

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/228480209>

One-Step Synthesis of Dipyrromethanes in Water.

Article in *Tetrahedron Letters* · August 2003

DOI: 10.1016/S0040-4039(03)00785-8

CITATIONS

81

READS

753

9 authors, including:



Abilio Sobral

University of Coimbra

240 PUBLICATIONS 1,547 CITATIONS

[SEE PROFILE](#)



Manuela Ramos Silva

University of Coimbra

518 PUBLICATIONS 2,534 CITATIONS

[SEE PROFILE](#)



Ana Matos Beja

Faculdade de Ciências e Tecnologia da Universidade de Coimbra (Portugal)

367 PUBLICATIONS 1,990 CITATIONS

[SEE PROFILE](#)



José António Paixão

University of Coimbra

557 PUBLICATIONS 3,551 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Manuela Ramos Silva's Lab [View project](#)



Molecular Spintronics (MOLSPIN) @ CFisUC, Universidade de Coimbra [View project](#)



One-step synthesis of dipyrromethanes in water

Abílio J. F. N. Sobral,^{a,*} Nuno G. C. L. Rebanda,^a Melo da Silva,^a Sandra H. Lampreia,^a M. Ramos Silva,^b A. Matos Beja,^b J. A. Paixão^b and António M. d'A. Rocha Gonsalves^a

^aChemistry Department, FCT, University of Coimbra, Portugal

^bCEMDRX, Physics Department, FCT, University of Coimbra, Portugal

Received 20 February 2003; accepted 18 March 2003

Abstract—In this communication we describe the first results of an efficient synthesis of β -free-dipyrromethanes in water. This new method affords very pure products in moderate to high yields, using a cheap, non-toxic, environment friendly solvent, in a one-step procedure from pyrrole and carbonyl compounds, needing little or no work up procedures. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

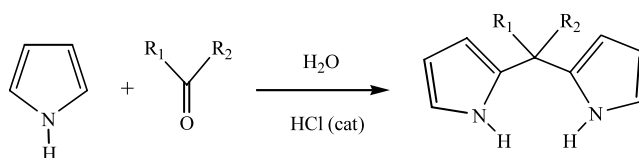
Polypyrrolic compounds are of wide interest in several areas, namely in porphyrins and related macrocycles,¹ science materials,² optics³ and medicine.⁴

Dipyrromethanes are important building blocks for many of the structures of interest in the above-mentioned areas. Although the stability of dipyrromethanes to oxidation is always a cause for concern during the synthetic procedure, isolation and storage of such compounds, a diversity of conditions have been established allowing good to excellent yields of dipyrromethanes to

be obtained in the case where adequate substituents are present on the pyrrole rings. Those substituents provide for the stability of both the pyrrole precursors and the product dipyrromethanes.^{5,6}

In the case of unsubstituted pyrrole rings, the dipyrromethanes are then prone to give further reactions leading to polymeric and highly labile products, except in the specific case of some polypyrrolic macrocycles.

The ready availability of pyrrole unsubstituted dipyrromethanes is, however, of significant interest due to their importance as synthetic building blocks and



	R ₁	R ₂	Yield (%); Solvent: Water; (with 2:1 pyrrole/carbonyl compound), cat.: HCl	Lit. ^{7c} Yield (%) Solvent: pyrrole;(with 25:1 pyrrole/carbonyl compound); cat.: TFA
1	CH ₂ CH ₃	CH ₂ CH ₃	90	—
2	CH ₃	C ₆ H ₅	82	—
3	H	C ₆ H ₅	75	53
4	H	H	25	41
5	H	(<i>p</i> -NO ₂)C ₆ H ₄	37	56

Scheme 1.

Keywords: pyrrole; dipyrromethanes; reactions in water; X-ray crystallography.

* Corresponding author. Fax: +351 239 827703; e-mail: asobral@ci.uc.pt

efforts have been made at their preparation. Those methods, mainly due to the work of Lindsey et al.,⁷ are generally based on the acid-catalyzed condensation of the aldehydes and pyrrole, in the presence of a large excess of pyrrole, using strong organic acids like trifluoroacetic acid. They imply necessarily a delicate time control to stop the reaction when the dipyrromethane concentration is at its maximum and involve a final workup that requires, at least, the distillation of the excess pyrrole.

