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Short Note

Benzyl 2-Phenyl-1*H*-pyrrole-1-carboxylate

Sung-Gon Kim

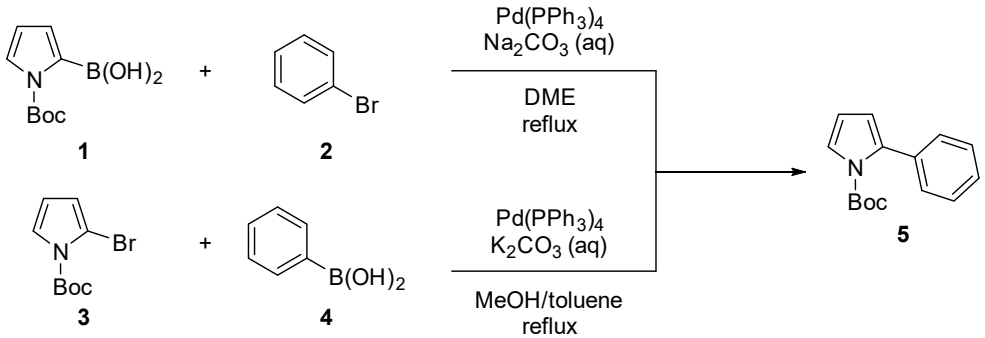
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Abstract: A highly novel method for the preparation of benzyl 2-phenyl-1*H*-pyrrole-1-carboxylate has been developed. The intramolecular reaction of benzyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)carbamate with oxalyl chloride provided title compound in good yields. The structure of the newly synthesized compound was determined using ^{1}H-, ^{13}C-NMR, IR, and mass spectral data.

Keywords: pyrrole; intramolecular reaction; oxalyl chloride

1. Introduction

Pyrrole is one of the most valuable structural scaffolds, frequently encountered in a variety of biologically active natural products [1,2], pharmaceuticals [3,4], and materials science and industry [5]. Well-established synthetic methods—such as the Paal–Knorr reaction [6], the Hantzsch reaction [7], and the Barton–Zard reaction [8]—have been widely employed to prepare biologically active pyrroles. Additionally, multicomponent reactions using transition-metal catalysis have been developed for synthesizing pyrrole derivatives [9,10]. Among these, functionalized 2-arylpyrroles serve as promising precursors for novel selective dopamine D_3 receptor antagonists and BODIPY dyes or chromophores [11,12]. Accordingly, several strategies have been devised for 2-arylpyrrole synthesis, with Suzuki coupling being predominantly used for *N*-protected 2-arylpyrroles (Scheme 1) [13,14]. Recently, visible-light-mediated direct C–H arylation of *N*-protected pyrroles with aryl diazonium salts using a photoredox catalyst has also been employed for the synthesis of 2-arylpyrroles [15]. However, although *N*-Boc-protected 2-arylpyrroles have been extensively synthesized via Suzuki coupling, to our knowledge, *N*-Cbz-protected 2-arylpyrroles have not yet been reported. Herein, we describe the synthesis of benzyl 2-phenyl-1*H*-pyrrole-1-carboxylate through the intramolecular reaction of benzyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)carbamate.



Scheme 1. Synthesis of *N*-Boc-2-phenylprrole through Suzuki coupling.

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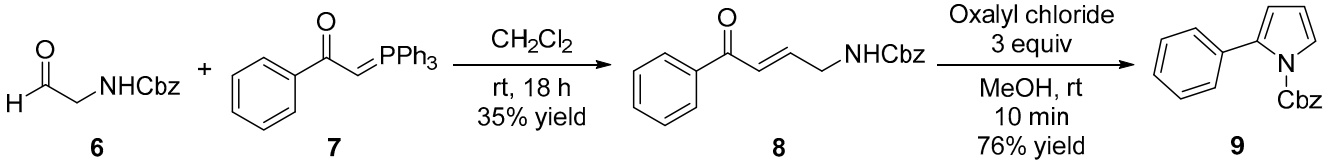
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2. Results and Discussion

In our previous studies [16], an asymmetric intramolecular Michael reaction of α,β-unsaturated carbonyl compounds containing benzyl alcohol afforded enantioenriched 1-substituted phthalans. Building on this work, we anticipated that a Lewis acid-catalyzed intramolecular reaction of an γ-amino-α,β-unsaturated carbonyl compound would yield pyrrole derivatives. Accordingly, we prepared benzyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)carbamate (**8**) via the Wittig reaction of Cbz glycinal **6** with 1-phenyl-2-(triphenylphosphoranylidene)ethanone **7** with a 35% yield. Next, we carried out an intramolecular reaction of compound **8** using oxalyl chloride in MeOH at room temperature. In this reaction, HCl is generated in situ from $SOCl_2$ and MeOH, acting as a Lewis acid. This process successfully yielded the desired benzyl 2-phenyl-1*H*-pyrrole-1-carboxylate (**9**) with a 76% yield (Scheme 2). The structure of compound **9** was confirmed by by ^{1}H-, and ^{13}C-NMR, IR, and mass spectral data, all of which were consistent with the proposed structure.



