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Synthesis of (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates), a new type of 2,2′-azopyridine dyes

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ABSTRACT

An unexpected, but simple method for the efficient synthesis of new 2.2′-azopyridine dyes, such as (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates) (**2**, **4**, **6**, **8**, **10**, and **12**), based on the treatment of ethyl 6-amino-5-cyano-2-methyl-4-arylnicotinates (**1**, **3**, **5**, **7**, **9**, and **11**) with NBS/benzoyl peroxide, is described. The X-ray diffraction analysis and the UV–vis absorption spectra of dye **2** are reported and discussed.

Aromatic azo molecules have been traditionally used in dye and food industries.[1] Current synthetic methods for the synthesis of azo compounds include either the oxidation of anilines, using permanganate,[2] lead tetraacetate,[2] or *N*-chloroacetanilide,[3] and the reduction of nitro aromatic derivatives by stoichiometric amounts of metals.[4] Symmetric aromatic azo compounds have been synthesized by coupling aryl diazonium salts, prepared from anilines and the toxic nitrous acid,[5] with electron-rich substituted aromatic derivatives.[6] As a typical example, 2,2′-azopyridine has been prepared by oxidation of 2-aminopyridine with aqueous sodium hypochlorite in 30% yield.[7] In spite of this, no satisfactory methodologies in terms of experimental conditions and environmental consequences are available. On the other hand, and from the perspective of green chemistry, new, more friendly and sustainable chemical processes are mandatory. In this context, it has been recently reported that gold nanoparticles on TiO_2 (Au/TiO_2) catalyze the aerobic oxidation of aromatic anilines to aromatic azo compounds in high yields and mild reaction conditions.[8] Regarding the possible applications, azobenzene derivatives have been used for several switching processes in which chirality is critical[9] and for the stabilization of the helical structures.[10] Similarly, the photochemical *E/Z* isomerization of azobenzene derivatives has been exploited extensively to modulate the conformational and biological properties of folded peptides and helical polymers.[11] In biology, the introduction of azobenzene photo-switches has led to the development of photocontrolled ion channels and enzymes.[12] Congo red, for instance, the sodium salt of benzidinediazo-bis-1-naphthylamine-4-sulfonic acid, due to its strong affinity for fibrillar amyloid proteins, is a paradigmatic marker used to examine in vitro tissue sections for amyloid deposits.[13] Finally, 2,2′-azopyridines are known to form a variety of dinuclear complexes showing unusual electronic and structural features.[14]

In this Letter we report a new, simple, and efficient method for the synthesis of 2,2′-azopyridines from 2-aminopyridines, which has been particularly useful for the synthesis of (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates). The method is based on the unexpected reactivity of ethyl 6-amino-5-cyano-2-methyl-4-arylnicotinates with *N*-bromosuccinimide (NBS), in the presence of benzoyl peroxide.

In the course of a project in progress in our laboratory for the synthesis of new multipotent drugs for the treatment of Alzheimer's disease,[15] and when trying to prepare the bromomethyl derivative of ethyl 6-amino-5-cyano-2-methyl-4-phenylnicotinate (**1**),[16a] by typical free radical bromination conditions (NBS, benzoyl peroxide), instead of the expected molecule, a new compound (**2**)

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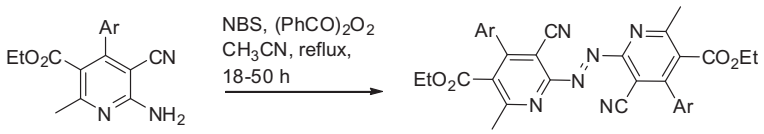


1	Ar= C_6H_5	**2** (79%)
3	Ar= *p*-ClC_6H_4	**4** (68%)
5	Ar= *o*-MeC_6H_4	**6** (74%)
7	Ar= 4'-pyridyl	**8** (40%)

Scheme 1. Synthesis of (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates) **2**, **4**, **6**, and **8**.

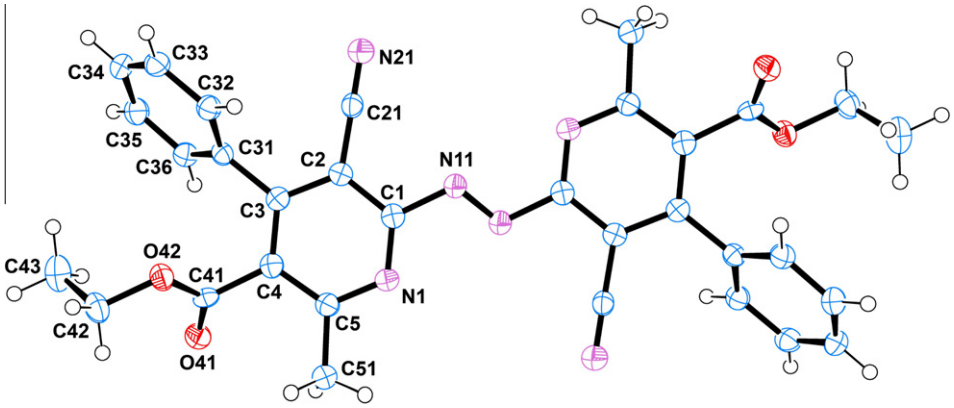


Figure 1. X-ray molecular structure of the compound **2** showing the atomic numbering scheme. Ellipsoids are drawn at the 50% probability level for non-H atoms, and the H atoms are denoted as spheres of 0.1 Å radius.

