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1-(2-Pyridyl)-2-propen-1-ol: a multipurpose reagent in organic synthesis

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ABSTRACT

A peculiar thermal behaviour of hydroxyallylpyridyl derivatives, likely associated to the weak acidity of the 'picoline-type' hydrogen atom and responsible for the formation of allyl inversion products, has been reported. The 'mobility' of the same hydrogen atom allowed the unprotected title compound to behave regioselectively as C-1, C-2 or C-3 carbon nucleophile depending on the thermal or base-promoted experimental conditions and on the kind of electrophile; moreover, the corresponding Hantzsch-type pyridine tautomer displayed a biomimetic ability to transfer hydrogen to aromatic and heteroaromatic nitro derivatives.

1. Introduction

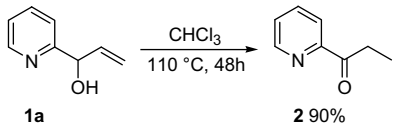
The wide range of synthetic applications of α- and γ-picolines and alkylpyridines mainly arise from the weak acidity of the alkyl protons, easily removed in base-catalysed processes. The presence of the nitrogen atom makes the alkyl substitutents in the α- and γ-positions more reactive with respect to the corresponding benzene derivatives. As a consequence, treatment of α- and γ-alkylpyridines with strong bases, such as sodium amide in liquid ammonia or organolithiums, results in an essentially quantitative deprotonation affording stabilized carbanions, as a result of charge delocalisation on the ring nitrogen. These intermediates are able to react with a wide range of electrophiles, such as alkyl halides and tosylates, acyl halides, carbon dioxide, aldehydes, ketones, etc., in a large array of different reactions.[1]

Moreover, the one-pot isomerization of allyl alcohols to the corresponding saturated carbonyl compounds is a very attractive synthetic approach, corresponding to an internal redox process with total atom economy.[2] Even though some thermal conversions at high temperatures or in the presence of mineral acids or bases are reported,[3] the above rearrangement has been mainly and efficiently performed under catalysis of transition-metal complexes.[4]

On this ground and in the light of preliminary data supporting a peculiar thermal behaviour for allyl pyridyl alcohol derivatives **1a**–**c**,[5] likely ascribed to the weak acidity of the picoline-type hydrogen atom, we decided to gain better insight into the thermal isomerisation processes as well as the possibility to exploit the above compounds as carbon nucleophiles in reactions with different electrophilic counterparts. On the other hand, a new reactivity of **1a** as a hydrogen donor towards aromatic and heteroaromatic nitro derivatives,[6] again amenable to the 'mobility' of the picoline-type hydrogen atom, has been investigated.

2. Results and discussion

By heating a solution of allyl alcohol **1a**[7] in chloroform in a sealed tube at 110 °C for 48 h, we observed the complete disappearance of the starting material with the resultant formation of 2-propionylpyridine (**2**)[8] in 90% yield (Scheme 1).[9]



1a **2** 90%

Scheme 1. Thermal isomerization of alcohol **1a**.

In contrast, the acetyl derivative **1b**,[10] the *tert*-butyldimethylsilyl ether **1c**[11] and the new acryloyl derivative **1d** proved to be more stable. While **1c** was synthesized according to the Uenishi procedure, **1b** and **1d** were prepared in 85% and 94% yields by treatment of the alcohol **1a** with acetic anhydride and acryloyl chloride, respectively, in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine at 0 °C (Experimental

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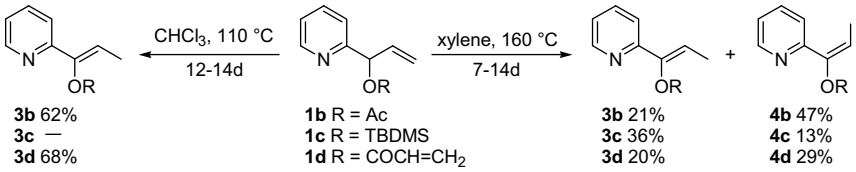
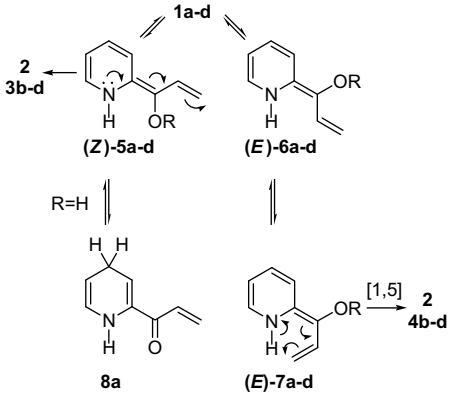


Scheme 2. Thermal isomerization of compounds **1b**–**d**.

section). When **1b** was heated at 110 °C in a sealed tube for 12 days, the vinyl acetate **3b** was obtained in 62% yield. On the other hand, by heating **1b** in xylene at 160 °C for 14 days the diastereomeric vinyl acetates **3b** and **4b** were isolated in 21% and 47% yields, respectively (Scheme 2). When submitted to heating in xylene at 160 °C, compound **3b** was recovered completely unchanged, ruling out the possibility of its thermal isomerization into **4b**. The *tert*-butyldimethylsilyl ether **1c** appeared perfectly stable in chloroform at 110 °C for weeks and only after 10 days at 160 °C in xylene was partially converted (ca. 66%, ^{1}H NMR) into **3c** and **4c**, isolated by flash column chromatography in 36% and 13% yields, respectively (Scheme 2).[12] As observed for **1b**, when the acryloyl derivative **1d** was heated at 110 °C in chloroform in a sealed tube for 14 days only compound **3d** was recovered in 68% yield whereas, operating in xylene at 160 °C for 7 days, the two diastereomers **3d** and **4d** were isolated respectively in 20% and 29% yields (Scheme 2). As compound **3b**, also the (*Z*) isomers **3c**,**d** resulted completely stable in xylene at 160 °C.

The structures of (*Z*) and (*E*) diastereomers were easily assigned on the basis of NOESY-1D experiments; moreover the quartet of the H-2 proton (J=7.1 Hz and 7.4–7.5 Hz, respectively) appears at higher frequencies in diastereomers **3b**–**d** (δ 5.98–6.63) with respect to **4b**–**d** (δ 5.29–5.80), likely due to the anisotropy of the pyridine ring.

A mechanistic rational of the above results could be proposed taking into account the weak acidity of the 'picoline-type' hydrogen atom on the C-1 carbon of the allyl residue of compounds **1a**–**d**. A 1,3-proton shift can give rise to the fully conjugated diastereomeric enamines (*Z*)-**5a**–**d** and (*E*)-**6a**–**d**. While **5a**–**d** could evolve into the (*Z*) enol derivatives **3b**–**d** and ketone **2** (coming from the corresponding enol form) by simple intermolecular proton transfer, **6a**–**d** could give rise to the (*E*) isomers **4b**–**d**, as well as compound **2**, through a [1,5] sigmatropic hydrogen shift involving the higher energy *s-cis* conformers (*E*)-**7a**–**d**. When R=H also the tautomer **8a** can form (Scheme 3).



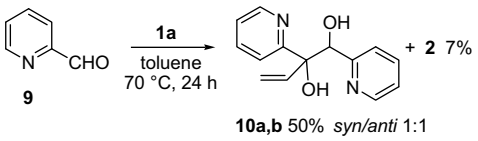
Scheme 3. Proposed mechanism for thermal isomerization of **1a**–**d**.

