Mendeleev Communications

Mendeleev Commun., 2025, **35**, 258–260

A reaction of hexafluoro-1,4-naphthoquinone with 2-aminopyridines

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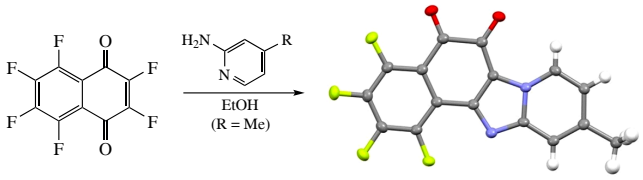
DOI: 10.71267/mencom.7737

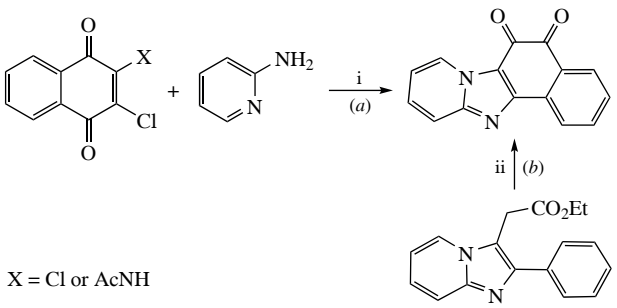
A reaction of hexafluoro-1,4-naphthoquinone with 2-aminopyridines leads to fluorinated naphtho[1′,2′:4,5]-imidazo[1,2-*a*]pyridine-5,6-diones. Advantages of the proposed one-step procedure are easily available starting materials, atom economy, and simple isolation of products without chromatographic purification.



Keywords: naphthoquinones, 2-aminopyridines, condensation, fused heterocyclic quinones, naphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridine-5,6-diones, organofluorine compounds.

Fused heterocyclic quinones are widely used for the treatment of various infectious diseases and constitute one of the largest classes of antitumor agents.[1–3] These compounds get involved in numerous biochemical processes because of their facile redox reactions. They play an important role in electron transport and oxidative phosphorylation processes. Furthermore, their biological activities include enzyme inhibition, and some members of this class have therapeutic value as antitumor (*e.g.*, anticancer), antibacterial, and antifungal agents. These compounds also leave a substantial imprint in the domain of dyes and pigments, particularly in the textile industry, because their conjugated structure imparts vibrant and stable coloration to fabrics and various other materials.[4,5] In addition, heterocyclic quinonoid compounds have found applications as visible photosensitizers for free-radical polymerization, charge-transporting materials,[6,7] and redox flow batteries and in other fields.[8,9]

Naphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridine-5,6-diones (NIPDs) were among the first obtained representatives of fused heterocyclic quinones. The first NIPD system was constructed by Mosby and Boyle in 1959 *via* the refluxing of 2,3-dichloro- or 2-acetamido-3-chloro-1,4-naphthoquinones with 2-aminopyridine (Scheme 1, path *a*),[10] which found further application.[11–14] An alternative cyclization of ethyl 2-(2-phenylimidazo[1,2-*a*]-pyridin-3-yl)acetate or related compounds with polyphosphoric acid involved an intramolecular Friedel–Crafts acylation and *in situ* oxidation of the methylene unit (see Scheme 1, path *b*).[15,16]

