Catalytic Cycloisomerization

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Platinum-Catalyzed Intramolecular Cyclizations of Alkynes: Efficient Synthesis of Pyrroloazepinone Derivatives**

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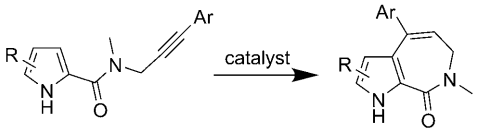
Dedicated to Professor Hans Jürgen Wernicke on the occasion of his 60th birthday

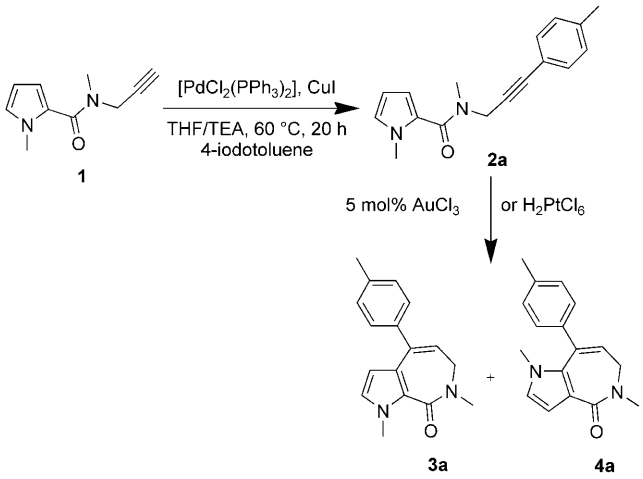
Transition-metal-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes have attracted much attention in the last decade. In particular, intramolecular gold- and platinum-catalyzed hydroarylations,[1] cycloisomerizations,[2] and cycloadditions[3] offer new ways for the efficient construction of biologically interesting carbo- and heterocycles. Recent elegant examples also include the use of *N*-heterocycles; for example, Echavarren et al.[4] and England and Padwa[5] reported intramolecular cyclizations of indol derivatives in the presence of gold catalysts. Inspired by this work and our interest in the application of catalytic coupling and amination reactions for the synthesis of bio-active compounds,[6] we started a program on the catalytic synthesis of novel pyrroloazepinone derivatives.

The pyrroloazepinone motif (Scheme 1)[7] is present in a variety of natural and pharmaceutical products, such as hymenialdisine,[8] stevensine,[9] latonduine,[10] and the paullones.[11] From a biological point of view, pyrroloazepinones have been found to selectively inhibit a number of different kinases and cytokines.[12–14] Therefore, these kinase inhibitors have emerged as promising therapeutic molecules for treatment of a range of diseases, including cancer.[13,15] Some of the pyrrole-based alkaloid intermediates were shown to have also neuroprotective activity against the agonists serotonin and glutamate in vivo.[16] It is thus not surprising that this class of compounds has become an important target for organic synthesis. For example, Joseph and co-workers reported the preparation of Latonduine derivatives in five steps with a intramolecular Heck reaction as the key step.[17] In addition, Taddei et al. synthesized (pyrroloazepinyl)acetamides by a Beckmann rearrangement.[18]



Scheme 1. Planned formation of pyrroloazepinones from propargylamide-substituted pyrroles.

Our initial investigations aimed at the straightforward synthesis of the pyrrolo[2,3-*c*]azepin-8-one **3a** (Scheme 2). *N*,*N*′-Dimethyl-*N*-(prop-2-ynyl)-1*H*-pyrrole-2-carboxamide



Scheme 2. Synthesis of pyrroloazepinones **3a** and **4a**.

(**1**) was formed in 91% yield by addition of *N*-methylpropargylamine to *N*-methyl-1*H*-pyrrole-2-carboxylic acid activated by 4-(dimethylamino)pyridine and 1,1′-carbonyldiimidazole in tetrahydrofuran at 40 °C.[19] A subsequent palladium-catalyzed Sonogashira reaction in the presence of the $[PdCl_2(PPh_3)_2]$ and CuI catalyst system gave *N*,*N*′-dimethyl-*N*-(3-*p*-tolylprop-2-ynyl)-1*H*-pyrrole-2-carboxamide (**2a**) in 73% yield.[20] The intramolecular cyclization of **2a** was then examined in the presence of different metal salts and complexes of Au, Pt, Pd, Cu, Zn, Fe, Ru, and others. High activity and full conversion were observed only in the presence of $AuCl_3$ and $H_2PtCl_6{\cdot}6H_2O$ as catalysts.

