Tetrahedron Letters 67 (2021) 152871

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of bis(benzoxazole) frameworks chiralized by planar chiral [2.2]Paracyclophane

Emrah Polat, Ozge Turbedaroglu, Murat Cakici *

Faculty of Sciences, Department of Chemistry, Ataturk University, Erzurum 25240, Turkey

ARTICLE INFO

Article history:
Received 9 December 2020
Revised 15 January 2021
Accepted 21 January 2021
Available online 4 February 2021

Keywords:
Bis(benzoxazole)
[2.2]Paracyclophane
Planar chirality
Horeau principle

ABSTRACT

In this study, a new class of chiral bis(benzoxazole) has been synthesized. The bis(benzoxazole) framework, which has an achiral structure was chiralized by a planar chiral [2.2]paracyclophane moiety. Both enantiomeric forms of the bis(benzoxazole) derivatives were successfully obtained in 99% *ee*. Even though the starting material was not completely enantiomerically pure, enantiomeric enrichment was afforded by the Horeau principle in the synthesis route.

Introduction

Chiral bis(oxazolines) are one of the most popular classes of ligands used in coordination chemistry and asymmetric synthesis. Many C_2-symmetric chiral oxazoline-based ligands have been synthesized and they are employed in a wide range of asymmetric reactions [1–4]. These ligands consist of two oxazoline moieties separated by a spacer unit, which is most commonly based on a single carbon atom (Box) or a pyridine ring (PyBox). The chirality in the box ligands is caused by two adjacent tetrahedral carbon atoms with sp^3 hybridization in the oxazoline ring, which is available from enantiomerically pure amino alcohols [5].

Benzoxazoles are also an important class of heterocycle in which an oxazole moiety is fused onto a benzene ring (Fig. 1). Benzoxazole and their derivatives exhibit a broad spectrum of biological activities [6] and are also used as brighteners [7], photochromatic and fluorescent agents [8–9], and laser dyes [10–11]. Box- and PyBox-like bis(benzoxazole) derivatives have been synthesized and used in various applications [12–17]. However, the achiral properties of the benzoxazole backbone caused by the plane and symmetrical structure have restricted their chiral applications [18]. Due to their unique three-dimensional structural properties, [2.2]paracyclophanes have important applications in several areas such as asymmetric synthesis and material science [19–20].

In this study, we report the synthesis of novel C_2-symmetric bis(benzoxazole) derivatives that exhibit planar chirality by replacing the phenyl group with a [2.2]paracyclophane backbone to introduce chirality (Fig. 2). Thus, we introduce a new type of planar chiral Box- and Pybox-like bis(benzoxazole) ligands.

Result and discussion

This paper provides a concept for the design and synthesis of novel C_2-symmetric bis(benzoxazole) ligands which are chiralized by fusing the planar chiral [2.2]paracyclophane moiety.

The study was initiated with the synthesis of the optically pure 2-aminophenol moiety, (S_P)-**6** (Scheme 1). 4-Formyl[2.2]paracyclophane (**PC-CHO**) was prepared with the Rieche formylation of [2.2]paracyclophane (**PC**). Resolution of the racemic 4-formyl[2.2]-paracyclophane (**PC-CHO**) was achieved as described in the literature [21] by converting the two enantiomers into their diastereomeric imines. (S_P,*R*)-**4** was obtained in ca. 20% yield and >99% *de* after two crystallization steps. After hydrolyzing of diastereomerically pure imine (S_P,*R*)-**4** over a column of silica, Dakin oxidation of the (S_P)-**PC-CHO** resulted in (S_P)-4-hydroxy [2.2]paracyclophane ((S_P)-**PC-OH**) [22–23]. Synthesis of the *ortho*-substituted planar chiral aminophenol derivative ((S_P)-**6**) was performed according to the following synthetic steps [24]: MOM protection, *ortho*-directed metalation of MOM-protected (S_P)-**PC-OH** with butyllithium, nucleophilic attack of the corresponding lithium derivative with *p*-toluenesulfonyl azide, and reduction of azido-derivative (S_P)-**5** with $LiAlH_4$.