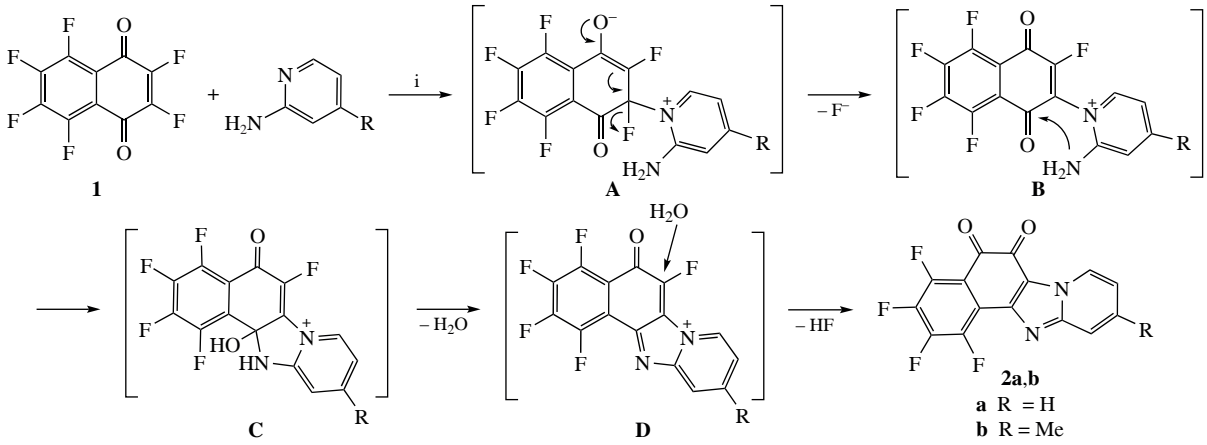


Scheme 1 *Reagents and conditions*: i, EtOH, 8 h, reflux; ii, polyphosphoric acid, 140 °C.

Among NIPD derivatives, dyes possessing strong fluorescence or positive solvatochromism or serving as efficient photoinitiators of free-radical polymerization in visible light have been obtained and comprehensively investigated.[11,17] Furthermore, an NIPD-based fluorescence probe has been designed and synthesized. The signal of this probe positively correlated with the α-helix content of proteins and could distinguish between human serum albumin and glycated forms of human serum albumin *via* typical modulation of aggregation-induced enhanced emission and excited-state intermolecular proton transfer-based dual-channel emission properties.[18] Certain NIPD derivatives were highly reactive substrates of NADPH-dependent single- and two-electron-transferring flavoenzymes.[13] Additionally, these NIPD derivatives have emerged as promising compounds for treating functional and organic venous insufficiency and inflammatory edema.[19,20]

Within the framework of our research aimed at using 2,3,5,6,7,8-hexafluoro-1,4-naphthoquinone **1** as a super-electrophilic compound for the preparation of polyfunctionalized derivatives,[21–25] here we focused on the synthesis of a new family of fluorinated NIPD derivatives. For the first time, we investigated a reaction of **1** with 2-aminopyridines. Starting perfluoro quinone **1** was obtained from octafluoronaphthalene by a literature procedure.[26] The reaction of **1** with model 2-aminopyridine was tested with variation of solvents, reaction duration, and temperatures. The best results with respect to the yield and purity of 1,2,3,4-tetrafluoronaphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridine-5,6-dione **2a** were achieved upon reflux in EtOH for 1 h. With these conditions, condensation product **2a** was isolated in pure form by simple filtration in 58% yield. The same conditions were most suitable for the synthesis of methyl-substituted derivative **2b** (62% yield).

The obtained compounds **2** are orange crystalline substances possessing low solubility in most organic solvents. They were characterized by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy and high-resolution mass spectrometry. ^{1}H NMR spectra of quinones **2** contain signals for protons of the pyridine moieties. Their ^{19}F NMR spectra show four peaks for the fluorine atoms at the benzene core. Structure of compound **2b** was ultimately confirmed by X-ray analysis. To the best of our knowledge, this is the first structure of methylnaphtho[1′,2′:4,5]imidazo-



Scheme 2 *Reagents and conditions*: i, EtOH, reflux, 1 h.

[1,2-*a*]pyridine-5,6-diones deposited in The Cambridge Crystallographic Data Centre.

The X-ray diffraction analysis indicates that compound **2b** crystallizes in the monoclinic $P2_1/n$ space group (Figure 1).† The C(11)–O(1) and C(12)–O(2) bond lengths are 1.212(2) and 1.229(2) Å, respectively, whereas C(13)–N(2) and C(4)–N(1) bond lengths are 1.391(2) and 1.346(2) Å. Analysis of crystal packing revealed short contacts O(2)···C(3) and C(12)···N(1) of 3.096 and 3.167 Å, respectively, which formally bind the molecules into chains along the *b* axis (Figure 2). Every chain is connected with another one by short contacts O(1)···C(8), O(1)···F(3), and O(1)···C(9) of 3.005, 3.167, and 3.061 Å. These contacts give rise to centrosymmetric pairs of chains (Figure 3). In turn, the pairs of chains are linked by a network of short contacts F···H–C.

