Supplementary Information

On-Water Synthesis of Dipyrrromethanes via bis-Hetero-Diels–Alder Reaction of Azo- and Nitrosoalkenes with Pyrrole

Nelson A. M. Pereira\textsuperscript{a}, Susana M. M. Lopes\textsuperscript{a}, Américo Lemos\textsuperscript{b,*} and Teresa M. V. D. Pinho e Melo\textsuperscript{a,*}

\textsuperscript{a}Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal
\textsuperscript{b}CIQA, FCT, University of Algarve, Campus de Gambelas, 8005-139 Faro, Portugal
E-mail: tmelo@ci.uc.pt.

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Experimental procedures and characterization data

General

$^1$H NMR spectra were recorded on an instrument operating at 400 MHz. $^{13}$C NMR spectra were recorded on an instrument operating at 100 MHz. The solvent is deuteriochloroform except where indicated otherwise. IR spectra were recorded on a Nicolet 6700 FTIR spectrometer. Mass spectra were recorded under electrospray ionization (ESI). HRMS spectra were recorded on a Finnigan MAT95 S instrument. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

Synthesis and characterization of compounds

1,1-Dichloroacetone t-butoxycarbonyl hydrazone (1a)$^1$, 2,2-dichloro-1-phenylethanone oxime (4b)$^2$ and 2,2-dibromo-1-(4’-bromophenyl)ethanone oxime (4c)$^2$ were synthesized from the corresponding 1-aryl-2,2-dihalogenoethanones according to literature procedures.

2,2-Dichloro-4’-bromoacetophenone t-butoxycarbonyl hydrazone (1c)

Hydrazone 1c was prepared from chlorination of 4-bromoacetophenone t-butoxycarbonyl hydrazone$^3$ following a literature procedure.$^4$

Obtained as a white solid in 86% yield. mp 162-164 °C (diethyl ether / n-hexane); IR: $\nu_{\text{max}}$(KBr) = 3124, 2977, 1508, 1365, 1236, 1151, 1095, 1012, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.72 (d, $J$ = 8.0 Hz, 2H, Ar), 7.44 (bs, 1H, NH), 6.63 (s, 1H, CH), 1.47 (s, 9H, t-Bu) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 151.5, 146.2, 132.8, 131.2, 125.9, 125.4, 82.7, 71.9, 28.1 ppm; HRMS (ESI): calcd. 380.9767 for C$_{13}$H$_{16}$BrCl$_2$N$_2$O$_2$ [M + H]+, found 380.9780.
Oxime 4a was prepared following a literature procedure.1 Oxime 4a was obtained as colorless crystals in 57% yield. mp °C 37-39 (n-hexane); IR: \( \nu_{\text{max}}(\text{KBr}) = 3445, 1715, 1399, 740 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.28 \) (bs, 1H, OH), 6.25 (s, 1H, CH), 2.12 (s, 3H, Me) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 155.7, 70.6, 8.6 \text{ ppm} \); HRMS (ESI): calcd. 141.9821 for C\(_3\)H\(_6\)Cl\(_2\)NO [M + H]\(^+\), found 141.9817.

General procedure for the synthesis of dipyrromethanes from hetero-Diels–Alder azo- and nitrosoalkenes with pyrrole:

**Method A**

Hydrazone 1 (1.66 mmol) or oxime 4 were added to a suspension of Na\(_2\)CO\(_3\) (8.49 mmol) in pyrrole (144 mmol) and the reaction mixture was stirred at room temperature for 66 hours. Unreacted pyrrole was recovered by distillation under reduced pressure and the residue dissolved in dichloromethane. The mixture was then filtered through a Celite pad, which was washed with dichloromethane. The solvent was evaporated and the product was purified by flash chromatography.

**Method B**

Hydrazone 1 (0.83 mmol) or oxime 4 were added to a solution of Na\(_2\)CO\(_3\) (8.30 mmol) in water (11 mL) and pyrrole (16.6 mmol). The reaction mixture was stirred at room temperature for 4 hours. After this time the mixture was extracted with dichloromethane (3 x 20 mL) and dried over Na\(_2\)SO\(_4\). The solvent and the excess of pyrrole were removed under reduced pressure. The product was crystallized with diethyl ether/n-hexane, filtered, washed with hexane and dried under vacuum.

