HETEROCYCLES, Vol. 96, No. 1, 2018, pp. 67 - 73. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 12th October, 2017, Accepted, 16th November, 2017, Published online, 22nd November, 2017
DOI: 10.3987/COM-17-13822

A CONVENIENT SYNTHESIS OF INDOLE AND 1,4-DIHYDROPYRIDINE HYBRID MACROMOLECULES BY DIMERIZATION OF [2-(1*H*-INDOL-3-YL)ETHYL]PYRIDINIUM SALTS

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Abstract – The design and synthesis of a novel type of macrocyclic compounds containing indole and 1,4-dihydropyridine heterocyclic subunits is presented. The key reaction involved in the synthesis was a base-mediated dimerization of [2-(1*H*-indol-3-yl)ethyl]pyridinium salts. The structure of the macrocycles was unambiguously confirmed by NMR and HRMS spectroscopic and X-ray single crystal diffraction.

INTRODUCTION

The design and synthesis of heteroarene-based macromolecules possessing defined structural architectures are the focus of intense research in the area of molecular and ion recognition,[1] supramolecular chemistry,[2] and drug design.[3] In this regard, the nitrogen containing heterocycles such as pyridine and pyrrole,[4] thiazoline and thiazole,[5] and oxazole and oxazoline[6] have been preferentially selected as fundamental subunits since these classess of subunits may participate in a wide varieties of non-covalent interactions, such as dipole–dipole and π-π interactions, hydrogen-bonding, and chelation. On the other hand, the indole nucleus are prevailing structural motifs in natural products and synthetic molecules for pharmaceuticals and materials.[7] However, to our knowledge, the indole skeleton has been rarely considered as a useful substructure for the fabrication of macrocycles.

Previously, we and others have designed and synthesized a variety of thiazoline/thiazole- and oxazole-based macrocycles[5,6] (Figure 1), and have investigated the recognition property of some of these macrocycles serving as host compounds toward small organic molecules or metal ions. With the aim of

developing new macrocyclic compounds for potential applications in host-guest chemistry together with our longstanding interests in the development of new methodology for the synthesis of artificial and naturally occurring indole compounds,[8] we become interested in carrying out the synthetic studies on the indole-derived macrocycles. In principle, the nature of large π-system paired with the presence of N-heteroatom of indole unit would make the indole-containing macrocycles appealing in molecule or ion recognition. Herein, we present an efficient synthesis and detailed structure characterization of macrocyclic compounds composed of indole and 1,4-dihydropyridine heterocyclic substructures.

