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Rhodium-catalyzed carbonylation of 2-alkynylbenzylamine: a new route to the synthesis of benzazepinones ☆

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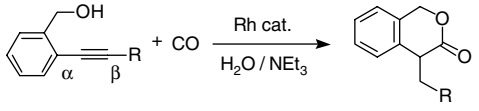
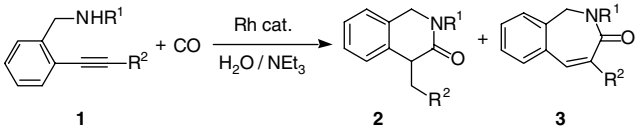
Abstract—Rhodium-catalyzed carbonylation of 2-alkynylbenzylamines under water–gas shift reaction conditions gives a seven-membered heterocyclic product, 2,4-disubstituted-1,4-dihydrobenz[*c*]azepin-3-ones, in a good yield.

Heterocyclic compounds are very important for agricultural and medical chemicals, and belong to one of target molecules in synthetic organic chemistry. Recent development in synthetic chemistry has shown that metal-mediated cyclocarbonylation of unsaturated compounds such as alkenes and alkynes may be a promising reaction for the efficient synthesis of heterocyclic compounds.[1] Previously we have developed a new type of cyclocarbonylation of alkynes catalyzed by a rhodium complex, by which phenylacetylene is effectively converted to furanone under water–gas shift reaction conditions. The Rh-catalyzed carbonylation has a wide application, and phenylacetylene derivatives bearing functional groups such as hydroxy, amino, and formyl groups adjacent to the ethynyl group smoothly undergo cyclocarbonylation, in which the functional groups take part in the cyclization reaction and give five- and six-membered heterocyclic compounds in good yields.[2–4] For example, 2-alkynylphenols were carbonylated at 170 °C to give five- and six-membered heterocyclic products, bezofuranone, and coumarin derivatives, in a good total yield,[2] but the product selectivity was not high. The five- and six-membered products apparently come from a CO attack at the α- and β-carbon of the triple bond, respectively. Mechanistic consideration attempting a higher product selectivity has led us to an experimental trial of the carbonylation of 2-alkynylbenzylalcohol instead of 2-alkynylphenols as a substrate, and we have found a selective cyclocarbonylation producing a six-membered heterocycle, isochromanone derivatives, by the carbonylation at α-carbon of the triple bond[3] (Eq. 1). The success of improving product selectivity prompted us to examine the carbonylation of 2-alkynylbenzylamine by our catalytic system since 2-alkynylanilines also gave five- and six-membered heterocyclic products, indolone and quinolone.[4] Here we report the experimental results that the carbonylation of 2-alkynylbenzylamines gives an unexpected seven-membered product, hydrobenzazepinone, in a good yield.



(1)



1 2 3

	R^1	R^2
a:	H	^{n}Bu
b:	H	^{t}Bu
c:	H	Me
d:	H	Ph
e:	H	Mes

	R^1	R^2
f:	H	4-MeOC$_6$H$_4$
g:	^{i}Pr	^{n}Bu
h:	^{t}Bu	^{n}Bu
i:	Cy	^{n}Bu

(2)

Thus, a mixture of 2-(1-hexynyl)benzylamine **1a** ($R^1 = H$, $R^2 = {}^n$Bu) (1 mmol), $Rh_6(CO)_{16}$ (0.5 mol%),

Keywords: Carbonylation; Alkynylbenzylamine; Rhodium catalyst; Water–gas shift reaction; Benzazepinone; Heterocycle.