This mechanistic assumption allowed us to explain the experimental results. While the enol forms coming from the free alcohol **1a**, immediately evolve into pyridyl ketone **2**, the protected alcohols **1b**–**d** afford different enol derivatives **3b**–**d** or **4b**–**d**, depending on the reaction conditions and, consequently, on the inter- or intramolecular operating mechanism. In particular, the higher energy pathway associated with the intramolecular sigmatropic hydrogen shift leading to diastereomers **4b**–**d**, could justify the exclusive formation of **3b** and **3d** at lower temperature. The higher reactivity of **1a** with respect to **1b**–**d** could be likely ascribed to the contribution of an intramolecular hydrogen bond between the OH group and the ring nitrogen, which could favour the initial proton abstraction. Moreover, the poor reactivity of **1c** with respect to **1b** and **1d** could be justified by the presence of the strongly electron-donating silyl ether group, unable to stabilize a vicinal negative charge.

On the basis of this new reactivity of **1a**–**d**, and their likely behaviour as enamines or, even vinilogous enamines, we investigated their reactions towards different electrophiles.

The studies were rapidly focused on alcohol **1a**, because, working under neutral thermal conditions, the less reactive oxygen-protected derivatives **1b**–**d** required long reaction times and drastic conditions leading to complex reaction mixtures.

Alcohol **1a** was totally inert towards benzaldehyde and furaldehyde at 110 °C, in toluene or chloroform in a sealed tube, while the reaction with an excess (3 equiv) of 2-pyridyl carbaldehyde (**9**) in dry toluene at 70 °C for 24 h gave an almost 1:1 mixture of the diastereomeric diols **10a**,**b**, isolated in 50% yield, along with a minor amount of pyridyl ketone **2** (7%)[13] (Scheme 4).

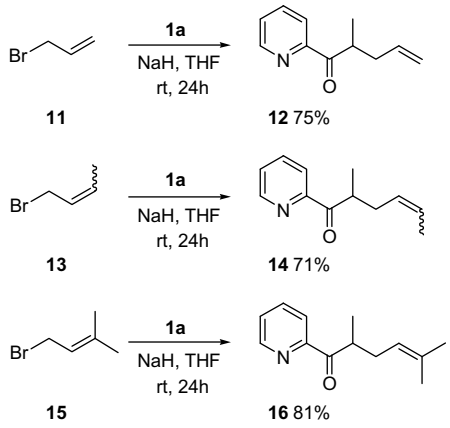


Scheme 4. Reaction of **1a** with 2-pyridyl carbaldehyde (**9**).

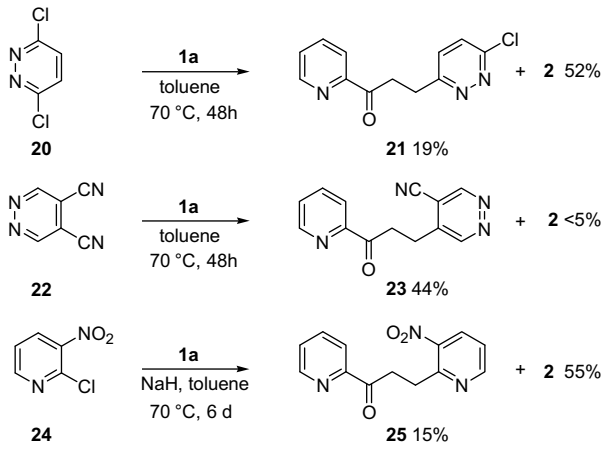
The vicinal diols **10a**,**b** are the products of an aldol reaction occurring through nucleophilic attack of the C-1 carbon atom of the allyl residue of **1a** (via enamines **5a** and **6a**) on the carbonyl group of **9**. The stability of diols, not undergoing H_2O elimination, could be likely due to intramolecular hydrogen bonds between the OH groups and the pyridine rings nitrogen atoms.

The enamine reactivity in aldol type reactions, therefore, seems to be limited to activated aromatic aldehydes. Switching to study the alkylation with halides, the thermal reaction of **1a** with an excess of allyl bromide **11** in dry toluene at 70 or 110 °C for 24–48 h led to the exclusive formation of ketone **2**. Nevertheless, operating in the presence of bases alkylation products were obtained. By treatment with an equivalent amount of sodium hydride at room temperature in THF, **1a** reacted with allyl bromides **11**, **13** and **15** in 24 h to give compounds **12**,[14] **14** and **16**, in 75%,[12] 71% and 81% yields, respectively. The products **12**, **14** and **16** result from the nucleophilic substitution of bromides by the C-2 carbon of the allyl moiety of **1a** (Scheme 5). In such reaction conditions, operating at room temperature, the formation of ketone **2** was almost completely avoided allowing the isolation of the substitution products in satisfactory yields.

A reasonable mechanistic hypothesis could involve the formation of the enolate **19** as reactive species from the deprotonated alcohol **17**, via the mesomeric allyl anions **18** (Scheme 6).



Scheme 5. Reactions of **1a** with allyl bromides.



Scheme 7. Reactions of **1a** with heterocyclic electrophiles.

Considering the easy isomerisation of allyl alcohols into the corresponding ketones by treatment with bases,[3b,c] the above alkyation derivatives might derive also from ketone **2**, as the first reaction product, via enolate formation and nucleophilic substitution. In fact, in the same reaction conditions, compound **2** gave similar results under deprotonation with NaH. However, the recovery of unreacted alcohol **1a** in the reaction with allyl bromide (**11**, Scheme 5) after 24 h (Experimental section) seems to rule out the conversion of alcohol into ketone **2** before nucleophilic substitution.

As previously observed with aldehydes, the non catalysed thermal reactions of allyl pyridine **1a** as carbon nucleophile seem to require highly activated electrophiles. For this reason heterocyclic electrophiles were investigated. When **1a** was allowed to react in a sealed tube with an excess (8 equiv) of 3,6-dichloropyridazine (**20**) in anhydrous toluene at 70 °C for 48 h the substitution product **21** was isolated by flash column chromatography in 19% yield, along with a significant amount (ca. 52%) of the volatile pyridyl ketone **2** (Scheme 7). Analogously, treatment of **1a** with 2 equiv of 4,5-dicyanopyridazine (DCP)[15] (**22**) gave, together with minor amount of ketone **2** (<5%, ^{1}H NMR), compound **23**, coming from nucleophilic attack on DCP and HCN elimination, in 44% yield (Scheme 7). Attempts to improve the formation of compounds **21** and **23** by varying the experimental conditions (amounts of electrophile, solvent, reaction temperature) were unsuccessful likely due to the competitive isomerization affording compound **2**.

A peculiar behaviour was observed with 2-chloro-3-nitropyridine (**24**). Nucleophilic substitution product **25** was isolated in poor 15% yield, together with ketone **2** as the major product (55% yield), only after longer reaction times (six days) and addition of 1.3 equiv of NaH (Scheme 7).[16]

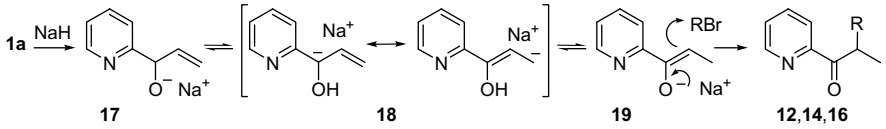
Compounds **21**, **23** and **25** derive from nucleophilic attack of the C-3 carbon atom of the allyl residue of alcohol **1a** on the electrophilic C-3, C-4, and C-2 carbons, respectively, of **20**, **22** and **24** followed by leaving group elimination. The products are the results of a 'vinylogous picolination' that is unprecedented, to our knowledge, in the literature. The sizeable enhancement of reactivity observed for 4,5-dicyanopyridazine (**22**) could be tentatively associated to the presence of the leaving group (the CN group, in this case) in γ-position with respect to the nitrogen atom, rather than in α-position as in compounds **20** and **24**. Likely, as reported for nucleophilic attack on ribopyranoside derivatives,[17] a repulsive dipolar interaction due to the proximity of the lone pair of an heteroatom could hamper the approach of the incoming nucleophile. An analogous repulsive effect involving the nitrogen lone pair could be invoked to explain the lower reactivity of 2-cyanopyridine with respect to the 4-cyano derivative in nucleophilic aromatic substitutions with lithium amides,[18] as well as the weaker acidity determined in THF of 2-picoline compared with the 4-isomer.[19]

Unfortunately, alcohol **1a** was absolutely inert towards mono- and bis-halo substituted pyrazines, pyrimidines, and pyridines and even rising the reaction temperature to 110 °C the exclusive isomerisation into ketone **2** was observed.

