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Synthesis of a New Class of C_2-Symmetrical Biheteroaryls by Ammonium Cerium(IV) Nitrate Mediated Dimerization of 2-(Furan-3-yl)pyrroles

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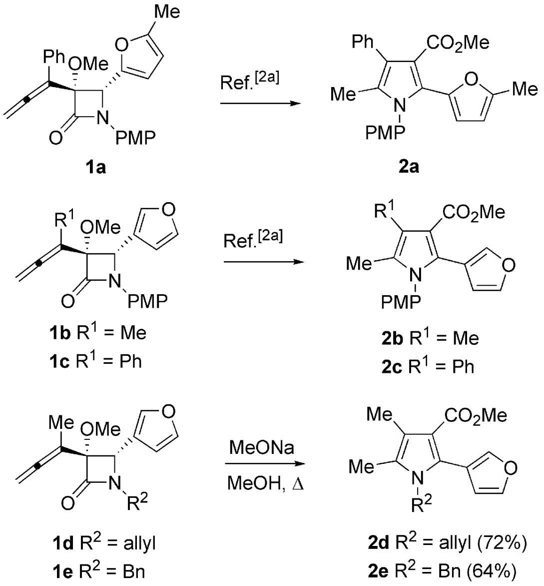
Polyfunctionalized 2-(furan-2-yl)pyrroles and 2-(furan-3-yl)pyrroles derived from 2-azetidinone-tethered allenes by two independent cerium(IV)-mediated single-electron oxidations provided a (4-oxopent-2-enoyl)pyrrole and 3,3′-bis(pyrrol-2-yl)-2,2′-bifurans, respectively. Access to the oxidation precursors was achieved by regiocontrolled cyclization of β-allenamine intermediates derived from selective β-lactam nucleus breakage of 2-azetidinone-tethered allenols.

Introduction

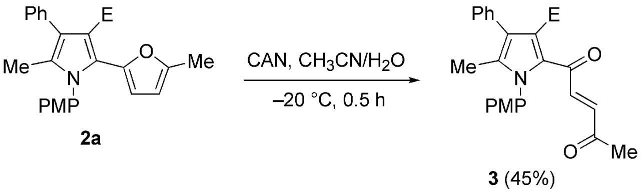
Cerium is a member of the lanthanides, whose electronic configuration facilitates that it can exist in both tri- and tetrapositive states. The strong oxidising power of the cerium(IV) ion has been recognised for many years, being of valuable synthetic utility for organic chemists.[1] We wish to report herein the use of CAN as an efficient and selective reagent for generating molecular diversity from furanylpyrroles.

Results and Discussion

We have recently reported a novel regiocontrolled preparation of functionalized *N*-substituted pyrroles **2** from 2-azetidinone-tethered allenes **1** (Scheme 1).[2] To strengthen the synthetic utility of this methodology, procedures for the effective removal of the *N*-protecting groups in the pyrrole core were then surveyed. In an attempt to perform the CAN-promoted oxidative cleavage of the *N*-(4-methoxyphenyl) substituent in 2-(5-methylfuran-2-yl)pyrrole (**2a**), surprisingly, we found that the pyrrole-based 1,4-dicarbonyl compound **3** was isolated as the sole product (Scheme 2).[3]



Scheme 1. Preparation of pyrroles **2** from allenic β-lactams **1**. PMP = 4-$MeOC_6H_4$.



Scheme 2. CAN-mediated reaction of (furan-2-yl)pyrrole **2a**. Synthesis of α,β-unsaturated 1,4-diketone **3**. E = CO_2Me; PMP = 4-$MeOC_6H_4$; CAN = ammonium cerium(IV) nitrate.

To our delight, in contrast to the 2-(furan-2-yl)pyrrole **2a**, the 2-(furan-3-yl)pyrrole **2b** does not undergo oxidative cleavage of the furan ring under CAN exposure, but the

