Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 345–347

TETRAHEDRON LETTERS

Electrophilic substitution reactions of dipyrroheptane

Stefaan Depraetere and Wim Dehaen*

Laboratory of Organic Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium

Received 20 August 2002; revised 31 October 2002; accepted 8 November 2002

Abstract—Dipyrroheptanes have been reacted with a number of electrophiles, including aryldiazonium salts, acyl chlorides and isocyanates to give selectively the mono- or disubstituted derivatives. The bis(trichloroacetyl) dipyrroheptane can be used for the synthesis of amide and ester derivatives.

1. Introduction

Dipyrromethanes have emerged as useful intermediates for the synthesis of porphyrins[1] and porphyrin-like[2] macrocycles. In most cases, the *meso* position has either no substituents or a single aryl or alkyl substituent. Dialkyl[3] or diaryldipyrromethanes[4] have been much less studied. However, we showed recently[5] that dialkyldipyrromethanes can show similar recognition as calix[4]pyrroles[6] towards neutral phenols in membrane systems. Sessler recently reported that quinoxaline derivatives, bearing dipyrromethane substituents, act as improved anion receptors as compared to the unsubstituted dipyrrolylquinoxaline core.[7]

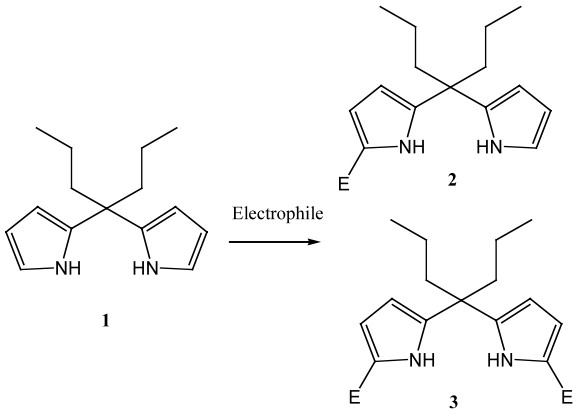
Therefore, we wanted to explore the substitution reactions of dipyrromethanes in order to use them as alternatives for calix[4]pyrroles in supramolecular chemistry. The latter are not easily derivatized at the β-position,[6] limiting their application. On the contrary, the free α-positions of dipyrromethanes should be very reactive towards electrophilic substitution. Of course, conditions will have to be found that will leave the acid-labile dipyrromethanes intact.

2. Results and discussion

We could prepare dipyrroheptane **1** in good yield, and on a scale of >20 g, starting from 4-heptanone and an excess of pyrrole with trifluoroacetic acid as the catalyst. As expected, the solubility of **1** in organic solvents (ranging from heptane to DMSO) is excellent, which makes it easier to prepare and to purify its derivatives. Initial experiments with the dipyrropropane analog were much more cumbersome due to its limited solubility.

Pyrroles are known to react with aryldiazonium salts at the α-position, giving products which were used as bidentate ligands for Ni(II) and Cu(II) cations.[8]

We investigated the substitution of the α-hydrogens of the dipyrroheptane **1** with aryldiazonium salts. An aqueous solution of excess phenyldiazonium salt, prepared from aniline, hydrochloric acid and sodium nitrite did not give the expected products **2** or **3** but rather the monopyrrole degradation product **4**. Indeed, in the literature several examples were described[9] of the reaction of dipyrromethanes with aryldiazonium salts, leading to similar degradation products. This can occur either via preliminary proton-catalyzed degradation of the dipyrromethane (at low pH), followed by aryldiazo-

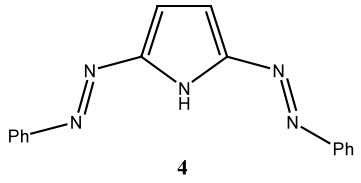


Scheme 1. Synthesis of mono- and disubstituted dipyrroheptanes **2** and **3**.