According to the work of Echavarren et al., the best catalyst for the formation of azepinone derivatives by an *endo*-dig process should be an gold(III) complex, and the expected product should have been the pyrrolo[2,3-*c*]azepin-8-one **3a**.[4] Surprisingly, an intramolecular hydroarylation reaction gave 1,5-dimethyl-8-*p*-tolyl-5,6-dihydropyrrolo[3,2-*c*]azepin-4-one (**4a**) as the major product (Scheme 2). To our knowledge, this type of alkyne cyclization, including rear-

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rangement of carbonyl groups, has not been previously reported.[4,18]

The yields of products **3a** and **4a** varied significantly depending on the catalysts, solvents, and reaction temperature used (Table 1). $H_2PtCl_6{\cdot}6H_2O$ and toluene as solvent

Table 1: Variation of reaction conditions in the presence of $AuCl_3$ and $H_2PtCl_6{\cdot}6H_2O$ catalysts.[a]

Entry	Catalyst	Solvent	*T* [°C]	Conv.[b] [%]	Yield[b] **3a** [%]	Yield[b] **4a** [%]
1	$AuCl_3$	toluene	120	76	13	40
2	$AuCl_3$	dioxane	120	100	31	55
3	$AuCl_3$	dioxane	60	100	51	48
4	$AuCl_3$	dioxane	20	29	19	10
5	H_2PtCl_6	toluene	120	100	7	78
6	H_2PtCl_6	toluene	60	19	0	3
7	H_2PtCl_6	dioxane	120	100	36	60
8	H_2PtCl_6	dioxane	60	100	35	64
9	H_2PtCl_6	CH_2Cl_2	20	9	0	8

[a] Reaction conditions: catalyst (5 mol%), *N*,*N*′-dimethyl-*N*-(3-*p*-tolyl-prop-2-ynyl)-1*H*-pyrrole-2-carboxamide (**2a**; 0.2 mmol), solvent (10 mL), 20 h. [b] Determined by GC with hexadecane as internal standard.

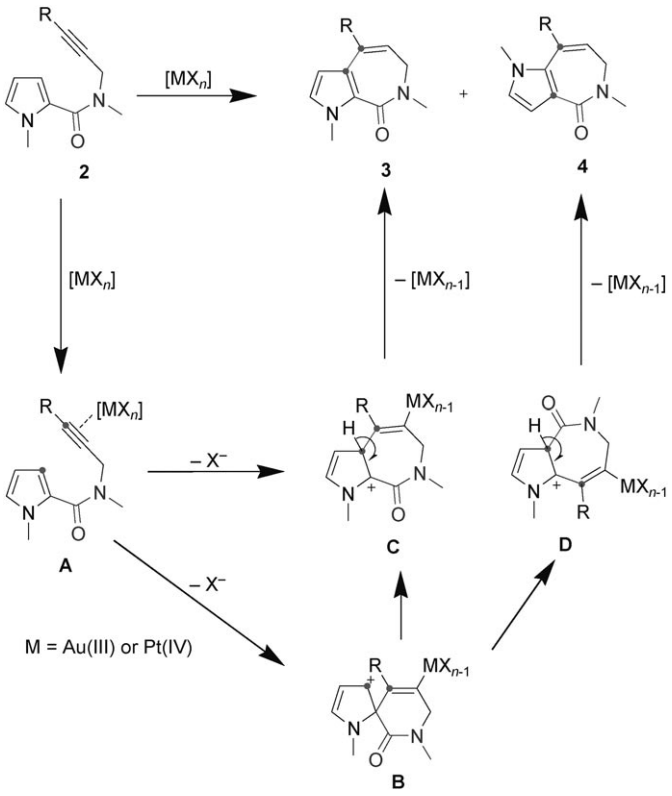
turned out to be the optimal catalyst at higher temperatures, and product **4a** is formed in 78% yield (Table 1, entry 5). Notably, in this case only a small amount (7%) of the originally expected cyclization isomer **3a** is observed. However, in 1,4-dioxane in the presence of both gold or platinum catalysts, the regioselectivity is low. In these cases, the pyrroloazepinones **3a** and **4a** were formed in a ratio that ranged from 1:1 to 1:2 (Table 1, entries 2, 3, 7–8).

In few cases, traces of other compounds apart from **3a** and **4a** and degradation products were detected in the crude reaction mixture. Indeed, we observed pyrrolo[2,3-*c*]pyridin-7-one derivatives (< 1% yield) corresponding to the product with a six-membered ring, which was probably formed by an 6-*exo*-dig process.[5] A simplified proposal for the mechanism of this novel gold- and platinum-catalyzed cycloisomerization reaction is shown in Scheme 3.

