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(2-Pyridyl)phenyl methanol: a new reagent for metal-free reduction of nitro aromatic compounds

Donatella Giomi *, Renzo Alfini, Alberto Brandi *

Dipartimento di Chimica 'Ugo Schiff', Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Biologicamenti Attivi (HeteroBioLab), Università di Firenze, Polo Scientifico e Tecnologico, Via della Lastruccia 3-13, I-50019 Sesto Fiorentino, Italy

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ABSTRACT

As previously reported for 1-(2-pyridyl)-2-propen-1-ol, (2-pyridyl)phenyl methanol is able to react as hydrogen donor towards nitro aromatic and heteroaromatic compounds. Operating in the presence of methyl acrylate as an aza-Michael acceptor, a domino process involving reduction and conjugate addition steps allows the one pot formation of β-amino esters. The crucial role of the pyridine nucleus in making this purely thermal reactivity of carbinols possible has been shown.

1. Introduction

In biological systems, reductions proceed smoothly under mild conditions in cascade processes involving metalloenzymes and organic hydride reduction cofactors, such as nicotinamide adenine dinucleotide (NADH) and the corresponding phosphate ester (NADPH).[1] In order to understand the mechanism of the hydride transfer, many 1,4-dihydropyridine derivatives have been extensively investigated as NADH models for the reduction of unsaturated organic compounds[2] in the absence of metal ions, under thermal or Brùnsted acid-catalyzed conditions. In particular, after the pioneering works of Braude and Dittmer,[3] noteworthy results in the last 50 years demonstrate that Hantzsch ester (HEH) and other 1,4-dihydropyridine systems work as efficient and versatile reducing agents.[4]

Moreover, even if the most common methods applied for the reduction of organic compounds exploit metal catalysts in conjunction with a hydrogen source, in the last decade great attention has been devoted to the development of organocatalysis,[5] namely the acceleration of chemical reactions through the addition of a substoichiometric amount of an organic compound, which does not contain a metal atom. This combines significant preparative advantages (reactions performed under aerobic conditions, in wet solvents, with inexpensive catalysts, etc.) and in many cases extremely high enantioselectivities.[6] On this basis, new metal-free organocatalytic strategies based on the use of small molecules as organocatalysts and 1,4-dihydropyridine systems as hydrogen donors have been described.[7]

Concerning nitro compounds, their synthetic applications and, hence, their reduction processes have been extensively reviewed.[8] The reduction of aromatic nitro derivatives to amines has been mainly performed with metals and acid, by catalytic hydrogenation, or with hydrides and various catalysts.[9] Aniline derivatives have also been obtained in alcoholic media in the presence of dodecacarbonyltriiron[10] or bases,[11] although in the last case different reaction products were isolated depending on the experimental conditions. Recently, hydrogenation of nitrobenzene to give aniline has been performed in the presence of fullerene, as a non-metal catalyst for the activation of molecular hydrogen, under UV irradiation or by heating under a high pressure of H_2.[12] Only few examples of purely thermal metal-free reductions of aromatic nitro derivatives exploiting 9,10-dihydroanthracene[13] or 1,4-dihydropyridine systems[3,14,15] as hydrogen source have been reported.

In this context, we recently described a surprising reactivity of 1-(2-pyridyl)-2-propen-1-ol as 1,4-dihydropyridine HEH mimic for the metal-free reduction of nitro groups to amino functions in aromatic and heteroaromatic nitro compounds.[16,17] A low chemical efficiency of the reduction was, however, observed due to competitive thermal isomerization of the allyl alcohol into the corresponding ethyl ketone. Other pyridyl carbinols were taken into consideration to avoid such

* Corresponding authors. Tel.: +39 055 4573475; fax: +39 055 4573575 (D.G.); Tel.: +39 055 4573485; fax: +39 055 4573572 (A.B.); e-mail addresses: donatella.giomi@unifi.it (D. Giomi), alberto.brandi@unifi.it (A. Brandi).

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drawbacks and, in this paper, (2-pyridyl)phenyl methanol (**1**)[18] demonstrated its efficiency as hydrogen donor.

