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Mendeleev Commun., 2015, **25**, 13–14
Mendeleev Communications

Aryne approach towards 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles

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DOI: 10.1016/j.mencom.2015.01.003

Reaction between 3-(2-pyridyl)-1,2,4-triazines and *in situ* generated 4,5-difluorobenzyne in toluene affords 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles. The structure of one representative compound was confirmed by X-ray diffraction analysis.

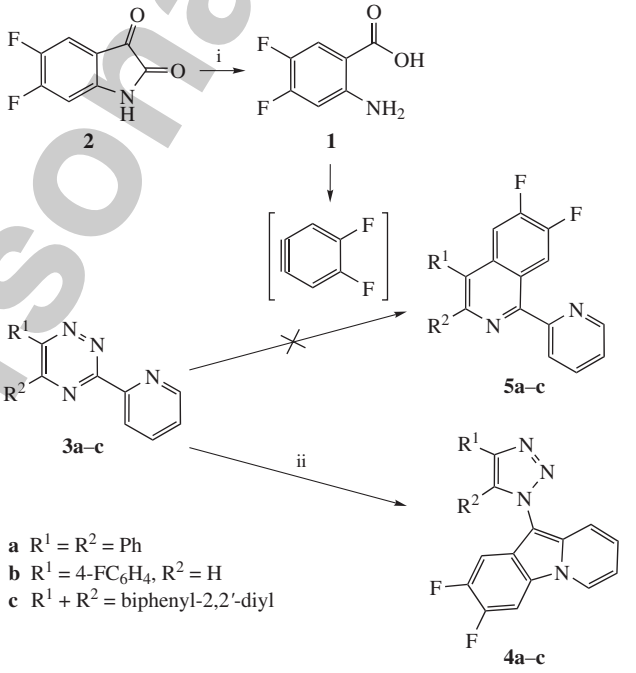
Pyrido[1,2-*a*]indoles are of practical interest due to their cytostatic,[1] antiviral[2] and antitumor[3] activities. Introduction of fluorine atoms into poly(hetero)cyclic systems in most cases improves their photophysical properties,[4] biological activity[5] and electrochemical properties.[6] For now fluorinated pyrido[1,2-*a*]indoles are known scarcely,[7] while substituted 2,3-difluoropyrido[1,2-*a*]-indoles are not reported. As for 1,2,3-triazoles, they are of interest[8] as common pharmacophores[9] as well as components of photoluminescent sensors for various analytes,[10] including explosives.[11]

The methods for the synthesis of pyrido[1,2-*a*]indoles are mostly limited by availability of the starting materials and/or the application of harsh conditions.[12] As for 1,2,3-triazole-substituted pyrido[1,2-*a*]indoles, recently the convenient one-pot approach *via* the benzyne-mediated rearrangement of 3-(2-pyridyl)-1,2,4-triazines was reported by our group.[13] In this paper the convenient one-pot approach to 10-substituted 2,3-difluropyrido[1,2-*a*]-indoles by reaction between 3-(2-pyridyl)-1,2,4-triazines and 4,5-difluorobenzyne is reported.

During the last decade, aryne chemistry is experiencing a renaissance, due to the development of new methods for the smooth and effective aryne generation.[14] In particular, 4,5-difluorobenzyne can be generated from 4,5-difluoro-2-trimethylsilylphenyl trifluoromethanesulfonate[15] by the action of fluoride anion or from 1,2-dibromo-4,5-difluorobenzene[16] by the action of *n*-butyllithium. On the other hand, 3,4-difluoroanthranilic acid, which can be easily obtained by 3,4-difluoroaniline[17]–5,6-difluoroisatine sequence, is a rare 4,5-difluorobenzyne source.[18] In this work, 3,4-difluoroanthranilic acid–derived 4,5-difluorobenzyne is used to prepare 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles in one step in good yields.

For the synthesis of 3,4-difluoroanthranilic acid **1**, the modified method based on 5,6-difluoroisatine **2**[19] was used (Scheme 1).

1,2,4-Triazines **3** were synthesized according to reported procedures[20] by the reaction of isonitrosoacetophenone hydrazones with pyridine-2-carbaldehyde or by the reaction between α-diketones and amidrazones. The fluorination of the aryl substituent of the triazine core as well as the aryl precursor of the 4,5-difluorobenzyne did not influence the reaction pathway giving 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles **4** in moderate yields (see Scheme 1).† No isoquinolines **5** were observed in a reaction mixture. A plausible mechanism of this transformation is represented in Scheme 2.

