

Regioselective Addition of 2-Pyridinone to C-2 of a Haloalkyne

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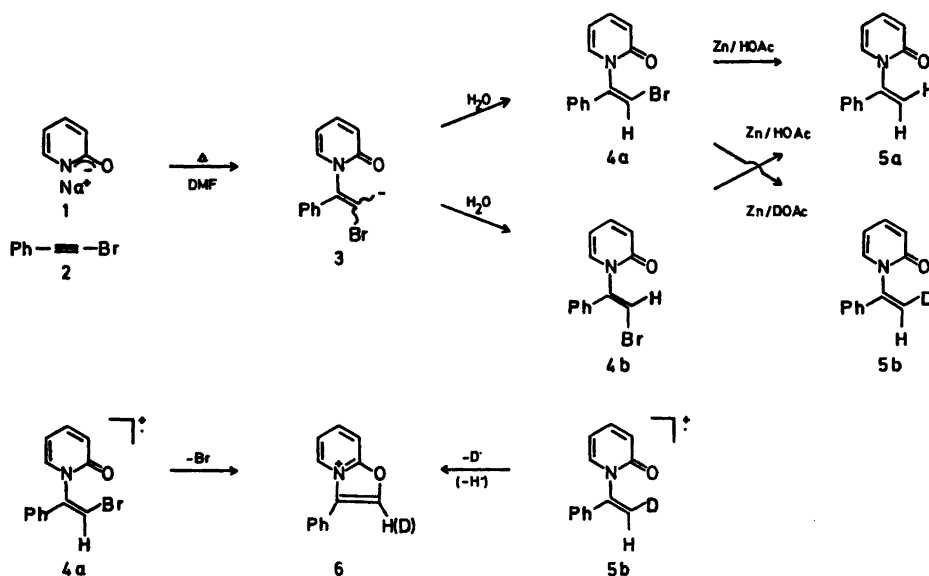
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2-Pyridinone is *N*-vinylated by adduct formation with 1-bromophenylacetylene. The N—C bond is formed with C-2 in the alkyne. Stereochemical assignments are based on spectroscopy and X-ray structure determination.

Nucleophilic attack on 1-haloalkynes may occur at either C-1, C-2 or at the halogen atom; the latter pathway leads *via* an ion-molecular pair to an alkyne.¹ Attack at C-1 followed by halide expulsion from the carbanionic intermediate also results in alkyne formation. Attack at C-2, however, requires migration of a C-2 substituent to C-1 for alkyne formation.¹ Vinyl derivatives are formed when the intermediates from attack at C-1 or C-2 are trapped by protonation. In the case of phenyl

substituted alkynes, nucleophilic attack at C-1 by sulfur,^{2,3} by amino⁴ and by hydroxy nucleophiles⁵ seems to be favoured. From a study of 1-haloalkynes and lactams we herein report on the reaction between 1-bromophenylacetylene and 2-pyridinone.

When the sodium salt of 2-pyridinone was heated with 1-bromophenylacetylene in DMF at 50 °C two isomeric 1:1 adducts were formed in equal amounts. On further heating at higher temperature (100 °C) the isomer mixture was converted into one of the isomers. When the isomers were heated in the absence of a base no isomerisation took place. Neutralisation of the cold reaction mixture with acetic acid-*d*₁ gave no deuterium incorporation, probably due to the presence of water in the solvent



Scheme 1.

despite attempted drying, or due to protonation of the carbanionic intermediate **3** by DMF. The latter course is related to the formation of lithium *N,N*-dimethylformamide from DMF and lithium diisopropylamide.⁶

