Synthesis of 3,4-Dihydro-2H-pyrans by Hetero-Diels-Alder Reactions of Functionalized α,β-Unsaturated Carbonyl Compounds with Styrenes

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Hetero-Diels-Alder Reaction, α,β-Unsaturated Ketones, Styrenes

Cycloadditions of 3-aryl-2-benzoyl-2-propenenitriles 1a,b to styrene (2a) and its methyl- or methoxy-substituted derivatives 2b–d proceed regio- and diastereoselectively yielding cis and trans diastereoisomers of 2,4,6-triaryl-3,4-dihydro-2H-pyran-5-carbonitriles 3 and 4 in 59–72% yield. Cycloadducts cis-3 were the major products. Reaction of 5-(4-nitrobenzylidene)-1,3-dimethylbarbituric acid (5) with styrenes 2a–d afforded diastereoisomeric mixtures of 2H-pyran[2,3-d]pyrimidine-2,4(3H)-diones cis-6 and trans-7 in 71–78% yield.

Introduction

Hetero-Diels-Alder reactions of compounds containing an 1-oxa-1,3-butadiene system with electron-rich olefins lead to 3,4-dihydro-2H-pyran containing an 1-oxa-1,3-butadiene system with rated carbonyl compounds [19, 20]. To improve reports describe their reactions with α,β-unsaturated cyclic addition with inverse electron demand [9]. The reactivity of α,β-unsaturated carbonyl compounds as dienes is generally low and the reactions require high temperature [9–10] or high pressure [11–13]. The reactivity can be enhanced by introducing electron-withdrawing substituents into the 1-oxa-1,3-butadiene system [14–17]. These groups lower the LUMO energy so that this orbital can more easily interact with the HOMO of the dienophile.

Styrenes are known as efficient dienophiles in conventional Diels-Alder cycloadditions [18], however in cycloadditions with inverse electron demand they react reluctantly. Only a few literature reports describe their reactions with α,β-unsaturated carbonyl compounds [19, 20]. To improve the reactivity of styrenes and the diastereoselectivity of these reactions, Lewis acids such as ZnI₂ [21], AlCl₃ [22], SnCl₄ [23] and europium complexes [24, 25] were used. Introduction of electron-donating groups in para position of the phenyl ring of styrenes also increases their reactivity towards α,β-unsaturated carbonyl compounds [26].

Recently, we have reported that Diels-Alder reactions of some 3-cyano-1-oxa-1,3-butadienes with enol ethers lead efficiently to 2-alkoxy-3,4-dihydro-2H-pyran-5-carbonitriles [27]. In this paper we present the results of an extension of this work, namely cycloadditions to styrenes.

Results and Discussion

One main aim of the present work was to investigate reactivity of styrene (2a) and its 4-methyl-phenyl-, α-methyl, 4-methoxyphenyl-substituted derivatives 2b–d as dienophile components in hetero-Diels-Alder reactions with inverse electron demand, and to determine the influence of these substituents on the diastereoselectivity of cycloadditions. In our experiments we used 3-aryl-2-benzoyl-2-propenenitriles 1a,b and 5-(4-nitrobenzylidene)-1,3-dimethylbarbituric acid (5) as dienes possessing electron-withdrawing groups. Compounds 1a,b and 5 were obtained according to the methods described in the literature [28, 29]. Compounds 1a,b and 5 exist as E isomers with s-Z conformation [27], which is suitable for Diels-Alder cycloaddition. The reactions of dienes 1a,b with styrenes 2a–d were performed in boiling toluene (Scheme 1). Most of these reactions go to completion within 36 h producing mixtures of the cis and trans diastereoisomers of 2,4,6-triaryl-3,4-dihydro-2H-pyran-5-carbonitriles 3/4 with the cis-3 diastereoisomers as the main products. The yields of pro-
ducts were between 59 and 72%. The diastereoisomers could be separated only partially by column chromatography. We managed to isolate all pure cis-3 compounds but only one pure trans diastereoisomer (4e). Cycloadducts 3 and 4 were characterized by $^1$H, $^{13}$C NMR, IR, and mass spectra.

Scheme 1.