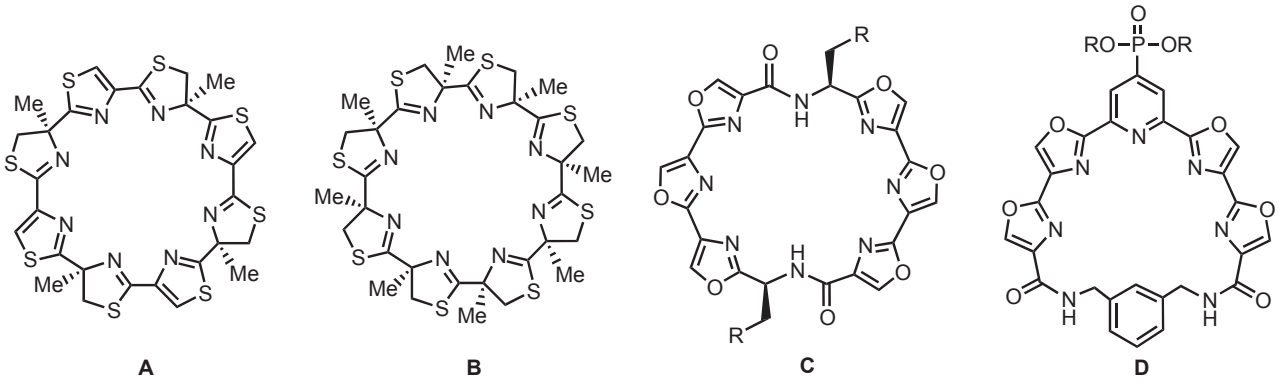
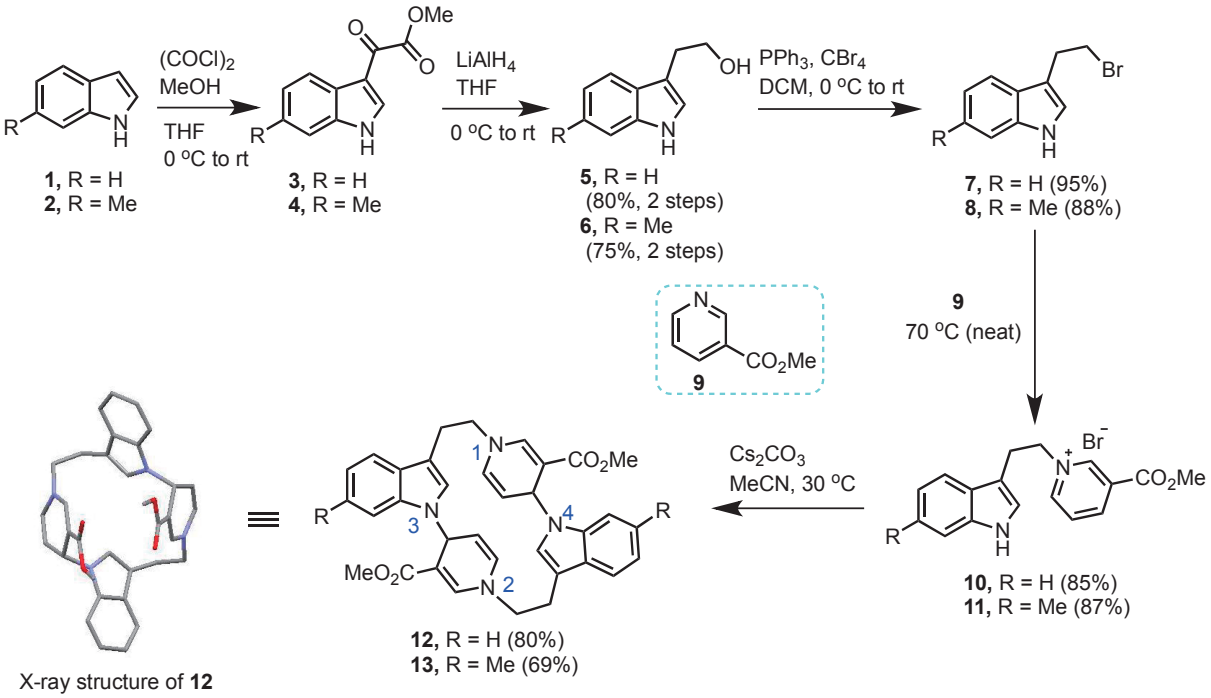


Figure 1. Representative macrocyclic compounds synthesized in previous works

RESULTS AND DISCUSSION



Scheme 1. Synthesis of macrocycles containing indole subunit

Our synthesis commenced with the commercially available indole derivatives **1** and **2** (Scheme 1). Respective Friedel-Crafts acylation of **1** and **2** with oxalyl dichloride afforded methyl 2-(1*H*-indol-3-yl)-2-oxoacetate **3** and **4**.[9] TLC monitoring indicated that the reaction proceeded cleanly without apparent formation of other appreciable regioisomers. Therefore, the crude **3** and **4** were subjected to the reduction with $LiAlH_4$ without careful purification to give 2-(1*H*-indol-3-yl)ethan-1-ol **5** and **6**, respectively, in high yields over two steps. Conversion of the hydoxy group in **5** and **6** into the corresponding brominated derivatives **7** and **8** was carried out efficiently under the effect of PPh_3 and CBr_4.[10] Subsequently, treatment of **7** and **8** with methyl nicotinate **9** according the conditions described by Xia and co-workers[11] afforded the pyridinium salts **10** and **11** in high yields. For the dimerization of **10** and **11**, we examined an array of conditions by varying bases and solvents, and eventually found that the dimerization proceeded efficiently with the presence of Cs_2CO_3 base in MeCN. The desired macrocyclic compounds **12** and **13** could be obtained in 80% and 69% yields respectively. The dimerization reaction could be reliably performed on gram scale. In addition, the dimerization could also proceed in THF using NaH as base.[12] However, the reaction was somewhat sluggish to give the product in a lowered yield (*ca.* 50% for **12**).