In the IR spectra the absorption at 1660 cm⁻¹ (CO) is consistent with N–C rather than O–C bond formation. Also vinylation of 2-pyridinones with other alkyne reactants normally occurs at the nitrogen atom.^{7–9} In the alkyne a nucleophilic attack at C-2 was expected since the products of the reaction are olefinic. The products were identified as the stereoisomers **4a** and **4b**. The vinyl proton of the thermodynamically more stable isomer in the ¹H NMR spectrum resonated as a singlet at δ 7.05; the vinyl proton in the less stable isomer appeared at δ 7.40. Hydrogenolysis of the pure isomer or the isomer mixture using zinc in acetic acid gave a product with two terminal vinyl protons at δ 5.41 and 5.92 with a *J* 1.3 Hz coupling in accordance with structure **5a**. After hydrogenolysis of the pure isomer in acetic acid-*d*₁ using zinc, the signal for the vinyl proton in the product was at δ 5.92. Therefore the terminal vinyl proton responsible for the signal at δ 5.41 has been introduced by hydrogenolysis of the bromine atom.

The mass spectrum of the pure isomer is characterised by a very small molecular ion and by [M–Br] as the base peak. On the other hand, the isomer mixture gave rise to an additional strong primary fragment due to [M–H]. Previously we have pointed out that the mass spectra of *N*-vinylpyridine-2-thiones are characterised by loss of a substituent from the β -carbon of the vinyl group.¹⁰ The ready expulsion of a β -substituent from **4** can be rationalised by formation of the oxazolo[3,2-*a*]pyridinium ion **6**. In the formation of **6** preferential expulsion of the bromine radical may be expected when the bromine atom and the pyridine ring are *cis*, and hence the product has the (*Z*) configuration. Accordingly, hydrogen elimination is plausible from the (*E*)-isomer. The mass spectrum of the debrominated product has [M–H] as base peak and relative intensity 88 % for [M]. The major primary ions in the mass spectrum of the stereochemically homogeneous monodeuterio derivative, however, were due to [M] 100, [M–H] 89 and

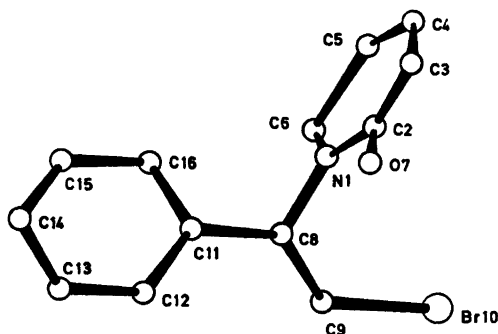


Fig. 1. Molecular geometry.

[M–D] 39 %. This observation may be rationalised by loss of the configuration after electron impact or by the difference in the ease of breakage of the C–D and C–H bonds.

The tentatively assigned structure for the pure bromo isomer has been confirmed as (*Z*)-*N*-(2-bromo-1-phenylvinyl)pyridin-2-one **4a** by X-ray structure determination. A view of the molecule including atomic numbering is given in Fig. 1.* The angle between the planes of the phenyl and pyridine rings is 84°. The bromine atom lies close to the plane of the phenyl ring, and the dihedral angle C9–C8–C11–C16 is 160°. Hence, the 2-bromo-1-phenylvinyl moiety is almost planar and the pyridine ring stands almost perpendicular onto this plane.

The ¹³C NMR spectra for the vinyl isomers **4** are very similar (Fig. 2). In the (*E*)-isomer, in which the bromine and phenyl substituents have the *cis* configuration, the chemical shift for C-2 of the phenyl group is at slightly lower field than in the (*Z*)-isomer.

Gated-(1) decoupled spectra were used in the relative assignments of ¹³C chemical shifts. The α -carbon atoms in pyridine have the highest short range coupling ¹*J*_{CH}.¹¹ Hence, in the spectrum of **5a** the signal at δ 138.4, ¹*J*_{CH} 189 Hz, is assigned to C-6. The latter is also *meta* coupled to H-4, ³*J*_{CH} 7.2 Hz, and *ortho* coupled to H-5, *J* 4.1 Hz. C-2 is identified by its high chemical shift δ 162.0. C-4 resonates at δ 140.1 and is *meta* coupled ³*J*_{CH} 8.8 Hz to H-6 and weakly (< 1 Hz) ²*J*_{CH} coupled to H-3

* A complete list of bond lengths, bond angles and dihedral angles may be obtained from the authors upon request.

