Natural aldehyde extraction and direct preparation of new blue light-emitting imidazo[1,5-a]pyridine fluorophores

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Abstract

This work describes the extraction of natural aldehydes and the use of extracts to synthesize new fluorescent imidazo[1,5-a]pyridine derivatives. The characterization of the extracted aldehydes by different techniques and the optical study of the fluorescent products allow the design of new compounds suitable for pharmaceutical, down-shifting, microscopy, and electronic applications. The fluorophores are generated by an easy one-pot cyclization reaction in mild conditions without catalyst and with only water as by-product.

1 Introduction

The extraction of natural products from plants dates back to ancient times [Industrial Scale Natural Products Extraction, Hans-Jorg Bart (Editor), Stephan Pilz (Editor), Wiley 314 pages April 2011, ISBN: 978-3-527-32504-7] and medicinal aromatic plants offer nowadays a wide range of natural compounds. Extracts from seeds, leaves, flowers of aromatic and curative plants present a large number of chemical products, which make them interesting for food, cosmetic, pharmaceutical and chemical industries.

Imidazo[1,5-a]pyridine derivatives have attracted a growing consideration due to their particular biological, chemical, and optical properties. The imidazo[1,5-a]pyridine core is present in several pharmaceutical compounds and biologically dynamic agents (as HIV protease inhibitors (Kim et al. 2005), cardiotonic agents (Davey et al. 1987), aromatase inhibitors in estrogen dependent diseases (Browne et al. 1991), thromboxane A2 synthetase inhibitors (Ford et al. 1985), RORc inverse agonists in inflammatory diseases (Fauber et al. 2015), 5-HT4 receptor partial agonists in Alzheimer's disease (Nirogi et al. 2015) and antitumor agents (Roy et al. 2011). Furthermore imidazo[1,5-a]pyridines also represent a class of aromatic derivatives for fluorescence microscopy and down-shifting luminescent layer technologies (Song et al. 2016; Volpi et al. 2017; Ge et al. 2017). This class of heterocyclic compounds finds application in several research areas, from pharmaceutical fields to material technologies (Weber et al. 2016).

From the synthetic point of view, the imidazo[1,5-a]pyridine nucleus can be achieved by different approaches involving the use of Pd-catalyzed (Yamaguchi et al. 2011) and Cu-catalyzed (Wang et al. 2015) reactions on different substrates or using sensitive Lewis acid (Krapcho & Powell 1986) or of a stoichiometric amount of elemental sulphur (S8) (Krapcho & Powell 1986) as an oxidant, or from the oxidation of a Schiff base (Grigg et al. 1992). Among them, efficient synthetic methods for the preparation of the imidazo[1,5-a]pyridine core have also been reported via two or three reagent condensation reactions, using an aldehyde and 2-cyanopyridine (Fulwa et al. 2009; Fulwa & Manivannan 2012a; Fulwa & Manivannan 2012b), or pyridyl-ketones, aromatic aldehydes and ammonium acetate in acetic acid (See Figure 1) (Wang et al. 2003). In the present work, we selected the last synthetic approach, due to its simplicity and low cost of reagents.

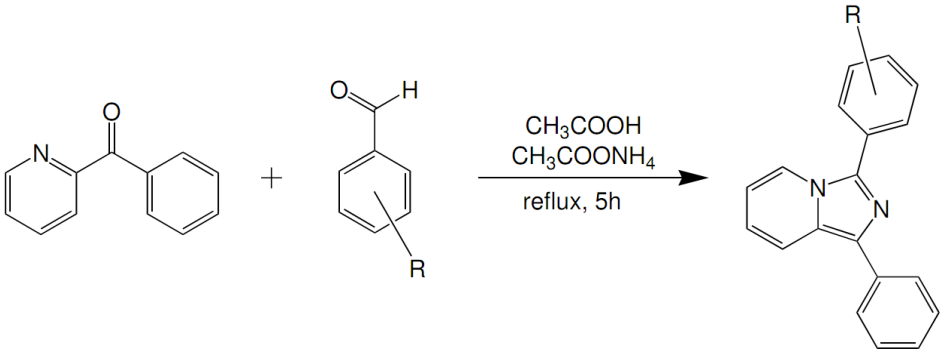

Fig. 1 One pot cyclization of pyridyl-ketones and aromatic aldehydes to obtain substituted imidazo[1,5-a]pyridines.

