SHORT PAPER

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Synthesis of tricyclic β-lactams via palladium acetate-induced Heck reaction

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Synthesis of tricyclic β-lactams *via* palladium acetate mediated cyclization of the unsaturated bromo β-lactam was accomplished in good yield.

Keywords: tricyclic β-lactams, palladium acetate, Heck reaction

Synthesis of novel β-lactams is still the subject of intensive investigation in spite of the drug resistance to some β-lactam antibiotics.[1] At the beginning of β-lactam research, only bicyclic compounds were shown potent biological activity.[2] Later, some monocyclic β-lactams with antibacterial properties were reported.[2] However, in comparison, the synthesis of tricyclic β-lactams was not actively investigated. Recently, syntheses of tricyclic β-lactams have appeared in the literature.[3]

In continuation of our research on β-lactams,[4] biologically active polycyclic aromatic compounds[5] and metal-mediated reactions,[6] we became interested in the development of an expeditious synthesis of functionalised tricyclic β-lactam using Heck methodology.[7] To our knowledge, this is the first report of synthesis of tricyclic β-lacatm by palladium acetate[8] mediated cyclization of unsaturated monocyclic β-lactam.

Synthesis of the starting monocyclic β-lactams[9] was achieved by the cycloaddition reaction of imines with acid chlorides in the presence of a tertiary base. We used allyl amine and 2-bromobenzaldehyde for the preparation of the imine **1**. With phenoxy and benzyloxy acid chloride (**2**), the imine **1** produced β-lactam **3** in 70% yield (Scheme 1).

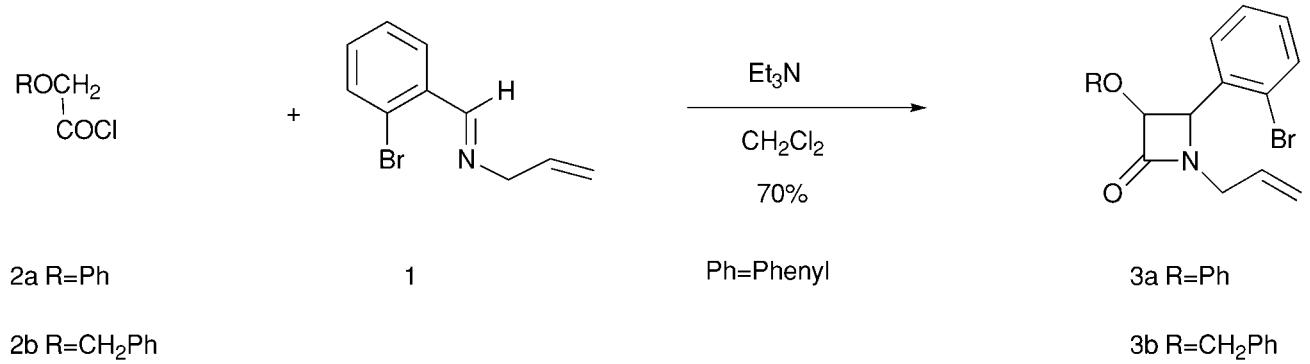
Heck reaction mediated by palladium acetate in the presence of triethyl amine was then performed to accomplish the synthesis of tricyclic β-lactams. The phenoxy β-lactam **3a** and the benzyloxy β-lactam **3b** under identical conditions afforded three tricyclic β-lactams **4a**, **5a** and **6a**. The structure of the major product was deduced to be an olefinic product **4a** with excocyclic double bond. The structure of the minor product was found to be the olefinic β-lactam **5a** with endocyclic double bond and the third compound **6a** was the unsaturated β-lactam with a 7-membered ring. Experiments were performed to improve the ratio of **4a**, but the proportion could not be increased, presumably because of the stability of the conjugated system and basic media (partial isomerization). Similarly, β-lactam **3b** produced **4b**, **5b** and **6b** in a ratio of 4:1:1. The β-lactams reported herein are functionalised at the middle rings and several chemical transformations can be performed for the preparation of different tricyclic analogues. For example, oxidative cleavage of the double bond in 4 and base-catalysed alkylation can provide carbacephem type of system.[10] Similar transformations with tributyltin hydride mediated radical cyclizations[9] produced mixtures of saturated β-lactams.[11] We believe the present methodology has great potential for further elaboration because of the presence of the double bond in each of the products.

