Tetrahedron Letters 53 (2012) 4824–4827

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An easy route for the synthesis of pyrazine-2,3-dicarbonitrile 5,6-bis-substituted derivatives using a palladium catalyst

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ARTICLE INFO

Article history:
Received 5 June 2012
Revised 19 June 2012
Accepted 24 June 2012
Available online 14 July 2012

Keywords:
5,6-Disubstituted-2,3-pyrazine
Porphyrazines
Pd-catalyst cross coupling reaction
PDT
Phthalocyanines

ABSTRACT

An easy synthetic method for the preparation of pyrazine-2,3-dicarbonitrile 5,6-bis-substituted derivatives using Pd-catalyzed cross coupling reaction (Sonogashira, Suzuki, Heck) is described. The reaction conditions allow preparing symmetrical and unsymmetrical bis-substituted products in moderate to high yields, as precursors for the preparation of highly substituted symmetrical and non-symmetrical aza-phthalocyanines with well-defined spectral properties.

Photodynamic therapy (PDT) is a new alternative treatment of cancer involving the combined action of a photosensitizer (PS), molecular oxygen, and light.[1] Most PS advanced for PDT are based on the porphyrin and phthalocyanine (Pc) chromophore. The aza analogs of Pc (aza-Pc) are heterocyclic Pc analogs that likewise can serve as PS for PDT.[2] The interest in such structural modification is related to the simultaneous introduction of both electron-donating and -accepting groups across a delocalized organic framework. The extent of the hypsochromic shift of the Q-band in the electronic spectra of the aza analogs of Pc, naphthalocyanines (NPc), and anthracyanines is strongly influenced by the presence of exocyclic nitrogen atoms resulting from the aza substitution in the fused benzo rings. Applications of these macrocyclic chromophores range from optical data storage, signal processing, and optical imaging, to biological, diagnostic, and therapeutic applications.[3] The significance of organic materials chemistry is contrasted by its limited synthetic accessibility. The ability to form C–C bonds in a single step makes this one of the most attractive approaches to create or modify organic molecules. Transition metal catalysts with wide spread activities expand the application of metal-catalyzed coupling reactions to a variety of functionalities to be introduced into selected substrates. This in turn allows the preparation of more elaborate and multifunctional synthons to access a variety of building blocks.[4] Pd-catalysts have emerged as extremely powerful tools for the construction of carbon–carbon bonds.[5] Considerable progress has been made in the use of cross coupling reactions developed by Sonogashira,[6] Suzuki,[7] Heck,[8] Stille,[9] and Buchwald.[10]

Consequently Pd-catalysts have also been exploited for modifications of porphyrins and Pc derivatives.[11] The phthalonitriles and their nitrogen-rich congeners, the pyrazines, serve as convenient starting materials for the preparation of functionalized Pc and aza-Pc. The generation of suitable precursors has been the key to the success of these reactions.

Tetrapyrazinoporpyrazines are conveniently assembled by a base-induced cyclotetramerization of dicyanopyrazines, which in turn are obtained by the condensation of diaminomaleonitrile (**3**) with an appropriate α-diketone in acetic acid. Compared to the availability of phthalonitrile derivatives, methods for the preparation of pyrazine-2,3-dicarbonitrile are limited and thus there exists a need for efficient methods to synthesize such building blocks. In this communication we studied Pd-catalyzed coupling procedures to obtain a variety of 5,6-substituted pyrazine-2,3-dicarbonitrile derivatives.

The strong electron withdrawing capability of the 2,3-dicyanopyrazine moiety makes it possible to afford various nucleophilic substitutions at 5- and 6-positions. Thus various nucleophiles,[12] including amines,[13] thiolates,[14] or alkyloxides[15] were used to synthesize many types of pyrazine oriented heterocyclics.[16]

The effect of aza substitution on the absorption spectra becomes more pronounced in the case of linearly conjugated aza-Pc. Acetylenic units enlarge the π-systems of the chromophore, inducing bathochromic shifts in the electron absorption and emission spectra. Furthermore, terminal alkynyl groups can serve as covalent linkers for the assembly of delocalized multi-chromosphere chains.

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0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.102

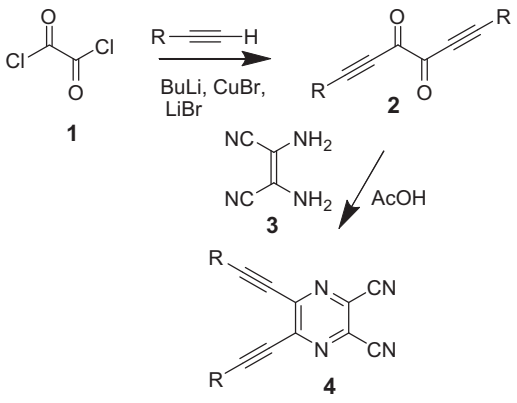
This structural motif can be exploited to devise materials with unique electronic and/or optical properties for organic light-emitting diodes, chromophores with non-linear optical properties, and efficient PS for PDT.