The purpose of this work is to obtain new luminescent imidazo[1,5-a]pyridine moieties from natural aldehydes extracted directly by steam distillation from medicinal or aromatic spices. For this purpose, an important requirement in choosing the natural product for the extraction was that the obtainable aldehyde could be acquired through steam distillation, without purification, in high quantities and with sufficient purity to be used in the subsequent cyclization reaction. To this end, cumin-aldehyde constitutes one of the major components of *Cuminum Cyminum* essential oil (Bankar 2011; Morshedi et al. 2015) and vanillin-aldehyde constitutes the primary component of the extract of the *Vanilla Planifolia* bean (Ainscough & Brodie 1990; Sinha et al. 2008; Cicchetti et al. 2010).

The synthetic approach here employed to obtain two new imidazo[1,5-a]pyridines represents a strongly selective reaction mechanisms and avoids any purification of the extracted essential oils because such one-pot cyclization mechanism only involves aromatic aldehydes.

2 Results and discussion

Natural aldehydes extraction

The natural aldehydes (cumin-aldehyde and vanillin-aldehyde) were collected by steam distillation, as previously reported (Dignum et al. 2001; Zheljazkov et al. 2015).
The synthetic approach here employed to obtain two new imidazo[1,5-a]pyridines (Figure 2) represents a strongly selective reaction mechanisms and avoids any purification of the extracted essential oils because such one-pot cyclization mechanism only involves aromatic aldehydes.
[Figure 2 near here]

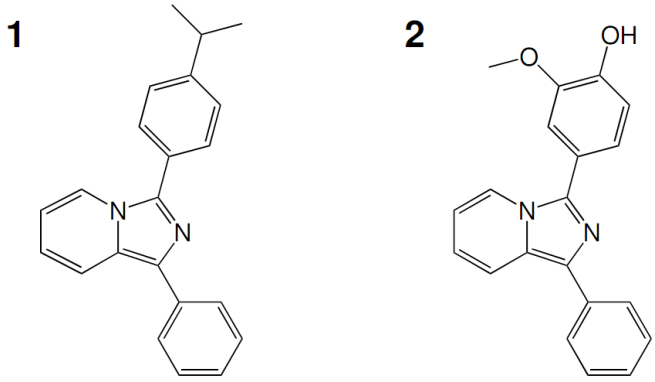

Fig. 2 3-substituted-1-phenylimidazo[1,5-a]pyridines derived **1** from cuminaldehyde and **2** from vanillin.

The obtained solutions were extracted with CH_2Cl_2. The organic layers were separated, dried and evaporated under vacuum. The resulting essential oils were analysed using TLC, MS and NMR and compared with commercial pure compounds (see supplemental material). The TLC developing solvent efficiently separates cumin and vanillin aldehyde from other compounds in the essential oils (Rf = 0.71 and Rf = 0.26 respectively in 100% CH_2Cl_2) and **1**, **2** (Rf = 0.32 and Rf = 0.09 respectively in 100% CH_2Cl_2). The obtained products containing natural aromatic aldehydes were directly employed for the one-pot reaction cyclization to obtain compound **1** and **2** (see Figure 2).

General synthetic approach

As previously reported, different interesting 1,3-diarylated imidazo[1,5-a]pyridine derivatives can be synthesized in high yields with a one-step cyclization approach via condensation of different pyridyl-ketones with several aromatic aldehydes in the presence of ammonium acetate (Scheme 1) (Volpi, Magnano, et al. 2017). In this work, in order to synthesize and characterize the optical properties of this class of fluorophores, two new phenylimidazo[1,5-a]pyridines have been synthetized using both vanillin aldehyde (from *Vanilla Planifolia* beans) and cumin aldehyde (from *Cuminum cyminum* seeds).