The anomalous behaviour of 2-chloro-3-nitropyridine (**24**) in the substitution reaction with **1a** allowed, however, the discovery of another reaction path for 1-(2-pyridyl)-2-propen-1-ol (**1a**). In fact, when pure samples of **1a** were allowed to react with an excess (5 equiv) of **24** in toluene at 110 °C for 18 h, the amino compound **26** was obtained as the only reaction product isolated in 31% yield (Table 1, entry 1).[6]

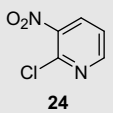
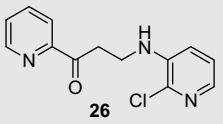
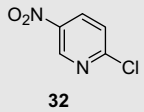
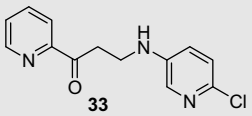
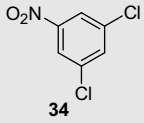
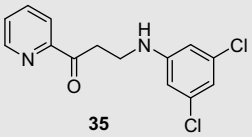
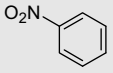
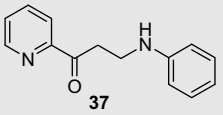
The structure of compound **26**, and the lack in the reaction mixture of any rearrangement product of 1-(2-pyridyl)-2-propen-1-ol (**1a**), together with the absence of side products,[6] suggested that **26** derived from a very straightforward redox process of **1a** able to reduce the nitro group of 2-chloro-3-nitropyridine to the corresponding amino function which adds to the pyridyl vinyl ketone **28**, the product of oxidation of alcohol **1a**. In the light of the proposed mechanistic hypothesis (see below) 3 equiv of **1a** are necessary to reduce 2-chloro-3-nitropyridine to 2-chloro-3-aminopyridine and then the yield of the reaction should be calculated as 93% (Scheme 8). The excess of the unstable pyridyl vinyl ketone likely undergoes polymerization under the reaction conditions.

The mechanistic rationale for this new behaviour of **1a** as reducing agent can be ascribed again to the weak acidity of the 'picoline-type' hydrogen atom, likely involving the 1,4-dihydropyridine tautomeric form **8a** able to react as Hantzsch ester (HEH) mimic in metal-free redox processes. Hydrogen transfer to **24** could produce the vinyl ketone **28** and nitroso pyridine **29**; the involvement of two more molecules of **1a** could then allow the formation of the amino derivative **31** able to give aza-Michael addition to **28** affording **26** through a novel domino process (Scheme 8).[6]

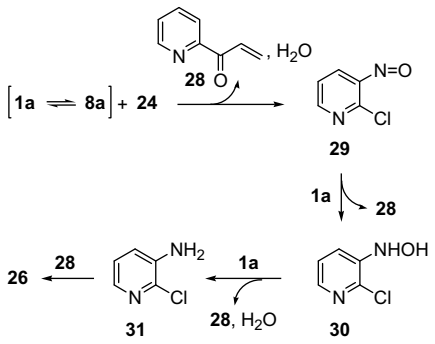


Scheme 6. Proposed mechanism accounting for the formation of **12**, **14** and **16**.

Table 1
Thermal reactions of **1a** with nitro derivatives (RNO_2)[a]

Entry	RNO_2	T (°C)	Time	Products	Yield[b,c] %
1	 **24**	110	18 h	 **26**	31 (93)
2	 **32**	70	48 h	 **33**	15 (45)
3	 **34**	110	18 h	 **35**	10 (30)
4	 **36**	150[d]	4 h	 **37**	11 (33)

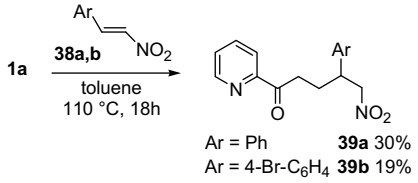
[a] Reactions performed in a sealed tube in toluene with an excess (5 equiv) of RNO_2 to reduce the competitive thermal isomerisation of **1a** to ethyl ketone **2**.
[b] Isolated yields.
[c] Yields in brackets refer to a reaction stoichiometry **1a**/RNO_2 3:1, according to the proposed mechanism.
[d] Reaction performed in xylene with 9 equiv of nitrobenzene.



Scheme 8. Mechanistic hypothesis accounting for the formation of compound **26**.

The synthetic potential of alcohol **1a** as reducing agent was tested with other nitro derivatives. Chloronitropyridine **32** was able to react at lower temperature, likely due to reduced steric hindrance, leading to the amino ketone **33**, albeit in lower yield (45%, Table 1, entry 2).

Operating at higher temperatures, less activated nitroarenes were also reduced to the corresponding amino derivatives. 3,5-Dichloro-1-nitrobenzene (**34**) was allowed to react at 110 °C for 18 h with **1a** to give amino compound **35** (Table 1, entry 3) while nitrobenzene (**36**) was converted into **37**[20] only by heating in xylene at 150 °C for 4 h (Table 1, entry 4).



Scheme 9. Reactions of **1a** with nitroalkenes.

A different behaviour was observed with nitro alkenes. In fact, when alcohol **1a** was reacted with *trans*-β-nitrostyrene (**38a**) in toluene at 110 °C for 18 h, the reduction process did not occur either for the NO_2 group or for the C=C double bond, and only the conjugate addition product **39a** was isolated in 30% yield along with ketone **2** (Scheme 9).

p-Bromonitrostirene (**38b**)[21] gave similar results leading to **39b** in 19% yield. Again, the formation of **39a**,**b** could be ascribed to the reactivity of **1a** as vinylogous picoline C-3 carbon nucleophile, now able to give conjugate addition to the electrophilic nitro alkenes **38a**,**b**.

3. Conclusions

In summary, the reported results clearly show a peculiar thermal behaviour of hydroxyallylpyridyl derivatives likely associated to the weak acidity of the 'picoline-type' hydrogen atom and responsible for the formation of allyl inversion products. In fact, the alcohol **1a** and its oxygen protected derivatives **1b**–**d** can be easily isomerised to ketone **2** and vinyl derivatives **3b**–**d** and **4b**–**d**, respectively, under thermal neutral conditions.

From a synthetic viewpoint, the allyl alcohol **1a** can behave regioselectively as C-1, C-2 or C-3 carbon nucleophile depending on the experimental conditions and the electrophilic counterparts.

In particular, reactivity as C-1 carbon nucleophile was observed in the thermal aldol reaction with pyridine carbaldehyde, while allyl bromides, in the presence of NaH at room temperature, afforded in good yields the corresponding propionylpyridines allyl substituted at position 2 of the lateral chain through reaction of the C-2 carbon atom. On the other hand, treatment of **1a** with activated heterocyclic electrophiles as well as nitroalkenes allowed a 'vinylogous picolination', via nucleophilic attack of the C-3 carbon of the allyl moiety of **1a**, leading to new polyfunctionalized nitrogen heterocycles and β-substituted nitroalkanes, respectively. Moreover, a new reactivity as 1,4-dihydropyridine HEH mimic allowed the metal-free reduction of the nitro group of aromatic and heteroaromatic nitro derivatives leading to aminoalkyl pyridyl ketones through domino processes involving direct trapping of the produced amino species. Mechanistic hypothesis have been proposed to rationalize the experimental results.