* Corresponding author.
E-mail address: mcakici@atauni.edu.tr (M. Cakici).

https://doi.org/10.1016/j.tetlet.2021.152871
0040-4039/

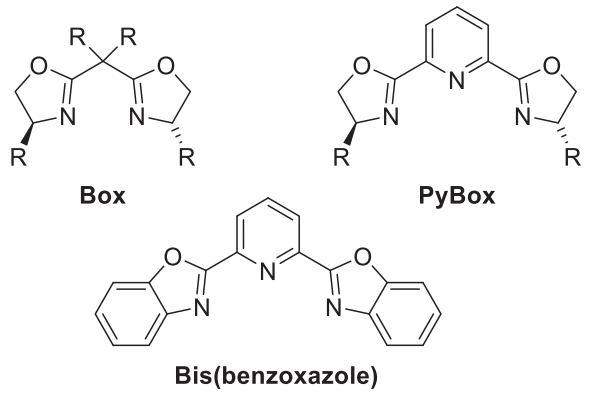


Fig. 1. Typical bis(oxazoline) and bis(benzoxazole) structures.

Fig. 2. Structures of planar chiral bis(benzoxazole) in this study.

We tried different methods to form a benzoxazole structure and found that a direct ring closure after removing the MOM group was not a suitable method. As a synthesis strategy, we decided to follow the amidation of (S_P)-**6**, MOM-deprotection, and ring closure steps.

The amidation of (S_P)-**6** with 2,6-pyridinedicarbonyl dichloride (**7**) as a linker was investigated under various reaction conditions (data not given). The optimum reaction conditions are shown in Scheme 2. 2,6-Pyridinedicarbonyl dichloride (**7**), which is obtained from 2,6-pyridinedicarboxylic acid by treatment of $SOCl_2$, was reacted with (S_P)-**6** in presence of NEt_3. The corresponding diamide (S_P,S_P)-**8** was obtained with a 96% yield. In this reaction, a little excess of (S_P)-**6**, which is synthetically valuable, was used to complete the conversion. Later, unconsumed (S_P)-**6** was recovered in the purification step via column chromatography.

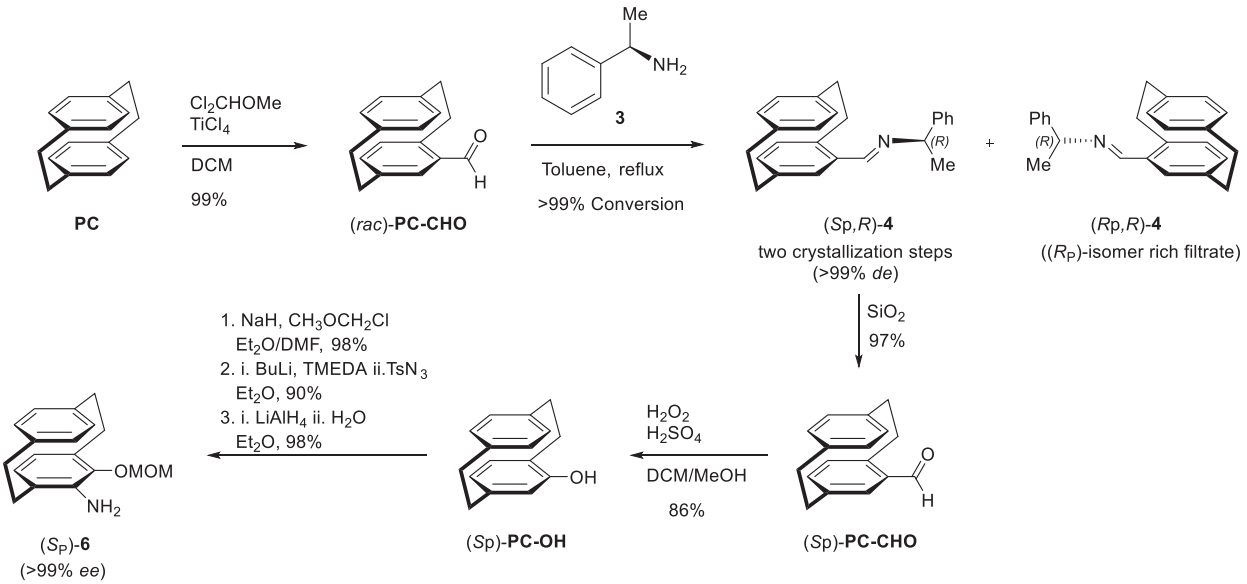
After deprotection of the (S_P,S_P)-**8** with HCl, (S_P,S_P)-**9** was refluxed with methanesulfonic acid in 1,4-dioxane for 8 h, which resulted in the desired planar chiral [2.2]paracyclophane-based bis(benzoxazole) derivative (S_P,S_P)-**1**. The structure of (S_P,S_P)-**1** was characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra. Chiral HPLC analysis showed that the enantiomeric purity was >99% *ee*.