In agreement with earlier reports,[1,4,5,21] we assume that pyrrole derivative **2** is initially activated at the triple bond by coordination to the electrophilic gold(III) or platinum(IV) catalyst. Several modes of cycloisomerization reactions are then possible depending on reaction conditions (Table 1 and Scheme 3).

It appears that the pyrroloazepinone **3** is obtained by a 7-*endo*-dig process from compound **2**. Following the initial activation of the triple bond, cation **C** is formed either directly from intermediate **A** or via cation **B**. Subsequent protonolysis of the carbon–metal bond and deprotonation leads to **3**. In contrast, cation **D** might be formed from **B** by rearrangement. After deprotonation followed by demetalation, compound **4** is obtained.

Apart from being mechanistically interesting, our new cycloisomerization procedure provides an original β-amino acid scaffold in only two steps, which is an attractive motif for novel biologically active compounds. Therefore, we were interested in the scope and limitations of the procedure with

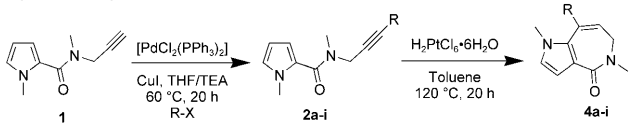


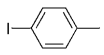
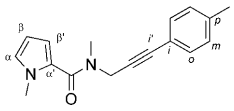
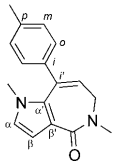
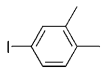
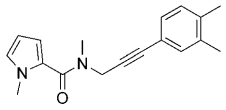
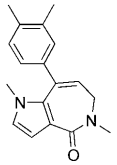
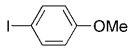
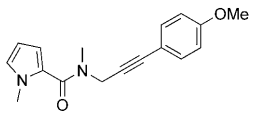
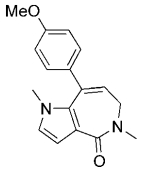
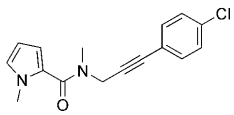
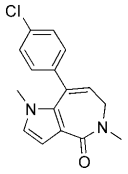
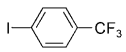
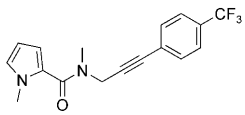
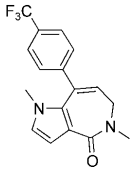
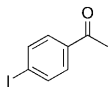
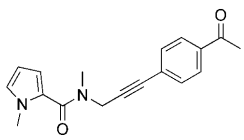
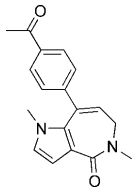
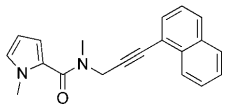
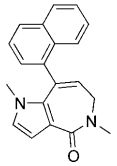
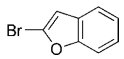
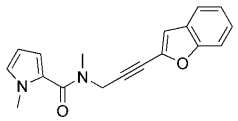
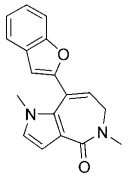
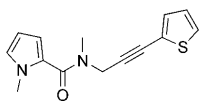
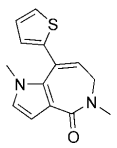
Scheme 3. Proposed mechanism for the formation of seven-membered-ring-containing compounds **3** and **4**.

different arylated substrates. Selected examples of the newly synthesized pyrroles **2a–i** and azepinones **4a–i** are listed in Table 2. The first step, the Sonogashira reaction of *N*-propargylpyrrole-2-carboxamide **1** with various substituted aryl or heteroaryl iodides and bromides proceeded smoothly in a 1:1 mixture of tetrahydrofuran and triethylamine at 60°C in presence of $[PdCl_2(PPh_3)_2]$ and CuI.[19] We typically obtained the desired pyrroles **2** in 70–80% yield. Next, the cyclization of pyrroles **2a–i** was performed using 5 mol% of $H_2PtCl_6{\cdot}6H_2O$ in toluene at 120°C to afford pyrrolo[3,2-*c*]azepin-4-ones **4a–i** with yields of isolated products between 18 and 76%. If the alkyne moiety is substituted with tolyl, *o*-xylyl, anisyl, chlorophenyl, *p*-acetylphenyl, or naphthyl groups, the cycloisomerization process afforded the corresponding products **4a–d** and **4f,g** (Table 2, entries 1–4, 6, 7) in good yields. With trifluoromethylbenzene, benzofuran, or thiophene substituents (Table 2, entries 5, 8, 9), the desired coupling products were obtained in lower yields. Obviously the electronic and steric nature of the attached aryl group influences the reactivity; however, is no clear trend is observed between reactivity and electronic nature of the aryl substituent. It is important to note that in all cases, the major cycloisomerization product was compound **4**, and the regioisomer **3** was obtained only in traces (< 5%).