These new complementary features of reactivity of alcohol **1a** appear quite intriguing from a synthetic viewpoint and encourage further studies to find conditions which reduce the drawbacks of the processes, mainly reaction yields, and to expand the synthetic application of the new synthesized products.

4. Experimental section

4.1. General

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230–400 mesh) were used for TLC and flash chromatographies (FC), respectively; petroleum ether (PE) employed for chromatographic workup refers to the fractions of bp 40–70 °C. IR spectra were recorded with a Perkin–Elmer Spectrum BX FT-IR System spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions with Varian-Gemini and Varian Mercuryplus 400 instruments, operating at 200 and 50 MHz and 400 and 100 MHz, respectively. Elemental analyses were performed in our Department with a Perkin–Elmer 2400 analyzer.

Unless otherwise stated, the thermal reactions were performed in a sealed tube (Pyrex N. 13). In the following reactions, the reagents used in large excess to reduce the competitive thermal isomerisation of alcohol **1a** to ethyl ketone **2** were recovered via FC.

4.2. Preparation of derivatives 1b and 1d. General procedure

Acetic anhydride (0.613 g, 0.566 mL, 6.0 mmol) or acryloyl chloride (0.543 g, 0.487 mL, 6.0 mmol), triethylamine (0.911 g, 1.25 mL, 9.0 mmol) and DMAP (0.073 g, 0.6 mmol) were added at 0 °C to a solution of alcohol **1a** (0.405 g, 3 mmol) in dry dichloromethane (17 mL). After 5 h at room temperature, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (17 mL) and extracted with dichloromethane (3×30 mL). The extract was washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated to dryness under reduced pressure giving a reaction crude which was resolved by FC.

4.2.1. 1-(2-Pyridyl)-2-propenyl acetate (**1b**)[7]

Colourless oil (0.505 g, 95%); R_f (PE/EtOAc 3:1) 0.33.

4.2.2. 1-(2-Pyridyl)-2-propenyl acrylate (**1d**)

Colourless oil (0.539 g, 94%); [Found: C, 69.91; H, 5.83; N, 7.34. $C_{11}H_{11}NO_2$ requires: C, 69.83; H, 5.86; N, 7.40%.] R_f (PE/EtOAc 7:1) 0.39; ν_{max} (film) 3087, 3014, 2990, 1728, 1590, 1405, 1186 cm^{-1}; δ_H (200 MHz) 5.32 (br d, J=10.3 Hz, 1H, CHCH=CH_2), 5.41 (br d, J=17.2 Hz, 1H, CHCH=CH_2), 5.89 (dd, J=10.3 and 1.5 Hz, 1H, COCH=CH_2), 6.06–6.31 (m, 2H, 2×CH=CH$_2$), 6.38 (d, J=6.2 Hz, 1H, CHCH=CH$_2$), 6.50 (dd, J=17.4 and 1.6 Hz, 1H, COCH=CH_2), 7.22 (dd, J=7.0 and 5.5 Hz, 1H, 5-H), 7.38 (d, J=7.7 Hz, 1H, 3-H), 7.70 (ddd, J=7.7, 7.7 and 1.8 Hz, 1H, 4-H), 8.61 (d, J=4.4 Hz, 1H, 6-H); δ_C (50 MHz) 76.9 (d), 117.7 (t), 121.0 (d), 122.7 (d), 128.0 (d), 131.3 (t), 134.8 (d), 136.7 (d), 149.3 (d), 157.9 (s), 164.8 (s); m/z (EI) 189 (4, M^+), 118 (100%).

4.3. Thermal isomerizations of compounds 1a–d. General procedure

A solution of the allyl pyridyl derivative (1.0 mmol) in chloroform or xylene (2 mL) was heated in a sealed tube at 110 °C or 160 °C, respectively, for the reported time. After evaporation to dryness, the reaction crude was subjected to FC.

4.3.1. 2-Propionylpyridine (**2**)[8]

FC (PE/EtOAc 6:1) of the reaction crude obtained by heating **1a** at 110 °C for 2 days gave compound **2** (R_f=0.51, 0.122 g, 90%).

4.3.2. (1Z)-1-(2-Pyridyl)-1-propenyl acetate (**3b**)

Purification by FC (PE/EtOAc 6:1) of the residue coming from heating **1b** at 110 °C for 12 days led to compound **3b** (0.110 g, 62%) as a colourless oil; [Found: C, 68.02; H, 6.13; N, 8.09. $C_{10}H_{11}NO_2$ requires: C, 67.78; H, 6.26; N, 7.90%.] R_f (PE/EtOAc 6:1) 0.33; ν_{max} (film) 3055, 3008, 2919, 1759, 1585, 1470, 1432, 1370, 1205 cm^{-1}; δ_H (400 MHz) 1.76 (d, J=7.2 Hz, 3H, CH_3), 2.34 (s, 3H, $OCOCH_3$), 6.56 (q, J=7.1 Hz, 1H, =CHCH$_3$), 7.17 (dd, J=7.5 and 4.9 Hz, 1H, 5-H), 7.30 (d, J=8.0 Hz, 1H, 3-H), 7.66 (ddd, J=7.8, 7.8, and 1.5 Hz, 1H, 4-H), 8.54 (d, J=4.9 Hz, 1H, 6-H); δ_C (100 MHz) 11.5 (q), 20.5 (q), 117.1 (d), 118.5 (d), 122.6 (d), 137.1 (d), 145.7 (s), 148.7 (d), 151.7 (s), 168.7 (s); m/z (EI) 177 (3, M^+), 135 (82), 106 (29), 79 (100%).

4.3.3. (1E)-1-(2-Pyridyl)-1-propenyl acetate (**4b**)

Operating as above, chromatographic resolution of the reaction crude obtained by heating **1b** at 160 °C for 14 days allowed the isolation of, along with compound **3b** (R_f=0.33, 0.038 g, 21%), the diastereomer **4b** (0.084 g, 47%) as colourless oil; [Found: C, 68.15; H, 6.01; N, 8.22. $C_{10}H_{11}NO_2$ requires: C, 67.78; H, 6.26; N, 7.90%.] R_f (PE/EtOAc 6:1) 0.24; ν_{max} (film) 3048, 3012, 2911, 1741, 1580, 1451, 1210 cm^{-1}; δ_H (400 MHz) 2.00 (d, J=7.6 Hz, 3H, CH_3), 2.21 (s, 3H, $OCOCH_3$), 5.75 (q, J=7.5 Hz, 1H, =CHCH$_3$), 7.18 (ddd, J=7.6, 4.8, and 1.0 Hz, 1H, 5-H), 7.37 (ddd, J=8.0, 1.0, and 1.0 Hz, 1H, 3-H), 7.69 (ddd, J=7.8, 7.8, and 1.9 Hz, 1H, 4-H), 8.63 (ddd, J=4.9, 1.8, and 1.0 Hz, 1H, 6-H); δ_C (100 MHz) 12.7 (q), 20.8 (q), 118.2 (d), 122.5 (d), 122.7 (d), 136.1 (d), 145.4 (s), 149.2 (d), 152.8 (s), 169.9 (s); m/z (EI) 177 (4, M^+), 135 (78), 106 (31), 79 (100%).