2. Results and discussion

As aromatic amines are often quite unstable compounds, they are preferably trapped during their synthesis. Indeed, in a preliminary study,[16] (2-pyridyl)phenyl methanol (**1**) and 2-chloro-3-nitropyridine (**2**) completely disappeared after heating in toluene at 110 °C for 96 h, leading to a complex reaction mixture mainly containing ketone **3**[18a,18d,19] and only trace amounts of 3-amino-2-chloropyridine (**4**). It is likely that the free amine, coming from the reduction of **2**, undergoes different competitive reaction pathways. Among them, however, the condensation of **4** with ketone **3** should be ruled out as the corresponding product was never observed in the reaction crude.

Performing the above reaction in the presence of methyl acrylate as aza-Michael acceptor, the amino ester **5** was isolated in 65% yield.[16] Thus, the method provided an excellent access to β-amino esters in a domino multicomponent process. β-Amino acids and their derivatives are valuable synthetic intermediates.[20] The reaction was then optimized using an excess of methyl acrylate (see Experimental section) in acetonitrile to favour the trapping of the free amine (Scheme 1). Careful chromatographic separation allowed isolation of amino derivatives **4** and **5** in 8 and 68% yields, respectively, along with ketone **3** (recovered in 89% yield, based on reacted alcohol **1**). Attempts to complete the conversion of **4** into **5** by operating with a larger excess of acrylate or by addition of a catalytic amount of acetic acid were unsuccessful.

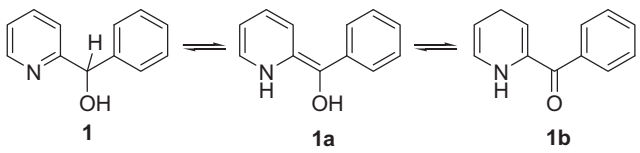
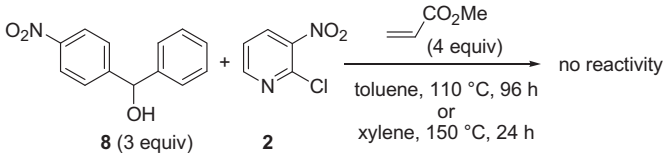


Fig. 1. Tautomeric forms of alcohol **1**.

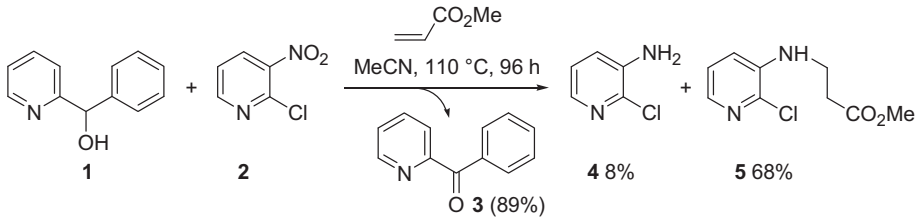
from the reaction mixture mainly containing the starting reagents (Scheme 3). This result clearly showed the key role of the pyridine ring in promoting the reactivity of **1** as a reducing agent.



Scheme 3. Reactions of carbinol **8** with 2-chloro-3-nitropyridine (**2**).

Reactions of other nitro heterocycles with alcohol **1** were studied to demonstrate the generality of the process (Table 1).

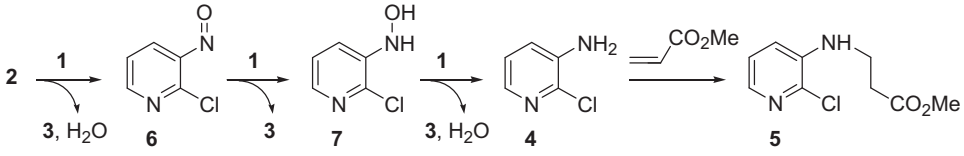
Under the same reaction conditions, a complex reaction mixture was obtained from the isomeric 2-chloro-5-nitropyridine (**9**): the amino ester **10** was isolated in only 30% yield, with ketone **3** recovered in 84% yield (Table 1, entry 2). The switch to acetonitrile as solvent did not change the poor result, probably due to side reactions of the formed 5-amino-2-chloropyridine.[24]



Scheme 1. Reaction of alcohol **1** with 2-chloro-3-nitropyridine (**2**).