According to the proposed reaction mechanism (see Scheme 2), 2-aminopyridine is initially added to the double bond of the quinone moiety resulting in intermediate **A**. Subsequent elimination of a fluoride anion produces pentafluoro quinone **B**. At the next stage, the amino group prefers to attack the carbon atom of the C=O group thereby giving fused system **C**. Next, dehydration of intermediate **C** results in salt **D**. Final product **2** is formed *via* the hydrolysis of the bond of the remaining fluorine atom in the iminoquinone unit.

To conclude, we investigated a reaction of perfluoronaphthoquinone with 2-aminopyridines which afforded 1,2,3,4-tetrafluoronaphtho[1′,2′:4,5]imidazo[1,2-*a*]pyridine-5,6-diones. Structure of one of the synthesized compounds was proved by X-ray diffraction. The polyfluorinated fused system prepared in this work can be a good starting point for further chemical modification in the search for novel materials and drugs.

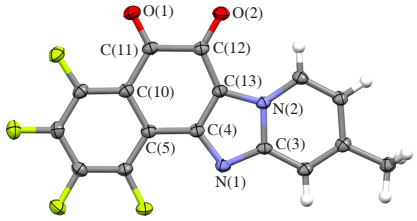


Figure 1 Molecular structure of 1,2,3,4-tetrafluoro-10-methylnaphtho-[1′,2′:4,5]imidazo[1,2-*a*]pyridine-5,6-dione **2b**. Characteristics of atomic displacement are shown with a 50% probability.

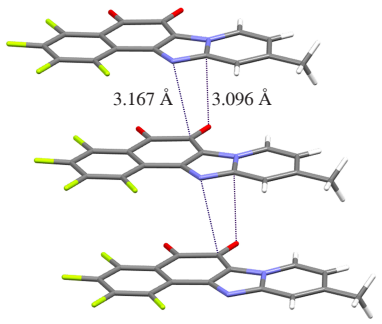


Figure 2 A fragment of crystal structure of compound **2b** with short contacts O(2)···C(3) and C(12)···N(1).

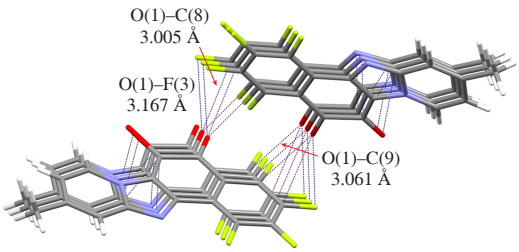


Figure 3 Centrosymmetric pairs of chains in the structure of compound **2b** with short contacts O(1)···C(8), O(1)···F(3), and O(1)···C(9).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7737.

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† *Crystal data for* **2b**. $C_{16}H_6F_4N_2O_2$ (M_w = 334.23), monoclinic, space group $P2_1/n$, a = 10.4653(2), b = 5.20120(10) and c = 23.1232(3) Å, β = 94.9100(10)°, V = 1254.03(4) Å^3, and μ(CuKα) = 1.400 mm^{-1}. The analysis was performed at 100.00(10) K on an XtaLAB Synergy, DualFlex, HyPix diffractometer by a standard procedure (graphite monochromated CuKα radiation, ω-scanning). The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.[27] At angles 3.83° < θ < 79.52°, a total of 14169 reflections were measured, including 2720 unique reflections (R_{int} = 0.0447) and 2462 reflections with $I > 2\sigma(I)$. The structure was solved and refined using the SHELXT software suite.[28] The structure was determined by direct statistical methods and refined by full-matrix anisotropic approximation for F^2 for all nonhydrogen atoms by means of the SHELXL software[29] in the OLEX2 program.[30] Hydrogen atoms were localized by the direct method and refined in the isotropic approximation. A rotating group model was applied for methyl groups. GOOF = 1.072; final R values: R_1 = 0.0481, wR_2 = 0.1392 [$I > 2\sigma(I)$]; R_1 = 0.0512, and wR_2 = 0.1417 (all data). Residual electronic density (max/min) was 0.351/–0.282 e Å^{-3}.

CCDC 2419430 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk.

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Received: 3rd February 2025; Com. 25/7737