It should be noted that in an earlier report in 1986, a similar dimerization reaction was proposed by Wenkert and co-workers during the synthetic study of indole alkaloids.[12] However, the structure of the macrocyclic product was not definitely established due to the lack of rigorous proof. Herein, we could unambiguously confirm the structure of the macrocycles by a combination of ^{1}H- and ^{13}C-NMR spectroscopic, HRMS, and X-ray single crystal analysis.[13] Interestingly, the NMR spectroscopic and X-ray single crystal analysis revealed that the indole-dihydropyridine hybrid macrocycles have C_2 symmetry both in solution and solid state. The two indole and two dihydropyridine rings form a well-defined cavity with an estimated pore size of l = *ca.* 5.19 Å (l = length, N_1 to N_2) and b = *ca.* 4.21 Å (b = breadth, N_3 to N_4).[14] In the cavity, there are four nitrogen atoms which may serve as the binding sites for guest molecules or ions. In addition, there are two methyl ester groups pointed toward outward of the cavity. These functionalities are anticipated to be acting as extra binding sites to further tune the interaction property between the host and guest when molecule or ion recognition is under consideration.

In conclusion, we have designed and synthesized a new type of macrocycles via the base-mediated dimerization of [2-(1*H*-indol-3-yl)ethyl]pyridinium salts. The synthetic procedure developed herein would provide an efficient and general way for flexible synthesis of indole-based macrocycles. The structure of the macrocyclic compounds was clearly established by multi-spectroscopic and X-ray single crystal analysis. The well-defined cavity associated with the presence of four nitrogen heteroatoms in the cavity and two arm-like ester functionalities makes such type of the macrocycles great potential in

application of host-guest chemistry. Synthesis of other indole-derived macrocycles with structural diversity and study on their molecule/ion recognition properties are the focus of our future work.

EXPERIMENTAL

All oxygen or moisture sensitive reactions were performed under argon atmosphere in dry glassware. All commercial reagents were used without further purification, unless otherwise noted. Anhydrous solvents were distilled according to standard methods. ^{1}H NMR spectra were recorded at 300 MHz (Bruker AV) the ^{13}C NMR spectra were recorded at 125 MHz. All chemical shifts are given in ppm. All coupling constants (*J* values) were reported in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on an IonSpec Ultima 7.0 T FT-ICR-MS (IonSpec, USA) with a Waters Z-spray source. X-Ray crystallographic analysis was performed on a Bruker D8 ADVANCE diffractometer with Mo-Ka radiation (λ = 0.71073 Å).

Synthesis of compounds 5. To a solution of indole (10.0 mmol, 1.0 equiv) in dry Et_2O (50 mL) was added dropwise oxalyl chloride (2.7 mL, 30.0 mmol, 3.0 equiv) at 0 °C. Then the ice bath was removed and the resulting yellow slurry was stirred for 6 h at room temperature. The reaction mixture was then cooled to 0 °C and quenched with MeOH (2.0 mL, 50.0 mmol, 5.0 equiv). The crude precipitate was collected by filtration and was washed with cold Et_2O. The solid **3** was dried under vacuum and used directly for the next step without further purification.

A solution of compound **3** in THF (20 mL) was added dropwise to a suspension of $LiAlH_4$ (1.5 g, 4.0 equiv) in THF (40 mL) at 0 °C. The reaction mixture was stirred for 4 h at room temperature and quenched with H_2O (1.5 mL), 10% aqueous NaOH (3.0 mL), and H_2O (4.5 mL) slowly at 0 °C. The reaction mixture was then filtered and the filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, v/v = 1:1) to give tryptophol **5** (1.3 g, 80% for two steps) as a yellow solid. NMR data were in consistent with those reported.[15]

Synthesis of compound 6. The compound was synthesized from **2** according to the same procedure as for **5** in 75% yield over two steps. NMR data were in consistent with those reported.[16]

Synthesis of compound 7. A solution of CBr_4 (5.4 g, 1.3 equiv) in CH_2Cl_2 (15 mL) was added dropwise to a solution of Ph_3P (4.2 g, 1.3 equiv) and **5** (2.0 g, 1.0 equiv) in CH_2Cl_2 (20 mL) under nitrogen atmosphere at 0 °C. The reaction mixture was allowed to stir at room temperature for 1 h. Solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (petroleum ether:EtOAc, v/v = 25:1) to afford compound **7** (2.6 g, 95%) as a yellow oil. NMR data were in consistent with those reported.[16]

Synthesis of compound 8. The compound was synthesized from **6** according to the same procedure as for **7** in 88% yield as a white solid.