From a mechanistic viewpoint, the reaction stoichiometry (alcohol/nitro derivative ratio at least 3:1), associated with the recovery of ketone **3**, seems to confirm the hypothesis of a domino process. Alcohol **1** acts as a reducing agent able to transform 2-chloro-3-nitropyridine (**2**), via the nitroso and hydroxylamino intermediates **6** and **7**, into the amino derivative **4**, converted into the final product through aza-Michael addition to methyl acrylate (Scheme 2).

On the basis of the interest in 4-aminopyridine in the pharmacological domain,[25] and with the aim to test monofunctional nitropyridines to limit competitive pathways, 4-nitropyridine (**11**)[26] was allowed to react with **1**. However, a completely different behaviour was observed. Operating in acetonitrile at 110 °C, only the pyridone derivative **12** was isolated in 57% yield (Table 1, entry 3).[27] Control experiments showed that the same compound formed



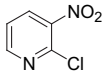
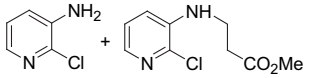
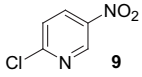
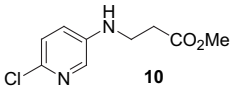
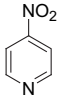
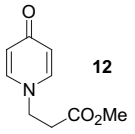
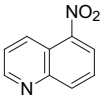
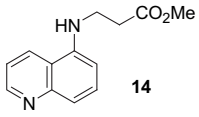
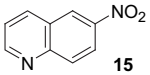
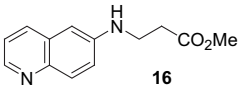
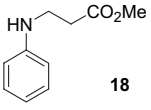
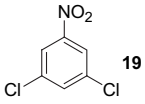
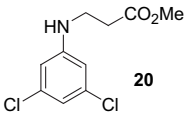
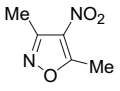
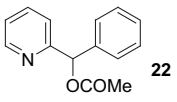
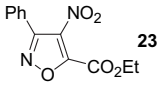
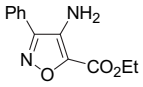
Scheme 2. Mechanistic rationale accounting for the formation of compound **5**.

Such reactivity of alcohol **1** could be ascribed to its behaviour as a HEH mimic[16,17] through the involvement of a 1,4-dihydropyridine tautomer **1b** generated as a consequence of the mobility of the hydrogen atom of the methanol residue (Fig. 1).

Moreover, the crucial role of the pyridine ring is demonstrated in the lack of reactivity towards 2-chloro-3-nitropyridine (**2**) of the apparently analogous nitrophenyl derivative **8**.[21] In toluene at 110 °C or in xylene at 150 °C, alcohol **8** was only poorly converted to 4-nitrobenzophenone,[22,23] and reduction products were absent also in absence of **1**, likely due to the hydrolysis of 4-nitropyridine to 4-pyridone[28,29] followed by aza-Michael addition to methyl acrylate. However, 4-nitropyridine (**11**) was recovered unchanged after heating at 110 °C in dry toluene in the presence of alcohol **1** and molecular sieves.

Better results were obtained with monofunctionalized nitro heterocycles, such as 5-nitroquinoline (**13**) and 6-nitroquinoline (**15**) which gave, in acetonitrile as solvent, the valuable β-amino esters **14** and **16** in 57 and 55% yields, respectively (Table 1, entries 4 and 5).

Table 1
Reduction of nitroarenes to aminoarenes and aza-Michael addition to methyl acrylate

Entry	Reagent	Reaction conditions[a]	Product	Yield[b]
1	 **2**	MeCN 110 °C, 96 h	 **4** **5**	**4** 8% **5** 68%
2	 **9**	toluene 110 °C, 63 h	 **10**	30%
3[c]	 **11**	MeCN 110 °C, 43 h	 **12**	57%
4	 **13**	MeCN 110 °C, 6 days	 **14**	57%
5	 **15**	MeCN 110 °C, 7 days	 **16**	55%
6	 **17**	MeCN 110 °C, 10 days, 20 mol % AcOH	 **18**	63%
7	 **19**	Toluene 110 °C, 67 h, 20 mol % AcOH	 **20**	15%
8[c, d]	 **21**	Xylene 150 °C, 46 h	 **22**	29%
9[d]	 **23**	Toluene 110 °C, 64 h	 **24**	48%

[a] (2-Pyridyl)phenyl methanol (**1**) (3.5 equiv), methyl acrylate (4 equiv), screw-cap tube (Pyrex N. 15). Reaction times refer to disappearance of starting nitro derivative.
[b] Isolated yields.
[c] The reaction product is not related to the reduction process.
[d] Reaction performed without methyl acrylate.

