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Reaction of 3-chloropyrazine 1-oxide (**1**) with 1-hexyne (**2a**) in the presence of tetrakis(triphenylphosphine)-palladium(0) and potassium acetate in DMF afforded 3-(1-hexynyl)pyrazine 1-oxide (**3a**) and 3-(2-butyl-1-octen-3-ynyl)pyrazine 1-oxide (**4a**). The novel formation of **4a** was elucidated to result from codimerization of **3a** with **2a**. The details of reaction are discussed on the basis of findings in palladium(0)-catalyzed reaction of other chloroheterocycles.

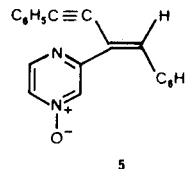
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Palladium-catalyzed coupling reactions of terminal acetylenes with halogenated six-membered *N*-heteroaromatics are a method of choice to connect carbon substituents to the heterocyclic ring [2]. Unlike the extremely poor reactivity of chlorobenzene in the Heck arylation, chloropyrazines [2-4] and their *N*-oxides [4] are capable of undergoing carbon-carbon bond formation with acetylenes in the presence of palladium catalyst to yield the alkynyl substituted pyrazines. We report here the novel formation of another class of compounds, alkenynylpyrazines, a codimeric product of the alkynylpyrazine with terminal acetylene employed initially, in the above reaction.

Under the standard reaction conditions using copper (I) iodide and an alkylamine solvent [5], the palladium-catalyzed alkylation of 3-chloropyrazine 1-oxide (**1**) with 1-hexyne (**2a**) could not be effected. When the *N*-oxide **1** was treated with 1.5 equivalents each of **2a** and potassium acetate [4] in DMF at 70° for 2 hours in the presence of 5 mole % of tetrakis(triphenylphosphine)palladium(0), the coupling reaction ensued leading to a 78% yield of 3-(1-hexynyl)pyrazine 1-oxide (**3a**) together with an 8% yield of codimeric product whose spectral data identified it as (*E*)-enyne **4a**. Regiospecific codimerization on the side chain has been fully established by ¹H nmr spectrum showing a singlet at δ 6.47 as a sole vinyl hydrogen.

Assignment of the (*E*) configuration depends on the low-field shift of the allyl hydrogens which arises from deshielding by diamagnetically anisotropic effects of the *cis*-situated pyrazine ring [6]. The ¹³C nmr spectrum was unequivocally consistent with the assigned structure. Its ir spectrum, however, exhibits very weak absorption of acetylenic group.

A similar codimerization was observed in the palladium mediated reaction of **1** with phenylacetylene (**2b**). In addition of arylation product **3b**, heating at 100° for 2 hours gave two codimeric isomers, which were tentatively identified with (*E*)-**4b** and (*Z*)-**5** by comparing their vinyl hydrogen shifts at δ 8.28 and 7.03, respectively, with those of (*E*)-3-(2-phenylethenyl)pyrazine 1-oxide [7] at δ 7.80 and 6.97 (*J* = 16 Hz). Their geometric arrangement is speculated from the fashion of codimerization in **4a**. 2-Propyn-1-ol and 3-methoxy-1-propyne reacted with the *N*-oxide **1** in the presence of palladium catalyst under the similar conditions, but any of the isolated products could not be identical with the anticipated compounds **3** and **4** and/or its regioisomers.



Changing the substrate in the palladium-catalyzed reaction with **2a** revealed the scope of arylation as well as codimerization. 2-Chloropyrazine (**6**) was converted into arylation product 2-(1-hexynyl)pyrazine (**7**) along with two regioisomeric codimers **8** and **9**. Stereochemistry of those codimers was definitely confirmed by their ¹H nmr spectra in the similar manner described in that of **4a**. A supplementary proof for structural assignment of **9** is the appearance of a triplet at δ 6.40 corresponding to the vinyl hydrogen coupled (7.6 Hz) with allyl ones. On the other hand, palladium-catalyzed reaction of 2-chloropyrazine

