Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2031-2034, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00287-6

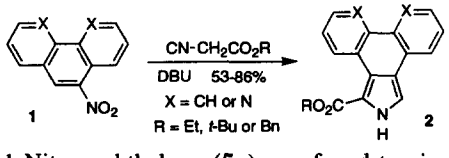
Synthesis of Novel Porphyrin Chromophores from Nitroarenes: Further Applications of the Barton-Zard Pyrrole Condensation

Timothy D. Lash,* Chaminda Wijesinghe, Augustine T. Osuma and Jyoti R. Patel
Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160

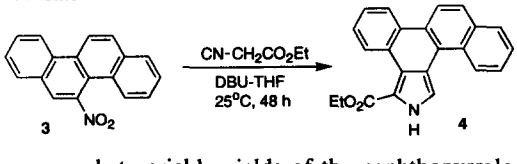
Abstract: *Porphyrins with fused nitronaphthalene and benzothiadiazole subunits have been synthesized by the "2 + 2" and "3 + 1" methodologies; the key pyrrolic intermediates were prepared by the base catalyzed condensation of dinitronaphthalenes or 4-nitro-2,1,3-benzothiadiazole with isocyanoacetates.* © 1997 Elsevier Science Ltd.

The influence of fused aromatic ring systems on the spectroscopic properties of the porphyrin chromophore has been poorly studied, in contrast to their tetraaza analogs the phthalocyanines.[1] Modified porphyrin chromophores have many potential applications, such as the development of molecular wires,[2] photosynthetic antenna arrays[3] and as photosensitizers in photodynamic therapy,[4] and have additional value as geochemical standards in the analysis of sedimentary metalloporphyrins.[5] Recently, these considerations have spurred a resurgence of interest in the synthesis of benzoporphyrins[5,6] and naphthoporphyrins.[5,7] We have initiated a program to methodically investigate the effects of one or more fused aromatic subunit on the porphyrin system.[1,5,7-10] Efficient routes for the synthesis of pyrroles bearing *c*-face fused aromatic systems are a necessary prerequisite for these studies. Barton and Zard demonstrated that nitroalkenes condense with isocyanoacetates in the presence of a non-nucleophilic base to give pyrrole-2-carboxylates[11] and this chemistry has been adapted for the synthesis of *c*-annelated pyrroles (e.g., Scheme 1).[12,13] Although nitrobenzene does not react in this fashion, nitroarenes with a significant amount of double bond character such as 9-nitrophenanthrene (**1a**), 5-nitro-1,10-phenanthroline (**1b**) (Scheme 1) and 1-nitroacenaphthylene,[1,8-10,12] condense with isocyanoacetates and DBU in tetrahydrofuran to give the related pyrroles **2** in good yields.[12] Similarly, 6-nitrochrysene (**3**) condensed with ethyl isocyanoacetate to give chrysopyrrole ethyl ester **4** (Scheme 2).[14] Following our initial report,[12] several groups have independently explored different aspects of this chemistry,[1,8-10,15,16] including the formation of anomalous products.[15b,16] The high level of current interest in this area has prompted us to relate additional observations and applications of this versatile chemistry.

Scheme 1

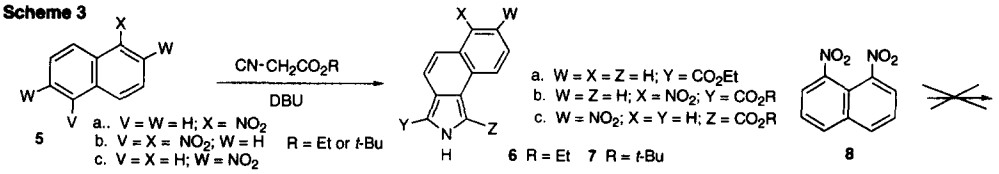


Scheme 2



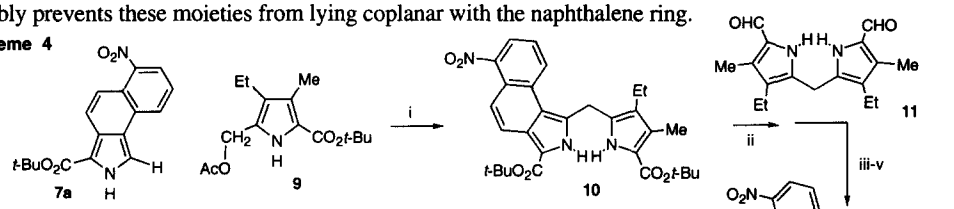
1-Nitronaphthalene (**5a**) was found to give low, somewhat variable yields of the naphthopyrrole **6a** (Scheme 3; see also ref. 15a). This chemistry was generally accompanied by the formation of dark tarry biproducts and the yield of isolated product was always less than 10%. Interestingly, at higher dilutions (>100 mL of THF for 1.00 g of **5a**) no pyrrole formation was observed even after prolonged reflux, but no degradation to tarry biproducts occurred either under these conditions. The poor results for **5a** were not unexpected, but we