The structures of 2H-dihydropyrans 3 and 4 were assigned on the basis of $^1$H NMR spectra. Their relative cis and trans configuration and the half-chair conformation were inferred from the chemical shift values and coupling constants of protons attached to C-2, C-4 of the dihydropyran ring. For diastereoisomers 3 (R = H) proton 2-H resonates as a doublet of doublets at $\delta = 5.21-5.30$ ppm with large and small coupling constants ($^{3}J = 11.1-11.5$ and $1.3-1.6$ Hz) due to coupling with two protons at C-3. The large coupling constant refers to coupling of 2-H with the axial proton 3-H, and the small coupling constant results from the coupling of 2-H with the equatorial proton 3-H. Thus, the proton at C-2 in 3 obviously adopts the axial position, and the aryl group Ar$^2$ occupies the equatorial position (Fig. 1). In the spectra of 3b and 3d, the signal of 2-H appeared only as a doublet due to a large $^{3}J$ coupling constant (11.5 and 11.1 Hz), while the small vicinal coupling was obviously too small to be observed. The signal of 4-H appears as a doublet of doublets at $\delta = 4.01-4.17$ ppm with the coupling constants $^{3}J = 10.4-12.1$ and 5.8-6.5 Hz, also due to coupling with two protons at C-3. Thus, 4-H occupies a pseudo-equatorial position, and the aryl groups Ar$^1$ adopt a pseudo-equatorial orientation (Fig. 1).

In compounds 3c, 3g (R$^2$ = CH$_3$) the aryl group Ar$^1$ at C-4 is in pseudo-equatorial position because proton 4-H resonates as a doublet of doublets at $\delta = 3.87-4.02$ ppm with two large coupling constants ($^{3}J = 6.4-6.5$ and 10.4-10.5 Hz). The orientation of methyl and phenyl groups at C-2 was assigned on the basis of a NOESY spectrum of compound 3c. In this spectrum there is a strong cross peak correlating 4-H with the protons of 2-CH$_3$. Thus, in compounds 3c,g the methyl group occupies the axial position and the phenyl group is oriented equatorially. The considered compounds 3 are cis diastereoisomers (Fig. 1).

To assign the stereochemistry of cycloadducts 4 we considered the appropriate signals in the proton spectra of a mixture of cis and trans diastereoisomers. The proton at C-2 appears as doublet of doublets (for 4a only doublet) at $\delta = 4.92-5.0$ ppm with a large and a small coupling constant ($^{3}J = 11.0-11.4$ and 2.2-2.3 Hz). This indicates the axial position of 2-H (Fig. 1). Proton 4-H resonates as a doublet of doublets at $\delta = 3.93-4.06$ ppm with the coupling constants $^{3}J = 5.7-6.2$ and 2.3-2.4 Hz. Thus, it is oriented pseudo-equatorially and the aryl group Ar$^1$ occupies the pseudo-axial position. The compounds 4 are trans diastereoisomers (Fig. 1).

![Fig. 1. Preferred conformations of cycloadducts 3 and 4.](image)

The results of the reactions of propenenitrites 1a,b with styrenes 2a-d are summarized in Table 1. In the next experiments we studied the reactions of 5-(4-nitrobenzylidene)-1,3-dimethylbarbituric acid 5 with styrenes 2a-d (Scheme 2).

The cycloadditions were conducted in boiling toluene and most of them were completed within 24 h providing diastereoisomeric mixtures of 2H-pyrano[2,3-d]pyrimidine-2,4(3H)-diones 6 and 7 in
Table 1. Reaction conditions, yields, and diastereoisomeric ratios of cycloadducts 3 and 4.

<table>
<thead>
<tr>
<th>Cycloadducts</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>Ratio of 3:4</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a:4a</td>
<td>36</td>
<td>67</td>
<td>5.1:1</td>
</tr>
<tr>
<td>3b:4b</td>
<td>30</td>
<td>69</td>
<td>14.0:1</td>
</tr>
<tr>
<td>3c</td>
<td>28</td>
<td>65</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>3d</td>
<td>24</td>
<td>72</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>3e:4e</td>
<td>36</td>
<td>62</td>
<td>3.0:1</td>
</tr>
<tr>
<td>3f:4f</td>
<td>30</td>
<td>59</td>
<td>4.5:1</td>
</tr>
<tr>
<td>3g:4g</td>
<td>30</td>
<td>63</td>
<td>2.4:1</td>
</tr>
<tr>
<td>3h:4h</td>
<td>24</td>
<td>65</td>
<td>6.0:1</td>
</tr>
</tbody>
</table>

* All reactions were carried out at 110 °C;
* determined by $^1$H NMR spectroscopy.