Optical properties

The imidazo[1,5-a]pyridine nucleus is known in literature for its electronic absorption and emission behavior (Volpi et al. 2016; Volpi, Magnano, et al. 2017; Volpi, Garino, et al. 2017). Products **1** and **2** show different absorption peaks in the wavelength range from 250 nm to 400 nm (as shoulders), while almost no absorption beyond 420 nm is observed. The products show large Stokes' shifts (179 and 181 nm) and strong emissions at wavelengths in the 420–500 nm range. The absorption and emission spectra of **1** and **2** are presented in

Figures S8 and S9 respectively, and their optical properties are summarized in Table 1.

Table 1. Photophysical properties and solvent effects (both solvatochromism and halochromism) on the electronic absorption and emission maxima of **1** and **2**.

	1			**2**		
	λ_{abs} (nm)	λ_{em} (nm)	Stokes' shift (nm)	λ_{abs} (nm)	λ_{em} (nm)	Stokes' shift (nm)
CH_3CN	297	478	181	310 380sh	489	179
CH_3CN + ac	276	438	162	303sh 325	458	155
CH_2Cl_2	300	484	184	308 378sh	489	181
CH_2Cl_2 + ac	270	450	180	296 323	464	168
EtOH	292	487	195	304 375sh	488	184
EtOH + ac	270	470	200	303	464	161

The solvent effects (both solvatochromism and halochromism) on the absorption and emission properties of **1** and **2** have been evaluated in dichloromethane, acetonitrile and ethanol solutions prior to and after the addition of formic acid (ac) to the sample (1% v/v) (Table 1). Solvent polarity barely influences the absorption and emission spectra of **1** and **2** heterocycles, suggesting low charge transfer character of their ground state. A strong halochromic effect characterizes product **1** and **2**, with a hypsochromic shift in both cases (see Figures S8 and S9 and Table 1).

All the compounds show deep absorptions in the near UV, intense emissions in the visible region (400–500 nm), and large Stokes' shifts, as required for UV absorption and down-shifting materials.

3 Experimental

Materials and techniques

All solvents and raw materials were used as received from commercial suppliers (Sigma-Aldrich and Alfa Aesar) without further purification.

Column chromatography was performed on Sigma-Aldrich silica gel 60 (70e230 mesh ASTM). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 200 spectrometer at 200 MHz and 50 MHz, respectively, in $CDCl_3$ or CD_3OD. Mass spectra were recorded on a Thermo-Finnigan Advantage Max Ion Trap Spectrometer equipped with an electrospray ion source (ESI) in positive or negative ion acquiring mode. High-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap Hybrid Mass Spectrometer.

UV-Vis absorption spectra were recorded on a Cary60 spectrometer. Photoemission spectra were acquired with a HORIBA Jobin Yvon IBH Fluorolog-TCSPC spectrofluorometer. The spectral response was corrected for the spectral sensitivity of the photomultiplier.

TLC was performed on 10×20 cm TLC sheets, coated with 0.25 mm layers of silica gel 60 F254 (E. Merck). After the application of the extract (about 10 µl), the sheets were developed in paper-lined all-glass chambers with 10 ml of dichloromethane-methanol (96-4), previously left to equilibrate for at least 15 min.

Spots are visualized with a UV lamp. The distance to the centre of the spot (dspot) and the solvent (dichloromethane) front distance (dsolv) from the spot line are measured with a ruler, and the Rf (retention factor) for the spot is calculated from Rf = dspot/dsolv. The TLC developing solvent efficiently separates cumin and vanillin aldehyde (Rf=0.71 and Rf=0.26 respectively in 100% CH_2Cl_2) and 1, 2 (Rf=0.32 and Rf=0.09 respectively in 100% CH_2Cl_2).

Syntheses

A mixture of phenyl(pyridin-2-yl)methanone (800 mg, 4.37 mmol, 1 eq), aldehyde (6.55 mmol, 1.5 eq), and ammonium acetate (1704 mg, 21.85 mmol, 5 eq) in glacial acetic acid (25 mL) was stirred at reflux. After 5 h, the reaction mixture was cooled to room temperature and the acetic acid was removed by evaporation under reduced pressure. The obtained solid was dissolved in a saturated aqueous solution of Na_2CO_3 and the mixture extracted with CH_2Cl_2. The organic layer was separated, dried and the solvent evaporated under vacuum. The obtained yellow crude product was purified via column chromatography on silica gel (CH_2Cl_2/CH_3OH 98:2).