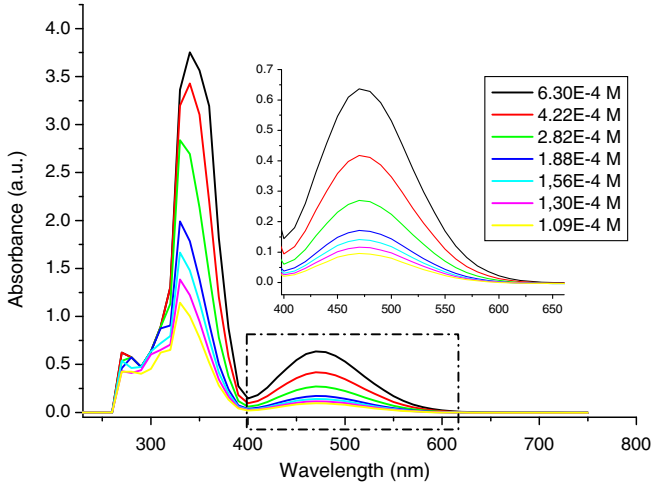


Figure 2. UV–vis absorption spectra of 2,2′-azopyridine **2** in acetone at different concentrations.

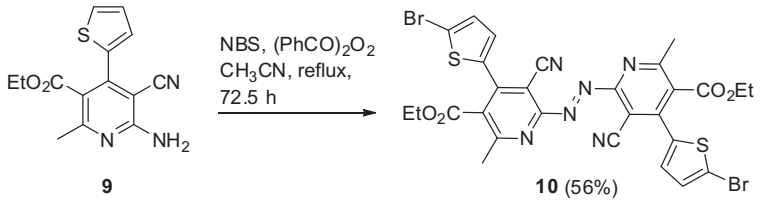
(Scheme 1) was obtained in 79% yield, and isolated as a strong red colored dye solid ('***MarcoRed***') whose structure was established by inspection of its spectroscopic and analytical data.[17a] Final confirmation of this structure was obtained by X-ray diffraction analysis (Fig. 1).

Molecules of compound **2** crystallize with an inversion center at the middle point of the N=N azo bond. Therefore, the crystal shows a half independent molecule. Primary distances and angles are normal compared with those in similar moieties contained in the Cambridge Structural Database.[18] The phenyl ring and the carboxylate group are twisted 60° and 52° with respect to the pyridine ring (Fig. 1).[19]

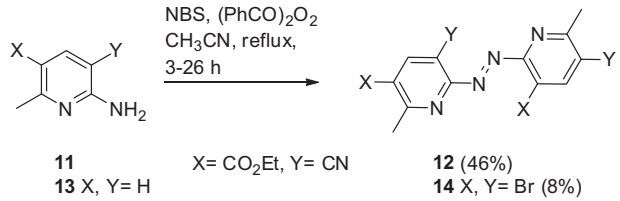
We have also measured the UV–vis absorption spectra of the azo derivative **2** in acetone, at different concentrations (6.3×10^{-4} M–1.09×10^{-4} M). The absorption spectra of 2,2′-azopyridine **2** shows two bands, the first at 330 nm (strong) (ε_{max} = 10,613 M^{-1} cm^{-1}) and the second (weak) with a maximum intensity at 470 nm (ε_{max} = 986 M^{-1} cm^{-1}) (Fig. 2). UV–vis spectroscopic studies were carried out also in other solvents.[20] These spectra show bands at 330 nm and at 470 nm with similar molar extinction coefficients (ε_{max}) at 470 nm.

This result was completely unexpected, as neither the bromomethyl derivative of compound **1** or brominated aromatic molecules were detected or isolated. Instead, the 2,2′-azopyridine **2** was formed in good yield, possibly by oxidation of the 2-aminopyridine to the corresponding diazonium salt, followed by the reaction with 1 equiv of the starting material, but we cannot exclude a free radical mechanism[2] involving a secondary aminyl radical (RNH·) followed by dimerization and oxidation to give the azo derivative.