2. Results and discussion

In our synthetic endeavors in the area of porphyrin chemistry we came to find that the drop-wise addition of pyrrole to an aqueous solution of required ketone or aldehyde in the presence of hydrochloric acid, gave the corresponding dipyrromethane in good to excellent yields, after 30–45 min at 90°C. In the cases where aldehydes were used, the experiments were conducted under nitrogen to avoid the atmospheric oxidation of the dipyrromethane to dipyrromethene (Scheme 1).

Apparently the success of our approach resides on the fact that the reaction between the pyrrole and the carbonyl compound occurs at the interface between the pyrrole and the acidic aqueous aldehyde or ketone solution. The release of the dipyrromethane from the aqueous layer as it is formed, forces the reaction to completion and protects the product from further reactions, revealing another case of success in the use of water in organic reactions.⁸

A continuous GC–MS analysis during the course of the reactions showed the exclusive formation of the dipyrromethane in the first half hour at 90°C for all cases. Only forcing the reaction conditions far beyond the necessary time for the consumption of the carbonyl compound and pyrrole, some secondary products were observed. In fact, a 3 h reflux experiment in water was required to detect two new compounds whose mass and fragmentation patterns correspond to those of the ‘*N*-confused-dipyrromethane’ isomer and to the tripyrromethane.

These compounds were detected in several other methods of dipyrromethane or porphyrin synthesis as by-products.^{9,10} The low production of secondary products is an advantage of our method, which gives directly dipyrromethane samples of great purity. That purity is evident not only in the GC–MS analysis but also the elemental analysis.

Samples obtained directly from the reaction medium, with no purification process whatsoever, showed a total absence of tripyrromethane in the crystals, and allowed us to resolve for the first time the crystal structure of dipyrromethanes **1** and **2** (Figs. 1 and 2). To the best of our knowledge, despite two reports of *meso*-mono-substituted dipyrromethanes,¹¹ our work is the first to describe the crystal and molecular structure of *meso*-di-substituted dipyrromethanes.

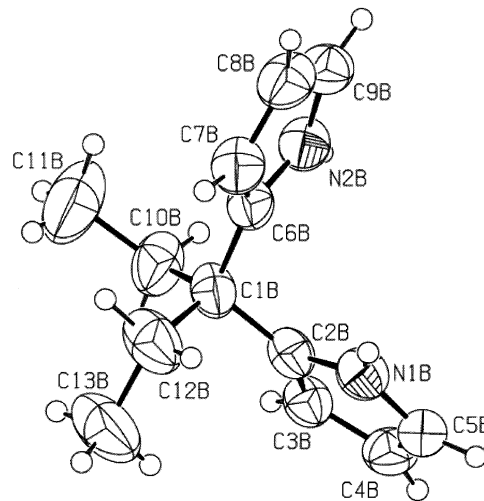


Figure 1. ORTEP¹² diagram for compound **1**, *meso*-diethyl-2,2'-dipyrromethane, with the displacement ellipsoids drawn at the 50% probability level. Crystal data: $C_{13}H_{18}N_2$, $M = 202.29$, monoclinic, $a = 13.2770(17)$ Å, $b = 14.0750(19)$ Å, $c = 13.152(2)$ Å, $\beta = 90.186(12)^\circ$, $V = 2457.7(6)$ Å³, $T = 293(2)$ K, space group $C2$, $Z = 8$, (MoK α) = 0.065 mm⁻¹, 2676 reflections measured, of which 2360 unique ($R_{int} = 0.035$), used for direct methods structure determination¹³ and full matrix least-squares refinement.¹³ The H atoms were placed at calculated idealized positions and refined as riding atoms. The final R (F^2) was 0.042 (for $I > 2\sigma(I)$) and $wR(F^2)$ was 0.123 (for all reflections).