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NEt_3 (1 mmol), and H_2O (4 mmol) in 1,4-dioxane was heated at 175 °C for 7 h under 70 atm of carbon monoxide. After usual work-up, isolation by column chromatography on silica gave six-membered **2a** and seven-membered **3a** in 23% and 12% yield, respectively. Compounds **2a** and **3a** were identified by spectral analyses. The mass spectra showed an m/z of 217 (M^+, **1a**+2CO+2H) for **2a** and of 215 (M^+, **1a**+2CO) for **3a**. Product **2a** showed absorptions at 3222 and 1668 cm^{-1} due to amino and carbonyl groups in the IR spectrum and a signal at δ 175.7 ppm due to a carbonyl group in the ^{13}C NMR spectrum, indicating **2a** to be 4-butyl-1,4-dihydro-2*H*-isoquinolin-3-one.[5] On the other hand the spectral analyses[6a] suggested a dihydrobenzazepinone structure for product **3a**. The molecular structure of **3a**, 4-butyl-1,2-dihydrobenz[*c*]azepin-3-one, was finally determined by an X-ray crystallographic method (Fig. 1).[6b] Six-membered lactam **2a** was an expected product, whereas the formation of seven-membered **3a** was not presurmised because of high ring strain for an eight-membered rhodanacycle intermediate postulated in the carbonylation mechanism.[2] On the other hand, a new synthetic method for hydrobenzazepinone may be attractive since a few papers[5–8] reported the synthesis of the seven-membered heterocyclic compound; dihydrobenzazepinones may be synthesized from allylaniline, azides,[7,8] *o*-propargylaryl nitrones[9,10] or benzophenone-2-carboxylic acid,[11] but these synthetic methods need three to six reaction steps and are not applicable to the synthesis of benzazepinones with no substituents on the nitrogen.[9,10] Therefore, we focused our attention on improving the product selectivity of the carbonylation, and searched the best reaction conditions for the high-yield synthesis of dihydrobenzazepinones **3**. The cyclocarbonylation of **1a** was chosen as a model system to establish the reaction conditions suitable for the selective synthesis of **3a**. The experimental results obtained from the carbonylation under various reaction conditions are summarized in Table 1.

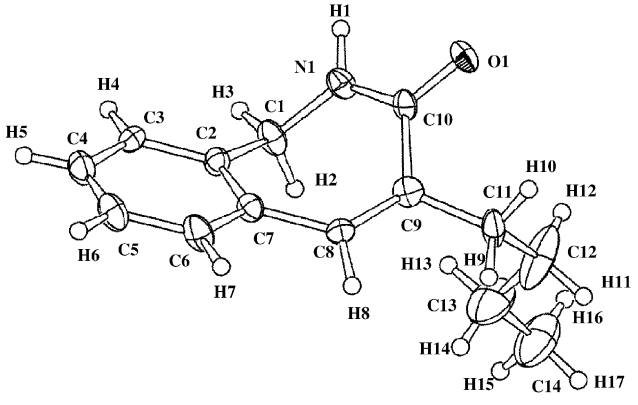

Figure 1. ORTEP drawing of the molecular structure of 4-butyl-1,2-dihydrobenz[*c*]azepin-3-one.

The results reveal that the yields of **2a** and **3a** were strongly influenced by reaction temperature and the amount of additive water as well as by CO pressure. Carbonylation at a temperature above 150 °C gave **2a** as a main product (runs 1–3), whereas a reaction at 100 °C gave **3a** as a main product and **2a** was not detected in the products. From the reactions of runs 2 and 3, unidentified product **4a**, of which the mass spectrum showed m/z = 241 (**1a**+2CO−2H), was isolated in 15% and 18% yields, respectively. Then, the reaction temperature was fixed at 100 °C, and the effects of additive water and CO pressure were examined. Use of large amounts of water depressed the formation of **2a**, and 30 atm of CO pressure gave the best result in terms of the selectivity for **3a** (run 11). The reason why the formation of seven-membered azepinone prefers the reaction conditions has not yet been clear, although a strong influence of reaction temperature on product selectivity has often observed for the cyclocarbonylation of alkynes catalyzed by rhodium carbonyl clusters.[2] As a catalyst other than the Rh carbonyls, carbonyl complexes such as $Co_2(CO)_8$, $Fe_3(CO)_{12}$, and $Ru_3(CO)_{12}$ did not show an appreciable catalytic activity. Thus, to investigate the scope of the present system we employed the reaction conditions adopted for run 11, and examined the carbonylation of a variety of 2-alkynylbenzylamines. The results obtained are summarized in Table 2. In the case of a primary amine ($R^1 = H$) with an aliphatic R^2 on the triple bond the carbonylation gave product **3** in a good yield (runs 1–3). When R^2 is an aromatic group, the reaction gave a

Table 1. Carbonylation of 2-(1-hexynyl)benzylamine **1a**[a]

Run	Temperature (°C)	H_2O (mol)	CO (atm)	Conversion (%)	Yield (%)	
					2a	**3a**
1	200	4	70	100	37	15
2[b]	175	4	70	100	23	12
3[b]	150	4	70	100	28	14
4	100	4	70	100	Trace	10
5	100	60	70	100	Trace	34
6	100	110	70	100	0	45
7	100	220	70	100	0	58
8	100	330	70	100	0	57
9	100	220	5	100	0	26
10	100	220	20	100	0	55
11	100	220	30	100	0	70
12	100	220	90	100	0	51

[a] Reaction conditions: substrate **1a**, 1 mmol; $Rh_6(CO)_{16}$, 0.5 mol%; 1,4-dioxane, 15 mL; NEt_3, 1 mmol; 7 h.
[b] Unidentified product **4a** was isolated.