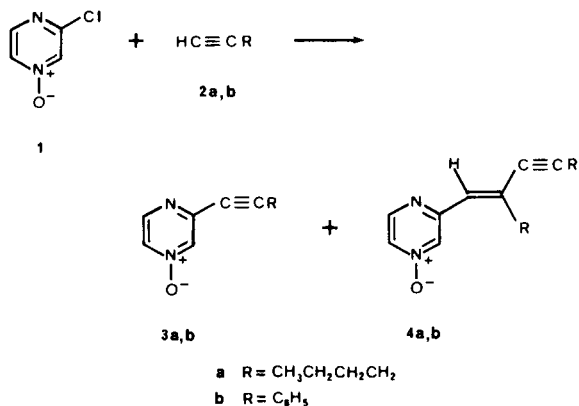


Table 1

Reaction of Chloroheterocycles with Terminal Acetylenes 2 [a]

Substrate	Acetylene	Reaction conditions °C/hours	Yield/% (Product)		
			ethyne	1-en-2-yne	1-en-1-yne
1	2a	70/2	79 (3a)	8 ((E)-4a)	0
1	2b	100/2	27 (3b)	17 ((E)-4b)	21 ((Z)-5)
6	2a	70/4	69 (7)	10 ((E)-8)	5 ((Z)-9)
10	2a	70/4	0	0	0
11	2a	70/4	0	0	0
12	2a	70/4	61 (13)	0	0

[a] The reaction was carried out by using 1.5 equivalents each of the terminal acetylene 2 and potassium acetate with 5 mole % of tetrakis(triphenylphosphine)palladium(0) in DMF.

1-oxide (10) resulted in the recovery of only 39% of the starting material. The failure of coupling reaction is believed to be due to catalyst agglomeration or metal formation from pyrazinyl palladium complex formed initially with the adjacent oxygen atom in the *N*-oxide function prior to reacting the metal complex with terminal acetylene 2a. Although 3-bromopyridine has been shown to undergo palladium-catalyzed coupling with 2a [8], 3-chloropyridine (11) did not react. In contrast, 2-chloropyridine (12) afforded a 61% yield of 2-(1-hexynyl)pyridine (13) as a single product. These results are summarized in Table 1.

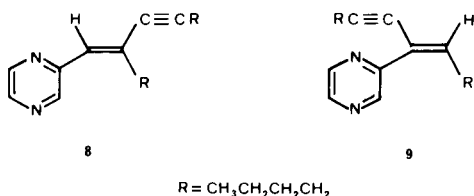


Table 2

Reaction of 1 with 2a [a]

Equivalents of 2a	Reaction time/hours	Yield/%		total
		3a	4a	
1.5	2	79	8	87
1.5	4	71	15	86
1.5 [b]	4	71	14	85
3.0	4	59	30	89

[a] The reaction was performed by using equimolar amounts of 2a and potassium acetate with 5 mole % of tetrakis(triphenylphosphine)palladium(0) in DMF at 70°. [b] 18-Crown-6 (10 mole %) was added to the reaction mixture

In terms of simplicity of products and ease of their separation, the palladium-catalyzed reaction of 1 with 2a was further examined to define the details of codimerization. Prolonging the reaction time to 4 hours at 70° increased a proportion of 4a in almost the same total yields. Using more acetylene 2a enhanced the trend, nevertheless complete conversion into 4a could not be achieved even by treating with 3 equivalents of 2a. An addition of crown ether [9] to the above reaction mixture had no effect on the yields and ratio of 3a and 4a. These results are summarized in Table 2.

Pathway to 4a was clearly elucidated by pursuing the progress of reaction by tlc chromatography, *i.e.*, the alkynylpyridazine 3a initially formed, and after consumption of the starting material 1, which underwent additional codimerization with the acetylene 2a leading to 4a. This sequence can not conflict with the findings in experiments of the longer reaction time or using the large excess acetylene. Furthermore, we have found that the codimerization proceeds in the presence of acetic acid, *i.e.*, such a palladium-mediated reaction starting from 3a afforded a 14% yield of 4a together with 47% of recovered starting material after heating at 70° for 2 hours. The palladium-catalyst requirement in the above conversion was evident by a control experiment excluding the catalyst.