* Corresponding author. Tel.: +32-16-327436; fax: +32-16-327990; e-mail: wim.dehaen@chem.kuleuven.ac.be

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02521-2

tation, or via direct *ipso* attack of the phenyldiazonium salt on the dipyrromethane (at higher pH).[10] However, with the tetrafluoroborate aryldiazonium salts, and the ability to work in organic solvents, products **2a–c** and **3a**,**b** could be obtained from dipyrroheptane **1**. The reaction time is very short (0.5–1 h) and all reactions can be carried out at room temperature. The addition of base (triethylamine) was not required to obtain a high yield. We synthesised mono- and disubstituted dipyrroheptanes starting from different diazonium salts (see Scheme 1).



4

When we used the *p*-nitrophenyl diazonium tetrafluoroborate we selectively obtained the desired mono- or disubstituted product **2a** and **3a**, depending on the number of equivalents we used, i.e. one and two, respectively. As we generated the 2-diazonium benzoate inner salt in situ by diazotation of anthranilic acid, we only worked with an excess of this reagent. Thus, we only obtained the disubstituted product **3b**, which is water-soluble. However, with the less reactive *p*-methoxyphenyldiazonium tetrafluoroborate we obtained only the monosubstituted product **2c**, even when we added 2 equiv. of the diazonium salt and triethylamine.

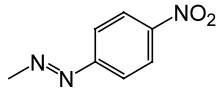
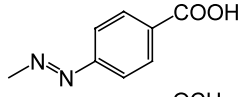
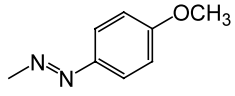
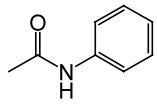
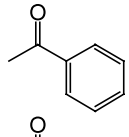
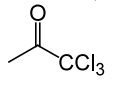
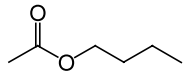
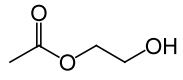
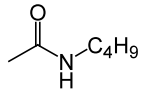
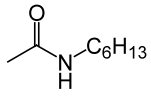
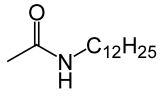
Pyrroles are known to react with isocyanates at the α-position.[11] The resulting amides may be used as receptors for anions by analogy with work carried out recently by Gale et al. on mono- and dipyrrolediamides.[12] We investigated the substitution of the α-hydrogens of the dipyrroheptane **1** with phenyl isocyanate under different conditions. Either with phenyl isocyanate as solvent under reflux[11] or with THF as solvent and different bases: Et_3N/reflux, EtMgCl (–78°C to rt), the monosubstituted product **2d** was obtained in a good yield (up to 60%). However, we never observed the disubstituted product **3d** even with an excess of reagent. To our surprise, an isomeric dipyrroheptane derivative **5** was formed when 2 equiv. BuLi were used to deprotonate **1** before the addition of isocyanate. In product **5**, one α-hydrogen and one nitrogen hydrogen are substituted. Possibly, hydrogen bonding in the intermediate directed the second addition to the nitrogen atom. Reaction of **1** with only 1 equiv. BuLi gives only **2d**, also in 60% yield.

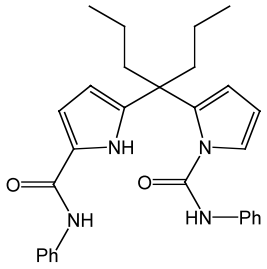
The reaction of dipyrroheptane **1** with benzoyl chloride, carried out at ambient temperature with EtMgCl as base, yielded the expected mono- or disubstituted products **2e** and **3e** in fair yield, depending on the equivalents of base and benzoyl chloride used.