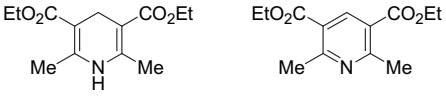
Nitrobenzene derivatives could be also reduced by alcohol **1**. The reactions were performed in the presence of 20 mol % of AcOH to favour the aza-Michael addition.[20,30] Nitrobenzene (**17**) gave the β-anilino ester **18** in 63% yield by prolonged heating in MeCN (10 days, Table 1, entry 6), whereas the more activated dichloro derivative **19** was more quickly converted in toluene into the amino ester **20**, isolated in only 15% yield (Table 1, entry 7).

The reactivity of **1** was also tested towards available heterocycles like nitroisoxazoles. 3,5-Dimethyl-4-nitroisoxazole (**21**) was recovered unchanged after heating with an excess of **1** in toluene at 110 °C for 96 h, while when operating in xylene at 150 °C only the acetate **22** was isolated in 29% yield (Table 1, entry 8). It is likely that thermal decomposition of the isoxazole **21** prevails in these conditions, showing its reactivity as a masked acetate.[31] Nucleophilic attack of the alcohol **1** on the C-5 carbon atom of the isoxazole ring and subsequent ring opening gave the acetate **22**.

In contrast, a chemoselective reduction of the NO_2 group of the nitro ester **23**[32] leading to the corresponding amino isoxazole **24** in

48% yield was achieved (Table 1, entry 9). Attempts to convert **24** into the corresponding β-amino ester operating in the presence of methyl acrylate were unsuccessful, likely due to the less nucleophilic character of the amino function.

To evaluate the potential of (2-pyridyl)phenyl methanol (**1**) in the reduction of nitro aromatics and heteroaromatics, its reactivity towards the poorly activated nitrobenzene (**17**) was compared with that of Hantzsch ester **25**. When nitrobenzene was heated in a screw-cap tube with an excess of **25** (3 equiv) in toluene or MeCN, after 72 h at 70 °C the reaction mixture appeared unchanged. Raising the temperature to 110 °C for 5 days, the conversion of **25** into the corresponding pyridine derivative **26** was the only significant process,[33] and only trace amounts of aniline were observed (GC–MS) along with unreacted **17**. Operating under the same conditions described for alcohol **1** (MeCN, in the presence of methyl acrylate and AcOH as catalyst), after 5 days at 110 °C, **18** was completely absent in the reaction mixture containing pyridine **26** and nitrobenzene (**17**). The same result was also observed when the more activated 2-chloro-3-nitropyridine (**2**) was heated with ester **25** and methyl acrylate at 110 °C in MeCN for 4 days: only unreacted **2** and the aromatic derivative **26** were detected in the reaction mixture.



25 **26**

The lack of reactivity of the Hantzsch ester is remarkable, as this popular reagent has been employed in a vast array of hydrogen transfer reductions,[4,7] and provides even more interest in (2-pyridyl)phenyl methanol (**1**) as a new reducing agent. An explanation of the different reactivity is rather premature, although a brief structural comparison of the two compounds shows the presence of sterically bulky substituents in the dihydropyridine ring of Hantzsch ester that might slow down its reactivity compared to **1**.

