Palladium-Catalyzed Intramolecular Addition of Amines to Acetylenes. Synthesis of Cyclic Imines

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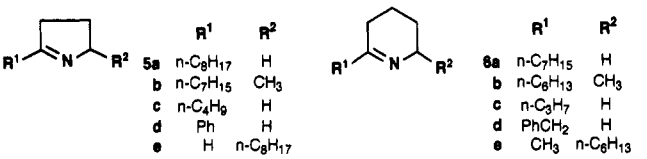
Intramolecular aminopalladation of alkynylamines gave intermediary alkenylpalladium compounds that hydrolyzed and isomerized to thermodynamically stable cyclic imines. Treatment of 3-alkynylamines with a catalytic amount of $PdCl_2(MeCN)_2$ gave exclusively 1-pyrrolines in good yields; 5-alkynylamines afforded 2,3,4,5-tetrahydropyridines selectively. Treatment of 4-alkynylamines with Pd(II) afforded mixtures of both 5- and 6-membered cyclic imines. Applications to the synthesis of some naturally occurring alkaloids are also described.

Synthesis of nitrogen heterocycles, important skeletal fragments of biologically active natural products, has attracted considerable attention in these decades.[1] Among various approaches to such compounds, syntheses using cyclic imines as intermediates have been extensively studied;[2,3] reaction of organometallic reagents to cyclic oxime derivatives[4] as well as palladium-promoted intramolecular aminations of olefins[5] are representative of recently developed methods for the synthesis of such cyclic imines.[4-18] In the case of Pd(II)-catalyzed intramolecular aminopalladation of alkenylamines giving cyclic imines, unexpected products were sometimes obtained owing to the lack of regioselectivity of the reaction.[5] In contrast, intramolecular reaction of alkynylamines has been preliminarily reported to possess high regioselectivity affording the expected product exclusively.[19-22] This paper describes in detail the intramolecular reaction of alkynylamines by Pd(II) catalysis.

Intramolecular reaction of 3-alkynylamines **1** was tried first. Treatment of 3-dodecynylamine (**1a**) with 5 mol % $PdCl_2$ in refluxing acetonitrile containing a few percent of water afforded 2-octyl-1-pyrrolidine (**5a**) as the sole product, which was obtained in 63% yield after distillation. The reaction proceeded sluggishly in refluxing anhydrous acetonitrile. In the absence of a catalytic amount of water, protonolysis of the intermediary alkenylpalladium species is slow; tarry materials were obtained by the intermolecular reaction of the organopalladium intermediate with the starting alkynylamine. This reaction can be explained by the following reactions: A 5-*Endo-Dig* aminopalladation occurred intramolecularly to give A, protonolysis of C–Pd bond was accelerated by water, and an initially produced cyclic enamine isomerized into a stable imine C (Scheme I). As 4-*Exo-Dig* cyclizations to give B are disfavored processes,[23] the intramolecular reaction of 3-alkynylamines proceeded in an allowed 5-*Endo-Dig* process exclusively.

Various 3-alkynylamines **1** gave the expected imines **5** by the catalytic action of the same Pd(II) species. Results are summarized in Table I. The reaction in THF also gave substituted 1-pyrrolines **5** exclusively, but the reaction proceeded slowly. Although internal acetylenic amines gave corresponding pyrrolines in good yields, reaction of a terminal acetylenic amine afforded 1-pyrroline in a poor yield. In this case, a palladium acetylide would be formed,[24] which could not be transformed into nitrogen heterocycles.

Palladium-catalyzed reaction of 4-alkynylamines **2** proceeded under the above described reaction conditions. Treatment of 4-dodecynylamine (**2a**) with $PdCl_2$ (5 mol %) in refluxing acetonitrile afforded a mixture of 2-



octyl-1-pyrroline (**5a**) and 6-heptyl-2,3,4,5-tetrahydropyridine (**6a**) in a ratio of 83:17. In contrast to the regioselective cyclizations of 3-alkynylamines **1**, intramolecular reaction of a 4-alkynylamine **2** proceeded by two competitive processes; a major 5-*Exo-Dig* cyclization giving a 5-membered ring (D through B) and a minor 6-*Endo-Dig* one affording a 6-membered ring (C through A). Another 4-alkynylamine gave a similar result. These results are summarized in Table II.

† On leave from Kyowa Yuka Co. Ltd., Yokkaichi, Mie, Japan.