Recent works [10,11] have shown that homo-coupling and cross-coupling of terminal acetylenes with transition metal complex involve *cis* addition of the acetylene across the carbon-carbon triple bond of another molecule to yield a single geometric isomer of enyne compound. The observed stereochemistry in 4a, 8 and 9 is attributed to cross-coupling in the same fashion. On the other hand, incorporating an electron-deficient internal acetylene conjugated with methoxycarbonyl or phenylsulfonyl group in the reaction of a terminal acetylene with palladium acetate

and triarylphosphine has proved to lead only to the cross-coupling products [12]. Therefore, the difference of reactivity between pyrazine and pyridine compounds is rationalized to electron-withdrawing effects of those heterocyclic rings on the carbon-carbon triple bond. Another work [13] demonstrated that success of the cross-coupling reaction rests on less sterically crowded circumstances around the metal of the complex. Presumably, acetic acid formed on the arylation step would take part in reduction of bulky trisphenylphosphine ethynyl palladium complex to smaller species of high reactivity.

EXPERIMENTAL

General

All melting points were determined in capillary tubes on a Büchi 535 apparatus and are uncorrected. The boiling points are uncorrected. The ir spectra were recorded on a Hitachi 260-10 or a JASCO IR-810 spectrometer, ^1H and ^{13}C nmr spectra (deuteriochloroform) on a JEOL JNM FX-90Q, GX-400, GSX-500 or a Bruker AM-250, AM-400 instrument with tetramethylsilane as the internal standard, and high resolution mass spectra on JEOL JMS DX-300 mass spectrometer.

Palladium-catalyzed Reaction of 3-Chloropyrazine 1-Oxide (1) with 1-Hexyne (2a)

A mixture of **1** (0.262 g, 2.01 mmoles), potassium acetate (0.290 g, 2.95 mmoles), and tetrakis(triphenylphosphine)palladium(O) (0.116 g, 0.10 mmole) was purged by the passage of argon, and DMF (10 ml) and **2a** (0.345 ml, 3.00 mmoles) was respectively added to the above mixture through a septum by syringe. The reaction mixture was heated at 70° for 2 hours and then concentrated to a dark oil under reduced pressure. The residue was passed through a Florisil plug (20 g), eluting with 2:1 hexane-ethyl acetate. The elution was condensed, and the residue was purified by flash chromatography over 45 g of silica gel, eluting with the same solution. The early fractions contained 0.041 g (8%) of **4a**, which was purified by recrystallization from hexane. Later fraction containing **3a** was concentrated to afford 0.279 g (79%), purified by bulb-to-bulb distillation.

Other palladium-catalyzed reactions were performed in the same manner. The physical properties of these products are described below. Assignments in ^1H and ^{13}C nmr spectra were confirmed by H-C two-dimensional nmr spectroscopy.

3-(1-Hexynyl)pyrazine 1-Oxide (3a)

This product had mp $40-41^\circ$; bp $140-145^\circ$ (air bath temperature)/4 mm; ir (potassium bromide): 2230 cm^{-1} ($\text{C}\equiv\text{C}$); ^1H nmr: $\delta = 0.95$ (t, 3H), 1.48 (sextet, 2H), 1.63 (quintet, 2H), 2.48 (t, 2H), 8.00 (dd, 1H, $J = 4.2, 1.5$ Hz), 8.10 (dd, 1H, $J = 1.5, 0.7$ Hz), 8.36 (dd, 1H, $J = 4.2, 0.7$ Hz); ^{13}C nmr: $\delta = 13.49, 19.05, 21.96, 29.89, 76.03, 97.08, 132.15, 135.55, 143.05, 146.67$; ms: m/e 176 (M^*).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}$: C, 68.15; H, 6.87; N, 15.90. Found: C, 68.50; H, 7.08; N, 16.01.