Table 2. Carbonylation of 2-alkynylbenzylamine **1**[a]

Entry	R^1	R^2		Time (h)	Product	Yield (%)[b]
1	H	Bu^n	**1a**	7	**3a**	70
2	H	Bu^t	**1b**	7	**3b**	70
3	H	Me	**1c**	7	**3c**	59
4	H	Ph	**1d**	3	**3d**	36
5	H	Mes	**1e**	24	**3e**	60
6	H	4-$MeOC_6H_4$	**1f**	7	**3f**	48[c]
7	Pr^i	Bu^n	**1g**	7	**3g**	47
8	Bu^t	Bu^n	**1h**	12	**3h**	72[c]
9	Cy	Bu^n	**1i**	12	**3i**	41[c]

[a] Reaction conditions: substrate, 1 mmol; $Rh_6(CO)_{16}$, 0.5 mol%; 1,4-dioxane, 15 mL; NEt_3, 1 mmol; H_2O, 220 mmol; CO pressure, 30 atm; reaction temperature, 100 °C; reaction time, 7 h.
[b] Yields are based on 2-ethylbenzylamine **1** and determined by GC.
[c] Isolated yield.

lower yield (run 4) or needed a longer reaction time (run 5). Secondary amines **1** bearing an ^{i}Pr, ^{t}Bu, or Cy group on the nitrogen atom were also converted to azepinones **3g–i** in a good or moderate yield. Products **3** were confirmed to be hydrobenzazepinone derivatives by spectral and elemental analyses.

In summary we have reported here the new synthesis of dihydrobenz[*c*]azepinones by the carbonylation of 2-alkynylbenzylamines, which may provide an effective method for the direct and convenient synthesis of seven-membered azepinone derivatives from easily prepared alkynylbenzylamines.

General procedure. A mixture of 2-(1-hexynyl)benzylamine **1a** ($R^1 = H$, $R^2 = {}^n$Bu) (1 mmol), $Rh_6(CO)_{16}$ (0.5 mol%), NEt_3 (1 mmol), and H_2O (220 mmol) in 1,4-dioxane (15 mL) was placed in a 100 mL stainless steel autoclave under 30 atm of an initial carbon monoxide pressure and stirred at 100 °C for 7 h. After usual work-up, purification by column chromatography on silica using a mixture of ethyl acetate and hexane as an eluent gave **3a** as colorless crystals,[6] which was recrystallized from ethyl acetate and hexane.

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6. (a) Data for 4-butyl-1,2-dihydrobenz[*c*]azepin-3-one **3a**: colorless crystals; mp 135 °C; ^{1}H NMR (acetone-d_6, 400 MHz) δ 7.40–7.28 (m, 4H, Ph), 7.03 (s, 1H, CH), 4.11 (d, 5.3 Hz, 2H), 2.84 (d, 13.1 Hz, 1H, NH), 2.58 (t, 7.3 Hz, 2H, CH_2), 1.58–1.51 (m, 2H, CH_2), 1.45–1.36 (m, 2H, CH_2), 0.94 (t, 7.3 Hz, 3H, CH_3); ^{13}C NMR (acetone-d_6, 100 MHz) δ 168.3 (C=O), 140.7 (C), 139.3 (C), 137.0 (C), 132.4 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 127.3 (CH), 44.8 (CH_2), 35.4 (CH_2), 32.1 (CH_2), 22.9 (CH_2), 14.0 (CH_3); IR (KBr) ν N–H 3196, C=O 1644, C=C 1601 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.82; H, 8.26; N, 6.66; (b) Crystal data for 4-butyl-1,2-dihydrobenz[*c*]azepin-3-one **3a**: $C_{14}H_{17}NO$, $M = 215.29$, crystal dimensions $0.5 \times 0.35 \times 0.13$ mm, orthorhombic, space group $Pna2_1$, $a = 11.106(6)$, $b = 8.906(4)$, $c = 24.322(7)$ Å, $V = 2405(1)$ Å^3, $Z = 8$, $D_c = 1.189$ g/cm^3, graphite monochromated Mo Kα radiation with $\lambda = 0.71069$ Å, $\mu = 0.74$ cm^{-1}, 2840 reflections were collected at −75 °C on a Rigaku AFC7R four circle diffractometer in the ω–θ scan mode to $2\theta_{max} = 55.0°$. The structure was solved by direct methods and expanded using Fourier techniques, and refined to give $R = 0.058$, $Rw = 0.077$ for 2138 observed reflections ($F > 3\sigma F$). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 230077.
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