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SYNTHESIS OF NEW MULTIVALENT FURO[3,2-*c*]PYRIDINE AND BIFURO[3,2-*c*]PYRIDINE DERIVATIVES

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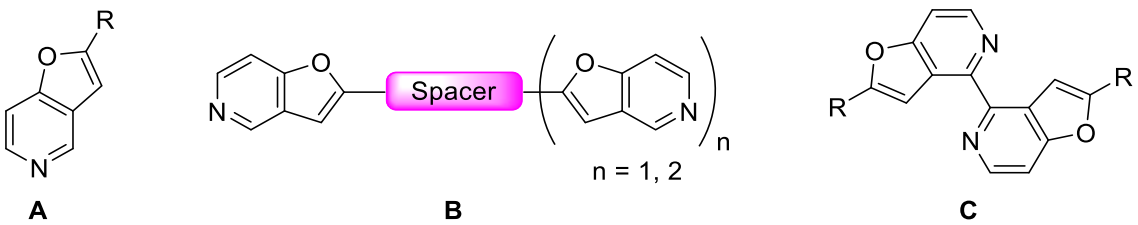
Abstract – A series of furo[3,2-*c*]pyridine derivatives was prepared by an efficient cascade process involving Sonogashira reactions of 4-hydroxy-3-iodopyridine with suitable terminal alkynes followed by an immediate 5-*endo-dig* cyclization to generate the furan ring. Several multivalent furo[3,2-*c*]pyridines were prepared by employing dialkynes or trialkynes. Two bifuro[3,2-*c*]pyridine derivatives were prepared by alternative coupling methods. The photophysical properties of several of these compounds are compared.

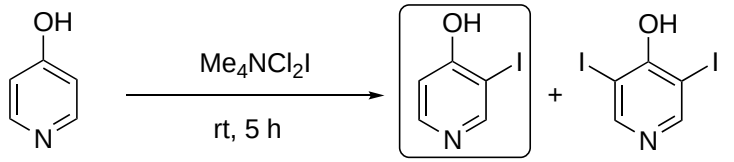
During the last decade our group studied syntheses and properties of a series of multivalent heterocycles,[1] in particular of oxazole[2] and of pyridine derivatives.[3] The 2D self-assembly at a solution-graphite interface[2,3a,c,e,g] and the photophysical properties[3d,j] of these multivalent compounds were thereby of special interest. During these investigations efficient routes to furo[2,3-*c*]- and furo[3,2-*c*]pyridines were developed employing a very flexible building block system.[4] Since furopyridines are a very interesting class of heterocycles[5-7] we extended our synthetic efforts to the preparation of a series of new multivalent furo[3,2-*c*]pyridine derivatives (Scheme 1). Simple furo[3,2-*c*]pyridines **A**, spacer-connected divalent or trivalent compounds **B**, and directly connected bifuropyridine derivatives of type **C** should be synthesized.



Scheme 1

‡ Dr. Maurice Taszarek died on February 24, 2018.
This paper is dedicated to the memory of Professor Dr. Akihiro Ohta (1934–2022).

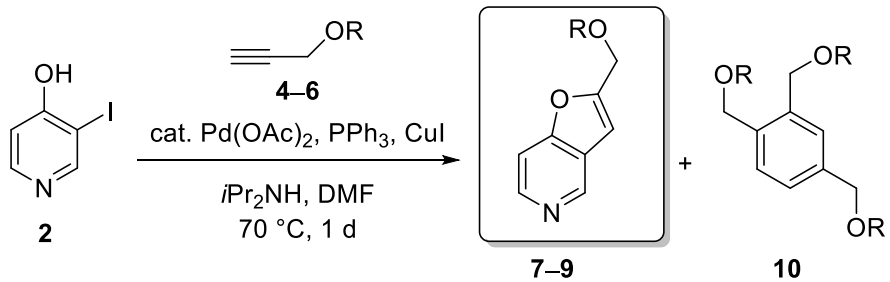
As crucial starting material for the synthesis of furo[3,2-*c*]pyridines we required 4-hydroxy-3-iodopyridine (**2**). Following the literature reported method[8] and treating 4-hydroxypyridine (**1**) with elemental iodine and potassium iodide under basic conditions, we obtained a mixture of **2** and the corresponding diiodo derivative (**3**), which were isolated in 26% and 23% yield. An alternative method with tetramethylammonium dichloroiodate (Me_4NCl_2I) as mild iodination reagent[9] delivered a much better result (Scheme 2). After slow addition of 0.5 equivalents of Me_4NCl_2I to 4-hydroxypyridine (**1**) and chromatographic purification the desired compound **2** was obtained in 81% yield (based on the amount of the iodination reagent) and the side-product **3** was isolated only in 5%.



