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Aust. J. Chem. **2004**, *57*, 677–680

Cyclization of Acetylenic Amides Using a Cationic Rhodium(I) Complex*

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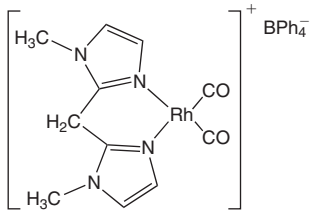
The cationic Rh(I) dicarbonyl complex [{Rh(bim)$(CO)_2$}$^+$$BPh_4^-$] **1**, containing a bidentate bisimidazolylmethane ligand [bim refers to bis(*N*-methylimidazol-2-yl)methane] acts as a catalyst for the cyclization of alkynyl amides to produce lactams and *N*-acyl heterocyclic compounds.

Manuscript received: 10 February 2004.
Final version: 6 April 2004.

The formation of C—N bonds by the addition of N—H to carbon—carbon double and triple bonds (hydroamination) is a process of fundamental importance in the synthesis of organic compounds.[1] Compounds containing C—N bonds are common in biologically active natural and synthetic products[2] and new catalysts for alkene and alkyne hydroamination are improving synthetic routes to a range of amino compounds. More recently, several examples of intermolecular hydroamination reactions have been reported using Rh and Ir phosphine complexes[3] and organoactinide[4] complexes as catalysts.

The scope of catalyzed hydroamination is very catalyst-dependent, and limited to relatively narrow classes of substrates. Most reports of hydroamination have involved the addition of primary amines to carbon—carbon double or triple bonds, although hydroamination using *N*-substituted amines has also been reported. Successful hydroamination of primary amides would provide a significant advance in the scope of hydroamination reactions, as amines are commonly protected with amide functionality and because of the utility of the *N*-substituted hydroamination products. The early transition metal catalysts, as well as the lanthanide catalysts are highly oxophilic, and generally unsuitable for the addition of amides to alkynes or alkenes. Palladium-catalyzed addition of tosylamides to alkenes has been used as a route to form nitrogen-containing heterocycles where the parent amine bound too aggressively to the catalyst and inhibited the cyclization.[5] The palladium-catalyzed cyclization of alkynylacetanilides to form *N*-acyl indole derivatives has also been reported.[6]

We have recently reported the synthesis of a new reactive cationic Rh(I) dicarbonyl complex [{Rh(bim)$(CO)_2$}$^+$$BPh_4^-$] **1** (Scheme 1), with a bidentate bisimidazolylmethane ligand [bim refers to bis(*N*-methylimidazol-2-yl)methane].[7]



1

Scheme 1.

Complex **1** acts as a catalyst for a range of organic reactions including the hydrosilation of double and triple bonds, the alcoholysis of silanes, and the cyclization of alkynols and alkynoic acids to oxygen-containing heterocycles.[8] Complex **1** also acts as a catalyst for hydroamination reactions, specifically for the facile intramolecular cyclization of amino alkyne substrates. In this paper, we report the intramolecular cyclization of both aromatic and aliphatic alkynamides to form nitrogen-containing heterocycles.

Complex **1** was prepared by reaction of the bidentate imidazole ligand bim **2** with $[Rh(CO)_2Cl]_2$ as described previously.[9] *N*-Acetyl-2-ethynylaniline **3** was cyclized by **1** in acetone solvent at 55°C with 1.5 mol% catalyst to give *N*-acetylindole **4**. The reaction was slow compared to that using the free amine substrate and, after 3 days, **4** was obtained in a yield of 23% (Scheme 2).

In a similar fashion, 1,5-bis(acetamido)-2,4-diethynylbenzene **5** was synthesized in five steps from 1,3-dibromobenzene and cyclized with **1** at a loading of 30 mol% to form the bisacetylated pyrrolo[3,2-*f*]indole **6** (Scheme 3).

This approach, via the intramolecular cyclization of substituted alkynylanilines, clearly provides a relatively direct entry

* This paper is dedicated to Professor Lew Mander in recognition of his great contribution to organic chemistry in Australia.