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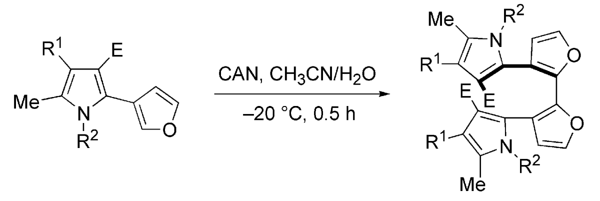
product obtained was the C_2-symmetrical 3,3′-bis(pyrrol-2-yl)-2,2′-bifuran **4a** (Scheme 3), probably through the formation of a C–C bond by the coupling of two aromatic units.[4,5] The structure of biheteroaryl **4a** was established by X-ray crystallography (Figure 1).[6] Similar behaviour was observed for phenyl derivative **2c**, which is readily amenable for the CAN-promoted conversion to 3,3′-bis(pyrrol-2-yl)-2,2′-bifuran **4b**, as depicted in Scheme 3. Although no precedent could be found for this reactivity in the literature, further investigation of its potential scope was of interest. As a result, *N*-allyl- and *N*-benzyl-substituted pyrroles **2d** and **2e** were treated with CAN under the same conditions as *N*-PMP-substituted pyrroles. Again, the reaction yielded only one product, namely, the homodimers **4c** and **4d** (Scheme 3). Thus, for the first time the controlled dimerization reaction of furanylpyrrole derivatives can be achieved, eliminating the need to prepare halogen or metal derivatives of the aryl fragments prior to their actual union.



2b R^1 = Me, R^2 = PMP
2c R^1 = Ph, R^2 = PMP
2d R^1 = Me, R^2 = allyl
2e R^1 = Me, R^2 = Bn

4a R^1 = Me, R^2 = PMP (54%)
4b R^1 = Ph, R^2 = PMP (60%)
4c R^1 = Me, R^2 = allyl (63%)
4d R^1 = Me, R^2 = Bn (50%)

Scheme 3. CAN-mediated reactions of (furan-3-yl)pyrroles **2b**–**e**. Synthesis of 3,3′-bis(pyrrol-2-yl)-2,2′-bifurans **4a**–**d**. E = CO_2Me; PMP = 4-$MeOC_6H_4$; CAN = ammonium cerium(IV) nitrate.

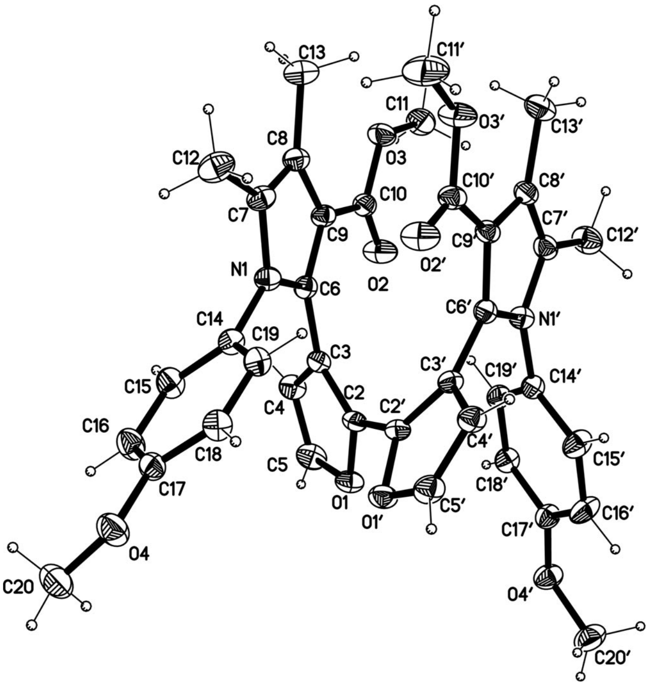
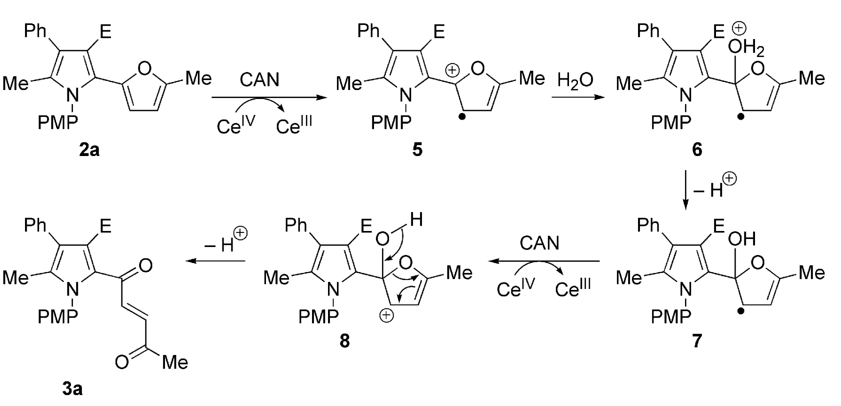


Figure 1. X-ray diffraction analysis of bis(pyrrol-2-yl)-2,2′-bifuran **4a**.