*Compound **1**:* 3-(4-isopropylphenyl)-1-pheny-lH-imidazo[1,5-a]pyridine.

Reaction yield: 53.4%. MP: 79–80°C. Rf: 0.32 (CH_2Cl_2). ESI-MS spectrum m/z 313.23 $[M+H]^+$. HRMS (ESI) spectrum m/z 313.1511 $[M+H]^+$. ^{1}H NMR spectrum in $CDCl_3$: δ 8.24 (dt, J = 7.3, 1.1 Hz, 1H), 7.95 (d, J = 7.7 Hz, 2H), 7.84 (dt, J = 9.3, 1.2 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 7.3 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.31 (dt, J = 7.7, 1.6 Hz, 1H), 6.79 (ddd, J = 9.3, 6.4, 1.0 Hz, 1H), 6.57 (td, J = 6.8, 1.2 Hz, 1H), 3.00 (sept, J = 6.9 Hz, 1H), 1.31 (d, J = 6.9 Hz, 6H). ^{13}C NMR spectrum in $CDCl_3$: δ 150.08, 138.34, 134.80, 131.65, 128.85 (2C), 128.52 (2C), 127.56, 127.36, 127.27 (2C), 126.99 (2C), 126.71, 122.04, 119.85, 119.28, 113.37, 34.22, 24.03 (2C). ATR: 2960, 1664, 1602, 1492, 1260, 1053, 839, 692 cm^{-1}.

*Compound **2**:* 2-methoxy-4-(1-phenylH-imidazo[1,5-a]pyridin-3-yl)phenol.

Reaction yield: 41.1%. MP: 109–110°C. Rf: 0.09 (CH_2Cl_2). ESI-MS spectrum m/z 317.16 $[M+H]^+$. HRMS (ESI) spectrum m/z 317.1097 $[M+H]^+$. ^{1}H NMR spectrum in $CDCl_3$: δ 8.18 (dt, J = 7.3, 1.0 Hz, 1H), 7.93 (d, J = 7.1 Hz, 2H), 7.81 (dt, J = 9.3, 1.2 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.36-7.21 (m, 3H), 7.01 (d, J = 8.2 Hz, 1H), 6.78 (ddd, J = 9.3, 6.4, 1.0 Hz, 1H), 6.56 (td, J = 6.8, 1.2 Hz 1H), 3.91 (s, 3H). ^{13}C NMR spectrum in $CDCl_3$: δ 147.53, 146.90, 138.32, 134.64, 131.31, 128.84 (2C), 127.38, 126.99 (2C), 126.72, 121.97, 121.62, 121.00, 119.80, 119.18, 114.86, 113.40, 112.06, 56.18. ATR: 2960, 2835, 1594, 1515, 1254, 1217, 1129, 768, 692 cm^{-1}.

4 Conclusion

Two new 1,3-diarylated-imidazo[1,5-a]pyridine derivatives have been synthesized by means of the easy to scale up, one-pot condensation of phenyl(pyridin-2-yl)methanone with natural aldehydes directly obtained by steam distillation and solvent extraction.

Reaction yields were good and the obtained imidazo[1,5-a]pyridines show remarkable optical properties depending on the chemical structure of the substituent in position 3 derived from the employed aromatic aldehydes. Compound **1** and **2** display intense fluorescent emissions, large Stokes' shifts and typical halochromic and solvatochromic effect.

Theoretical design of such compounds and investigation on the introduction of some other systems into imidazo[1,5-a]pyridines for functional materials can be considered in choosing other aromatic plants or natural starting materials. These compounds represent an interesting class of fluorescent molecules easily tuneable with potential interest in the fields of fluorescence microscopy, down-shifting luminescent layer technologies and for pharmaceutical applications. Moreover, high reaction yields, absence of catalysts, high accessibility and stability, nontoxicity of reagents accounts for promising scale up perspectives of this synthetic approach.

