Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 2113–2115
Tetrahedron Letters

New reactivity of hydroxyallylpyridyl derivatives as C-3 carbon nucleophiles

Donatella Giomi,* Michela Piacenti and Alberto Brandi

Dipartimento di Chimica Organica 'Ugo Schiff', Polo Scientifico, Università di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Italy

Received 22 December 2003; revised 9 January 2004; accepted 13 January 2004

Abstract—Hydroxyallylpyridyl derivatives exhibited a peculiar thermal behavior likely ascribed to the weak acidity of the 'picoline-type' hydrogen atom on the C-1 carbon of the allyl residue, leading to allyl inversion products. The unprotected alcohol reacted as 'vinylogous picoline' carbon nucleophile with strongly activated heterocyclic counterparts. A mechanistic rationale for this unprecedented reactivity was proposed.

Picolines have been widely used in organic synthesis, especially in base-catalyzed processes exploiting the weak acidity of methyl protons in α- or γ-positions. The ring nitrogen makes alkyl substituents in α- and γ-positions more reactive with respect to the corresponding benzene derivatives and different bases can convert 2- and 4-alkyl-pyridines and -quinolines into the corresponding carbanions able to react with different electrophiles.[1]

In the light of our interest towards synthetic applications of nitrogen heterocycles,[2] we decided to investigate the reactivity of 1-(2-pyridyl)-2-propen-1-ol (**1a**)[3] as a vinylogous functionalized picoline system and we encountered an unprecedented reactivity of this compound and its derivatives under simple thermal conditions.

When a solution of allyl alcohol **1a** in chloroform was heated in a sealed tube at 110 °C for 48 h, we observed the complete disappearance of the starting material affording 2-propionylpyridine (**2**)[4] in 85% yield.[5]

The acetyl derivative **1b**[6] appeared more stable and it was converted into the vinyl acetate **3b** in 62% yield, by heating in the above conditions for 8 days. Nevertheless, operating in xylene at 160 °C (sealed tube) for 14 days we succeeded in the isolation of the diastereomeric vinyl acetates **3b** and **4b** in 21% and 47% yields, respectively. Compound **3b** resulted absolutely stable in xylene at 160 °C excluding the possibility of its thermal isomerization into **4b**.

The *t*-butyldimethylsilyl ether **1c**[7] appeared particularly stable and, after 7 days at 160 °C in xylene, it was only partially converted (64%) into **3c** and **4c** in 36% and 13% yields (Scheme 1).[8]

The above results could be tentatively rationalized on the basis of the weak acidity of the 'picoline-type' hydrogen atom on the C-1 carbon of the allyl residue of **1a–c**, which could allow the formation of the fully conjugated diastereomeric dienamines (*Z*)-**5a–c** and (*E*)-**6a–c**. The former could then evolve into the enol derivatives **3a–c** by simple intermolecular proton transfer, while the conversion of the latter into the *E* isomers **4a–c** could be ascribed to a [1,5] sigmatropic hydrogen shift involving the *s-cis* conformers (*E*)-**7a–c** (Scheme 2).

This mechanistic hypothesis could explain the different thermal behavior of **1a–c**.

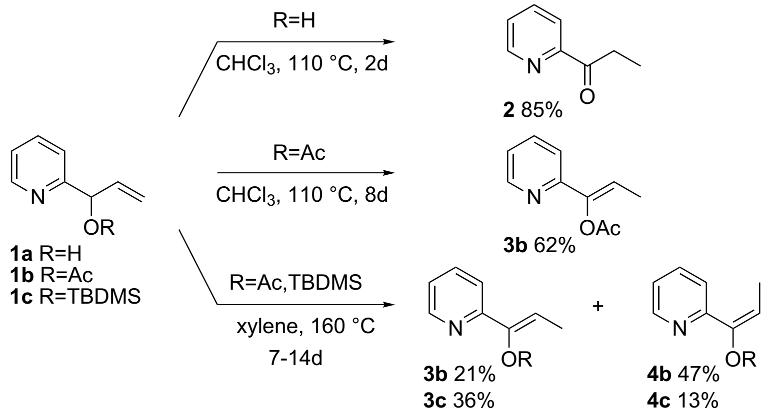
The obtainment at lower temperature of vinyl acetate **3b** could be rationalized on the basis of the higher energy pathway required for the formation of **4b**. Of course, starting from the alcohol **1a**, the enol forms **3a** and **4a** immediately give rise to the same pyridyl ketone **2** as the only reaction product. The higher reactivity of **1a** with

Keywords: Hydroxyallylpyridyl derivatives; Picoline derivatives; Nucleophilic substitution; Heterocyclic electrophiles; Thermal reactions.

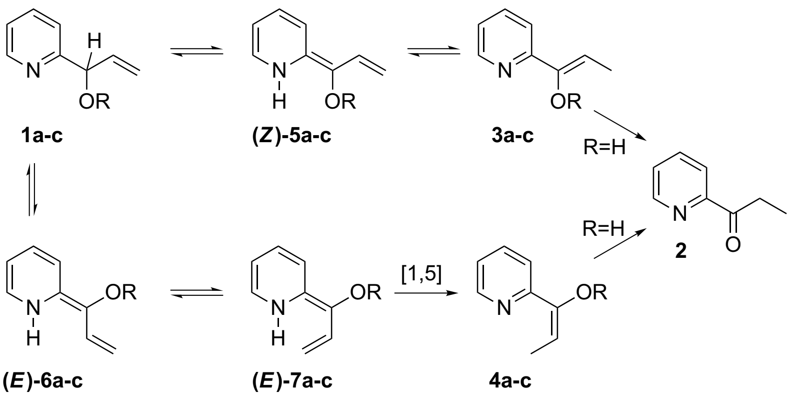
---

* Corresponding author. Tel.: +39-055-4573475; fax: +39-055-4573575; e-mail: donatella.giomi@unifi.it

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.01.049



Scheme 1.