(E)-3-(2-Butyl-1-octen-3-ynyl)pyrazine 1-Oxide ((E)-4a)

This product has mp $72-73^\circ$ (hexane); ir (potassium bromide): 2210 cm^{-1} (weak) ($\text{C}\equiv\text{C}$); ^1H nmr: $\delta = 0.92$ (t, 3H), 0.95 (t, 3H), 1.37 (sextet, 2H), 1.46 (sextet, 2H), 1.57 (quintet, 2H), 1.60

(quintet, 2H), 2.33 (t, 2H, $\text{C}\equiv\text{CCH}_2$), 2.75 (t, 2H, $\text{C}\equiv\text{CCH}_2$), 6.47 (s, 1H, $\text{C}=\text{CH}$), 7.89 (dd, 1H, $J = 4.0, 1.6$ Hz), 7.95 (dd, 1H, $J = 1.6, 0.7$ Hz), 8.39 (dd, 1H, $J = 4.0, 0.7$ Hz); ^{13}C nmr: $\delta = 13.56, 13.94, 19.24, 21.99, 22.43, 30.58, 30.69, 32.37, 82.73, 94.57, 126.77, 130.45, 133.04, 136.82, 146.28, 155.47$; ms: m/e 258 (M^*), Calcd. 258.1732. Found: 258.1728.

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$: C, 74.09; H, 8.94; N, 10.80. Found: C, 74.48; H, 8.66; N, 10.87.

3-(2-Phenylethynyl)pyrazine 1-Oxide (3b)

This product had mp 156° (ethanol); ir (potassium bromide): 2220 cm^{-1} ($\text{C}\equiv\text{C}$); ^1H nmr: $\delta = 7.38-7.47$ (m, 3H), 7.60-7.62 (m, 2H), 8.04 (dd, 1H, $J = 4.3, 1.5$ Hz), 8.25 (dd, 1H, $J = 1.5, 0.6$ Hz), 8.43 (dd, 1H, $J = 4.3, 0.6$ Hz); ^{13}C nmr: $\delta = 84.06, 94.81, 120.76, 128.63, 130.16, 132.34, 132.88, 136.22, 143.33, 147.42$; ms: m/e 176 (M^*).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.50; H, 4.15; N, 14.17.

(E)-3-(2,4-Diphenyl-1-buten-3-ynyl)pyrazine 1-Oxide ((E)-4b)

This product had mp $156-157^\circ$ (ethanol); ^1H nmr: $\delta = 7.39-7.48$ (m, 6H), 7.57-7.60 (m, 2H), 8.02 (dd, 1H, $J = 4.0, 1.5$ Hz), 8.10-8.12 (m, 2H), 8.28 (s, 1H, $\text{C}=\text{CH}$), 8.43 (dd, 1H, $J = 4.0, 0.9$ Hz), 8.75 (dd, 1H, $J = 1.5, 0.9$ Hz); ^{13}C nmr: $\delta = 85.22, 98.93, 115.15, 122.26, 128.57, 128.65, 129.24, 130.05, 130.22, 131.65, 131.86, 132.20, 135.28, 140.08, 146.13, 155.23$; ms: m/e 298 (M^*), Calcd. 298.1106. Found: 298.1119.

Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.63; H, 4.74; N, 9.31.

(Z)-3-(1-Benzylidene-3-phenyl-2-propynyl)pyrazine 1-Oxide ((Z)-5)

This product had mp 156° (ethanol); ^1H nmr: $\delta = 7.03$ (s, 1H, $\text{C}=\text{CH}$), 7.34-7.36 (m, 3H), 7.40 (s, 5H), 7.47-7.50 (m, 2H), 7.57 (dd, 1H, $J = 1.5, 0.9$ Hz), 7.83 (dd, 1H, $J = 4.3, 1.5$ Hz), 8.35 (dd, 1H, $J = 4.3, 0.9$ Hz); ^{13}C nmr: $\delta = 90.61, 94.74, 122.45, 128.44, 128.46, 129.06, 129.24, 129.39, 130.88, 131.44, 131.85, 132.35, 133.81, 136.28, 146.84, 155.11$; ms: m/e 298 (M^*), Calcd. 298.1106. Found: 298.1073.

Anal. Calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$: C, 80.52; H, 4.73; N, 9.39. Found: C, 80.34; H, 4.69; N, 9.34.

