Synthetic Methods

DOI: 10.1002/anie.201202850

Straightforward Acid-Catalyzed Synthesis of Pyrrolyldipyrromethenes**

Changjiang Yu, Lijuan Jiao, Xujun Tan, Jun Wang, Yajun Xu, Yangchun Wu, Gaosheng Yang, Zhaoyun Wang, and Erhong Hao**

Conjugated oligopyrroles are the core component of many natural products including porphyrins, expanded porphyrins, streptorubin B, tambjamines, and prodigiosins (Figure 1). They have found wide applications in organic synthesis, medicinal chemistry, material science, supramolecular chemistry, and nanotechnology[1] as anion binding and cation coordination reagents,[1b,2] and photosensitizers,[1f] as well as key synthetic precursors for the construction of conducting polymers,[3] liquid crystals,[4] and nonlinear optical devices.[5] Among these, pyrrolyldipyrromethenes, wherein each of the pyrrole units is either covalently linked at the 2,2′-positions or through a methylene bridge, serves as the core structure of prodigiosins and analogues and have received special attention because of the wide range of interesting biological activities associated with these structures.[6–8]

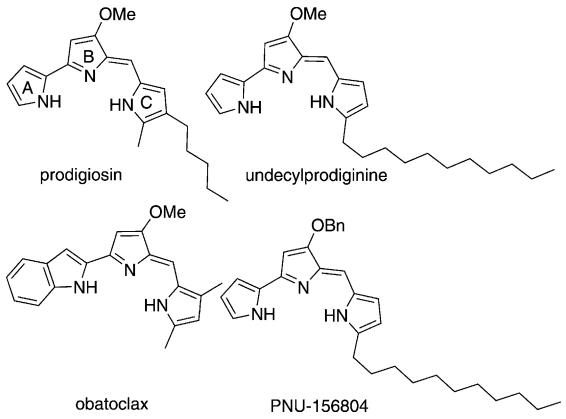


Figure 1. Naturally occurring pyrrolyldipyrromethenes (prodigiosin and undecylprodiginine) and their corresponding synthetic analogues (Obatoclax and PNU-156804).

Currently, only limited methods are available for the construction of 2,2′-linked oligopyrroles, including the Vilsmeier condensation,[9] Paal–Knorr cyclization,[10] oxidative coupling of α-unsubstituted pyrroles,[11] Ullmann coupling,[12] and other metal-mediated coupling reactions.[13] Among these, few strategies are applicable for the construction of pyrrolyldipyrromethenes in which the key synthetic step is also the construction of the 2,2′-bipyrrole unit, that is, the direct covalent bond between the pyrrole unit A and azafulvene unit B (Figure 1). The available synthetic methods[1c,14–18] for pyrrolyldipyrromethenes, although elegant, involve multiple steps, often require the use of expensive catalysts, and suffer from limited diversity of bipyrrole units. Such diversity is desirable for studying the structure–activity relationships of these pyrrole alkaloids. For example, the derivation of the C-ring alkyl substituents of prodigiosin or undecylprodiginine to produce Obatoclax and PNU-156804 (Figure 1) has improved the therapeutic potential of their natural analogues.[19,20]

Herein we report a straightforward $POCl_3$-promoted synthesis of pyrrolyldipyrromethenes in good yields from the condensation of 5-halogenated-2-formylpyrrole derivatives or analogues thereof (isoindoles) with suitable pyrrole (or indole) fragments through a novel nucleophilic aromatic substitution (S_NAr) of the protonated azafulvene rings. Our synthesis features the use of a common acid catalyst to generate the target pyrrolyldipyrromethenes within two steps, and is also diversity oriented.

Initially, the reaction was performed by condensing 5-chloro-2-formylisoindole (**2a**) with excess amounts of pyrrole in the presence of $POCl_3$ in dichloromethane at room temperature under argon (Scheme 1), and the desired pyrroledipyrromethene **1a** was smoothly generated as the major product in 61% yield. Subsequently, our synthetic strategy was extended to the condensation of **2a** with a set of alkyl-substituted pyrroles, from which the corresponding pyrrolyldipyrromethenes **1b–d** were obtained in 57–75% yields upon isolation. Among these, the use of 3-acetyl-2,4-dimethyl pyrrole, possessing an electron-withdrawing acetyl group, for the reaction led to the lowest yield (**1d**).

