Pergamon

Tetrahedron Letters 43 (2002) 2299–2302

TETRAHEDRON LETTERS

A new synthesis of 'push–pull' naphthalenes by condensation of nitro-2-methylbenzoate esters with dimethylacetamide dimethyl acetal

See-Mun Wong, Bhavini Shah, Priyal Shah, Ian C. Butt, Esther C. Y. Woon, James A. Wright, Andrew S. Thompson, Christopher Upton and Michael D. Threadgill*

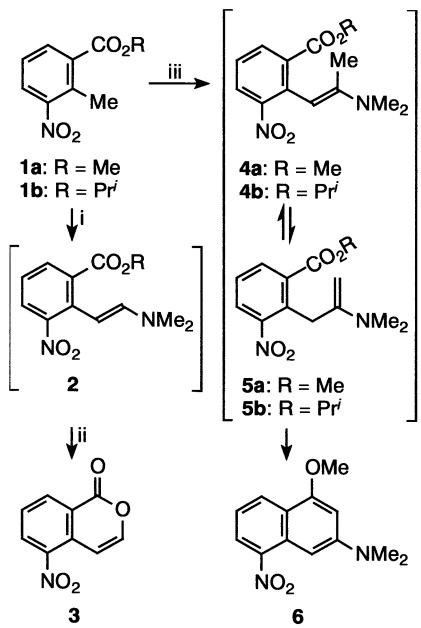
Department of Pharmacy & Pharmacology, University of Bath, Bath BA2 7AY, UK

Received 2 January 2002; revised 21 January 2002; accepted 30 January 2002

Abstract—Whereas condensation of 2-methyl-3-nitrobenzoate esters with dimethylformamide dimethyl acetal gives 5-nitroisocoumarin, analogous condensation with dimethylacetamide dimethyl acetal proceeds via a different route, affording 1-methoxy-3-dimethylamino-5-nitronaphthalene in good yield. Extension of the reaction to other naphthalenes with this novel 'push–pull' substitution motif has been explored. A deuterium labelling study revealed that equilibration of the alkoxy groups in the reaction mixture took place before the final carbocyclisation.

Most syntheses of polysubstituted naphthalenes involve modification and substitution of a preformed bicyclic naphthalene core, with a few employing construction of the rings with the substituents already attached to the acyclic or monocyclic precursors. Examples of the latter ring-closure routes include Diels–Alder cyclisations of dienes with benzoquinones,[1,2] acid-catalysed cyclisations of phenylethylidenemalononitriles to 2-cyanonaphthyl-1-amines[3] and base-catalysed cyclisation of 2-allyl-*N*,*N*-dialkylbenzamides to naphth-1-ols.[4] However, these routes are not generally amenable to synthesis of substituted alkoxy- and amino-naphthalenes. We report here a new synthesis of novel polysubstituted naphthalenes, which bear the 'push–pull' motif of electron-withdrawing substituents on one ring and electron-donating substituents on the other.

We[5,6] and others[7] have previously reported that condensation of methyl 2-methyl-3-nitrobenzoate **1a** with dimethylformamide dimethyl acetal (dimethoxymethyl dimethylamine, DMFDMA) gives the enamine **2** (Scheme 1). Treatment of this crude enamine with silica gel provides sufficient acid catalysis to hydrolyse the enamine and cyclise the intermediate enol to the isocoumarin **3**. In an initial attempt to explore the scope and mechanism of this reaction, the isopropyl ester **1b**[8] was treated similarly with DMFDMA; the condensation followed a similar path but the cyclisation with silica gel was much slower and gave lower yields of **3** (Scheme 1). This observation is consistent with steric obstruction by the bulky isopropyl group during cyclisation.



Scheme 1. Reactions of 2-methyl-3-nitrobenzoate esters with orthoamides. *Reagents and conditions*: (i) $HC(OMe)_2NMe_2$, DMF, 150°C, 16 h, 53%; (ii) SiO_2, EtOAc; (iii) $MeC(OMe)_2NMe_2$, $MeCONMe_2$, 150°C, 16 h, 77%.

* Corresponding author. Tel.: +44-1225-826840; fax: +44-1225-826114; e-mail: m.d.threadgill@bath.ac.uk

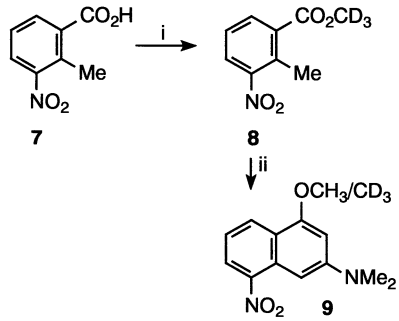
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00228-9