Scheme 2.

respect to **1b** and **1c** could be tentatively ascribed to the contribution of an intramolecular hydrogen bond between the OH group and the ring nitrogen, which probably could favor the initial proton abstraction. The resulting carbanion **8a** assumes, in fact, high stability as pseudo-aromatic form (Fig. 1).

The poor reactivity of **1c** could be associated to the presence of the strongly electron-donating silyl ether group, obviously unable to stabilize a vicinal negative charge, as evidenced in the carbanion **8c** ($R = SiMe_2{}^tBu$) (Fig. 1).

Allowing alcohol **1a** to react under thermal conditions with electrophiles should lead to a 'vinylogous picolination' of electrophiles under neutral conditions. In fact, when **1a** was heated in a sealed tube in anhydrous toluene at 70 °C with 5 equiv of 2-chloro-3-nitropyridine (**9**) for 24 h, we succeeded in the isolation of the new bipyridyl derivative **10** and the volatile ketone **2** in 26% and 29% yields, respectively. Several attempts were made to optimize the reaction yield, and disfavor the formation of ketone **2**, by increasing the amount of electrophile or changing solvent and reaction temperature. Obviously, the reaction pathway of hydrogen transfer cannot be eliminated, especially if it occurs in an intramolecular fashion. Other heterocyclic electrophiles were tested. For example, operating as above for 48 h with 3,6-dichloropyridazine (**11**) (8 equiv) the substituted chloropyridazine **12** and compound **2** were isolated in 18% and 22% yields, respectively. Better results were obtained by heating **1a** with 4,5-dicyanopyridazine (**13**) (2 equiv), in the previously reported conditions for 36 h, affording the cyanopyridazine **14** in 44% yield, together with a minor amount of product **2** (<5%) (Scheme 3).[9]

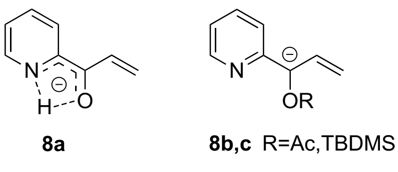
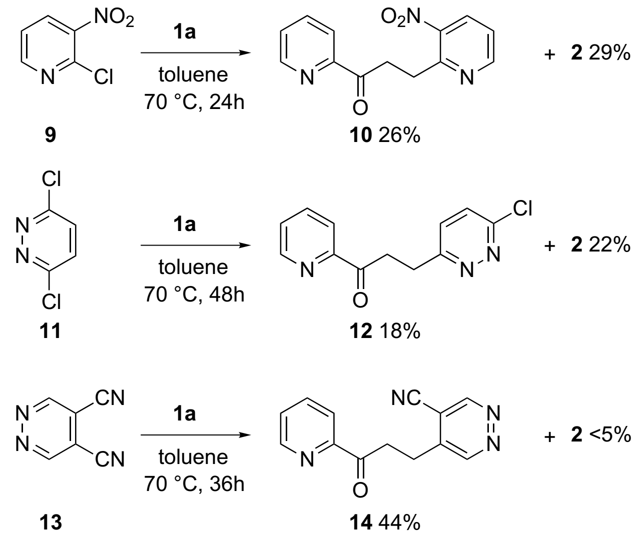


Figure 1.

These results suggest that only very reactive electrophiles can participate in the reaction.

All the more, a new reactivity of hydroxyallyl substituted pyridines has been evidenced. The reaction can be considered a 'vinylogous picolination' of reactive het-



Scheme 3.

erocyclic electrophiles leading to interesting polyfunctionalized heteroaromatic compounds. The study of the general scope and synthetic applications of this new reaction is underway in our laboratories.

Acknowledgements

Authors thank MIUR (Rome, Italy) for financial support (PRIN 2002, 2003).

References and notes

1. (a) Uff, B. C. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, UK, 1984; Vol. 2, pp 329–335; (b) Dennis, N. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A., Ed.; Pergamon: Oxford, UK, 1996; Vol. 5, pp 101–104.
2. Cicchi, S.; Cordero, F. M.; Giomi, D. *Prog. Heterocycl. Chem.* **2003**, *15*, 261.
3. Uenishi, J.; Hiraoka, T.; Hata, S.; Nishiwaki, K.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 2481.
4. Sato, N.; Narita, N. *Synthesis* **2001**, 1551.
5. The same conversion was observed by heating **1a** at 70 °C for three days.
6. For the synthesis of **1b** in enantiopure form, see Ref. 3.
7. Uenishi, J.; Hiraoka, T.; Yuyama, K.; Yonemitsu, O. *Heterocycles* **2000**, *52*, 719.
8. The reported yields were determined on the basis of the recovered starting material.
9. For examples of 4,5-dicyanopyridazine (**13**) acting as an electrophile, see: (a) Giomi, D.; Cecchi, M. *Tetrahedron* **2002**, *58*, 8067; (b) Giomi, D.; Cecchi, M. *J. Org. Chem.* **2003**, *68*, 3340.