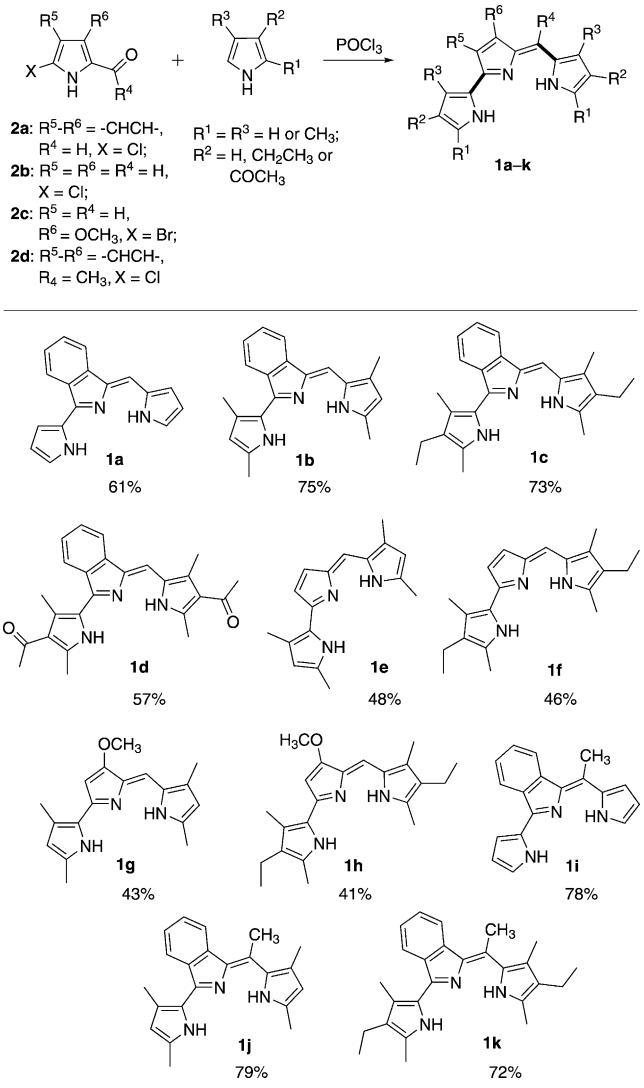
By contrast, 5-chloro-2-formylpyrrole (**2b**) and 5-bromo-2-formyl-3-methoxylpyrrole (**2c**) slowly condensed with pyrroles under the above reaction conditions. By replacing dichloromethane with 1,2-dichloroethane under refluxing conditions, we were still able to obtain the desired pyrrolyldipyrromethenes **1e–h** in 41–48% yields upon isolation.

To demonstrate the versatility of our one-pot synthesis of pyrrolyldipyrromethenes **1** and to introduce functionality onto the methene bridge in the pyrroledipyrromethene chromophore, we used 5-chloro-2-acetylisoindole (**2d**), an

[*] C. Yu, Prof. Dr. L. Jiao, X. Tan, J. Wang, Y. Xu, Y. Wu, Prof. Dr. G. Yang, Z. Wang, Prof. Dr. E. Hao
Laboratory of Functional Molecular Solids, Ministry of Education
Anhui Laboratory of Molecule-Based Materials
School of Chemistry and Materials Science
Anhui Normal University, Wuhu, 241000 (China)
E-mail: jiao421@mail.ahnu.edu.cn
haoehong@mail.ahnu.edu.cn

[**] This work is supported by the National Nature Science Foundation of China (Grants 20802002, 20902004 and 21072005), Anhui Province (Grants 090416221 and KJ2009A130), and the Ministry of Education of China (Grant 20093424120001).