In summary, a series of biologically interesting scaffolds were synthesized in a straightforward fashion in only two steps. For the first time, gold- and platinum-catalyzed intramolecular cyclization reactions that give pyrrolo[3,2-*c*]azepin-4-one derivatives have been performed. Interestingly, the 7-

Table 2: General synthesis of pyrroloazepin-4-one products.[a]



Entry	Substrate	Product **2**		Yield of **2** [%][b]	Product **4**		Yield of **4** [%][b]
1			**2a**	73		**4a**	76
2			**2b**	75		**4b**	75
3			**2c**	52		**4c**	68
4			**2d**	82		**4d**	54
5			**2e**	81		**4e**	18
6			**2f**	80		**4f**	58
7			**2g**	72		**4g**	70
8			**2h**	78		**4h**	33
9			**2i**	65		**4i**	29

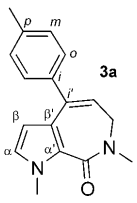
[a] Sonogashira conditions: $[PdCl_2(PPh_3)_2]$ (2 mol%), CuI (4 mol%), **2** (1.15 mmol), THF/triethylamine (1:1; 8 mL), 60°C, 20 h. Cyclization conditions: $H_2PtCl_6{\cdot}6H_2O$ (5 mol%), **4** (0.2 mmol), toluene (10 mL), 120°C, 20 h. [b] Yield of isolated product.

endo-dig cyclization process involved a concomitant rearrangement of the amidocarbonyl group from the 2- to the 3-position of the pyrrole ring. $H_2PtCl_6 \cdot 6H_2O$ is the best catalyst for the formation of seven-membered pyrrolo[3,2-*c*]azepin-4-one derivatives; the corresponding products **4a–i** were obtained in up to 76% isolated yield. Further extensions of this chemistry towards indoles and other heterocycles can be easily envisioned, and are being currently explored in our laboratory.

Experimental Section

N,*N*′-Dimethyl-*N*-(3-*p*-tolylprop-2-ynyl)-1*H*-pyrrole-2-carboxamide (**2a**): $[PdCl_2(PPh_3)_2]$ (0.023 mmol, 16 mg, 2 mol%) and CuI (0.046 mmol, 9 mg, 4 mol%) were placed in an ACE pressure tube under an argon atmosphere. A solution of *N*,*N*′-dimethyl-*N*-(prop-2-ynyl)-1*H*-pyrrole-2-carboxamide (**1**; 1.15 mmol, 202.7 mg) in THF/TEA (1:1; 8 mL) was then added. The pressure tube was sealed and the reaction mixture was heated at 60 °C for 20 h. After removal of the solvent in vacuo, the residue was purified by column chromatography (heptane/ethyl acetate 1:1) to give pyrrole **2a** as yellow liquid (223 mg, 73%). ^{1}H NMR (500.13 MHz; $CDCl_3$; numbering according to Table 2): $\delta = 7.34$ (m, 2H, *o*-Ph); 7.14 (m, 2H, *m*-Ph); 6.70 (dd, $^3J_{\alpha,\beta} = 2.5$ Hz, $^4J_{\alpha,\beta'} = 1.8$ Hz, 1H, H-α); 6.61 (br, 1H, H-β′); 6.09 (dd, $^3J_{\beta,\beta'} = 3.8$ Hz, $^3J_{\alpha,\beta} = 2.5$ Hz, 1H, H-β); 4.53 (s, 2H, CH_2); 3.80 (s, 3H, NCH_3); 3.23 (br, 3H, $OCNCH_3$); 2.34 ppm (s, 3H, aryl CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 163.8$ (CO); 138.6 (C-*p*); 131.6 (C-*o*); 129.0 (C-*m*); 126.7 (C-α); 124.8 (C-α′); 119.6 (C-*i*); 113.5 (C-β′); 106.9 (C-β); 84.4 (br), 83.6 (H_2C-*C*, C-*i*′); 40.3 (br, CH_2); 35.9 (NCH_3); 34.8 (br, $OCNCH_3$); 21.4 ppm (aryl CH_3). GC-MS (EI, 70 eV): *m/z* (%) 266 (22) [M^+], 251 (27), 238 (65), 224 (43), 209 (91), 194 (27), 175 (12), 156 (13), 129 (28), 115 (15), 108 (100), 91 (4), 81 (30), 63 (6), 53 (29), 39 (20). HRMS (EI): $C_{17}H_{18}ON_2$ calcd 266.14136, found 266.140787.