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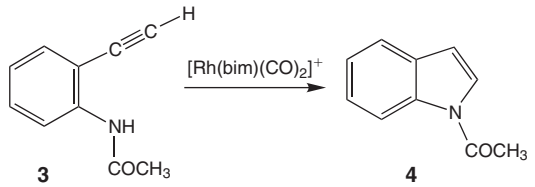
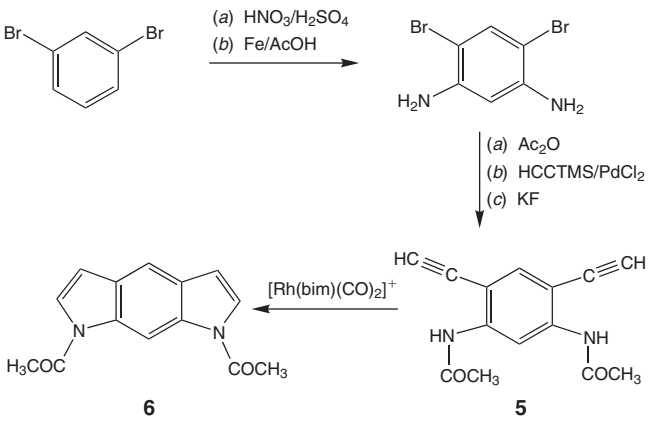
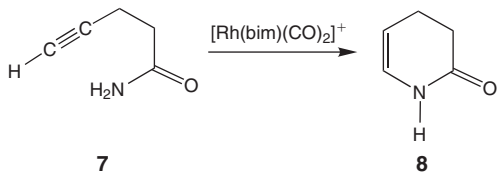


Scheme 2.



Scheme 3.



Scheme 4.

to the indoles. Since it is known that non-terminal alkynes also undergo cyclization with **1**, this scheme has the flexibility to access a range of indoles with substituents on the indole nitrogen or at the 2-position.

Complex **1** also successfully cyclized non-aromatic acetylenic amides. 1-Pentynamide **7** was cyclized to 3,4-dihydro-2-pyridone **8** (Scheme 4) albeit slowly at a loading of 10 mol% and in modest yield (11%). In principle, the intramolecular cyclization could give two possible isomers resulting from either the 5-*exo-dig* or 5-*endo-dig* ring closure. *exo*-Cyclization gives a five-membered ring, while *endo*-cyclization would give the six-membered ring product. With **1** as catalyst, only the six-membered ring product **8** was observed.

The mechanism of addition of N─H bonds to carbon─carbon double and triple bonds has been investigated for several of the metal-mediated systems. Classical oxidative addition/reductive elimination reaction pathways have been proposed using catalysts containing metal centres such as lanthanides,[10] actinides,[11] and Rh(I).[12] This mechanism involves oxidative addition of the N─H bond of the amine to the metal centre followed by a migratory insertion to the tethered alkene to produce a metal-coordinated heterocyclic enamine. Li and Marks[10] have previously identified enamine intermediates in the cyclization of primary and secondary amino alkynes by an organolanthanide complex.

To conclude, the cyclization of alkynamides to *N*-acylindoles and to other nitrogen-containing heterocycles provides a useful preparative route to a range of heterocyclic systems. The reaction of amides is significantly slower than their free-amine counterparts. It should be noted that amino alkynes are cyclized by a range of related cationic Rh(I) and Ir(I) complexes, and the efficiency of the catalyst changes remarkably even with small changes to the ligand donor set as well as with the nature of the counter ion. So far, no attempt has been made to optimize product yields or assess the best metal complex for the cyclization of alkynamides.

Experimental

All manipulations of metal complexes and air-sensitive reagents were carried out using standard Schlenk or vacuum techniques, or in a nitrogen- or argon-filled dry box.

All organic starting materials were obtained from Aldrich and were distilled before use. $[Rh(bim)(CO)_2]^+[BPh_4]^-$ **1** was synthesized according to literature methods.[9] *N*-Acetyl-2-ethynylaniline **3** was prepared by the method of Rudisill and Stille.[6a] 1,5-Diamino-2,4-dibromobenzene was synthesized following the method of Dumont and Slegers.[13] Pent-4-ynoic acid was synthesized according to the procedure of Holland and Gilman.[14]

Tetrahydrofuran was stored over sodium wire and distilled under nitrogen immediately before use from sodium benzophenone ketyl. Deuterated solvents for NMR purposes were obtained from Merck and Cambridge Isotopes. Deuterated chloroform was used as supplied. Deuterated acetone was dried over P_2O_5 and deuterated tetrahydrofuran was stored over Na. Solvents were degassed using three consecutive freeze–pump–thaw cycles and vacuum distilled immediately before use.