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Table I. Pd(II)-Catalyzed Cyclization of 3-Alkylnylamines 1

entry	amine	R^1	R^2	solvent	conditions, reflux (h)	product	yield[a] (%)
1	**1a**	n-C_8H_{17}	H	MeCN	5	**5a**	40
2				MeCN–H_2O	5		67[b]
3				THF–H_2O	10		60[b]
4	**1b**	n-C_7H_{15}	CH_3	MeCN–H_2O	5	**5b**	70[b]
5	**1c**	n-C_4H_9	H	MeCN	5	**5c**	31
6				MeCN–H_2O	5		70[b]
7	**1d**	Ph	H	MeCN–H_2O	5	**5d**	63[b]
8	**1e**	H	n-C_8H_{17}	MeCN–H_2O	5		0

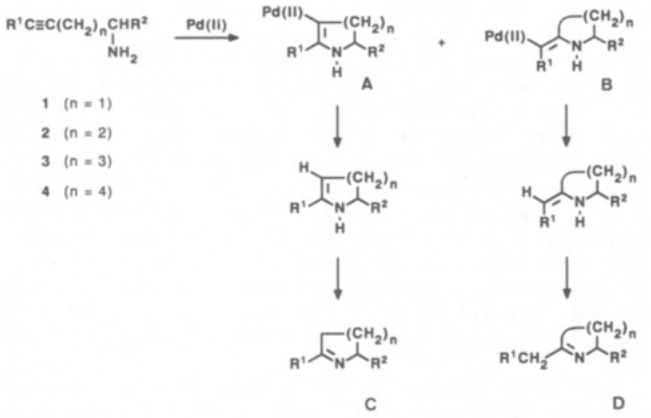
[a] Isolated yield by distillation. [b] Complete conversion to **5** was observed by TLC analysis.

Table II. Pd(II)-Catalyzed Cyclization of 4-Alkynylamines 2

entry	amine	R^1	R^2	products (yield (%))[a]
1	**2a**	n-C_7H_{15}	H	**5a** (83), **6a** (17)
2	**2b**	n-C_6H_{13}	CH_3	**5b** (80), **6b** (20)

[a] Yields of the products were determined by ^1H NMR.

Scheme I. Palladium-Catalyzed Reaction of Alkynylamine



Intramolecular reaction of 5-alkynylamines **3** proceeded smoothly at slightly higher reaction temperatures. Treatment of 5-dodecynylamine (**3a**) with Pd(II) catalysts did not give any cyclized product in refluxing acetonitrile, which was successfully employed in the above cyclizations; unchanged starting material was recovered quantitatively (Table III, entry 1). In refluxing butyronitrile, on the other hand, 5-dodecynylamine (**3a**) afforded 6-heptyl-2,3,4,5-tetrahydropyridine (**6a**) exclusively in good yield (Table III, entry 3). The cyclization occurred in refluxing propionitrile too.

A variety of 5-alkynylamines **3** were allowed to react in the presence of Pd(II) catalyst to give tetrahydropyridine derivatives **6**. 1-Hexyl-5-hexynylamine (**3e**) afforded the expected cyclized product in low yield; 6-phenyl-5-hexynylamine (**3d**) gave a complex mixture. Results are summarized in Table III.

The cyclization of 5-alkynylamines proceeded exclusively in 6-*Exo-Dig* manner, although both 6-*Exo-Dig* and 7-*Endo-Dig* cyclizations are favored processes.[23] Compared

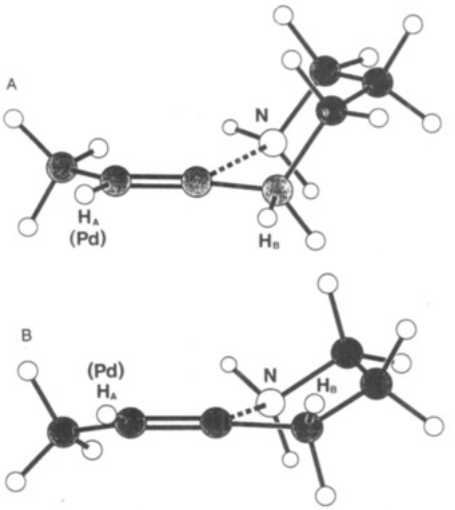
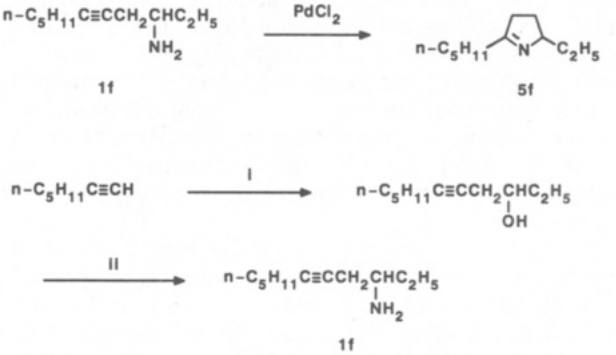


Figure 1. (A) Calculated transition structure of 6-*Exo-Dig* cyclization of 5-heptynylamine. (B) Calculated transition structure of 5-*Exo-Dig* cyclization of 4-hexynylamine.

Scheme II[a]



[a] Key: (i) (1) BuLi, (2) 1,2-epoxybutane/Me_3Ga; (ii) (1) TsCl/pyridine, (2) NaN_3, (3) LAH.