The same strategy was also followed to synthesize the methylene bridged bis(benzoxazole) derivative (S_P,S_P)-**2**. First, the starting material dimethylmalonic acid was treated with oxalyl chloride in the presence of *N*,*N*-dimethylformamide to give corresponding acyl chloride **10**. Bis(benzoxazole) (S_P,S_P)-**2** was obtained with high yields as a result of the amidation of acyl chloride **10** with (S_P)-**6**, removal of the MOM protecting group, and ring closure to form benzoxazole (Scheme 3). The structure of the methylene bridged bis(benzoxazole) (S_P,S_P)-**2** was also confirmed by mass spectrometry, IR, and NMR spectroscopy including ^{1}H NMR and ^{13}C NMR. The spectral data were in agreement with the desired structure.

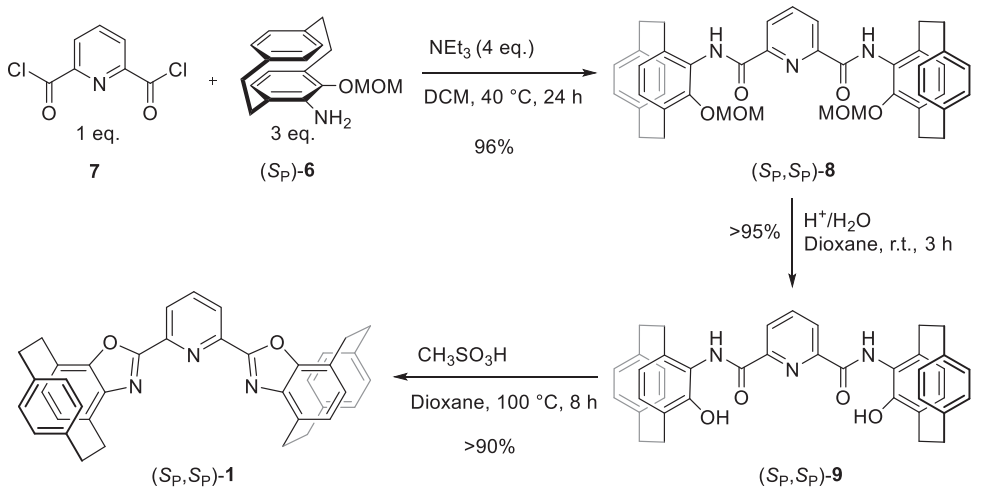
We planned to synthesize the other enantiomer of the bis(benzoxazole) **1** as well. However, after crystallization of the diastereomeric imine mixture of **4**, only the (S_P,*R*)-**4** isomer could be obtained in pure form. To the best of our knowledge, (R_P,*R*)-**4** isomer remains a waste product in the crystallization filtrate (Scheme 1).

We found that (R_P,*R*)-**4** can be obtained up to 90–95% *de* by recrystallization of the (R_P)-isomer rich filtrate remaining from first crystallization of the diastereomeric mixture of **4** (Scheme 4).

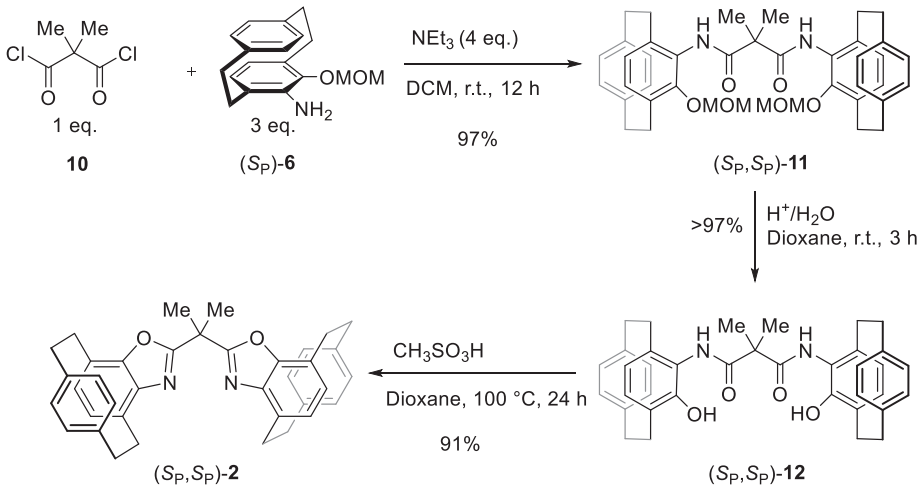
Actually, this enantiomeric purity is not sufficient for an asymmetric synthesis. However, we thought that the enantiomeric excess of the product in the amidation step would increase by removing of the minor enantiomer through the statistical formation of diastereomeric forms of **8** (the Horeau principle) [25]. To test this idea, (*R*p)-**6**, obtained from (R_P,*R*)-**4** under the described procedure in 90% *ee*, was reacted with 2,6-pyridinedicarbonyl dichloride (**7**). The ^{1}H NMR spectrum of the crude product showed the presence of two diamide **8** diastereomers at a 92:8 ratio. The resulting diastereomeric mixture was successfully separated by column chromatography to give (R_P,R_P)-**8** and (R_P,S_P)-**8** (*meso*) with