3. Conclusions

The above results demonstrate the ability of pyridyl carbinol **1** to react as hydrogen donor towards nitro aromatic and heteroaromatic derivatives. The observed reactivity extends that already reported for 1-(2-pyridyl)-2-propen-1-ol.[16,17] Pyridyl carbinol **1** proves to be a superior reagent for this chemistry, as the replacement of the vinyl group with the phenyl ring prevents competitive reactions observed for pyridylpropenol, such as thermal isomerisation or nucleophilic substitutions/additions, allowing the use of almost stoichiometric amounts of the reducing agent. Moreover, the oxidation product, ketone **3**, can be recovered and recycled through reduction with $NaBH_4$.[34]

Despite the isolation of the free amines being impractical, operating in the presence of methyl acrylate as aza-Michael acceptor, a domino process involving reduction and conjugate addition allows the one pot formation of β-amino esters as the product of multicomponent reactions (3-MCR)[35] involving alcohol **1**, the nitro compound, and methyl acrylate. Comparing the reactivity of carbinols **1** and **8**, the crucial role of the pyridine nucleus to make this purely thermal reactivity of **1** possible is well evidenced. Moreover, the reducing ability of **1** is even more striking if compared with the inertness of Hantzsch ester **25** in reducing 2-chloro-3-nitropyridine (**2**) and nitrobenzene (**17**) in purely thermal conditions.

In the light of the great interest associated with multicomponent and organocatalytic metal-free processes, further studies are underway in our laboratories to test the reactivity of pyridyl carbinols as reducing agents towards different substrates.

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 (FCs), respectively; petroleum ether (PE) employed for crystallizations and chromatographic workup refers to the fractions of bp 30–50 and 40–70 °C, respectively. 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 a Varian Mercuryplus 400 instrument, operating at 400 and 100 MHz, respectively. Elemental analyses were performed with a Perkin–Elmer 2400 analyzer.

Accurate mass spectra were recorded on an LTQ-Orbitrap high-resolution mass spectrometer (Thermo, San Jose, CA, USA), equipped with a conventional ESI source.

4.2. Reaction of 1 with nitro derivatives 2, 9, 11, 13. General procedure

Nitro compound (0.5 mmol), alcohol **1** (0.324 g, 1.75 mmol) and methyl acrylate (0.180 mL, 2 mmol) were mixed in toluene or acetonitrile (1 mL) degassed by several vacuum–nitrogen cycles to reduce the air oxidation of alcohol **1** to ketone **3**. The resulting mixture was heated at 110 °C in a screw-cap tube (Pyrex N. 15) until the disappearance of the starting nitro compound. Removal of the solvent in vacuo and purification by FC gave the β-amino esters and ketone **3**. The excess alcohol **1** was recovered and recycled.

*4.2.1. 3-Amino-2-chloropyridine (**4**).* In the reaction crude obtained by heating 2-chloro-3-nitropyridine (**2**) (0.079 g, 0.5 mmol) and alcohol **1** (0.324 g, 1.75 mmol) in toluene (1 mL) at 110 °C for 96 h, without methyl acrylate, ketone **3** was the predominant product (ca. 90%, ^1H NMR spectroscopy) while only trace amounts of amine **4** (ca. 5%, ^1H NMR spectroscopy) were detected.

*4.2.2. Methyl 3-[(2-chloro-3-pyridyl)amino]propanoate (**5**).* The reaction mixture obtained by heating 2-chloro-3-nitropyridine (**2**) (0.079 g, 0.5 mmol), alcohol **1** (0.324 g, 1.75 mmol) and methyl acrylate (0.180 mL, 2 mmol) in acetonitrile (1 mL) at 110 °C for 96 h, was resolved by FC (DCM/EtOAc 100:3), leading to ketone **3** (R_f=0.43, 0.244 g, 89% referred to reacted **1**), 3-amino-2-chloropyridine (**4**) (R_f=0.20, 0.005 g, 8%) and compound **5** (R_f=0.18, 0.073 g, 68%) as a dark yellow oil: IR (film) 3402, 3059, 2954, 2918, 1734, 1586, 1495, 1176 cm^{-1}; ^1H NMR δ 2.66 (t, J=6.4 Hz, 2H, CH_2CO_2Me), 3.50 (t, J=6.4 Hz, 2H, CH_2NH), 3.71 (s, 3H, OCH_3), 4.90 (br s, 1H, NH), 6.95 (dd, J=8.0 and 1.5 Hz, 1H, 4-H), 7.12 (dd, J=8.0 and 4.7 Hz, 1H, 5-H), 7.73 (dd, J=4.7 and 1.4 Hz, 1H, 6-H); ^{13}C NMR δ 33.4 (t), 38.7 (t), 52.0 (q), 117.7 (d), 123.5 (d), 136.2 (d), 136.9 (s), 140.4 (s), 172.1 (s). HRMS (ESI): MH^+, found 215.0582, $C_9H_{12}{}^{35}ClN_2O_2$ requires 215.0586.

