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Tetrahedron Letters 46 (2005) 5683–5685
Tetrahedron Letters

Facile conversion of pyridine propargylic alcohols to enones: stereochemistry of protonation of allenol

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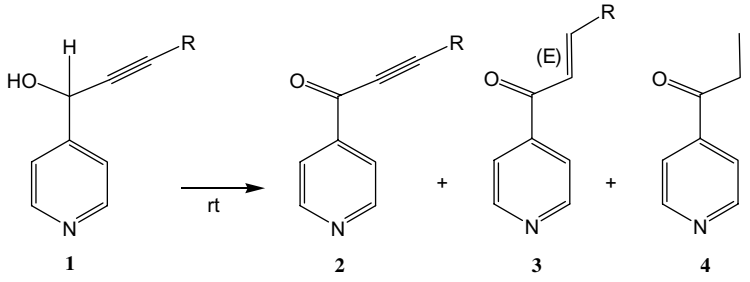
Received 10 May 2005; revised 10 June 2005; accepted 17 June 2005
Available online 6 July 2005

Abstract—The conversion of 4-pyridyl propargylic alcohols **1** to the (*E*)-propenones **3** and propynones **2** occurs under mild reaction conditions, pyridinium chloride in methanol at room temperature. (Z)-4-Pyridyl propenones **11** are detected as initial products when large substituents such as trimethylsilyl, *tert*-butyl and phenyl are attached at C-3 of the propynols and these (*Z*)-enones **11** are isomerised to the (*E*)-isomers **3** under the reaction conditions. In the presence of deuterated solvent, both hydrogens at the double bond of enone **3d** are deuterated. An allenol is proposed as intermediate whose preferential protonation occurs at the less hindered side giving the (Z)-enone. The propargylic alcohols, pyridin-2-yl **12** and quinolin-4-yl **5**, are converted to (*E*)-enones **13** and **7**, respectively.

In a synthetic scheme, we planned to use alcohols of the type 1-(pyridin-4-yl)prop-2-yn-1-ol and found that they are not well documented. Only one reference mentions the compound **1d** as a pink solid that slowly decomposes (NMR in $CDCl_3$).[1] Based on the reported transformation of quinine to quinotoxine under acid–base catalysis,[2] we suspected that the acidic deuterochloroform may contribute to the instability of this propargylic alcohol. Soon we found out that this alcohol **1d** was more stable in THF solution. Since pyridine hydrochloride



1 **2** **3** **4**

Comp.	Reaction condition		Yld (%)	
a R = CH_3	MeOH, PyHCl	15	49	-
b R = Ph	MeOH, PyHCl	10	55	-
c R = t-butyl	MeOH, PyHCl	12	75	-
d R = $SiMe_3$	MeOH, PyHCl	26	52	-
e R = $SiMe_3$	CH_2Cl_2	15	28	8

Keywords: Isomerisation; Propargylic alcohol; Enone; Ynone; Heterocyclic; Pyridinium chloride.
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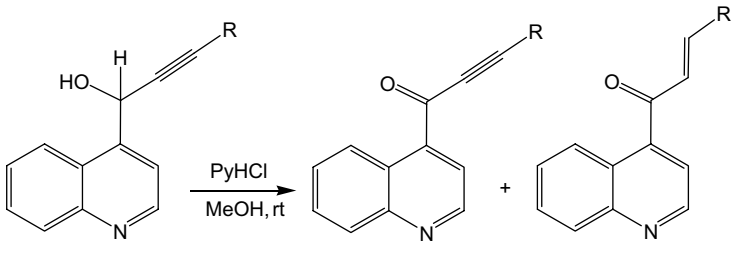
doi:10.1016/j.tetlet.2005.06.087



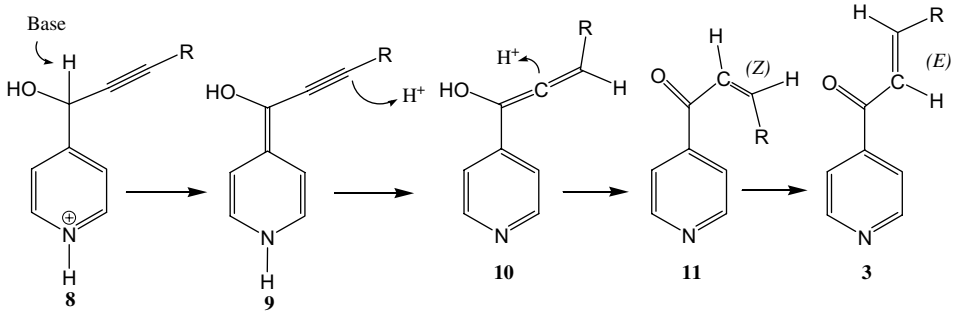
5 **6** **7**

Comp.	Yld (%)	
a R = CH_3	30	36
b R = $SiMe_3$	-	55

is a good acid–base catalyst,[3] we treated the propargylic alcohol **1d** in methanol with pyridine hydrochloride in catalytic amount (5% molar ratio) and found that greater yields of the reaction products were obtained in methanol than those in chloroform and dichloromethane. We isolated two ketones ynone **2d** and (*E*)-enone **3d** by chromatography.[4] Besides the ynone **2d** and enone **3d**, the saturated ketone **4e**[5] was obtained in the reaction of alcohol **1d** in dichloromethane (without addition of pyridinium hydrochloride). We explored the generality of this transformation by variation of the acetylenic substituent. The three alcohols **1a**, **1b** and **1c** underwent the same transformation and the results are presented as well as those obtained for the 1-(quinolin-4-yl)but-2-yn-1-ol **5a** and compound **5b**.