On the basis of these promising synthetic success, further studies are in progress to test other medicinal and aromatic spices or natural products to obtain new imidazo[1,5-a]pyridines derivatives as tuneable and low-cost fluorescent materials.

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References

Ainscough E, Brodie A. 1990. The Determination of Vanillin in Vanilla Extract - an Analytical-Chemistry Experiment. J Chem Educ. 67:1070–1071.

Bankar R. 2011. Comparative studies of the major components present in the essential oil of Indian Cumin (Cuminum cyminum L.) from different origin. Asian J Exp Chem. 6:31–34.

Browne LJ, Gude C, Rodriguez H, Steele RE, Bhatnager A. 1991. Fadrozole Hydrochloride - a Potent, Selective, Nonsteroidal Inhibitor of Aromatase for the Treatment of Estrogen-Dependent Disease. J Med Chem. 34:725–736.

Cicchetti E, Silvestre V, Fieber W, Sommer H, Remaud G, Akoka S, Chaintreau A. 2010. Procedure for the isolation of vanillin from vanilla extracts prior to isotopic authentication by quantitative C-13-NMR. Flavour Fragr J. 25:463–467.

Davey D, Erhardt PW, Lumma WC, Wiggins J, Sullivan M, Pang D, Cantor E. 1987. Cardiotonic Agents .1. Novel 8-Aryl-Substituted Imidazo[1,2-a] and [1,5-a]Pyridines and Imidazo[1,5-a]Pyridinones as Potential Positive Inotropic Agents. J Med Chem. 30:1337–1342.

Dignum MJW, Kerler J, Verpoorte R. 2001. Vanilla Production: Technological, Chemical, and Biosynthetic Aspects. Food Rev Int. 17:119–120.

Fauber BP, Gobbi A, Robarge K, Zhou A, Barnard A, Cao J, Deng Y, Eidenschenk C, Everett C, Ganguli A, et al. 2015. Discovery of imidazo[1,5-a]pyridines and -pyrimidines as potent and selective RORc inverse agonists. Bioorg Med Chem Lett. 25:2907–2912.

Ford NF, Browne LJ, Campbell T, Gemenden C, Goldstein R, Gude C, Wasley JWF. 1985. Imidazo[1,5-a]Pyridines - a New Class of Thromboxane-A2 Synthetase Inhibitors. J Med Chem. 28:164–170.

Fulwa VK, Manivannan V. 2012a. Synthesis of some 1,3-disubstituted imidazo[1,5-a]pyridines using 2-cyanopyridine. Tetrahedron Lett. 53:2420–2423.

Fulwa VK, Manivannan V. 2012b. Synthesis of 3-substituted imidazo[1,5-a]pyridines having 1-(N-picolinamidin-2-yl) group. Tetrahedron. 68:3927–3931.

Fulwa VK, Sahu R, Jena HS, Manivannan V. 2009. Novel synthesis of 2,4-bis(2-pyridyl)-5-(pyridyl)imidazoles and formation of N-(3-(pyridyl)imidazo[1,5-a]pyridine)picolinamidines: nitrogen-rich ligands. Tetrahedron Lett. 50:6264–6267.

Ge Y, Ji R, Shen S, Cao X, Li F. 2017. A ratiometric fluorescent probe for sensing Cu2+ based on new imidazo[1,5-a]pyridine fluorescent dye. Sens Actuators B Chem. 245:875–881.

Grigg R, Kennewell P, Savic V, Sridharan V. 1992. X=Y-Zh Systems as Potential 1,3-Dipoles .38. 1,5-Electrocyclization of Vinyl-Azomethine and Iminyl-Azomethine Ylides - 2-Azaindolizines and Pyrrolo-Dihydroisoquinolines. Tetrahedron. 48:10423–10430.

Kim D, Wang LP, Hale JJ, Lynch CL, Budhu RJ, MacCross M, Mills SG, Malkowitz L, Gould SL, DeMartino JA, et al. 2005. Potent 1,3,4-trisubstituted pyrrolidine CCR5 receptor antagonists: effects of fused heterocycles on antiviral activity and pharmacokinetic properties. Bioorg Med Chem Lett. 15:2129–2134.

