FACILE SYNTHESIS OF BIS(CROWN ETHER)BENZILS: PROSPECTIVE BUILDING BLOCKS FOR METAL ION SENSORS

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GRAPHICAL ABSTRACT

Abstract A new facile synthetic route to benzils containing fragments of 12-crown-4, 15-crown-5, and 18-crown-6 by oxidation of corresponding stilbenes was developed. The first representative of a new family of fluorescent sensors was obtained by reaction of bis(15-crown-5)benzil with o-phenylenediamine. The latter exhibits great fluorescence enhancement upon association with K⁺ and Rb⁺ compared to Na⁺ and Cs⁺.

Keywords Benzil; chemosensor; crown compounds; host–guest systems; stilbene; supramolecular chemistry

INTRODUCTION

The design and synthesis of chemosensors capable of selective binding of neutral and charged substrates is one of the most urgent tasks of supramolecular chemistry.[1] Molecular sensors for the recognition of alkali and alkaline earth metal ions have attracted extensive attention over the past few years.[2] To date, structures based on calixarenes[3] and crown ethers[4] are mostly used for these purposes. In recent
years, interest in biscrown ethers with preorganized crown ether subunits as a potent and selective complexones of alkali and alkaline earth metal cations has increased significantly. These chemosensors generally comprise crown ether blocks capable effectively capturing a substrate and a fragment providing an analytical response.

Benzils, or diaryl-1,2-diketones, are convenient precursors to obtain a wide range of compounds. Benzils with fragments of crown ethers will be promising in the synthesis of chemosensors, chelators, and supramolecular structures. To date, just one biscrown-containing benzil based on benzo-15-crown-5 has been reported. For the first time it was obtained by Huang et al. as a by-product with a trace yield in 4′-formylbenzo-15-crown-5 benzoin condensation. Yield of this benzil for two steps was <1%. It was synthesized by Kimura et al. purposefully in three steps using an organolithium derivative and dimethyl piperazinedione. However, the overall yield based on the starting benzo-15-crown-5 was less than 6%. It is obvious that the first and second methods are not of preparative value. The approach was improved by the same authors by obtaining and oxidizing the bis(15-crown-5)tolan, which raised the total yield up to 50%.

Although the last method allows obtaining target product in an acceptable yield, it requires the use of expensive palladium catalysts.

The aim of the present study was the search for alternative syntheses of crown-containing benzils and exploration of the possibility for preparation of potential chemosensors on their base.

RESULTS AND DISCUSSION

Retrosynthetic analysis revealed five main pathways for the synthesis of symmetrical crown-containing benzils (Scheme 1).

The formation of two polyether macrocycles based on 1,2-bis(3,4-dihydroxyphenyl)ethane-1,2-dione (method A) is not very promising as the starting material is commercially unavailable, and its synthesis presents another task. Simultaneous creation of two crown residues at the cyclization step is not expected to give the desired products in good yields. Synthetic pathway B (the formation of C–C bond through benzoin condensation followed by oxidation, as has been mentioned) resulted in extremely poor
yield of the target compound. Its disadvantages include the use of toxic cyanides. α-Diketone moiety may also be introduced using the Friedel–Crafts reaction with oxalyl chloride\[^{[8a]}\] or via organotin compounds\[^{[8b]}\] (method C). However, using of veratrole in this reaction leads to desired product in very poor (1.7\%) yield.\[^{[8a]}\]

When using crown ethers, isolation of target products may be complicated by the formation of strong and insoluble complexes with Lewis acids. The conversion of 1,3-diketones to benzils is a relatively new synthetic approach (method D).\[^{[8c, d]}\] The strategy E—oxidation of unsaturated C=\(\equiv\)C\[^{[8e]}\] or C\(\equiv\)C\[^{[7b, 8f]}\] bonds up to α-diketones—is the most promising. However, all these examples are not free of some disadvantages such as the use of expensive catalysts both at a final step and in the preparation of starting materials. Difficulty of obtaining of benzils “precursors” is caused by complicated and multistep synthesis.

We report herein an efficient facile synthesis of benzils with crown ethers moieties using catalyst-free oxidative protocol.

