Journal of Photochemistry and Photobiology A: Chemistry 222 (2011) 263–265

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

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

Photochemical synthesis and properties of axially chiral naphthylpyridines

Pablo Wessig*, Charlotte Pick

Institut für Chemie Universität Potsdam Karl-Liebknecht-Str. 24-25 D-14476 Potsdam, Germany

ARTICLE INFO

Article history:
Received 19 April 2011
Received in revised form 2 June 2011
Accepted 4 June 2011
Available online 12 June 2011

Keywords:
Photochemistry
Axial chirality
Photo-Dehydro-Diels-Alder reaction
Dynamic NMR
Dynamic HPLC
Molecular modeling

ABSTRACT

Five alkynyl pyridines were prepared and cyclized to naphthylpyridines as the main products in the course of a *Photo-Dehydro-Diels-Alder* reaction. Four of the final products are axially chiral and the determination of the rotational barrier by DFT calculations, dynamic NMR and HPLC experiments is demonstrated.

1. Introduction

Heterocyclic biaryls play an important role as ligands in countless metal complexes. Especially, pyridyl moieties are part of many mono- and polydentate ligands. The ligands are closely associated with catalytic activity, which hallmark many of the metal complexes, in particular those of transition metals [1]. Therefore, there is a great demand for new synthetic methods for the preparation of structurally complex ligands.

Synthetic methods for the preparation of biaryls were summarized in several reviews and books and here we refer to this literature [2]. Most methods for the preparation of heterocyclic biaryls are based on coupling of already existing rings and in only few cases one or both aryl moieties are built up in the key step of the synthesis [3]. One of the latter methods is the *Dehydro-Diels-Alder* reaction [4]. Its photochemical version (the *Photo-Dehydro-Diels-Alder* reaction, PDDA) has been intensively investigated in our group in recent years [5]. Herein, we report on the PDDA synthesis of some naphthylpyridines as well as on the conformational flexibility of the biaryl axis.

2. Materials and methods

Experimental procedures, spectroscopic data, X-ray structure analysis of compounds **4** and **6**, and the details of the DFT calculations, DNMR and DHPLC experiments are presented in the Electronic Supplementary Information (ESI).

3. Results and discussion

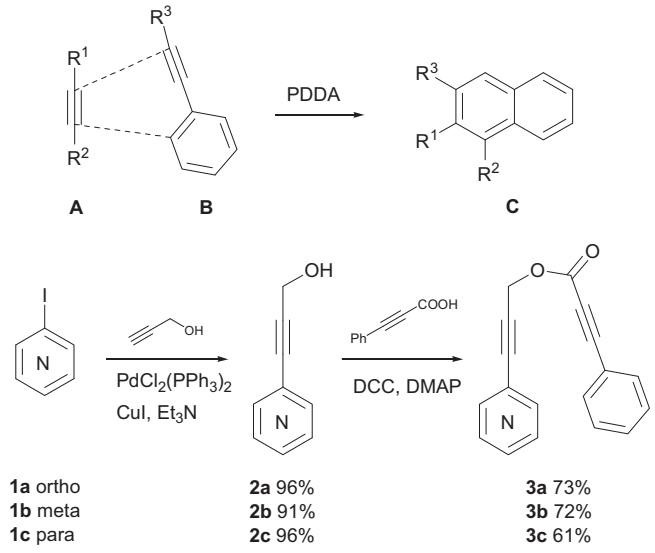
The PDDA reaction has proved its worth for the preparation of highly substituted naphthalenes. The cycloaddition takes place between an alkyne **A** and an alkynyl-arene **B**, giving substituted naphthalenes **C** (Scheme 1). If both reactants are alkynyl-arenes and/or the arenes are not monosubstituted, several regioisomers are possible [4]. To investigate whether alkynyl-pyridines undergo the PDDA reaction and how the nitrogen atom influences regioselectivity, we first prepared the three isomeric 3-pyridyl-2-propynyl 3-phenylpropynoates **3a**–**c**. Commencing with commercially available iodopyridines **1a**–**c**, the 2-propyn-1-ols **2a**–**c** were prepared by *Sonogashira* coupling in excellent yields [5]. Esterification with 3-phenyl-propynoic acid provided the target compounds **3a**–**c** (Scheme 1).

