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New reactivity of 1-(2-pyridyl)-2-propen-1-ol with nitro derivatives

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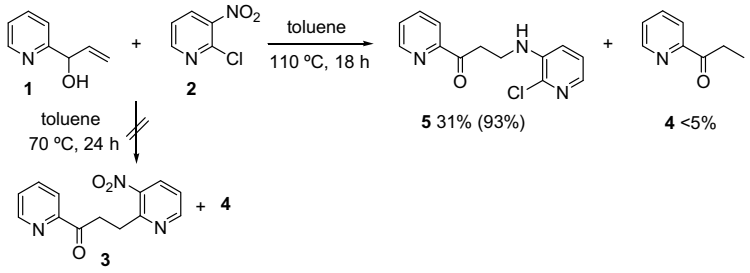
ABSTRACT

1-(2-Pyridyl)-2-propen-1-ol showed an unprecedented reactivity behaving as Hantzsch ester 1,4-dihydropyridine mimic for the metal-free reduction of the nitro group of electron-deficient aromatic and heteroaromatic nitro compounds to the corresponding amino function. The redox mechanism is part of a domino process involving a direct trapping of the amino derivatives through aza-Michael addition to the vinyl ketone intermediate leading to the one-pot formation of new functionalised aminoacylpyridines.

In the chemical domain, the most common broad-spectrum reducing agents are certainly metal hydrides, used in stoichiometric amounts, and hydrogen in conjunction with metal catalysts. On the other hand, biochemical processes rely on organic cofactors such as nicotinamide adenine dinucleotide (NADH) in combination with metalloenzymes.[1] Metal-free catalytic hydrogenations, rare even in nature, had been unknown in chemical synthesis until a few years ago. Nowadays, a great interest has been devoted to the development of environmentally friendly organocatalysis, namely new catalytic methods based on the use of metal-free organic molecules and able to join efficiency and preparative advantages deriving from the absence of metals in the reaction mixtures.[2] Recently, new biomimetic organocatalytic strategies have been performed replacing enzymes and cofactors with small molecule organocatalysts and Hantzsch ester dihydropyridine (HEH) as hydrogen donor. These methodologies were successfully exploited in enantioselective transfer hydrogenation of unsaturated carbonyl compounds, imines, heteroaromatic compounds, reductive amination,[3] as well as in biomimetic reduction of conjugated nitroalkenes.[4] Due to their behaviour as NADH mimics and with the aim to elucidate the mechanism of action of the coenzyme, over the past century 1,4-dihydropyridines have been extensively studied as hydrogen transfer agents for the reduction of unsaturated organic compounds.[5] After the former pioneering works related to metal-free reduction of thio ketones, keto acids, quinones, derivatives of maleic and fumaric acids, nitro compounds,[6] over the last fifty years the above methodology has been successfully applied to different substrates and recent results concern HEH metal-free reduction of activated olefins,[7] exocyclic double bonds,[8] tertiary amides,[9] as well as new applications



Scheme 1.

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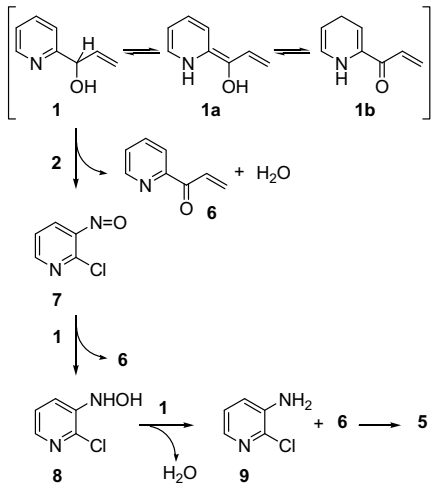
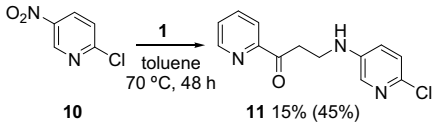


Scheme 2.