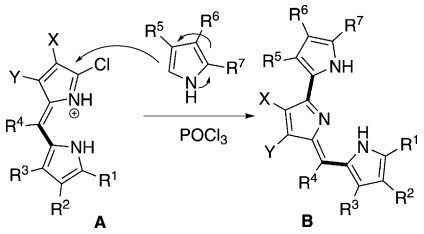
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202850.



Scheme 1. $POCl_3$-promoted one-pot syntheses of pyrrolyldipyrromethenes **1a–k.** Reaction conditions for **1a–d** and **1i–k**: dichloromethane, room temperature, 2 h. Reaction conditions for **1e–f** and **1g–h**: 1,2-dichloroethane, refluxing, 7–8 h.

isoindole ketone, for the condensation. Interestingly, a high reactivity was observed for **2d** as compared to that of **2a**: the condensation can be performed at room temperature, and the desired pyrrolyldipyrromethenes **1i–k** were obtained in 72–79% yields upon isolation.

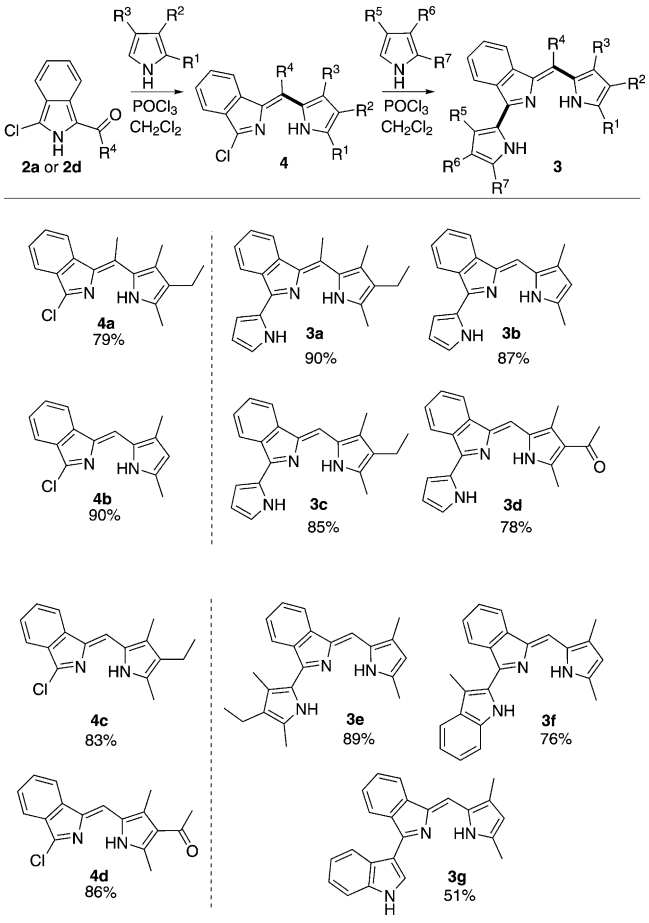
This interesting one-pot formation of pyrrolyldipyrromethenes prompted us to study the possible mechanism for this reaction. The acid-catalyzed condensation of a 2-formylpyrrole with an α-unsubstituted pyrrole is known to form dipyrromethenes in a salt form[21] before subsequent work-up with base. Since their initial synthesis, by Hans Fischer in 1934, dipyrromethenes as dipyrrinato ligands have been widely studied and continually attract interest because of their synthetic utility as porphyrin precursors and their rich photophysical properties.[22] In our case, the acid-catalyzed condensation of 5-halo-2-formylpyrroles (or isoindoles) with an α-unsubstituted pyrrole generated the 9-halodipyrromethene **A** in salt form (Scheme 2). Subsequently, the proton-



Scheme 2. Proposed mechanism for the formation of pyrrolyldipyrromethenes under $POCl_3$-promoted condensation conditions.

ated azafulvene unit in this in situ generated **A** could participate in an unexpected S_NAr reaction with a suitable α-unsubstituted pyrrole to form the pyrroledipyrromethene **B**. Therefore, the isolation of this intermediate **A** would provide opportunities for the construction of unsymmetrical pyrrolyldipyrromethenes in a two-step fashion.