In contrast, when the ester **1a** was treated with dimethylacetamide dimethyl acetal (1,1-dimethoxyethyl dimethylamine, DMADMA),[9] none of the expected 3-methyl-5-nitroisocoumarin was formed. The sole isolable product was a deep red solid, formed in high yield. The strong colour suggested that it was not an isocoumarin (most 5-nitroisocoumarins are pale yellow); this was borne out by the lack of a carbonyl absorption in the IR spectrum.[9] The ^{1}H NMR spectrum[9] showed five aromatic protons, together with signals for NMe_2 and OMe. One of the aromatic proton signals was shifted markedly upfield at δ 6.48, corresponding to a location between the electron-donating NMe_2 and OMe groups. These data, together with the mass spectrum, allowed the assignment of the naphthalene structure **6** to the condensation product. The locations of the NMe_2 and OMe substituents were confirmed by a NOESY spectrum, which showed NOE connectivity between OMe and the 2-H (δ 6.48, d, $J=2.3$ Hz) and between NMe_2 and the 2-H and 4-H (δ 7.37, d, $J=2.3$ Hz). The deep red colour is a consequence of the 'push–pull' substitution pattern of the naphthalene chromophore. Compounds with a nitro group at one end of a conjugated system and an amine at the other are often deeply coloured, ranging from simple 2-nitroethenamines[10] to laser dyes and dark red 1-nitro-7-aminonaphthalenes.[11–14] For this unprecedented synthesis of the naphthalene ring system, we propose the course of reaction shown in Scheme 1. Initial condensation with the DMADMA gives the enamine **4**, by analogy with the identified intermediate enamine **2** for the sequence employing DMFDMA. Whereas the C–H enamine **2** has no opportunity for further reaction under the conditions, the C–Me enamine **4** can tautomerise to the alternative enamine **5**, presumably via an iminium species. This second enamine **5** then provides a nucleophilic carbon correctly located to attack the ester carbonyl. It is noteworthy that water is the sole leaving group in the condensation of the enamine with the ester (giving **6**); no 3-dimethylamino-5-nitronaphth-1-ol was obtained (through loss of methanol).

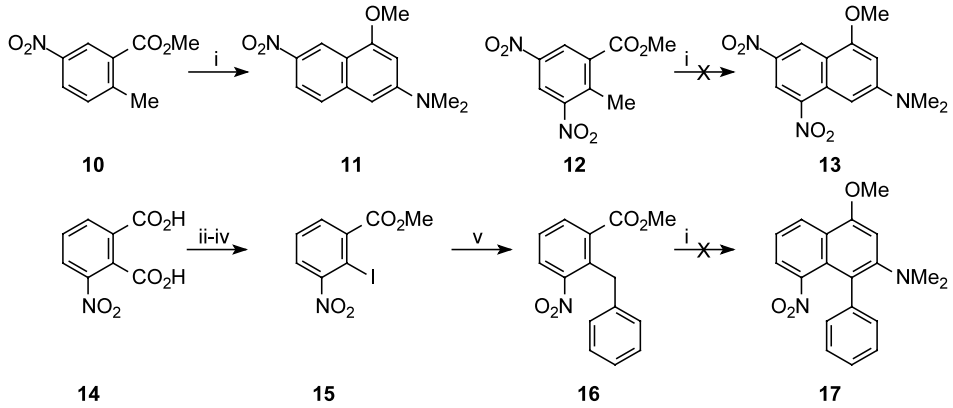
A short study revealed aspects of the mechanism, generality and limitations of this new synthesis of substituted naphthalenes. Firstly, condensation of the isopropyl ester **1b**[8] with DMADMA gave the methoxynaphthalene **6** as the sole naphthalene product (Scheme 1); no isopropoxynaphthalene was evident in the crude product mixture. This observation suggests either that the mechanism of the reaction is complex and involves intramolecular transfer of a methoxy group in an intermediate or that there is an equilibrium exchange of alkoxy groups ($Pr^iO \leftrightarrow MeO$) between the ester and the orthoamide before the final ring-closure. The complete absence of isopropoxynaphthalenes is consistent with the latter, since it is likely that ring-closure with the isopropyl ester **5b** will be much slower than that with the methyl ester **5a**, owing to the greater steric bulk of the Pr^iO; this steric retardation of ring-closure is analogous to that observed in the formation of the isocoumarin **3** from **1b**. Secondly, to select between these two alternative mechanisms (intramolecular MeO transfer and ester exchange), an isotopic competition experiment was performed (Scheme 2). 2-Methyl-3-nitrobenzoic acid **7** was converted to its trideuteromethyl (CD_3) ester **8**[15] in 88% yield. This isotopomer was then treated with DMADMA in which the methoxy groups were all OCH_3, under the standard reaction conditions. Mass spectroscopic and NMR analysis of the product **9** showed that the ratio of OCD_3 to OCH_3 corresponded to the ratio of OCD_3 (in **8**) to OCH_3 (in DMADMA) in the reaction mixture. Thus, as there is virtually no difference between the steric requirements of CD_3 and CH_3, the mechanism must involve full equilibration of the alkoxy groups between the ester and the orthoamide before final ring-closure. Hence, introduction of alternative alkoxy groups at position-1 of the naphthalene in this new condensation will require other appropriate orthoamides.