Scheme 2. Synthesis of benzyl 2-phenyl-1*H*-pyrrole-1-carboxylate (**9**).

The structure of compounds **8** and **9** were confirmed by ^{1}H-, ^{13}C-NMR, IR, and mass spectral data, all of which were consistent with the proposed structure. All data are available in the Supplementary Materials (Figures S1–S6 and Tables S1 and S2).

3. Materials and Methods

3.1. General

All reagents were used as received without further purification. Chromatographic purification was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63 (Merck, Darmstadt, Germany). Thin-layer chromatography (TLC) (Merck, Darmstadt, Germany) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Developed chromatograms were visualized by fluorescence quenching and anisaldehyde staining. ^{1}H- and ^{13}C-NMR spectra were recorded on 400 MHz instrument (Bruker BioSpin GmbH, Karlsruhe, Germany) as noted, and were internally referenced to residual protio solvent signals. Data for ^{1}H NMR were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublets), integration, coupling constant (Hz), and assignment. Data for ^{13}C-NMR were reported in terms of chemical shift. IR spectra were recorded on Perkin–Elmer 1600 FT-IR spectrometer (Bruker Optics GmbH, Ettlingen, Germany), and reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry data were recorded on a JEOL JMS-700 M Station mass spectrometer (JEOL, Tokyo, Japan).

3.2. Syntheis of (E)-(4-Oxo-4-phenylbut-2-en-1-yl)carbamate (**8**)

A solution of benzyl (2-oxoethyl)carbamate (**6**, 0.97 g, 5 mmol, 1 equiv) in CH_2Cl_2 (25 mL, 0.2 M) was added to 1-phenyl-2-(triphenylphosphoranylidene)ethanone (**7**, 1.9 g, 5 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature for 18 h. Then, the resulting mixture was concentrated in vacuo and was purified by flash column chromatography with EtOAc/hexanes (1/4) as an eluent to obtain desired product **8** (35%, 0.52 g). White solid; m.p. 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.60–7.53 (m, 1H), 7.48 (d, *J* = 1.5 Hz, 2H), 7.41–7.36 (m, 3H), 7.36 (s, 2H), 6.98 (s, 2H), 5.15 (s,

2H), 5.05 (s, 1H), 4.14–4.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 156.2, 144.2, 137.5, 136.3, 133.0, 128.64 (two peaks overlapping), 128.60, 128.3, 128.2, 125.6, 67.1, 42.3; IR (neat) 3553, 3056, 3035, 2930, 2898, 1714, 1692, 1670, 1625, 1537, 1486, 1254, 1241, 1211, 1177, 1151, 1053, 1021 cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{18}H_{17}NO_3$: 295.1208 Found: 295.1180.

3.3. Syntheis of Benzyl 2-Phenyl-1H-pyrrole-1-carboxylate (**9**)

A solution of benzyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)carbamate (**8**, 30 mg, 0.1 mmol, 1 equiv) in MeOH (1.0 mL, 0.1 M) was added to oxalyl chloride (26 µL, 0.3 mmol, 3.0 equiv). After stirring at room temperature for 10 min, the reaction mixture was quenched with water and was extracted with CH_2Cl_2. Afterwards, the combined organic layers was washed with brine and dried over Na_2CO_3. Then, the resulting mixture was concentrated in vacuo and was purified by flash column chromatography with EtOAc/hexanes (1/20) as an eluent to obtain desired product **9** (76%, 21 mg). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.37–7.33 (m, 2H), 7.33–7.28 (m, 6H), 7.20 (dd, *J* = 6.6, 2.9 Hz, 2H), 6.25 (t, *J* = 3.3 Hz, 1H), 6.22 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 135.7, 134.8, 133.8, 129.4, 128.7, 128.6, 128.4, 127.7, 127.5, 122.6, 115.1, 111.5, 68.9; IR (neat) 1784, 1732, 1714, 1399, 1381, 1328, 1293, 1215, 1179, 1147, 1112, 1074, 1042, 1026, 1001, cm^{-1}; HRMS (EI) *m/z* calcd for $[M]^+$ $C_{18}H_{15}NO_2$: 277.1103 Found: 277.1121.

Supplementary Materials: Figure S1: ^{1}H NMR spectrum of compound **8**, Figure S2: ^{13}C NMR spectrum of compound **8**, Figure S3: ^{1}H NMR spectrum of compound **9**, Figure S4: ^{13}C NMR spectrum of compound **9**, Figure S5: IR spectra of compound **8**, Table S1: High mass data of compound **8**, Figure S6: IR spectra of compound **9**, Table S2: High mass data of compound **9**.

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Data Availability Statement: Data are contained within the article and Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

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