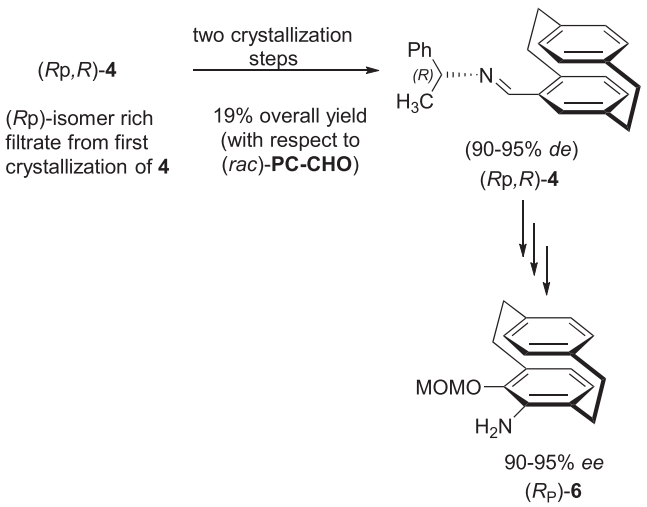
Scheme 1. Synthesis of 2-aminophenol moiety, (S_P)-**6**.



Scheme 2. Synthesis of the planar chiral bis(benzoxazole) (S_P,S_P)-**1**.



Scheme 3. Synthesis of the methylene bridged bis(benzoxazole) (S_P,S_P)-**2**.



Scheme 4. Synthesis of (R_P)-**6** (in 90–95% *ee*).

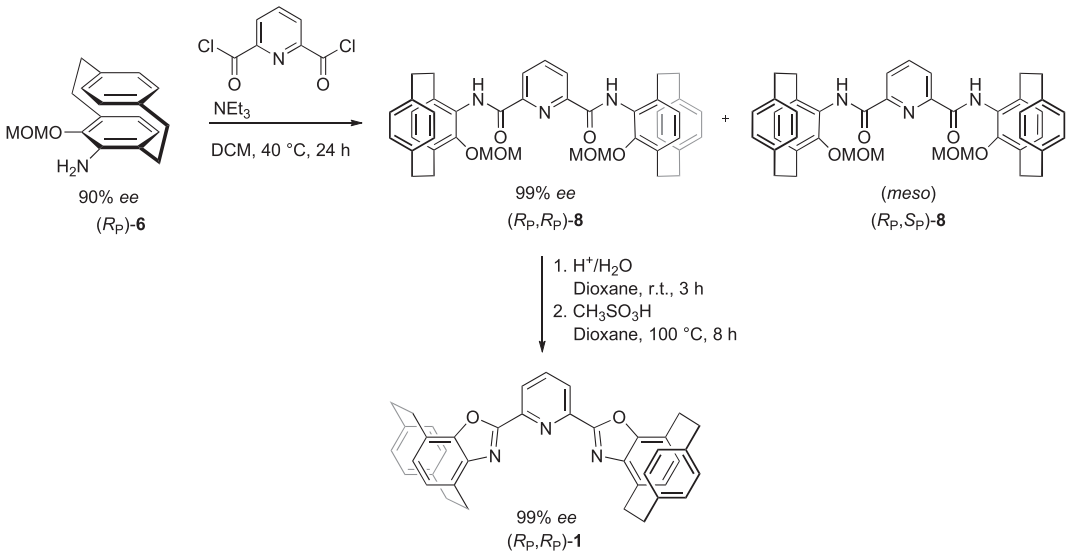
yields of 90% and 9%, respectively. Separation of these two diastereomers effectively removed the minor (S_P)-enantiomer from the major (R_P)-enantiomer and the enantiopurity of the (R_P,R_P)-**8** increased to 99% *ee* (determined by Chiral HPLC). (R_P,R_P)-**1** was successfully obtained with the ring closure after removal of the MOM group. All the spectral data of the (R_P,R_P)-**1** were in agreement with those of the (S_P,S_P)-isomer sample (Scheme 5).