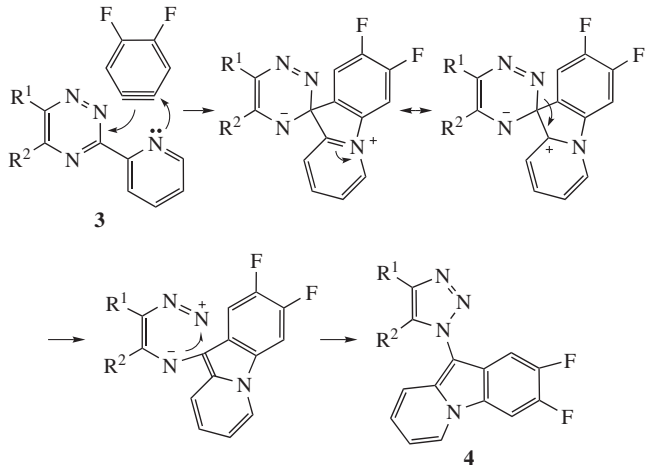


Scheme 1 *Reagents and conditions*: i, NaOH, H_2O_2, 55 °C, 2 h, then HCl, 15–20 °C; ii, toluene, isoamyl nitrite, 110 °C, 1.5 h.

The structure of the products **4** was confirmed by ^{1}H, ^{13}C, ^{19}F NMR spectroscopy and mass spectrometry, and by comparison of their spectral data with the previously reported ones for non-fluorinated products.[13] Ultimately, the structure of the representative compound **4b** was confirmed by X-ray crystallography (Figure 1).‡

Compound **4b** is crystallized in trigonal system. Face-to-face π–π stacking interactions between the pyrido[1,2-*a*]indole fragments are evident, the interplanar separations are in the range of

† *2,3-Difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-a]indoles* **4**. Corresponding triazine **3** (3 mmol) was suspended in dry toluene (130 ml). Isoamyl nitrite (1.61 ml, 12 mmol) was added to this mixture. The mixture was stirred under reflux while solution of 3,4-difluoroanthranilic acid (2.08 g, 12 mmol) in dry 1,4-dioxane (15 ml) was added dropwise within 30 min. The reaction mixture was refluxed for 1 h, then cooled to room temperature and washed with 3 M KOH solution (3×75 ml), the organic layer was separated and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure. Products **4** were isolated by column chromatography [silica gel, AcOEt–CH_2Cl_2 (3:1) as eluent, R_f = 0.8]. Analytically pure samples **4** were obtained by the recrystallization from dry acetonitrile. For the analytical data, see Online Supplementary Materials.



Scheme 2

3.5 Å, and the glide-related molecules are linked in a head-to-tail fashion to generate a supramolecular architecture of infinite chains (see Figure S1, Online Supplementary Materials). Hydrogen bonds between fluorine and hydrogen atoms are also observed, distances between them are in a range of 2.5–2.6 Å (see Figure S2, Online Supplementary Materials). Similar cases of intermolecular and intramolecular hydrogen bonds involving fluorine atoms were reported.[21]

In conclusion, a convenient one-step approach towards novel 2,3-difluoro-10-(1*H*-1,2,3-triazol-1-yl)pyrido[1,2-*a*]indoles *via* the aryne chemistry has been developed. These compounds can be very promising in view of their biological activities.

This work was supported by the Russian Ministry of Education and Science (state contract no. 8430), the Council for grants of the President of the Russian Federation (grant no. MK-1511.2013.3) and Act #211 of the Russian Federation Government (no. 02.A03.21.0006).

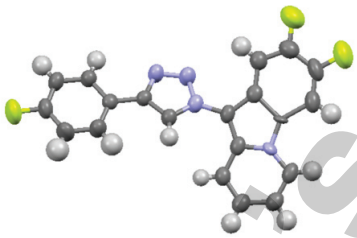


Figure 1 Molecular structure for product **4b**.