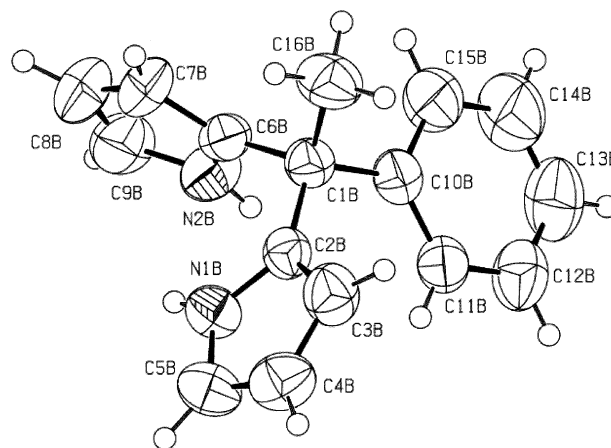


Figure 2. ORTEP¹² diagram for compound **2**, *meso*-methyl-*meso*-phenyl-2,2'-dipyrromethane, with the displacement ellipsoids drawn at the 50% probability level. Crystal data: $C_{16}H_{14}N_2$, $M = 236.31$, triclinic, $a = 10.330(5)$ Å, $b = 15.349(5)$ Å, $c = 17.051(5)$ Å, $\alpha = 97.30(5)^\circ$, $\beta = 100.16(5)^\circ$, $\gamma = 91.44(5)^\circ$, $V = 2636.6(17)$ Å³, $T = 293(2)$ K, space group $P\bar{1}$, $Z = 2$, (MoK α) = 0.545 mm⁻¹, 9613 reflections measured, of which 9131 unique ($R_{int} = 0.007$), used for direct methods structure determination¹³ and full matrix least-squares refinement.¹³ The H atoms were placed at calculated idealized positions and refined as riding atoms. The final R (F^2) was 0.080 (for $I > 2\sigma(I)$) and $wR(F^2)$ was 0.254 (for all reflections).

3. Conclusions

The synthesis of unsubstituted dipyrromethanes in water is an efficient process giving good yields of pure compounds. When pyrrole and an aldehyde or a ketone are made to react in an aqueous medium in the presence of an acid catalyst, the reaction proceeds with attack in a very selective way to the α -positions of the pyrrole and with direct isolation of the product dipyrromethane from the reaction medium, providing for its stabilization.

Besides being a cheap, non-toxic and environment friendly solvent, water joins the physico-chemical characteristics required to reach the goal of finding the way to make simple dipyrromethanes. The synthesis of dipyrromethanes in water involves little or no subsequent purification procedures and needs no excess of pyrrole, as previously known methods. Our approach is of value for *meso* mono and di-substituted or free *meso*-dipyrromethanes and has the advantage of avoiding the environmental disturbing solvents.

4. Experimental

In a typical experiment, to a solution of 15 ml (0.14 mol) of 3-pentanone in 100 ml boiling water, 0.5 ml of 37% aqueous HCl are added, followed by the dropwise addition of 5 ml (0.7 mol) of pyrrole. After refluxing for 30 to 45 min the suspension is left to cool to 40–50°C and then the upper layer is transferred and allowed to cool to room temperature. The product crystallizes in large pale white crystals. *meso*-Phenyl-2,2'-dipyrromethane **3**, dipyrromethane **4** and *meso*-(4-nitrophenyl)-2,2'-dipyrromethane **5** gave physical data in full concordance with the literature.^{7c} Dipyrromethanes **1** and **2** are new compounds and have the following physical data: (1) *meso*-diethyl-2,2'-pyrromethane: mp: 108.5–110°C. Elemental analysis for C₁₃H₁₈N₂: calcd% (C, 77.1; H, 8.9; N, 13.3). Found%: (C, 76; H, 8.9; N, 13.4). ¹H NMR (solvent: CDCl₃; internal standard: TMS): δ = 0.60 (6H, t, J = 7.4 Hz, CH₃-CH₂-C), 1.80 (4H, q, J = 7.4 Hz, CH₃-CH₂-C), 6.0 (4H, m, pyrrole-H), 6.40 (2H, m, pyrrole-H), 7.2 (2H, ls, NH). FT-IR (cm⁻¹; group): (2933, C=C), (3361, ν N-H). GC-MS: C₁₃H₁₈N₂ needs 202, found by EI+: M+ at m/z = 202. (2) *meso*-Methyl-*meso*-phenyl-2,2'-pyrromethane: mp: 102–104°C. Elemental analysis for C₁₆H₁₆N₂: calcd% (C, 81.3; H, 6.8; N, 11.8). Found%: (C, 81.4; H, 6.8; N, 11.3). ¹H NMR (solvent: CDCl₃; internal standard: TMS): δ = 2.0 (3H, s, CH₃-C), 5.97 (2H, m, pyrrole-H), 6.17 (2H, m, pyrrole-H), 6.60 (2H, m, pyrrole-H), 7.1 (2H, PhH^m, m), 7.2 (3H, PhH^{o-p}, m), 7.3 (2H, ls, NH). FT-IR (cm⁻¹; group): (2974, C=C), (3385, N-H). GC-MS: C₁₆H₁₆N₂ needs 236, found by EI+: M+ at m/z = 236.

