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Vinylpyridines as Building Blocks for the Photocatalyzed Synthesis of Alkylpyridines

Luca Capaldo, Maurizio Fagnoni, Davide Ravelli*

Abstract: The photocatalyzed addition of several hydrogen donors (ethers, aldehydes, alkanes, amides) onto vinylpyridines has been achieved. This approach gave access to alkylpyridines, important building blocks for the preparation of compounds having biological activity. The strategy is very simple and straightforward, since it requires only a small amount of a cheap decatungstate salt as the photocatalyst. As an added value, the reaction can be carried out under sunlight irradiation, as well as under flow conditions.

The pyridine ring is a scaffold of fundamental importance in many bioactive compounds and it is present in several antihistamine drugs (acrivastine, pheniramine, triprolidine), antibiotics (isoniazid) and vitamins (B3, B6).[1] Moreover, derivatives bearing a pyridine ring substituted with an alkyl chain were recently isolated from marine sponges of the Niphatidae (and other) family, showing antibiotic, antimycotic and cytotoxic activity (Figure 1).[2] Some examples of compounds having the 3-alkylpyridine motif are: nakinadine C,[3a] niphatesine C,[3b] ikimine A,[3c] haminol-1,[3d] topsendine A,[3e] along with pyrinodemin A,[3f] cribochalines A and B,[3g] and niphatoxin B.[3h]

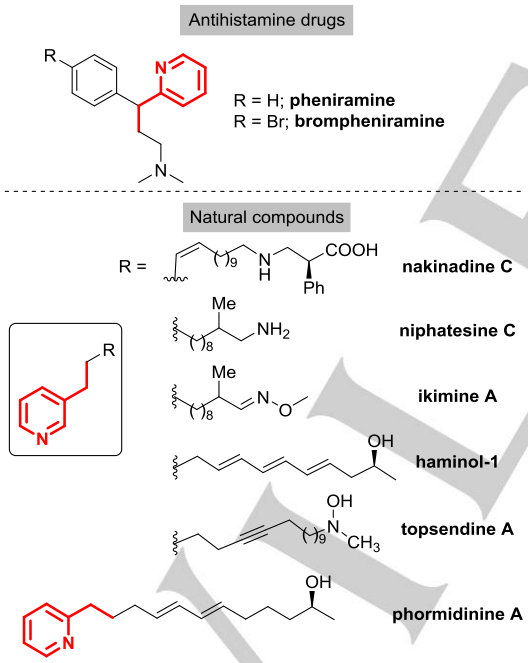
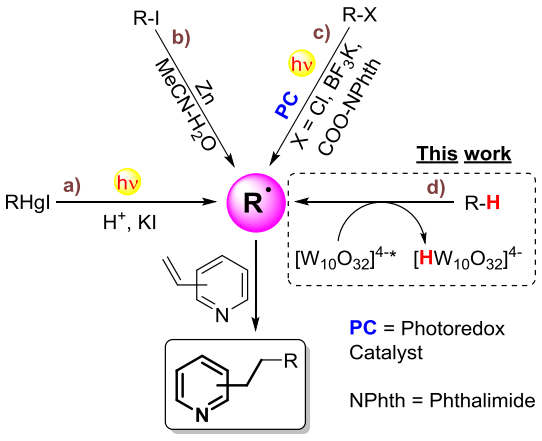


Figure 1. Alkylpyridine motifs in bioactive compounds.

2-Alkylpyridine alkaloids (*e.g.* phormidinine A, Figure 1) were isolated from marine organisms as well.[3i] Substituted alkylpyridines were recently investigated for their peculiar umami flavor[4] or as polar surfactants.[5]

From the synthetic point of view, vinylpyridines are useful substrates for the preparation of alkylpyridines via direct addition of nucleophiles onto the double bond. Different strategies are known for the C-alkylation of ethenylpyridines via addition of C-nucleophiles (benzyl anions[6a] or enolate anions[6b-d]), under reductive conditions,[6e] under acid-catalyzed,[6f] NHC-catalyzed[6g] or metal-catalyzed[6h-j] conditions. Recently, an interesting organocatalytic enantioselective addition of aldehydes onto vinylpyridines has been likewise described.[7]