The key building block for such reactions requires the presence of an acetylenic α-diketone (**2**). The earlier reported method to prepare **2** from pentyllithium and oxalyl chloride (**1**) is not generally applicable.[17] This rather lengthy, four-step procedure starts from the readily available propargyl aldehyde diethyl acetals. An alternative approach for the synthesis of this key component involves the reaction of two equivalents of LiBr, Cu-acetylide (prepared in situ by transmetallation of Li-acetylide with CuBr) to convert oxalyl chloride into the corresponding compound **2** in 50–80% yields (Scheme 1).[18]

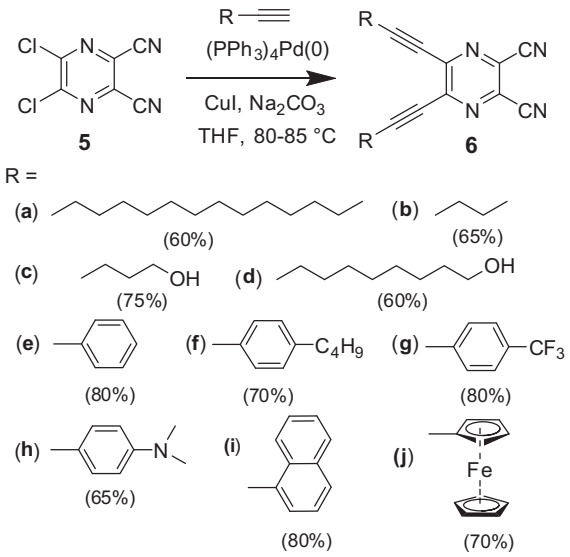
The Pd-catalyzed reaction of terminal alkynes with aryl/vinyl halides and triflated derivatives is usually achieved in the presence of copper, known as the Sonogashira reaction. Organic iodide, bromide, and triflate are frequently used as substrates while the use of organic chloride is noticeably uncommon, although the latter are available at low cost and with wider diversity. It has however been reported that coupling of activated arylchloride, particularly nitrogen containing heteroaryl chloride, affords N-heteroaromatic compounds.[19]

Based on this information we initially attempted Sonogashira cross coupling with alkynyl derivatives using the commercially available, low cost precursor 2,3-dicyano-5,6-bis-chloropyrazine (**5**). In a typical reaction, compound **5** was coupled with 1-hexadecyne using $(TPP_3)_4Pd(0)$, copper iodide and sodium carbonate as a base in THF at 80–85 °C for 4 h. After purification, the product was isolated in 60% yield. Using this protocol, the coupling reaction was also performed with various alkynyl derivatives having different functional groups and aromatic moieties (Scheme 2). Using triethylamine as a base either gave low yields or undesired products. Attempts to couple 3-ethynyl pyridine and 10-undecynoic acid under these reaction conditions failed. Attempted coupling reactions using other Pd-catalysts with or without ligand, also were unsuccessful.

A previously reported coupling procedure can only provide symmetrically, bis-substituted pyrazine derivatives.[16] In order to prepare unsymmetrical 5,6-bis-substituted derivatives we developed coupling conditions using stoichiometry, yielding isolated mono-chlorinated, mono-substituted products that were subjected to different Pd-catalyzed coupling reaction conditions to afford the desired unsymmetrical products. Thus coupling of compound **5** with phenyl acetylene or 4-ethynyl-*N*,*N*-dimethylaniline in equal molar ratio under Sonogashira catalyzed reaction conditions, gave mono-substituted mono-chlorinated derivatives **7** and **8** in 70–75% yields along with bis-substituted products **6e** and **6h** in 10–15%



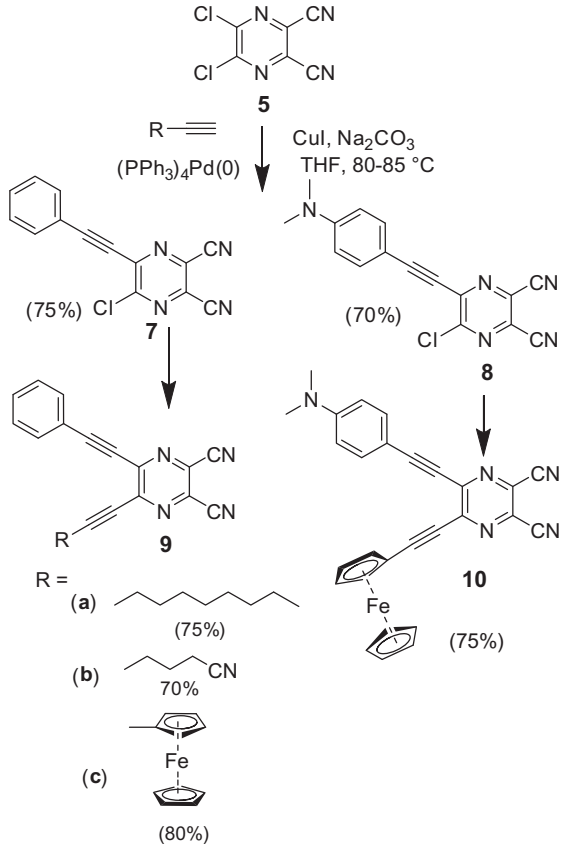
Scheme 1.