Mass spectra of organic compounds were recorded on a Finnigan Mat TSQ 4600 mass spectrometer by chemical ionization. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. Melting points were determined using a Gallenkamp apparatus and are uncorrected.

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX400 spectrometer at 400.13 and 100.62 MHz respectively. ^1H and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonances.

Cyclization of N-*Acetyl-2-ethynylaniline* ***3***

N-Acetyl-2-ethynylaniline **3** (42 mg, 0.26 mmol) was added to a solution of $[Rh(bim)(CO)_2]^+[BPh_4]^-$ **1** (3 mg, 4.6 μmol, 1.5 mol%) in $(CD_3)_2CO$ (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 55°C in an oil bath. *N*-Acetylindole **4** was formed with 23% conversion from starting material after 3 days. The material was spectroscopically identical to an authentic sample prepared by the acetylation of indole with acetic anhydride. δ_H (400 MHz, $(CD_3)_2CO$) 8.42 (d, 1H, $^3J_{4,5}$ 8.2, H4), 7.71 (d, 1H, $^3J_{7,6}$ 3.8, H7), 7.59 (m, 1H, H2), 7.32 (m, 1H, H6), 7.25 (m, 1H, H5), 6.68 (m, 1H, H3), 2.65 (s, 3H, CH_3). δ_C (100 MHz, $(CD_3)_2CO$) 169.7 (C=O), 137.0, 127.2, 125.9 (C2), 125.3 (C6), 122.2 (C4), 121.5 (C5), 116.9 (C7), 109.0 (C3), 23.9 (CH_3).

1,5-Bis(acetamido)-2,4-dibromobenzene

Acetic anhydride (0.3 mL) was added to a solution of 1,5-diamino-2,4-dibromobenzene (52 mg, 0.20 mmol) in dichloromethane (2 mL), and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum. The residue was recrystallized from ethanol to give 1,5-bis(acetamido)-2,4-dibromobenzene as a white powder (41 mg, 61%). (Found: *m*/*z* 347.9111; C 34.2, H 2.7, N 7.9%. $C_{10}H_{10}Br_2N_2O_2$ requires 347.9109; C 34.3, H 2.9, N 8.0%.)

δ_H (200 MHz, $(CD_3)_2SO$) 9.52 (br s, 2H, NH), 7.94 (s, 1H, H3), 7.88 (s, 1H, H6), 2.07 (s, 6H, CH_3). δ_C (75 MHz, $(CD_3)_2SO$) 168.7 (C=O), 136.1 (C1 and C5), 135.0 (C3), 124.3 (C6), 114.2 (C2 and C4), 23.3 (CH_3). *m/z* (EI^+) 350 (M^+, 3%), 271 (100), 269 (93), 266 (28), 229 (60), 227 (53), 189 (50).

1,5-Bis(acetamido)-2,4-bis(trimethylsilylethynyl)benzene

Palladium(II) chloride (111 mg, 0.626 mmol), copper(II) acetate (128 mg, 1.04 mmol), triphenylphosphine (482 mg, 1.84 mmol), and 1,5-bis(acetamido)-2,4-dibromobenzene (2.0 g, 5.7 mmol) were mixed under nitrogen with dry and degassed triethylamine (180 mL). (Trimethylsilyl)acetylene (2.6 mL, 18 mmol) was added and the reaction mixture was stirred and heated at 85°C under nitrogen for 8 h. The mixture was cooled to room temperature, filtered to remove the insoluble salts, and the triethylamine was removed under reduced pressure. The solid residue was dissolved in ethyl acetate, pre-adsorbed onto flash silica, and then purified by chromatography using flash silica (hexane/ethyl acetate, 1 : 1), R_F 0.46 (hexane/ethyl acetate, 1 : 1), to give 1,5-bis(acetamido)-2,4-bis(trimethylsilylethynyl)benzene as a light brown solid (1.1 g, 50%), mp 168–170°C. (Found: *m/z* 384.1685; C 63.0, H 7.4, N 7.2%. $C_{20}H_{28}N_2O_2Si_2$ requires 384.1689; C 62.5, H 7.3, N 7.3%.) δ_H (200 MHz, $CDCl_3$) 9.34 (br, 1H, H6), 7.90 (br s, 2H, NH), 7.46 (s, 1H, H3), 2.17 (s, 6H, $COCH_3$), 0.27 (s, 18H, $Si(CH_3)_3$). δ_C (75 MHz, $CDCl_3$) 167.9 (C=O), 140.7 (C1 and C5), 134.6 (C3), 109.7 (C6), 106.9 (C2 and C4), 102.1 (*C*CSiMe$_3$), 99.4 (C*C*SiMe$_3$), 24.9 (CO*C*H$_3$), 0.4 ($Si(CH_3)_3$). *m/z* (EI^+) 384 (M^+, 75%), 343 (100), 301 (40), 74 (18). ν_{max}/cm^{-1} (KBr) 3293w (N–H), 2958w (C–H aromatic), 2155m (C≡C), 1671s (C≡O), 1585s, 1412s, 1250s, 842s.

