ω-Methoxylation and Hydration of Ethynyl-*N*-heteroarenes

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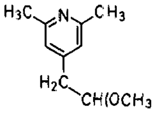
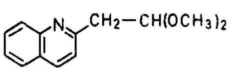
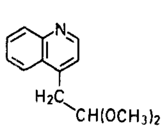
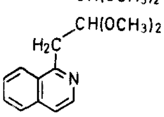
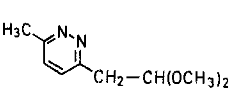
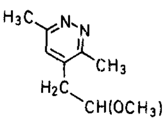
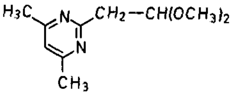
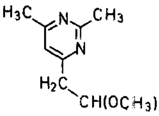
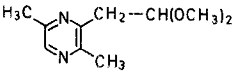
We have recently reported[1] a general method for the synthesis of ethynyl-*N*-heteroarenes (**1a–o**) by condensation of halogenated *N*-heteroarenes with trimethylsilylacetylene and desilylation of the resultant trimethylsilylethynyl-*N*-heteroarenes with potassium hydroxide in aqueous methanol. The present paper deals with the transformation of these ethynyl compounds into the corresponding 2-methoxyethenyl, 2,2-dimethoxyethyl, and acetyl compounds.

On investigating the addition of methanol to ethynyl-*N*-heteroarenes (**1**) under basic conditions we found that compounds **1** can be divided into two groups as regards their reactivity. The first group consists of the compounds having the ethynyl group at an active position (**1c, d, f, g, j–m, o**), the other group contains the ethynyl group at an inactive position (**1b, e, h, i, n**). When the compounds belonging to the first group were heated with sodium methoxide in methanol under reflux, heteroaryl-substituted acetaldehyde acetals (**2**) were obtained in satisfactory yields. For example, 4-ethynyl-2,6-dimethylpyridine (**1c**) was converted into 2,6-dimethylpyridine-4-acetaldehyde dimethyl acetal (**2c**; 67%) under these conditions. The ^{1}H-N.M.R. spectrum of compound **2c** shows the signals of two methoxy groups and of a CH_2—CH group and is thus in agreement with the assigned structure.

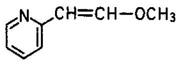
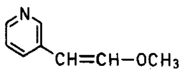
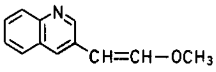
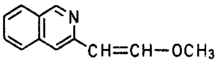
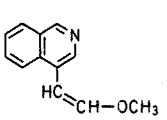
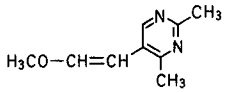
The ethynyl compounds of the second group are fairly resistent to the addition of methanol; even after prolonged reaction times, the products isolated are methoxyethenyl-*N*-heteroarenes (**3**) resulting from the addition of only one molecule of methanol. For example, the reaction of 3-ethynylpyridine (**1b**) with sodium methoxide in boiling methanol (72 h) afforded 3-(2-methoxyethenyl)-pyridine (**3b**, 55%) as the only product. According to the ^{1}H-N.M.R. spectrum, the side chain has the *Z* configuration (see Table 2).

Table 1. *C*-(2,2-Dimethoxyethenyl)-*N*-heteroarenes (**2**)

