Synthesis of β-Amino Acid Derivatives by Nickel(0)-mediated Sequential Addition of Carbon Dioxide and Dibenzoyldiazene onto Unsaturated Hydrocarbons

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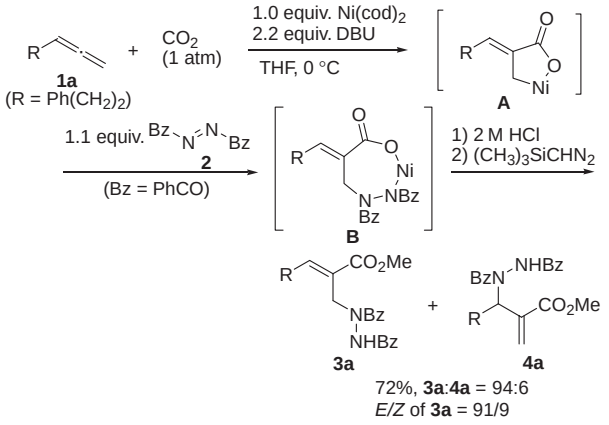
(Received January 18, 2007; CL-070063; E-mail: murakami@sbchem.kyoto-u.ac.jp)

A stoichiometric amount of nickel(0) complex mediated the aminative carboxylation of unsaturated hydrocarbons through oxidative cyclization with carbon dioxide followed by insertion of dibenzoyldiazene into the carbon–nickel bond, giving β-amino acid derivatives.

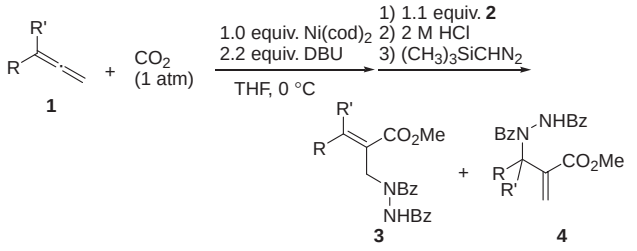
The development of reactions which incorporate carbon dioxide into organic molecules has been an important challenge in chemistry.[1] In recent years, oxidative cyclization on nickel(0) has emerged as an efficient elementary step to activate carbon dioxide[2] which is thermodynamically very stable. Oxanickellacycle intermediates formed by oxidative cyclization of carbon dioxide and unsaturated hydrocarbons can undergo further transformations including oxidation,[2b] carbon–carbon bond formation,[2d,f] rearrangement,[2h] etc. The nickel(0)-mediated carboxylation reactions possess good functional group compatibility, and thus, provide unique preparative methods of carboxylic acid derivatives. On the other hand, β-amino acid is an intriguing structural motif because it is a valuable constituent of designed peptides and biologically active compounds.[3] It would become a new synthetic method of amino acids if the carbon–nickel bond of an oxanickellacycle intermediate is transformed into a carbon–nitrogen bond. In this paper, we report the synthesis of β-amino acids via nickel(0)-mediated oxidative cyclization and subsequent amination of the carbon–nickel bond.

Terminal allene **1a** was reacted with bis(1,5-cyclooctadiene)nickel ($Ni(cod)_2$, 1.0 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.2 equiv.) at 0 °C in THF under atmospheric pressure of carbon dioxide for 2 h according to the literature procedure.[2f] The resulting reaction mixture containing an oxanickellacycle intermediate was then treated with various nitrogen nucleophiles such as potassium phthalimide and trimethylsilyl azide with the expectation that transmetallation with the nickel carboxylate moiety followed by reductive elimination would form a carbon–nitrogen bond. However, the reactions with nitrogen nucleophiles have all failed so far, which encouraged us to examine electrophilic aminating reagents. To our delight, dibenzoyldiazene (**2**, 1.1 equiv.) was successfully incorporated into the oxanickellacycle intermediate.[4,5] Acidic hydrolysis of the nickel carboxylate moiety followed by esterification with $(CH_3)_3SiCHN_2$ afforded β-amino carboxylate **3a** together with a small amount of the regioisomeric aminated product **4a** (72% total yield, **3a**:**4a** = 94:6).[6] The product **3a** in which the terminal allene carbon was aminated predominated over the regioisomeric aminated product **4a**. This regiochemical outcome is in marked contrast to that of the reaction of oxanickellacycles with aldehydes.[2f] The plausible mechanism is shown in Scheme 1. Initially, oxanickellacycle **A** having an allylnickel moiety[7] is formed by oxidative cyclization of carbon dioxide and the allene on nickel(0). Diazene **2** was subsequently inserted into the carbon–nickel bond of **A**, forming the seven-membered nickellacycle **B**. The intermediate **B** is protonated and the resulting acid is esterified.