4.3.4. tert-Butyl(dimethyl)silyl (1Z)-1-(2-pyridyl)-1-propenyl ether (**3c**) and tert-butyl(dimethyl)silyl (1E)-1-(2-pyridyl)-1-propenyl ether (**4c**)

The reaction crude coming from heating **1c** at 160 °C for 10 days was resolved by FC (PE/EtOAc 50:1). The first band gave compound **4c** (0.023 g, 9% absolute yield) as colourless oil; [Found: C, 67.04; H, 8.90; N, 5.98. $C_{14}H_{23}NSiO$ requires: C, 67.42; H, 9.29; N, 5.62%.] R_f (PE/EtOAc 50:1) 0.22; ν_{max} (film) 3043, 2966, 2941, 2864, 1647, 1581, 1331 cm^{-1}; δ_H (200 MHz) 0.08 [s, 6H, $Si(CH_3)_2$], 0.94 [s, 9H, $C(CH_3)_3$], 1.93 (d, J=7.3 Hz, 3H, CH_3), 5.29 (q, J=7.4 Hz, 1H, =CHCH$_3$), 7.15 (dd, J=7.6 and 5.1 Hz, 1H, 5-H), 7.49 (d, J=8.0 Hz, 1H, 3-H), 7.68 (ddd, J=7.8, 7.8, and 1.8 Hz, 1H, 4-H), 8.59 (d, J=5.0 Hz, 1H, 6-H); δ_C (50 MHz) −4.6 (q), 12.7 (q), 18.1 (s), 25.8 (q), 109.0 (d), 121.9 (d), 122.5 (d), 135.9 (d), 147.9 (s), 148.2 (d), 156.7 (s).

The second band afforded derivative **3c** (0.064 g, 26% absolute yield) as colourless oil; [Found: C, 67.02; H, 9.61; N, 6.00. $C_{14}H_{23}NSiO$ requires: C, 67.42; H, 9.29; N, 5.62%.] R_f (PE/EtOAc 50:1) 0.18; ν_{max} (film) 3054, 2956, 2929, 2858, 1653, 1584, 1472, 1326 cm^{-1}; δ_H (200 MHz) 0.04 [s, 6H, $Si(CH_3)_2$], 1.02 [s, 9H, $C(CH_3)_3$], 1.79 (d, J=7.3 Hz, 3H, CH_3), 5.98 (q, J=7.1 Hz, 1H, =CHCH$_3$), 7.12 (dd, J=7.6 and 5.0 Hz, 1H, 5-H), 7.45 (d, J=8.0 Hz, 1H, 3-H), 7.63 (ddd, J=7.8, 7.8, and 1.7 Hz, 1H, 4-H), 8.50 (d, J=4.9 Hz, 1H, 6-H); δ_C (50 MHz) −3.9 (q), 11.8 (q), 18.35 (s), 25.9 (q), 108.8 (d), 119.4 (d), 121.9 (d), 136.1 (d), 148.7 (d), 148.75 (s), 156.2 (s).

The slowest moving band gave unreacted **1c** (R_f=0.13, 0.072 g, 29%).

4.3.5. (1Z)-1-(2-Pyridyl)-1-propenyl acrylate (**3d**)

Chromatographic resolution (PE/EtOAc 8:1) of the reaction crude obtained by heating **1d** at 110 °C for 14 days led to compound **3d** (0.128 g, 68%) as a colourless oil; [Found: C, 69.46; H, 5.70; N, 7.37. $C_{11}H_{11}NO_2$ requires: C, 69.83; H, 5.86; N, 7.40%.] R_f (PE/EtOAc 8:1) 0.29; ν_{max} (film) 3055, 3008, 2983, 2918, 1741, 1584, 1470, 1404, 1238, 1160 cm^{-1}; δ_H (200 MHz) 1.78 (d, J=7.0 Hz, 3H, CH_3), 6.04 (dd, J=10.3 and 1.4 Hz, 1H, COCH=CH_2), 6.38 (dd, J=17.2 and 10.2 Hz, 1H, COCH=CH$_2$), 6.63 (q, J=7.1 Hz, 1H, =CHCH$_3$), 6.65 (dd, J=17.3 and 1.2 Hz, 1H, COCH=CH_2), 7.16 (dd, J=7.5 and 4.8 Hz, 1H, 5-H), 7.27 (d, J=7.7 Hz, 1H, 3-H), 7.64 (ddd, J=7.7, 7.7, and 1.5 Hz, 1H, 4-H), 8.55 (d, J=4.6 Hz, 1H, 6-H); δ_C (50 MHz) 11.4 (q), 116.6 (d), 118.2 (d), 122.4 (d), 127.3 (d), 132.7 (t), 136.7 (d), 145.8 (s), 149.1 (d), 151.8 (s), 163.7 (s); m/z (CI) 190 (48, MH^+), 189 (2, M^+), 136 (100%).

4.3.6. (1E)-1-(2-Pyridyl)-1-propenyl acrylate (**4d**)

Operating as above, chromatographic resolution of the reaction crude obtained by heating **1d** at 160 °C for 7 days allowed the isolation of, along with compound **3d** (R_f=0.29, 0.038 g, 20%), the diastereomer **4d** (0.055 g, 29%) as colourless oil; [Found: C, 69.57; H, 5.58; N, 7.19. $C_{11}H_{11}NO_2$ requires: C, 69.83; H, 5.86; N, 7.40%.] R_f (PE/EtOAc 8:1) 0.23; ν_{max} (film) 3048, 3011, 2976, 1735, 1578, 1468, 1411, 1231, 1172 cm^{-1}; δ_H (200 MHz) 2.04 (d, J=7.3 Hz, 3H, CH_3), 5.80 (q, J=7.4 Hz, 1H, =CHCH$_3$), 5.94 (dd, J=10.3 and 1.2 Hz, 1H, COCH=CH_2), 6.27 (dd, J=17.2 and 10.3 Hz, 1H, COCH=CH$_2$), 6.54 (dd, J=17.2 and 1.3 Hz, 1H, COCH=CH_2), 7.19 (dd, J=7.6 and 4.7 Hz, 1H, 5-H), 7.38 (d, J=8.0 Hz, 1H, 3-H), 7.70 (ddd, J=7.8, 7.8, and 1.5 Hz, 1H, 4-H), 8.63 (d, J=4.5 Hz, 1H, 6-H); δ_C (50 MHz) 12.7 (q), 118.4 (d), 122.5 (d), 122.6 (d), 127.8 (d), 132.2 (t), 136.1 (d), 145.0 (s), 149.1 (d), 152.7 (s), 164.9 (s); m/z (CI) 190 (39, MH^+), 189 (3, M^+), 136 (100%).

4.4. 1,2-Di(2-pyridyl)-3-butene-1,2-diol (10a,b)

A mixture of alcohol **1a** (0.068 g, 0.5 mmol) and 2-pyridyl carbaldehyde (**9**) (0.161 g, 0.14 mL, 1.5 mmol) in anhydrous toluene (1 mL) was heated at 70 °C for 24 h. Chromatographic resolution (PE/

