

A rational protocol for the synthesis of 1-(2-pyridyl)isoquinolines

Dmitry S. Kopchuk,^{a,b} Igor S. Kovalev,^a Albert F. Khasanov,^a Grigory V. Zyryanov,^{a,b}
Pavel A. Slepukhin,^b Vladimir L. Rusinov^{a,b} and Oleg N. Chupakhin^{a,b}

^a Department of Organic Chemistry, Ural Federal University, 620002 Ekaterinburg, Russian Federation

^b I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russian Federation. Fax: +7 343 374 1189; e-mail: dkopchuk@mail.ru

DOI: 10.1016/j.mencom.2013.05.007

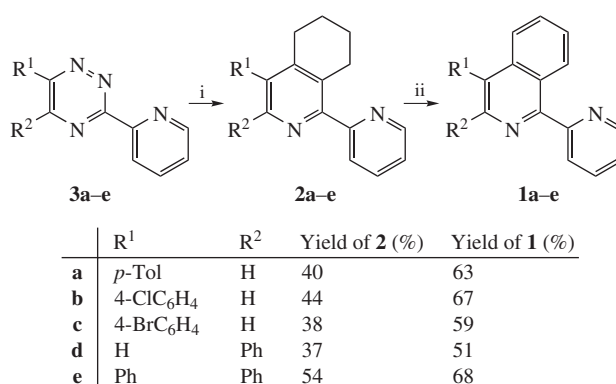
Aza-Diels–Alder reaction between 3-(2-pyridyl)-1,2,4-triazines and 1-morpholinocyclohexene followed by aromatization of the cyclohexene moiety affords 1-(2-pyridyl)isoquinolines. Crystal structures of two tetrahydroisoquinolines were confirmed by X-ray diffraction analysis.

Isoquinolines and tetrahydroisoquinolines are important class of heterocycles due to their presence in a wide range of naturally occurring compounds. Isoquinoline derivatives exhibit various biological activities,¹ including anti-HIV,² antimalarial,³ ion-channel blocking activity,⁴ act as dopamine agonists,⁵ and are present in some alkaloids.⁶ Pyridyl-substituted isoquinolines are of wide use as ligands for copper,⁷ as chiral catalysts⁸ and phosphorescent emitters for OLEDs.⁹ Traditional synthetic routes to isoquinolines are the Bischler–Napieralski, Pomeranz–Fritsch and Pictet–Spengler reactions, which involve the intramolecular cyclization under the drastic conditions.¹⁰ Pyridyl-substituted isoquinolines can also be accessed by cross-coupling reactions,¹¹ reactions mediated by organolithium compounds,¹² as well as some heterocyclization reactions.¹³ In addition, some new synthetic approaches to isoquinolines appeared in a literature, especially due to the development of metal-catalyzed organic synthesis¹⁴ as well as modern aryne chemistry.¹⁵ Thus, an efficient synthesis of isoquinolines from alkynes and iododiamines and ketimines,¹⁶ as well as palladium-catalyzed aryne annulation with *ortho*-haloaldehydes affording isoquinolines¹⁷ were reported. Recently¹⁸ we described the synthesis of pyridyl-substituted isoquinolines using non-catalyzed cycloaddition of substituted 1,2,4-triazines and arynes generated *in situ*.

Herein we propose a rational protocol for the synthesis of pyridyl-substituted isoquinolines by the inverse demand Diels–Alder reaction of 1,2,4-triazines (Scheme 1). The first precedent of such a reaction was reported¹⁹ in 1969 and nowadays this approach is of high demand.²⁰ However, the inverse demand Diels–Alder reactions have never been used for the preparation of pyridyl-substituted isoquinolines.

Starting 1,2,4-triazines **3** were synthesized by described²¹ cyclocondensation between the corresponding amidrazones and dicarbonyl compounds or between isonitrosoacetophenone hydrazones and pyridine-2-carboxaldehyde. Our investigations began with examining the reaction conditions for preparing tetrahydroisoquinolines. According to the published data, various dienes can be efficiently applied for obtaining pyridine derivatives from 1,2,4-triazines. In most cases 1,2,4-triazines and enamines of pyrrolidine²² were utilized to prepare the corresponding pyridocyclopentenes. Only in a very few cases 1-morpholinocyclohexene was used for similar purposes.²³

We found that in case of enamine as the dienophile the product yield depended on the reactant ratio and the reaction temperature. Thus, refluxing of corresponding 1,2,4-triazines and 1 to 5 equiv. of 1-morpholinocyclohexene in aromatic solvents afforded the



Scheme 1 Reagents and conditions: i, 1-morpholinocyclohexene (neat), 200 °C, 4 h; ii, DDQ, *o*-xylene, 143 °C, 10 h.

corresponding tetrahydroisoquinolines in yields less than 25%. The solvent-free procedure²⁴ at the same ratio of reactants (*ca.* 1:5) and the temperature of 195–200 °C was significantly more effective: the target tetrahydroisoquinolines **2** were isolated in 37–54% yields.[†] Note that all the products were simply purified by recrystallization and in most cases no column chromatography was needed.[‡]

Structures of products **2** were confirmed by spectral data. In addition, the crystal structures of compounds **2c** and **2e** were proved by X-ray diffraction analysis (Figure 1).[§]

The subsequent aromatization of products **2**, for instance by the solvent-free heating over 10% Pd on carbon²⁵ afforded isoquinolines **1** only in 10–15% yield, and a significant amount of oily by-products was detected in the reaction mixture. The procedure using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in

[†] Preparation of bipyridines **2** (general procedure). A mixture of the corresponding triazine **3** (2 mmol) and 1-morpholinocyclohexene (1.68 ml, 10 mmol) was stirred at 200 °C for 2 h under argon. Then the additional portion of 1-morpholinocyclohexene (0.84 ml, 5 mmol) was added and the mixture was stirred for additional 2 h. The resulting solution was cooled to room temperature. Acetonitrile (20 ml) was added and the reaction mixture was kept at –18 °C for 15 h. The fine crystalline precipitate formed was filtered off, washed with acetonitrile and dried. Analytically pure sample was obtained by recrystallization from acetonitrile.