A milder approach, however, involves the addition of carbon-centered radicals onto the double bond. A dated example is the functionalization of 4-vinylpyridine by photodecomposition of alkylmercury halides (Scheme 1, *path a*).[8a] In another instance, the thermal generation of radicals was achieved starting from alkyl halides, through a Zn-promoted reaction (*path b*).[8b] Quite surprisingly, only a few examples were reported for the functionalization of vinylpyridines by means of photoredox catalysis (*path c*), notwithstanding the several examples published on styrenes.[9] Actually, only α-carbonyl,[10a] α-oxy[10b] and α-amino radicals[10c,d] were smoothly generated and used for the preparation of alkylpyridines (*path c*). Carbon-centered radicals obtained by a photocatalyzed proton-coupled electron transfer on *N*-arylamide derivatives were likewise trapped by 2-vinylpyridine.[11]



Scheme 1. Generation of carbon based radicals (R•) by cleavage of a R-X (*paths a-c)* and a R-H bond (this work, *path d*) for the synthesis of alkylpyridines.

In all of the radical-based strategies discussed so far, an X group must be present in the radical precursor to facilitate the cleavage of the C-X bond and the ensuing radical formation. By contrast, the direct generation of radicals by cleavage of a C-H bond still represents a harsh challenge and has not been exploited for vinylpyridines derivatization so far.

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We surmised that the formation of (carbon-centered) radicals could be attained by a homolytic C-H cleavage via a hydrogen atom transfer (HAT)[12] by using a decatungstate salt (TBADT, $(n\text{Bu}_4\text{N})_4[\text{W}_{10}\text{O}_{32}]$) as the photocatalyst (Scheme 1, *path d*).[13,14] Firstly, we optimized the reaction conditions by studying the photocatalyzed addition of cyclohexane (**1g**) onto 4-vinylpyridine (**2a**) to give 4-(2-cyclohexylethyl)pyridine (**9**) as a model reaction. As reported in Table S1, the highest yield of **9** (68%) was obtained by irradiating (λ_{IRR} centered at 310 nm; 10×15 W phosphor-coated lamps were used) a MeCN solution of **2a** (0.1 M) for 16 h in the presence of TBADT (2 mol%; λ_{MAX} = 323 nm) and an excess of **1g** (5 equiv.). We then investigated the scope of our approach by testing several hydrogen donors (ethers **1a,b**, acetal **1c**, amides **1d,e**, nitrile **1f**, cyclohexane **1g**, silane **1h** and aldehydes **1i-m**, Figure 2) in the reaction with vinylpyridines **2a-g**, adopting the optimized conditions by using the minimum excess of **1**.

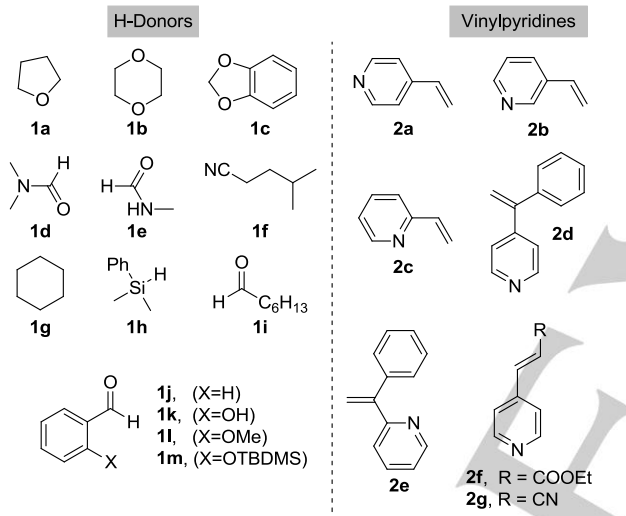
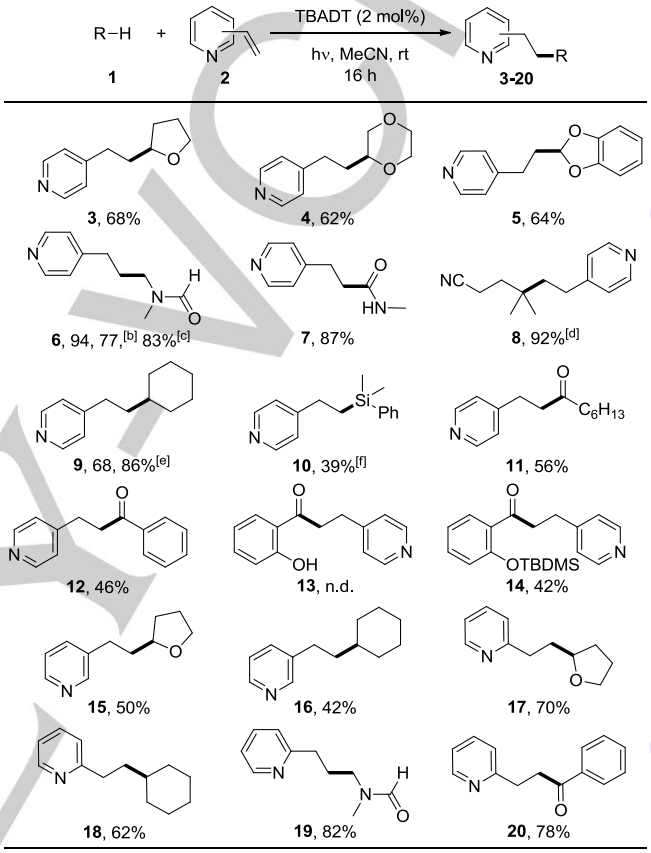


