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Synthesis and atropisomerism of 2,2′-ortho disubstituted biphenyls

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ABSTRACT

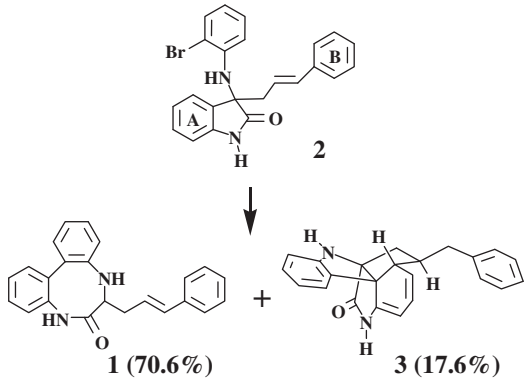
The role of substitution on the aromatic rings for the synthesis of 2:2 disubstituted biphenyls has been investigated. Atropisomerism involved in the above ring system has been studied using NMR spectroscopy. The outcome of inter and intramolecular Heck reaction is discussed.

1. Introduction

Recently[1] we reported a novel synthesis of ortho–ortho disubstituted biphenyls represented by structure **1**. Thus when compound **2** was treated with TBTH in refluxing toluene solution it yielded **1** as the major product along with a minor component **3** (Scheme 1). Intrigued by the complexity of the structure represented by compound **3** and the possibility of it being a novel pharmacophore in drug discovery, we reinvestigated the above reaction to determine whether we could change the proportion of **1** and **3** in the above reaction either by changing the substrate or the reaction condition. Thus we investigated the substitution effects on ring A and B. In this Letter, we wish to report our findings and also disclose the outcome of the inter/intra molecular Heck reaction[2] used during the synthesis. We also wish to record atropisomerism amongst a class of compounds reported in this Letter.

2. Present study

To study the effect of the substitution on ring A, we prepared[3] **8** and **9** starting with appropriately substituted isatins **4** and **5** and following the sequence of steps[4,5] involving **6** and **7** (see Scheme 2). Radical induced cyclization[6] of **8** yielded **10** and **11**. Similarly **9** yielded **12** and **13**. From the yields obtained in these cases it appears that there is a trend of aromatic substitution effect in the outcome of the radical reaction described above, however no generalization about it can be made with the limited number of examples studied.



Scheme 1.

We then investigated the effect of substitutions on ring B. Synthesis of **2** involves addition of cinnamyl bromide in the presence of indium to the imine **14**. To prepare the B ring-substituted derivatives represented by structures **15** and **16** (see Scheme 3), we needed a good procedure for the preparation of substituted cinnamyl bromides which proved to be unsatisfactory following several literature[7] procedures for their synthesis. Perhaps the substituted cinnamyl bromides were not very stable. We therefore studied whether we could prepare **15** and **16** starting with **17**. We were aware that the outcome of this reaction could be complicated by the competition involving intramolecular Heck reaction[8] of **17** to yield **18** and intermolecular Heck reaction[9] when the reaction was carried out in the presence of bromo substituted benzenes. To our surprise the major product in the above reaction was the outcome of the intermolecular reaction pathway. Thus compound **17** yielded **2** as the major product along with compound **18** (5%) as a minor