EtOAc 6:1) of the residue left by evaporation to dryness gave, after the isolation of ketone **2** (R_f = 0.36, 0.005 g, 7%), a 1:1 mixture of compounds **10a**,**b** (0.061 g, 50%) as pale yellow solid; [Found: C, 69.27; H, 6.08; N, 11.51. $C_{14}H_{14}N_2O_2$ requires: C, 69.41; H, 5.82; N, 11.56%.] R_f (PE/EtOAc 6:1) 0.14; ν_{max} (KBr) 3158, 2890, 1597, 1571, 1468, 1061 cm^{-1}; δ_H (400 MHz) 4.98 (s, 1H, 1-H), 5.00 (dd, *J*=10.7 and 1.8 Hz, 1H, 4-H), 5.10 (s, 1H, 1-H), 5.21 (dd, *J*=10.6 and 1.7 Hz, 1H, 4-H), 5.26 (dd, *J*=17.2 and 1.8 Hz, 1H, 4-H), 5.36 (v br s, 2H, 2×OH), 5.41 (dd, *J*=17.2 and 1.6 Hz, 1H, 4-H), 5.80 (v br s, 2H, 2×OH), 6.32 (dd, *J*=17.1 and 10.6 Hz, 1H, 3-H), 6.55 (dd, *J*=17.1 and 10.6 Hz, 1H, 3-H), 7.04–7.09 (m, 2H, Ar-2H), 7.18–7.23 (m, 2H, Ar-2H), 7.57–7.64 (m, 4H, Ar-4H), 7.62–7.76 (m, 4H, Ar-4H), 8.30–8.32 (m, 2H, Ar-2H), 8.45–8.49 (m, 2H, Ar-2H); δ_C (100 MHz) 76.4 (d), 78.0 (d), 78.1 (s), 78.5 (s), 114.65 (t), 114.75 (t), 121.3 (d), 121.4 (d), 122.0 (d), 122.15 (d), 122.2 (d), 122.25 (d), 122.3 (d), 122.4 (d), 136.8 (d), 136.95 (d), 137.1 (d), 137.5 (d), 139.2 (d), 141.2 (d), 146.7 (d), 146.8 (d), 146.9 (d), 146.95 (d), 160.3 (s), 161.4 (s), 163.3 (s), 164.0 (s).

4.5. Reactions of 1a with allyl bromides 11, 13, and 15. General procedure

A solution of alcohol **1a** (0.068 g, 0.5 mmol) in anhydrous THF (1 mL) was added dropwise, under nitrogen, at room temperature to a solution of NaH (0.012 g, 0.5 mmol) in the same solvent (0.25 mL). The reaction mixture was stirred at room temperature for 2 h and then the suitable allyl bromide (1 mmol) was added. The resulting mixture (which turned red during the addition) was stirred at room temperature overnight and then decomposed with aqueous hydrochloride (10%, 0.5 mL) and water (1 mL). Extraction with diethyl ether (3×3 mL), evaporation to dryness, and prolonged evacuation gave pure alkylation products.

*4.5.1. 2-Methyl-1-(2-pyridyl)-4-penten-1-one (**12**)*[14]

Compound **12** (0.050 g, 57%) was obtained as a pale yellow oil; [Found: C, 75.08; H, 7.74; N, 7.68. $C_{11}H_{13}NO$ requires: C, 75.40; H, 7.48; N, 7.99%.] ν_{max} (film) 3076, 3055, 2975, 2932, 1699, 1641, 1583 cm^{-1}; δ_H (200 MHz) 1.20 (d, *J*=7.0 Hz, 3H, CH*CH*$_3$), 2.40 (m, 2H, 3-CH_2), 4.18 (sextet, *J*=7.0 Hz, 1H, 2-H), 5.00 (m, 2H, 5-CH_2), 5.80 (m, 1H, 4-H), 7.47 (m, 1H, 5′-H), 7.85 (ddd, *J*=7.7, 7.7, and 1.5 Hz, 1H, 4′-H), 8.05 (d, *J*=7.9 Hz, 1H, 3′-H), 8.70 (d, *J*=4.4 Hz, 1H, 6′-H); δ_C (50 MHz) 16.3 (q), 37.1 (t), 38.8 (d), 116.4 (t), 122.3 (d), 126.9 (d), 136.0 (d), 136.8 (d), 148.8 (d), 152.9 (s), 204.7 (s); *m*/*z* (EI) 175 (2, M^+), 160 (16), 147 (17), 106 (19), 79 (100%).

Neutralization of the aqueous phase with a saturated solution of $NaHCO_3$, and extraction with diethyl ether (3×3 mL) allowed the recovery of unreacted **1a** (0.016 g, 24%).

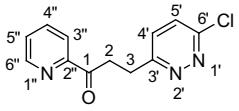
*4.5.2. 2-Methyl-1-(2-pyridyl)-4-hexen-1-one (**14**)*

Compound **14** was obtained (0.067 g, 71%) as pale orange oil; [Found: C, 75.81; H, 8.25; N, 7.15. $C_{12}H_{15}NO$ requires: C, 76.16; H, 7.99; N, 7.40%.] ν_{max} (film) 3054, 3018, 2969, 2934, 1697, 1583, 1456 cm^{-1}; δ_H (200 MHz) 1.17 (d, *J*=7.0 Hz, 3H, CH*CH*$_3$), 1.59 (m, 3H, 6-CH_3), 2.09–2.53 (m, 2H, 3-CH_2), 4.11 (sextet, *J*=6.9 Hz, 1H, 2-H), 5.42 (m, 2H, 4-H and 5-H), 7.46 (m, 1H, 5′-H), 7.84 (ddd, *J*=7.8, 7.8, and 1.4 Hz, 1H, 4′-H), 8.04 (d, *J*=8.0 Hz, 1H, 3′-H), 8.69 (d, *J*=4.0 Hz, 1H, 6′-H); δ_C (50 MHz) (the values in square brackets refer to some resonances of the minor diastereomer) [12.9 (q)], 16.3 (q), 17.9 (q), [30.4 (t)], 36.1 (t), 39.4 (d), 122.2 (d), [125.5 (d)], 126.6 (d), 126.8 (d), [127.4 (d)], 128.2 (d), 136.6 (d), 148.6 (d), 152.8 (s), 204.7 (s); *m*/*z* (EI) 189 (5, M^+), 161 (18), 146 (14), 106 (30), 91 (80), 79 (100%).

*4.5.3. 2,5-Dimethyl-1-(2-pyridyl)-4-hexen-1-one (**16**)*

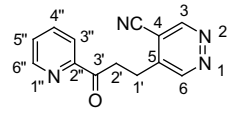
Compound **16** was obtained (0.082 g, 81%) as pale orange oil; [Found: C, 76.49; H, 8.64; N, 6.54. $C_{13}H_{17}NO$ requires: C, 76.81; H, 8.43; N, 6.89%.] ν_{max} (film) 3054, 2970, 2930, 1697, 1583, 1456 cm^{-1}; δ_H (200 MHz) 1.18 (d, *J*=7.0 Hz, 3H, CH*CH*$_3$), 1.58 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 2.30 (m, 2H, 3-CH_2), 4.09 (sextet, *J*=6.9 Hz, 1H, 2-H), 5.12 (t, *J*=7.1 Hz, 1H, 4-H), 7.46 (m, 1H, 5′-H), 7.85 (ddd, *J*=7.8, 7.8, and 1.5 Hz, 1H, 4′-H), 8.04 (d, *J*=8.0 Hz, 1H, 3′-H), 8.69 (d, *J*=4.8 Hz, 1H, 6′-H); δ_C (50 MHz) 16.1 (q), 17.7 (q), 25.7 (q), 31.6 (t), 39.8 (d), 121.7 (d), 122.3 (d), 126.8 (d), 133.2 (s), 136.8 (d), 148.8 (d), 153.1 (s), 205.3 (s); *m*/*z* (EI) 203 (1, M^+), 188 (2), 175 (11), 160 (9), 106 (11), 79 (100%).