Figure 2. Hydrogen donors (**1a-m**) and vinylpyridines (**2a-g**) used in this work.

4-Vinylpyridine (**2a**) was first tested and in most cases the expected products were formed in good to excellent yields (Table 1). As for ethers, tetrahydrofuran (**1a**) and 1,4-dioxane (**1b**) gave the Giese adducts **3** and **4** in 68 and 62% yields, respectively. A similar yield (64%; compound **5**) was achieved when shifting to 1,3-benzodioxole (**1c**) as hydrogen donor. Elective substrates for this reaction appeared to be aliphatic amides, since both *N*,*N*-dimethylformamide (**1d**) and *N*-methylformamide (**1e**) gave excellent yields of **6** and **7** (94 and 87%, respectively). Accordingly, the reactivity of **1d** was also investigated under different conditions, by changing the light source. As an example, formamide **6** was obtained in a very good yield (77%) when the reaction was performed in a solar simulator and in 83% yield when the solution was irradiated with direct sunlight in a Pyrex vessel on a window ledge (Table 1). Isocapronitrile (**1f**) reacted with **2a** to afford **8** as the only product in 92% yield, with a regioselective C-H cleavage at the methine site. Noteworthy, in the preparation of alkylpyridine **9** a higher yield (86% vs 68%) was obtained when carrying out the reaction under flow conditions[15] (flow rate = 0.2 mL min^{-1}). The flow photoreactor (total volume: 12 mL) employed here is based on a PTFE tubing (internal diameter: 1.3 mm) wrapped around an immersion well apparatus (125 W Hg vapors lamp as the light source).[14f]

Table 1. TBADT photocatalyzed synthesis of alkylpyridines **3-20**.[a]

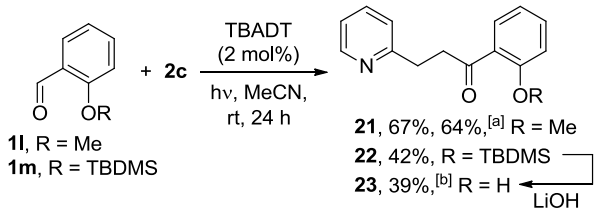


[a] Conditions: A MeCN solution (15 mL) of **1a-m** (1.5-7.5 mmol, 0.1-0.5 M, 1-5 equiv.) and **2a-c** (1.5 mmol, 0.1 M, 1 equiv.), in the presence of TBADT (2×10^{-3} M, 2 mol%) irradiated with 10×15 W phosphor-coated lamps (λ_{IRR} centered at 310 nm) for 16 h. Isolated yields reported, see SI for details. [b] Irradiation carried out by placing the solution (50 mL) in a solar simulator (500 $W\cdot m^{-2}$). [c] Irradiation carried out by placing the solution (50 mL) in a Pyrex vessel exposed on a window ledge for 8 h. [d] 1.6 M **1f**. [e] Reaction carried out under flow conditions (see text and SI). [f] TBADT 4 mol%.