The structures of cycloadducts 6 and 7 were deduced from chemical shift values and coupling constants of protons 5-H and 7-H. The signal of proton 5-H of compound cis-6 (R = H) is a doublet of doublets at $\delta = 4.22-4.24$ ppm with the coupling constants $^3J = 11.1-11.2$ and 6.8 Hz, hence 5-H must be pseudoequatorial, and the nitrophenyl group is in the pseudoequatorial position (Fig. 2). Proton 7-H resonates as a doublet of doublets at $\delta = 5.23-5.29$ ppm with a large and a small coupling constant ($^3J = 11.0-11.8$ and 1.4-1.8 Hz), thus this proton is obviously axial (Fig. 2). For diastereoisomers trans-7 (R = H) 5-H appears as a doublet of doublets at $\delta = 4.33-4.34$ ppm with the coupling constants $^3J = 5.0-6.5$ and 1.8-1.9 Hz. This indicates the pseudo-equatorial position of the 5-H and the nitrophenyl group is oriented pseudoequatorially (Fig. 2). Proton 7-H of cycloadducts trans-7 (R = H) resonates as a doublet of doublets at $\delta = 4.97-5.03$ ppm with the coupling constants $^3J = 12.0-12.1$ and 1.9-2.1 Hz. Thus, proton 7-H must be axial, and the aryl groups Ar^2 occupy the equatorial position (Fig. 2).

In compound 6c (R = CH$_3$) the 4-nitrophenyl group at C-5 is pseudoequatorial whereas in 7c it is pseudoequatorial, since the signal of proton 5-H is a doublet of doublets at $\delta = 4.15$ ppm with the coupling constants $^3J = 7.2$ and 6.8 Hz (6c) and a doublet of doublets at $\delta = 3.60$ ppm with the coupling constants $^3J = 11.9$ and 6.2 Hz (7c). The stereoechemical orientations of methyl and phenyl groups at C-7 were assigned on the basis of NOESY spectra. The spectrum of compound 6c reveals a strong correlation signal of 5-H with protons 7-CH$_3$ but in the spectrum of compound 7c the same cross peak is weak. We can conclude that in compounds 6c and 7c the phenyl group at C-7 occupies the axial position and the methyl group is oriented equatorially. The cis configuration was assigned to compound 6c and the trans configuration to compound 7c (Fig. 2).

The results of the reactions compound 5 with styrenes 2a-d are given in Table 2.

In conclusion, the [4+2]-cycloadditions of selected 4-aryl-1-oxa-1,3-butadienes to styrene and its derivatives have been shown to proceed in good yield leading to functionalized 3,4-dihydro-2H-pyrans. The cis diastereoisomers or mixtures of cis- and trans-products in which the cis-product predominates were obtained.
The presence of methyl and methoxy groups in the dienophile increases the rate and the yield of these reactions. 4-Methoxystyrene 2d is the most reactive dienophile. Styrenes were found to be less reactive than enol ethers because similar reactions of dienes 1a,b with enol ethers occurred at room temperature [27] whereas reactions with styrenes required heating in boiling toluene.

Experimental

Melting points were determined on a Boetius hot stage apparatus. – IR spectra: Bruker IFS 48 in KBr pellets. – NMR spectra: Bruker AMX 500 (1H: 500.14 MHz, 13C: 125.76 MHz) in CDCl3 with TMS as an internal standard. 13C signal assignments were confirmed by XHCO R and DEPT methods. – Mass spectra: Finnigan Mat 95 (70 eV). Microanalyses were performed with Euro EA 3000 Elemental Analyzer.

2-Benzoyl-3-(4-nitrophenyl)-2-propenenitrile (1a) and 2-benzoyl-3-(4-pyridyl)-2-propenenitrile (1b) were obtained according to lit. [27, 28]. The preparation of 5-(4-nitrobenzylidene)-1,3-dimethylbarbituric acid (5) is described in lit. [29]. Styrenes 2a-d were purchased from Aldrich.

General procedure for the synthesis of cycloadducts

The solution of the α,β-unsaturated carbonyl compounds 1a,b or 5 (5 mmol) in anhydrous toluene (10 ml) and styrenes 2a-d (5 mmol) was refluxed for 15–36 hours. The progress of the reactions was monitored by TLC. The solvent was evaporated and the mixture was separated and purified by column chromatography on silica gel using chloroform or chloroform/methanol (20:1) as an eluent. Recrystallization from t-butylmethyl ether or t-butylmethyl ether/ethanol 5:1 gave colourless crystals.

