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Alternative approaches to (*Z*)-1,2-bis(2-bromopyridin-3-yl)ethenes, key intermediates in the synthesis of the 1,10-phenanthroline core

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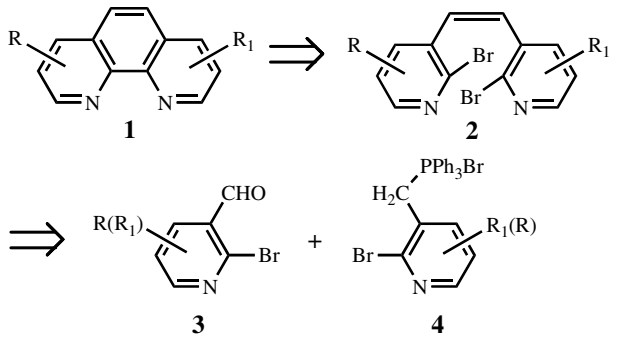
Abstract

A study on the synthesis of (*Z*)-1,2-bis(2-bromopyridin-3-yl)ethenes, key intermediates in the preparation of 1,10-phenanthrolines, based on selective Sonogashira and Suzuki–Miyaura cross-coupling reactions has been carried out.

Keywords: (*Z*)-Alkenes; Alkynes; Nitrogen heterocycles; Sonogashira reaction; Suzuki–Miyaura reaction; Palladium catalysts

We have recently reported a new protocol for the synthesis of substituted 1,10-phenanthrolines **1**, which serve as essentially universal ligands for metals,[1] by the de novo construction of the phenanthroline core (Scheme 1).[2] The approach is hinged upon the Ullmann intramolecular coupling of *cis*-1,2-bis(2-bromopyridin-3-yl)ethenes **2** that are in turn obtained by Wittig reaction of 2-bromonicotinaldehydes **3** with phosphonium salts **4** prepared from 2-bromo-3-(bromomethyl)pyridines.



Scheme 1.

Since the crucial point of this approach is the obtainment of **2**, we decided to explore alternative routes to the Wittig reaction that affords **2** in high yields, but in several cases fails to give good cis/trans stereoselectivity. Moreover, the phosphonium salts **4** are not easily available. Besides the Wittig and related reactions,[3] the main routes to the preparation of (*Z*)-alkenes are the cis-hydrogenation of alkynes[4] and the metal-catalyzed cross-coupling reactions of stereodefined substituted alkenes.[5] Based on this background, we herein report the results obtained in the synthesis of **2** tackling the last two approaches by selective Sonogashira and Suzuki–Miyaura cross-coupling reactions.

In order to prepare **2** via semihydrogenation of alkynes, a valuable method to obtain dipyridylethynes was required. Among the several approaches to obtain internal alkynes[6] we devoted our attention to Sonogashira palladium-catalyzed cross-coupling reaction,[7] taking into account that the reactivity of halogens toward coupling reactions is known to be I > Br ≫ Cl and that the positions *ortho* or *para* to the nitrogen of pyridine are usually reactive enough with chlorine to give acceptable yields of coupled products,

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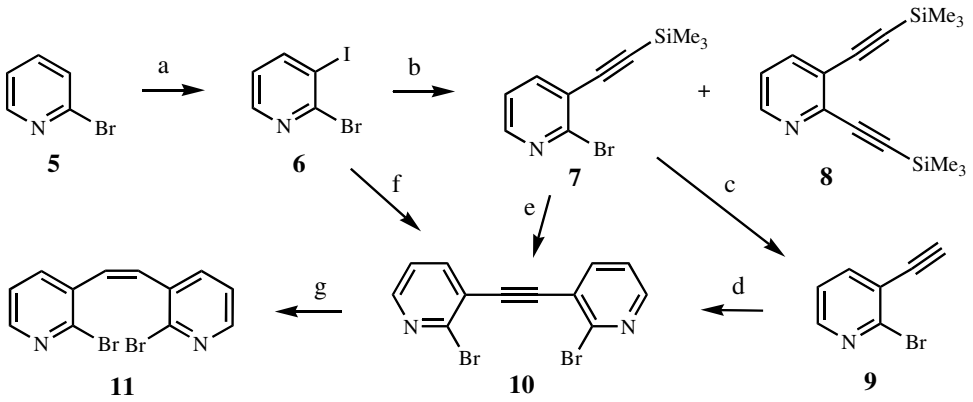

Scheme 2. Reagents and conditions: (a) LDA, THF, −95 °C, then I_2–THF, 82%; (b) $Pd(PPh_3)_2Cl_2$, TMS–acetylene, CuI, Et_3N, 1.5 h, 85%; (c) KOH, MeOH, 1.5 h, 83%; (d) **6**, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, rt, 2.5 h, 46%; (e) **6**, $Pd(PPh_3)_2Cl_2$, CuI, DBU, H_2O, benzene, 7 h, 70%; (f) $Pd(PPh_3)_2Cl_2$, CuI, DBU, H_2O, benzene, 7 h, 65%; (g) H_2 (4 atm), 5% Pd on $BaSO_4$, benzene, 24 h, 51%.