Krapcho AP, Powell JR. 1986. Syntheses of 1,3-Disubstituted Imidazo[1,5-a]Pyridines. Tetrahedron Lett. 27:3713–3714.

Morshedi D, Aliakbari F, Tayaranian-Marvian A, Fassihi A, Pan-Montojo F, Perez-Sanchez H. 2015. Cuminaldehyde as the Major Component of Cuminum cyminum, a Natural Aldehyde with Inhibitory Effect on Alpha-Synuclein Fibrillation and Cytotoxicity. J Food Sci. 80:H2336–H2345.

Nirogi R, Mohammed AR, Shinde AK, Bogaraju N, Gagginapalli SR, Ravella SR, Kota L, Bhyrapuneni G, Muddana NR, Benade V, et al. 2015. Synthesis and SAR of Imidazo[1,5-a]pyridine derivatives as 5-HT4

receptor partial agonists for the treatment of cognitive disorders associated with Alzheimer's disease. Eur J Med Chem. 103:289–301.

Roy M, Chakravarthi BVSK, Jayabaskaran C, Karande AA, Chakravarty AR. 2011. Impact of metal binding on the antitumor activity and cellular imaging of a metal chelator cationic imidazopyridine derivative. Dalton Transactions. 40(18):4855–4864.

Sinha AK, Sharma UK, Sharma N. 2008. A comprehensive review on vanilla flavor: Extraction, isolation and quantification of vanillin and others constituents. Int J Food Sci Nutr. 59:299–326.

Song G-J, Bai S-Y, Dai X, Cao X-Q, Zhao B-X. 2016. A ratiometric lysosomal pH probe based on the imidazo[1,5-a]pyridine–rhodamine FRET and ICT system. RSC Adv. 6:41317–41322.

Volpi G, Garino C, Conterosito E, Barolo C, Gobetto R, Viscardi G. 2016. Facile synthesis of novel blue light and large Stoke shift emitting tetradentate polyazines based on imidazo[1,5-a]pyridine. Dyes and Pigments. 128:96–100.

Volpi G, Garino C, Priola E, Diana E, Gobetto R, Buscaino R, Viscardi G, Barolo C. 2017. Facile synthesis of novel blue light and large Stoke shift emitting tetradentate polyazines based on imidazo[1,5- a] pyridine – Part 2. Dyes and Pigments. 143: 284–290.

Volpi G, Magnano G, Benesperi I, Saccone D, Priola E, Gianotti V, Milanesio M, Conterosito E, Barolo C, Viscardi G. 2017. One pot synthesis of low cost emitters with large Stokes' shift. Dyes Pigments. 137:152–164.

Wang H, Xu W, Wang Z, Yu L, Xu K. 2015. Copper-Catalyzed Oxidative Amination of sp(3) C-H Bonds under Air: Synthesis of 1,3-Diarylated Imidazo[1,5-alpha]pyridines. J Org Chem. 80:2431–2435.

Wang J, Mason R, VanDerveer D, Feng K, Bu XR. 2003. Convenient preparation of a novel class of imidazo[1,5-a]pyridines: Decisive role by ammonium acetate in chemoselectivity. J Org Chem. 68:5415–5418.

Weber MD, Garino C, Volpi G, Casamassa E, Milanesio M, Barolo C, Costa RD. 2016. Origin of a counterintuitive yellow light-emitting electrochemical cell based on a blue-emitting heteroleptic copper(I) complex. Dalton Trans. 45:8984–8993.

Yamaguchi E, Shibahara F, Murai T. 2011. 1-Alkynyl- and 1-Alkenyl-3-arylimidazo[1,5-a]pyridines: Synthesis, Photophysical Properties, and Observation of a Linear Correlation between the Fluorescent Wavelength and Hammett Substituent Constants. J Org Chem. 76:6146–6158.

Zheljazkov VD, Shiwakoti S, Astatkie T, Salamon I, Grul'ová D, Mudrencekova S, Schlegel V. 2015. Yield, Composition, and Antioxidant Capacity of Ground Cumin Seed Oil Fractions Obtained at Different Time Points during the Hydrodistillation. HortScience. 50:1213–1217.