4.6. 3-(6-Chloropyridazin-3-yl)-1-(2-pyridyl)-1-propanone (21)



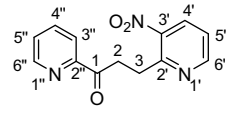
The reaction mixture obtained by heating 3,6-dichloropyridazine (**20**) (1.192 g, 8 mmol) and alcohol **1a** (0.135 g, 1 mmol) in anhydrous toluene (2 mL) at 70 °C for 48 h was resolved by FC (PE/EtOAc 1:1) to afford, after the isolation of ketone **2** (R_f=0.82, 0.070 g, 52%), compound **21** (0.048 g, 19%) as a white solid, mp 92–93 °C (from pentane); [Found: C, 57.81; H, 3.98; N, 16.71. $C_{12}H_{10}ClN_3O$ requires: C, 58.19; H, 4.07; N, 16.97%.] R_f (PE/EtOAc 1:1) 0.28; ν_{max} (KBr) 3087, 3049, 2921, 1701, 1676, 1581, 1437 cm^{-1}; δ_H (400 MHz) 3.74 (t, *J*=7.2 Hz, 2H, 2-CH_2), 4.56 (t, *J*=7.2 Hz, 2H, 3-CH_2), 6.90 (d, *J*=9.7 Hz, 1H, 4′-H), 7.15 (d, *J*=9.7 Hz, 1H, 5′-H), 7.45 (ddd, *J*=7.6, 4.8, and 1.3 Hz, 1H, 5″-H), 7.85 (ddd, *J*=7.7, 7.7, and 1.6 Hz, 1H, 4″-H), 8.04 (dd, *J*=7.8 and 1.2 Hz, 1H, 3″-H), 8.65 (ddd, *J*=4.8, 1.5, and 0.9 Hz, 1H, 6″-H); δ_C (100 MHz) 36.2 (t), 47.65 (t), 121.8 (d), 127.35 (d), 131.8 (d), 133.5 (d), 137.0 (d), 137.3 (s), 149.0 (d), 152.9 (s), 158.9 (s), 199.0 (s).

4.7. 5-[3-Oxo-3-(2-pyridyl)propyl]-4-pyridazinecarbonitrile (23)



4,5-Dicyanopyridazine (**22**) (0.130 g, 1 mmol) was added to a solution of alcohol **1a** (0.068 g, 0.5 mmol) in anhydrous toluene (1 mL) and. the resulting mixture was heated at 70 °C for 48 h. The crude product left by evaporation to dryness was subject to FC (PE/EtOAc 1:1) to afford compound **23** (0.053 g, 44%) as a pale orange solid, mp 89–90 °C (from diethyl ether/dichloromethane); [Found: C, 65.44; H, 4.22; N, 23.21. $C_{13}H_{10}N_4O$ requires: C, 65.54; H, 4.23; N, 23.52%.] R_f (PE/EtOAc 1:1) 0.28; ν_{max} (KBr) 3071, 3051, 2930, 2236, 1698, 1583, 1567, 1362 cm^{-1}; δ_H (400 MHz) 3.31 (t, *J*=7.1 Hz, 2H, 1′-CH_2), 3.76 (t, *J*=7.1 Hz, 2H, 2′-CH_2), 7.50 (ddd, *J*=7.6, 4.8, and 1.3 Hz, 1H, 5″-H), 7.85 (ddd, *J*=7.7, 7.7, and 1.7 Hz, 1H, 4″-H), 8.02 (dd, *J*=7.8 and 1.2 Hz, 1H, 3″-H), 8.65 (ddd, *J*=4.8, 1.6, and 0.9 Hz, 1H, 6″-H), 9.23 (d, *J*=1.0 Hz, 1H, 3-H), 9.42 (d, *J*=1.0 Hz, 1H, 6-H); δ_C (100 MHz) 25.8 (t), 36.8 (t), 113.35 (s), 113.6 (s), 121.9 (d), 127.7 (d), 137.1 (d), 143.5 (s), 149.1 (d), 150.2 (d), 152.3 (s), 152.65 (d), 198.5 (s); *m*/*z* (EI) 238 (11, M^+), 222 (5), 210 (13), 209 (26), 132 (31), 106 (24), 79 (100), 78 (92), 51 (95%).

4.8. 3-(3-Nitro-2-pyridyl)-1-(2-pyridyl)-1-propanone (25)



2-Chloro-3-nitropyridine (**24**) (0.396 g, 2.5 mmol) was added to a solution of alcohol **1a** (0.068 g, 0.5 mmol) and NaH (0.016 g, 0.67 mmol) in anhydrous toluene (1 mL), previously stirred at room

temperature for three hours. The reaction mixture was then heated at 70 °C for six days. The resulting crude was treated with aqueous hydrochloride (10%, 0.5 mL) and water (1 mL) and extracted with dichloromethane (3×5 mL). The crude product left by evaporation to dryness was subjected to FC with PE/EtOAc 2:1 as eluent leading to ketone **2** (R_f=0.70, 0.027 g, 40%) and with PE/EtOAc 1:2 to isolate the nitro derivative **25** (0.020 g, 15%) as a pale orange solid, mp 144–145 °C (from ethyl acetate); [Found: C, 60.37; H, 4.24; N, 16.10. $C_{13}H_{11}N_3O_3$ requires: C, 60.70; H, 4.31; N, 16.33%.] R_f (PE/EtOAc 1:2) 0.24; ν_{max} (KBr) 3120, 3052, 2923, 1694, 1679, 1598, 1523, 1355 cm^{-1}; δ_H (400 MHz) 3.86 (t, J=6.0 Hz, 2H, 2-CH_2), 4.49 (t, J=6.0 Hz, 2H, 3-CH_2), 6.28 (dd, J=7.7 and 6.6 Hz, 1H, 5′-H), 7.48 (ddd, J=7.7, 4.7, and 1.4 Hz, 1H, 5″-H), 7.83 (ddd, J=7.7, 7.7, and 1.6 Hz, 1H, 4″-H), 7.98 (ddd, J=7.7, 1.1, and 1.1 Hz, 1H, 3″-H), 8.07 (dd, J=6.6 and 2.1 Hz, 1H, 6′-H), 8.30 (dd, J=7.7 and 2.0 Hz, 1H, 4′-H), 8.65 (ddd, J=4.7, 1.6, and 1.0 Hz, 1H, 6″-H); δ_C (100 MHz) 36.35 (t), 47.0 (t), 102.9 (d), 121.6 (d), 127.7 (d), 136.9 (d), 138.6 (s), 138.8 (d), 146.1 (d), 149.2 (d), 152.4 (s), 154.4 (s), 199.6 (s); m/z (EI) 257 (1, M^+), 212 (13), 133 (62), 132 (42), 105 (88), 80 (49), 78 (100%).

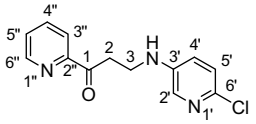
4.9. Reactions of 1a with nitro derivatives 24, 32, 34, 36, and 38a,b. General procedure

Alcohol **1a** (0.068 g, 0.5 mmol) was heated at 70 or 110 °C in toluene or xylene (1 mL) with the suitable nitro compound until its complete disappearance. Removal of the solvent in vacuo and purification by FC allowed, after the recovery of unreacted nitro compound, to isolate the reaction products along with different amounts of ketone **2**.

*4.9.1. 3-[(2-Chloro-3-pyridyl)amino]-1-(2-pyridyl)-1-propanone (**26**)*

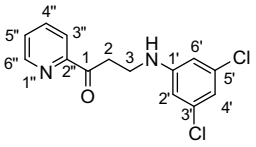
See Ref. 6.