2-(1-Hexynyl)pyrazine (7)

This product had bp 125° (air bath temperature)/2 mm; ir (neat): 2230 cm^{-1} ($\text{C}\equiv\text{C}$); ^1H nmr: $\delta = 0.96$ (t, 3H), 1.50 (sextet, 2H), 1.64 (quintet, 2H), 2.49 (t, 2H), 8.42 (d, 1H, $J = 2.8$ Hz), 8.50 (dd, 1H, $J = 2.8, 1.5$ Hz), 8.61 (d, 1H, $J = 1.5$ Hz); ^{13}C nmr: $\delta = 13.65, 19.11, 22.04, 30.23, 77.82, 95.76, 142.37$ (2C), 144.32, 147.64; ms: m/e 160 (M^*).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.65; H, 7.54; N, 17.46.

(E)-2-(2-Butyl-1-octen-3-ynyl)pyrazine ((E)-8)

This product had bp 125° (air bath temperature)/2 mm; ir (neat): 2210 cm^{-1} (weak) ($\text{C}\equiv\text{C}$); ^1H nmr: $\delta = 0.92$ (t, 3H), 0.95 (t, 3H), 1.38 (sextet, 2H), 1.47 (sextet, 2H), 1.59 (quintet, 2H), 1.62 (quintet, 2H), 2.39 (t, 2H, $\text{C}\equiv\text{CCH}_2$), 2.78 (t, 2H, $\text{C}\equiv\text{CCH}_2$), 6.67 (s, 1H, $\text{C}=\text{CH}$), 8.31 (d, 1H, $J = 2.4$ Hz), 8.41 (d, 1H, $J = 1.5$ Hz), 8.52 (dd, 1H, $J = 2.4, 1.5$ Hz); ^{13}C nmr: $\delta = 13.61, 13.98, 19.25, 22.00, 22.43, 30.61, 30.81, 32.05, 83.16, 93.35, 128.78, 134.43, 141.47, 143.81, 145.45, 152.22$; ms: m/e 242 (M^*).

Anal. Calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.29; H, 11.36; N, 14.48.

(Z)-2-(1-Pentylidene-2-heptynyl)pyrazine ((Z)-9).

This product had bp 125° (air bath temperature)/2 mm; ¹H nmr: δ = 0.87 (t, 3H), 0.93 (t, 3H), 1.32 (sextet, 2H), 1.43 (quintet, 2H), 1.45 (sextet, 2H), 1.58 (quintet, 2H), 2.37 (t, 2H, C≡CCH₂), 2.48 (q, 2H, C=CCH₂), 6.40 (t, 1H, C=CH), 8.42 (d, 1H, J = 2.4 Hz), 8.55 (dd, 1H, J = 2.4, 1.5 Hz), 8.82 (d, 1H, J = 1.5 Hz); ¹³C nmr: δ = 13.54, 13.78, 19.01, 21.99, 22.29, 29.29, 30.76, 31.46, 80.27, 89.63, 119.71, 142.15, 143.11, 143.73, 145.02, 145.20; ms: m/e 242 (M⁺), Calcd. 242.1783. Found: 242.1775.

Anal. Calcd for C₁₆H₂₂N₂: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.41; H, 11.31; N, 14.54.

2-(1-Hexynyl)pyridine (13).

This product had bp 110° (air bath temperature)/2 mm, lit [14] bp 79-81°/1 mm; ir (neat): 2230 cm⁻¹ (C≡C); ¹H nmr: δ 0.94 (t, 3H), 1.49 (sextet, 2H), 1.62 (quintet, 2H), 2.45 (t, 2H), 7.17 (ddd, 1H, J = 7.6, 4.9, 1.2 Hz), 7.36 (dt, 1H, J = 7.6, 1.2 Hz), 7.60 (td, 1H, J = 7.6, 1.8 Hz), 8.54 (ddd, 1H, J = 4.9, 1.8, 0.9 Hz); ¹³C nmr: δ = 13.61, 19.04, 22.06, 30.44, 80.45, 91.22, 122.20, 126.76, 136.00, 144.19, 149.81.

Anal. Calcd for C₁₁H₁₃N: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.79; H, 8.25; N, 8.81.

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