Scheme 3.

involving polymer-supported HEH.[10] In particular, concerning nitro derivatives, few literature data proved 1,4-dihydropyridines to be able to reduce aromatic nitro compounds under purely thermal conditions leading to the corresponding anilines.[6,11]

Recently, a new reactivity of 1-(2-pyridyl)-2-propen-1-ol (**1**) as 'vinilogous picoline' C-3 carbon nucleophile towards strongly activated heterocyclic electrophiles was reported, and ascribed to the weak acidity of the 'picoline type' hydrogen atom on the C-1 carbon of the allyl residue.[12]

For the sake of a generalization of the 'vinilogous picoline' reactivity of **1** with 2-chloro-3-nitropyridine (**2**), the expected compound **3** was not observed,[13] whereas a new product **5** formed besides ethyl ketone **4**,[14] a common side product derived from thermal isomerisation of **1** (Scheme 1). In fact, when alcohol **1** was heated with 5 equiv of **2**[15] in toluene at 110 °C for 18 h, compound **5** was isolated by flash chromatography in 31% yield (referred to the moles of alcohol **1**) that corresponds to 93% yield on the basis of the proposed reaction mechanism (see below).[16,17]

The presence of an amino functionality in compound **5** suggested a novel behaviour of **1** as reducing agent. The reactivity of **1** is likely justified by its isomerisation to the 1,4-dihydropyridine form **1b**, promoted by the weak acidity of the C(1)–H hydrogen of the allyl moiety (Scheme 2). This equilibration allows **1** to react as an HEH mimic which is able to reduce the heteroaromatic nitro group and to convert into the oxidation product **6**. Then, a novel domino process occurs involving cascade reduction of the nitro group of **2** to the corresponding amino function (with a reaction stoichiometry alcohol/nitro compound **3:1**) followed by aza-Michael addition of **9** to the pyridyl vinyl ketone **6** (Scheme 2). Likely, the vinyl ketone **6** being an optimal acceptor, the free amine **9** was never observed in the reaction mixture.[18]

To test the synthetic potential of this new reactivity of **1**, the study was extended to other nitro derivatives.

Similar results, albeit lower yields, were obtained when compound **1** was allowed to react with 5 equiv of 2-chloro-5-nitropyridine (**10**).[15] However, in this case a better result was obtained operating at lower temperature (70 °C rather than 110 °C) for a longer time (48 h) and compound **11** was then isolated in 15% (45%) yield (Scheme 3).[19] Ethyl ketone **4** was always the only side product formed in variable yields according to the reaction conditions.[14] Compared to compound **2**,[20] reaction of **10** was faster, likely due to the reduced steric hindrance of the 2,5-disubstituted substrate.

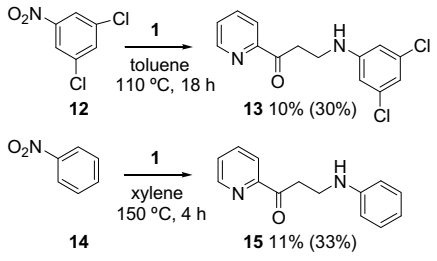
Also, less electron-poor nitrobenzenes participated in the reduction process, although at higher temperatures. The reaction of **1** with 5 equiv[15] of 3,5-dichloro-1-nitrobenzene (**12**) in toluene at 110 °C for 18 h led to aminoketone **13** in 10% (30%) yield[19] (Scheme 4).[21]

Nitrobenzene (**14**) resulted even less reactive at 110 °C, but rising the temperature at 150 °C in xylene led to the formation of compound **15**[22] in 11% (33%) yield[19] (Scheme 4).