1 **2** 81% **3** 5%

Scheme 2

With sufficient material of precursor **2** in hand we could prepare three simple furo[3,2-*c*]pyridine derivatives. The applied cascade process is based on a Sonogashira reaction[10] which is immediately followed by a base-induced 5-*endo-dig* cyclization of the pyridine oxygen to the alkynyl moiety to form the furan ring.[4,11] Reaction of **2** with three differently protected propargylic ethers **4**–**6** (1.2–2 equivalents) in the presence of catalytic amounts of palladium catalysts, copper iodide and diisopropylamine in DMF at 70 °C furnished the desired compounds **7**–**9** in good yields (Scheme 3). In all reactions we detected small amounts of compounds **10** which apparently result from a palladium-catalyzed trimerization of the starting propargylic ethers.



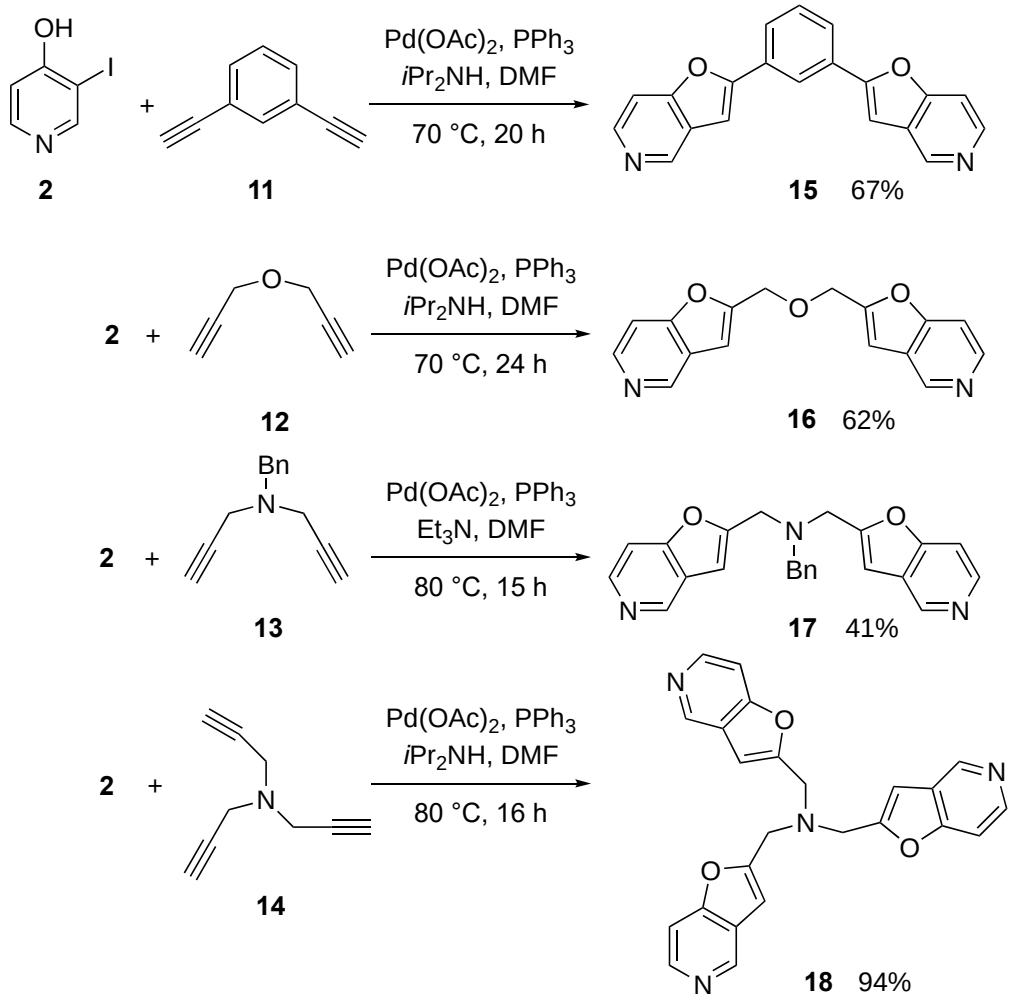
2 **7–9** **10**

4 R = Me, **5** R = Bn, **6** R = TBS **7** R = Me 76%, **8** R = Bn 75%, **9** R = TBS 75%

[for the transformation of **5** to **8** $Pd(PPh_3)_4$ was used instead of $Pd(OAc)_2$]