*4.9.2. 3-[(6-Chloro-3-pyridyl)amino]-1-(2-pyridyl)-1-propanone (**33**)*



The reaction mixture obtained by heating **1a** and **32** (0.396 g, 2.5 mmol) in toluene at 70 °C for 48 h was resolved with PE/EtOAc 2:1, leading to ketone **2** (R_f=0.70, 0.013 g, 19%) and compound **33** (0.020 g, 15%) as ivory coloured needles, mp 112–113 °C (from *n*-hexane/acetone); [Found: C, 59.53; H, 4.53; N, 15.77. $C_{13}H_{12}ClN_3O$ requires: C, 59.66; H, 4.62; N, 16.06%.] R_f (PE/EtOAc 2:1) 0.14; ν_{max} (KBr) 3395, 3055, 2858, 1690, 1585, 1459, 1326 cm^{-1}; δ_H (400 MHz) 3.54 (m, 2H, 2-CH_2), 3.58 (m, 2H, 3-CH_2), 4.25 (br s, 1H, NH), 6.93 (dd, J=8.6 and 3.1 Hz, 1H, 4′-H), 7.08 (d, J=8.6 Hz, 1H, 5′-H), 7.50 (m, 1H, 5″-H), 7.80 (d, J=2.9 Hz, 1H, 2′-H), 7.86 (ddd, J=7.7, 7.7, and 1.7 Hz, 1H, 4″-H), 8.05 (d, J=7.8 Hz, 1H, 3″-H), 8.68 (d, J=4.3 Hz, 1H, 6″-H); δ_C (100 MHz) 37.2 (t), 39.4 (t), 122.2 (d), 122.7 (d), 124.4 (d), 127.9 (d), 135.0 (d), 137.4 (d), 139.3 (s), 143.3 (s), 149.4 (d), 153.2 (s), 200.9 (s).

*4.9.3. 3-(3,5-Dichloroanilino)-1-(2-pyridyl)-1-propanone (**35**)*



Chromatographic resolution (PE/EtOAc 4:1) of the crude obtained by heating **1a** and **34** (0.48 g, 2.5 mmol) in toluene at 110 °C for 18 h afforded ketone **2** (R_f=0.49, 0.009 g, 13%) and compound **35** (0.015 g, 10%) as pale yellow oil; R_f (PE/EtOAc 4:1) 0.21; ν_{max} (film) 3395, 3057, 2916, 1694, 1590, 1569 cm^{-1}; δ_H (400 MHz) 3.49 (m, 2H, 2-CH_2), 3.55 (m, 2H, 3-CH_2), 4.41 (br s, 1H, NH), 6.49 (d, J=1.6 Hz, 2H, 2′-H and 6′-H), 6.63 (t, J=1.7 Hz, 1H, 4′-H), 7.49 (ddd, J=7.7, 4.7, and 1.2 Hz, 1H, 5″-H), 7.84 (ddd, J=7.8, 7.8, and 1.6 Hz, 1H, 4″-H), 8.04 (dd, J=7.8 and 1.0 Hz, 1H, 3″-H), 8.69 (ddd, J=4.8, 1.8. and 1.0 Hz, 1H, 6″-H); δ_C (100 MHz) 37.0 (t), 38.8 (t), 111.0 (d), 117.0 (d), 121.9 (d), 127.5 (d), 135.5 (s), 137.1 (d), 149.0 (d), 149.5 (s), 152.9 (s), 200.6 (s); HRMS (ESI): MNa^+, found 317.0222. $C_{14}H_{12}Cl_2N_2NaO$ requires 317.0219.

*4.9.4. 3-Anilino-1-(2-pyridyl)-1-propanone (**37**)[20]*

Chromatographic resolution (PE/EtOAc 3:1) of the crude obtained by heating **1a** and **36** (0.554 g, 0.46 mL, 4.5 mmol) in xylene at 150 °C for 4 h afforded ketone **2** (R_f=0.59, 0.010 g, 15%) and amino ketone **37** (0.013 g, 11%) as a pale solid, mp 78–79 °C (from methanol–ether); R_f (PE/EtOAc 3:1) 0.28; δ_H (400 MHz) 3.62 (m, 4H, 2-CH_2 and 3-CH_2), 5.45 (br s, 1H, NH), 6.81–6.85 (m, 3H, Ar-3H), 7.19–7.23 (m, 2H, Ar-2H), 7.47 (ddd, J=7.6, 4.9, and 1.2 Hz, 1H, 5′-H), 7.83 (ddd, J=7.7, 7.7, and 1.8 Hz, 1H, 4′-H), 8.03 (dd, J=7.8 and 1.2 Hz, 1H, 3′-H), 8.65 (ddd, J=4.8, 2.0. and 0.8 Hz, 1H, 6′-H); δ_C (100 MHz) 36.8 (t), 40.7 (t), 114.8 (d), 119.5 (d), 121.8 (d), 127.4 (d), 129.4 (d), 136.95 (d), 149.0 (d), 149.05 (s), 152.95 (s), 200.6 (s).

*4.9.5. 5-Nitro-4-phenyl-1-(2-pyridyl)-1-pentanone (**39a**)*

The reaction mixture obtained by heating **1a** and **38a** (0.373 g, 2.5 mmol) in toluene at 110 °C for 18 h was resolved with PE/EtOAc 4:1, leading to ketone **2** (R_f=0.49, 0.021 g, 30%) and compound **39a** (0.043 g, 30%) as a pale oil; R_f (PE/EtOAc 4:1) 0.16; ν_{max} (film) 3053, 2922, 1695, 1541, 1379 cm^{-1}; δ_H (400 MHz) 2.16 (m, 2H, 3-CH_2), 3.14 (m, 2H, 2-CH_2), 3.60 (m, 1H, 4-H), 4.63 (AB part of an ABX system, J=12.2 and 7.7 Hz, 2H, 5-CH_2), 7.22–7.36 (m, 5H, Ph), 7.43 (ddd, J=7.6, 4.8, and 1.0 Hz, 1H, 5′-H), 7.80 (ddd, J=7.7, 7.7, and 1.7 Hz, 1H, 4′-H), 7.98 (ddd, J=7.8, 1.2 and 1.2 Hz, 1H, 3′-H), 8.60 (ddd, J=4.6, 1.7, and 0.9 Hz, 1H, 6′-H); δ_C (100 MHz) 27.1 (t), 35.0 (t), 43.75 (d), 80.8 (t), 121.7 (d), 127.2 (d), 127.6 (d), 127.8 (d), 128.9 (s), 129.0 (d), 136.9 (d), 148.9 (d), 153.0 (s), 200.7 (s); HRMS (ESI): MH^+, found 285.1237. $C_{16}H_{17}N_2O_3$ requires 285.1234.

*4.9.6. 5-Nitro-4-(4-bromophenyl)-1-(2-pyridyl)-1-pentanone (**39b**)*

Operating as above with **38b** (0.570 g, 2.5 mmol), chromatographic resolution (PE/EtOAc 3:1) gave ketone **2** (R_f=0.59, 0.012 g, 18%) and compound **39b** (0.035 g, 19%) as a pale yellow oil; R_f (PE/EtOAc 3:1) 0.21; ν_{max} (film) 3051, 2926, 1690, 1546, 1383 cm^{-1}; δ_H (400 MHz) 2.12 (m, 2H, 3-CH_2), 3.12 (m, 2H, 2-CH_2), 3.58 (m, 1H, 4-H), 4.61 (AB part of an ABX system, J=12.5 and 7.6 Hz, 2H, 5-CH_2), 7.11 (m, 2H, Ar-2H), 7.43–7.46 (m, 3H, 5′-H and Ar-2H), 7.81 (ddd, J=7.7, 7.7, and 1.8 Hz, 1H, 4′-H), 7.98 (ddd, J=7.8, 1.0 and 1.0 Hz, 1H, 3′-H), 8.60 (ddd, J=4.7, 1.7. and 0.9 Hz, 1H, 6′-H); δ_C (100 MHz) 27.1 (t), 34.8 (t), 43.2 (d), 80.5 (t), 121.7 (d), 127.3 (d), 129.1 (s), 129.4 (d), 132.0 (s), 132.2 (d), 136.9 (d), 148.9 (d), 152.9 (s), 200.5 (s); HRMS (ESI): MH^+, found 363.0342. $C_{16}H_{16}BrN_2O_3$ requires 363.0339.

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