‡ *Crystal data for* **4b**. The single crystal (brown needle, 0.25×0.08×0.02 mm) of compound **4b** ($C_{20}H_{11}F_3N_4$) was used for X-ray analysis. Analysis was performed at 295(2) K on an Xcalibur E diffractometer using graphite monochromated MoKα (λ = 71.073 pm) and CCD detector. Crystal is trigonal, space group *R*-3 with $a = b = 47.097(5)$ and $c = 3.8351(5)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 7367.1(15)$ Å^3, $Z = 18$. On the angles $2.29 < \theta < 26.36°$ 10614 reflections were measured, among them 3323 unique reflections ($R_{int} = 0.0490$), 1679 reflections with $I > 2\sigma(I)$. Completeness to $\theta_{max} = 26.38$ is 99.3%. The structure was solved by direct method and refined by full-matrix least squares at F^2 using the SHELXTL program package. All non-hydrogen atoms were refined anisotropically, the positions of the hydrogen atoms were calculated as a riding model in isotropic approximation. An absorption correction was not applied (μ = 0.115 mm^{-1}). Goodness of fit at F^2 1.003; final *R* values [$I > 2\sigma(I)$], $R_1 = 0.0548$, $wR_2 = 0.0846$; *R* value (all reflections) $R_1 = 0.1326$, $wR_2 = 0.1024$. Largest difference peak and hole were 0.143 and –0.139 eÅ^{-3}.

CCDC 984078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.01.003.

References

1 (*a*) R. Ambros, S. Von Angerer and W. Wiegrebe, *Arch. Pharm.*, 1988, **321**, 481; (*b*) R. Ambros, M. R. Schneider and S. Von Angerer, *J. Med. Chem.*, 1990, **33**, 153.

2 T. W. Hudyma, X. Zheng, F. He, M. Ding, C. P. Bergstrom, P. Hewawasam, S. W. Martin and R. G. Gentles, *U.S. Pat. Appl. Publ.*, 2006, 318, *Cont.-In-Part of U.S. Ser. No. 181, 639* (*Chem. Abstr.*, 2006, **145**, 189063).

3 E. O. M. Orlemans, W. Verboom, M. W. Scheltinga, D. N. Reinhoudt, P. Lelieveld, H. H. Fiebig, B. R. Winterhalter, J. A. Doublell and M. C. Bibbyll, *J. Med. Chem.*, 1989, **32**, 1612.

4 (*a*) S. Donga and W. Wanga, *Synth. Met.*, 2009, **159**, 385; (*b*) T. V. Trashakhova, E. V. Nosova, M. S. Valova, P. A. Slepukhin, G. N. Lipunova and V. N. Charushin, *Russ. J. Org. Chem*, 2011, **47**, 753 (*Zh. Org. Khim.*, 2011, **47**, 748).

5 G. N. Lipunova, E. V. Nosova, A. A. Laeva and V. N. Charushin, *Pharm. Chem. J.*, 2012, **45**, 709 (*Khim.-Farm. Zh.*, 2012, **45**, 12).

6 (*a*) I. N. Kang, H. K. Shim and T. Zyung, *Chem. Mater.*, 1997, **9**, 746; (*b*) R. M. Gurge, A. M. Sarker, P. M. Lahti, B. Hu and F. E. Karasz, *Macromolecules*, 1997, **30**, 8286.

7 (*a*) D. C. Rogness, N. A. Markina, J. P. Waldo and R. C. Larock, *J. Org. Chem.*, 2012, **77**, 2743; (*b*) L.-L. Sun, Z.-Y. Liao, R.-Y. Tang, C.-L. Deng and X.-G. Zhang, *J. Org. Chem.*, 2012, **77**, 2850.

8 G. T. Sukhanov, G. V. Sakovich, Yu. V. Filippova, I. Yu. Bagryanskaya and A. G. Sukhanova, *Mendeleev Commun.*, 2014, **24**, 280.

9 S. G. Agalave, S. R. Maujan and V. S. Pore, *Chemistry – An Asian Journal*, 2011, **6**, 2696.

10 (*a*) H. Kim, S. Lee, J. Lee and J. Tae, *Org. Lett.*, 2010, **12**, 5342; (*b*) K. Ghosh, D. Kar, S. Joardar, D. Sahu and B. Ganquly, *RSC Adv.*, 2013, **3**, 16144.