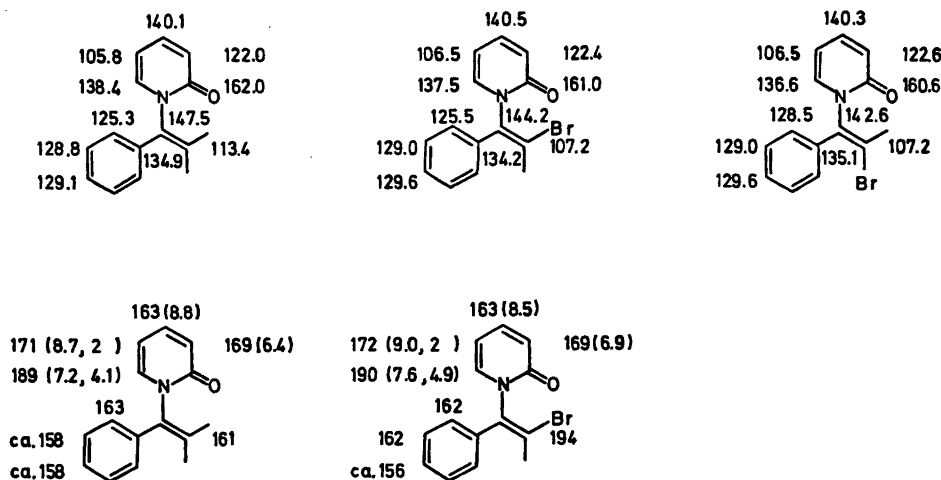


Fig. 2. ^{13}C NMR spectral data.

and H-5. Both C-3 and C-5 are strongly *meta* coupled to H-5 and H-3, respectively, $^3J_{\text{CH}}$ 6.8 and 8.3 Hz, and weakly (<1 Hz) *ortho* coupled to H-4. C-5 is also *ortho* coupled to H-6, $^3J_{\text{CH}}$ ca. 2 Hz. The relative assignments of the chemical shifts for C-3 and C-5 are in agreement with data in the literature for 2-pyridinone and *N*-methyl-2-pyridinone. The data for the latter were derived from analyses of heteronuclear double resonance spectra and fine splittings.^{11,12} In the vinyl group the α -carbon atom is at the lower field δ 147.5 since it is attached to a nitrogen atom and lacks one bond coupling. The assignment of chemical shifts in the phenyl substituent is based on a comparison with benzene (δ 128.7) using the relative intensities of the signals as well as influences of steric and electronic factors.¹³ The chemical shifts for the (*E*)-isomer were obtained from a 1:1 isomer mixture of 4.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded in ca. 0.5 M CDCl_3 using a Jeol FX-60 Fourier transform NMR spectrometer operating at 25.2 MHz. The temperature was ca. 32°C. Proton-noise decoupled and gated-(1) decoupled spectra were obtained. The shifts are relative to TMS.

(*Z*)-*N*-(1-Phenyl-2-bromovinyl)pyridin-2-one 4a. Pyridin-2-one was converted into its sodium salt by heating with sodium in toluene and the salt was isolated by evaporation of the solvent.

The sodium salt (1.8 g, 0.015 mol) and 1-bromophenylacetylene¹⁴ (2.9 g, 0.016 mol) in anhydrous DMF (75 ml) were heated at 60°C for 3 h. The reaction was monitored and the products analysed by TLC on silica gel using the system MeCN-PhMe-AcOH 10:10:1; R_F value 0.55 and 0.61 for the (*Z*)- and (*E*)-isomer, respectively. The isomer ratio was 1:1 when the reaction was run as above. When the reaction mixture was heated under reflux for another 30 min only the (*Z*)-isomer was present in the reaction mixture. The cold reaction mixture was neutralised with acetic acid and the solvent distilled off. Water was added to the residue and the mixture extracted with ether. The dried (MgSO_4) ether extracts were evaporated and the residue recrystallised from acetone; m.p. 158–159°C, yield 1.2 g (30%). Anal. $\text{C}_{13}\text{H}_{10}\text{BrNO}$: C, H. ^1H NMR (CDCl_3): δ 7.05 (H-vinyl), aromatic protons not resolved. UV [MeOH, (log ϵ): 303 (3.72), 296(3.72), 257(4.24), 230(4.09) nm. IR (CHCl_3): 1660 cm^{-1} (CO). MS [70 eV; m/e (% rel.int.)]: 275 (<1, [M]), 197(14), 196(100, [M-Br]), 168(7), 167(30), 102(32), 78(16).