Scheme 3 shows three further studies on the generality of the reaction. Treatment of methyl 2-methyl-5-nitrobenzoate **10**[16] with DMADMA under the standard reaction conditions gave the corresponding 1-methoxy-3-dimethylamino-7-nitronaphthalene **11**.[17] In contrast, similar treatment of the 3,5-dinitro analogue **12**,[18] in which the arylmethyl group is further activated, gave only degradation products. To explore an alternative approach to activating the arylmethyl further and, simultaneously, to introduce a 4-substituent into the naphthalene, methyl 2-benzyl-3-nitrobenzoate **16** was synthesised. 3-Nitrophthalic acid **14** was decarboxylated/mercurated with $Hg(OAc)_2$ and the intermediate aryl-Hg compound was treated with iodine to give 2-iodo-3-nitrobenzoic acid, by the method of Seno et al.;[19] this was converted to its methyl ester **15**. Negishi coupling with benzyl zinc bromide/DIBAL-H/$Pd(PPh_3)_2Cl_2$ then afforded the novel 2-benzylbenzoate ester **16** in moderate yield.[20] However, this failed to afford the target 4-phenylnaphthalene **17** on treatment with DMADMA.

In this letter, we report a novel method for the synthesis of substituted naphthalenes by treatment of nitro-2-methylbenzoate esters with dimethylacetamide dimethyl acetal (DMADMA), together with early studies on its



Scheme 2. Studies on the source of the naphthalene 1-substituent. *Reagents and conditions*: (i) CD_3OD, H_2SO_4, reflux, 72 h; (iii) $MeC(OCH_3)_2NMe_2$ (3 equiv.), $MeCONMe_2$, 150°C, 16 h.



Scheme 3. Synthesis of 1-methoxy-3-dimethylamino-7-nitronaphthalene **11** and preliminary exploration of the limitations of the naphthalene-forming condensation reaction. *Reagents and conditions*: (i) $MeC(OMe)_2NMe_2$, $MeCONMe_2$, 150°C, 16 h, 5.3%; (ii) $Hg(OAc)_2$, aq. NaOH (10%), reflux, 3 days; (iii) I_2, aq. NaOH (3.4%), reflux, 16 h; (iv) MeOH, H_2SO_4, 62% from **14**; (v) $PhCH_2ZnBr$, $Bu^i{}_2AlH$, $Pd(PPh_3)_2Cl_2$, THF, 45°C, 72 h, 32%.

mechanism and generality. This condensation has considerable potential for construction of 'push-pull'-substituted polycyclic arenes. The results of a more comprehensive study on this reaction will be published later.

Acknowledgements

We thank Mr. R. R. Hartell and Mr. D. J. Wood for the NMR spectra and Mr. C. Cryer for the mass spectra. J.A.W. held a Research Studentship from the Department of Pharmacy & Pharmacology, University of Bath. Part of this work was carried out by S.-M.W., B.S., P.S. and I.C.B. as an Undergraduate Research Project for the MPharm degree.