1,5-Bis(acetamido)-2,4-diethynylbenzene ***5***

1,5-Bis(acetamido)-2,4-bis(trimethylsilylethynyl)benzene (0.44 g, 1.2 mmol) was dissolved in methanol (40 mL), potassium fluoride (0.70 g, 12 mmol) was added, and the reaction mixture was stirred for 1 h at room temperature. Water (30 mL) was added, and the reaction mixture was extracted with diethyl ether (5 × 50 mL). The combined organic layers were washed with water (2 × 25 mL) and brine (25 mL), then dried over magnesium sulfate and the solvent was removed under vacuum to give the *title compound* **5** as a creamy brown solid (106.8 mg, 39%), mp 300°C (dec.). (Found: *m/z* 240.0897. $C_{14}H_{12}N_2O_2$ requires 240.0899.) δ_H (400 MHz, [D_8]THF) 9.08 (s, 1H, H6), 8.42 (br s, 2H, NH), 7.44 (s, 1H, H3), 3.92 (s, 2H, C≡C–H), 2.11 (s, 6H, CH_3). δ_C (100 MHz, [D_8]THF) 168.2 (C=O), 142.1 (C1 and C5), 136.6 (C3), 133.9 (C6), 108.1 (C2 and C4), 84.8 (*C*≡C–H), 79.3 (C≡*C*–H), 24.2 (CH_3). *m/z* (EI^+) 240 (M^+, 30%), 198 (77), 156 (100), 104 (26). ν_{max}/cm^{-1} (KBr) 3392m (N–H), 3278s, 3206s (C≡*C*–*H*), 2097w (*C*≡*C*–H), 1699s, 1686s, 1664s (C=O), 1577s, 1529s, 1497s, 1417s.

Cyclization of ***5*** *to 1,7-Diacetylpyrrolo[3,2-*f*]indole* ***6***

Complex **1** (48.0 mg, 73.1 μmol; 30 mol%) was added to compound **5** (60.1 mg, 250 μmol) in deuterated tetrahydrofuran (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60°C and ^{1}H NMR spectra were recorded at regular intervals. The product was formed after 72 h. The tube was opened to the atmosphere and the residue was poured into a mixture of hexane (2.5 mL) and ethyl acetate (7.5 mL) to give a solid precipitate. The supernatant liquid was decanted and the precipitate was washed with hexane/ethyl acetate (1 : 3; 8 × 20 mL). The washings and the supernatant liquid were combined, reduced in volume, and purified by chromatography using flash silica (hexane/ethyl acetate, 1 : 3) to give compound **6** as an orange solid (21.5 mg, 36%), mp 205–207°C. (Found: *m/z* 240.0899. $C_{14}H_{12}N_2O_2$ requires 240.0899.) δ_H (400 MHz, $CDCl_3$) 9.47 (br s, 1H, H8), 7.65 (d, $^4J_{4,3/5}$ 0.77, 1H, H4), 7.50 (d, $^3J_{2,3}$ 3.8, 2H, H2 and H6), 6.67 (dd, $^3J_{3,2}$ 3.8, $^4J_{3,4}$ 0.77, 2H, H3 and H5), 2.67 (s, 6H, CH_3). δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 134.3 (C2′), 128.0 (C3′), 126.2 (C2 and C6), 111.9 (C4), 109.1 (C3 and C5), 104.6 (C8), 24.3 (CH_3). *m/z* (EI^+) 240 (M^+, 53%), 198 (32), 156 (100). ν_{max}/cm^{-1} (KBr) 1704s, 1688s (C=O), 1263s, 1213s, 1094m, 1029s (C–N), 1378s, 805s.