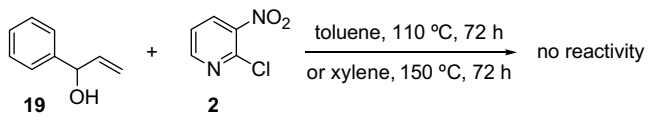
Finally, operating in toluene at 110 °C for 18 h with an α,β-unsaturated nitro compound, *trans*-β-nitrostyrene (**16**), none of the nitro group reduction derivative **17** was isolated but only the conjugate addition product **18** of the vinylogous picoline **1** with nitrostyrene **16** (Scheme 5).

To confirm the proposed mechanistic hypothesis (Scheme 2), involving as key intermediates the dihydropyridine systems **1a,b**, the behaviour of the corresponding phenyl derivative **19**[23] towards nitro pyridine **2** was investigated. Operating in toluene at 110 °C for 72 h alcohol **19** appeared totally inert towards compound **2**. After heating in xylene at 150 °C for 72 h, only traces of the corresponding ethyl ketone (deriving from the thermal isomerisation of **19**) were observed (^{1}H NMR) along with the unchanged starting materials (Scheme 6).

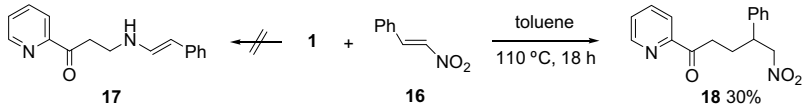
Moreover, the crucial role of the pyridine ring in these reduction processes was well evidenced by studying the reactivity of carbinol **20**.[24] When alcohol **20** (3 equiv) was allowed to react with nitro pyridine **2** in toluene at 110 °C for 96 h, ketone **21**[25] was evidenced



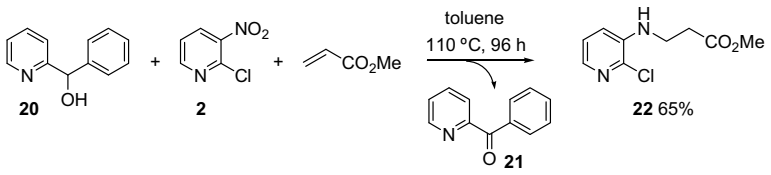
Scheme 4.



Scheme 6.



Scheme 5.



Scheme 7.

as the predominant product in the reaction mixture (^{1}H NMR), while the formation of 3-amino-2-chloropyridine, originating from the reduction of **2**, was only observed via GC/MS analysis. The above reaction was then repeated in the presence of methyl acrylate (1 equiv) with the aim to trap the reduction product and confirm the reactivity of **20** as reducing agent (Scheme 7). The conjugate addition product **22** was isolated in 65% yield by flash chromatography along with ketone **21** recovered in 83% yield, referred to the full amount of alcohol **20** used. By-the-way, this is a further confirmation of the proposed mechanism involving a reaction stoichiometry alcohol/nitro derivative 3:1.

In conclusion, these preliminary results clearly show an unprecedented and unexpected reactivity of pyridyl allyl alcohol **1**, related to the weak acidity of the 'picoline-type' hydrogen atom. This compound, in fact, not only is able to react as C-3 carbon nucleophile towards strongly activated electrophilic counterparts as previously reported,[12] but also in the presence of electron-poor aromatic and heteroaromatic nitro derivatives it behaves as 1,4-dihydropyridine HEH mimic for the metal-free reduction of the nitro group to the corresponding amino function. Moreover, the redox mechanism becomes part of a domino process involving a direct trapping of the amino intermediates, undergoing the one-pot formation of new functionalised aminoacylpyridines. The facile thermal methodology appears clearly limited to activated aromatic and heteroaromatic nitro compounds, as both nitro and alkene functions of nitro olefins seem unaffected by the redox ability of **1**, and suffers of the large excess of recoverable nitro reagent necessary to overcome the spontaneous thermal isomerisation of pyridyl allyl alcohol **1** to pyridyl ethyl ketone **4**. On the other hand, from a mechanistic viewpoint, the data related to alcohols **19** and **20** seem to confirm the key role played by the pyridine ring in the redox processes, that is, unprecedented for this kind of compounds. Therefore, the reactivity of compounds **1** and **20** appears worthy of further investigations to establish their real potential as new metal-free reducing agents, and studies in this direction are underway in our laboratories.