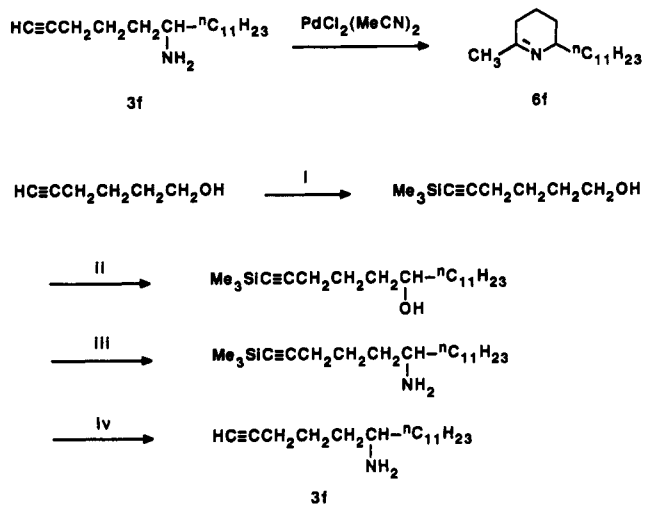
to the cyclizations of 3-alkynylamines and 4-alkynylamines, the cyclization of the 5-alkynylamines required higher reaction temperature; the activation energy of the 6-*Exo-Dig* cyclization seems slightly higher than that of 5-*Exo-Dig* one. The geometry of the transition state structure

Table III. Pd(II)-Catalyzed Cyclization of 5-Alkynylamines 3

entry	amine	R^1	R^2	solvent	conditions, reflux (h)	product	yield[a] (%)
1	**3a**	n-C_6H_{13}	H	MeCN	20	**6a**	0
2				EtCN	20		70[b]
3				PrCN	20		71[b]
4	**3b**	n-C_5H_{11}	CH_3	EtCN	10	**6b**	69[b]
5	**3c**	C_2H_5	H	EtCN	20	**6c**	68[b]
6	**3d**	Ph	H	EtCN	20		0
7	**3e**	H	n-C_6H_{13}	EtCN	20	**6e**	15

[a] Isolated yield by distillation. [b] Complete conversion to **6** was determined by TLC analysis.

Scheme III[a]



[a] Key: (i) (1) EtMgBr, (2) Me_3SiCl; (ii) (1) P.C.C., (2) n-$C_{11}H_{23}MgBr$; (iii) (1) TsCl/pyridine, (2) NaN_3, (3) LAH; (iv) KF/DMSO.

for the assumed 6-*Exo-Dig* cyclization of 5-heptynylamine was calculated by the MNDO method where the forming C–N bond length was fixed to 2.500 Å, Pd(II) was replaced by H^+, and other bond lengths and angles were optimized (Figure 1A). The assumed transition state structure for 5-*Exo-Dig* cyclization of 4-hexynylamine was obtained analogously and is shown in Figure 1B. The calculation gave slightly higher value for the activation energy of the 6-*Exo-Dig* cyclization compared to the 5-*Exo-Dig* one.[25] The distance between H_A and the allylic hydrogen (H_B) is calculated to be 3.25 Å in the transition structure for 5-*Exo-Dig* cyclization and 3.11 Å in that for the 6-*Exo-Dig* alternative. This result indicates that allylic repulsion might destabilize the transition state for the 6-*Exo-Dig* cyclization. In the actual reaction, H_A should be a bulky $Pd(II)L_n$ species, and hence the actual difference of the activation energy between 6-*Exo-Dig* and 5-*Exo-Dig* cyclizations would be greater than the calculated value. The above consideration would explain the experimental result that 6-*Exo-Dig* cyclization required a higher reaction temperature.

Application to the synthesis of large cyclic imines was fruitless; treatment of 6-tridecynylamine (4; $R^1 = n$-C_6H_{13}, $R^2 = H$) with 5 mol % of $PdCl_2(MeCN)_2$ in refluxing butyronitrile resulted in a quantitative recovery of the starting amine.

The reactions described above were applied to the synthesis of some cyclic imines isolated as venom constituents from ant species belonging to the family Formicidae.[26]

5-Ethyl-2-pentyl-1-pyrroline (**5f**; $R^1 = n$-C_5H_{11}, $R^2 = C_2H_5$) is one of the venom alkaloids from the South African fire ant, *Solenopsis punctaticeps*.[27] This compound was synthesized from 1-ethyl-3-nonynylamine (**1f**, $R^1 = n$-C_5H_{11}, $R^2 = C_2H_5$) by palladium catalysis in excellent yield. The starting material, 1-ethyl-3-nonynylamine (**1f**), was easily prepared from 5-undecyn-3-ol, as shown in Scheme II.