Synthesis of compound 10. Compound **7** (0.47 g, 2.1 mmol) was added to methyl nicotinate (0.86 g, 6.3 mmol, 3.0 equiv). The mixture was then stirred at 70 ºC for 8 h. The reaction mixture was dispersed in a mixed solvent of Et_2O/DCM (v/v = 1:1). The solid was collected by filtration and washed further with Et_2O/DCM (v/v = 1:1) to afford pure compound **10** (0.53 g, 85%) as a solid. NMR data were in consistent with those reported.[17]

Synthesis of compound 11. The compound was synthesized from **8** according to the same procedure as for **10** in 88% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.91–10.74 (br, 1H), 9.45 (s, 1H), 9.01 (d, J = 6.1 Hz, 1H), 8.94 (d, J = 8.1 Hz, 1H), 8.17 (dd, J = 8.1, 6.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 6.96 (d, J = 2.3 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.95 (t, J = 7.0 Hz, 2H), 3.95 (s, 3H), 3.40–3.29 (t, J = 6 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.10, 147.89, 145.81, 145.00, 136.66, 130.40, 129.44, 127.90, 124.59, 123.50, 120.41, 117.84, 111.37, 108.01, 61.72, 53.45, 26.97, 21.38. HMRS Calcd for $C_{18}H_{19}N_2O_2$ $[M]^+$: 295.1441; Found: 295.1434.

Synthesis of compound 12. To a solution of **10** (0.72 g, 2.0 mmol) in dry MeCN (10 mL) was added Cs_2CO_3 (0.98 g, 3.0 mmol, 1.5 equiv) at room temperature. The mixture was stirred at 30 ºC for 1 h. To the reaction mixture was added H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford pure compound **12** (0.47 g, 80%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 1H), 7.53 (dt, J = 7.9, 1.0 Hz, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.30–7.22 (m, 1H), 7.17–7.09 (m, 1H), 6.88 (s, 1H), 6.07 (d, J = 4.9 Hz, 1H), 5.43 (dd, J = 7.7, 1.7 Hz, 1H), 4.72 (dd, J = 7.7, 4.9 Hz, 1H), 3.76–3.67 (m, 2H), 3.53 (s, 3H), 3.27–2.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.18, 140.02, 135.92, 135.61, 129.88, 129.60, 125.53, 125.33, 124.87, 121.19, 118.42, 117.49, 109.89, 109.50, 102.82, 102.32, 98.57, 76.16, 55.17, 50.53, 50.25, 44.98, 27.75, 27.32. HMRS Calcd for $C_{34}H_{33}N_4O_4$ $[M+H]^+$: 561.2502; Found: 561.2492; $C_{34}H_{32}N_4O_4Na$ $[M+Na]^+$: 583.2321; Found: 583.2299.

Synthesis of compound 13. The compound was synthesized from **11** according to the same procedure as for **12** in 69% as solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 3H), 6.95 (d, J = 8.0 Hz, 1H), 6.78 (s, 1H), 6.01 (d, J = 4.9 Hz, 1H), 5.37 (d, J = 7.6 Hz, 1H), 4.67 (dd, J = 7.7, 4.9 Hz, 1H), 3.70 (dd, J = 7.3, 3.2 Hz, 2H), 3.54 (s, 3H), 3.30–2.80 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 166.88, 141.01, 140.74, 136.35, 136.12, 130.33, 129.93, 125.16, 124.95, 124.06, 123.80, 120.22, 117.95, 110.29, 102.89, 102.67, 97.42, 54.94, 54.68, 50.56, 50.35, 44.86, 27.47, 27.26, 21.67. HMRS Calcd for $C_{36}H_{37}N_4O_4$ $[M+H]^+$: 589.2815; Found: 589.2809.

ACKNOWLEDGEMENTS

Financial support from NSFC (21572215, 21772191) is acknowledged.