4-Vinylpyridine was also capable of trapping silyl radicals, even though a higher amount of TBADT was required (4 mol%). Thus, the Si-H bond in dimethylphenylsilane (**1h**) was homolytically broken and trapping of the thus-formed radical afforded silane **10** in a modest yield (39%). Activation of $C(sp^2)$-H bonds in aldehydes (whether aliphatic or aromatic) allowed the preparation of unsymmetrical ketones. In particular, heptanal (**1i**) gave ketone **11** in 56% yield, whereas aromatic aldehydes gave contrasting results. While unsubstituted benzaldehyde (**1j**) reacted quite well with **2a**, giving **12** in 46% yield, the reaction of salicylaldehyde (**1k**) to give **13** failed, probably due to the presence of the phenolic group.[14g] Protection of the -OH group as TBDMS ether restored the usual reactivity (product **14** formed in 42% yield, Table 1, and **13** from it by basic treatment, see SI).

The reaction was also extended to 3-vinyl (**2b**) and 2-vinylpyridine (**2c**, Table 1). Alkylated pyridines **15** and **16** were formed in 50 and 42% yield, respectively, in the photocatalyzed addition of **1a** and **1g** onto **2b**. By contrast, 2-vinylpyridine gave results comparable with those of **2a** (products **17-20** obtained in up to 82% yield, Table 1). Attempted alkylation of 2-vinylpyrazine failed due to polymerization.

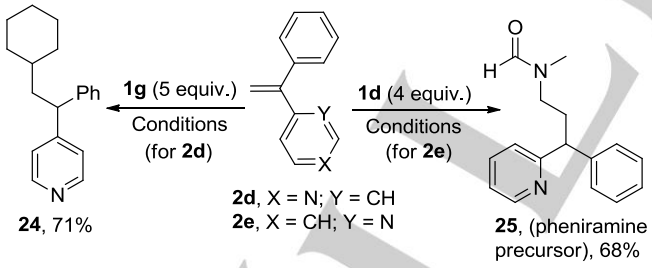
With the aim to prepare compounds of potential industrial interest, **2c** was reacted with protected salicylaldehydes **1l** and **1m** to give ketones **21** and **22** (Scheme 2). In the former case, compound **21** was formed in roughly the same yield under flow conditions in only 5 h. In the latter case, treatment of crude **22** under basic conditions (LiOH) formed phenol **23**. Notably, compounds **21** and **23** belong to a class of compounds mimicking the umami flavour.[4]



[a] Flow conditions (time: 5 h, see SI); [b] Yield over two steps

Scheme 2. Photocatalyzed synthesis of derivatives **21** and **23** having umami flavor.

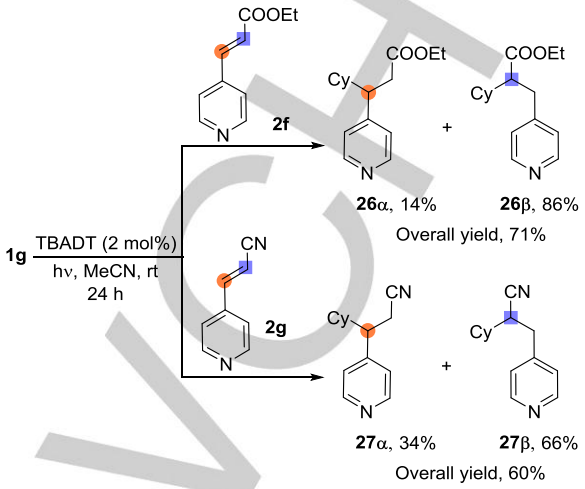
We then tested phenyl substituted vinylpyridines **2d** and **2e** (Scheme 3). Photocatalytic addition of cyclohexane onto **2d** led to compound **24** in a good yield (71%). The versatility of our approach made possible the smooth preparation of **25** (precursor of the antihistamine drug pheniramine, see Figure 1) in a single step and in 68% yield starting from DMF and **2e**.