6-Methyl-2-undecyl-2,3,4,5-tetrahydropyridine (**6f**; $R^1 = CH_3$, $R^2 = n$-$C_{11}H_{23}$) is present as a venom species of *S. xyloni*.[28] It could be synthesized from corresponding alkynylamine **3f** ($R^1 = H$, $R^2 = n$-$C_{11}H_{23}$) in moderate yield, as shown in Scheme III. The starting material, 1-undecyl-5-hexynylamine (**3f**) was prepared from 5-hexyn-1-ol as shown in Scheme III.

Solenopsin A, one of the venoms of the fire ant *Solenopsis* (*Solenopsis*),[29] can be derived from cyclic imine **6f** by stereocontrolled reduction.[4,30]

In conclusion, intramolecular addition of an amine to an acetylene moiety described in this paper has opened a facile route to various nitrogen heterocycles.

Experimental Section

^1H NMR spectra were measured at 200 MHz.

Preparation of Alkynylamines (1–4) (General Procedure). Alkynylamines were prepared by the reduction of corresponding azides (Method A) or oximes (Method B). These precursors were readily available from appropriate acetylenic alcohols, which can be prepared by standard methods.[31]

Method A. Acetylenic alcohol (20 mmol) was converted into the corresponding tosylate by the treatment with *p*-toluenesulfonyl chloride (4.58 g, 24 mmol, 1.2 equiv) in pyridine (150 mL).[32] Acetylenic tosylate was alternatively synthesized by the reaction of lithium salt of acetylenic alcohol, which was prepared by the reaction of the alcohol (20 mmol) with *n*-BuLi (20 mmol, hexane solution) in THF and with *p*-toluenesulfonyl chloride (4.58 g, 24 mmol, 1.2 equiv) in THF.[33] The tosylate was treated with sodium azide (3.25 g, 50 mmol, 2.5 equiv) in DMF (150 mL) at 60–70 °C for 4 h. The reaction mixture was diluted with ether (200 mL) and washed with two portions (100 mL) of water and one portion (100 mL) of aqueous LiBr. The ethereal solution was dried (Na_2SO_4) and concentrated to give corresponding azide. The azide was reduced with LAH (759 mg, 20 mmol, 4 equiv) in ether (200 mL) at 0 °C giving alkynylamine, which was purified by distillation.

Method B. Acetylenic ketone was prepared by the oxidation of corresponding alcohol with Jones reagent.[34] An alternative method for the synthesis of methyl ketone was the reaction of the corresponding acetylenic acid with methyllithium in ether.[35] The acetylenic ketone (20 mmol) was treated with hydroxylamine hydrochloride (1.95 g, 28 mmol, 1.4 equiv) in EtOH (50 mL)–water (50 mL) in the presence of sodium carbonate (1.48 g, 14 mmol, 1.4 equiv) to give acetylenic oxime. The oxime was reduced with LAH (1.52 g, 40 mmol, 4 equiv) in ether (200 mL) at 0 °C to give alkynylamine. The product was purified by distillation.

3-Dodecynylamine (1a): prepared by method A; bp 82 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.0 Hz), 1.20–1.47 (14 H, m), 2.16 (2 H, tt, J = 2.4, 6.4 Hz), 2.29 (2 H, tt, J = 2.4, 6.2 Hz), 2.79 (2 H, t, J = 6.2 Hz); IR (neat) 3500–3000, 1080, 810 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.66; H, 13.04; N, 7.48.

1-Methyl-3-undecynylamine (1b): prepared by method A; bp 80 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.8 Hz), 1.12 (3 H, d, J = 6.4 Hz), 1.20–1.62 (12 H, m), 2.10–2.30 (4 H, m), 3.03 (1 H, tq, J = 6.7, 6.4 Hz); IR (neat) 3400–3100, 1260, 1110, 1090, 810 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.33; H, 12.96; N, 7.65.

3-Octynylamine (1c): prepared by method A; bp 80 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J = 7.0 Hz), 1.30–1.57

(25) Heats of formation are as follows: 4-hexynylamine, 21.18 kcal mol^{-1}; transition structure, 217.69 kcal mol^{-1}; 5-heptynylamine, 16.48 kcal mol^{-1}; transition structure, 214.53 kcal mol^{-1}. Thus, H of the cyclizations are calculated to be as follows: 5-*Exo-Dig* cyclization, 196.51 kcal mol^{-1}; 6-*Exo-Dig* cyclization, 198.05 kcal mol^{-1}.

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(6 H, m), 2.17 (2 H, tt, J = 2.4, 7.1 Hz), 2.30 (2 H, tt, J = 2.4, 6.4 Hz), 2.79 (2 H, t, J = 6.4 Hz); IR (neat) 3600–3100, 1272 cm^{-1}. Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.48; H, 12.32; N, 10.92.

1-Octyl-3-butynylamine (1d): prepared by method A; bp 85 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.5 Hz), 1.15–1.58 (16 H, m), 2.02 (1 H, t, J = 3.0 Hz), 2.15 (1 H, ddd, J = 3.0, 7.0, 16.1 Hz), 2.38 (1 H, ddd, J = 3.0, 5.2, 16.1 Hz), 2.91 (1 H, m); IR (neat) 3600–3100, 3300, 1380 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.77; H, 13.05; N, 7.70.