In accordance with previously reported findings [6b], the 3-phenylpropynoates **3** are unreactive upon direct irradiation. This phenomenon was attributed to an inefficient intersystem crossing (ISC) to the triplet state, which is necessary for a successful PDDA reaction [6]. The problem can be circumvented by irradiation of such compounds in acetone as triplet sensitizer [7].

The irradiation of alkynyl pyridines **3a**–**c** in acetone afforded in all three cases products of a PDDA reaction, even though the overall yields were rather low in the range of 20–30%. Furthermore, we found that in each case, both the pyridyl and the phenyl ring were attacked in the course of the cycloaddition, albeit with a clear

* Corresponding author. Tel.: +49 331 977 5401; fax: +49 331 977 5065.
E-mail address: wessig@uni-potsdam.de (P. Wessig).

1010-6030/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jphotochem.2011.06.006

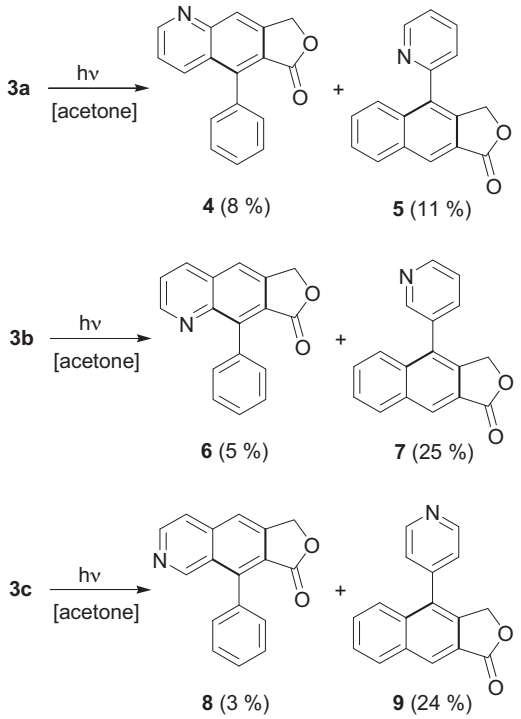


Scheme 1. Preparation of alkynyl pyridines **3a–c**.

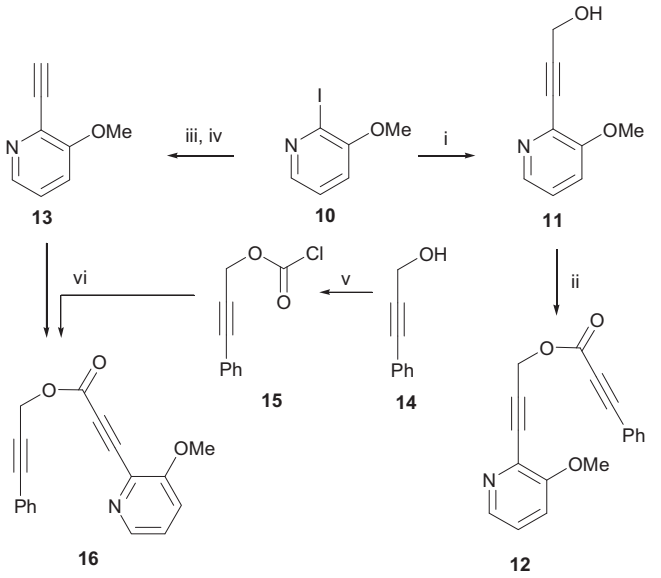
preference for the phenyl ring. X-ray crystal structure analysis of compounds **4** and **6** permitted an unambiguous assignment of the structures of heterocyclic biaryls **4**–**9** (Scheme 2) [8].

The most important conclusion from these first-cut experiments was that both *ortho*-positions of one of the two arene moieties must be interlocked to avoid attack and increase the selectivity. Because the irradiation of compounds **3** furnished no evidence at all that the nitrogen atom is attacked, we focused in the second part of this work on 2-alkynyl pyridines, supplied with a second substituent in the 3-position of the pyridine moiety.