Scheme 3



speculated that dinitronaphthalenes might be more prone to nucleophilic attack by the isocyanoacetate anion and might therefore yield pyrrolic products in synthetically useful yields. With this in mind, the reactivities of 4 commercially available dinitronaphthalenes have been investigated. 1,5- (**5b**) and 2,7-dinitronaphthalene (**5c**) were found to condense with 1.25 equiv. of ethyl isocyanoacetate in the presence of DBU in refluxing THF to give the related nitronaphthopyrroles **6b**[17] and **6c** in 44-45% yield (Scheme 3). The corresponding *tert*-butyl esters **7a** and **7b** were prepared similarly in comparible yields. Hence, the additional nitro group appears to tip the balence sufficiently to allow the Barton-Zard chemistry to occur efficiently. It is noteworthy, however, that further reaction to form dipyrrolic products was never observed in these studies. This was to be expected as the aromaticity of the remaining benzo moiety would be lost to generate a second isoindole unit. Surprisingly, 1,8-dinitronaphthalene (**8**) failed to give any pyrrolic products under any of the conditions that we examined.[18] The inability of **8** to facilitate pyrrole formation may be due to the proximity of the two nitro groups, a factor that presumably prevents these moieties from lying coplanar with the naphthalene ring.

Scheme 4

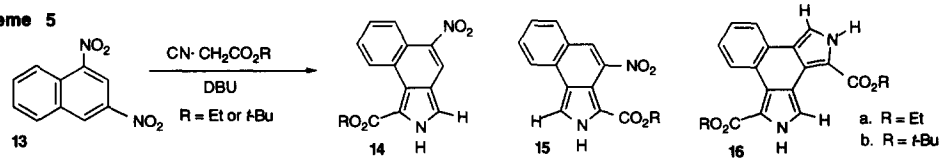


i Montmorillonite clay, CH_2Cl_2, 16 h. ii TFA iii *p*-TSA-CH_2Cl_2-MeOH iv $Zn(OAc)_2$, air v TFA

The utility of nitronaphthopyrroles in porphyrin synthesis was investigated using the MacDonald "2 + 2" condensation (Scheme 4).[19] Naphthopyrrole **7a** was condensed with acetoxymethylpyrrole **9** in the presence of Montmorillonite clay[20] to give **10** in 86% yield. Cleavage of the *tert*-butyl esters with TFA, followed by condensation with dialdehyde **11** under conventional conditions[19b] gave only trace amounts of the targeted porphyrin **12**. However, when the deprotected naphthodipyrrylmethane and **11** were added dropwise to a stirred solution of *p*-toluenesulfonic acid in methanol-dichloromethane to simulate high dilution conditions,[21] and the mixture was further air oxidised in the presence of zinc acetate and demetallated with TFA, the desired porphyrin **12** was obtained in 15% yield. The electronic spectrum of **12** was unusual in that the Soret band was split into two absorptions at 396 and 421 nm, respectively.[22] As this effect was not observed for a naphthoporphyrin lacking the nitro group,[7] this result indicates that the NO_2 unit significantly alters the porphyrin chromophore. On the other hand, the longer wavelength "Q bands" remained essentially unalterred.

