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Lithium perchlorate accelerated Friedel-Crafts addition of furans to β-nitrostyrenes

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Abstract—The Friedel-Crafts alkylation of furans by the Michael acceptor, β -nitrostyrene, is greatly accelerated by the use of the Lewis acid catalyst and solvent, 5 M lithium perchlorate in diethyl ether (LDPE). © 2013 Elsevier Science. All rights reserved

Furan is generally acknowledged¹ to be among the weaker dienes in Diels-Alder and other cycloaddition reactions. In particular, its reaction with singly activated olefins such as acrylic esters is usually sluggish unless performed either under ultra-high pressure conditions² or in the presence of Lewis acid catalysts.³ As part of an ongoing project aimed at the synthesis of aryl-coupled 7-oxabicyclo-[2.2.1]heptanes within the ambient field of the alkaloid epibatidine, we sought to examine the Diels-Alder reaction of a number of readily available β -nitrostyrenes with furan.⁴ The current work illustrates the results obtained when Lewis acid catalysed reaction conditions were used.

In preliminary work,⁴ it was envisaged that classical Lewis acids such as zinc chloride/iodide could be used to accelerate the Diels-Alder reaction of β -nitrostyrene and furan (Scheme 1).



Scheme 1. Outcome of the furan and nitrostyrene addition reaction.

However, in this case the desired reaction did not occur, and the only product obtained was the adduct **4** of Friedel-Crafts addition at C2, in low yield. Indeed zinc iodide has been reported⁵ to catalyse the production of **4** in good yield, however, in our hands the yields of the product varied widely due to extensive polymerisation of the furan. Compound **4** and related indolyl compounds have also been prepared by the reversed process of 1,4-addition of arylboronic esters to 2-(2-nitroethenyl)furan.⁵

The observed product could be envisaged as either arising from a direct Friedel-Crafts addition on the strongly polarised nitroolefin, (Scheme 2) or via cycloaddition followed by a rearrangement (Scheme 3). In this experiment and all other following Lewis acid catalysed reactions, no trace of cycloaddition products **5** with furan were ever found, before or after column chromatography. Campbell *et al.*⁶ also reported no evidence of a cycloaddition pathway.



Scheme 2. Direct Friedel-Crafts alkylation route

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Nitroethylene⁷ has been previously reported to react with furan in the absence of any catalyst to yield a related





nitroethyl product, and recently, Itoh8 has reported the addition of the highly reactive 2-methoxyfuran to nitrostyrenes, also in the absence of Lewis catalysts. However, in this instance, furan and 2-methylfuran were unreactive.⁸ These authors speculate that the reaction may proceed through a bicyclic intermediate as in Scheme 3 which undergoes a rearrangement to yield the final product. Sera et al.9 have also reported a Michael-type product in of furan the addition to diethyl (acetoxymethylene)malonate when a combination of Lewis acid (ZnI₂) catalysis and high pressure (1 GPa) was used. In the absence of a Lewis acid, the expected cycloaddition products and some multiaddition products were observed.

We then sought to optimise the yield of 4, as these compounds could be of interest in the synthesis of more complex molecules. Reduction of the nitro group would lead to furyl ethanamines, previously incorporated into dopamine antagonists,¹⁰ appetite suppressants,¹¹ and inhibitors of platelet aggregation.¹² The use of lithium perchlorate in diethyl ether (hereafter LPDE) as a Diels-Alder accelerant has received widespread attention following the landmark work of Grieco.¹³ We thought that if these reactions were proceeding via a cycloaddition or other polarised transition state pathway, then this solvent could be of use in maximising yields and shortening reaction times. Interestingly, the reaction did produce the desired alkylated product **4** in 93% yield,¹⁴ however, the reaction still required two days at room temperature. We propose that the lithium perchlorate is providing additional activation of the reaction by further stabilizing the nitrostyrene in the polarised nitronic acid-benzyl cation form. In order to examine the generality of this reaction, a number of readily available nitrostyrenes were synthesised simply from the aromatic aldehydes by Henry methodology, and then subjected to the LDPE reaction with furan.¹⁵ In all cases (Table 1), excellent yields of the

Friedel-Crafts products were obtained. The presence of electron-donating substituents on the aromatic ring of the nitrostyrene slowed the reaction somewhat as observed by monitoring the reactions by GC, but the reactions were generally complete after 2-3 days.