Product	Yield [%]	b.p. [°C]/ torr	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]			
				—CH_2—	—CH=	—$(OCH_3)_2$	other protons
2c 	67	137–138°/4	$C_{11}H_{17}NO_2$ (195.25)	2.95 (d, 2H, *J*=6 Hz)	4.73 (t, 1H, *J*=6 Hz)	3.26 (s, 6H)	6.85 (s, 2H)
2d 	89	145–148°/1	$C_{13}H_{15}NO_2$ (217.3)	3.30 (d, 2H, *J*=6 Hz)	4.91 (t, 1H, *J*=6 Hz)	3.36 (s, 6H)	7.2–8.3 (m, 6H)
2f 	85	134–136°/1	$C_{13}H_{15}NO_2$ (217.3)	3.38 (d, 2H, *J*=6 Hz)	4.70 (t, 1H, *J*=6 Hz)	3.33 (s, 6H)	7.38 (d, 1H, *J*=5 Hz); 7.5–7.9 (m, 2H); 7.9–8.3 (m, 2H); 8.80 (d, 1H, *J*=5 Hz)
2g 	92	145–153°/1	$C_{13}H_{15}NO_2$ (217.3)	3.63 (d, 2H, *J*=6 Hz)	5.02 (t, 2H, *J*=6 Hz)	3.35 (s, 6H)	7.4–8.0 (m, 4H); 8.0–8.5 (m, 1H); 8.48 (d, 1H, *J*=6 Hz)
2j 	63	131–132°/4	$C_9H_{14}N_2O_2$ (182.2)	3.10 (d, 2H, *J*=6 Hz)	4.62 (t, 1H, *J*=6 Hz)	3.30 (s, 6H)	2.62 (s, 3H); 7.10 (s, 2H)
2k 	60	140–143°/3	$C_{10}H_{16}N_2O_2$ (196.2)	3.00 (d, 2H, *J*=6 Hz)	4.73 (t, 1H, *J*=6 Hz)	3.34 (s, 6H)	2.56 (s, 3H); 2.59 (s, 3H); 7.07 (s, 1H)
2l 	81	110–114°/5	$C_{10}H_{16}N_2O_2$ (196.2)	3.05 (d, 2H, *J*=6 Hz)	4.99 (t, 1H, *J*=6 Hz)	3.27 (s, 6H)	2.30 (s, 6H); 6.76 (s, 1H)
2m 	78	131–133°/20	$C_{10}H_{16}N_2O_2$ (196.2)	3.10 (d, 2H, *J*=6 Hz)	4.85 (t, 1H, *J*=6 Hz)	3.32 (s, 6H)	2.32 (s, 3H); 2.43 (s, 3H); 6.81 (s, 1H)
2o 	75	137–139°/4	$C_{10}H_{16}N_2O_2$ (196.2)	2.93 (d, 2H, *J*=6 Hz)	4.73 (t, 1H, *J*=6 Hz)	3.30 (s, 6H)	2.48 (s, 3H); 2.52 (s, 3H); 8.10 (s, 1H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.34; H, ±0.19; N, ±0.27.

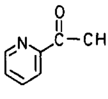
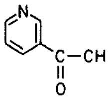
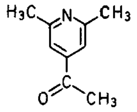
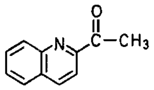
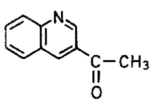
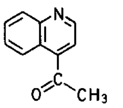
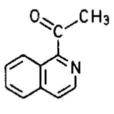
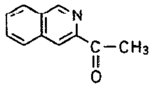
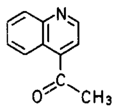
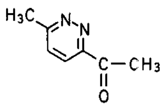
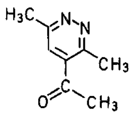
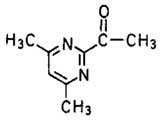
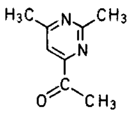
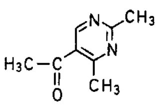
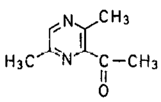
Table 2. (*Z*)-(2-Methoxyethenyl)-*N*-heteroarenes (3)