Experimental procedure

To a solution of β-lactam **3** (1mmol) in acetonitrile (50 ml) was added triphenyl phospine (1 mmol), triethyl amine (1mmol) and palladium acetate (1mmol). The mixture was refluxed under argon atmosphere for 8 h. Most of the solvents were distilled off under reduced pressure and then the residue was extracted with dichloromethane (50 ml), washed with brine and purified by column chromatography over silica gel (ethyl acetate: hexanes, 10:90).

4a: IR CH_2Cl_2): 1760cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ: 7.38 (d, *J*=8Hz, 1H), 7.25–7.14 (m, 8H), 6.47 (dd, J_1=3Hz, J_2=10Hz, 1H), 5.80 (d, *J*=5.5Hz, 1H), 5.69 (d, *J*=5.5Hz, 1H), 5.17–5.10 (m, 1H), 4.15–4.03 (m, 1H), 3.06–2.94 (dd, J_1=8.8Hz, J_2=12Hz, 1H); *m/e* 278 $(M+H)^+$.

6a: IR (CH_2Cl_2): 1755cm^{-1}; H NMR ($CDCl_3$, 300MHz) δ: 7.29–7.02 (m, 9H), 6.40 (d, *J*=8Hz, 1H), 5.81–5.75 (m, 1H), 5.60 (d,



Scheme 1

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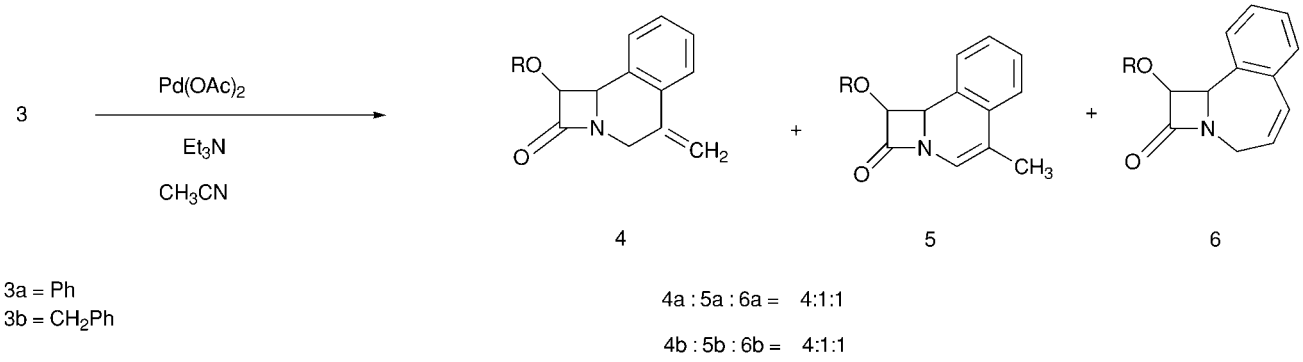
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 2

J=4.85Hz, 1H), 5.27 (d, *J*=4.80Hz, 1H), 4.67 (dd, J_1=8Hz, J_2=13Hz, 1H), 3.89 (m, 1H); *m/e* 278 $(M+H)^+$

4b: IR (CH_2Cl_2): 1750cm^{-1}; 1H NMR ($CDCl_3$, 200MHz) δ: 7.95 (m, 1H), 7.45–7.00 (m, 8H), 6.40 (dd, J_1=3Hz, J_2=11Hz, 1H), 5.50 (d, *J*=5.6Hz, 1H), 5.21 (d, *J*=5.52Hz, 1H), 5.0–4.95 (m, 1H), 4.95 (d, *J*=12Hz, 1H), 4.85 (d, *J*=12Hz, 1H) 4.1–4.0 (m, 1H), 3.0 (dd, J_1=8Hz, J_2=12Hz, 1H); *m/e* 292 $(M+H)^+$.

6b: IR (CH_2Cl_2): 1755cm^{-1}. 1H NMR ($CDCl_3$, 200MHz) δ: 7.40–7.25 (m, 9H), 6.38–6.35 (m, 1H), 5.9–5.72 (m, 1H), 5.20 (d, *J*=4.9Hz, 1H), 5.05 (d, *J*=4.9Hz, 1H), 4.60 (d, *J*=12Hz, 1H), 4.52–4.50 (m, 1H), 4.40 (d, *J*=12Hz, 1H), 3.80–3.69 (m, 1H); *m/e* 292 $(M+H)^{+\cdot}$

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