Table 1. Yields and reaction times for furan additions



^a The value in parentheses represents the percentage yield of all GCdetectable products in the crude reaction mixtures. ^b Any impurities below the common threshold set for all experiments. ^c Reaction occurred at C3 (see Figure 1)

The electron-rich furan ring is required for these reactions to proceed as control experiments using benzene or anisole as the arene, and nitrostyrenes or succinic anhydride as the reaction partner, gave no product under LDPE conditions.

Replacement of furan with the more electron-rich 2methylfuran resulted in a dramatic improvement in reaction rate. Additions with 2-methylfuran were found to raise the temperature of the reaction mixture above the boiling point of ether at the onset of reaction. Brief initial cooling is therefore required to stop the reaction mixture becoming too dry to stir effectively. Subsequently, the reaction is complete within six hours at room temperature. In contrast, a recent paper reports the zinc iodide mediated addition of 2-methylfuran to nitrostyrene taking three days at room temperature.¹⁶ When 2,5-dimethylfuran is used the reaction occurs more slowly once again, this time however, Friedel-Crafts alkylation occurs at C3. We initially aimed to use 2methylfuran to aid in the elucidation of a cycloaddition mechanism, as the additional asymmetry could result in both regioisomers and exo-endo mixtures being formed. Unfortunately, both in this case and with 2,5dimethylfuran, no cycloaddition products were observed in the preparation of either 5 or 6, further hindering the elucidation of the reaction mechanism.

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Figure 1. Products from 2-methylfuran and 2,5-dimethylfuran

In conclusion, 5 M lithium perchlorate in diethyl ether is a versatile Lewis acid catalyst for the mild, and high-yielding Friedel-Crafts alkylation of furans. Furan and 2-methylfuran react exclusively at C2 or C5, whilst 2,5-dimethylfuran reacts more slowly at C3. Work is continuing on the application of this technique to the synthesis of more complex heterocyclic systems, and agents of biological interest.

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- 14 As with all acid-catalysed reactions of furans, some polymerisation occurs in these reactions. Polymeric material accounts for the remainder of material not converted into product.
- 15 General Procedure: To a mixture of the nitrostyrene (1.5 mmol) and furan (1 ml) was added a solution of LiClO₄ in Et₂O (5 M, 1.5 ml). The mixture was stirred at room temperature until GC analysis of small aliquots worked up as below indicated complete conversion of the starting styrene. The mixture was then partitioned between Et₂O (10 ml) and H₂O (10 ml). The organic layer was washed with saturated NaCl solution, dried over anhydrous Na₂SO₄, filtered and evaporated. The residues were purified where necessary by column chromatography (50 g, SiO₂) in CH₂Cl₂:petroleum ether (1:1) to >95% purity by ¹H NMR. The following