Conditions: hν, TBADT (2 mol%), MeCN, rt, 24h

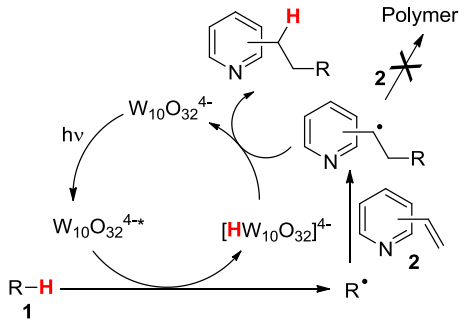
Scheme 3.

Finally, vinylpyridines bearing an electron-withdrawing group such as **2f** and **2g** were subjected to the photocatalyzed reaction with **1g** (Scheme 4**)**. Cyclohexyl radical attacked both the α and the β (preferred) position with respect to the pyridyl ring. Compound **2f** gave ethyl esters **26** as a mixture of isomers (α/β ratio of 14:86) in a 71% overall yield, whereas olefin **2g** afforded nitriles **27** (α/β ratio of 34:66) in a 60% yield. The regioselectivity observed in compound **2f** is similar to that found in the cyclohexyl radical addition onto ethyl cinnamate.[16]



Scheme 4. Regioselectivity in the addition of radicals onto substituted vinylpyridines.

As for the mechanism, the formation of carbon-centered radicals is promoted by excited TBADT via a hydrogen atom transfer reaction (Scheme 5).[12,13] Vinylpyridines behave as radical traps and regioselective addition at the β position smoothly took place. The efficient back hydrogen donation from $[HW_{10}O_{32}]^{4-}$ to the adduct radical hampered the otherwise fast polymerization of **2** to poly(vinylpyridines).[17]



Scheme 5. Proposed reaction mechanism.

Moreover, the high absorptivity of TBADT at the wavelength used prevented the light absorption of the starting vinylpyridines (see Figures S1, S2) and of the end compounds. This was beneficial to the overall process, since it avoided again a photopolymerization of **2**[17] and at the same time made negligible intramolecular hydrogen abstraction side reactions from the resulting 2-alkylpyridines.[18] The presence of a COOEt or a CN group on the double bond of vinylpyridines makes them more electrophilic, but shifts (at least in part) the regioselectivity of radical attack to the α position.

In conclusion, the present work demonstrates that vinylpyridines are interesting building blocks for the preparation of valuable alkylpyridines having biological application (**25**) or commercial importance (compounds **21** and **23** endowed with the umami flavor). The process is very simple and can be also carried out both under sunlight irradiation and under flow conditions.

Experimental Section

Typical Procedure for the TBADT-Photocatalyzed Functionalization of Vinylpyridines. An acetonitrile solution (15 mL) of cyclohexane **1g** (808 µL, 7.5 mmol, 0.5 M, 5 equiv.) and vinylpyridine **2a** (161 µL,1.5 mmol, 0.1 M, 1 equiv.), in the presence of TBADT ($2{\cdot}10^{-3}$ M, 2 mol%) was poured in a quartz tube and then purged for 3 min with nitrogen, capped with a septum, and irradiated for 16 h in a multi-lamp apparatus fitted with 10×15 W phosphor-coated lamps (emission centered at 310 nm). The solvent was removed under reduced pressure from the photolyzed solution and the product isolated by purification of the residue by column chromatography to yield 194 mg of **9** (68% yield) as an oil.

Acknowledgements

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Keywords: Decatungstate anion • Hydrogen transfer • Photocatalysis • Radical reactions • Vinylpyridines

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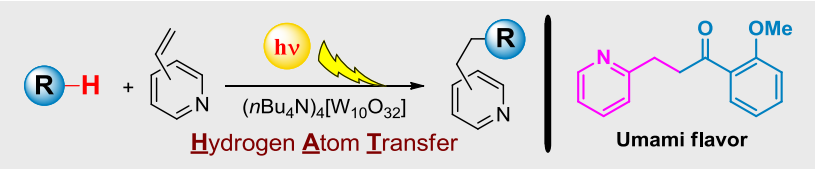

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Vinylpyridines as Building Blocks for the Photocatalyzed Synthesis of Alkylpyridines

The flavor of photocatalysis. The photocatalyzed addition of several hydrogen donors (R-H) onto vinylpyridines has been achieved. This approach gave access to alkylpyridines, important building blocks for the preparation of compounds having biological activity, including derivatives showing an umami flavor.