

Preparation of some heterocyclic enones and ynones by isomerisation of the propargylic alcohols

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The propargylic alcohols were synthesised by treatment of aldehydes with substituted acetylenes. The conversion of propargylic alcohols to propynones and propenones takes place with pyridine hydrochloride in methanol at room temperature. In presence of pyridinium triflate and *p*-toluenesulfonate the propynone was the only product isolated in the isomerisation of alcohol. The silylated propenone undergoes with cyclopentadiene a Diels–Alder cycloaddition to give ketone whose skeleton is related to that of quinine.

Keywords: isomerisation, propargylic alcohol, enone; ynone, heterocyclic

The pyridine ring plays a key role in several biological processes.^{1,2} The quinoline ring system is an important target in synthetic chemistry. It is found in a large number of natural products, many of which have important biological activities.^{3–7} In addition, they are used as dyestuffs and photographic sensitizers.⁸

In a preliminary communication we reported the facile isomerisation of heterocyclic propargylic alcohols to propenones and propynones in the presence of pyridine hydrochloride.⁹ We had shown that this isomerisation occurs when the propargylic hydrogen is activated at C-2 and C-4 in case of pyridine and that the ethylenic protons originated from protons of the solvent. An enolic allene was postulated as an intermediate and its protonation gives a (*Z*) enone subsequently isomerised to the (*E*) form. Related isomerisations have been reported on different systems under various conditions.^{10–20} We now report more examples of this isomerisation and the results obtained with two other pyridinium salts as catalysts and the Diels–Alder reaction of one of these enones whose chemistry has not been explored.

Results and discussions

We prepared in good yields the propargylic alcohols **3** from aldehydes **1** and substituted acetylenes **2**. These alcohols **3** except **3a**, **3m** and **3n** are not too stable and their isomerisation was carried out without delay. Table 1 shows the results of the preparation of the propargylic alcohols **3** and their isomerisation with pyridine hydrochloride catalyst to ynones **4** and enones **5**. The structure of enone **5d** was elucidated by X-ray diffraction (Fig. 1).

We tried with the quinoline alcohol other pyridinium salts: trifluoromethanesulfonate, *p*-toluenesulfonate, and compared the results with those obtained with pyridinium hydrochloride. (Table 2). The ynone **6** was the only product isolated in the presence of pyridinium triflate and pyridinium toluenesulfonate. Enone **7** was found only in the presence of pyridinium hydrochloride. The presence of air seemed to increase the yield of the ynone, but the ynone was also obtained under argon (Table 2). In addition to the ynone and enone, coloured and polar material was obtained.

Concerning the mechanism of the conversion of the propargylic alcohols, the protonation of the nitrogen is an essential step. So the first step is the protonation at the nitrogen to give the pyridinium or quinolinium cation. Now the hydrogen at the alpha position is activated and is abstracted by a base to give the anhydro base **8**. This base **8**

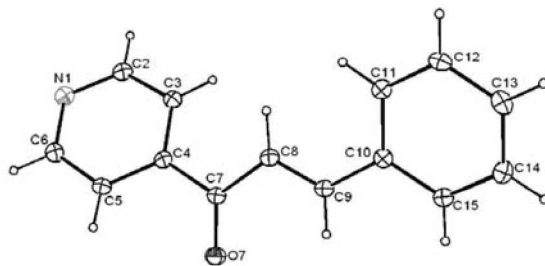
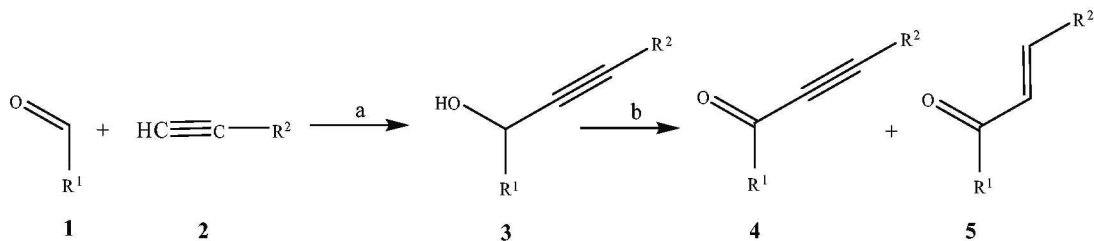


Fig. 1 ORTEP structure of **5d**.