4-Phenyl-3-butynylamine (1e): prepared by method A; bp 87 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 1.53 (2 H, s), 2.56 (2 H, t, J = 6.4 Hz), 2.93 (2 H, t, J = 6.4 Hz), 7.25–7.50 (5 H, m); IR (neat) 3600–3100, 3050, 1600, 1490, 1440, 1085, 765, 697 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.62; H, 7.82; N, 9.48.

4-Dodecynylamine (2a): prepared by method A; bp 83 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.1 Hz), 1.20–1.55 (12 H, m), 1.62 (2 H, quint, J = 7.0 Hz), 2.14 (2 H, tt, J = 2.4, 6.8 Hz), 2.23 (2 H, tt, J = 2.4, 7.0 Hz), 2.80 (2 H, t, J = 7.0 Hz); IR (neat) 3700–3100, 1100, 1070 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.20; H, 12.86; N, 7.46.

1-Methyl-4-undecynylamine (2b): prepared by method B; bp 80 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.0 Hz), 1.07 (3, H, d, J = 6.0 Hz), 1.25–1.60 (10 H, m), 1.49 (2 H, q, J = 6.0 Hz), 2.13 (2 H, tt, J = 2.3, 6.7), 2.23 (2 H, tt, J = 2.3, 6.0 Hz), 3.03 (1 H, six, J = 6.0 Hz); IR (neat) 3400–3000, 1380, 1080, 815 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.38; H, 13.04; N, 7.67.

5-Dodecynylamine (3a): prepared by method A; bp 87 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.0 Hz), 1.18–1.60 (14 H, m), 2.15 (4 H, m), 2.71 (2 H, t, J = 7.0 Hz); IR (neat) 3700–3050, 1380, 1340 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.38; H, 13.02; N, 7.52.

1-Methyl-5-undecynylamine (3b): prepared by method B; bp 82 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.0 Hz), 1.07 (3 H, d, J = 6.2 Hz), 1.20–1.65 (12 H, m), 2.10–2.25 (4 H, m), 2.91 (1 H, six, J = 6.2 Hz); IR (neat) 3400–3000, 1370, 1100, 810 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.62; H, 12.98; N, 7.84.

5-Octynylamine (3c): prepared by method A; bp 87 °C (15 mmHg); ^1H NMR ($CDCl_3$) δ 1.12 (3 H, t, J = 7.2 Hz), 1.45–1.64 (6 H, m), 2.42 (4 H, m), 2.72 (2 H, t, J = 6.5 Hz); IR (neat) 3600–3100, 1310, 1075 cm^{-1}. Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.69; H, 12.29; N, 10.89.

1-Hexyl-5-hexynylamine (3d): prepared by method A; bp 87 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.0 Hz), 1.15–1.70 (16 H, m), 1.97 (1 H, t, J = 2.6 Hz), 2.22 (2 H, dt, J = 2.6, 6.8 Hz), 2.73 (1 H, m); IR (neat) 3600–3100, 3300, 2200, 1376, 840 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.22; H, 13.06; N, 7.56.

6-Phenyl-5-hexynylamine (3e): prepared by method A; bp 107 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 1.35 (2 H, s), 1.62–1.78 (4 H, m), 2.44 (2 H, m), 2.76 (2 H, t, J = 7.0 Hz), 7.25–7.50 (5 H, m); IR (neat) 3600–3100, 3075, 3050, 1600, 1490, 1345, 1060, 970, 760, 965 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 82.94; H, 8.94; N, 7.99.

1-Ethyl-3-nonynylamine (1f): prepared by method A; bp 72 °C (3 mmHg); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.0 Hz), 0.90 (3 H, t, J = 7.0 Hz), 1.15–1.62 (10 H, m), 2.05–2.40 (4 H, m), 2.78 (1 H, m); IR (neat) 3600–3200, 1380 cm^{-1}. Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 79.08; H, 12.82; N, 8.13.

1-Undecyl-5-hexynylamine (3f): prepared by method A; bp 160 °C (1 mmHg, Kugelrohr); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 7.5 Hz), 1.10–1.71 (26 H, m), 1.78 (1 H, t, J = 2.5 Hz), 2.16 (2 H, dt, J = 2.5, 6.5 Hz), 2.64 (1 H, m); IR (neat) 3600–3100, 3310, 2120, 1380 cm^{-1}. Anal. Calcd for $C_{17}H_{33}N$: C, 81.20; H, 13.23; N, 5.57. Found: C, 81.06; H, 13.31; N, 5.48.