(*Z*)- and (*E*)-*N*-(1-Phenyl-2-bromovinyl)pyridin-2-one 4a and 4b. A 1:1 isomer mixture was prepared as above by heating the reactants together at 60°C for 3 h before the reaction was worked up. The yield was 30%. ^1H NMR (CDCl_3): δ 7.40 (H-vinyl for the (*E*)-isomer). MS [70 eV; m/e (% rel.int.)]: 277 and 275 (9+9, [M]), 276 and 274 (64+66, M-H), 197(13), 196(100).

N-(1-Phenylvinyl)pyridin-2-one 5a. The (*Z*)-isomer 4a or the (*Z*)/(*E*)-isomer mixture 4a and 4b (1:1) was dissolved in acetic acid and zinc dust added. The progress of the reaction was monitored by TLC. The reaction had gone

to completion after 4 d at room temperature. The reaction mixture was poured into water and filtered. The filtrate was extracted several times with ether. The dried (MgSO₄) ether extracts were evaporated, and the residual pale yellow oil could be made to crystallize from a small volume of ether; m.p. 88°C. Anal. C₁₃H₁₁NO: C, H. ¹H NMR (CDCl₃): δ 5.41 and 5.92 (CH₂=, *J* 1.3 Hz), aromatic protons not resolved. IR (CDCl₃): 1660 cm⁻¹ (CO). MS [70 eV; *m/e* (% rel.int.)]: 197 (88, [M]), 196 (100), 168 (20), 103 (42), 102 (46), 95 (22).

(*Z*)-*N*-(1-Phenyl-2-deuteriovinyl)pyridin-2-one 5b was prepared as 5a above by using acetic acid-*d*₁. ¹H NMR (CDCl₃): δ 5.92 (H-vinyl). MS [70 eV; *m/e* (% rel.int.)]: 198 (100, [M]), 197 (89), 196 (39), 169 (23), 168 (8), 105 (48), 104 (59), 103 (41), 102 (30), 96 (15), 95 (34).

Crystallographic structure determination. Oscillation and Weissenberg diagrams implied orthorhombic symmetry. The quality of the crystals was poor making a crystallographic determination difficult. The crystals were twinned such that the *c*-axis was doubled. The systematic absences in a close to single crystal were those characteristic of the space groups *Pna*2₁ and *Pmma*. The structure determination later showed the space group to be the non-centrosymmetric *Pna*2₁.

A computer-controlled Syntex P1 four-circle diffractometer with graphite monochromatised MoK α -radiation was used in the determination of cell parameters and the collection of intensity data. The dimensions of the crystal used were ca. 0.5 × 0.15 × 0.1 mm. The temperature was kept at 19 ± 1 °C. Cell parameters were refined by a least-squares treatment of the angular coordinates of fifteen reflections.

The intensity data were collected using the ω -scanning mode with scan speed variable from 2 to 12° min⁻¹ depending on the intensity of the reflection and a scan area of 1°. Background counts were taken for 0.35 × (scan time) with a displacement of 0.85° from the scan midpoint at each side. The intensities of three standard reflections which were remeasured regularly showed no significant variations. Estimated standard deviations were taken as the square root of the total counts with an addition of 2% for experimental uncertainties. Of the 921 reflections measured ($2\theta_{\max} = 45^\circ$), 598 had intensities larger than twice their standard deviations. These were regarded as observed and the remaining were excluded from further calculations. The computer program used, as well as programs subsequently employed, is described elsewhere.¹⁵

The atomic scattering factors for carbon, nitrogen, oxygen and bromine,¹⁶ and for hydrogen¹⁷ were taken from the literature.