Table 1 Preparation of propargylic alcohols (**3**) and their conversion to ynones (**4**) and enones (**5**) with pyridinium hydrochloride

Compound	R ¹	R ²	3 ^a	4 (ynone)	5 (enone)
			Yield/%	Yield/%	Yield/%
a	Phenyl	Me ₃ Si	100	–	–
b	4-Pyridyl	Me ₃ Si	83	26	52
c	4-Pyridyl	Me	82	15	49
d	4-Pyridyl	Phenyl	90	10	55
e	4-Pyridyl	<i>t</i> -Butyl	96	12	75
f	4-Quinolyl	Me ₃ Si	79	see Table 2	–
g	4-Quinolyl	Me	83	30	36
h	4-Quinolyl	<i>t</i> -Butyl	80	26	37 (<i>E</i>)–18 (<i>Z</i>)
i	4-Quinolyl	Phenyl	74	24	21
k	2-Pyridyl	Me ₃ Si	88	–	42
m	3-Pyridyl ^{21,22}	Me ₃ Si	97	Stable	–
n	3-Pyridyl ^{21,22}	H	–	Stable	–

^aExcept for **3n** prepared from **3m** by removal of the trimethylsilyl group by TBAF.

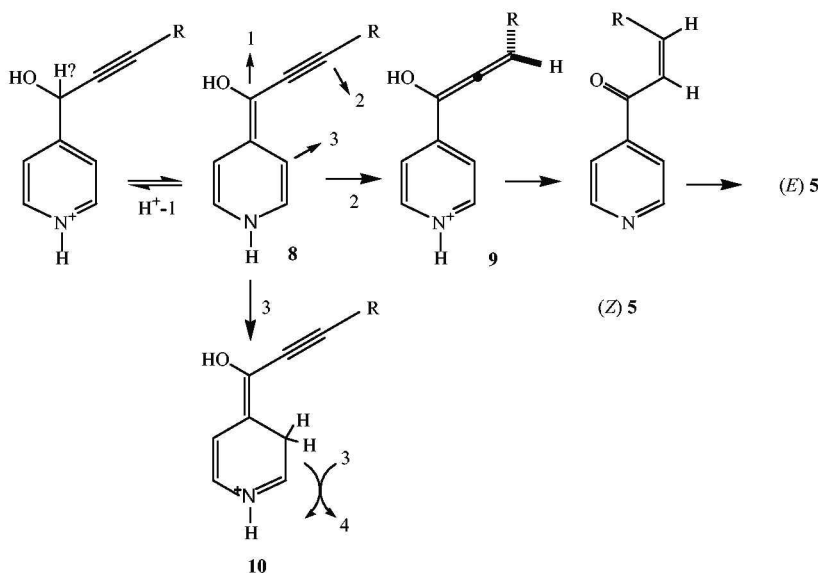


Scheme 1 Reagents and conditions: (a) *n*-BuLi, THF, -78°C (b) $\text{C}_6\text{H}_6\text{NCl}$, MeOH.

Table 2 Conversion of **3f** using various pyridinium salts

PyH ⁺ salt	Atmosphere	Additive	6	7
CF ₃ SO ⁻	Air	–	36%	–
	Ar	–	32%	–
<i>p</i> -Me-C ₆ H ₄ -SO ₃ ⁻	Air	–	67%	–
	Ar	–	49%	–
Cl ⁻	Ar	Na ₂ CO ₃	33%	–
	Air	–	40%	–
	Ar	–	40%	50%

may be protonated at several positions: 1, 2 and 3. At position 1 to give back the pyridinium salt, resulting in the exchange of this hydrogen. With the protonation at position 2, the terminal carbon of the triple bond, the pyridinium allenol **9** is obtained. The deprotonation of the nitrogen and the ketonisation of the allenol gives at first the (*Z*) isomer of ketone later isomerised to the (*E*) isomer. The kinetic product of the protonation of the allenol **9** to (*Z*) isomer of ketone is documented in the cases where allenols are intermediates.^{23–27} The protonation at C-3 (position 3) gives iminium salt **10** which could be involved in the oxidation of the alcohol to the ynones. We have not tried to isolate the reduced products resulting from this dismutation. If we follow the reaction by NMR using MeO²H, the exchange of the alpha hydrogen of propargylic alcohol is observed