6-Tridecynylamine (4): prepared by method A; bp 103 °C (1 mmHg); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.6 Hz), 1.17–1.63 (16 H, m), 2.15 (4 H, m), 2.70 (2 H, t, J = 6.5 Hz); IR (neat) 3600–3200, 1327 cm^{-1}. Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.70; H, 12.98; N, 7.08.

Preparation of 1-Pyrrolines 5 from 3-Alkynylamine 1 (General Procedure). 3-Alkynylamine (5 mmol) was dissolved in a mixture of acetonitrile (20 mL) and water (1 mL). To this solution was added $PdCl_2(MeCN)_2$ (32 mg, 0.12 mmol, 5 mol %), and the whole was heated at reflux for 5–10 h. The reaction mixture was diluted with ether (50 mL) and washed with a 1:1 mixture of aqueous NH_3 and brine (50 mL). After the solution was dried over Na_2SO_4, the ethereal layer was concentrated to give crude product. The product was purified by Kugelrohr distillation.

2-Octyl-1-pyrroline (5a): yield 606 mg (67%); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6.4 Hz), 1.20–1.48 (10 H, m), 1.59 (2 H, br t, J = 7.6 Hz), 1.85 (1 H, quint, J = 7.3 Hz), 1.86 (1 H, quint, J = 7.3 Hz), 2.32 (2 H, tt, J = 1.7, 7.6 Hz), 2.46 (2 H, tt, J = 1.7, 7.3 Hz), 3.80 (2 H, tt, J = 1.7, 7.3 Hz); IR (neat) 1645, 1380, 1300, 1014, 975 cm^{-1}; MS m/z (relative intensity) 180 (3.3, $M^+ - 1$), 152 (8.5), 138 (14.0), 124 (14.4), 110 (51.3), 96 (94.1), 83 (100), 68 (31.3), 55 (73.1). Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.69; H, 13.02; N, 7.77.

2-Heptyl-5-methyl-1-pyrroline (5b): yield 634 mg (70%); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 6.0 Hz), 1.25 (3 H, d, J = 6.2 Hz), 1.20–1.83 (10 H, m), 2.14 (2 H, m), 2.36 (2 H, t, J = 7.0 Hz), 2.50 (2 H, m), 4.06 (1 H, m); IR (neat) 1643, 1375, 1338, 903 cm^{-1}; MS m/z (relative intensity) 181 (5.2, M^+), 166 (13.1), 152 (30.9), 138 (39.9), 124 (88.4), 110 (99.6), 97 (100), 96 (53.9), 82 (95.8). Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.48; H, 12.87; N, 7.69.

2-Butyl-1-pyrroline (5c): yield 438 mg (70%); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.4 Hz), 1.35 (2 H, six, J = 8.0 Hz), 1.58 (2 H, quint, J = 8.0 Hz), 1.83 (2 H, m), 2.33 (2 H, t, J = 7.8 Hz), 2.45 (2 H, tt, J = 1.9, 8.0 Hz), 3.80 (2 H, tt, J = 1.9, 7.5 Hz); IR (neat) 1644, 1380, 1300 cm^{-1}; MS m/z (relative intensity) 124 (1.5, $M^+ - 1$), 110 (4.9), 96 (25.0), 83 (100), 74 (37.4), 59 (76.8). Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.59; H, 12.29; N, 11.09.

2-Phenyl-1-pyrroline (5d): yield 570 mg (63%); ^1H NMR ($CDCl_3$) δ 2.04 (2 H, tt, J = 7.4, 8.1 Hz), 2.97 (2 H, tt, J = 2.1, 8.1 Hz), 4.18 (2 H, tt, J = 2.1, 7.4 Hz), 7.44 (3 H, m), 7.85 (2 H, m); IR (neat) 3054, 3028, 1616, 1575, 1495, 1459, 1447, 1341, 1046, 1026, 760, 692 cm^{-1}; MS m/z (relative intensity) 145 (100, M^+), 117 (97.0), 104 (28.2), 77 (25.2). Anal. Calcd for $C_{10}H_{11}N$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.55; H, 7.81; N, 9.65.

Preparation of 2,3,4,5-Tetrahydropyridines 6 from 5-Alkynylamines 3 (General Procedure). To a solution of $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol, 5 mol%) in 20 mL of propionitrile was added 5-alkynylamine (1 mmol), and the whole was heated at reflux for 10–20 h. The reaction mixture was diluted with ether (50 mL) and washed with a 1:1 mixture of aqueous NH_3 and brine (50 mL). The ethereal layer was dried (Na_2SO_4) and concentrated to give crude product. The product was purified by Kugelrohr distillation.

6-Heptyl-2,3,4,5-tetrahydropyridine (6a): yield 643 mg (71%); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6.4 Hz), 1.23–1.71 (14 H, m), 2.13 (4 H, m), 3.54 (2 H, m); IR (neat) 1663, 1365 cm^{-1}; MS m/z (relative intensity) 181 (3.5, M^+), 152 (4.4), 138 (4.7), 124 (12.4), 110 (48.9), 97 (100), 96 (34.9), 82 (15.2), 69 (13.7), 55 (35.5). Anal. Calcd for $C_{12}H_{23}N$: C, 79.49: H, 12.79; N, 7.73. Found: C, 79.36; H, 12.76; N, 7.66.