Scheme 2.

together with unreacted starting material. The chloro group of the mono-substituted product was further reacted to prepare unsymmetrical bis-substituted pyrazine derivatives. Treatment of **7** and **8** with substituted alkynyl derivatives, gave compounds **9** and **10** in good yields using the above Sonogashira Pd–Cu catalyzed reaction conditions (Scheme 3).

5-Amino-6-chloro-2,3-dicyanopyrazine (**11**) is also commercially available and was likewise used as a starting material for

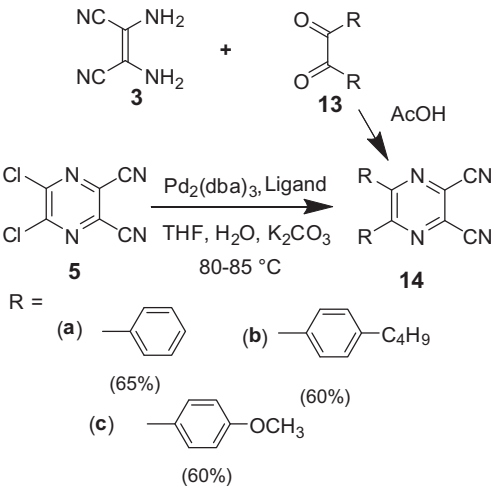


Scheme 3.

Pd-catalyzed coupling reactions. Compound **11** was treated with a number of alkynes using, CuI, Na_2CO_3 in THF at 80 °C. After purification the HRMS analysis of the products revealed a single coupling product. Furthermore both aliphatic and aromatic alkynes reacted under these conditions and various functional groups were tolerated (Scheme 4). Compared to the unsuccessful reaction of compound **5**, compound **11** gave coupling product with both 3-ethynyl pyridine and 10-undecynoic acid. While our work was in progress, Keivanloo et al.[20] reported the reaction of 5-(alkyl-arylamino)-6-chloropyrazine-2,3-dicarbonitrile with phenyl acetylene, catalyzed by Pd–Cu in the presence of sodium lauryl sulfate as a surfactant in water, which gave 5,6-bis-substituted-5H-pyrrole{2,3-b}pyrazine-2,3-dicarbonitrile, while aliphatic alkynes gave only reduced product. In contrast to this recent report our reaction conditions did not yield any cyclized product, instead a broad range of non-cyclized coupling products were obtained.

Pyrazine derivatives directly attached to aryl and heteroaryl derivatives were prepared using diaminomaleonitrile and corresponding α-diketone (Scheme 5).[21] Among Pd-catalyzed cross-coupling processes, the Suzuki reaction using aryl or vinyl halide with boronic acids has emerged as the most versatile reaction amiable to industrial application. A general and efficient synthesis of 5-aryl imidazo[1,5-*a*]pyrazines by palladium-catalyzed coupling of the corresponding 8-substituted derivatives with aryl halides has been described.[22] We developed an alternative method to prepare such compounds using the Suzuki reaction. Compound **5** treated with phenylboronic acid as the coupling partner, in the presence of aq. sodium bicarbonate, $(TPh_3)_4Pd(0)$ in toluene did not afford the desired product. Using K_3PO_4, $Pd(OAc)_2$, and 2-(di-*t*-butylphosphino)biphenyl as ligand, gave bis-substituted **14a** in very low yields along the mono-chlorinated substituted product and its reduced analog.

Changing the ligand to 2′-dicyclohexylphosphino-2,6-dimethoxy-3-sulfonato-1,1′biphenyl hydrate sodium salt in the presence of K_2CO_3 in H_2O:CH_3CN resulted in 60% conversion providing product **14a** in 50% yield. Trifluoroborate coupling systems proved to be more reactive than the corresponding boronic acids. Thus compound **5** treated with Pot.2-methoxyphenyltrifluoroborate and 4-*t*-Bu-phenyltrifluoroborate in the presence of tris(dibenzylideneacetone)dipalladium(0) and cesium carbonate