REFERENCES AND NOTES

1. For selected reviews, see: X. X. Zhang, J. S. Bradshaw, and R. M. Izatt, *Chem. Rev.*, 1997, **97**, 3313; T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev.*, 1993, **22**, 383.
2. 'Supramolecular Chemistry: Concepts and Perspectives,' ed. by J.-M. Lehn, Wiley-VCH, Weinheim, 1995.
3. E. Izbicka, R. T. Wheelhouse, E. Raymond, K. K. Davidson, R. A. Lawrence, D. Sun, B. E. Windle, L. H. Hurley, and D. D. Von Hoff, *Cancer Res.*, 1999, **59**, 639; J. Seenisamy, S. Bashyam, V. Gokhale, H. Vankayalapati, D. Sun, A. Siddiqui-Jain, N. Streiner, K. Shin-ya, E. White, W. D. Wilson, and L. H. Hurley, *J. Am. Chem. Soc.*, 2005, **127**, 2944.
4. J. Breitenbach, J. Boosfeld, and F. Vögtle, 'Comprehensive Supramolecular Chemistry,' ed. by J. L. Atwood, J. E. D. Davies, D. D. MacNicol, and F. Vögtle, Pergamon, Oxford, 1996, Vol. 2, pp. 29–67.
5. F. S. Han, H. Tokuyama, and T. Fukuyama, *Chem. Commun.*, 2007, 3444; F. S. Han, H. Osajiama, M. Cheung, H. Tokuyama, and T. Fukuyama, *Chem. Commun.*, 2006, 1757; F. S. Han, H. Osajima, M. Cheung, H. Tokuyama, and T. Fukuyama, *Chem. Eur. J.*, 2007, **13**, 3026.
6. F. Qi, L. Gao, and F. Han, *Chin. J. Chem.*, 2014, **32**, 585, and references therein; F. Qi, L. Gao, and F. Han, *Chem. Res. Chin. Univ.*, 2014, **30**, 587, and references therein.
7. For selected reviews, see: M. S. Shchepinov and V. A. Korshun, *Chem. Soc. Rev.*, 2003, **32**, 170; M. Shiri, M. A. Zolfigol, H. G. Kruger, and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250.
8. For selected publications, see: C.-Y. Liu and F.-S. Han, *Chem. Commun.*, 2015, **51**, 11844; X. Zhong, Y. Li, J. Zhang, and F.-S. Han, *Org. Lett.*, 2015, **17**, 720; X. Zhong, Y. Li, J. Zhang, W.-X. Zhang, S.-X. Wang, and F.-S. Han, *Chem. Commun.*, 2014, **50**, 11181; S. Qi, C.-Y. Liu, J.-Y. Ding, and F.-S. Han, *Chem. Commun.*, 2014, **50**, 8605; X. Zhong, Y. Li, and F.-S. Han, *Chem. Eur. J.*, 2012, **18**, 9784; F.-Q. Yuan, L.-X. Gao, and F.-S. Han, *Chem. Commun.*, 2011, **47**, 5289.
9. L. Han, C. Liu, W. Zhang, X.-X. Shi, and S.-L. You, *Chem. Commun.*, 2014, **50**, 1231.
10. Q. T. Do, G. T. Nguyen, V. Celis, and R. S. Phillips, *Arch. Biochem. Biophys.*, 2014, **560**, 20.
11. J. Xu, L.-D. Shao, D. Li, X. Deng, Y.-C. Liu, Q.-S. Zhao, and C. Xia, *J. Am. Chem. Soc.*, 2014, **136**, 17962.
12. E. Wenkert, E. C. Angell, J. Drexler, P. D. R. Moeller, J. S. Pyrek, Y. J. Shi, M. Sultana, and Y. D. Vankar, *J. Org. Chem.*, 1986, **51**, 2995.
13. CCDC 1575752 contains the supplementary crystallographic data for compound **12**.

14. For atomic radii used for estimating the pore size of the synthesized macrocyclic compounds, see: E. Clementi, D. L. Raimondi, and W. P. Reinhardt, *J. Chem. Phys.*, 1967, **47**, 1300.
15. M. Szostak, M. Spain, A. J. Eberhart, and D. J. Procter, *J. Am. Chem. Soc.*, 2014, **136**, 2268.
16. S. Tong, Z. Xu, M. Mamboury, Q. Wang, and J. Zhu, *Angew. Chem. Int. Ed.*, 2015, **54**, 11809.
17. C. Galvez, F. Garcia, J. Ribera, and P. Viladoms, *J. Heterocycl. Chem.*, 1980, **17**, 1355.