whereas meta positions require bromine, iodine, or triflates for sufficient reactivity.[8]

On this basis we examined the Sonogashira reaction of 2-bromo-3-iodopyridine **6**[9] with an excess of TMS–acetylene under Sogonashira conditions (Scheme 2). The reaction [$Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 25 °C] after 18 h afforded only the diacetylene adduct **8**[10] in 65% yield, but when the reaction was stopped after 1.5 h the desired monoacetylene product **7** was isolated in 85% yield. After TMS deprotection with methanolic KOH (MeOH, 1.5 h, 83%), the resulting 2-bromo-3-ethynylpyridine **9** was coupled in the usual way (2.5 h) with **6** to give dipyridylethyne **10** in 46% yield. In order to avoid the silane deprotection step, the direct conversion of **7** to **10** was then examined. Treatment of **7** with **6** under modified Sonogashira conditions[11] [$Pd(PPh_3)_2Cl_2$, CuI, DBU–H_2O, benzene, rt, 7 h] afforded **10** in 70% yield. This satisfactory result encouraged us to carry out two sequential cross-coupling reactions starting from **6** in one-pot. Thus, the treatment of **6** with TMS–acetylene in the presence of DBU [$Pd(PPh_3)_2Cl_2$, CuI, DBU–H_2O, benzene, rt, 7 h] afforded **10** in 65% yield.[12]

The semihydrogenation of **10** was initially pursued using Lindlar's catalyst at atmospheric pressure, but although a variety of conditions (substrate/catalyst = 1/0.1 to 1/1; MeOH or benzene; 25–50 °C) were examined, no reaction was observed. The hydrogenation was then performed using 5% palladium on Ba_2SO_4 at atmospheric pressure. With MeOH as the solvent complete hydrogenation to 1,2-bis(2-bromopyridin-3-yl)ethane occurred after 3.5 h, and without it was possible to detect the formation of the intermediate semihydrogenation alkene **11**. On the other hand, the formation of **11** took place using benzene as the solvent, though the reaction was very slow and a large amount of the catalyst was required. Therefore, the reaction was performed in a Parr apparatus under pressure. The best conditions to obtain **11** were found by carrying out the hydrogenation in benzene for 24 h at 4 atm and using a w/w ratio of substrate/catalyst = 1/2 (51% yield).

We next went on to carry out the preparation of **10** following a different coupling reaction that considers the cross-coupling of a 1-haloalkyne with a pyridyl metal reagent. Among the possible 3-metalated 2-bromopyridines we decided to exploit organoboron derivatives because boronated pyridines have been profitably used for Suzuki–Miyaura cross-coupling reactions.[13] Moreover, 2-bromopyridin-3-yl-boronic acid or esters are now easily available via halogen–metal exchange or directed *ortho*-metalation.[14]

The first step in this direction was the preparation of 2-bromo-3-(2-bromoethynyl)pyridine **14** by dehydrobromination of 1,1-dibromoalkene **13** (*t*-BuOK, THF, 0 °C to rt, 3 h, 95%) that was in turn obtained from 2-bromonicotinaldehyde **12**[15] according to Corey and Fuchs procedure[16] (CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 1 h, 85%) (Scheme 3). With 1-bromoalkyne **14** in hand its coupling with pyridylborate ester **17** was examined under a variety of palladium-catalyzed cross-coupling conditions. Initially, carrying out the coupling of **14** with **17** [$Pd(PPh_3)_4$, KOH, Bu_4NBr, THF, reflux, 6 h], the disappearance of the starting material was observed, but no dipyridylalkyne derivative **10** was detected. Disappointing results were also obtained by changing the base and the solvent [$Pd(PPh_3)_4$, K_2CO_3, THF–H_2O (or 1,4-dioxane–H_2O), reflux, up to 72 h]. In order to determine if the results were imputable to bromoalkyne **14** or to **17**, the cross-coupling of **14** with 3-(diethylboryl)pyridine **18** was inspected.[17] Under the usual conditions the reaction failed to give alkyne **15** that on the contrary was obtained in 17% yield when Cs_2CO_3 was used as the base [$Pd(PPh_3)_4$, Cs_2CO_3, 1,4-dioxane–H_2O, 65 °C, 72 h]. Similar results (20% yield) were obtained when catalytic Bu_4NBr was employed.

These disappointing results prompted us to examine an alternative procedure that starting from **13** inverts the dehydrobromination-coupling steps (Scheme 3). Thus, **13** was cross-coupled with **17** in the presence of Pd_2dba_3 and TFP[18] to give the expected monoarylated compound **16** in 90% yield[19] and then dehydrobrominated with DBU[20]