Starting with 2-iodo-3-methoxy-pyridine **10** [9], we prepared two 2-alkynyl pyridines **12** and **16** according to the routes depicted in Scheme 3. Whereas **12** was accessible by the same route described above for compounds **3**, **16** needed another approach. 2-



Scheme 2. Photochemical behavior of compounds **3a–c**.

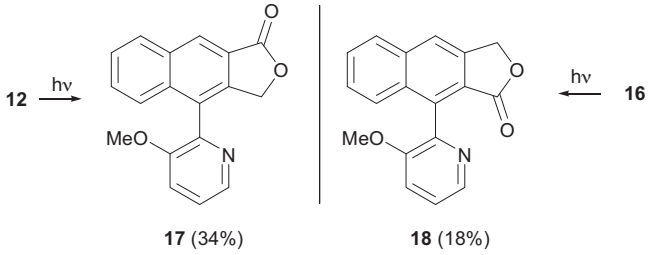


Scheme 3. Synthesis of compounds **12** and **16** (i: $PdCl_2(PPh_3)_2$/CuI/Et_3N, 82%, ii: 3-phenylpropynoic acid, DCC, DMAP, 75%, iii trimethyl-silylethyne, $PdCl_2(PPh_3)_2$/CuI/Et_3N, 70%, iv: K_2CO_3/MeOH, 97%, v: phosgene, vi: 1. *n*-BuLi, 2. **15**, 10%).

Ethynyl-3-methoxypyridine **13** was prepared from **10** in two steps and treated with the chloro formate **15** after lithiation with BuLi giving **16**. **15** was obtained from 3-phenyl-propyn-1-ol and phosgene and was used without further purification (Scheme 3).

Upon irradiation of compounds **12** and **16** in acetone, we isolated only one product in each case (**17** and **18**, respectively, Scheme 4).

Naphthylpyridines **5**, **7**, **17**, and **18** are axially chiral and we were interested in the rotational barrier E_R of the aryl-aryl-bond to evaluate the usability of such compounds as chiral ligands. First, we calculated E_R by means of two different density functional methods (B3LYP [10] and M06-2X [11]). The B3LYP functional, which is very often used in routine calculations [12], results in consistently lower activation barriers (1–2 kcal/mol) compared with the M06-2X functional (Table 1). These results indicate the well-known underestimation of weak non-bonding interactions by



Scheme 4. Irradiation of compounds **12** and **16** (solvent: acetone).

Table 1
Rotational barriers of compounds **5**, **7**, **17**, **18**.

Compound	E_{calc} [a]	E_{calc} [b]	E_{exp}
5	7.5	8.6	–
7	17.0	18.0	16.0[c]
17	16.5	18.5	19.0[c]
18	24.4	26.0	25.8[d]

[a] B3LYP/6-31G* in kcal/mol.
[b] M06-2X/TZVP in kcal/mol.
[c] DNMR.
[d] DHPLC. For details, see ESI.

B3LYP, which should be important for an accurate calculation of the rotational barrier of biaryls [13].

To evaluate the calculated E_{calc} values, we decided to determine the rotational barriers experimentally, if possible. Depending on the height of the rotational barrier, two different methods are appropriate for this problem. If the barrier amounts to 15–20 kcal/mol, dynamic NMR (DNMR) [8,14] is the method of choice, whereas barriers between 20 and 30 kcal/mol are accessible by dynamic HPL chromatography (DHPLC) [8,15]. The experimentally determined rotational barriers are summarized in Table 1 and are in good agreement with the calculated values.

4. Conclusion

In summary, we reported on the synthesis of eight heterocyclic biaryls **4**–**9**, **17**, **18** with the *Photo-Dehydro-Diels-Alder* (PDDA) reaction as a key step. Half of these compounds are axially chiral and we calculated the rotational barriers by means of DFT methods. Furthermore, we succeeded in the experimental determination of these barriers with DNMR (**7** and **17**) and DHPLC (**18**), respectively. The values calculated with the M06-2X/TZVP method are in excellent accordance with experimental values and we therefore emphatically recommend this method for such problems.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jphotochem.2011.06.006.