Table 2. Reaction conditions, yields, and diastereoisomeric ratios of cycloadducts 6 and 7.

<table>
<thead>
<tr>
<th>Cycloadducts</th>
<th>Reaction time (h)a</th>
<th>Yield (%)</th>
<th>Ratio of 3:4b</th>
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<tbody>
<tr>
<td>6a:7a</td>
<td>24</td>
<td>73</td>
<td>1.4:1</td>
</tr>
<tr>
<td>6b:7b</td>
<td>20</td>
<td>75</td>
<td>1.3:1</td>
</tr>
<tr>
<td>6c:7c</td>
<td>20</td>
<td>78</td>
<td>2.9:1</td>
</tr>
<tr>
<td>6d:7d</td>
<td>15</td>
<td>71</td>
<td>0.7:1</td>
</tr>
</tbody>
</table>

a The all reactions were carried out at temperature 110 °C; b determined by 1H NMR spectroscopy.

(2RS,4SR)-3,4-Dihydro-4-(4-nitrophenyl)-2,6-diphenyl-2H-pyran-5-carbonitrile (3a)

Yield 56%. – M.p. 192 °C. – IR (KBr): ν = 3105, 2923, 2848 (CH), 2195 (CN), 1611, 1594 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl3): δ = 2.12 (dd, J1 = 14.1 Hz, J2 = 11.6 Hz, J3 = 11.6 Hz, 1H, 3-Hax), 2.55 (dd, J2 = 14.2 Hz, J3 = 1.7 Hz, J4 = 6.5 Hz, 1H, 3-Heq), 4.17 (dd, J2 = 11.6 Hz, J3 = 6.5 Hz, 1H, 4-Hax), 5.30 (dd, J3 = 11.5 Hz, J4 = 1.5 Hz, 1H, 2-Heq). 7.35–8.27 (m, 14H, CHarom). – 13C[NH] NMR (125.76 MHz, CDCl3): δ = 39.27 (C-3), 41.98 (C-4), 79.60 (C-2), 86.79 (C-5), 119.14 (CN), 124.36, 125.94, 125.99, 128.36, 128.45, 128.58, 129.46, 131.30, 132.64, 135.49, 138.81, 147.50, 148.77 (CHarom), 167.50 (C-6). – MS (EI, 70 eV): m/z (%) = 382 (21) [M+], 104 (100) [C6H5C2H3N+], 77 (23) [C6H5C+]. – C25H18N2O3 (382.44): calcld. C 75.38, H 4.74, N 7.33; found C 75.28, H 4.90, N 7.33.

(2RS,4SR)-3,4-Dihydro-2-(4-tolyl)-4-(4-nitrophenyl)-6-phenyl-2H-pyran-5-carbonitrile (3b)

Yield 65%. – M.p. 166 °C. – IR (KBr): ν = 3049, 2923, 2854 (CH), 2201 (CN), 1605, 1595 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl3): δ = 2.12 (m, 1H, 3-H), 2.36 (s, 3H, CH3), 2.51 (m, 1H, 3-H), 4.14 (dd, J1 = 11.4 Hz, J2 = 6.1 Hz, 1H, 4-Hax), 5.26 (d, J3 = 11.5 Hz, 1H, 2-Heq), 7.17–8.26 (m, 13H, CHarom). – 13C[NH] NMR (125.76 MHz, CDCl3): δ = 21.13 (CH3), 39.15 (C-3), 42.07 (C-4), 79.62 (C-2), 86.74 (C-5), 119.15 (CN), 124.34, 125.99, 128.36, 128.45, 128.58, 129.46, 131.30, 132.64, 135.49, 138.81, 147.50, 148.77 (CHarom), 167.50 (C-6). – MS (EI, 70 eV): m/z (%) = 396 (9) [M+], 118 (100) [CH3C6H5C2H3N+], 105 (19) [C6H5CO+]. – C26H21N2O3 (396.44): calcld. C 75.74, H 5.08, N 7.07; found C 75.66, H 5.07, N 7.07.