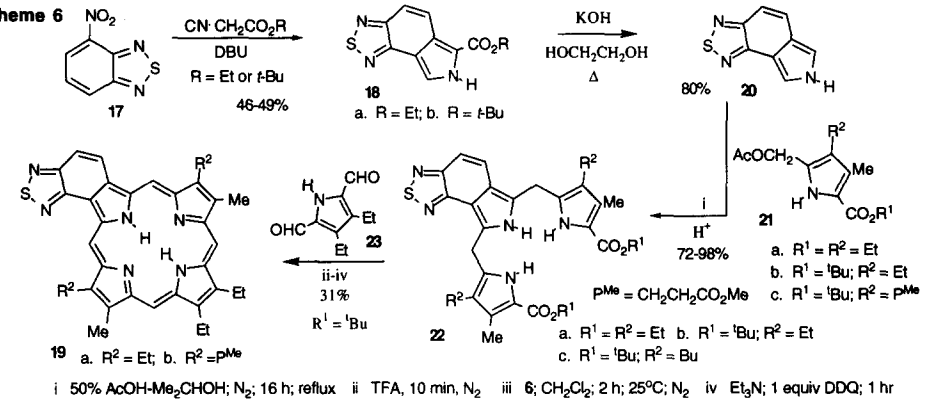
A fourth isomer, 1,3-dinitronaphthalene (**13**), was also investigated (Scheme 5). Reaction of **13** with 1.3 equiv. of ethyl isocyanoacetate gave a mixture of three pyrrolic products **14a**, **15a** and **16a** in 25%, 26% and 13% yield, respectively. These compounds were easily separated by column chromatography on silica gel, eluting with dichloromethane. When 5 equiv. of the isocyanoacetate was used, **16a** was the sole isolatable product (25%), but a far greater proportion of tarry biproducts were formed under these conditions. The corresponding *tert*-butyl esters **14b**-**16b** were prepared similarly (Scheme 5). The availability of dipyrroles **16** suggests the tantalizing possibility that helicene-like diporphyrin structures could be constructed from these precursors. Realization of this speculation remains a future goal in this laboratory.

Scheme 5



The reactivity of heteroaromatic systems with isocyanoacetates has also been investigated. However, 2-nitrofuran and 2-nitrothiophene gave no useful products in our hands, producing mostly dark tarry biproducts, and 4-nitropyridine failed to give any reaction with ethyl isocyanoacetate. However, 4-nitro-2,1,3-benzothiadiazole (**17**) reacted with ethyl isocyanoacetate to give pyrrole **18a**, albeit in rather low yields under conventional conditions (see also ref. 15a). When the reaction was carried out with 1.00 g of **17** in 60 mL of THF, **18a** was isolated in 15% yield. However, in 300 mL of THF, **18a** was isolated in 27% yield and in 450 mL, a respectable 46-48% yield was obtained. The corresponding *tert*-butyl ester **18b** was obtained in 49% yield under these latter conditions. These observations are not easily explained, and in fact show the opposite trend to reactions of 1-nitronaphthalene where the chemistry appears to essentially shut down under dilute conditions.

Scheme 6



i 50% AcOH-Me_2CHOH; N_2; 16 h; reflux ii TFA, 10 min, N_2 iii 6; CH_2Cl_2; 2 h; 25°C; N_2 iv Et_3N; 1 equiv DDQ; 1 hr

We have taken the opportunity to prepare thiadiazoloporphyrins **19** from the tricyclic pyrrole system **18**, in this case using the "3 + 1" methodology.[23] Treatment of **18a** with KOH in refluxing ethylene glycol afforded the unsubstituted tricycle **20** and subsequent reaction with 2 equiv. of an acetoxymethylpyrrole **21a-c** in refluxing acetic acid-ethanol[23b] gave a series of tripyrranes **22a-c** in good yields. Tripyrranes **22b** and **22c**, which possess terminal *tert*-butyl esters, were treated with TFA, diluted with dichloromethane and condensed with diformylpyrrole **23**.[23b,24] Following neutralization with triethylamine, and oxidation with DDQ, porphyrins **19** were obtained in 31% yield. The electronic spectra for **19** again showed split Soret bands,[22] although the Q band region was unexceptional.

The synthesis of *c*-annelated pyrroles and the related conjugated porphyrin structures from nitroarenes clearly shows great promise and this chemistry will allow synthetic entry into many new porphyrinoid systems. The use of phosphorus "superbases" in Barton-Zard chemistry[25] has also shown some potential in extending this valuable synthetic methodology.[15c] However, the reactivity of nitroaromatic compounds is highly variable and generalization of this chemistry must be approached with caution.

Acknowledgements: This material is based upon work supported by the National Science Foundation under Grant No. CHE-9500630.