For characteristics of compounds **2a–e**, see Online Supplementary Materials.

[‡] In case of bipyridine **2d** column chromatography (CHCl₃, *R*_f = 0.2) was used to purify the product.

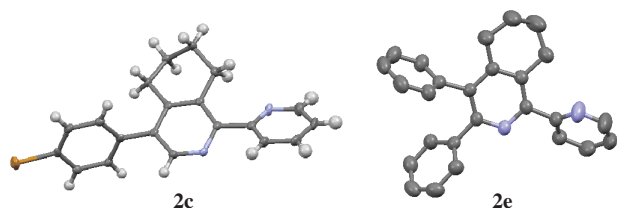


Figure 1 Molecular structures of bipyridines **2c** and **2e**. Hydrogen atoms in **2e** are omitted for clarity.

aromatic solvents was more successful. In a typical case refluxing of compounds **2** and **3** equiv. DDQ in *o*-xylene afforded isoquinolines **1** in yields up to 68%.[†]

It should be mentioned that although the synthesis of compound **1d** was reported previously by R. Ziessel and co-authors,²⁶ their spectral data differed from those observed by us. In particular, in the ¹³C NMR spectrum of compound **1d** obtained by us, the resonances of all 18 aromatic carbons are revealed *versus* 15 carbon atoms reported by R. Ziessel and co-authors. In addition, its ¹H NMR spectrum contained the characteristic resonance for C⁴H proton of isoquinoline system as one proton singlet at 8.15 ppm and several multiplets for other protons *versus* broad multiplet reported for this compound.²⁶

Thus, we have developed an efficient and novel synthetic route to aryl-substituted 1-(2-pyridyl)isoquinolines *via* the corresponding tetrahydroisoquinolines readily accessed from 1,2,4-triazines by the aza-Diels–Alder reaction. This approach allows one to obtain isoquinolines with a fairly wide variation of substituents in core.

The work was supported by the Russian Ministry of Education and Science (state contract nos. 14.740.11.1020 and 14.A18.21.0817),

§ *Crystal data for 2c*. Brown crystals (0.33×0.18×0.03 mm), triclinic, space group *P* $\bar{1}$, at 150(2) K: *a* = 8.6964(7), *b* = 13.8034(11) and *c* = 15.4544(19) Å, α = 112.724(11)°, β = 99.166(10)°, γ = 103.960(7)°, *V* = 1593.2(3) Å³, *Z* = 4, *d*_{calc} = 1.523 g cm^{−3}. 9057 reflections were collected (2.67° < θ < 28.29°), 7639 independent (*R*_{int} = 0.0261) and 4429 with *I* > 2σ(*I*). Analytical correction for absorption was applied (μ = 2.581 mm^{−1}).²⁷ The final refinement parameters were: *R*₁ = 0.0408, *wR*₂ = 0.0874 for reflections with *I* > 2σ(*I*); *R*₁ = 0.0839, *wR*₂ = 0.0919 for all reflections; GOF = 1.005.

Crystal data for 2e. Colourless crystals (0.25×0.20×0.15 mm), monoclinic, *P*₂/c, at 295(2) K: *a* = 9.9141(12), *b* = 10.5438(7) and *c* = 18.7699(17) Å, β = 99.358(9)°, *V* = 1935.9(3) Å³, *Z* = 4, *d*_{calc} = 1.244 g cm^{−3}. 8513 reflections were collected (2.777° < θ < 28.28°), 4594 independent (*R*_{int} = 0.0309) and 1750 with *I* > 2σ(*I*). Analytical correction for absorption was not applied (μ = 0.073 mm^{−1}).²⁷ The final refinement parameters were: *R*₁ = 0.0429, *wR*₂ = 0.079 for reflections with *I* > 2σ(*I*); *R*₁ = 0.1312, *wR*₂ = 0.0852 for all reflections; GOF = 1.002.

The structures were solved by direct methods and refined by full-matrix least-squares procedure on *F*² with the SHELXTL-97²⁸ program in the anisotropic approximation for non-hydrogen atoms. The positions of the H atoms were calculated geometrically and included in the refinement with the ‘riding model’.

CCDC 913339 and 913340 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2013.

† *Preparation of isoquinolines 1 (general procedure)*. A mixture of the corresponding bipyridine **2** (0.5 mmol), DDQ (114 mg, 0.5 mmol) and *o*-xylene (40 ml) was refluxed for 3 h. Additional portion of DDQ (114 mg, 0.5 mmol) was added and the reaction mixture was refluxed for additional 3 h. Then the final portion of DDQ (114 mg, 0.5 mmol) was added and the resulting mixture was refluxed for 4 h. The solvent was removed under reduced pressure, the residue was purified by column chromatography (neutral Al₂O₃, chloroform).

For characteristics of compounds **1a–e**, see Online Supplementary Materials.

the Russian Foundation for Basic Research (grant no. 12-03-31726) and the Council for grants of the President of the Russian Federation (grant no. MK-1511.2013.3).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.05.007.

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Received: 5th February 2013; Com. 13/4063