(2RS,4SR)-3,4-Dihydro-2-methyl-4-(4-nitrophenyl)-2,6-diphenyl-2H-pyran-5-carbonitrile (3c)

Yield 65%. – M.p. 132 °C. – IR (KBr): ν = 3086, 3038, 2848 (CH), 2208 (CN), 1620, 1596 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl3): δ = 1.83 (s, 3H, 2-CH3), 2.15 (dd, J1 = 14.1 Hz, J2 = 10.5 Hz, 1H, 3-Hax), 2.50 (dd, J2 = 14.2 Hz, J3 = 6.5 Hz, 1H, 3-Heq), 4.02 (dd, J2 = 10.5 Hz, J3 = 6.5 Hz, 1H, 4-Hax), 7.25–8.19 (m, 14H, CHarom). – 13C[NH] NMR (125.76 MHz, CDCl3): δ = 24.96 (CH3), 39.19 (C-3), 42.51 (C-4), 80.98 (C-2), 85.04 (C-5), 119.35 (CN), 124.06, 124.13, 127.81, 128.24, 128.55, 128.74, 131.24, 133.15, 143.87, 147.16, 148.48 (CHarom), 165.56 (C-6). – MS (EI, 70 eV): m/z
(2RS,4SR)-3,4-Dihydro-2-(4-methoxyphenyl)-4-(4-nitrophenyl)-6-phenyl-2H-pyran-5-carbonitrile (3d)

Yield 72%. - M.p. 136 °C. - IR (KBr): ν = 3067, 2935, 2835 (CH), 2201 (CN), 2979, 2935 (CH), 2201 (CN), 1599 (C=C) cm⁻¹. - 1H NMR (500.14 MHz, CDCl₃): δ = 2.12 (dd, 2J = 14.0 Hz, 3J = 11.6 Hz, 3J = 11.6 Hz, 1H, 3-H₂ax), 2.46 (dd, 2J = 14.0 Hz, 3J = 1.6 Hz, 3J = 6.5 Hz, 1H, 3-H₂eq), 3.80 (s, 3H, OCH₃), 4.14 (dd, 2J = 11.4 Hz, 3J = 6.5 Hz, 1H, 4-H₂ax), 5.24 (d, 3J = 11.1 Hz, 1H, 1-H), 2-H₂ax). 6.89–8.26 (m, 13H, CH₃). - MS (EI, 70 eV): m/z (%) = 388 (25) [M+], 104 (100) [C₆H₅C₂H₅⁺], 77 (13) [C₆H₅⁺], - C₂₈H₂₁N₂O₂ (368.41): calcd. C 78.17, H 5.67, N 7.58.

Yield 94%. - M.p. 145 °C. - IR (KBr): ν = 3067, 3029, 2933, 2201 (CN), 1598 (C=C) cm⁻¹. - 1H NMR (500.14 MHz, CDCl₃): δ = 2.07 (dd, 2J = 14.1 Hz, 3J = 11.6 Hz, 3J = 11.6 Hz, 1H, 3-H₂eq), 2.36 (s, 3H, CH₃), 2.47 (dd, 2J = 14.1 Hz, 3J = 1.8 Hz, 3J = 6.5 Hz, 1H, 3-H₂eq), 4.01 (dd, 3J = 11.5 Hz, 3J = 11.5 Hz, 1H, 1-H, 4-H₂ax), 5.23 (dd, 3J = 11.5 Hz, 3J = 1.3 Hz, 1H, 2-H₂ax), 7.15–8.63 (m, 13H, CH₃). - MS (EI, 70 eV): m/z (%) = 352 (12) [M⁺], 118 (100) [C₆H₅C₆H₃⁺], 105 (38) [C₆H₅CO⁺], 77 (24) [C₆H₅⁺], - C₂₈H₂₁N₂O₂ (352.44): calcd. C 81.79, H 5.72, N 7.95; found C 81.82, H 5.78, N 7.96.