Crystallographic data (excluding structure factors) for the structures **1** and **2** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 205932 and CCDC 205933. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road,

Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Chymiotecnnon and FCT Sapiens POCTI/QUI/42536/2001 for financial support. We would also like to thank Professor Hugh D. Burrows, for interesting discussions on the two-phase reactions and MSc. Sónia Ribeiro and Dr Alexandra Gonsalves, for assistance on the GC-MS analysis.

References

- (a) Lee, C.-H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothner-By, A. A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645–11672; (b) Shanmugathan, S.; Edwards, C.; Boyle, R. W. *Tetrahedron* **2000**, *56*, 1025–1046.
- Drain, C. M.; Hupp, J. T.; Suslick, K. S.; Wasielewski, M. R.; Chen, X. J. *Porphyrins Phthalocyanines* **2002**, *6*, 243–258.
- Okura, I. J. *Porphyrins Phthalocyanines* **2002**, *6*, 268–270.
- (a) Bonnett, R. *Chem. Soc. Rev.* **1995**, 4151–4202; (b) Sternberg, E. D.; Dolphin, D.; Bruckner, C. *Tetrahedron* **1998**, *54*, 4151–4202; (c) MacDonald, I. J.; Dougherty, T. J. *J. Porphyrins Phthalocyanines* **2001**, *5*, 105–129.
- (a) *Porphyrins and Metalloporphyrins*; Smith, K. M., Ed. Synthesis and preparation of porphyrin compounds; Elsevier, 1975; Chapter 2; (b) *The Porphyrins*; Dolphin, D., Ed. Synthesis of pyrroles and porphyrins via single step coupling of dipyrrolic intermediates. Academic Press, 1978; Chapter 4.
- (a) Okada, K.; Saburi, K.; Nomura, K.; Tanino, H. *Tetrahedron* **2001**, *57*, 2127–2131; (b) Montalban, A. G.; Herrera, A. J.; Johannsen, J.; Beck, J.; Godet, T.; Vrettou, M.; White, A. J. P.; Williams, D. J. *Tetrahedron Lett.* **2002**, *43*, 1751–1753.
- (a) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427–11440; (b) Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864–2872; (c) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391–1396; (d) Yu, L.; Lindsey, J. S. *Tetrahedron* **2001**, *57*, 9285–9298.
- (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (c) Ludwig, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1808–1827; (d) Engberts, J. B. F. N.; Bladamer, M. J. *Chem. Commun.* **2001**, 1701–1708.
- (a) Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 687–700; (b) Geier, G. R., III; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2002**, *6*, 159–185.
- Ka, J.-W.; Lee, C.-H. *Tetrahedron Lett.* **2000**, *41*, 4609–4613.
- (a) Jiuh, K.; Wu, J.-Y.; Chen, C.-T. *Acta Crystallogr.* **1996**, *C52*, 3114–3116; (b) Gallagher, J. F.; Moriarty, E. *Acta Crystallogr.* **1999**, *C55*, 1079–1082.
- Johnson, C. K. ORTEPII. Report ORNL-5138, Oak Ridge National Laboratory, TN, USA, 1976.
- Sheldrick, G. M. SHELXS-97 and SHELXL-97, Univ. of Göttingen, Germany, 1997.