Acknowledgements

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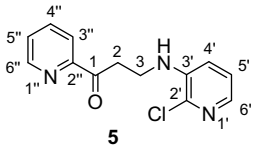
13. The formation of **3** was observed operating in the presence of bases such as KOH, ^{t}BuOK or NaH.
14. The amount of **4** was estimated via ^{1}H NMR analyses of the reaction crudes. In fact, due to its volatility (50 °C/4 Torr, see Ref.12 and references therein), the amounts of **4** recovered after evaporation of the solvent at reduced pressure and column chromatography are significantly lower compared to the original presence in the reaction mixtures.
15. The excess of the reagent (recovered by chromatography) allows to reduce the formation of **4**.
16. Operating under the same reaction conditions but with an excess of alcohol **1** (ratio **1**:**2** ca. 4:1) ethyl ketone **4** became the predominant product (ratio **4**:**5** ca. 2:1, ^{1}H NMR).
17. *Experimental procedure for the preparation of compound* **5**:



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A mixture of alcohol **1** (0.068 g, 0.5 mmol) and 2-chloro-3-nitropyridine (**2**) (0.396 g, 2.5 mmol) in toluene (1 mL) was heated at 110 °C in a sealed tube (Pyrex N. 13) for 18 h. Removal of the solvent in vacuo and purification by column chromatography (petroleum ether 40–70 °C/ethyl acetate 3:2 v/v) gave unreacted **2** (R_f = 0.41, 0.337 g) and 3-[(2-chloro-3-pyridyl)amino]-1-(2-pyridyl)-1-propanone (**5**) [R_f = 0.20, 0.041 g, 31% (93%)][19] as a pale yellow thick oil: IR (liquid film): 3394, 3059, 2916, 1694, 1584, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (ddd, J = 4.8, 1.6, and 1.0 Hz, 1H, H-6″), 8.07 (ddd, J = 7.8, 1.1 and 1.1 Hz, appears as dt, 1H, H-3″), 7.86 (ddd, J = 7.7, 7.7 and 1.7 Hz, appears as td, 1H, H-4″), 7.69 (dd, J = 4.5 and 1.6 Hz, 1H, H-6′), 7.50 (ddd, J = 7.6, 4.7, and 1.1 Hz, 1H, H-5″), 7.09 (dd, J = 8.1 and 4.6 Hz, 1H, H-5′), 6.98 (dd, J = 8.1 and 1.5 Hz, 1H, H-4′), 4.96 (br s, 1H, NH), 3.62 (m, 2H, 3-CH_2), 3.55 (m, 2H, 2-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 152.9, 149.1, 140.6, 137.2, 137.1, 136.3, 127.5, 123.4, 121.9, 117.3, 38.7, 36.9; MS (EI): *m/z* (%) 263 (4) $[M+2]^+$, 261 (13) $[M]^+$, 226 (2), 208 (13), 157 (9), 155 (24), 134 (27), 79 (100). HRMS(ESI) calcd for $C_{13}H_{12}ClN_3O$ $[M+H]^+$ 262.0742; found: 262.0742.
18. The unreacted vinyl ketone **6** was never isolated from the reaction mixture, likely due to concomitant decomposition/polymerisation processes.
19. Yields in brackets refer to a reaction stoichiometry alcohol **1**/nitro derivative 3:1, according to the proposed mechanism.
20. Operating with **2** in toluene at 70 °C, alcohol **1** disappeared only after 72 h.
21. Operating in toluene at 70 °C, the formation of **13** was too slow, and ketone **4** became the major product.
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