Symmetric crown-containing stilbenes are available and can be readily prepared by the procedure described (Scheme 2).\[^{[9]}\]

It has been established that the first stage can be carried out at higher temperatures (up to +20°C) without decreasing yield of the target stilbene. Also, it prevents precipitation of starting benzocrown ether from the reaction mixture. The oxidation of 2b in the dimethylsulfoxide (DMSO)/HBr system\[^{[9]}\] has resulted in the target benzil 3b in a good yield of 61%. The total yield based on the starting benzo-15-crown-5 1b is 42\%, which is less than that described by Kimura.\[^{[7b]}\] However, the method offered by us has several advantages. The precursor stilbene 2b is obtained without isolation of intermediates and does not require purification. There is no need to use low temperatures and expensive catalysts.

Within this approach, the following new benzils have been obtained: bis(12-crown-4)benzil 3a and bis(18-crown-6)benzil 3c (Scheme 2, Table 1).

Bis(crown ether) 4, where two fragments of benzo-15-crown-5 are attached to quinoxaline core, was synthesized to assess the prospects of using obtained benzils as building blocks in the synthesis of chemosensors. Synthesis was carried out by refluxing of o-phenylenediamine with benzil 3b in ethanol in the presence of p-toluenesulfonic acid (PTSA) (Scheme 3).\[^{[10]}\] The desired bis(crown ether) 4 was obtained in 89\% yield.

Fluorescence properties of 4 (50\,µM) were examined in methanol solution at room temperature. It exhibits emission with the maxima at 540 nm when excited at 367 nm. Addition of alkali metal chlorides leads to a blue shift of emission maximum and to dramatic increase in the intensity (Fig. 1).

**Scheme 2.** Reagents and conditions: (a) CH\(_2\)BrCH(OEt)\(_2\), H\(_2\)SO\(_4\)/AcOH, 0–20 °C; (b) AmOH, reflux, 6 h; and (c) DMSO, 48\% HBr, 115°C, 1.5 h.
The observed changes in the fluorescence spectrum are caused by the complexation between the crown ether 4 and alkali metal cations. Such behavior is a feature of internal charge transfer (ICT) fluorescence mechanism.\textsuperscript{[11]} Registered
luminescence intensity rise is substantially greater when K\(^+\) and Rb\(^+\) complexes are formed than in the case of Na\(^+\) and Cs\(^+\) complexes. This allows us to consider the synthesized compound 4 as a potential chemosensor with K\(^+\) ion concentration determination in the presence of an excess of Na\(^+\) ions.

**CONCLUSIONS**

In summary, we have developed an alternative convenient method for obtaining benzils with crown ether moieties, which can be used as building blocks in the synthesis of ionophores and chemosensors without the use of expensive palladium catalysts and poisonous cyanides. Synthesized ICT fluorescent chemosensor 4 shows significantly greater fluorescent response at binding to the K\(^+\) and Rb\(^+\) cations than to the Na\(^+\) and Cs\(^+\). Further research on obtaining a series of quinoxaline-based chemosensors with various crown ether moieties and study of their complexation properties with alkali metal cations are currently underway in our laboratory.

**EXPERIMENTAL**

Solvents were purified using standard procedures before use. All other reagent-grade chemicals were used as received. Silica gel 60 F\(_{254}\) (Merck) plates were used for TLC. Silica gel 60 (0.063–0.100 mm, Merck) was used for column chromatography. The plates were examined by UV light or spots were visualized, if required, by I\(_2\) vapor. \(^1\)H NMR spectra were obtained on a Varian VXR-300 (300 MHz) spectrometer. \(^{13}\)C NMR spectra were obtained on a Varian Gemini-2000 (100 MHz) spectrometer. All chemical shifts are quoted in parts per million (ppm) on the δ scale with tetramethylsilane (TMS) or residual solvent as an internal standard. The coupling constants are expressed in hertz. The melting points were determined by the open capillary tube method and were uncorrected. Electron impact (EI) mass spectrometry was performed on an MKh-1321 mass spectrometer, direct inlet, 70 eV. Fast atom bombardment (FAB) mass spectrometry was performed on an VG 70-70EQ mass spectrometer, equipped with an argon primary atom beam, and an \(m\)-nitrobenzyl alcohol matrix was utilized. Elemental analysis was carried out on a EuroVector EA3000 CHNS elemental analyzer. Steady-state emission spectra were acquired on a Horiba Jobin Yvon IBH FluoroLog-3 (FL-3-22) spectrofluorimeter.