References and Notes

1. Lash, T.D.; Novak, B.H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 683.
2. Crossley, M.J.; Burn, P.L. *J. Chem Soc., Chem. Commun.* **1991**, 1569.
3. E.g.: Wagner, R.W.; Johnson, T.E.; Lindsey, J.S. *J. Am. Chem. Soc.* **1996**, *118*, 11166.
4. Brown, S.B.; Truscott, T.G. *Chem. Br.* **1993**, *29*, 955; Bonnett, R. *Chem. Soc. Rev.* **1995**, *24*, 19.
5. Lash, T.D. *Energy Fuels* **1993**, *7*, 166.
6. a. Clezy, P.S.; Leung, C.W.F. *Aust. J. Chem.* **1993**, 46, 1705; b. Nguyen, L.T.; Senge, M.O.; Smith, K.M. *J. Org. Chem.* **1996**, *61*, 998; c. Bonnett, R.; McManus, K.A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2461.
7. a. Lash, T.D.; Roper, T.J. *Tetrahedron Lett.* **1994**, *35*, 7715; b. Lash, T.D.; Denny, C.P. *Tetrahedron* **1995**, *51*, 59.
8. Lash, T.D.; Novak, B.H. *Tetrahedron Lett.* **1995**, *36*, 4381. See also: Freemantle, M. *C&E News* **1994**, *72* (39), 25-27.
9. a. Lin, Y.; Lash, T.D. *Tetrahedron Lett.* **1995**, *36*, 9441; b. Chandrasekar, P.; Lash, T.D. *Tetrahedron Lett.* **1996**, *37*, 4873.
10. Lash, T.D.; Chandrasekar, P. *J. Am. Chem. Soc.* **1996**, *118*, 8767.
11. Barton, D.H.R.; Kervagoret, J.; Zard, S.Z. *Tetrahedron* **1990**, *46*, 7587.
12. Lash, T.D.; Novak, B.H.; Lin, Y. *Tetrahedron Lett.* **1994**, *35*, 2493.
13. Our studies on the synthesis of *c*-annelated pyrroles from nitroarenes and isocyanoacetates were reported, in part, at the following meetings: a. 207th National Meeting of the American Chemical Society, San Diego, CA, March 1994 (Abstract: Lash, T.D.; Roper, T.J.; Novak, B.H.; Lin, Y. *Book of Abstracts*, ORGN 154); b. 208th National Meeting of the American Chemical Society, Washington, DC, August 1994 (Abstract: Novak, B.H.; Lash, T.D. *Book of Abstracts*, ORGN 222); c. 209th National Meeting of the American Chemical Society, Anaheim, CA, April 1995 (Abstract: Lash, T.D.; Novak, B.H.; Lin, Y.; Melquist, M.J.; Patel, J.R. *Book of Abstracts*, ORGN 177); d. 210th National Meeting of the American Chemical Society, Chicago, Illinois, August 1995 (Abstracts: Lash, T.D.; Lin, Y. *Book of Abstracts*, ORGN 179; Chandrasekar, P.; Lash, T.D. *Book of Abstracts*, ORGN 80); e. 211th National Meeting of the American Chemical Society, New Orleans, Louisiana, March 1996 (Abstracts: Wijesinghe, C.; Lash, T.D. *Book of Abstracts*, ORGN 230; Osuma, A.; Lash, T.D. *Book of Abstracts*, ORGN 478).
14. Lash, T.D. Unpublished work.
15. a. Ono, N; Hironaga, H.; Ono, K.; Kaneko, S.; Murashima, T.; Ueda, T.; Tsukamura, C.; Ogawa, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 417; b. Murashima, T.; Fujita, K.; Ono, K.; Ogawa, T.; Uno, H.; Ono, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1403; c. Murashima, T.; Tamai, R.; Fujita, K.; Uno, H.; Ono, N. *Tetrahedron Lett.* **1996**, *37*, 8391.
16. a. Jaquinod, L.; Gros, C.; Olmstead, M.M.; Antolovich, M.; Smith, K.M. *J. Chem. Soc., Chem. Commun.* **1996**, 1475; b. Pelkey, E.T.; Chang, L.; Gribble, G.W. *ibid.*, 1909.