6-Hexyl-2-methyl-2,3,4,5-tetrahydropyridine (6b): yield 624 mg (69%); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.6 Hz), 1.23 (3 H, d, J = 6.9 Hz), 1.24–1.75 (12 H, m), 2.12 (4 H, m), 3.45 (1 H, m); IR (neat) 1658, 1369, 1312 cm^{-1}; MS m/z (relative intensity) 181 (16.2, M^+), 166 (8.4), 152 (12.5), 138 (27.6), 124 (56.0), 111 (100), 110 (37.2), 96 (92.8), 82 (10.3). Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.22; H, 12.90; N, 7.47.

6-Propyl-2,3,4,5-tetrahydropyridine (6c):[36-39] yield 425 mg (68%); ^1H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.4 Hz), 1.41–1.90 (6 H, m), 2.10 (4 H, m), 3.56 (2 H, m); IR (neat) 1662, 1375, 1361, 1328, 1145, 954 cm^{-1}; MS m/z (relative intensity) 125 (11.4, M^+),

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110 (23.7), 97 (100), 96 (30.5), 82 (13.6), 70 (32.6). Anal. Calcd for $C_8H_{15}N$: C, 76.74; H, 12.08; N, 11.19. Found: C, 76.46; H, 12.21; N, 11.08.

2-Hexyl-6-methyl-2,3,4,5-tetrahydropyridine (6e): yield 136 mg (15%); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.0 Hz), 1.02-1.83 (14 H, m), 1.89 (3 H, d, J = 2.0 Hz), 2.08 (2 H, m), 3.25 (1 H, m); IR (neat) 1660, 1376 cm^{-1}; MS m/z (relative intensity) 181 (18.8, M^+), 166 (4.7), 152 (33.2), 138 (10.1), 124 (11.0), 110 (100), 97 (97.1), 96 (96.4), 82 (40.4). Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73. Found: C, 79.21; H, 13.04; N; 7.61.

5-Ethyl-2-pentyl-1-pyrroline (5f): yield 601 mg (72%); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6.7 Hz), 0.93 (3 H, t, J = 7.0 Hz), 1.30-1.90 (8 H, m), 2.05 (2 H, m), 2.33 (2 H, t, J = 7.5 Hz), 2.45 (2 H, m), 3.88 (1 H, m); IR (neat) 1642, 1380, 1315 cm^{-1}; MS m/z (relative intensity) 166 (2.2, $M^+ - 1$), 152 (2.3), 138 (33.0), 124 (46.2), 111 (91.6), 110 (8.1), 96 (15.5), 82 (100). Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 79.08; H, 12.84; N, 8.15.

6-Methyl-2-undecyl-2,3,4,5-tetrahydropyridine (6f): yield 527 mg (42%); ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.5 Hz), 1.10-1.80 (24 H, m), 1.92 (3 H, d, J = 2.0 Hz), 2.08 (2 H, m), 3.25 (1 H, m); IR (neat) 1662, 1370 cm^{-1}; MS m/z (relative intensity) 251 (37.5, M^+), 236 (3.8), 222 (7.9), 208 (9.0), 194 (5.6), 180 (7.4), 166 (12.7), 152 (41.4), 138 (15.1), 124 (11.3), 110 (100), 97 (88.4). Anal. Calcd for $C_{17}H_{33}N$: C, 81.20; H, 12.23; N, 5.57. Found: C, 80.96; H, 12.25; N, 5.57.

Reaction of 4-Alkynylamine 2 in the Presence of Pd(II). 4-Dodecynylamine (**2a**, 500 mg, 2.76 mmol) was treated in refluxing acetonitrile (20 mL) in the presence of $PdCl_2$ (25 mg, 0.14 mmol, 5 mol %) for 8 h. The reaction mixture was diluted with ether (50 mL) and washed with a 1:1 mixture of aqueous NH_3 and brine (50 mL). The ethereal layer was dried (Na_2SO_4) and concentrated to give a mixture of 2-octyl-1-pyrroline (**5a**) and 6-heptyl-2,3,4,5-tetrahydropyridine (**6a**) in quantitative yield. NMR analysis of the product proved the ratio of **5a** and **6a** was 83:17: ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J = 6.4 Hz), 1.20-1.48 (9.66 H, m), 1.59 (2 H, m), 1.85 (0.83 H, quint, J = 7.3 Hz), 1.86 (0.83 H, quint, J = 7.3 Hz), 2.13 (1.36 H, m), 2.32 (1.66 H, tt, J = 1.7, 7.6 Hz), 2.46 (1.66 H, tt, J = 1.7, 7.6 Hz), 3.54 (0.34 H, m), 3.80 (1.66 H, tt, J = 1.7, 7.3 Hz).