**General Procedure for the Synthesis of Bis(crown ether)benzils 3a–c**

The corresponding stilbenes 2a–c (20 mmol) were dissolved in DMSO (100 mL) at 100–120 °C. The resulting solution was cooled to 80 °C and aqueous 48% HBr (20 mL) was added in one portion. The reaction mixture was stirred at 115 °C for 1.5 h. Water (120 mL) was added to the warm reaction mixture and the resulting slurry was cooled to rt. The precipitate was filtered off, washed with water, and air dried. The crude product was purified by recrystallization from the appropriate solvent.

**Bis(12-crown-4)benzil (3a)**

Thin colorless needles: 6.53 g, 65% yield; mp 179.5–180.5 °C (from BuOH). \(^1\)H NMR (300 MHz, CDCl\(_3\)) δ 3.72–3.95 (m, 16 H), 4.19–4.30 (m, 8 H), 6.98 (d,
cooled mixture and the solution was successively washed with water 1.87 mmol. Column chromatography was performed, and the solvent was removed at reduced pressure. The residue was subjected to aqueous HCl.

The solvent was removed at reduced pressure and the residue was subjected to column chromatography (SiO₂, eluent: CHCl₃-MeOH, 10:1). The crude product was purified by recrystallization from a benzene/hexane mixture to give 4 as yellowish crystals: 0.99 g, 89% yield; mp 146–147.5 °C. ¹H NMR (300 MHz, CDCl₃) δ 3.65–3.98 (m, 24 H), 3.99–4.24 (m, 8 H), 6.80 (d, J = 8.4 Hz, 2 H), 7.02 (dd, J = 8.4, 1.6 Hz, 2 H). 13C NMR (75 MHz, CDCl₃) δ 68.8, 68.9, 69.4, 69.4, 70.3, 70.4, 71.0, 71.0, 115.4, 123.4, 128.8, 129.5, 131.9, 140.8, 148.7, 149.8, 152.8. MS (FAB, Ar, 8 kV) m/z 663 [M+H⁺]. Calcd. for C₃₆H₄₂N₂O₁₀ (662.73): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.01; H, 6.46; N, 4.33.

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**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

**REFERENCES**

1. (a) Xue, G.; Savage, P. B.; Bradshaw, J. S.; Zhang, X. X.; Izaat, R. M. In *Advances in Supramolecular Chemistry*; G. W. Gokel (Ed.); Elsevier Science: Stamford, 2001; vol. 7, pp. 99–138; (b) Ansyn, E. V. *J. Org. Chem.* 2007, 72, 687–699.
2. (a) Sahana, S.; Bharadwaj, P. K. *Inorg. Chim. Acta* 2014, 417, 109–141; (b) Callan, J. F.; de Silva, A. P.; Magria, D. C. *Tetrahedron* 2005, 61, 8551–8588.
3. (a) Patra, S.; Maity, D.; Gunupuru, R.; Agnihotri, P.; Paul, P. *J. Chem. Sci.* 2012, 124, 1287–1299; (b) Arora, V.; Chawla, H. M.; Singh, S. P. *Arkivoc* 2007, 2, 172–200; (c) Ludwig, R.; Dzung, N. T. K. *Sensors* 2002, 2, 397–416.
4. (a) Ast, S.; Schwarze, T.; Müller, H.; Sukhanov, A.; Michaelis, S.; Wegener, J.; Wolfbeis, O. S.; Körzdörfer, T.; Dürkop, A.; Holdt, H. *Chem. Eur. J.* 2013, 19, 14911–14917; (b) Xia, W.-S.; Schmehl, R. H.; Li, C.-J.; Mague, J. T.; Luo, C.-P.; Guldi, D. M. *J. Phys. Chem. B* 2002, 106, 833–843; (c) Sakamoto, H.; Yamamura, T.; Takumi, K.; Kimura, K. *J. Phys. Org. Chem.* 2007, 20, 900–907; (d) Sankaran, N. B.; Nishizawa, S.; Watanabe, M.; Uchida, T.; Teramae, N. *J. Mater. Chem.* 2005, 15, 2755–2761; (e) Zhang, G.-J.; Agarwal, A.; Buddhharaju, K. D.; Singh, N.; Gao, Z. *Appl. Phys. Lett.* 2007, 90, 233903.
5. (a) Cao, J.; Jiang, Y.; Zhao, J.-M.; Chen, C.-F. *Chem. Commun.* 2009, 1987–1989; (b) Bogaschenko, T. Yu.; Lyapunov, A. Yu.; Kikot, L. S.; Mazepa, A. V.; Botoshansky, M. M.; Fonari, M. S.; Kirichenko, T. I. *Tetrahedron* 2012, 68, 4757–4764; (c) Kikot, L. S.; Lyapunov, A. Yu.; Kulygina, C. Yu.; Bogaschenko, T. Yu.; Zubatyuk, R. I.; Shishkin, O. V.; Kirichenko, T. I. *Incl. Phenom. Macrocycl. Chem.* 2014, 79, 343–348; (d) Fery-Forgues, S.; Al-Ali, F. *J. Photochem. Photobiol. C* 2004, 5, 139–153; (e) Shao, M.; Dongare, P.; Dawe, L. N.; Thompson, D. W.; Zhao, Y. *Org. Lett.* 2010, 12, 3050–3053; (f) Takeshita, M.; Irie, M. *J. Org. Chem.* 1998, 63, 6643–6649.