17. **6b**: DBU (1.74 g) was added dropwise to a solution of 1,5-dinitronaphthalene (2.00 g) and ethyl isocyanoacetate (1.31 g) in THF (100 mL) and the resulting mixture was stirred while heating under reflux overnight. The mixture was cooled to room temperature, diluted with chloroform and washed with water. The solution was dried over sodium sulfate, concentrated on a rotary evaporator and the residue taken up in a minimal amount of dichloromethane. The solution was chromatographed on a silica column, eluting with dichloromethane, and a yellow band was collected. Recrystallization from dichloromethane-hexane gave **6a** as bright yellow crystals, m.p. 244-245°C; ir (nujol mull): v 3262 (NH), 1683 cm^{-1} (C=O); ^1H NMR (300 MHz, d_6-DMSO): δ 1.37 (3H, t, J = 7 Hz, CH_2CH_3), 4.36 (2H, q, J = 7 Hz, OCH_2), 7.70 (1H, t, J = 8.0 Hz), 7.83 (1H, d, J = 9.6 Hz), 8.06 (1H, d, J = 7.8 Hz), 8.18 1H, d, J = 9.6 Hz), 8.40 (1H, s, pyrrole-H), 8.73 (1H, d, J = 8.1 Hz), 13.38 (1H, br s, NH); ^{13}C NMR (d_6-DMSO): δ 14.23, 59.88, 113.64, 118.19, 118.83, 120.61, 121.29, 121.34, 123.96, 123.99, 126.20, 128.71, 129.73, 147.69, 160.83; Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found C, 63.04; H, 4.19; N, 9.76. **18a**: 4-Nitro-2,1,3-benzothiadiazole (4.00 g) in THF (800 mL) was added to a solution of ethyl isocyanoacetate (2.50 g) and DBU (3.36 g) in THF (1000 mL) and the resulting dark mixture was stirred under reflux overnight. The solution was concentrated under reduced pressure, diluted with chloroform, washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed with silica gel eluting with chloroform. A reddish brown fraction was collected and recrystallized from methanol to afford **18a** (2.50 g, 46%) as pale brown crystals, m.p. 173-174°C; ir (nujol mull): v 3300 (NH), 1691 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 1.48 (3H, t, J = 7 Hz, CH_2CH_3), 4.49 (2H, q, J = 7 Hz, OCH_2), 7.61 (1H, d, J = 9.6 Hz, benzo-H), 7.96 (1H, d, J = 2.7 Hz, pyrrole-H), 8.19 (1H, d, J = 9.6 Hz, benzo-H), 10.09 (1H, br, NH); ^{13}C NMR (d_6-DMSO): δ 14.32, 60.20, 115.34, 115.69, 118.32, 119.18, 125.11, 125.57, 150.56, 154.09, 160.62; Anal. Calcd for $C_{11}H_9N_3O_2S$: C, 53.43; H, 3.67; N, 16.99. Found C, 53.30; H, 3.67; N 16.68.
18. In an independent study,[15a] both **6b** and **8** were claimed to react with ethyl isocyanoacetate to give pyrrolic products. However, the proton NMR spectrum for the product obtained from **8** was essentially identical to the one reported for the pyrrole produced from **6b**. Given the very different positioning of the nitro moiety relative to the pyrrole subunit in the presumed product structure, this coincidence is somewhat implausible. Therefore, we suggest that this result is treated with skepticism.
19. a. Arsenault, G.P.; Bullock, E.; MacDonald, S.F. *J. Am. Chem. Soc.* **1960**, *82*, 4384; b. Cavaleiro, J.A.S.; Rocha Gonsalves, A.M. d'A.; Kenner, G.W.; Smith, K.M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1771.
20. Jackson, A.H.; Pandey, R.K.; Rao, K.R.N.; Roberts, E. *Tetrahedron Lett.* **1985**, *26*, 793.
21. Burns, D.H.; Caldwell, T.M.; Burden, M.W. *Tetrahedron Lett.* **1993**, *34*, 2883.
22. **12**: uv-vis (CH_2Cl_2): λ_{max} ($\log_{10}\varepsilon$) 396 (5.01), 421 (5.15), 520 (3.97), 556 (4.48), 576 (4.23), 630 (3.61); **19a**: uv-vis ($CHCl_3$): λ_{max} ($\log_{10}\varepsilon$) 380 (4.85), 438 (5.06), 528 (3.86), 566 (4.47), 588 nm (4.45).
23. a. Lash, T.D. *Chem. Eur. J.* **1996**, 2, 1197; b. Lash, T.D. *J. Porph. Phthal.*, **1997**, in press.
24. Vogel, E.; Jux, N.; Rodriguez-Val, E.; Lex, J.; Schmickler, H. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1387.
25. a. Tang, J.; Verkade, J.G. *J. Org. Chem.* **1994**, *59*, 7793; b. Bag, N.; Chern, S.-S.; Peng, S.-M.; Chang, C.K. *Tetrahedron Lett.* **1995**, *36*, 6409.

(*Received in USA* 6 *January* 1997; *revised* 29 *January* 1997; *accepted* 3 *February* 1997)