Scheme 1. Sequential addition of carbon dioxide and dibenzoyldiazene (**2**) onto (2-phenylethyl)allene (**1a**).

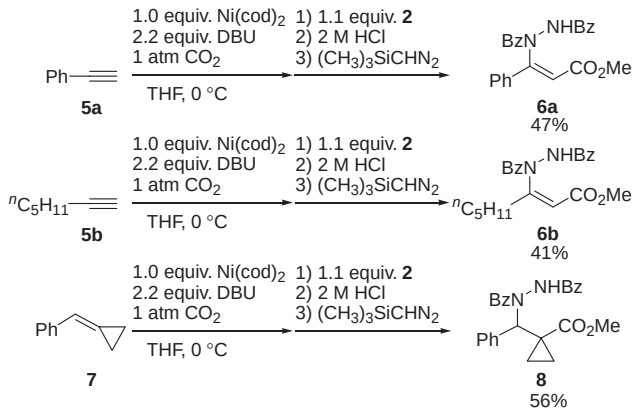
Table 1. Sequential addition of carbon dioxide and **2** onto allenes[a]



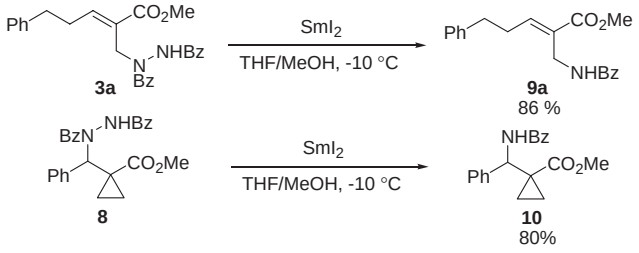
Entry	Substrate (R, R′)	Yield/%[b]	Ratio[c] **3**:**4**	*E*/*Z* of **3**[d]
1	**1b** ($BnO(CH_2)_2$, H)	68	92:8	87/13
2	**1c** ($BzO(CH_2)_2$, H)	64	94:6	94/6
3	**1d** ($PhthN(CH_2)_2$, H)	74	94:6	94/6
4	**1e** (Ph, Me)	82	>99:1	>99/1
5	**1f** (Ph, H)	47	94:6	>99/1

[a]For the experimental procedure, see the Ref. 6. [b]Total yield. [c]Ratio was determined by ^1H NMR. [d]The geometry of the olefin was determined by ^1H NMR. Phth: phthaloyl.

The results of the nickel(0)-mediated aminative carboxylation of allenes are shown in Table 1. Ether and ester functionalities were tolerated under the reaction conditions (Entries 1 and 2). A phthalimide remained intact (Entry 3). 1-Methyl-1-phenylallene (**1e**) selectively gave **3e** in 82% yield (Entry 4). The lower yield observed with phenylallene (**1f**) can be ascribed to its com-



Scheme 2. Reactions with other unsaturated hydrocarbons.



Scheme 3. Reductive cleavage of the hydrazine moiety.

petitive oligomerization (Entry 5).