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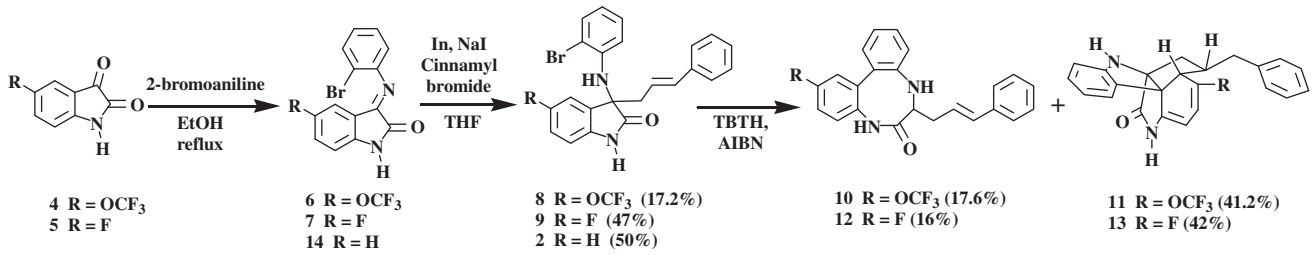
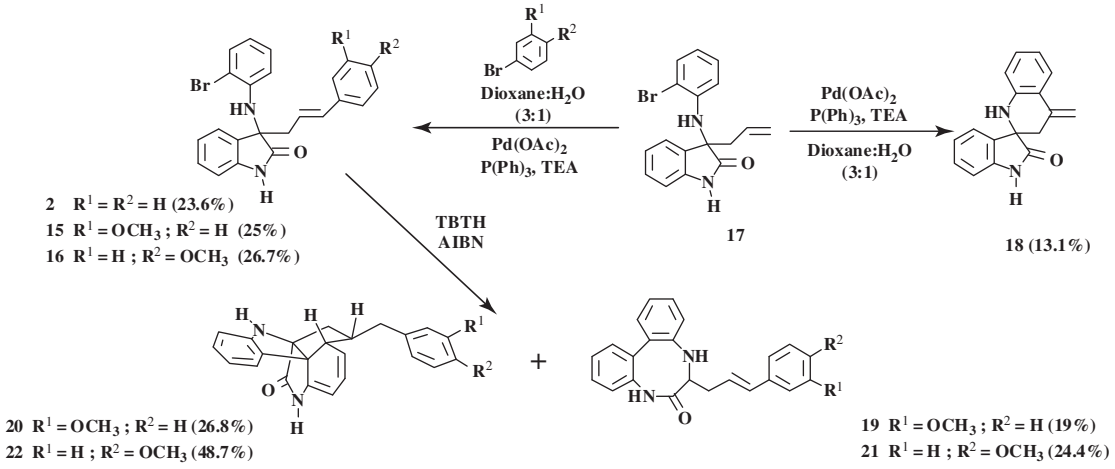
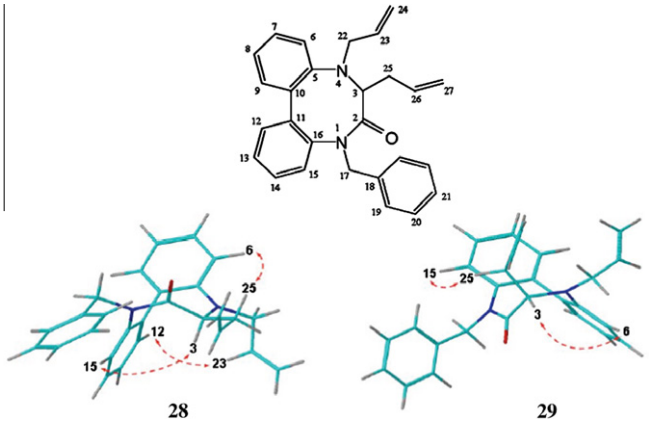


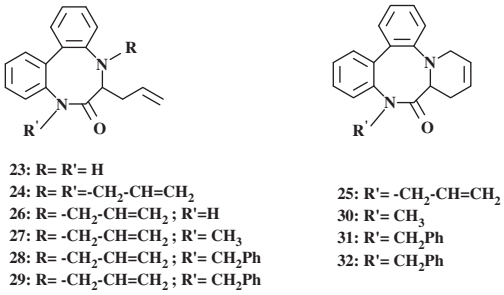
Scheme 2.



Scheme 3.



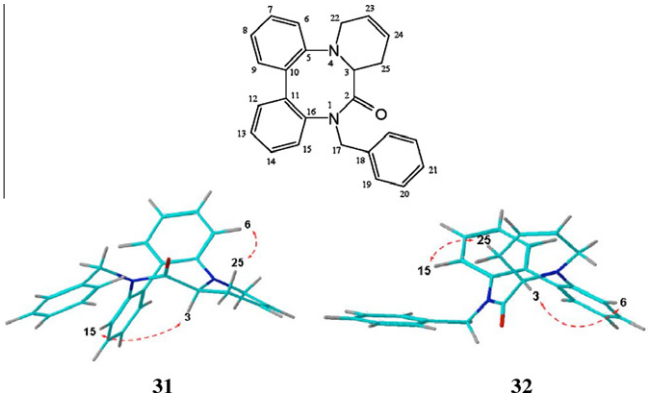
Scheme 4.



Scheme 5.

component. We repeated the reaction of **17** with para-methoxy and meta-methoxy bromobenzenes and obtained **16** and **15** also in modest yield, respectively. Radical cyclization of **15** yielded **19** and **20** whereas **16** yielded **21** and **22**. It would appear that para electron-donating substitution has the desired effect for the formation of the ring system represented by the structure **22**.

