture was stirred at room temperature for 24 hours after which it was filtered and the pure white powder product was washed with acetone. Yield: 82%. M.p. 100–102 °C.  $^1\text{H}$  NMR (500 MHz, DMSO),  $\delta$ : 12.05 (s, 1H, OH), 3.02 (t, 2H,  $J = 7.0$  Hz,  $\text{NCH}_2$ ), 2.90 (s, 4H,  $\text{O}=\text{CH}_2\text{CH}_2=\text{O}$ ), 2.41 (t, 2H,  $J = 6.0$  Hz,  $\text{OOCCH}_2$ ), 2.32–2.15 (m, 4H,  $\text{CH}_2$ ), 1.52–1.24 (m, 2H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR (125 MHz, DMSO),  $\delta$ : 174.25, 173.66, 38.27, 33.52, 28.72, 28.62, 25.83, 24.11. IR ( $\text{cm}^{-1}$ ) 3315, 2929, 1688, 1560, 1414, 1250, 1183.

### Ethyl-2-bromo-6-(2,5-dioxopyrrolidin-1-yl)hexanoate (2)

To the organic acid **1** (45.8 g, 214.8 mmol), held at 30 °C, thionyl chloride (29.4 g, 247.0 mmol, 17.9 mL) was added slowly dropwise and the mixture was stirred at 60–80 °C until the gas evolution essentially stopped. At 80 °C  $\text{Br}_2$  (36.1 g, 225.5 mmol, 11.6 mL) was added dropwise at approximately the rate that the  $\text{Br}_2$  was consumed. Stirring continued for several hours until the evolution of HBr nearly stopped. Absolute ethanol (27 mL) was added slowly to the crude acid chloride at 20–30 °C. After stirring overnight, the mixture was evaporated until dry under vacuum and the residue was dissolved in diethyl ether (50 mL). The solution was washed with dilute  $\text{NaHSO}_3$  and water, the organic layer was dried over anhydrous  $\text{MgSO}_4$ , filtered and the organic solvent was removed under rotary evaporation. The crude product (yield: 94.2%) was purified by vacuum distillation using a Vigreux column (b.p. 160–165 °C/ 0.35 mbar) to yield 55.9 g (81%) of mixture **2** and **3**. The mixture was separated using HPLC system Hewlett Packard. SI semi-preparative column Supelcosil, 250  $\times$  10 mm, 5  $\mu\text{m}$  and propan-2-ol as a mobile phase were used. A flow rate of the column was 3 mL/min. Retention time was 5.15 min for **3** and 6.62 min for **2**. HPLC separation showed the ratio of **2** and **3** as 2:1.

**2**:  $R_F$  0.44 (propan-2-ol 100%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.16 (q, 2H,  $J = 7.0$  Hz,  $\text{OCH}_2$ ), 4.11 (t, 1H,  $J = 7.3$  Hz,  $\text{BrCH}$ ), 3.44 (t, 2H,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 2.64 (s, 4H,  $\text{O}=\text{CH}_2\text{CH}_2=\text{O}$ ), 1.99 (q, 2H,  $J = 7.3$  Hz,  $\text{CHCH}_2$ ), 1.54 (qi, 2H,  $J = 7.0$  Hz,  $\text{CH}_2$ ), 1.43–1.15 (m, 2H,  $\text{CH}_2$ ), 1.23 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 176.94, 169.43, 61.84, 45.63, 38.23, 34.17, 28.08, 26.77, 24.43, 13.82. IR ( $\text{cm}^{-1}$ ) 2939, 1730, 1692, 1436, 1399, 1143, 818.

### Ethyl-2-bromo-6-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)hexanoate (3)

Generated as a by-product during vacuum distillation of crude product **2**, light yellow oil, yield 18.3 g.  $R_F$  0.69 (pro-

pan-2-ol 100%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 6.70 (s, 2H,  $\text{CH}=\text{CH}$ ), 4.23 (q, 2H,  $J = 7.0$  Hz,  $\text{OCH}_2$ ), 4.14 (t, 1H,  $J = 7.3$  Hz,  $\text{BrCH}$ ), 3.52 (t, 2H,  $J = 7.0$  Hz,  $\text{NCH}_2$ ), 2.06 (q, 2H,  $J = 7.3$  Hz,  $\text{CHCH}_2$ ), 1.63 (qi, 2H,  $J = 7.0$  Hz,  $\text{CH}_2$ ), 1.49–1.21 (m, 2H,  $\text{CH}_2$ ), 1.29 (t, 3H,  $J = 7.0$  Hz,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 170.69, 169.55, 134.08, 61.94, 45.66, 37.43, 34.27, 27.74, 24.45, 13.90. IR ( $\text{cm}^{-1}$ ) 3140, 2934, 1678, 1720, 1441, 1406, 1148, 825.