References

1. Bailey, A. S.; Shuttleworth, A. J. *J. Chem. Soc. C* **1968**, 1115.
2. House, H. O.; Koepsell, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003.
3. Sepiol, J. J.; Wilamowski, J. *Tetrahedron Lett.* **2001**, *42*, 5287.
4. Sibi, M. P.; Dankwart, J. W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 271.
5. McDonald, M. C.; Mota-Filipe, H.; Wright, J. A.; Abdelrahman, M.; Threadgill, M. D.; Thompson, A. S.; Thiemermann, C. *Br. J. Pharmacol.* **2000**, *130*, 843.
6. Parveen, I.; Naughton, D. P.; Whish, W. J. D.; Threadgill, M. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2031.
7. Somei, M.; Karasawa, Y.; Shoda, T.; Kaneko, C. *Chem. Pharm. Bull.* **1981**, *29*, 249.
8. Rohr, O. US Patent 4048217, **1997**.
9. **Synthesis of 6**. Ester **1a** (1.01 g, 5.2 mmol) was heated at 150°C with $MeC(OMe)_2NMe_2$ (2.5 g, 18.8 mmol) in $MeCONMe_2$ (6 mL) for 16 h. Evaporation and chromatography (hexane/EtOAc, 10:1) gave **6** (990 mg, 77%) as dark red needles; mp 123–124°C; IR ν_{max} 1522, 1343 cm^{-1}; NMR ($CDCl_3$) δ_H 3.13 (6H, s, NMe_2), 4.00 (3H, s, OMe), 6.48 (1H, d, $J=2.3$ Hz, 2-H), 7.11 (1H, dd, $J=8.2$, 7.8 Hz, 7-H), 7.37 (1H, d, $J=2.3$ Hz, 4-H), 8.24 (1H, dd, $J=7.8$, 1.2 Hz, 8-H), 8.37 (1H, dd, $J=8.2$, 1.2 Hz, 6-H); MS (EI) m/z 246 (M). Found: C, 63.4; H, 5.72; N, 11.4. $C_{13}H_{14}N_2O_3$ requires C, 63.41; H, 5.69; N, 11.38%.
10. Gate, E. N.; Meek, M. A.; Schwalbe, C. H.; Stevens, M. F. G.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 251.
11. Schurman, J. V.; Becker, E. I. *J. Org. Chem.* **1953**, *18*, 211.
12. Friedländer, P.; Szymanski, S. *Chem. Ber.* **1892**, *25*, 2076.
13. Machida, M.; Bando, M.; Migata, Y.; Machida, M. I.; Kanaoka, Y. *Chem. Pharm. Bull.* **1976**, *24*, 3045.
14. Gould, R. G.; Jacobs, W. A. *J. Biol. Chem.* **1939**, *130*, 407.
15. **Data for 8**: Mp 62–65°C; IR (KBr) ν_{max} 2186, 1724, 1524, 1363 cm^{-1}; NMR ($(CD_3)_2SO$) δ_H 2.40 (3H, s, Me), 7.56 (1H, dd, $J=8.2$, 7.8 Hz, 5-H), 8.00 (1H, d, $J=7.8$ Hz, 6-H), 8.04 (1H, d, $J=8.2$ Hz, 4-H). Found: C, 54.4; H, 4.59; N, 7.05. $C_9H_6D_3NO_4$ requires C, 54.5; H, 4.54; N, 7.07%.
16. Phadnis, A. P.; Nanda, B.; Patwardhan, S. A.; Gupta, A. S. *Indian J. Chem. B* **1984**, *23*, 1098.
17. **Data for 11**: Dark red needles; mp 172–174°C; NMR ($CDCl_3$) δ_H 3.15 (6H, s, NMe_2), 4.03 (3H, s, OMe), 6.52 (1H, brs, 2-H), 6.56 (1H, brs, 4-H), 7.54 (1H, d, $J=9.5$ Hz, 5-H), 8.08 (1H, dd, $J=9.5$, 2.6 Hz, 6-H), 9.00 (1H, d, $J=2.6$ Hz, 8-H); δ_C 40.5, 55.5, 95.1, 98.3, 117.0, 120.4, 120.6, 126.0, 138.7, 141.0, 151.8, 158.0; MS (EI) m/z 246.0998 (M) ($C_{13}H_{14}N_2O_3$ requires 246.1004). Found: C, 63.2; H, 5.80; N, 11.2. $C_{13}H_{14}N_2O_3$ requires C, 63.41; H, 5.69; N, 11.38%.
18. Racine, S. *Liebigs Ann. Chem.* **1887**, *239*, 71.
19. Seno, K.; Hagishita, S.; Sato, T.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2012.
20. **Synthesis of 16**. Compound **15** (2.5 g, 8.1 mmol) and benzyl zinc bromide (0.5 M in THF, 24.5 mL, 12.2 mmol) in dry THF (30 mL) were added to $Pd(PPh_3)_2Cl_2$ (330

mg, 500 μmol) and $Bu^{i}_{2}AlH$ (1.0 M in hexane, 1.0 mL, 1.0 mmol) in dry THF (15 mL) under Ar and the mixture was stirred for 72 h at 45°C. Extraction ($CHCl_3$), evaporation and chromatography (hexane/EtOAc, 9:1) gave **16** (700 mg, 32%) as a yellow oil: IR (film) ν_{max} 1731, 1532, 1362 cm^{-1}; NMR ($CDCl_3$) δ_H 3.77 (3H, s, Me), 4.52 (2H, s, CH_2), 7.02 (2H, d, $J=7.4$ Hz, Ph 2,6-H_2), 7.14 (1H, t, $J=7.4$ Hz, Ph 4-H), 7.21 (2H, t, $J=7.4$ Hz, Ph 3,5-H_2), 7.42 (1H, t, $J=7.8$ Hz, 5-H), 7.81 (1H, dd, $J=7.8$, 1.6 Hz, 6-H), 7.95 (1H, dd, $J=7.8$, 1.6 Hz, 4-H); MS (FAB) m/z 272.0921 (M+H) ($C_{15}H_{14}NO_4$ requires 272.0923).