Dipyrromethane 2a was isolated as a white solid by column chromatography [n-hexane / ethyl acetate (3/2)] in 75% yield (Method A) and 82% yield (Method B). mp 137-138 °C (diethyl ether / n-hexane); IR: \( \nu_{\text{max}}(\text{KBr}) = 3337, 2979, 1720, 1529, 1369, 1245, 1164, 715 \text{ cm}^{-1} \); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 8.74 \) (bs, 2H, NH), 7.51 (s, 1H, NH), 6.70 (bs, 2H, \( \alpha \)-H pyrrolic), 6.13 (bs, 2H, \( \beta \)-H pyrrolic), 6.05 (bs, 2H, \( \beta \)-H pyrrolic), 5.05 (s, 1H, meso), 1.83 (s, 3H, Me), 1.53 (s, 9H, t-Bu) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 156.0, 152.9, 129.1, 117.6, 108.3, 106.9, 81.4, 46.4, 28.3, 13.9 \text{ ppm} \); HRMS (ESI): calcd. 303.1815 for C\(_{16}\)H\(_{23}\)N\(_4\)O\(_2\) [M + H]\(^+\), found 303.1813.
Dipyrromethane 2b was isolated by column chromatography \([n\text{-hexane} / \text{ethyl acetate (2/1)}]\) followed by compound 3. Obtained as a yellow solid in 17% yield (Method A) and 21% yield (Method B). mp 138-140 °C (diethyl ether / \(n\text{-hexane}\)); IR: \(\nu_{\max}(\text{KBr}) = 3370, 3301, 2977, 1743, 1486, 1369, 1236, 1157, 1097, 1029, 734 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.88 \text{ (bs, 2H, NH)}, 7.65 \text{ (s, 1H, NH)}, 7.41-7.40 \text{ (m, 3H, Ph)}, 6.99 \text{ (bs, 2H, Ph)}, 6.70-6.69 \text{ (m, 2H, \(\alpha\)-H pyrrolic), 6.09-6.08 \text{ (m, 2H, \(\beta\)-H pyrrolic)}}, 5.94 \text{ (bs, 2H, \(\beta\)-H pyrrolic)}, 5.29 \text{ (s, 1H, \textit{meso})}, 1.48 \text{ and 1.42 \textit{(2s, 9H, \textit{t-Bu}) ppm); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 152.7, 145.6, 136.9, 123.6, 129.7, 129.4, 128.3, 127.2, 117.8, 108.1, 107.1, 81.6, 45.8, 28.3 \text{ ppm}; HRMS (ESI): calced. 365.1972 for C\(_{21}\)H\(_{25}\)N\(_4\)O\(_2\) [M + H]\(^+\), found 365.1980.}

Di-\(t\)-butyl 5-phenyl-1,4-dihydro-1,2,3,4-tetrazine-2,3-dicarboxylate (3)

Obtained as a white solid in 50% yield (Method A) and 31% yield (Method B). mp 165-167 °C (diethyl ether / \(n\text{-hexane}\)); IR: \(\nu_{\max}(\text{KBr}) = 3345, 3212, 3068, 2979, 1712, 1569, 1481, 1432, 1378, 1301, 1141 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.41 \text{ (bs, 1H, NH)}, 8.01 \text{ (bs, 1H, NH)}, 7.90 \text{ (s, 1H, CH)}, 7.53-7.44 \text{ (m, 2H, Ph)}, 7.31-7.29 \text{ (m, 2H, Ph)}, 1.48 \text{ (s, 9H, \(t\)-Bu)}, 1.45 \text{ (s, 9H, \(t\)-Bu)} \text{ ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 151.9, 149.3, 144.2, 129.9, 129.3, 128.9, 128.6, 82.1, 81.4, 28.2, 28.2. \text{ ppm; HRMS (ESI): calced. 385.1846 for C\(_{18}\)H\(_{26}\)N\(_4\)NaO\(_4\) [M + Na]^+\), found 385.1841.}