In our earlier publication[1], we also reported the conversion of **17** to **23** using radical cyclization process. Compound **23** when treated[10] in DMF solution with allyl bromide and cesium carbonate yielded only the diallyl compound **24** (see Scheme 5) which underwent ring-closing metathesis[11] to yield **25**, which was found to decompose on standing at room temperature. We presumed that the allyl group on the non-basic nitrogen atom contributed towards the instability of the molecule. We tried a variety of reaction conditions to selectively allylate the basic nitrogen which is needed for the ring-closing metathesis without much success till we found out that the treatment[12] of **23** with allyl bromide in DMF solution without any base yielded exclusively **26**. This appears to be a general reaction and could be very useful for the preparation of mono-substituted anilines. Further work is in progress to determine the scope of this reaction and will be published at a future date. Treatment of **26** in DMF solution and methyl iodide in the presence of cesium carbonate yielded **27** (77%). Similarly **26** when treated[13] in DMF solution with benzyl bromide and sodium iodide yielded **28** (50.9%) and **29** (23.5%). Structure elucidation of **28** and **29** was carried out by NMR spectroscopy. 1D and 2D homonuclear COSY and NOESY and heteronuclear HSQC, HSQCTOCSY and HMBC experiments were performed on a Varian INOVA 600 MHz spectrometer in $CDCl_3$ at 25 °C. MMX force field calculations of **28** (**29**) structure (PCModel software[14]) predicted the lowest energy conformations with a boat-like eight-membered ring structure and the H3 proton in either axial or equatorial orientation. Long-range NOE's between the H3 and H15, between the H12 and H23 and between the H6 and H25 protons in **28** (shown as red arrows in Scheme 4) proved that the



Scheme 6.

H3 proton occupies an axial orientation relative to the eight-membered ring plane. In turn an equatorial orientation of the H3 proton in **29** was confirmed by NOE's between the H3 and H6 and between the H15 and H25 protons. We have observed a slow overnight transition of **29** to **28** at 65 °C in toluene-d_8. Since the rate of isomerization was very slow even at 65 °C, **28** and **29** can be classified as atropisomers. Atropoisomers are stereoisomers with a significantly restricted rotation about a single bond which allows isolation of two isomers (rotamers).[15] Atropoisomersim is frequently observed in biphenyl systems that have bulky substituents in ortho positions.[15] In **28** and **29** a restricted rotation about the C10–C11 sp^2–sp^2 single bond is caused by a rigid four-atom linker which connects two ortho positions of the biphenyl subunit. Isomerization of **28** and **29** atropisomers is a complex multistep process which we are currently investigating. Results of this study will be published in the future.

Ring-closing metathesis[11] of **27** yielded **30** (67%). Similarly **28** under ring-closing metathesis condition yielded **31** (75.8%) and **29** yielded **32**(72%). Unlike **25** compounds **30**, **31** and **32** were stable at room temperature.

Similar to **28** and **29,** structure elucidation of **31** and **32** was carried out by 1D and 2D NMR spectroscopy. Initially conformations of **31** and **32** were generated from corresponding 3D structures of **28** and **29**. Then energy-minimized conformations of **31** and **32** were verified by long-range NOE's. Thus, NOE's between the H3 and H15 and between the H6 and H25 protons in **31** (shown as red arrows in Scheme 6) were consistent with predicted conformation with an axial H3 proton, whereas NOE's between the H15 and H25 and between the H3 and H6 protons in **32** were consistent with the conformation in which the H3 proton occupies an equatorial orientation relative to the eight-membered ring.