1,7-Dimethyl-4-*p*-tolyl-6,7-dihydropyrrolo[2,3-*c*]azepin-8(1*H*)-one (**3a**) and 1,5-dimethyl-8-*p*-tolyl-5,6-dihydropyrrolo[3,2-*c*]azepin-4(1*H*)-one (**4a**): $H_2PtCl_6 \cdot 6H_2O$ (0.01 mmol, 5.2 mg, 5 mol%) was placed in an ACE pressure tube under an argon atmosphere. A solution of product **2a** (0.2 mmol, 53.3 mg) in toluene (10 mL) was then added. The pressure tube was sealed and the reaction mixture was heated at 120 °C for 20 h. After removal of the solvent in vacuo, the residue was purified by column chromatography (ethyl acetate) to give pyrroloazepinones **3a** and **4a** as brown powders (5% and 76%, respectively). **3a**: ^{1}H NMR (500.13 MHz; $CDCl_3$): $\delta = 7.27$ (m, 2H, *o*-Ph); 7.14 (m, 2H, *m*-Ph); 6.71 (d, $^3J_{\alpha,\beta} = 2.7$ Hz, 1H, H-α); 6.03 (t, $^3J_{CH,CH_2} = 7.0$ Hz, 1H, =CH); 5.94 (d, $^3J_{\alpha,\beta} = 2.7$ Hz, 1H, H-β); 3.98 (s, 3H, NCH_3); 3.75 (d, $^3J_{CH,CH_2} = 7.0$ Hz, 2H, CH_2); 3.15 (s, 3H, $OCNCH_3$); 2.36 ppm (s, 3H, $CH_{3(aryl)}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 162.2$ (CO); 142.4 (C-*i*′); 137.6, 137.6 (C-*i*,*p*); 128.8 (C-*m*); 128.4 (C-*o*); 127.1, 126.8 (C-α′,β′); 126.7 (C-α); 119.0 (=CH); 107.7 (C-β); 47.5 (CH_2); 36.6 (NCH_3); 34.6 ($OCNCH_3$); 21.1 ppm (aryl CH_3). GC-MS (EI, 70 eV): *m/z* (%) 266 (100) [M^+], 251 (20), 237 (31), 224 (23), 209 (52), 194 (10), 175 (18), 165 (5), 152 (8), 115 (5), 91 (3), 77 (3), 63 (3), 51 (2), 42 (9). HRMS (EI): $C_{17}H_{18}ON_2$ calcd 266.14136, found 266.141082.



4a: ^{1}H NMR (500.13 MHz; $CDCl_3$; numbering according to Table 2): $\delta = 7.14$ (m, 2H, *m*-Ph); 7.09 (m, 2H, *o*-Ph); 6.73 (d, $^3J_{\alpha,\beta} = 2.9$ Hz, 1H, H-β); 6.61 (d, $^3J_{\alpha,\beta} = 2.9$ Hz, 1H, H-α); 6.09 (t, $^3J_{CH,CH_2} = 7.5$ Hz, 1H, =CH); 3.71 (d, $^3J_{CH,CH_2} = 7.5$ Hz, 2H, CH_2); 3.15 (s, 3H, $OCNCH_3$); 3.07 (s, 3H, NCH_3); 2.35 ppm (s, 3H, aryl CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 166.0$ (CO); 137.9, 137.7 (C-*i*′,*p*); 136.6 (C-*i*); 131.6 (C-α′); 129.3 (C-*m*); 127.4 (C-*o*); 124.6 (C-α); 123.8 (=CH); 123.5 (C-β′); 109.6 (C-β); 47.5 (CH_2); 36.4 (NCH_3); 35.2 ($OCNCH_3$); 21.1 ppm (aryl CH_3). GC-MS (EI, 70 eV): *m/z* (%) 266 (100) [M^+], 251 (14), 237 (48), 224 (29), 210 (29), 194 (11), 175 (20), 165 (4), 152 (9), 115 (5), 91 (3), 77 (3), 63 (3), 51 (2), 42 (11). HRMS (EI): $C_{17}H_{18}ON_2$ calcd 266.14136, found 266.141372.

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