To check the generality of this reaction, a number of related precursors (**3**,[16a] **5**,[16b] and **7**[16c]) have been synthesized and submitted to the same experimental conditions, to give the azo compounds **4**, **6,** and **8**, respectively, in moderate to good yields (Scheme 1). The reaction was also possible in ethyl 6-amino-5-cyano-2-methyl-4-(2-thienyl)nicotinate (**9**),[19,16c] but in this case, the resulting symmetric azo compound (**10**) (Scheme 2) was monobrominated at the thiophene ring at C-5′.[17a,b] This is also in good agreement with the known tendency of thiophenes to undergo free radical substitutions reactions at C-2.[21] Next, and in order to simplify the structure of the precursor, we submitted compound **11**,[15] bearing no aryl ring at C-4, to the same experimental conditions. We isolated the expected azo compound **12** in 46% yield (Scheme 3).[17a] Next, but as expected, due to the aromatic free available positions, the reaction of the commercially available 2-amino-6-methylpyridine (**13**) with NBS/benzoyl peroxide gave a complex reaction mixture formed by polybrominated derivatives, where we were able to



Scheme 2. Synthesis of (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(4-(5-bromothiophen-2-yl)-5-cyano-2-methylnicotinate) (**10**).



Scheme 3. Synthesis of (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates) **12** and **14**.

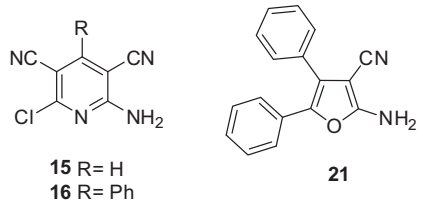
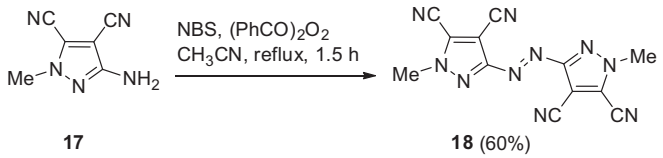
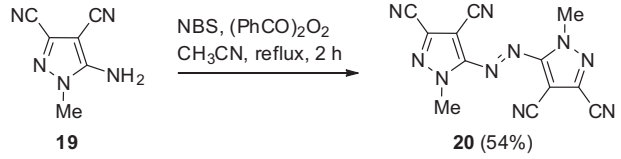


Figure 3. Structure of compounds **15**, **16** and **21**.



Scheme 4. Synthesis of (*E*)-3,3′-(diazene-1,2-diyl)bis(1-methyl-1*H*-pyrazole-4,5-dicarbonitrile) (**18**).



Scheme 5. Synthesis of (*E*)-5,5′-(diazene-1,2-diyl)bis(1-methyl-1*H*-pyrazole-3,4-dicarbonitrile) (**20**).

isolate only the azo compound **14**, albeit in poor yield (8%) (Scheme 3).[17a,c] In view of these results, next we explored this reactivity on related compounds **15**[22] and **16**[23] (Fig. 3), but surprisingly, no reaction or decomposition was observed. In order to extend the potential interest of this process to new heterocyclic precursors, the readily available pyrazoles **17**[24] and **19**[24] were submitted to the standard experimental conditions to give the azo compounds **18** (Scheme 4) and **20** (Scheme 5), in 60% and 54% yields, respectively. However, commercial 2-aminofuran-3-carbonitrile **21** (Fig. 3) did not react under the usual conditions.

To sum up, a new, mild, and simple synthetic method has been found to transform 2-aminopyridines into the corresponding azo compounds, using NBS in the presence of benzoyl peroxide. The present exploratory experiments suggest that the method is general for a wide structural diversity of substrates, but point out also that special requirements in the type and functionalization of the precursors are mandatory. These conditions seem to be particularly suitable for ethyl 6-amino-4-aryl-5-cyano-2-methylnicotinates, a large number of useful and easily available molecules,[25] that have afforded a new type of 2,2′-azopyridines, such as (*E*)-diethyl 6,6′-(diazene-1,2-diyl)bis(5-cyano-2-methyl-4-phenylnicotinates). These are new dyes of wide potential application in different areas of interest, such as catalysis, biology, and new materials. These issues are being currently investigated in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data (general methods and synthesis of compounds **2**, **4**, **5**, **6**, **8**, **10**, **12**, **14**, **18,** and **20**; and UV–vis analyzes of compound **2**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.095.

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Soto, J. L. *Liebigs Ann. Chem.* **1989**, 145) (see Supplementary data).; (c) León, R.; Marco-Contelles, J.; García, A. G.; Villarroya, M. *Bioorg. Med. Chem.* **2005**, *13*, 1167.
17. (a) All new compounds gave satisfactory analytical and spectroscopic data, in good agreement with their structures (see Supplementary data). (b) In the ^{1}H NMR spectrum of compound **10**, two doublets at δ 7.19 and 7.17, for one proton each, with a vicinal coupling constant of 3.9 Hz were observed and assigned to H-3′ and H-4′ thienyl protons, according to the literature data (see Ref. 16c). (c) In the ^{1}H NMR spectrum of compound **14**, the aromatic proton appears at δ 8.25, and shows two cross peaks with the signals at δ 157.3 and 156.8 (C-2, C-6) in the ^{1}H–^{13}C HSQC spectrum, data that are in good agreement with the location of the two bromine atoms at C-3 and C-5, leaving free the C-4 position.
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20. For the UV–vis analyzes of compound **2** in dichloromethane and ethyl acetate, as well as the experiments for the determination of the molar extinction coefficients, see the Supplementary data.
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