11 V. Bhalla, H. Singh and M. Kumar, *Dalton Trans.*, 2012, **41**, 11413.

12 (*a*) N. von Braun, *Chem. Ber.*, 1937, **70**, 1760; (*b*) A. Deegan and F. L. Rose, *J. Chem. Soc. C: Org. Chem.*, 1971, 2756; (*c*) R. R. Naredla, C. Zheng, S. O. Nilsson Lill and D. A. Klumpp, *J. Am. Chem. Soc.*, 2011, **133**, 13169; (*d*) A. T. Soldatenkov, M. V. Bagdadi, A. A. Fomichev and N. S. Prostakov, *J. Org. Chem. USSR*, 1982, **18**, 783 (*Zh. Org. Khim.*, 1982, **18**, 902); (*e*) A. Ohsawa, T. Kawaguchi and H. Igeta, *Chem. Lett.*, 1981, 1737; (*f*) L. M. Gaster and P. A. Wyman, *Patent US 5998409A*, 1995 (*Chem. Abstr.*, 1995, **122**, 265390).

13 I. L. Nikonov, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. F. Khasanov, P. A. Slepukhin, V. L. Rusinov and O. N. Chupakhin, *Tetrahedron Lett.*, 2013, **54**, 6427.

14 (*a*) I. S. Kovalev, D. S. Kopchuk, G. V. Zyryanov, P. A. Slepukhin, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2012, **48**, 536 (*Khim. Geterotsikl. Soedin.*, 2012, 576); (*b*) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191.

15 (*a*) K. S. Gebara, G. A. Casagrande and C. Raminelli, *Tetrahedron Lett.*, 2011, **52**, 2849; (*b*) L. Castedo, S. Escudero, D. Ferez, E. Guitian and D. Pena, *Angew. Chem., Int. Ed. Engl.*, 1997, **37**, 2659; (*c*) R. C. Larock, Z. Liu and C. Raminelli, *J. Org. Chem.*, 2006, **71**, 4689.

16 (*a*) R. Luo, W. Tang, J. Liao, R. Luo, L. Xie and A. S. Chan, *Chem. Commun.*, 2013, **49**, 9959; (*b*) H. F. Bettinger, R. P. Bula and I. M. Oppel, *J. Org. Chem.*, 2012, **77**, 3538; (*c*) R. Webster, C. Boeing and M. Lautens, *J. Am. Chem. Soc.*, 2009, **131**, 444.

17 A. A. Layeva, E. V. Nosova, G. N. Lipunova and V. N. Charushin, *Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 947 (*Izv. Akad. Nauk., Ser. Khim.*, 2008, 931).

18 (*a*) U. N. Rao, R. Sathunuru, J. A. Maguire and E. Biehl, *J. Heterocycl. Chem.*, 2004, **41**, 13; (*b*) D. M. Hodgson, M. W. P. Bebbington and P. Willis, *Org. Biomol. Chem.*, 2003, **1**, 3787; (*c*) M. W. P. Bebbington, D. M. Hodgson and P. Willis, *Org. Lett.*, 2002, **4**, 4353.

19 F. R. Busch, S. J. Hecker, P. R. McGuirk, B. T. O'Neill and H. A. Watson, Jr., *Patent EP0342849*, 1989 (*Chem. Abstr.*, 1990, **113**, 406177).

20 (*a*) F. H. Case, *J. Org. Chem.*, 1965, **30**, 931; (*b*) V. N. Kozhevnikov, O. V. Shabunina, D. S. Kopchuk, M. M. Ustinova, B. König and D. N. Kozhevnikov, *Tetrahedron*, 2008, **64**, 8963; (*c*) D. S. Kopchuk, G. V. Zyryanov, I. S. Kovalev, A. F. Khasanov, A. S. Medvedevskikh, V. L. Rusinov and O. N. Chupakhin, *Chem. Heterocycl. Compd.*, 2013, **49**, 500 (*Khim. Geterotsikl. Soedin.*, 2013, 535).

21 (*a*) C. Dalvit and A. Vulpetti, *ChemMedChem*, 2012, **7**, 262; (*b*) J. D. Dunitz and R. Taylor, *Chem. Eur. J.*, 1997, **3**, 89.

Received: 14th April 2014; Com. 14/4350