Scheme 3

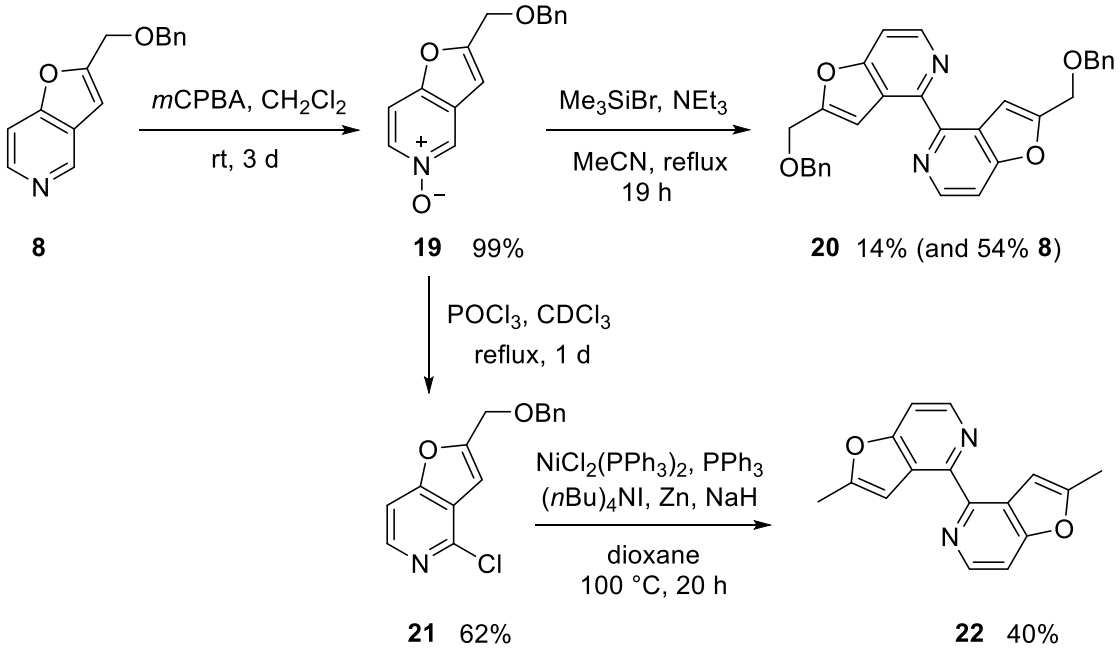
For the preparation of multivalent furo[3,2-*c*]pyridine derivatives we examined Sonogashira reactions of an excess of precursor **2** (2–4.4 equivalents) with dialkynes **11**–**13** and trialkyne **14** (Scheme 4). The fully conjugated bifuro[3,2-*c*]pyridine derivative **15** was obtained from the rigid diyne **11** in 67% yield whereas the couplings of the flexible dialkynes **12** and **13** were slightly less efficient providing **16** and **17** in 62% and 41% yield, respectively. Finally, the trivalent compound **18** was very efficiently prepared from **2** and the trialkyne **14**. We did not try to optimize these reactions.



Scheme 4

We also tried to connect furo[3,2-*c*]pyridine moieties without spacer units to afford the corresponding bifuro[3,2-*c*]pyridine derivatives (Scheme 5). For this purpose, furo[3,2-*c*]pyridine (**8**) was oxidized to the *N*-oxide **19** employing *m*-chloroperoxybenzoic acid.[12] Applying a method of Shiotani and Taniguchi,[13] bromotrimethylsilane and triethylamine in acetonitrile converted **19** into the desired product **20** in low yield; as major product of this experiment we isolated the deoxygenated compound **8** in 54% yield. Despite of the low yield of **20** the regioselectivity of this coupling process (as indicated by the NMR data) is very

remarkable. However, due to the moderate mass balance we cannot rigorously exclude the formation of small amounts of isomers of **20**. Although a mechanism was proposed in the original report[13] this interesting reaction deserves further studies to establish all details of this unique homo-coupling to bifuropyridine derivatives and the deoxygenation process.[14]