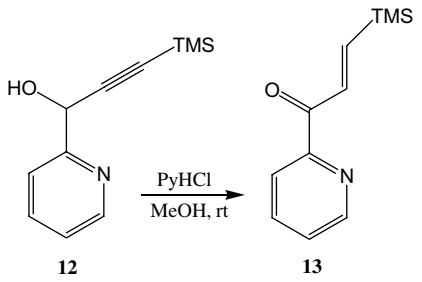
The mechanism shown below was considered. Isomerisation of propargylic alcohols to enones has been described in numerous instances with acid–base (under harsher conditions) or metallic catalysts.[6] It is surprising that the reaction of propargylic alcohol **1** goes to completion under much milder reaction conditions at room temperature in 5 h. So a special feature facilitates the reaction and this is the protonation of the nitrogen to salt **8** which loses the propargylic proton under base catalysis to give the anhydro base **9**. The protonation at the terminal position of the triple bond of **9** with the loss of the proton at the nitrogen gives allenol **10**. The protonation of the allenol **10** at the enolic position gives enone **3**. Model examination of this protonation suggested that the less hindered direction gives the (*Z*)-enone **11**. The approach of the acid cis to the large substituent as trimethylsilyl, phenyl or *t*-butyl is strongly hindered and the protonation occurs at the opposite face leading to the (*Z*)-enone **11**. When the reactions were followed by NMR, the (*Z*)-enones **11b**, **11c** and **11d** were detected initially. These (*Z*)-enone **11** gave rise to the (*E*)-enone **3** by acid isomerisation. With methyl substituted **1a**, the (*Z*) enone **11a** was not detected. When the reaction with **1d** was carried out in MeO^2H, the two vinylic hydrogens of enone **3d** are deuterated. Hence, these two deuteriums must be derived from the deuterated methanol. The protonation of allenol and related species such as allenyl ethers has been described to give at least some (*Z*) isomer.[7] A less likely explanation could be that the isomerisation of methyl (*Z*)-enone **11a** (R = Me) to the (*E*)-enone **3a** is faster than that of the other (*Z*)-enones **11b**, **11c** and **11d**. The isomerisation of the propargylic alcohol, 3-(trimethylsilyl)-1-phenylprop-2-yn-1-ol, was not detected under these conditions even on longer reaction times and higher temperature. So the activation of the propargylic proton by formation of the pyridinium salt is crucial.

The related allylic alcohols at C-4 of pyridine are not more described than the propargylic ones. It is mentioned where the preparation of the allylic alcohol was attempted by addition of the vinylic Grignard reagent to isonicotinaldehyde and the 1-(pyridin-4-yl)propan-1-one was isolated.[8] However, another substituted allylic alcohol is mentioned without comments about its stability.[9]



8 **9** **10** **11** **3**

We prepared the propargylic alcohol at C-2 **12**. The treatment of this alcohol **12** with pyridinium chloride gives the enone **13** in an yield of 42%. The same reasoning as for alcohols **1** applies here. It has been reported that heating of the related allylic alcohol, 1-(pyridin-2-yl)prop-2-en-1-ol, in chloroform at 110 °C for two days gave 1-(pyridin-2-yl)propan-1-one and that the intermediate was trapped.[10]



12 **13**

The ynones **2** and **6** originate from oxidation and were found even when the reaction was carried out under nitrogen. But the saturated ketone **4e** was observed only when the reaction was carried out in CH_2Cl_2. The dismutation of **1** to equal amount of ynone **2** and saturated ketone **4** does not seem to occur in the presence of pyridinium hydrochloride.

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4. To a solution of product **1d** (0.97 mmol) in MeOH (4.0 mL) was added pyridinhydrochloride (49 μmol) at rt. After 5 h, the usual extraction with CH_2Cl_2 was performed. By column chromatography (silica, hexane/EtOAc, 4:1) we separated two products: 3-(trimethylsilyl)-1-(pyridine-4-yl)prop-2-yn-1-one **2d**: Yellow liquid (26%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.30 (s, 9H), 7.87 (dd, J = 6.0, 3.0 Hz, 2H), 8.81 (dd, J = 6.0, 3.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.7, 100.1, 103.2, 122.1, 142.1, 150.9, 176.7; UV/vis (CH_2Cl_2), λ_{max} (ε) = 237 (6610); Ms (FAB$^+$), 204 [M$^+$+H]. Anal. Calcd for $C_{11}H_{13}NOSi$: C, 64.98; H, 6.44; N, 6.89. Found: C, 64.95; H, 6.41; N, 6.85. (*E*)-3-(trimethylsilyl)-1-(pyridine-4-yl)prop-2-en-1-one **3d**: Colourless liquid (52%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11(s, 9H), 7.05 (d, J = 18.8 Hz, 1H), 7.25 (d, J = 18.8 Hz, 1H), 7.60 (dd, J = 6.0, 2.0 Hz, 2H), 8.70 (dd, J = 6.0, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.8, 121.8, 137.4, 143.9, 150.7, 152.7, 189.9; UV/vis (CH_2Cl_2), λ_{max} (ε) = 195 (2900), 231 (4500), 277(2300); Ms (EI): 205 [M$^+$]. Anal. Calcd for $C_{11}H_{15}NOSi$: C, 64.34; H, 7.36; N, 6.82. Found: C, 64.30; H, 7.34; N, 6.85.
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