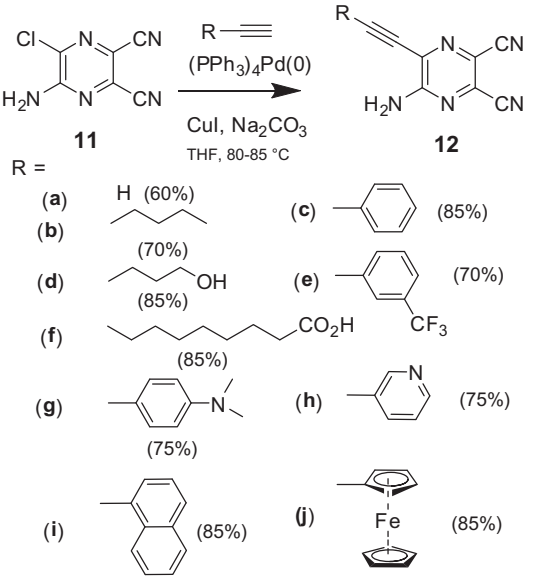


Scheme 5.

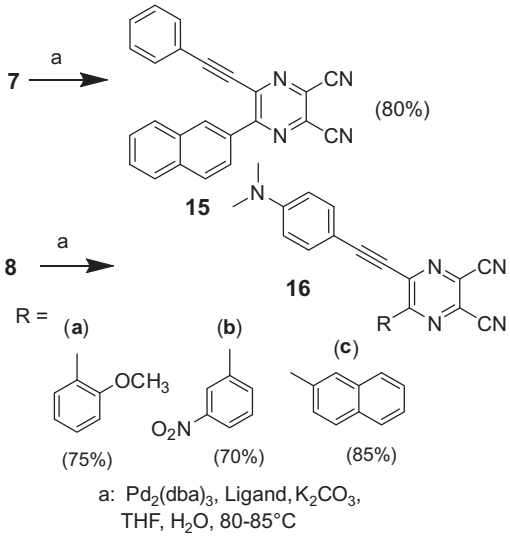
gave symmetrical bis-substituted derivatives **14b–c** in 70–80% yields (Scheme 5).

In order to prepare unsymmetrical pyrazine derivatives, compounds **7** and **8** were used as staring materials. Using the above reaction conditions products **15** and **16** substituted with two different groups, one directly attached and the second group attached via a triple bond, were obtained (Scheme 6). Subsequently compound **11** was also treated under the Suzuki reaction condition, which gave pyrazine derivatives **17** bearing an amino and directly attached aryl group (Scheme 7).

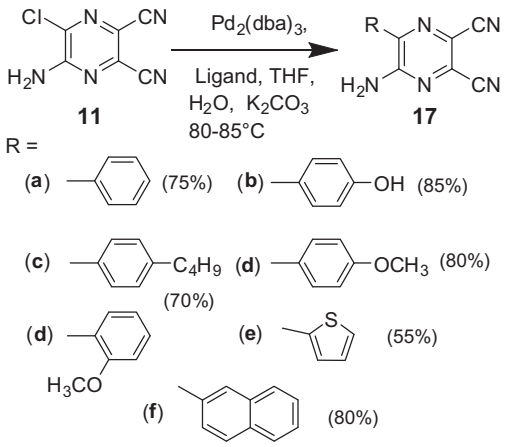
The UV spectra of the bis-substituted pyrazines bearing alkyl substitutions were similar to those of the parent molecule. In contrast aryl substituted pyrazines showed a red-shift when compared to the parent molecule (e.g., **6b** vs **6e**, 346 vs 379 nm). The aryl derivative containing an *N*-methyl group gave a pronounced blue-shift (e.g., **6h** vs **6b**, 494 vs 379 nm). The effect of the naphthalene substituent on the absorption spectrum is an even stronger bathochromic shift, showing a maximum at 424 nm compared to 378 nm for the analog substituted with a phenyl group. The site of attachment of the aryl substituent also affects the absorption maximum. Thus when the aryl group is directly attached to the pyrazine moiety, as in **14a**, the bathochromic shift is less



Scheme 4.



Scheme 6.



Scheme 7.

pronounced as compared to the analog with the aryl group attached via the ethynyl side chain, as in **6e**. The presence of an amino group also affects the spectral properties of the pyrazine derivatives. Thus compounds containing both an amino group and an ethynyl phenyl or phenyl group gave a bathochromic shift when compared to the mono-substituted analog.

In conclusion, we have developed an efficient synthetic method for the preparation of pyrazine-2,3-dicarbonitrile 5,6-bis-substituted derivatives using Pd-catalyzed cross coupling reactions. This procedure greatly increases the access to a large variety of homo and hetero bis-substituted pyrazine derivatives that in turn can serve as precursors for the synthesis of selected aza-phthalocyanine analogs using commercially available substrates.

Acknowledgments

Supported by the Jeanne and J.-Louis Lévesque Chair in radiobiology of the Université de Sherbrooke.

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