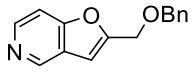
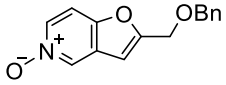
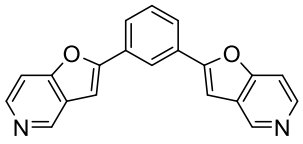
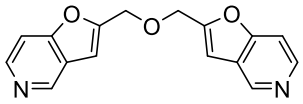
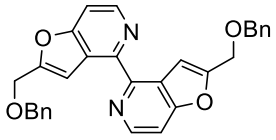


Scheme 5

Alternatively, *N*-oxide **19** was regioselectively chlorinated with phosphorus oxychloride[12] at C-2 of the pyridine moiety and the obtained product **21** was subsequently treated with a mixture of a nickel catalyst, activated zinc, sodium hydride, triphenylphosphine and tetrabutylammonium iodide as additives[15] to give the homo-coupled product 2,2´-dimethyl-4,4´-bifuro[3.2-*c*]pyridine (**22**) in moderate yield. Unexpectedly, the benzyloxy groups were removed under the employed reductive reaction conditions.

UV-Vis-spectra of selected furo[3,2-*c*]pyridines were measured (Table 1). The two monovalent compounds **8** and **19** have absorptions approximately at 250 nm. Compound **8** did not show an emission whereas for *N*-oxide **19** an emission at 388 nm was recorded. As expected, the fully conjugated divalent furo[3,2-*c*]-pyridine (**15**) absorbs at a longer wavelength (298 nm), but compared to **19** its Stokes shift is less pronounced. Divalent compound **16** shows the corresponding values at 247 nm and 344 nm. Bifuro[3,2-*c*]-pyridine derivative **20** is very likely not planar, but due to partial overlap of the two aromatic units a longer wavelength absorption at 322 nm and an emission at 374 nm were observed.

Table 1. Absorptions and emissions of furo[3,2-*c*]pyridine derivatives **8**, **19**, **15**, **16**, and **20**

Compound	Absorption in MeCN[a] λ_{max} [nm] (log ε)	Emission in MeCN[b,c] λ_{max} [nm]	Stokes shift [cm^{-1}]
8 	252 (3.9)[d]	--	--
19 	241 (4.4)	388	15700
15 	298 (4.8)	374	6800
16 	247 (4.4)	344	11400
20 	322 (4.5)	374	4300

[a] Absorption; recorded at c = 10^{-5} mol/L in 1-cm cuvettes; [b] after excitation at λ_{max} (absorption); [c] Recorded at c = 10^{-5}–10^{-6} mol/L in 1-cm cuvettes. [d] Measured in $CHCl_3$.

EXPERIMENTAL

General Information, all experimental procedures and analytical data with full assignments of spectroscopic data can be found in the Supporting Information.

2-Benzyloxymethylfuro[3,2-*c*]pyridine (8): 4-Hydroxy-3-iodopyridine (**2**) (730 mg, 3.30 mmol), $Pd(PPh_3)_4$ (289 mg, 0.25 mmol), and CuI (36 mg, 0.19 mmol) were added to a two-necked bottom flask, dissolved in DMF (23 mL) and *i*Pr_2NH (7.6 mL). After addition of benzyl propargyl ether (**5**) (578 mg, 3.96 mmol) the mixture was stirred at 70 °C for 23 h. After cooling to room temperature the mixture was concentrated under reduced pressure. The obtained residue was dissolved in AcOEt and filtrated through alumina. Column chromatography (silica gel, hexanes/AcOEt, 1:1) provided 488 mg (75%) of **8** as yellowish oil. The product is not very stable at room temperature and discolored to brownish after a few weeks; IR 3085–3010, 2985–2805, 1605–1585, 1270–1235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 2H), 4.63 (s, 2H), 6.74 (s, 1H), 7.20–7.38 (m, 5H), 7.40–7.48 (m, 1H), 8.42–8.47 (m, 1H), 8.86 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.2, 72.7, 103.8, 107.2, 125.5, 128.1, 128.2, 128.6, 137.4, 144.1, 144.7, 155.3, 159.6; Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.43; H, 5.67; N, 5.70.