(2RS,4SR)-3,4-Dihydro-2-methyl-2,6-diphenyl-4-(4-pyridyl)-2H-pyran-5-carbonitrile (3g)

Yield 45%. - M.p. 180 °C. - IR (KBr): ν = 3061, 2979, 2935 (CH), 2201 (CN), 1599 (C=C) cm⁻¹. - 1H NMR (500.14 MHz, CDCl₃): δ = 1.81 (s, 3H, 2-CH₃), 2.47 (dd, 2J = 14.0 Hz, 3J = 6.4 Hz, 1H, 3-H₂ax), 2.11 (dd, 2J = 14.0 Hz, 3J = 10.6 Hz, 1H, 1-H, 3-H₂eq), 3.87 (dd, 3J = 10.4 Hz, 3J = 6.35 Hz, 1H, 4-H₂ax). 7.19–8.55 (m, 14H, CH₃). - MS (EI, 70 eV): m/z (%) = 352 (14) [M⁺], 118 (100) [C₆H₅(CH₃)C₂H₅⁺], 105 (38) [C₆H₅CO⁺], 77 (25) [C₆H₅⁺], - C₂₈H₂₁N₂O₂ (352.44): calcd. C 81.79, H 5.72, N 7.95; found C 81.62, H 5.92, N 7.78.

(2RS,4SR)-3,4-Dihydro-2-(4-methyl-2-phenyl-4-pyridyl)-2H-pyran-5-carbonitrile (3h)

Yield 56%. - M.p. 123 °C. - IR (KBr): ν = 3029, 2967, 2835 (CH), 2201 (CN), 1613, 1572 (C=C) cm⁻¹. - 1H NMR (500.14 MHz, CDCl₃): δ = 2.08 (dd, 2J = 14.2 Hz, 3J = 11.5 Hz, 1H, 3-H₂ax), 2.50 (dd, 2J = 14.2 Hz, 3J = 1.8 Hz, 3J = 6.5 Hz, 1H, 3-H₂eq), 4.01 (dd, 3J = 11.5 Hz, 3J = 6.5 Hz, 1H, 4-H₂ax), 5.27 (dd, 3J = 11.5 Hz, 3J = 1.7 Hz, 1H, 1-H, 2-H₂ax), 7.28–8.63 (m, 14H, CH₃). - MS (EI, 70 eV): m/z (%) = 368 (5) [M⁺], 134 (100) [C₆H₅OC₆H₄C₂H₅⁺], 105 (38) [C₆H₅CO⁺], 77 (17) [C₆H₅⁺], - C₂₉H₂₆N₂O₂ (368.43): calcd. C 78.24, H 5.47, N 7.60; found C 78.17, H 5.67, N 7.58.
(5RS,7SR)-1,5,6,7-Tetrahydro-1,3-dimethyl-7-phenyl-5-(4-nitrophenyl)-2H-pyrano[2,3-d]-pyrimidine-2,4(3H)-dione (6a)

Yield 42%. – M.p. 229 °C. – IR (KBr): ν = 3036, 3005, 2961 (CH), 1693, 1630 (C=O), 1517 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl₃): δ = 2.06 (dd, 3J = 14.4 Hz, 3J = 11.3 Hz, 1H, 6-Hax), 2.56 (dd, 3J = 14.4 Hz, 3J = 6.8 Hz, 1H, 6-Heq), 3.25 (s, 3H, 6-CH₃), 4.24 (dd, 3J = 11.1 Hz, 1H, 5-Hax), 5.29 (dd, 3J = 11.3 Hz, 1H, 5-Heq), 3.26 (s, 3H, 1-CH₃), 3.46 (s, 3H, 3-CH₃), 4.99 (dd, 3J = 12.1 Hz, 1H, 5-Heq), 4.99 (dd, 3J = 12.1 Hz, 1H, 7-Hax), 7.14–8.22 (m, 9H, CH₆ arom). – C₂₁H₁₉N₃O₅ (393.39): calcd. C 64.12, H 4.87, N 10.68; found C 64.22, H 4.88, N 10.61.

(5RS,7RS)-1,5,6,7-Tetrahydro-1,3-dimethyl-7-(4-nitrophenyl)-2H-pyrano[2,3-d]-pyrimidine-2,4(3H)-dione (6b)