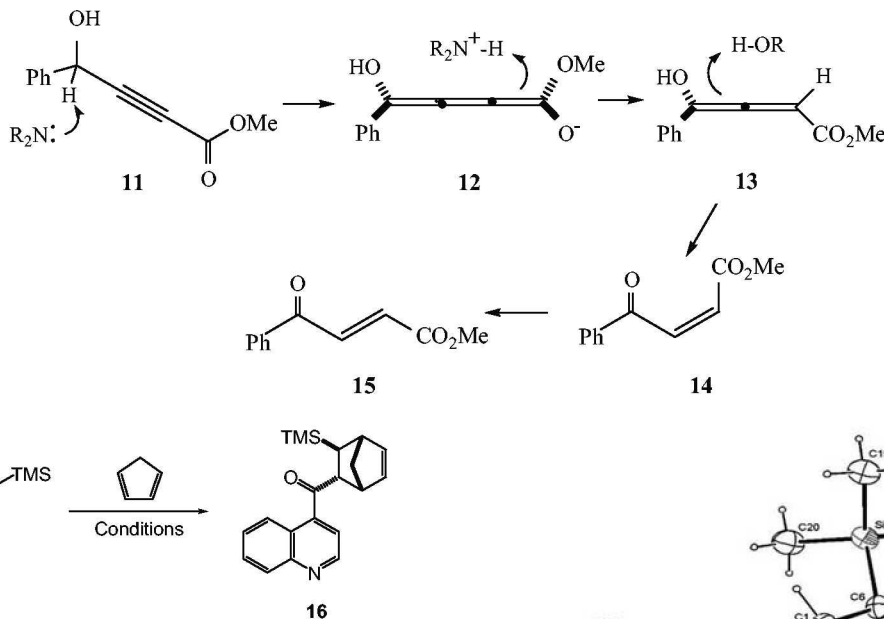


and later the appearance of the (*Z*) enone is observed and its transformation to the (*E*) enone and both hydrogens at the ethylenic positions are exchanged with a deuterium as shown by ¹H NMR and mass spectrometry. A related intramolecular dismutation reaction has been observed in the reaction of vinylmagnesium bromide with isonicotinaldehyde.²⁸

The isomerisation of γ -hydroxy- α,β -alkynoates **11** to γ -oxo- α,β -alkenoates with the organic base (DABCO) or sodium bicarbonate in DMSO-water has been studied.²⁹ The base removes the propargylic proton giving rise to a cumulene **12** which is protonated by the conjugated acid to an allenol **13** which in turn is protonated by an external proton. The protonation occurs to give first the (*Z*) isomer **14** later isomerised to the (*E*) isomer **15**. The propargylic proton is transferred to the vinylic position with little exchange and the other proton originates from solvent. In the propargylic alcohol, the ester group provides the acidity so that the proton can be removed. In the propargylic alcohols in Table 1, the protonation at the nitrogen lowers the pK_a of the proton so that it can be removed by a base.

The easy preparation of heterocyclic enone induced us to try the Diels–Alder reaction with cyclopentadiene to prepare a cyclic system related to quinine. The Diels–Alder adduct **16** with cyclopentadiene was obtained at 120°C (neat) in a yield of 25%.

In boron trifluoride etherate at -78°C in toluene, no adduct was isolated. So, we turned to lithium chloride as a catalyst and obtained in THF at 25°C the adduct **16** in a yield of 50%.³⁰ The *endo* cycloaddition product is obtained as expected.^{31,32} This has been ascertained by the structure determination by X-ray diffraction (Fig. 2).



These enones and yrones not previously prepared should open a new strategy for the synthesis of some complex heterocyclic systems such as alkaloids. They also could be the precursors of synthetically and pharmaceutically valuable compounds.