An interesting disubstituted product **3f** was formed by reaction of dipyrroheptane **1** with 2 equiv. of the reactive trichloroacetyl chloride without the use of base. The trichloroacetyl functions of **3f** can be seen as stable forms of acid chlorides.[13] Thus, we found that phenol/potassium carbonate is a good catalyst for the synthesis of esters **3g–i** and amides **3j**,**k** from **3f** and alcohols and amines,[14] respectively (see Table 1). This is a non-toxic alternative catalyst to cyanide anion which was used previously.[13]

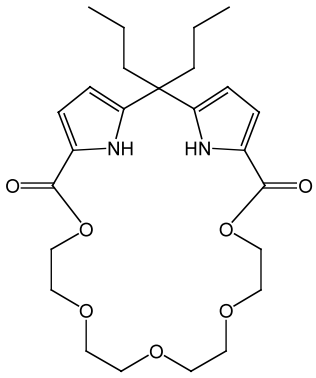
When an equimolecular mixture of the product **3f** and tetraethylene glycol was used in this reaction, again with phenol/potassium carbonate as the catalyst, we obtained the interesting macrocycle **6** in 20% yield. The compound **6** may be regarded as a hybrid of the crown ether and calixpyrrole ligands.

Table 1. Isolated yields

	E	**2** (%)	**3** (%)
a		50	40
b			40
c		75	
d		60	
e		50	40
f			50
g			55
h			75
i			80
j			80
k			85



5



6

3. Conclusion

These results clearly show that functionalisation of dipyrroheptane, as a model for other compounds of the dipyrromethane type, can be readily and selectively carried out to obtain mono- or disubstituted derivatives by adjusting the amount of reagent. The selectivity may seem remarkable if one considers that the two pyrrole rings are not electronically linked. However, an N–H···π interaction exists between the pyrrole rings as proven from crystal structures of other dipyrromethanes.[15]

Thus, an electron withdrawing substituent on one pyrrole ring will increase its N–H acidity and the interaction with the other pyrrole ring. The latter then becomes less reactive towards electrophilic substitution in comparison to the starting material **1**.

Difunctional amides are not directly obtainable from dipyrroheptane **1** and isocyanates but can be prepared from the bis(trichloroacetyl) derivative **3f**. The latter compounds can also be subjected to macrocyclisation reactions.

Acknowledgements

Support from the FWO, the University of Leuven, the 'Ministerie voor Wetenschapsbeleid' and a bilateral grant Poland/Flanders (BIL/01/24) is gratefully acknowledged.