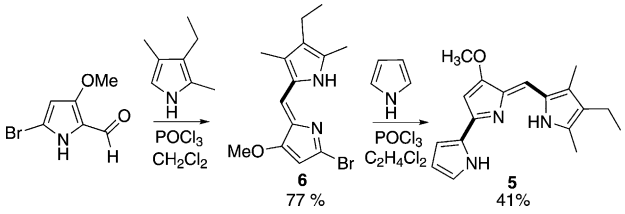
To test our hypothesis, 9-chlorodipyrromethene (**4a**) was prepared in 79% yield, using a modified literature procedure,[23] from the acid-catalyzed condensation of equal equivalents of 5-chloro-2-acetylisoindole (**2d**) with 3-ethyl-2,4-dimethylpyrrole, and was applied for the subsequent condensation with pyrrole (Scheme 3). The pyrroledipyrromethene **3a** was smoothly generated in 90% yield upon isolation.



Scheme 3. Syntheses of 9-chlorodipyrromethenes **4a–d** and pyrrolyldipyrromethenes **3a–g**.

As shown in Scheme 3, condensation of the 9-chlorodipyrromethenes **4b–d** with pyrrole and various substituted pyrroles at room temperature efficiently generated the corresponding pyrrolyldipyrromethenes **3b–e** in 76–90% yields upon isolation. Interestingly, indole derivatives also showed good reactivities in this reaction and gave **3f** and **3g** in 76 and 51% yields, respectively.

Most natural prodigiosin analogues have a B-ring 3-methoxy group in their structure, and it is closely associated with their many biological activities. To further study the versatility of our synthetic method and to investigate its possible applicability for the preparation of certain natural prodigiosin analogues, the pyrrolyldipyrromethene **5** was synthesized in 41% yield from the reaction of pyrrole with dipyrromethene **6**, which was generated from the reaction of 5-bromo-2-formyl-3-methoxylpyrrole (**2c**) with 2,4-dimethyl-3-ethylpyrrole by adopting a modified literature procedure[23] (Scheme 4).



Scheme 4. Syntheses of the B-ring methoxy pyrrolyldipyrromethene **5**.

The single-crystal X-ray structures of **1g** and **3d** are shown in Figures 2 and 3, respectively. The pyrroledipyrromethene framework of these two compounds are extremely flat with only the methyl, methoxy, and acetyl groups lying out of the plane of these pyrrolyldipyrromethene cores. In both cases, the azafulvene ring is clearly identifiable as the B ring and the three nitrogen atoms of the rings are all oriented in the same direction on the same side of the chormophore. All three NH

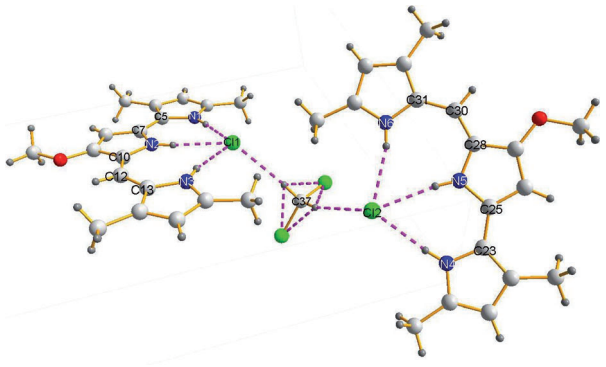


Figure 2. X-Ray structure of the **1g**·HCl dimer. Selected bond lengths [Å]: N1H–Cl1 2.30, N2H–Cl1 2.36, N3H–Cl1 2.33, N4H–Cl2 2.33, N5H–Cl2 2.38, N6H–Cl2 2.35. Selected torsional angles [°]: N1-C5-C7-N2 2.3, N2-C10-C13-N3 1.5, N4-C23-C25-N5 0.8, N5-C28-C31-N6 2.5. C grey, N blue, O red, Cl green. For details of the X-ray analysis results, including the CCDC number, see the Supporting Information.[25]