Experimental

General procedures

Commercial reagents were purchased from standard chemical suppliers and purified if needed. Solvents were purified and dried by passing through activated aluminum oxide under argon pressure. Flash column chromatography was carried out on Silica Gel 60 (230–400 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25 mm, E. Merck); detection was done by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$, $(NH_4)_6Mo_7O_{24}$, and H_2SO_4 in water or ninhydrin and acetic acid solution in *n*-butanol and subsequent heating on a hot plate. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. 1H and ^{13}C NMR spectra were recorded with Bruker AV400 and 500 MHz instruments. Chemical shifts are in ppm from TMS as internal standard, generated from the $CDCl_3$. IR spectra were taken with a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Elemental analysis was done with a Perkin-Elmer 2400CHN instrument. Mass spectra were obtained with a FAB JMS-700 double focusing mass spectrometer (JEOL, Tokyo, Japan).

1-Phenyl-3-trimethylsilylprop-2-yn-1-ol (3a): Prepared according to the literature and its physical data were in agreement with those published.²¹

4-(1-Hydroxy-3-trimethylsilylprop-2-ynyl)pyridine (3b): To a solution of (trimethylsilyl) acetylene (1.7 mL) in THF (20 mL) at $-78^\circ C$ was added a solution of *n*-BuLi (7 mL, 1.6 M in hexane). The reaction mixture was allowed to warm to $-10^\circ C$, then a solution of 4-pyridinecarboxaldehyde (1.0 g) in THF (3 mL) was added. After 1 h stirring, saturated NH_4Cl solution in water was added and the organic layer was washed with brine (2×30 mL), extracted with CH_2Cl_2 and dried over $MgSO_4$ and concentrated *in vacuo*. Product **3b** is a colourless solid (1.6 g, 83%), m.p. $94-95^\circ C$. (lit. m.p. $83-85^\circ C$).²⁴ 1H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 4.60 (brs, 1H), 5.48 (s, 1H), 7.49 (d, $J = 6.0$ Hz 2H), 8.53 (d, $J = 6.0$ Hz 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.18, 63.2, 92.0, 104.2, 121.5, 149.4, 150.3. MS (EI): m/z 205 [M]⁺.

4-(1-Hydroxy-3-butynyl)pyridine (3c): To a solution of propyne (1.12 g) in THF (10 mL), was added a solution of *n*-BuLi (7.0 mL, 1.6 M in hexane) as for **3b**. A solution of 4-pyridinecarboxaldehyde (1.0 g) in THF (5 mL) was added. The product **3c** was isolated as for **3b**, and as a liquid (1.12 g, 82%). UV (CH_2Cl_2): λ_{max} (ϵ) 255 (3540 $M^{-1} cm^{-1}$). IR (CH_2Cl_2): 1230, 1414, 1564, 1602, 1716, 2232, 2874, 2959, 3018, 3026, 3061 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 3H), 5.37 (d, $J = 1.6$ Hz, 1H), 6.30 (brs, 1H), 7.41 (d, $J = 5.9$ Hz, 2H),

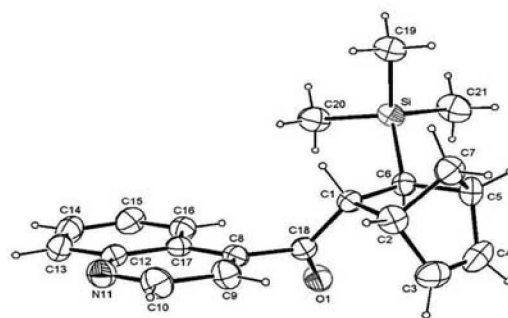


Fig. 2 ORTEP structure of 16.

8.36 (d, $J = 5.9$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8, 62.5, 78.8, 82.8, 121.6, 149.0, 151.1. MS (FAB⁺): m/z 148 ($M + H$)⁺. Anal. Calcd for C_9H_9NO : C, 73.45; H, 6.16; N, 9.52. Found: C, 73.40; H, 6.12; N, 9.47%.

