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Access to 2,3-bis(buta-1,3-diynyl)pyridines

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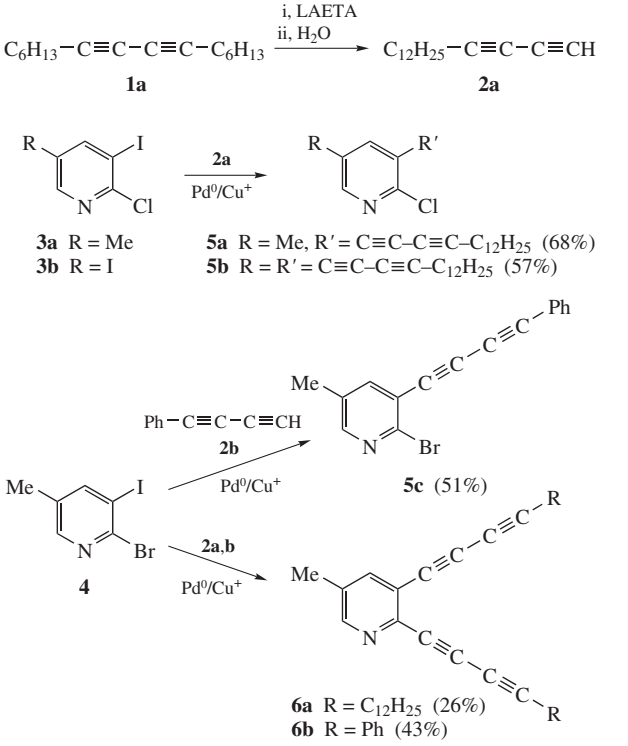
Sonogashira cross-coupling of 2-chloro-3-iodopyridines with buta-1,3-diynes gave products of only iodine substitution; in the case of 2-bromo-3-iodopyridine either 2-bromo-3-(buta-1,3-diynyl)- or 2,3-bis(buta-1,3-diynyl)pyridines were obtained depending on the reaction conditions.

Reversible cyclization of compounds containing a (*Z*)-hex-3-ene-1,5-diyne moiety to form the reactive *p*-benzyne biradical was first reported in 1972 and has become known as the Bergman cyclization.[1] This rather esoteric reaction has attracted a lot of attention in the past two decades when it was found to be the cause of extreme cytotoxicity of natural enediyne antibiotics.[2] The development of safer and more selective analogues of Neocarzinostatin, Esperamicin, and other natural enediynes is an important goal of the modern medicinal chemistry.[3,4] Thermal Bergman cycloaromatization of bis-*ortho*-ethynylarenes is also used in preparation of novel materials with unique optical properties.[5] There is only a single example of such cyclization of enetetraynes,[6] apparently due to the complexity of their preparation. In addition, 'double' Bergman cyclization can be considered as a facile access to acenes and heteroacenes, which are of interest as organic electronics, for example, semiconductors including organic thin film transistors[7] and organic light-emitting diodes.[8] It is also known that enediynes fused to electron-deficient nitrogen-containing heterocycles, for example, 2,3-diethylpyridine, have a lower activation energy in cycloaromatization compared with carbocyclic enediynes.[9]

We present here the first example of the synthesis of a pyridine-based enetetrayne system, 2,3-bis(buta-1,3-diynyl)pyridines (Scheme 1). 2-Chloro-3-iodopyridines **3** and 2-bromo-3-iodopyridine **4**, which were prepared from commercially available 2-aminopyridines,[10] were introduced into Pd/Cu-catalyzed Sonagashira cross-coupling[11] with two terminal diacetylenes: hexadeca-1,3-diyne **2a** and phenylbuta-1,3-diyne **2b**. Because of low stability of terminal diynes, the synthesis was carried out as one-pot procedure. Hexadeca-1,3-diyne **2a** was obtained by multipositional prototropic isomerization ('diacetylene zipper reaction') of internal isomer hexadeca-7,9-diyne **1a** upon treatment with lithium 2-aminoethylamide (LAETA). This approach was previously successfully used to produce functionalized 1-(het)arylalka-1,3-diynes.[12] 2-Methyl-6-phenylhexa-3,5-diyn-2-ol **1b** served as a synthetic precursor of the diyne **2b** in the *retro*-Favorskii reaction.[13]

The rate of halogen substitution in the cross-coupling reactions is known to decrease in the rank I > Br > Cl. At the same time, halogen atoms at the 2- or 4-positions of pyridine ring are more active in the cross-coupling reactions, as compared to halogen at the 3-position.[9,14] However, to the best of our knowledge, comparative rates of different halogen atoms substitution in pyridine have not been investigated earlier.

In fact, Sonogashira cross-coupling of 2-chloro-3-iodopyridines **3a**,**b** with the terminal diyne **2a** using $PdCl_2(PPh_3)_2$ or



Scheme 1

$Pd(PPh_3)_4$ catalyst at 65 °C gave only products of iodine substitution, namely, the corresponding 2-chloro-5-methyl-3-(hexa-1,3-diynyl)pyridine **5a**† and 2-chloro-3,5-bis(hexa-1,3-diynyl) pyridine **5b** (Scheme 1). Conducting the reactions at a higher temperature led to the decomposition of unstable terminal diynes.