*4.2.3. Methyl 3-[(6-chloro-3-pyridyl)amino]propanoate (**10**).* The crude obtained by heating alcohol **1** (0.324 g, 1.75 mmol), compound **9** (0.079 g, 0.5 mmol) and methyl acrylate (0.180 mL, 2 mmol) in toluene (1 mL) for 63 h was subjected to FC with DCM/EtOAc 20:1 as eluent leading to ketone **3** (R_f=0.47, 0.229 g, 84% referred to reacted **1**) and with DCM/EtOAc 6:1 to isolate compound **10** (R_f=0.23, 0.032 g, 30%) as ivory needles, mp 86–87 °C (from PE/Et_2O 4:1); [found: C, 50.08; H, 4.96; N, 12.97. $C_9H_{11}ClN_2O_2$ requires: C, 50.36; H, 5.17; N, 13.05%]. IR (KBr) 3397, 3051, 2947, 2890, 2853, 1723, 1594, 1461, 1441, 1209 cm^{-1}; ^1H NMR δ 2.62 (t, J=6.1 Hz, 2H, CH_2CO_2Me), 3.43 (q, J=6.2 Hz, 2H, CH_2NH), 3.71 (s, 3H, OCH_3), 4.16 (br s, 1H, NH), 6.88 (dd, J=8.4 and 3.3 Hz,

1H, 4-H), 7.09 (d, J=8.3 Hz, 1H, 5-H), 7.77 (d, J=3.4 Hz, 1H, 2-H); ^{13}C NMR δ 33.3 (t), 39.2 (t), 51.9 (q), 122.4 (d), 124.1 (d), 134.7 (d), 139.4 (s), 142.7 (s), 172.4 (s).

*4.2.4. Methyl 3-[4-oxo-1-(4H)-pyridyl]propanoate (**12**)*[36]. 4-Nitropyridine (**11**) (0.062 g, 0.5 mmol), alcohol **1** (0.324 g, 1.75 mmol) and methyl acrylate (0.180 mL, 2 mmol) were heated in MeCN (1 mL) at 110 °C for 43 h. Chromatographic resolution (EtOAc/MeOH/NEt$_3$ 7:2:2) gave alcohol **1** and ketone **3** as a 3:1 mixture (^{1}H NMR spectroscopy) (R_f=0.86, 0.310 g) and compound **12** (R_f=0.33, 0.052 g, 57%) as a pale yellow oil. IR (film) 3004, 2956, 1737, 1641, 1578, 1190 cm^{-1}; ^{1}H NMR δ 2.78 (t, J=6.3 Hz, 2H, CH_2CO$_2$Me), 3.69 (s, 3H, OCH$_3$), 4.09 (t, J=6.3 Hz, 2H, CH_2NH), 6.35 (d, J=7.8 Hz, 2H, 3-H and 5-H), 7.35 (d, J=7.8 Hz, 2H, 2-H and 6-H); ^{13}C NMR δ 35.0 (t), 51.9 (t), 52.3 (q), 118.8 (d), 139.9 (d), 170.5 (s), 178.7 (s). HRMS (ESI): MH$^+$, found 182.0814, $C_9H_{12}NO_3$ requires 182.0817.

