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

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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. © 2002 Elsevier Science Ltd. All rights reserved.

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, acid-catalysed cyclisations of phenylethylidenemalononitriles to 2-cyanonaphthyl-1-amines and base-catalysed cyclisation of 2-allyl-N,N-dialkylbenzamides to naphth-1-ols. 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-donating substituents on one ring and electron-donating substituents on the other.

We and others 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 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)2NMe2, DMF, 150°C, 16 h, 53%; (ii) SiO2, EtOAc; (iii) MeC(OMe)2NMe2, MeCONMe2, 150°C, 16 h, 77%.
In contrast, when the ester 1a was treated with dimethylacetamide dimethyl acetal (1,1-dimethoxyethyl dimethylamine, DMADMA), none of the expected dimethylacetamide dimethyl acetal (1,1-dimethoxyethyl isopropyl ester) before the absence of isopropoxynaphthalenes is consistent with the methyl ester 5a; no isopropoxynaphthalene was evident in the crude product mixture. This observation suggests either that there is an equilibrium exchange of the alkoxyl groups between the ester and the orthoamide before final ring-closure. Hence, introduction of alternative alkoxyl 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 with DMADMA under the standard reaction conditions gave the corresponding 1-methoxy-3-dimethylamino-7-nitronaphthalene. In contrast, similar treatment of the 3,5-dinitro analogue 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/mercured 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., this was converted to its methyl ester. Negishi coupling with benzyl zinc bromide/DIBAL-H/Pd(PPh3)4Cl2 then afforded the novel 2-benzylbenzoate ester 16 in moderate yield. However, this failed to afford the target 4-phenynaphthalene 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 transfer and ester exchange), an isotopic competition experiment was performed (Scheme 2). 2-Methyl-3-nitrobenzoic acid 7 was converted to its trideuteromethyl (CD3) ester 8 in 88% yield. This isotopomer was then treated with DMADMA in which the methoxy groups were all OCH3, under the standard reaction conditions. Mass spectroscopic and NMR analysis of the product 9 showed that the ratio of OCD3 to OCH3 corresponded to the ratio of OCD3 (in 8) to OCH3 (in DMADMA) in the reaction mixture. Thus, as there is virtually no difference between the steric requirements of CD3 and CH3, the mechanism must involve full equilibration of the alkoxyl groups between the ester and the orthoamide before final ring-closure.

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 with DMADMA gave the methoxy- naphthalene 6 as the sole naphthalene product (Scheme 1); no isoproxyoxynaphthalene 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 alkoxyl groups (PrO→MeO) between the ester and the orthoamide before the final ring-closure. The complete absence of isoproxyoxynaphthalenes 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 PrO; 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 (CD3) ester 8 in 88% yield. This isotopomer was then treated with DMADMA in which the methoxy groups were all OCH3, under the standard reaction conditions. Mass spectroscopic and NMR analysis of the product 9 showed that the ratio of OCD3 to OCH3 corresponded to the ratio of OCD3 (in 8) to OCH3 (in DMADMA) in the reaction mixture. Thus, as there is virtually no difference between the steric requirements of CD3 and CH3, the mechanism must involve full equilibration of the alkoxyl groups between the ester and the orthoamide before final ring-closure. Hence, introduction of alternative alkoxyl groups at position-1 of the naphthalene in this new condensation will require other appropriate orthoamides.

Scheme 2. Studies on the source of the naphthalene 1-substituent. Reagents and conditions: (i) CD3OD, H2SO4, reflux, 72 h; (ii) MeC(OCH3)2NMe2 (3 equiv.), MeCONMe2, 150°C, 16 h.
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.

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References

9. Synthesis of 6. Ester 1a (1.01 g, 5.2 mmol) was heated at 150°C with MeO(CO)Me2NMe2 (2.5 g, 18.8 mmol) in MeCONMe2 (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 νmax 1522, 1343 cm⁻¹; NMR (CDCl3) δH 2.13 (6H, s, NMe2), 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. C13H14N2O3 requires C, 63.41; H, 5.69; N, 7.05. C 9H6D3NO4 requires C, 54.5; H, 4.54; N, 11.4.
15. Data for 8: Mp 62–65°C; IR (KBr) νmax 2186, 1724, 1524, 1363 cm⁻¹; NMR ((CD3)2SO) δH 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. C6H4D2NO2 requires C, 54.5; H, 4.54; N, 7.07%.
17. Data for 11: Dark red needles; mp 172–174°C; NMR (CDCl3) δH 3.15 (6H, s, NMe2), 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); δC 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) (C13H14N2O3 requires 246.1004). Found: C, 63.2; H, 5.80; N, 11.2. C13H14N2O3 requires C, 63.41; H, 5.69; N, 11.38%.
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(PPh3)2Cl2 (330
mg, 500 μmol) and Bu'3AlH (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 (CHCl3), evaporation and chromatography (hexane/ EtOAc, 9:1) gave 16 (700 mg, 32%) as a yellow oil: IR (film) νmax 1731, 1532, 1362 cm⁻¹; NMR (CDCl3) δH 3.77 (3H, s, Me), 4.52 (2H, s, CH2), 7.02 (2H, d, J=7.4 Hz, Ph 2,6-H2), 7.14 (1H, t, J=7.4 Hz, Ph 4-H), 7.21 (2H, t, J=7.4 Hz, Ph 3,5-H2), 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) (C15H14NO4 requires 272.0923).