Acknowledgements

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3. NMR spectra were recorded with 400 MHz and/or 600 MHz spectrometers using $CDCl_3$ as solvent with TMS as an internal standard unless otherwise stated. NMR and high resolution mass spectra of all the compounds described in this letter were consistent with the assigned structures. Assignments were further confirmed using 2D NMR and NOE experiments. The figures in parenthesis in all the schemes represent yields in the reactions. It should be noted that the yields reported in this letter are not optimised. The purity of the compounds was established using various chromatographic techniques. Compounds **10**, **11**, **15**, **18**, **19**, **20**, **21**, **22**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, and **32** were not crystalline. All other compounds described in the Letter were crystalline. Crystals were obtained from DCM–hexane for compounds **2**, **8**, **9**, **16**, and **23** and from THF–hexane for compounds **12** and **13**. The melting points of compounds **2**, **8**, **9**, **12**, **13**, **16**, and **23** were 163–165, 139–141, 214–216, 108–110 (decomposes), >235, 199–200, and 179–181 °C, respectively.
4. Preparation of imine **6**. A solution of 5-(trifluoro-methoxy)isatin (500 mg, 2.77 mmol) and 2-bromoaniline (372 mg, 2.77 mmol) in ethanol was refluxed for 6 h. The mixture was evaporated to dryness and the product used for the next step without purification.
5. Preparation of **8**. To a solution of **6** (800 mg, 2.08 mmol) in DMF, indium (238.6 mg, 2.08 mmol) and sodium iodide (467 mg, 3.12 mmol) were added. To the stirred reaction mixture cinnamyl bromide (0.41 mL, 3.12 mmol) was added dropwise. After completion of the reaction it was filtered and evaporated to dryness. The crude reaction mixture was extracted with DCM, the organic layer washed with water, dried over anhydrous sodium sulfate, filtered and evaporated, followed by column chromatography to yield compound **8**.
6. Example of radical cyclisation: Preparation of **10** and **11**. To a solution of **8** (170 mg, 0.34 mmol) in toluene (30 mL), AIBN (11.1 mg, 0.07 mmol)) was added. TBTH (0.10 mL, 0.37 mmol) was then added dropwise to the reaction mixture which was then heated for 1 h at 110 °C at which point another 0.2 equiv of AIBN and 1.1 equiv of TBTH were added. The mixture was evaporated to dryness followed by extraction with DCM. The organic layer was washed with water, dried over anhydrous sodium sulfate and after evaporation purified by column chromatography to obtain pure products.
7. (a) Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. *Tetrahedron Lett.* **2006**, *47*, 1771–1775; (b) Yadav, V. K.; Babu, K. G. *Tetrahedron* **2003**, *59*, 9111–9116; (c) Hajipour, A. R.; Falahatia, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 4191–4196.
8. Example of intramolecular Heck reaction: Preparation of **18**. To a solution of **17** (200 mg, 0.58 mmol) in CH_3CN (9 mL) and water (3 mL), $Pd(OAc)_2$ (6.54 mg, 0.03 mmol), PPh_3(15.3 mg, 0.06 mmol) and triethylamine (0.10 mL, 2.56 mmol) were added. The reaction mixture was refluxed for 24 h and then evaporated to dryness, extracted with DCM and the organic layer washed with water, dried over anhydrous sodium sulfate, filtered, evaporated, followed by column chromatography to yield pure product.
9. Example of intermolecular Heck reaction: Preparation of **2**. To a solution of **17** (300 mg, 0.87 mmol) in CH_3CN (24 mL) and water (8 mL), $Pd(OAc)_2$ (9.8 mg, 0.05 mmol) and PPh_3(25.2 mg, 0.09 mmol) were added. The reaction mixture was stirred under nitrogen to which triethylamine (0.14 mL, 0.96 mmol) and bromobenzene (0.325 mL, 2.56 mmol) were added dropwise. The mixture was refluxed for 2 days, evaporated to dryness and extracted with DCM. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered, evaporated, followed by column chromatography to yield compound **2**.
10. Preparation of **24**. To a solution of **23** (100 mg, 0.38 mmol) in DMF, cesium carbonate (246.8 mg, 0.76 mmol), sodium iodide (114 mg, 0.76 mg), and allyl bromide (0.08 mL, 0.84 mmol) were added. The reaction was refluxed for 3 h. The mixture was filtered, evaporated to dryness and extracted with DCM. Compound **24** was obtained using column chromatography of the crude reaction mixture.
11. Example of ring closing metathesis: Preparation of **31**. To a solution of **28** (127.9 mg, 0.32 mmol) in DCM, 1st generation Grubbs catalyst (13.3 mg, 0.02 mmol) was added. The reaction was refluxed for 2 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, evaporated, and the crude product was chromatographed to yield compound **31**.
12. Preparation of **26**. To a solution of **23** (300 mg, 1.14 mmol) in DMF, sodium iodide (204.1 mg, 1.36 mmol) and allyl bromide (0.118 mL, 1.36 mmol) were added. The reaction mixture was stirred at room temperature for one day. It was evaporated to dryness and the residue extracted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness. Purification by column chromatography yielded compound **26**.
13. Preparation of **28** (**29**). To a solution of **26** (250 mg, 0.82 mmol) in DMF (7 mL), cesium carbonate (321.1 mg, 0.99 mmol), sodium iodide (147.7 mg, 0.986 mmol), and benzyl bromide (0.12 mL, 0.99 mmol) were added. The reaction mixture was stirred at room temperature over night, filtered, evaporated and chromatographed to yield **28** (**29**).
14. PCModel v. 8.5 Serena Software, Bloomington IN 47402-3076.
15. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons, 1994. pp 1142–1145.