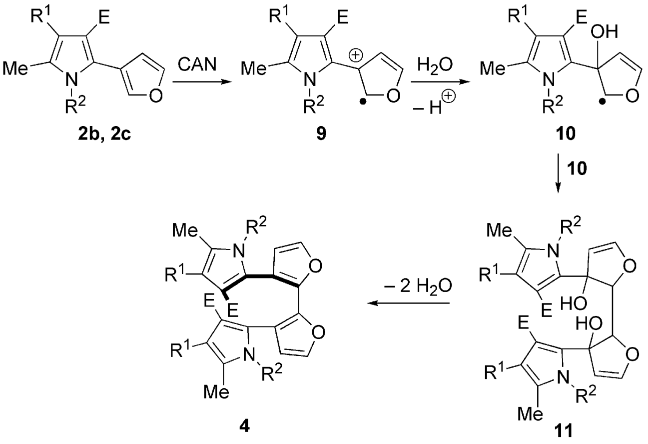
The following mechanism for the formation of pyrrole-based α,β-unsaturated γ-ketone **3a** was considered (Scheme 4). The reaction begins with the electron transfer from 2-(5-methylfuran-2-yl)pyrrole **2a** to Ce^{IV} to generate the radical cation **5**. The cationic center of **5** is trapped by water to afford species **6**, which after proton elimination gave radical **7**. One-electron oxidation of radical **7** followed by rearrangement of intermediate **8** into 1,4-dicarbonyl compound **3a** complete the proposal. Arguably, formation of the stable allyl-like carbocation is the major driving force for this oxidative cleavage.

A possible pathway for the oxidative dimerization of 2-(furan-3-yl)pyrroles may initially involve the CAN-mediated formation of the radical cation **9**. Next, addition of water followed by proton elimination should afford radical **10**, which dimerizes to intermediate **11**. Double dehydration of bis(dihydrofuran) **11** may be the final step for the achievement of 3,3′-bis(pyrrol-2-yl)-2,2′-bifurans **4** (Scheme 5).[7] The success of the reaction rests on the dimerization of radical **10** in opposition to abstraction of hydrogen, probably due to the higher stability of the radical because of the proximal oxygen atom. The presence of the



Scheme 4. Mechanistic explanation for the CAN-mediated preparation of pyrrole-based α,β-unsaturated 1,4-diketone **3a**. E = CO_2Me.

methoxycarbonyl group is probably necessary; otherwise the radical cation should have charge and spin mainly localized on the pyrrole ring.



Scheme 5. Mechanistic explanation for the CAN-mediated preparation of 3,3′-bis(pyrrol-2-yl)-2,2′-bifurans **4**. E = CO_2Me.

Conclusions

Using a simple reagent we have successfully accomplished two mild cerium(IV)-mediated single-electron oxidations of polyfunctionalized 2-(furan-2-yl)pyrroles and 2-(furan-3-yl)pyrroles to form a pyrrole-based 1,4-dicarbonyl compound and a new class of C_2-symmetrical biheteroaryls, namely 3,3′-bis(pyrrol-2-yl)-2,2′-bifurans, respectively.

Experimental Section

General Procedure for the CAN-Mediated Homodimerization of (Furan-3-yl)pyrroles 2b–e. Preparation of 3,3′-Bis(pyrrol-2-yl)-2,2′-bifurans 4a–d: A solution of CAN (171 mg, 0.313 mmol) in water (2 mL) was slowly added to a stirred solution of the appropriate (furan-3-yl)pyrrole **2** (0.136 mmol) in acetonitrile (2 mL) at –20 °C. The reaction mixture was stirred at –20 °C for 0.5 h. Aqueous (10%) sodium sulfite (1.0 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with brine, water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue using ethyl acetate/hexanes mixtures gave analytically pure compounds **4**.

Supporting Information (see also the footnote on the first page of this article): Compound characterization data and experimental procedures as well as copies of NMR spectra for all new compounds.

Acknowledgments

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[1] The most extensively used cerium(IV) reagent in organic chemistry is ammonium cerium(IV) nitrate (CAN). For reviews on the use of CAN as a versatile single-electron oxidant, see: a) V. Nair, A. Deepthi, *Tetrahedron* **2009**, *65*, 10745; b) V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862; for selected examples on CAN-promoted oxidative dimerization and oxidative arylation, see: c) C. Xi, Y. Jiang, X. Yang, *Tetrahedron Lett.* **2005**, *46*, 3909; d) J. C. Conrad, J. Kong, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640.