4-(1-Hydroxy-3-phenyl-2-propynyl)pyridine (3d): Phenylacetylene (1.04 g) in THF (10 mL) was treated as for **3b** with *n*-BuLi (7.0 mL) and 4-pyridinecarboxaldehyde (1.0 g) in THF (5 mL) was added. The product (1.75 g, 90%) was a liquid. UV (CH_2Cl_2): λ_{max} (ϵ) 242 (5100), 309 (1300). IR (CH_2Cl_2): 1042, 1243, 1376, 1461, 1733, 2869, 2926, 2960, 3583. 1H NMR (500 MHz, $CDCl_3$): δ 3.95 (brs, 1H), 5.68 (s, 1H), 7.27 (m, 3H), 7.40 (m, 2H), 7.53 (d, $J = 6.0$ Hz, 2H), 8.55 (d, $J = 6.0$ Hz 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 63.2, 86.7, 87.9, 121.4, 121.6, 128.2, 128.6, 131.7, 146.2, 149.4. MS (FAB⁺): m/z 201 [$M + H$]⁺. Anal. Calcd for $C_{14}H_{11}NO$ (209.2): C, 80.36; H, 5.30; N, 6.69. Found: C, 80.20; H, 5.34; N, 6.74%.

4-(1-Hydroxy-4,4-dimethyl-2-pentynyl)pyridine (3e): 3, 3-Dimethyl-1-butene (0.46 g) in THF (10 mL) was treated as for **3b** with *n*-BuLi (3.5 mL, 1.6 M in hexane) and 4-pyridinecarboxaldehyde (0.50 g) in THF (3.0 mL) was added. The product **3e** (0.85 g, 96%) was a solid, m.p. $85-88^\circ C$. UV ($CHCl_3$): λ_{max} (ϵ) 257 (2000). IR (CH_2Cl_2): 1068, 1404, 1599, 2232, 2333, 2363, 2970, 3060, 3596, 3685 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 9H), 3.50 (brs, 1H), 5.42 (s, 1H), 7.44 (d, $J = 4.7$ Hz, 2H), 8.50 (d, $J = 4.7$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.4, 30.7, 62.8, 77.6, 95.9, 121.4, 149.3, 151.0. MS (FAB⁺): m/z 190 [$M + H$]⁺. Anal. Calcd for $C_{12}H_{15}NO$ (189.3): C, 76.16; H, 7.99; N, 7.40. Found: C, 76.11; H, 8.03; N, 7.47%.

4-(1-Hydroxy-3-trimethylsilylprop-2-ynyl)quinoline (3f): Trimethylsilylacetylene (0.39 g) in THF (10 mL) was treated as for **3b** with *n*-BuLi (2.5 mL, 1.6 M, in hexane) and 4-quinolinecarboxaldehyde (0.5 g) in THF (2 mL) was added. The product **3f** was a solid (0.64 g, 78%). m.p. $95-96^\circ C$; UV (CH_2Cl_2): λ_{max} (ϵ) 234 (13900), 281 (4800 $M^{-1} cm^{-1}$). IR (CH_2Cl_2): 1510, 1573, 1607, 1636, 1654, 1686, 1717, 1734, 1750, 1774, 1801, 1830, 1884, 1963, 2174, 2305, 2339, 2360 cm^{-1} . 1H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 9H), 4.80 (brs, 1H), 6.10 (s, 1H), 7.55 (dd, $J = 7.6$ Hz, $J = 15.6$ Hz, 1H), 7.65 (dd, $J = 7.6$ Hz, $J = 15.6$ Hz, 1H), 7.69 (d, $J = 4.4$ Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.72 (d, $J = 4.4$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.4, 61.3, 92.4, 104.1, 118.2, 124.1, 125.6, 126.7, 129.3, 129.4, 146.1, 147.7, 149.8. MS (FAB⁺): m/e (%): 256 [$M + H$]⁺ (100), 180(5), 154 (6), 130 (10). Anal. Calcd for $C_{15}H_{17}NOSi$: C, 70.54; H, 6.71; N 5.48. Found: C, 70.50; H, 6.69; N, 5.52%.

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