The same treatment of 1-methyl-4-undecynylamine (**2b**) as above gave a mixture of 2-heptyl-5-methyl-1-pyrroline (**5b**) and 6-hexyl-2-methyl-2,3,4,5-tetrahydropyridine (**6b**) quantitatively in the ratio of 80:20: ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.0 Hz), 1.23 (0.6 H, d, J = 6.8 Hz), 1.25 (2.4 H, d, J = 6.8 Hz), 1.20-1.75 (10.8 H, m), 2.13 (2 H, m), 2.36 (1.6 H, m), 2.50 (1.6 H, m), 3.45 (0.2 H, m), 4.06 (0.8 H, m).

Registry No. **1a**, 135469-67-9; **1a** alcohol, 55182-73-5; **1b**, 135469-68-0; **1b** alcohol, 135469-87-3; **1c**, 98551-99-6; **1c** alcohol, 14916-80-4; **1d**, 135469-69-1; **1d** alcohol, 135469-88-4; **1e**, 135469-70-4; **1e** alcohol, 10229-11-5; **1f**, 135469-77-1; **1f** alcohol, 135469-85-1; **2a**, 135469-71-5; **2a** alcohol, 92051-75-7; **2b**, 135469-72-6; **2b** ketone, 132716-18-8; **3a**, 112218-11-8; **3a** alcohol, 88109-70-0; **3b**, 135469-73-7; **3b** ketone, 135469-84-0; **3c**, 135469-74-8; **3c** alcohol, 41547-21-1; **3d**, 135469-75-9; **3d** alcohol, 135504-80-2; **3e**, 135469-76-0; **3e** alcohol, 69936-53-4; **3f**, 135469-78-2; **3f** alcohol, 135469-86-2; **4**, 135469-79-3; **4** alcohol, 37011-88-4; **5a**, 135469-80-6; **5b**, 128741-64-0; **5c**, 64319-86-4; **5d**, 700-91-4; **5f**, 135469-83-9; **6a**, 5832-27-9; **6b**, 135469-81-7; **6c**, 1604-01-9; **6e**, 135469-82-8; **6f**, 83019-11-8; $PdCl_2(MeCN)_2$, 14592-56-4; n-$C_5H_{11}C{\equiv}CH$, 628-71-7.

Synthesis of Substituted Furans by Palladium-Catalyzed Cyclization of Acetylenic Ketones

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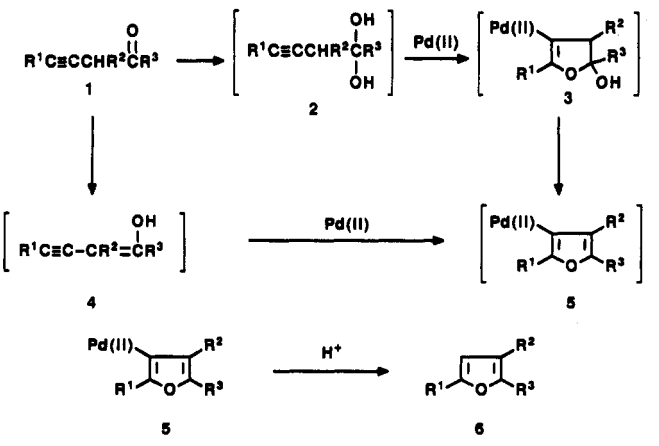
Palladium-catalyzed cyclization of β,γ-acetylenic ketones gives furans by intramolecular oxypalladation and subsequent protodemetalation. 3-Allylfurans were exclusively obtained by trapping the intermediate 3-furylpalladium species with allyl halides in the presence of 2,2-dimethyloxirane as a proton scavenger.

Substituted furans have been usually synthesized either by intramolecular reactions of 1,4-diketones or by the introduction of substituents to furan rings.[1-3] Various modifications of these methods have been extensively studied.[4-7] The recently reported Ta- or Nb-mediated coupling reaction of an alkyne, an aldehyde, and an isocyanide[8] as well as the Ag(I)-catalyzed cyclization of allenyl ketones[9] have opened novel methodologies for the synthesis of 2,3,5-trisubstituted furans. Danheiser et al. reported another synthesis of substituted furans by the reaction of allenylsilanes with acid chlorides in the presence of aluminum chloride.[10] Furans have also been prepared from acetylenic alcohols;[11-23] 2,5-dimethylfuran was prepared from 3-hexen-5-yn-1-ol,[11] and 2,5-di- or 2,3,5-trisubstituted furans were obtained from 2-methoxy-3-alkyn-1-ols by means of palladium catalysis.[24] A key step of the latter method is an intramolecular oxypalladation of the starting acetylenic alcohols to give 3-furylpalladium intermediates.

Scheme I



The same intramolecular oxypalladation was expected to proceed from an appropriate acetylenic ketone when an

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