References

[1] G.W. Parshall, S.D. Ittel, Homogeneous Catalysis: The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes, John Wiley & Sons, New York, 1992.
[2] (a) I. Cepanec, Synthesis of Biaryls, Elsevier, Amsterdam, 2004;
(b) G. Bringmann, A.J. Price Mortimer, P.A. Keller, M.J. Gresser, J. Garner, M. Breuning, Angew. Chem. Int. Ed. 44 (2005) 5384–5427.
[3] Due to lack of space, only the asymmetric reactions are cited. With respect to achiral variants, we refer to the references cited therein:
(a) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann, C. Sundermann, Angew. Chem. Int. Ed. 43 (2004) 3795–3797;
(b) T. Shibata, T. Fujimoto, K. Yokota, K. Takagi, J. Am. Chem. Soc. 126 (2004) 8382–8383;
(c) Y. Nishii, K. Wakasugi, K. Koga, Y. Tanabe, J. Am. Chem. Soc. 126 (2004) 5358–5359;
(d) J. Bao, W.D. Wulff, M.J. Fumo, E.B. Grant, D.P. Heller, M.C. Whitcomb, S.-M. Yeung, J. Am. Chem. Soc. 118 (1996) 2166–2181;
(e) A.V. Vorogushin, W.D. Wulff, H.-J. Hansen, J. Am. Chem. Soc. 124 (2002) 6512–6513;
(f) J.C. Anderson, J.W. Cran, N.P. King, Tetrahedron Lett. 44 (2003) 7771–7774.
[4] P. Wessig, G. Müller, Chem. Rev. 108 (2008) 2051–2063.
[5] Preparation of compounds **2a**–**c** were already reported but with lower yields;
(a) F.Y. Kwong, H.W. Lee, W.H. Lam, L. Qiu, A.S.C. Chan, Tetrahedron: Asymmetry 17 (2006) 1238–1252 (**2a**);
(b) M. Feuerstein, H. Doucet, M. Santelli, Tetrahedron Lett 46 (2005) 1717–1720 (**2b**);
(c) N. Inoue, O. Sugimoto, K. Tanji, Heterocycles 72 (2007) 665–671 (**2b**,**c**);
(d) N.A. Bumagin, A.B. Ponomarev, I.P. Beletskaya, Bull. Acad. Sci. USSR 33 (1984) 1433–1438 (**2c**).
[6] (a) P. Wessig, G. Müller, A. Kühn, R. Herre, H. Blumenthal, S. Troelenberg, Synthesis (2005) 1445–1454;
(b) P. Wessig, G. Müller, Chem. Commun. (2006) 4524–4526;
(c) P. Wessig, G. Müller, R. Herre, A. Kühn, Helv. Chim. Acta 89 (2006) 2694–2791;
(d) P. Wessig, G. Müller, C. Pick, A. Matthes, Synthesis (2007) 464–477;
(e) P. Wessig, G. Müller, Aust. J. Chem. 61 (2008) 569–572.
[7] M. Yamaji, J. Kobayashi, S. Tobita, Photochem. Photobiol. Sci. 4 (2005) 294–297.
[8] See Electronic Supplementary Information (ESI).
[9] H.-Q. Do, O. Daugulis, Org. Lett. 12 (2010) 2517–2519.
[10] A.D. Becke, J. Chem. Phys. 98 (1993) 5648–5652.
[11] (a) Y. Zhao, D.G. Truhlar, J. Phys. Chem. 110 (2006) 5121–5129;
(b) Y. Zhao, D.G. Truhlar, Theor. Chem. Acc. 120 (2008) 215–241.
[12] (a) W. Koch, M.C. Holthausen, A Chemist's Guide to Density Functional Theory, Wiley-VCH, Weinheim, 2001;
(b) D. Sholl, J.A. Steckel, Density Functional Theory: A Practical Introduction, John Wiley & Sons, New York, 2009.
[13] S. Grimme, Angew. Chem. Int. Ed. 45 (2006) 4460–4464.
[14] J. Sandström, Dynamic NMR Spectroscopy, Academic Press, New York, 1982.
[15] O. Trapp, Chirality 18 (2006) 489–497.