† *2-Chloro-3-(hexa-1,3-diynyl)-5-methylpyridine* **5a** was obtained from hexadeca-7,9-diyne **1a** and 2-chloro-3-iodo-5-methylpyridine **3a** in 68% yield (for details of the sequence 'diacetylene zipper'–Sonogashira cross-coupling, see ref. 12). Mp 33–34 °C. IR (CCl_4, ν/cm^{-1}): 3028, 2934, 2912, 2848, 2243, 1854, 1556, 1471, 1407, 1383, 1135, 1065, 902. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (t, 3H, Me, *J* 7 Hz), 1.26–1.63 [m, 20H, $(CH_2)_{10}$], 1.29 (s, 3H, *Me*C_{Ar}), 2.38 (t, 2H, ≡CCH_2, *J* 7 Hz), 7.60 (s, 1H), 8.14 (s, 1H, HC_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 17.44, 19.67, 22.67, 28.06, 28.88, 29.06, 29.34, 29.44, 29.58, 29.62, 29.63, 31.90, 64.65, 69.13, 81.27, 87.86, 119.00, 131.70, 142.73, 142.76, 148.85, 150.18. MS, *m*/*z* (I_{rel}, %): 345 $[M+2]^+$ (6), 343 $[M]^+$ (18), 308 (24), 246 (18), 231 (59), 230 (88), 208 (76), 194 (100), 182 (65), 168 (76), 152 (76), 140 (71), 126 (75), 105 (21). Found (%): C, 76.87; H, 8.78; N, 4.12. Calc. for $C_{22}H_{30}ClN$ (%): C, 76.83; H, 8.79; N, 4.07.

In contrast to **3**, the outcome of the cross-coupling of 2-bromo-3-iodo-5-methylpyridine **4** with terminal diacetylenes depended on the reaction conditions. At 20 °C, the reaction with phenyl-1,3-butadiyne **2b** in the presence of either $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ results in a selective replacement of iodine at the 3-position, with the formation of 2-bromo-5-methyl-3-(4-phenylbuta-1,3-diynyl) pyridine **5c**. Substitution products of both iodine and bromine – 2,3-bis(buta-1,3-diynyl)pyridines **6a**,**b**‡ were obtained only in the presence of $Pd(PPh_3)_4$ at 45 °C. The yields of **6a**,**b** are lower in comparison with those of **5a**–**c**, because the increase in temperature led to decomposition of unstable 1,3-diynes.

In conclusion, we showed that the rate of substitution of iodine atoms at the 3- and 5-positions of pyridine ring is significantly higher compared to that of bromine and chlorine atoms at the 2-position in the cross-coupling reactions. This phenomenon gives a possibility for selective introduction of butadiynyl substituents at the 3-position of pyridine ring. In the meanwhile, the use of 2-bromo-3-iodopyridines as the starting material provided access to 2,3-bis(butadiynyl)-substituted pyridine for the first time, the product being a pyridine enetetrayne derivative. Moreover, selectivity of different halogen reactivity can be further exploited for synthesis of unsymmetrical 2,3-butadiynylpyridines.

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‡ *General procedure for 1,3-diyne* **2** *coupling with* **4**. Hexadeca-7,9-diyne **1a** or 2-methyl-6-phenylhexa-3,5-diyn-2-ol **1b** (6 mmol) were used for *in situ* 1,3-diyne **2** preparation. When the 'diacetylene zipper'[12] (for obtaining **2a**) or the *retro*-Favorskii reaction[13] (for obtaining **2b**) was complete, 2-bromo-3-iodopyridine **4** (2 mmol), $Pd(PPh_3)_4$ (120 mg, 0.1 mmol), PPh_3 (52.5 mg, 0.2 mmol), Et_3N (5 ml) and CuI (57 mg, 0.3 mmol) were added sequentially, in this order to a solution of the 1,3-diyne **2**. The reaction mixture was stirred for a further 8–12 h at 45 °C (TLC control). Upon completion, the reaction mixture was poured into water and the resulting mixture was extracted with diethyl ether (4×25 ml). The combined organic extracts were washed with water and dried over $MgSO_4$. After solvent evaporation, the product was isolated by flash chromatography on silica gel, eluting with hexane, then hexane–diethyl ether (1:1, v/v) mixtures. 5-Methyl-2,3-bis(4-phenylbuta-1,3-diynyl)pyridine **6b** was obtained in 43% yield (293 mg, 0.86 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.54 (s, 3H, Me), 7.32–7.40 (m, 6H), 7.55–7.57 (m, 4H, HC_{Ph}), 7.62 (d, 1H, *J* 1 Hz), 8.39 (d, 1H, HC_{Py}, *J* 1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3, 73.7, 73.8, 78.8, 80.3, 83.6, 83.7, 84.0, 84.1, 121.4, 122.2, 122.8, 128.9, 128.5, 128.6, 129.5, 132.6, 132.7, 132.8, 140.3, 141.9, 150.5. MS, *m*/*z* (I_{rel}, %): 342 $[M + 1]^+$ (30), 341 $[M]^+$ (100), 313 (16), 170 (16), 150 (14).