Product		Yield [%]	b.p. [°C]/torr	Molecular formula[a]	^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$) δ [ppm] —OCH$_3$	—CH=CH—	other protons
3a		60	76-77°/20	C_8H_9NO (135.2)	3.83 (s, 3H)	5.36 (d, 1H, *J*=7 Hz); 6.33 (d, 1H, *J*=7 Hz)	6.9-8.0 (m, 3H); 8.3-7.6 (m, 1H)
3b		55[b]	123-125°/18	C_8H_9NO (135.2)	3.75 (s, 3H)	5.20 (d, 1H, *J*=7 Hz); 6.57 (d, 1H, *J*=7 Hz)	7.0-7.2 (m, 1H); 7.5-7.8 (m, 1H); 8.4-8.7 (m, 2H)
3e		83	135-139°/1	$C_{12}H_{11}NO$ (185.2)	3.71 (s, 3H)	5.27 (d, 1H, *J*=7 Hz); 6.18 (d, 1H, *J*=7 Hz)	7.2-7.8 (m, 3H); 7.9-8.2 (m, 1H); 8.2-8.6 (m, 1H); 8.97 (d, 1H, *J*=2 Hz)
3h		77	132-140°/1	$C_{12}H_{11}NO$ (185.2)	3.90 (s, 3H)	5.65 (d, 1H, *J*=7 Hz); 6.27 (d, 1H, *J*=7 Hz)	7.3-8.0 (m, 4H); 8.13 (s, 1H); 9.02 (s, 1H)
3i		85	140-142°/1	$C_{12}H_{11}NO$ (185.2)	3.70 (s, 3H)	5.67 (d, 1H, *J*=7 Hz); 6.32 (d, 1H, *J*=7 Hz)	7.4-8.0 (m, 4H); 9.00 (s, 2H)
3n		65[b]	102-104°/16	$C_9H_{12}N_2O$ (164.2)	3.79 (s, 3H)	5.13 (d, 1H, *J*=7 Hz); 6.60 (d, 1H, *J*=7 Hz)	2.37 (s, 3H); 2.55 (s, 3H); 8.80 (s, 1H)

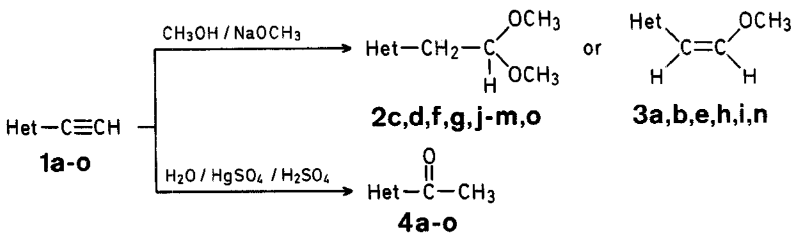
[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.30; H, ±0.30; N, ±0.35.

[b] Reflux time 72 h.

Table 3. Acetyl-*N*-heteroarenes (4)

Product		Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a] or Lit. Data
4a		60	b.p. 76-77°/20	b.p. 188-189°/760[2]
4b		72	b.p. 96-97°/16	b.p. 222-223°/760[3]
4c		56	b.p. 94-97°/4	$C_9H_{11}NO$ (149.2)
4d		75	m.p. 49-51° b.p. 117-119°/1	m.p. 50-52°[4] b.p. 93-95°/0.45[4]
4e		94	m.p. 101-102°	m.p. 100-102°[4]
4f		75	b.p. 115-120°/1	b.p. 118-121°/1[4]
4g		75	b.p. 115-118°/1	b.p. 145-149°/11[5]
4h		60	m.p. 87-88°	88°[6]
4i		58	m.p. 71-72° b.p. 160-170°/1	m.p. 70-71°[5] b.p. 160-164°/8[5]
4j		58	b.p. 124-127°/6	$C_7H_8N_2O$ (136.15)
4k		22	b.p. 97-100°/20	$C_8H_{10}N_2O$ (150.2)
4l		33	b.p. 81-83°/5	b.p. 70-72°/3[7]
4m		52	b.p. 90-92°/16	b.p. 96-98°/20[7]
4n		57	b.p. 122-122°/20	b.p. 62-64°/3[8]
4o		27	b.p. 85-87°/16	$C_8H_{10}N_2O$ (150.2)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.19; H, ±0.22; N, ±0.25.



2-Ethynylpyridine (**1a**) seems to represent an exception. The product obtained from this compound was 2-(2-methoxyethenyl)-pyridine (**3a**), although the ethynyl group of **1a** is located at the 2-position of the pyridine ring. These results show that the addition of methanol to **1a–o** is remarkably affected by the electron-withdrawing ability of the nitrogen atoms located in *N*-heteroaromatic rings.

N-Heteroarenes having an acetaldehyde type side chain may be considered to be useful intermediates in organic synthesis, but prior to our present work no systematic investigation on the preparation of these compounds has been reported.