Yield 33%. – M.p. 237 °C. – IR (KBr): ν = 3105, 2979, 2929 (CH), 1701, 1642 (C=O), 1603 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl₃): δ = 2.22 (ddd, 3J = 14.3 Hz, 3J = 1.9 Hz, 3J = 1.9 Hz, 1H, 6-Hax), 2.43 (ddd, 3J = 14.3 Hz, 3J = 6.0 Hz, 1H, 6-Hax), 3.35 (s, 3H, 6-CH₃), 3.47 (s, 3H, 3-CH₃), 3.44 (dd, 3J = 5.0 Hz, 1H, 5-Hax), 5.03 (dd, 3J = 12.1 Hz, 1H, 7-Hax), 7.26–8.24 (m, 9H, CH₆ arom). – 13C¹H NMR (125.76 MHz, CDCl₃): δ = 28.06 (1-CH₃), 28.89 (3-CH₃), 35.01 (C-5), 37.29 (C-6), 77.41 (C-7), 87.02 (C-4a), 124.03, 125.92, 128.49, 128.91, 129.12, 137.60, 146.94, 151.04, 151.47, (C arom), 157.36 (C-8a), 162.33 (C=O), 163.71 (C=O). – MS (EI, 70 eV): m/z (%) = 393 (38) [M⁺], 302 (88) [M⁺-CH₃C₆H₄CH₂⁺], 287 (21) [C₆H₅C₂H₃⁺], 73 (67). – C₂₂H₂₁N₃O₅ (407.42): calcd. C 64.86, H 5.19, N 10.31; found C 64.94, H 5.26, N 10.26.

(5RS,7RS)-1,5,6,7-Tetrahydro-1,3,7-trimethyl-7-(4-nitrophenyl)-2H-pyrano[2,3-d]-pyrimidine-2,4(3H)-dione (6c)

Yield 58%. – M.p. 224 °C. – IR (KBr): ν = 3105, 2979, 2929 (CH), 1708, 1647 (C=O), 1603 (C=C) cm⁻¹. – 1H NMR (500.14 MHz, CDCl₃): δ = 2.75 (s, 3H, 7-CH₃), 2.38 (dd, 3J = 14.5 Hz, 3J = 7.2 Hz, 1H, 6-Hax), 2.52 (dd, 3J = 14.5 Hz, 3J = 6.8 Hz, 1H, 6-Hax), 3.29 (s, 3H, 1-CH₃), 3.59 (s, 3H, 3-CH₃), 4.15 (t, 3J = 7.0 Hz, 1H, 4-H), 7.06–7.94 (m, 9H, CH₆ arom). – 13C¹H NMR (125.76 MHz, CDCl₃): δ = 27.58 (7-CH₃), 27.95 (1-CH₃), 28.95 (3-CH₃), 34.99 (C-5), 42.55 (C-6), 84.11 (C-7), 87.69 (C-4a), 123.36, 123.89, 127.63, 127.87, 128.49, 142.28, 145.99, 150.94 (C arom), 151.13 (C-8a), 156.41 (C=O), 161.99 (C=O). – MS (EI, 70 eV): m/z (%) = 407 (23) [M⁺], 302 (64), 118 (100) [C₆H₅C₂H₃C₂H₂⁺], 83 (21). – C₂₂H₂₁N₃O₅ (407.42): calcd. C 64.86, H 5.19, N 10.31; found C 64.84, H 5.09, N 10.15.
1-CH₃), 3.60 (dd, 3J = 11.9 Hz, 3J = 6.2 Hz, 1H, 5-H), 3.63 (s, 3H, 3-CH₃). 7.22–8.16 (m, 9H, CH₉arom). – C₂H₂N₂O₆ (407.42): calcd. C 64.86, H 5.19, N 10.31; found C 65.01, H 5.42, N 10.10.

(5RS,7SR)-1,5,6,7-Tetrahydro-1,3-dimethyl-7-(4-methoxyphenyl)-5-(4-nitrophenyl)-2H-pyrano[2,3-d]pyrimidine-2,4(3H)-dione (6d)

Yield 29%. – M.p. 207 °C. – ¹H NMR (500.14 MHz, CDCl₃): δ = 2.07 (ddd, 3J = 14.4 Hz, 3J = 11.5 Hz, 3J = 11.5 Hz, 1H, 6-Hₓeq), 2.51 (ddd, 3J = 14.4 Hz, 3J = 7.7 Hz, 3J = 1.9 Hz, 1H, 6-Hₓax), 3.25 (s, 3H, 1-CH₃), 3.42 (s, 3H, 3-CH₃), 4.22 (dd, 3J = 11.2 Hz, 3J = 6.8 Hz, 1H, 5-Hₓeq), 5.23 (dd, 3J = 11.8 Hz, 3J = 12.0 Hz, 1H, 7-Hₓeq), 5.90–8.16 (m, 8H, CH₉arom). – C₂H₂N₂O₆ (423.42): calcd. C 62.41, H 4.99, N 9.92; found C 62.48, H 5.12, N 9.87.