Pent-4-ynamide ***7***

A solution of pent-4-ynoic acid (94.5 mg, 1.00 mmol) in chloroform (2 mL, anhydrous) was stirred for 30 min in a stoppered Ace pressure tube, and 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (morpho-CDI; 0.45 g, 1.0 mmol) was added. After the addition was complete, the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was cooled to −78°C and then treated with condensed ammonia (1 mL, excess). The pressure tube was immediately stoppered and the mixture stirred at room temperature for 18 h. The tube was cooled to −78°C, the lid was removed, and the excess ammonia and solvent were evaporated in a stream of nitrogen at room temperature. The residue was extracted with ethyl acetate (5 × 20 mL). The ethyl acetate extracts were combined and the solvent was removed to give a yellow oily residue. The residue was chromatographed using flash silica (hexane/ethyl acetate, 1 : 3), R_F 0.28 (hexane/ethyl acetate, 1 : 3; $KMnO_4$ indicator), and recrystallized from ethyl acetate to give pent-4-ynamide **7** as a colourless crystalline solid (44.5 mg, 47%), mp 110–111°C (lit.[15] 112–113°C). δ_H (400 MHz, [D_8]THF) 6.76 (br, 1H, NH), 6.57 (br, 1H, NH), 2.41 (m, 2H, H2), 2.33 (m, 2H, H3), 2.22 (t, $^4J_{3,5}$ 2.6, 1H, H5). δ_C (100 MHz, [D_8]THF) 172.2 (C1), 84.0 (C4), 69.4 (C5), 35.1 (C2), 15.0 (C3). *m/z* (ES^+, methanol) 98 ($(M+H)^+$, 31%), 195 (50), 217 (35), 240 (20), 336 (100).

Cyclization of ***7*** *to 3,4-Dihydro-2-pyridone* ***8***

Complex **1** (136 mg, 207 μmol; 10 mol%) was added to pent-4-ynamide **7** (200 mg, 2.07 mmol) in deuterated tetrahydrofuran (0.5 mL) in an NMR tube under an atmosphere of nitrogen. The mixture was heated at 60°C and ^{1}H NMR spectra were recorded at regular intervals. The product **8** was formed after 24 h. Once the reaction was complete, the NMR tube was opened to the atmosphere. The residue was poured into a mixture of hexane (2.5 mL) and ethyl acetate (7.5 mL) to give a solid brown precipitate. The supernatant liquid was decanted and the brown precipitate was washed with hexane/ethyl acetate (1 : 3; 4 × 20 mL). The supernatant liquid and the washings were combined, reduced in volume, and chromatographed using flash silica (hexane/ethyl acetate, 1 : 3) to give 3,4-dihydro-2-pyridone **8** as a yellow oil (16 mg, 11%). (Found: *m/z* 97.0527. C_5H_7NO requires 97.0528.) δ_H (400 MHz, $CDCl_3$) 7.90 (br s, 1H, NH), 6.04 (ddt, $^3J_{6,5}$ 7.6, $^3J_{6,NH}$ 4.5, $^4J_{6,4}$ 1.6, 1H, H6), 5.04 (dtd, $^3J_{5,6}$ 7.6, $^3J_{5,4}$ 4.3, $^4J_{5,NH}$ 1.1, 1H, H5), 2.46 (m, 2H, H3), 2.29 (m, 2H, H4). δ_C (100 MHz, $CDCl_3$) 171.9 (C2), 125.1 (C6), 105.1 (C5), 30.5 (C3), 20.1 (C4). *m/z* (EI^+) 97 (M^+, 48%). *m/z* (ES^+, MeOH/$CDCl_3$) 485 ($(M \times 5)^+$, 46%), 418 (100), 316 (75), 217 (36), 152 (34), 120 (33), 98 (17). ν_{max}/cm^{-1} (NaCl) 3258m (N–H), 1679s, 1654s (C=O), 1367m, 1089m, 798m.

Acknowledgments

We gratefully acknowledge financial support from the Australian Research Council (ARC) and the generous loan of rhodium salts from Johnson Matthey Pty Ltd.

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