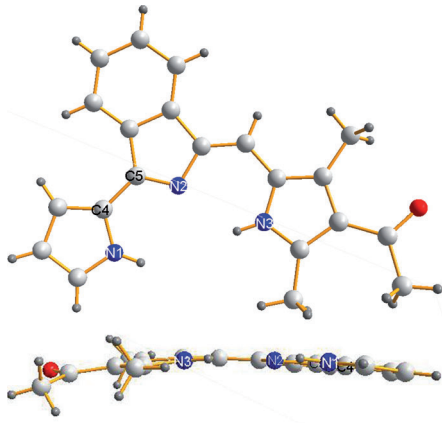


Figure 3. X-Ray structure of **3d**. Selected torsional angle [°]: N1-C4-C5-N2, −3.2. C grey, N blue, O red. For details of the X-ray analysis results, including the CCDC number, see the Supporting Information.[25]

hydrogen atoms of prodiginine **1g**·HCl are oriented towards the chloride counterion to form hydrogen-bonding interactions, and the NH···Cl distances are almost equal.

Beyond these hydrogen-bonding interactions, the chloride ion is hydrogen bonded to a methylene chloride molecule in the crystal lattice. The compound was crystallized from methylene chloride and in the absence of any other hydrogen-bonding partner, thus **1g**·HCl forms a dimer of two molecules in the asymmetric unit held together by a network of intermolecular hydrogen bonds to methylene chloride molecule in the crystal lattice. It bridges two such chlorides and helps the formation of a dimer structure in the lattice. Such a CH–Cl interaction is similar to those OH–Cl interactions reported in the literature.[24]

We have developed a new synthetic strategy for the facile preparation of a series of pyrrolyldipyrromethenes, and it features the usage of $POCl_3$ as promoter to generate the desired pyrrolyldipyrromethenes in good to excellent yields within two steps and is diversity oriented. Our methodology may provide an efficient way for the facile synthesis of 2,2′-bipyrroles and oligopyrroles. Additional investigations of their anticancer efficiency, their synthetic applications in building macrocyles, and the photophysical properties of their metal complexes are underway.

Received: April 13, 2012
Published online: ■■ ■■, ■■■■

Keywords: aromatic substitution · dyes/pigments · homogeneous catalysis · nitrogen heterocycles · synthetic methods

[1] a) S. Saito, A. Osuka, *Angew. Chem.* **2011**, *123*, 4432; *Angew. Chem. Int. Ed.* **2011**, *50*, 4342; b) B. M. Rambo, J. L. Sessler, *Chem. Eur. J.* **2011**, *17*, 4946; c) A. Fürstner, *Angew. Chem.* **2003**, *115*, 3706; *Angew. Chem. Int. Ed.* **2003**, *42*, 3582; d) M. O. Senge, *Angew. Chem.* **2011**, *123*, 4360; *Angew. Chem. Int. Ed.* **2011**, *50*, 4272; e) M. O. Senge, J. C. Brandt, *Photochem. Photobiol.* **2011**, *87*, 1240.