Dipyrromethane 2c was isolated as a yellow solid by column chromatography \([n\text{-hexane} / \text{ethyl acetate (2/1)}]\) in 38% yield (Method A) and 79% yield (Method B). mp 137-139 °C (diethyl ether / \(n\text{-hexane}\)); IR: \(\nu_{\max}(\text{KBr}) = 3369, 2977, 1735, 1484, 1238, 1159, 1093, 1010, 723 \text{ cm}^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.98 \text{ (bs, 2H, NH)}, 7.45 \text{ (s, 1H, NH)}, 7.39 \text{ (d, \(J = 8.2 \text{ Hz}, 2H, \text{ Ar}\)}, 6.67 \text{ (d, \(J = 8.2 \text{ Hz}, 2H, \text{ Ar}\)}, 6.58 \text{ (bs, 2H, \(\alpha\)-H pyrrolic)}, 5.98-5.97 \text{ (m, 2H, \(\beta\)-H pyrrolic)}, 5.79 \text{ (bs, 2H, \(\beta\)-H pyrrolic)}, 5.18 \text{ (s, 1H, \textit{meso})}, 1.36 \text{ (s, 9H, \(t\)-Bu)} \text{ ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 151.7, 144.8, 131.4, 129.8, 128.3, 127.4, 123.0, 116.8, 107.1, 106.4, 80.7, 45.1, 27.2 \text{ ppm; HRMS (ESI): calced. 443.1077 for C\(_{21}\)H\(_{25}\)BrN\(_4\)O\(_2\) [M + H]^+\), found 443.1081.}
Dipyrromethane 5 was isolated as a white solid by column chromatography \([n\text{-hexane} / \text{ethyl acetate (1/1)}]\) in 25% yield (Method A) and 74% yield (Method B). mp 142-144 ºC (diethyl ether / \(n\text{-hexane}\)); IR: \(\nu_{\text{max}}(\text{KBr}) = 3338, 1403, 1218, 1095, 1029, 948, 728 \text{ cm}^{-1}\); \(^1\text{H NMR (400 MHz, CDCl}_3/\text{DMSO-}\text{d}_6\)) \(\delta = 10.02 \text{ (s, 1H, OH)}, 9.37 \text{ (s, 2H, NH)}, 6.67 \text{ (bs, 2H, } \alpha\text{-H pyrrolic)}, 6.06 \text{ (bs, 2H, } \beta\text{-H pyrrolic)}\), 5.97 (bs, 2H, \(\alpha\text{-H pyrrolic)}\), 5.00 (s, 1H, \(\text{meso} \)), 1.84 (s, 9H, Me) ppm; \(^1\text{C NMR (100 MHz, CDCl}_3/\text{DMSO-}\text{d}_6\)) \(\delta = 157.0, 129.5, 117.2, 107.6, 106.5, 44.3, 12.3 \text{ ppm}; \) HRMS (ESI): calcd. 204.1131 for \(\text{C}_{11}\text{H}_{14}\text{N}_3\text{O} [\text{M + H}]^+\), found 204.1132.

\((Z)-5-(1'\text{-hydroxyimino-1'-phenylmethyl})\text{dipyrromethane (6a) and (E)-5-(1'-hydroxyimino-1'-phenylmethyl})\text{dipyrromethane (6b)}\)

Dipyrromethane 6b was isolated by column chromatography \([n\text{-hexane} / \text{ethyl acetate (3/2)}]\) in 3% yield followed by dipyrromethane 6a as a brown solid in 14% yield (Method A). A mixture of oximes \(Z/E\ (40/60)\) was obtained in 57% yield (Method B).

\(6a\) (Z form). mp 141-143 ºC (diethyl ether / \(n\text{-hexane}\)); IR: \(\nu_{\text{max}}(\text{KBr}) = 3374, 1637, 1402, 1095, 1027, 885, 779, 721 \text{ cm}^{-1}\); \(^1\text{H NMR (400 MHz, DMSO-}\text{d}_6\)) \(\delta = 10.75 \text{ (bs, 1H, OH)}, 10.56 \text{ (bs, 2H, NH)}, 7.29-7.27 \text{ (m, 3H, Ph)}, 7.16-7.14 \text{ (m, 2H, Ph)}, 6.61 \text{ (bs, 2H, } \alpha\text{-H pyrrolic)}, 5.88-5.87 \text{ (m, 2H, } \beta\text{-H pyrrolic)}, 5.67 \text{ (bs, 2H, } \beta\text{-H pyrrolic)}\), 5.23 (s, 1H, \(\text{meso} \)) ppm; \(^1\text{C NMR (100 MHz, DMSO-}\text{d}_6\)) \(\delta = 155.9, 134.4, 130.0, 128.2, 127.8, 127.3, 116.7, 106.9, 106.5, 43.8 \text{ ppm}; \) HRMS (ESI): calcd. 266.1288 for \(\text{C}_{16}\text{H}_{15}\text{BrN}_3\text{O} [\text{M + H}]^+\), found 266.1292.