[2] a) B. Alcaide, P. Almendros, R. Carrascosa, M. C. Redondo, *Chem. Eur. J.* **2008**, *14*, 637; b) B. Alcaide, P. Almendros, M. C. Redondo, *Chem. Commun.* **2006**, 2616.

[3] For a report available in the literature on the DDQ-mediated oxidative cleavage of 3-alkoxy-2,5-dihydrofurans to afford α,β-unsaturated γ-oxo aldehydes, see: a) M. Brasholz, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2007**, *46*, 1634; *Angew. Chem.* **2007**, *119*, 1659; for a report available in the literature on the CAN-mediated oxidative cleavage of a 3-ethoxycarbonyl-2-methylfuran to afford an oct-2-enoate, see: b) A. J. Moreno-Vargas, I. Robina, J. Fernández-Bolaños, J. Fuentes, *Tetrahedron Lett.* **1998**, *39*, 9271.

[4] Furans and pyrroles constitute an important structural component in pharmaceuticals and natural products, being some of the best-selling drug heterocycles of these types. For atorvastatin (a pyrrole used to control high cholesterol), see: a) M. E. M. Noble, J. A. Endicott, L. N. Johnson, *Science* **2004**, *303*, 1800; b) J. C. Reed, M. Pellecchia, *Blood* **2005**, *106*, 408; c) A. P. Lea, D. Mctavish, *Drugs* **1997**, *53*, 828; for ranitidine (a furan used to treat stomach ulcers), see: d) J. A. Joule, K. Mills, *Heterocyclic Chemistry*, 4th ed., Blackwell Science Ltd., Malden, MA, **2000**; in particular, bipyrroles are natural products belonging to the prodigiosins, and they are also capable of inducing apoptosis in human cancer cells, see: e) H. Rapoport, K. G. Holden, *J. Am. Chem. Soc.* **1962**, *84*, 635; f) B. Montaner, R. Pérez-Tomás, *Life Sci.* **2001**, *68*, 2025; on the other hand, bifurans are key motifs in natural products, such as licorice, present in foods and beverages, see: g) C. Frattini, C. Bicchi, C. Barettini, G. M. Nano, *J. Agric. Food Chem.* **1977**, *25*, 1238.

[5] Biaryls, important constituents of natural products and of pharmaceutical agents, have been recently recognized as a core functional group in organic molecular materials, and have received attention due to the use of axially chiral biaryls as ligands in asymmetric reactions; for selected reviews, see: a) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; b) J. Hagen, *Industrial Catalysis*, Wiley-VCH, Weinheim, 2nd ed., **2006**, pp. 59–80; c) A. O. King, N. Yasuda, in *Organometallics in Process Chemistry* (Ed.: R. D. Larsen), Springer-Verlag, Berlin, Heidelberg, **2004**, pp. 205–245; d) R. Noyori, *Chem. Soc. Rev.* **1989**, *18*, 187; e) K. Narasaka, *Synthesis* **1991**, 1.

[6] X-ray data of **4a**: crystallized from ethyl acetate/*n*-hexane at 20 °C. $C_{38}H_{36}N_2O_8$ (M_r = 648.69); monoclinic; space group $P2_1/c$; a = 17.0807(9), b = 10.4055(5); c = 19.0427(9) Å; β = 100.6450(10)°; V = 3326.3(3) Å^3; Z = 4; $d_{calcd.}$ = 1.295 mg m^{-3}; μ = 0.091 mm^{-1}; $F(000)$ = 1368. A transparent crystal of $0.45 \times 0.14 \times 0.08$ mm was used. 5630 [R(int) = 0.0550] independent reflections were collected with a Bruker Smart CCD difractomer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. Data were collected over a hemisphere of the reciprocal space by combination of three exposure sets. Each exposure of 20 s covered 0.3° in ω. The cell parameters were determined and refined by a least-squares fit of all reflections. The first 100 frames were recollected at the end of the data collection to monitor crystal decay, and no appreciable decay was observed. The structure was solved by direct methods and Fourier synthesis. It was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All

hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final *R*(*Rw*) values were *R*1 = 0.0394 and *wR*2 = 0.0941. CCDC-675795 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[7] A referee suggested an analogous mechanistic pathway involving the oxidation of the pyrrole segment first. Thus, an oxidation of the pyrrole nucleus and a delocalization of the charge into the furan moiety could be envisaged and would explain the selectivity observed and the difference of behavior between 2-furan (**2a**) and 3-furan (**2b**–**e**) compounds under such conditions. However, we think that both the presence of the ester group as well as the relatively low ionization potentials of the furan ring will undergo electron transfer particularly easily into the oxygenated heterocycle.

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