*4.2.5. Methyl 3-(5-quinolylamino)propanoate (**14**).* The residue coming from heating alcohol **1** (0.324 g, 1.75 mmol), 5-nitroquinoline (**13**) (0.087 g, 0.5 mmol) and methyl acrylate (0.180 mL, 2 mmol) at 110 °C in MeCN (1 mL) for 6 days, was resolved by FC with PE/EtOAc 3:1 as eluent leading to ketone **3** (R_f=0.43, 0.242 g, 88% referred to reacted **1**) and with PE/EtOAc 1:1 to isolate compound **14** (R_f=0.18, 0.065 g, 57%) as yellow needles, mp 79–80 °C (from PE/Et$_2$O 3:1); [found: C, 67.72; H, 6.41; N, 12.29. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17%]. IR (KBr) 3269, 3085, 2946, 1729, 1583, 1204, 1119 cm^{-1}; ^{1}H NMR δ 2.75 (t, J=6.4 Hz, 2H, CH_2CO$_2$Me), 3.59 (m, 2H, CH_2NH), 3.71 (s, 3H, OCH$_3$), 4.97 (br s, 1H, NH), 6.63 (d, J=7.6 Hz, 1H, 6-H), 7.30 (dd, J=8.4 and 4.3 Hz, 1H, 3-H), 7.48–7.57 (m, 2H, 7-H and 8-H), 8.16 (d, J=8.3 Hz, 1H, 4-H), 8.85 (dd, J=4.3 and 1.4 Hz, 1H, 2-H); ^{13}C NMR δ 33.1 (t), 39.5 (t), 51.8 (q), 104.7 (d), 118.7 (s), 118.8 (d), 119.4 (d), 128.8 (d), 130.2 (d), 143.1 (s), 149.2 (s), 150.0 (d), 172.9 (s).

*4.2.6. Methyl 3-(6-quinolylamino)propanoate (**16**).* Operating as above with compound **15** (0.087 g, 0.5 mmol) for 7 days, chromatographic resolution with DCM/EtOAc 4:1 as eluent gave ketone **3** (R_f=0.61, 0.230 g, 84% referred to reacted **1**) while the use of EtOAc/DCM 3:1 gave derivative **16** (R_f=0.20, 0.063 g, 55%) as a pale yellow oil; [found: C, 67.47; H, 6.35; N, 11.83. $C_{13}H_{14}N_2O_2$ requires: C, 67.81; H, 6.13; N, 12.17%]. IR (film) 3393, 3266, 3024, 2950, 1734, 1624, 1174 cm^{-1}; ^{1}H NMR δ 2.70 (t, J=6.3 Hz, 2H, CH_2CO$_2$Me), 3.57 (q, J=6.1 Hz, 2H, CH_2NH), 3.72 (s, 3H, OCH$_3$), 4.37 (br s, 1H, NH), 6.72 (d, J=2.7 Hz, 1H, 5-H), 7.09 (dd, J=9.2 and 2.5 Hz, 1H, 7-H), 7.26 (dd, J=8.4 and 4.1 Hz, 1H, 3-H), 7.87 (d, J=9.3 Hz, 1H, 8-H), 7.10 (dd, J=8.4 and 1.3 Hz, 1H, 4-H), 8.62 (dd, J=4.1 and 1.5 Hz, 1H, 2-H); ^{13}C NMR δ 33.3 (t), 39.3 (t), 51.8 (q), 103.1 (d), 121.3 (d), 121.4 (d), 130.0 (s), 130.3 (d), 133.7 (d), 143.3 (s), 145.5 (s), 146.3 (d), 172.6 (s).

*4.2.7. Methyl 3-anilinopropanoate (**18**)*[37]. The reaction mixture obtained by heating alcohol **1** (0.324 g, 1.75 mmol), nitrobenzene (**17**) (0.062 g, 0.052 mL, 0.5 mmol), methyl acrylate (0.180 mL, 2 mmol) and glacial acetic acid (0.006 g, 0.006 mL, 0.1 mmol) in acetonitrile (1 mL) at 110 °C for 10 days was resolved with DCM/EtOAc 100:1 as eluent to give compound **18** (R_f=0.19, 0.056 g, 63%) as a yellow sticky solid (lit.[37] mp 37–38 °C); ^{1}H NMR δ 2.64 (t, J=6.4 Hz, 2H, CH_2CO$_2$Me), 3.47 (t, J=6.5 Hz, 2H, CH_2NH), 3.70 (s, 3H, OCH$_3$), 4.01 (br s, 1H, NH), 6.64 (d, J=7.6 Hz, 2H, 2-H and 6-H), 6.73 (t, J=7.4 Hz, 1H, 4-H), 7.19 (t, J=7.5 Hz, 2H, 3-H and 5-H).

The slowest moving fractions gave ketone **3** (R_f=0.10, 0.260 g, 95% referred to reacted **1**).