The position of the bromine atom was found in a Patterson synthesis, and successive Fourier syntheses revealed the positions of all other non-hydrogen atoms. The structure

Table 1. Fractional atomic coordinates and thermal parameters with estimated standard deviations. The anisotropic temperature factor is given by: $\exp(-2\pi^2[U_{11}(a^*h)^2 + \dots + 2U_{23}(b^*c^*k)])$.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
N1	.135(1)	.669(3)	.293(6)	.034(10)	.035(9)	.074(21)	-.003(8)	.039(20)	.013(19)
C2	.164(1)	.720(5)	.419(6)	.026(15)	.017(16)	.093(29)	-.002(12)	.026(18)	.010(17)
C3	.210(2)	.800(7)	.483(6)	.048(23)	.048(23)	.157(36)	.002(15)	-.000(21)	-.003(24)
C4	.239(1)	.845(5)	.267(13)	.033(19)	.072(21)	.256(65)	.013(15)	-.004(45)	-.054(50)
C5	.220(2)	.809(7)	.130(7)	.062(34)	.050(24)	.127(44)	.004(23)	-.014(27)	.010(32)
C6	.145(2)	.688(5)	.020(7)	.074(45)	.028(19)	.128(38)	.005(24)	.114(36)	.037(25)
O7	.140(2)	.684(5)	.555(4)	.132(21)	.099(20)	.076(15)	.021(18)	-.019(15)	-.005(14)
C8	.079(1)	.567(2)	.243(9)	.038(9)	.043(10)	.046(19)	-.004(8)	.000(19)	.005(23)
C9	.079(1)	.382(2)	.269(9)	.039(9)	.044(11)	.100(18)	.003(8)	.018(30)	-.012(36)
Br10	.148(0)	.237(0)	.264(0)	.047(1)	.055(1)	.081(1)	.007(1)	.006(4)	-.001(4)
C11	.026(1)	.683(2)	.251(8)	.041(11)	.041(10)	.089(21)	-.001(8)	.028(27)	-.013(28)
C12	-.028(1)	.610(2)	.255(8)	.034(10)	.057(11)	.085(17)	-.012(9)	.013(27)	.010(26)
C13	-.078(1)	.719(3)	.247(11)	.055(12)	.058(13)	.073(23)	.022(10)	.003(24)	.001(28)
C14	-.075(1)	.900(3)	.274(7)	.056(12)	.064(15)	.109(24)	.002(11)	.052(28)	.022(30)
C15	-.025(1)	.974(3)	.155(13)	.063(13)	.069(14)	.102(22)	-.013(12)	-.024(12)	-.014(13)
C16	-.027(1)	.867(3)	.161(3)	.059(14)	.045(12)	.020(10)	-.008(11)	-.007(11)	-.001(11)

model was refined to an R of 0.064. Anisotropic thermal parameters were introduced for all non-hydrogen atoms and full-matrix least-squares refinements converged to an R of 0.059 and an R_w of 0.065.

The final structure model indicates some disorder, which may in part be due to the slightly twinned crystal. This and the relatively low overdetermination ratio (4.1) lead to large e.s.d.'s in molecular parameters.

Crystal data. (*Z*)-*N*-(2-Bromo-1-phenylvinyl)-pyridin-2-one, $C_{13}H_{10}BrNO$, space group: $Pna2_1$. Cell dimensions: $a = 22.891(7)$ Å, $b = 7.124(2)$ Å, $c = 9.119(2)$ Å, $V = 1128.4(7)$ Å³, $M = 276.13$ amu, $z = 4$, $D_{calc} = 1.626$ g/cm³. $F(000) = 552$.

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