1´,3´-Di(furo[3,2-*c*]pyridin-2-yl)benzene (15): 4-Hydroxy-3-iodopyridine (**2**) (603 mg, 2.73 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), PPh_3 (214 mg, 0.81 mmol) and CuI (29 mg, 0.15 mmol) were added to a two-necked bottom flask and dissolved in DMF (14 mL) and *i*Pr_2NH (8.2 mL). After addition of 1,3-

diethynylbenzene (**11**) (160 mg, 1.22 mmol) the mixture was stirred at 70 °C for 20 h. After cooling to room temperature the mixture was concentrated under reduced pressure. The residue was purified by multiple column chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 15:1, 10:1) to furnish 255 mg (67%) of **15** as pale yellow solid; mp 244–248 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.21 (s, 2H), 7.53 (d, *J* = 5.7 Hz, 2H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.90 (dd, *J* = 7.7, 1.7 Hz, 2H), 8.39 (t, *J* = 1.7 Hz, 1H), 8.54 (d, *J* = 5.7 Hz, 2H), 8.98 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.1, 107.2, 122.0, 126.1, 126.6, 129.8, 130.5, 144.3, 145.0, 156.2, 159.4; IR 3080–3005, 2960–2850, 1605–1555, 1260 cm^{-1}; Anal. Calcd for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 76.91; H, 3.85; N, 8.76.

2-(Benzyloxymethyl)furo[3,2-*c*]pyridine 5-Oxide (19): To a solution of compound **8** (110 mg, 0.459 mmol) in CH_2Cl_2 (3 mL) was added *m*-chloroperoxybenzoic acid (70%, 158 mg, 0.918 mmol) and the mixture was stirred at room temperature for 3 d. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Column chromatography (silica gel, AcOEt/MeOH, 15:1) provided 117 mg (quantitative) of **19** as colorless solid; mp 121–125 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.61 (s, 2H), 4.63 (s, 2H), 6.65 (s, 1H), 7.21–7.35 (m, 6H), 8.14 (dd, *J* = 7.1, 1.0 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 64.1, 73.2, 103.1, 109.0, 127.4, 128.0, 128.2, 128.7, 132.7, 136.4, 137.1, 151.8, 159.6; IR 3110–3020, 2960–2845, 1470–1435, 1200, 815 cm^{-1}; Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.68; H, 5.40; N, 5.59.

2,2-Di(benzyloxymethyl)-4,4-bifuro[3,2-*c*]pyridine (20): In a Schlenk flask, compound **19** (110 mg, 0.431 mmol) was dissolved in MeCN (6 mL) and 3Å molecular sieves (1.00 g) was added. After stirring at room temperature for 30 min, triethylamine (0.24 mL, 1.72 mmol) and bromotrimethylsilane (0.16 mL, 1.22 mmol) were added and the mixture was heated under reflux for 19 h. All volatile components were removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried (Na_2SO_4), filtrated and concentrated under reduced pressure. Column chromatography (silica gel, hexanes/AcOEt, 3:1) furnished 14 mg (14%) of **20** as pale yellow solid and 56 mg (54%) of **8** as yellowish oil. Data of **20**: melting range 156–162 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.66 (s, 4H), 4.72 (s, 4H), 7.29–7.41 (m, 10H), 7.47 (dd, *J* = 5.6, 0.8 Hz, 2H), 7.80 (s, 2H, 8.63 (d, *J* = 5.6 Hz, 2H, 6-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 64.4, 72.7, 107.2, 107.5, 124.4, 128.1, 128.1, 128.7, 137.7, 144.0, 151.4, 155.8, 161.2; IR 3140–2990, 2950–2860, 1595–1455, 1125 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{30}H_{25}N_2O_4$ (*m/z* $[M + H]^+$): 477.1814; Found: 477.1819; Anal. Calcd for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88. Found: C, 74.66; H, 5.47; N, 6.28.

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14. The authors propose a deoxygenation of *N*-oxide moieties by formal insertion of the oxygen into a carbon-silicon bond of bromotrimethylsilane (see Chart 1 of ref. 14). We are unsure about the feasibility of this mechanism and rather suggest participation of triethylamine as reducing agent.
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