*4.2.8. Methyl 3-(3,5-dichloroanilino)propanoate (**20**)*[38]. Chromatographic resolution (DCM/PE 1.5:1) of the material obtained by heating nitro derivative **19** (0.096 g, 0.5 mmol), alcohol **1** (0.324 g, 1.75 mmol), methyl acrylate (0.180 mL, 2 mmol) and glacial acetic acid (0.006 g, 0.006 mL, 0.1 mmol) in toluene (1 mL) at 110 °C for 67 h afforded compound **20** (R_f=0.32, 0.019 g, 15%) as a pale yellow oil; [found: C, 48.79; H, 4.83; N, 5.75. $C_{10}H_{11}Cl_2NO_2$ requires: C, 48.41; H, 4.47; N, 5.65%]. IR (film) 3394, 3102, 2951, 1731, 1594, 1572 cm^{-1}; ^{1}H NMR δ 2.61 (t, J=6.2 Hz, 2H, CH_2CO$_2$Me), 3.41 (t, J=6.2 Hz, 2H, CH_2NH), 3.71 (s, 3H, OCH$_3$), 4.23 (br s, 1H, NH), 6.46 (d, J=1.8 Hz, 2H, 2-H and 6-H), 6.67 (t, J=1.8 Hz, 1H, 4-H); ^{13}C NMR δ 33.3 (t), 39.0 (t), 51.9 (q), 111.0 (d), 117.3 (d), 135.5 (s), 149.2 (s), 172.4 (s).

Ketone **3** was recovered with DCM/EtOAc 3:1 as eluent (R_f=0.74, 0.216 g, 79% referred to reacted **1**).

*4.2.9. Phenyl-2-pyridylmethyl acetate (**22**)*[39]. Operating as above, but without methyl acrylate, chromatographic resolution (PE/EtOAc 3:1) of the material obtained by heating carbinol **1** (0.324 g, 1.75 mmol) and compound **21** (0.072 g, 0.5 mmol) in xylene (1 mL) at 150 °C for 46 h allowed the isolation of, along with ketone **3** (R_f=0.40, 0.163 g, 51% referred to **1**) coming from oxidation of alcohol **1**, derivative **22** (R_f=0.14, 0.031 g, 29%) as a pale yellow oil; ^{1}H NMR δ 2.18 (s, 3H, CH$_3$), 6.86 (s, 1H, C*H*OCOCH$_3$), 7.17 (ddd, J=7.6, 4.9, and 1.0 Hz, 1H, 5-H), 7.25–7.34 (m, 3H, Ar-3H), 7.39–7.42 (m, 3H, Ar-2H and 3-H), 7.67 (ddd, J=7.6, 7.6, and 1.8 Hz, 1H, 4-H), 8.56 (br d, J=4.8 Hz, 1H, 6-H); ^{13}C NMR δ 21.2 (q), 77.8 (d), 121.0 (d), 122.7 (d), 127.3 (d), 128.2 (d), 128.55 (d), 136.9 (d), 138.9 (s), 149.3 (d), 159.1 (s), 169.9 (s).

The slowest moving bands led to unreacted **1** (R_f=0.07, 0.099 g).

*4.2.10. Ethyl 4-amino-3-phenylisoxazole-5-carboxylate (**24**)*[40]. The reaction mixture obtained by heating compound **23** (0.132 g, 0.5 mmol) and alcohol **1** (0.324 g, 1.75 mmol) in toluene (1 mL) at 110 °C for 64 h, without methyl acrylate, was resolved by FC (DCM/EtOAc 120:1) to give amino ester **24** (R_f=0.44, 0.056 g, 48%) as pale yellow needles, mp 62–63 °C (from *n*-hexane) (lit.[40] 61–62 °C); ^{1}H NMR δ 1.42 (t, J=7.0 Hz, 3H, OCH$_2$CH_3), 4.45 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 4.68 (br s, 2H, NH$_2$), 7.48–7.61 (m, 3H, Ar-3H), 7.68–7.83 (m, 2H, Ar-2H).

The slowest moving bands gave ketone **3** (R_f=0.20, 0.230 g, 85% referred to reacted **1**).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.008.

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