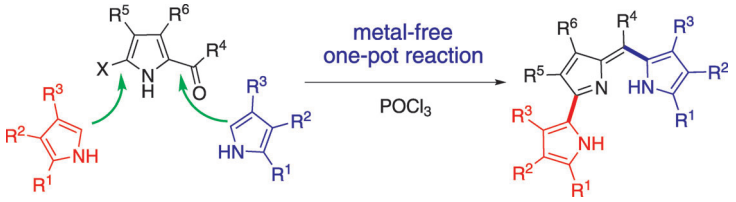
[2] a) P. A. Gale, *Acc. Chem. Res.* **2011**, *44*, 216; b) P. Plitt, D. E. Gross, V. M. Lynch, J. L. Sessler, *Chem. Eur. J.* **2007**, *13*, 1374.
[3] J. M. Nadeau, T. M. Swager, *Tetrahedron* **2004**, *60*, 7141.
[4] M. Stępień, B. Donnio, J. L. Sessler, *Angew. Chem.* **2007**, *119*, 1453; *Angew. Chem. Int. Ed.* **2007**, *46*, 1431.
[5] Z. S. Yoon, J. H. Kwon, M. H. Yoon, M. K. Koh, S. B. Noh, J. L. Sessler, J. T. Lee, D. A. Seidel, A. Aguilar, S. Shimizu, M. Suzuki, A. Osuka, D. Kim, *J. Am. Chem. Soc.* **2006**, *128*, 14128.
[6] M. S. Melvin, J. T. Tomlinson, G. R. Saluta, G. L. Kucera, N. Lindquist, R. A. Manderville, *J. Am. Chem. Soc.* **2000**, *122*, 6333.
[7] a) J. T. Davis, P. A. Gale, O. A. Okunola, P. Prados, J. C. Iglesias-Sanchez, T. Torroba, R. Quesada, *Nat. Chem.* **2009**, *1*, 138; b) P. A. Gale, M. E. Light, B. McNally, K. Navakhun, K. E. Sliwinski, B. D. Smith, *Chem. Commun.* **2005**, 3773.
[8] a) A. Fürstner, J. Grabowski, C. W. Lehmann, T. Kataoka, K. Nagai, *ChemBioChem* **2001**, *2*, 60; b) J. L. Sessler, L. R. Eller, W. S. Cho, S. Nicolaou, A. Aguilar, J. T. Lee, V. M. Lynch, D. J. Magda, *Angew. Chem.* **2005**, *117*, 6143; *Angew. Chem. Int. Ed.* **2005**, *44*, 5989; c) J. Regourd, A. Ali, A. Thompson, *J. Med. Chem.* **2007**, *50*, 1528; d) K. Papireddy, M. Smilkstein, J. X. Kelly, Shweta, S. M. Salem, M. Alhamadsheh, S. W. Haynes, G. L. Challis, K. A. Reynolds, *J. Med. Chem.* **2011**, *54*, 5296.
[9] J. Bordner, H. Rapoport, *J. Org. Chem.* **1965**, *30*, 3824.
[10] a) B. A. Merrill, E. LeGoff, *J. Org. Chem.* **1990**, *55*, 2904; b) J. L. Sessler, S. J. Weghorn, Y. Hiseada, V. Lynch, *Chem. Eur. J.* **1995**, *1*, 56; c) B. Jolicoeur, W. Lubell, *Org. Lett.* **2006**, *8*, 6107.
[11] a) J. L. Sessler, A. Aguilar, D. Sanchez-Garcia, D. Seidel, T. Kohler, F. Arp, V. M. Lynch, *Org. Lett.* **2005**, *7*, 1887; b) T. Dohi, K. Morimoto, A. Maruyama, Y. Kita, *Org. Lett.* **2006**, *8*, 2007; c) M. Zhang, E. Hao, J. Zhou, C. Yu, G. Bai, F. Wang, L. Jiao, *Org. Biomol. Chem.* **2012**, *10*, 2139.
[12] a) H. Ikeda, J. L. Sessler, *J. Org. Chem.* **1993**, *58*, 2340; b) A. Merz, S. Anikin, B. Lieser, J. Heinze, H. John, *Chem. Eur. J.* **2003**, *9*, 449.
[13] a) M. Yu, D. Pantos, J. L. Sessler, B. L. Pagenkopf, *Org. Lett.* **2004**, *6*, 1057; b) A. López-Pérez, R. Robles-Machín, J. Adrio, J. C. Carretero, *Angew. Chem.* **2007**, *119*, 9421; *Angew. Chem. Int. Ed.* **2007**, *46*, 9261; c) D. Sánchez-García, J. I. Borrell, S. Nonell, *Org. Lett.* **2009**, *11*, 77.
[14] a) H. Rapoport, K. G. Holden, *J. Am. Chem. Soc.* **1962**, *84*, 635; b) D. L. Boger, M. Patel, *J. Org. Chem.* **1988**, *53*, 1405; c) H. H. Wasserman, L. J. Lombardo, *Tetrahedron Lett.* **1989**, *30*, 1725; d) H. H. Wasserman, A. K. Peterson, M. Xia, J. Wang, *Tetrahedron Lett.* **1999**, *40*, 7587; e) A. Fürstner, H. Krause, *J. Org. Chem.* **1999**, *64*, 8281; f) R. D'Alessio, A. Rossi, *Synlett* **1996**, 513; g) K. Dairi, S. Tripathy, G. Attardo, J. Lavalle, *Tetrahedron Lett.* **2006**, *47*, 2605; h) M. I. Uddin, S. Thirumalairajan, S. M. Crawford, T. S. Cameron, A. Thompson, *Synlett* **2010**, 2561.