In addition to the above experiments, we investigated the hydration of compounds **1a–o** under acidic conditions. Without exception, the reaction of these compounds with mercury(II) sulfate/sulfuric acid in aqueous acetone afforded the methyl ketones **4a–o** in 22–94% yields. These results show that the hydration of ethynyl-*N*-heteroarenes provides a useful method for the synthesis of acetyl-*N*-heteroarenes since the starting compounds **1** are now readily available[1].

Methoxylation of Ethynyl-*N*-heteroarenes (1a–o); General Procedure:
A mixture of the ethynyl-*N*-heteroarene **1** (2 mmol) and methanolic sodium methoxide prepared from sodium (0.23 g, 10 mmol) and dry methanol (10 ml) is refluxed for 5 h. After removal of the solvent, water (20 ml) is added to the residue and the mixture is extracted with chloroform (3 × 20 ml). The organic extract is distilled under reduced pressure to give the pure product **2** or **3** as a liquid.

Table 4. Spectral Data of Acetyl-*N*-heteroarenes (**4**)

4	I.R. ($CHCl_3$) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]	
		—CO—CH_3	other protons
a	1700	2.62 (s, 3 H)	7.6–8.1 (m, 3 H); 8.5–8.8 (m, 1 H)
b	1700	2.60 (s, 3 H)	7.4–8.2 (m, 2 H); 8.6–9.3 (m, 2 H)
c	1700	2.65 (s, 3 H)	2.47 (s, 6 H); 7.05 (s, 2 H)
d	1695	2.87 (s, 3 H)	7.2–8.5 (m, 6 H)
e	1695	2.71 (s, 3 H)	7.3–8.4 (m, 4 H); 8.67 (d, 1 H, $J=3$ Hz); 9.37 (d, 1 H, $J=3$ Hz)
f	1685	2.73 (s, 3 H)	7.3–8.0 (m, 3 H); 8.0–8.7 (m, 2 H); 8.98 (d, 1 H, $J=4$ Hz)
g	1690	2.88 (s, 3 H)	7.4–8.4 (m, 4 H); 8.57 (d, 1 H, $J=7$ Hz); 8.8–9.1 (m, 1 H)
h	1690	2.85 (s, 3 H)	7.5–8.3 (m, 4 H); 8.46 (s, 1 H); 9.27 (s, 1 H)
i	1680	2.72 (s, 3 H)	7.4–8.2 (m, 3 H); 8.6–9.1 (m, 1 H); 9.00 (s, 1 H); 9.30 (s, 1 H)
j	1700	2.87 (s, 3 H)	2.80 (s, 3 H); 7.40 (d, 1 H, $J=8$ Hz); 8.03 (d, 1 H, $J=8$ Hz)
k	1695	2.75 (s, 3 H)	2.52 (s, 3 H); 2.70 (s, 3 H); 7.23 (s, 1 H)
l	1700	2.58 (s, 3 H)	2.50 (s, 6 H); 7.02 (s, 1 H)
m	1700	2.66 (s, 3 H)	2.52 (s, 3 H); 2.57 (s, 3 H); 7.45 (s, 1 H)
n	1700	2.67 (s, 3 H)	2.45 (s, 3 H); 2.68 (s, 3 H); 8.50 (s, 1 H)
o	1700	2.74 (s, 1 H)	2.45 (s, 3 H); 2.68 (s, 3 H); 8.50 (s, 1 H)

Hydration of Ethynyl-*N*-heteroarenes (1a–o); General Procedure:
A mixture of the ethynyl-*N*-heteroarene **1** (5 mmol), mercury(II) sulfate (1.484 g, 5 mmol), conc. sulfuric acid (0.981 g, 10 mmol), and 70–85% aqueous acetone (20 ml) is refluxed for 2 h. After removal of the solvent, the residue is made alkaline with aqueous potassium carbonate and extracted with chloroform (3 × 20 ml). The organic extract is purified by column chromatography on alumina using chloroform as eluent. Recrystallization or distillation of the product obtained upon evaporation affords the pure acetyl compound **4**.

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