References

1. See for instance: (a) Lee, C. H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427; (b) Nishino, N.; Wagner, R. W.; Lindsey, J. S. *J. Org. Chem.* **1996**, *61*, 7534; (c) Littler, B. J.; Ciringh, Y; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864; (d) Yu, L. H.; Lindsey, J. S. *Tetrahedron* **2001**, *57*, 9285; (e) Ogura, H.; Walker, F. S. *Inorg. Chem.* **2001**, *40*, 5729; (f) Cammidge, A. N.; Ozturk, O. *Tetrahedron Lett.* **2001**, *42*, 355; (g) Mamardashvili, N. Z.; Golubchikov, O. A. *Russ. Chem. Rev.* **2000**, *69*, 307.
2. See for instance: (a) Lee, C. H.; Cho, W. S. *Tetrahedron Lett.* **1999**, *40*, 8879; (b) Gryko, D. T.; Jadach, K. *J. Org. Chem.* **2001**, *66*, 4267; (c) Asokan, C. V.; Smeets, S.; Dehaen, W. *Tetrahedron Lett.* **2001**, *42*, 4483; (d) Kral, V.; Sessler, J. L.; Zimmerman, R. S.; Seidel, D.; Lynch, V.; Andrioletti, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 1055.
3. Brown, W. H.; Hutchinson, B. J.; MacKinnon, M. H. *Can. J. Chem.* **1971**, *49*, 4018.
4. (a) Turner, B.; Shterenberg, A.; Kapon, M.; Suwinska, K.; Eichen, Y. *Chem. Commun.* **2001**, 13; (b) Turner, B.; Botoshansky, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2475; (c) Turner, B.; Shterenberg, A.; Kapon, M.; Suwinska, K.; Eichen, Y. *Chem. Commun.* **2002**, 404.
5. Piotrowski, T.; Radecka, H.; Radecki, J.; Depraetere, S.; Dehaen, W. *Mat. Sci. Eng. (C)* **2001**, *C18*, 223.
6. For calixpyrroles reviews, see: (a) Gale, P. A.; Sessler, J. L.; Kral, V. *Chem. Commun.* **1998**, 1; (b) Gale, P. A. *Coord. Chem. Rev.* **2001**, *222*, 57; (c) Sliwa, W. *Heterocycles* **2002**, *57*, 169.
7. Sessler, J. L.; Maeda, H.; Mizuno, T.; Lynch, V. M.; Furuta, H. *Chem. Commun.* **2002**, 862.
8. (a) Fischer, O.; Hepp, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2251; (b) Pfeiffer, P.; Hesse, T.; Pfitzner, H.; Scholl, W.; Thielert, H. *J. Prakt. Chem.* **1937**, *149*, 249; (c) Butler, A. R.; Pogorzelec, P.; Shepherd, P. T. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1452; (d) Krowczynski, A.; Pyzuk, W.; Gorecka, E. *Polish. J. Chem.* **1994**, *68*, 281.
9. (a) Treibs, A.; Derra-Scherer, H. *Liebigs Ann. Chem.* **1954**, *589*, 196; (b) Treibs, A.; Fritz, G. *Liebigs. Ann. Chem.* **1958**, *611*, 162.
10. Butler, A. R.; Shepherd, P. T. *J. Chem. Soc., Perkin Trans. 2* **1980**, 113.
11. Papadopoulos, E. P. *J. Org. Chem.* **1972**, *37*, 351.
12. (a) Gale, P. A.; Camiolo, S.; Chapman, C. P.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2001**, *42*, 5095; (b) Gale, P. A.; Camolio, S.; Tizzard, G. J.; Capman, C. P.; Light, M. E.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2001**, *66*, 7849.
13. Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth. Coll.* **1988**, *50*, 618.
14. Experimental data for **3f**: mp: 197.6–198.2°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.28 (s, 2H, NH pyrrole), 7.35 (dd, 2H, pyrrole H adj. to CO), 6.27 (dd, 2H, pyrrole H); 1.99 (m, 4H, CH_2), 1.16 (m, 4H, CH_2), 0.92 (t, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.3 (C=O); 146.1 (α-C of pyrrole adj. to heptane chain); 122.9 and 122.1 (β-C); 110.9 (α-C of pyrrole adj. to C=O); 95.3 (CCl_3); 44.7 (quaternary C); 40.5; 17.7; 14.7 (alkyl Cs).
Data for **3j**: mp 323–324°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.10 (s, 2H, NH pyrrole); 7.48 (s, 2H, NH amide), 6.61 (br, 2H, pyrrole H adj. to C=O), 5.88 (br, 2H, pyrrole H), 3.21 (q, J=6.14 Hz, 4H, CH_2NH), 2.05 (m, 4H, CH_2 propyl), 1.52 (m, 4H, CH_2 hexyl), 1.31 (m, 12H, CH_2 hexyl), 1.10 m (4H, CH_2 propyl); 0.87 (m, 12H, CH_3 of propyl and hexyl); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.5 (C=O), 140.3 (α-C of pyrrole adj. to heptane chain), 126.0; 110.0; 106.3; 43.00, 38.6, 38.4, 30.9, 29.3, 26.0, 21.7, 16.8, 14.0, 13.4;
15. (a) Lin, K. J.; Wu, J. Y.; Chen, C. T. *Acta Crystallogr. (C)* **1996**, *52*, 3114; (b) Gallagher, J. F.; Moriarty, E. *Acta Crystallogr. (C)* **1999**, *55*, 1079.