Next, we examined the use of other unsaturated hydrocarbons (Scheme 2). Terminal alkynes **5a** and **5b**, afforded the corresponding alkenylhydrazine **6a** and **6b** in 47 and 41% yield, respectively. These results suggest that an oxanickellacycle containing a sp^2 carbon–nickel bond can also react with **2**. Methylenecyclopropane **7** yielded the aminative carboxylation product **8** without concomitant cleavage of the cyclopropane ring.[2h,8] In contrast to allenes (1,2-dienes), 1,3-dienes such as 1,3-cyclohexadiene and 1-phenyl-1,3-butadiene underwent only carboxylation[2d] but no insertion of **2** occurred, suggesting that the resulting allylic oxanickellacycle intermediate is less reactive than that derived from an allene.

Finally, reductive cleavage of the nitrogen–nitrogen bond was performed using SmI_2 (Scheme 3).[9] Treatment of the dibenzoylhydrazine **3a** with SmI_2 in THF/MeOH at $-10\,^{\circ}C$ gave the benzamide **9a** in 86% yield.[10] The α,β-unsaturated ester group remained at this temperature. The reaction of **8** with SmI_2 was also successful under the same reaction conditions, giving the product **10** in 80% yield.

In summary, we have described the synthesis of β-amino acid derivatives through a nickel(0)-mediated oxidative cyclization reaction of carbon dioxide with unsaturated hydrocarbons followed by an amination reaction with dibenzoyldiazene. Simple unsaturated hydrocarbons such as allenes, alkynes, and methylenecyclopropanes could be employed, giving β-hydrazinocarboxylic acids in one-pot. The present study provides a new example of utilization of carbon dioxide as C1 source.

The authors are grateful to Nippon Oil Corporation for a financial support. N.I. thanks Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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5 Diethyl diazodicarboxylate (DEAD) can be also used for amination. However, **2** was preferred over DEAD for the ease of isolation of the products.

6 A typical procedure is as follows: To a stirred suspension of $Ni(cod)_2$ (82.5 mg, 0.30 mmol) in a freshly distilled THF (2.5 mL) in a Schlenk-type flask under a nitrogen atmosphere at $0\,^{\circ}C$ was added DBU (100 μL, 0.66 mmol). The mixture was degassed by a freeze–pump–thaw method, and then carbon dioxide was introduced. To the resulting pale yellow solution at $0\,^{\circ}C$ was added a THF solution (0.5 mL) of substrate **1a** (47.6 mg, 0.33 mmol) dropwise (20 μL/min). After the reaction mixture was stirred at $0\,^{\circ}C$ for 2 h, a THF solution (1 mL) of dibenzoyldiazene (**2**, 79.2 mg, 0.33 mmol) was added. After 2 h, dilute hydrochloric acid (2 M) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was treated with $(CH_3)_3SiCHN_2$ in Et_2O/MeOH. The solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (dichloromethane:ethyl acetate = 10:1) to give the products. (*E*)-**3a**: IR (KBr): 3450, 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (br, 4H), 3.70 (s, 3H), 3.8–5.6 (br, 2H), 7.04 (t, $J = 6.9$ Hz, 1H), 7.1–7.6 (m, 15H), 8.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.37, 34.64, 45.75, 52.04, 125.95, 126.01, 126.62, 127.00, 127.76, 128.23, 128.28, 128.31, 128.52, 129.97, 131.80, 132.09, 134.67, 140.45, 148.26, 166.35, 171.89; HRMS (EI) Calcd for $C_{27}H_{26}N_2O_4$ (M^+): 442.1893. Found: 442.1895.

7 Both σ- and π-allyl structures are conceivable.

8 Methylenecyclopropane **7** was consumed and, besides **8**, a complex mixture of various products was obtained. However, it was hardly possible to identify other aminated products such as one in which the cyclopropane was opened.

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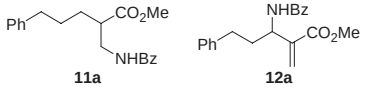
10 Because **3a** was contaminated with (*Z*)-isomer and the regioisomer **4a**, the product was obtained with the saturated ester **11a**, which probably resulted from (*Z*)-**3a,** and the regioisomeric ester **12a**.



Published on the web (Advance View) February 24, 2007; doi:10.1246/cl.2007.476