By-product **3** (18.3 g, 57.5 mmol) was dissolved in ethyl acetate (60 mL) and 10% Pd/C (0.2 g) was added. The mixture was kept under hydrogen and stirred under room temperature for 24 hours. After filtration of the catalyst the solvent was evaporated and 18.2 g (98%) of compound **2** was obtained.

### Ethyl-6-(2,5-dioxopyrrolidin-1-yl)-2-(2-oxopyrrolidin-1-yl)hexanoate (6)

Pyrrolidin-2-one (4.0 g, 46.9 mmol) was added slowly to a suspension of NaH (51.5 mmol, 60% dispersion in mineral oil) in dry DMF (100 mL). The mixture was stirred for a few minutes until the evolution of hydrogen gas stopped. Compound **2** (10.0 g, 31.2 mmol) and  $\text{Cu}_2\text{O}$  (1.1 g, 7.8 mmol) were then added, and the mixture was refluxed under argon for 9 hours. The cooled mixture was poured onto ice, filtered and extracted with chloroform. The combined organic extracts were washed with water, dried over anhydrous  $\text{MgSO}_4$ , filtered and the organic solvent was removed under rotary evaporation. The crude product was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether 3:1) provided a light yellow oil, yield 6.7 g (66%).  $R_F$  0.45 (propan-2-ol 100%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 4.66 (dd, 1H,  $J^1 = 5.0$  Hz,  $J^2 = 10.6$  Hz, CH), 4.16 (q, 2H,  $J = 7.1$  Hz,  $\text{OCH}_2$ ), 3.50 (t, 2H,  $J = 7.2$  Hz,  $\text{NCH}_2$ ), 3.54–3.29 (m, 2H,  $\text{CH}_2\text{pyrr.}$ ), 2.70 (s, 4H,  $\text{O}=\text{CH}_2\text{CH}_2=\text{O}$ ), 2.42 (t, 2H,  $J = 8.0$  Hz,  $\text{CH}_2\text{pyrr.}$ ), 2.17–1.95 (m, 2H,  $\text{CH}_2\text{pyrr.}$  and 1H from  $\text{CH}_2\text{CH}$ ), 1.78–1.56 (m, 2H,  $\text{CH}_2$  and 1H from  $\text{CH}_2\text{CH}$ ), 1.34–1.28 (m, 2H,  $\text{CH}_2$ ), 1.26 (t, 3H,  $J = 7.1$  Hz,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ),  $\delta$ : 177.13, 175.78, 170.76, 61.12, 53.51, 43.53, 38.26, 30.73, 28.08, 27.03, 23.35, 18.21, 14.07. IR ( $\text{cm}^{-1}$ ) 2927, 1767, 1687, 1401, 1284, 1187, 1153, 1027.

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- [14]  $R_F$  0.46 (ethyl acetate/petroleum ether 2:1).  $^1H$  NMR (500 MHz,  $CDCl_3$ ),  $\delta$ : 6.91 (dt, 1H,  $J' = 6.8$  Hz,  $J^2 = 15.8$  Hz, =CH), 5.84 (d, 1H,  $J = 15.8$  Hz, =CH), 4.18 (q, 2H,  $J = 7.2$  Hz,  $OCH_2$ ), 3.54 (t, 2H,  $J = 7.1$  Hz,  $NCH_2$ ), 2.71 (s, 4H,  $O=CH_2CH_2=O$ ), 2.23 (q, 2H,  $J = 7.5$  Hz,  $CH_2$ ), 1.76 (qi,  $J = 7.5$  Hz, 2H,  $CH_2$ ), 1.29 (t, 3H,  $J = 7.2$  Hz,  $CH_3$ ).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ),  $\delta$ : 176.98, 166.31, 147.0, 122.16, 60.14, 38.24, 29.46, 28.01, 26.01, 14.19. IR ( $cm^{-1}$ ) 3379, 2938, 1752, 1624, 1528, 1437, 1398, 1224, 1149.