\(6b\) (E form). Brown solid with low melting point; IR: \(\nu_{\text{max}}(\text{KBr}) = 3413, 1631, 1400, 1095, 1029, 927, 723 \text{ cm}^{-1}\); \(^1\text{H NMR (400 MHz, DMSO-}\text{d}_6\)) \(\delta = 11.47 \text{ (bs, 1H, OH)}, 10.53 \text{ (bs, 2H, NH)}, 7.28-7.20 \text{ (m, 5H, Ph)}, 6.59 \text{ (bs, 2H, } \alpha\text{-H pyrrolic)}, 6.27 \text{ (s, 1H, } \text{meso} \)), 5.89 \text{ (bs, 2H, } \beta\text{-H pyrrolic)}, 5.63 \text{ (bs, 2H, } \beta\text{-H pyrrolic)}\) ppm; \(^1\text{C NMR (100 MHz, DMSO-}\text{d}_6\)) \(\delta = 156.0, 136.1, 129.1, 127.9, 127.7, 127.4, 116.8, 107.0, 106.4, 35.0 \text{ ppm}; \) HRMS (ESI): calcd. 266.1288 for \(\text{C}_{16}\text{H}_{16}\text{N}_3\text{O} [\text{M + H}]^+\), found 266.1295.
(Z)-5-[1'-hydroxyimino-1'-(p-bromophenyl)methyl]dipyrromethane (7a) and (E)-5-[1’-hydroxyimino-1’-(p-bromophenyl)methyl]dipyrromethane (7b)

Dipyrromethane 7a was isolated as a brown solid by column chromatography [n-hexane / ethyl acetate (3/2)] in 11% yield (Method A). A mixture of oximes Z/E (28/72) was obtained in 76% yield (Method B).

7a (Z form). mp 130-132 °C (diethyl ether / n-hexane); IR: $\nu_{\text{max}}$(KBr) = 3392, 1587, 1486, 1392, 1074, 1027, 1012, 981, 734 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.18 (bs, 2H, NH), 7.46 (d, $J$ = 8.3 Hz, 2H, Ar), 7.03 (d, $J$ = 8.3 Hz, 2H, Ar), 6.69 (bs, 2H, $\alpha$-H pyrrolic), 6.15-6.14 (m, 2H, $\beta$-H pyrrolic), 6.02 (bs, 2H, $\beta$-H pyrrolic), 5.28 (s, 1H, meso) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 158.0, 132.0, 131.6, 131.4, 129.7, 128.5, 123.4, 117.9, 108.7, 107.6, 44.2 ppm; HRMS (ESI): calcd. 344.0393 for C$_{16}$H$_{15}$BrN$_3$O [M + H]$^+$, found 344.0392.

7b (E form). Brown solid with low melting point; IR: $\nu_{\text{max}}$(KBr) = 3388, 1589, 1486, 1394, 1074, 1029, 1010, 929, 833, 723 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 8.32 (bs, 2H, NH), 7.42 (d, $J$ = 8.4 Hz, 2H, Ar), 7.17 (d, $J$ = 8.3 Hz, 2H, Ar), 6.67 (bs, 2H, $\alpha$-H pyrrolic), 6.15-6.14 (m, 2H, $\beta$-H pyrrolic), 6.12 (s, 1H, meso), 6.02 (bs, 2H, $\beta$-H pyrrolic) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 158.2, 134.4, 131.5, 129.3, 127.3, 123.3, 117.6, 108.5, 107.8, 37.7 ppm; HRMS (ESI): calcd. 344.0393 for C$_{16}$H$_{15}$BrN$_3$O [M + H]$^+$, found 344.0391.
References

NMR spectra of new compounds

Fig. 1. $^1$H NMR and $^{13}$C NMR spectra of hydrazone 1b.
Fig. 2. $^1$H NMR and $^{13}$C NMR spectra of hydrazone 1c.
Fig. 3. $^1$H NMR and $^{13}$C NMR spectra of oxime 4a.
Fig. 4. $^1$H NMR and $^{13}$C NMR spectra of dipyromethane 2a.
Fig. 5. $^1$H NMR and $^{13}$C NMR spectra of dipyrrromethane 2b.
Fig. 6. $^1$H NMR and $^{13}$C NMR spectra of compound 3.
Fig. 7. $^{13}$C-DEPT135 NMR and $^1$H-$^1$H-NOESY NMR spectra of compound 3.
Fig. 8. $^1$H-$^{13}$C-HMQC NMR (upon) and $^1$H-$^{13}$C-HMBC NMR (bottom) spectra of compound 3.
Fig. 9. $^1$H NMR and $^{13}$C NMR spectra of compound 2c.
Fig. 10. $^1$H NMR and $^{13}$C NMR spectra of dipyromethane 5.
Fig. 11. $^1$H NMR and $^{13}$C NMR spectra of dipyrromethane 6a.
Fig. 12. $^1$H-$^1$H-NOESY NMR spectrum of compound 6a.
Fig. 13. $^1$H NMR and $^{13}$C NMR spectra of dipyrromethane 6b.
Fig. 14. $^1$H-$^1$H-NOESY NMR spectrum of compound 6b.
Fig. 15. $^1$H NMR and $^{13}$C NMR spectra of dipyromethane 7a.
Fig. 16. $^1$H NMR and $^{13}$C NMR spectra of dipyrrmethane 7b.