6. (a) Basu, B.; Das, S.; Das, P.; Nanda, A. K. *Tetrahedron Lett.* 2005, 46, 8591–8593; (b) Naimi-Jamal, M. R.; Mokhtari, J.; Dekamin, M. G.; Kaupp, G. *Eur. J. Org. Chem.* 2009, 3567–3572; (c) Cooksey, J. P.; Kocieński, P. J.; Schmidt, A. W.; Snaddon, T. N.; Kilner, C. A. *Synthesis* 2012, 44, 2779–2785; (d) Hu, P.; Wang, Q.; Yan, Y.; Zhang, S.; Zhang, B.; Wang, Z. *Org. Biomol. Chem.* 2013, 11, 4304–4307; (e) Kumbhar, A.; Kamble, S.; Barge, M.; Rashinkar, G.; Salunkhe, R. *Tetrahedron Lett.* 2012, 53, 2756–2760; (f) Sivakumar, K.; Kathirvel, A.; Lalitha, A. *Tetrahedron Lett.* 2010, 51, 3018–3021; (g) Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* 2000, 122, 12663–12674.

7. (a) Yuan, L.; Tian, B.; Huang, S. *Makromol. Chem.* 1993, 194, 1847–1862; (b) Kimura, M.; Shi, K.; Hashimoto, K.; Hu, Z. Z. *Heterocycles* 2006, 68, 2375–2380.

8. (a) Mohr, B.; Enkelmann, V.; Wegner, G. *J. Org. Chem.* 1994, 59, 635–638; (b) Kashiwabara, T.; Tanaka, M. *J. Org. Chem.* 2009, 74, 3958–3961; (c) Huang, L.; Cheng, K.; Yao, B.; Xie, Y.; Zhang, Y. *J. Org. Chem.* 2011, 76, 5732–5737; (d) Stergiou, A.; Bariotaki, A.; Kalaitzakis, D.; Smonou, I. *J. Org. Chem.* 2013, 78, 7268–7273; (e) Chen, S.; Liu, Z.; Shi, E.; Chen, L.; Wei, W.; Li, H.; Cheng, Y.; Wan, X. *Org. Lett.* 2011, 13, 2274–2277; (f) Moussset, C.; Provot, O.; Hamze, A.; Bignon, J.; Brion, J.-D.; Alami, M. *Tetrahedron* 2008, 64, 4287–4294.

9. Vedernikov, A. I.; Basok, S. S.; Gromov, S. P.; Kuz’mina, L. G.; Avakyan, V. G.; Lobova, N. A.; Kulygina, E. Yu.; Titkov, T. V.; Strelenko, Yu. A.; Ivanov, E. I.; Howard, J. A. K.; Alfimov, M. V. *Russ. J. Org. Chem.* 2005, 41, 843–854.

10. Gunbas, G. E.; Durmus, A.; Toppare, L. *Adv. Funct. Mater.* 2008, 18, 2026–2030.

11. (a) Fedorov, Yu. V.; Fedorova, O. A.; Andryukhina, E. N.; Gromov, S. P.; Alfimov, M. V.; Kuzmina, L. G.; Churakov, A. V.; Howard, J. A. K.; Aaron, J.-J. *New J. Chem.* 2003, 27, 280–288; (b) Panchenko, P. A.; Fedorov, Y. V.; Fedorova, O. A.; Jonusauskas, G. *Dyes Pigm.* 2013, 98, 347–357.