[15] a) S. R. Chawrai, N. R. Williamson, T. Mahandiran, G. P. C. Salmond, F. J. Leeper, *Chem. Sci.* **2012**, *3*, 447; b) P. K. Sydor, S. M. Barry, O. M. Odulate, F. Barona-Gomez, S. W. Haynes, C. Corre, L. Song, G. L. Challis, *Nat. Chem.* **2011**, *3*, 388.
[16] a) D. X. Hu, M. D. Clift, K. E. Lazarski, R. J. Thomson, *J. Am. Chem. Soc.* **2011**, *133*, 1799; b) S. W. Haynes, P. K. Sydor, C. Corre, L. Song, G. L. Challis, *J. Am. Chem. Soc.* **2011**, *133*, 1793; c) M. D. Clift, R. J. Thomson, *J. Am. Chem. Soc.* **2009**, *131*, 14579; d) A. Fürstner, K. Radkowski, H. Peters, G. Seidel, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 1929; e) J. T. Reeves, *Org. Lett.* **2007**, *9*, 1879; f) L. N. Aldrich, E. S. Dawson, C. W. Lindsley, *Org. Lett.* **2010**, *12*, 1048.
[17] a) X. Cai, X. Wu, B. B. Snider, *Org. Lett.* **2010**, *12*, 1600; b) S. G. Salamone, G. B. Dudley, *Org. Lett.* **2005**, *7*, 4443.
[18] D. M. Pinkerton, M. G. Banwell, A. C. Willis, *Org. Lett.* **2007**, *9*, 5127.
[19] a) M. Nguyen, R. C. Marcellus, A. Roulston, M. Watson, L. Serfass, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 19512; b) B. Díaz de Greñu, P. I. Hernández, M. Espona, D. Quiñonero, M. E. Light, T. Torroba, R. Pérez-Tomás, R. Quesada, *Chem. Eur. J.* **2011**, *17*, 14074.
[20] a) R. D'Alessio, A. Bargiotti, O. Carlini, F. Colotta, M. Ferrari, *J. Med. Chem.* **2000**, *43*, 2557.
[21] T. E. Wood, A. Thompson, *Chem. Rev.* **2007**, *107*, 1831.
[22] a) H. Fischer, H. Orth, *Die Chemie des Pyrrols*, *Vol. 2*, Akademische Verlagsgesellschaft, Leipzig, **1937**; b) H. Fischer, *Chem. Rev.* **1937**, *20*, 41.
[23] a) V. Leen, E. Braeken, K. Luckermans, C. Jackers, M. Van der Auweraer, N. Boens, W. Dehaen, *Chem. Commun.* **2009**, 4515; b) V. Leen, T. Leemans, N. Boens, W. Dehaen, *Eur. J. Org. Chem.* **2011**, 4386.
[24] S. Jenknis, C. D. Incarvito, J. Parr, H. H. Wasserman, *CrystEngComm* **2009**, *11*, 242.
[25] CCDC 875805 (**1g**·HCl) and CCDC 875806 (**3d**) contain 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

Communications

Synthetic Methods

C. Yu, L. Jiao,* X. Tan, J. Wang, Y. Xu, Y. Wu, G. Yang, Z. Wang, E. Hao* _____ ■■■■–■■■■

Straightforward Acid-Catalyzed Synthesis of Pyrrolyldipyrromethenes



Three for one: Pyrrolyldipyrromethenes having different functional groups were efficiently synthesized from $POCl_3$-promoted condensations between 5-chloro-2-formylpyrrole or isoindole derivatives and suitable pyrrole or indole fragments through a novel nucleophilic aromatic substitution of the initially formed protonated azafulvene rings.