compounds were prepared via the above procedure: (4a) Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.30-7.16 (6H, m), 6.21 (1H, dd, J 3.3, 1.8 Hz), 6.12 (1H, br d, J 3.3 Hz), 5.02 (1H, dd, J 12.2, 7.6 Hz), 4.94 (1H, t, J 7.6 Hz), 4.81 (1H, dd, J 12.2, 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 151.8, 142.2, 136.7, 128.7, 127.7, 127.6, 110.2, 107.1, 77.57, 43.12. *m/z* (EI): 217 (M^+ , 1%), 170 (100). $C_{12}H_{11}NO_3$ (217.07): calcd. 217.0739, found 217.0739. All data were in accordance with literature values.^{4,5} (**4b**) Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.20 (1H, dd, J 1.8, 0.5 Hz), 7.15 (2H, d, J 8.5 Hz), 7.06 (2H, d, J 8.5 Hz), 6.15 (1H, dd, J 3.3, 1.8 Hz), 5.96 (H, br d, J 3.3 Hz), 4.99 (1H, dd, J 11.9, 7.6 Hz), 4.92 (1H, t, J 7.6 Hz), 4.79 (1H, dd, J 11.9, 7.6 Hz). 13 C NMR (100 MHz, CDCl₃): δ 151.2, 142.5, 135.2, 133.7, 129.1, 129.0, 110.4, 107.3, 77.47, 42.6. m/z (EI): 251 (M⁺, 1%), 204 (100). C₁₂H₁₀ClNO₃ (251.03): calcd. C 57.3, H (40), N 5.6, found C 57.4, H 4.2, N 5.3. (**4c**) Colourless oil. ¹H NMR (400 MHz, CDCl₃): 8 7.31 (1H, d, *J* 2.0 Hz), 7.16 (2H, d, *J* 8.8 Hz), 6.83 (2H, d, *J* 8.8 Hz), 6.25 (1H, dd, *J* 3.3, 2.0 Hz), 6.06 (1H, br d, *J* 3.3 Hz), 4.98 (1H, dd, *J* 12.3, 7.6 Hz), 4.90 (1H, t, *J* 7.6 Hz), 4.77 (1H, dd, *J* 12.3, 7.6 Hz), 3.70 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ 159.0, 152.2, 142.2, 128.8, 128.6, 114.1, 110.2, 107.0, 77.9, 54.9, 42.5. m/z (EI): 247 (M⁺ 128.8, 128.6, 114.1, 110.2, 107.0, 77.9, 54.9, 42.5. m/z (EI): 247 (M⁺, 7%), 200 (100). $C_{13}H_{13}NO_4$ (247.08): calcd. C 63.2, H 5.3, N 5.7, found C 63.3, H 5.4, N 5.5. (**4d**) Brown oil. ⁻¹H NMR (400 MHz, CDCl₃): δ 7.32 (1H, dd, J 2.0, 0.8 Hz), 7.17 (1H, dd, J 4.5, 1.8 Hz), 6.95-6.87 (2H, m), 6.27 (1H, dd, J 3.3, 2.0, Hz), 6.16 (1H, ddd, J 3.3, 0.8, 0.8 Hz), 5.19 (1H, t, J 7.8 Hz), 4.92 (1H, dd, J 12.8, 7.8 Hz), 4.76 (1H, dd, J 12.8, 7.8 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 151.0, 142.4, 139.0, 126.9, 126.1, 125.3, 110.3, 107.4, 78.2, 38.4. m/z (EI): 223 (M⁺, 1%), 176 (100). $C_{10}H_{5}NO_{3}S$ (223.03): calcd. 