Conclusion

Benzoxazole units with planes of symmetry are achiral. This study introduces chirality into the framework of bis(benzoxazole) with a [2.2]paracyclophane fragment and developed a new family of Box- and PyBox-like ligands that may be useful in asymmetric synthesis and heterocyclic chemistry. We have also demonstrated the synthetic utility of the Horeau principle in the synthesis strategy to obtain the (R_P)-isomer derivative. Besides the synthesis of (S_P,S_P)-isomers **1** and **2**, subjecting (R_P)-**6** (90% *ee*), obtained from a waste scalemic mixture of crystallization filtrate, to the same synthesis route resulted in 99% *ee* of (R_P,R_P)-**1**. Studies on the applications of new bis (benzoxazole) derivatives are in progress.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Scheme 5. Synthesis of the (R_P,R_P)-isomer of **1** by the Horeau principle.

Acknowledgments

The authors thank The Scientific and Technological Research Council of Turkey (TUBITAK, Project No. 114Z184) for financial support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152871.

References

[1] H.A. McManus, P.J. Guiry, Chem. Rev. 104 (2004) 4151–4202.
[2] G. Desimoni, G. Faita, K.A. Jørgensen, Chem. Rev. 111 (2011) PR284–PR437.
[3] G.C. Hargaden, P.J. Guiry, Chem. Rev. 109 (2009) 2505–2550.
[4] G. Yang, W. Zhang, Chem. Soc. Rev. 47 (2018) 1783–1810.
[5] K. Tomioka, Y. Yamamoto, K.-I. Yamada, Compreh. Chiral. 3 (2012) 626–654.
[6] S. Pal, B. Manjunath, S. Ghorai, S. Sasmal, Alkaloids: Chem. Biol. 79 (2018) 71–137.
[7] S.-I. Um, Dyes Pigm. 75 (2007) 185–188.
[8] C. Carayon, S. Fery-Forgues, Photochem. Photobiol. Sci. 16 (2017) 1020–1035.
[9] Y. Chen, D.X. Zeng, J. Org. Chem. 69 (2004) 5037–5040.
[10] Y. Kanegae, K. Peariso, M.S. Studer, Appl. Spectrosc. 50 (1996) 316–319.
[11] C. Rullière, J. Joussot-Dubien, Opt. Commun. 24 (1978) 38–40.
[12] H.B. Ammar, J. Lenotre, M. Salem, M.T. Kaddachi, P.H. Dixneuf, J. Organomet. Chem. 662 (2002) 63–69.
[13] C. Fischmeister, L. Toupet, P.H. Dixneuf, New J. Chem. 29 (2005) 765–768.
[14] A. Singh, G. Das, B. Mondal, Polyhedron 27 (2008) 2563–2568.
[15] A.-K.-W. Chan, E.-S.-H. Lam, A.-Y.-Y. Tam, D.-P.-K. Tsang, W.H. Lam, M.-Y. Chan, W.-T. Wong, V.-W.-W. Yam, Chem. Eur. J. 19 (2013) 13910–13924.
[16] A. Garza-Ortiz, P.A. Martinez, A.M. Duarte-Hernandez, E. Mijangos, M. Flores-Alamo, C. Perez-Casas, C. Camacho-Camacho, R. Contreras, A. Flores-Parra, J. Reedijk, N. Barba-Behrens, J. Mol. Struct. 1032 (2013) 265–274.
[17] J. Honzíček, I. Honzíčková, J. Vinklárek, Z. Růžičková, J. Organomet. Chem. 772–773 (2014) 299–306.
[18] S. Yan, C. Zhang, Y.-H. Wang, Z. Cao, Z. Zheng, X.-P. Hu, Tetrahedron Lett. 54 (2013) 3669–3672.
[19] Z. Hassan, E. Spuling, D.M. Knoll, J. Lahann, S. Bräse, Chem. Soc. Rev. 47 (2018) 6947–6963.
[20] Z. Hassan, E. Spuling, D.M. Knoll, S. Bräse, Angew. Chem. Int. Ed. 59 (2020) 2156–2170.
[21] S. Banfi, A. Manfredi, F. Montanari, G. Pozzi, S. Quici, J. Mol. Catal. A: Chem. 113 (1996) 77–86.
[22] C.J. Friedmann, S. Ay, S. Bräse, J. Org. Chem. 75 (2010) 4612–4614.
[23] M. Cakici, S. Bräse, Eur. J. Org. Chem. (2012) 6132–6135.
[24] A. Cipiciani, F. Fringuelli, O. Piermatti, F. Pizzo, R. Ruzziconi, J. Org. Chem. 67 (2002) 2665–2670.
[25] J.P. Vigneron, M. Dhaenens, A. Horeau, Tetrahedron 29 (1973) 1055–1059.