223.0303, found 223.0303. (**4e**) Brown oil. ⁻¹H NMR (400 MHz, CDCl₃): δ 8.38 (1H, d, J 2.8, Hz), 7.64 (1H, dd, J 3.3, 2.8 Hz), 7.40 (1H, dd, J 2.0, 0.8 Hz), 7.34 (1H, d, J 8.3, Hz), 6.35 (1H, dd, J 3.3, 2.0 Hz). (1H, dd, J 2.0, 0.8 Hz), 7.34 (1H, d, J 8.3 Hz), 6.35 (1H, dd, J 3.3, 2.0 Hz), (1H, dd, J 2.0, 0.8 Hz), 1.34 (1H, d, J 8.5 Hz), 0.33 (1H, dd, J 3.3, 2.0 Hz), 6.17 (1H, d, J 3.3 Hz), 5.05 (1H, dd, J 12.3, 7.0 Hz), 4.96 (1H, app. t, J 7.6 Hz) 4.84 (1H, dd, J 12.3, 8.1 Hz). ¹³C NMR (100 MHz, CDCl₃): 8 150.8, 149.8, 148.9, 142.8, 138.0, 131.5, 124.3, 110.4, 107.7, 76.8, 39.9. m/z(EI): 207 (³⁷Cl, M-HNO₂, 31%), 206 (14), 205 (³⁵Cl, M-HNO₂, 100). C₁₁H₂ClN₂O₃ (252.03): calcd. 252.0302, found 252.0301. (dH) Colourless oil. ¹H NMR (400 MHz, CDCl₃): δ 7.40 (1H, dd, J 2.0, 0.8 Hz), 7.2-7.0 (4H, m), 6.23 (1H, dd, J 3.3, 2.0 Hz), 6.05 (1H, d, J 3.3 Hz), 4.98 (1H, app. t, J 7.4 Hz), 4.89 (1H, dd, J 11.8, 8.1 Hz), 4.82 (1H, dd, J 11.8, 7.0 Hz), 2.26 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ 152.1, 142.2, 137.6, 133.7, 129.5, 127.5, 110.2, 107.0, 77.8, 42.9, 20.8. *m/z* (EI): 231 (M⁺, 1%), 184 (100). C13H13NO3 (231.09): calcd. C 67.52, H 5.67, N 6.06, found C 67.50, H 5.95, N 6.07. Calcd. 231.0895, found C 231.0895. (4g) Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.34 (1H, d, J 2.0 Hz), 7.29 (1H, dd, J 2.0, 0.8 Hz), 7.14 (1H, dd, J 8.5, 2.0 Hz), 7.04 (1H, d, J 8.5 Hz), 6.24 (1H, dd, J 3.3, 2.0 Hz), 6.12 (1H, d, J 3.3 Hz), 5.35 (1H, dd, J 8.8, 7.0 Hz), 4.87 (1H, dd, *J* 13.3, 8.8 Hz), 4.72 (1H, dd, *J* 13.3, 7.0 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 150.0, 142.8, 134.4, 134.2, 133.0, 129.8, 129.7, 127.7, 110.5, 108.1, 75.8, 39.2. *m*/*z* (EI): 285 (³⁵Cl, ³⁵Cl, M⁺, <1%), 238 (100). C₁₂H₉Cl₂NO₃ (285.00): calcd. 284.9959, found 284.9959. (5) Pale yellow oil. ¹H NMR (400 MHz, CDCl₃): 8 7.28-7.18 (5H, m), 5.92 (1H, br d, J 3.1, Hz), 5.82 (1H, dq, J 3.1, 1.0 Hz), 4.93 (1H, dd, J 11.9, 7.6 Hz), 4.86 (1H, app. t, J 7.5 Hz), 4.73 (1H, dd, J 11.9, 7.2 Hz), 2.15 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ 151.9, 149.9, 136.9, 128.7, 127.7, 127.6, 107.7, 106.1, 77.7, 43.3, 13.1. m/z (EI): 231 (M⁺, 3%), 184 (100). C₁₃H₁₃NO₃ (231.09): calcd. C 67.52, H 5.67, N 6.06, found C 67.38, H 5.80, N 5.77. Calcd. 231.0895, found C 231.0895. (6) Pale yellow oil. NMR (200 MHz, CDCl₃): δ 7.5-7.0 (5H, m, ArH), 5.86 (1H, s), 4.84 (1H, dd, J 11.8, 8.0 Hz), 4.75 (1H, dd, J 11.8, 8.0 Hz), 4.66 (1H, br t, J 8.0 Hz), 2.13 (6H, s). 15 C NMR (50 MHz, CDCl₃) δ 150.1, 146.5, 139.14, 128.7, 127.2, 127.1, 117.3, 104.7, 79.1, 40.1, 13.2, 11.2. *m/z* (EI): 245 (M⁺, 72%), 155 (100). C₁₄H₁₅NO₃ (245.11): calcd. 245.1052, found 245.1052.
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