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TETRAHEDRON: ASYMMETRY

Diastereoselective synthesis of 3,6-dihydro-2*H*-1,3,4-thiadiazines

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Abstract

Thionation of the benzil hydrazones **3** with Lawesson's reagent afforded the 3,6-dihydro-2H-1,3,4-thiadiazines **4** by an intramolecular cyclisation. This reaction was shown to be diastereospecific and allowed the formation of the *exo* compounds **4b**–**e**. When the homochiral SAMP–hydrazone **3f** was used, the reaction afforded enantiomerically pure (4R,6R,9S)-**4f**. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

1,3,4-Thiadiazines are of great interest since many compounds possessing this structure have useful applications in very different areas such as pharmacology,¹ agriculture² or photography.³ Several reviews⁴ report the preparation of this six-membered heterocyclic system and its use in the synthesis of other heterocycles. In this report, we describe an original method leading to the 3,6-dihydro-2*H*-1,3,4thiadiazines **4** using a diastereospecific reaction.

2. Results and discussion

We have recently shown in our studies on 4-amino-1-thia-4-azabutadienes that the α -hydrazonothioamides 1 can isomerise into 3,6-dihydro-2*H*-1,3,4-thiadiazines 2 by simple heating⁵ (Scheme 1).

The dialkylhydrazones **3** were prepared as previously described⁶ by condensation of benzil with one equivalent of a dialkylhydrazine. The compounds **3** thus obtained were treated with Lawesson's reagent (LR) to give the dihydrothiadiazines **4** without isolation of any intermediates (Scheme 2).

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This type of intramolecular cyclisation has already been described by D. N. Reinhoudt⁷ and J. P. Pradère⁸ who obtained 1,3-thiazines from thioamide vinylogues. M. Hojo also prepared thiadiazines by a similar method.⁹

The mechanism for the transformation of 3 into 4 involves an intermediate thiocarbonyl compound 5 whose mesomeric form 6 is transformed by [1,5]-proton shift to the intermediate 7. Cyclisation resulting from nucleophilic addition of the thiolate to the iminium ion in 7 then leads to the dihydrothiadiazine 4 (Scheme 3).



When the cyclic hydrazines (*N*-aminopyrrolidine, *N*-aminopiperidine, *N*-aminomorpholine, *N*-aminohomopiperidine) were used in this reaction, the resultant compound **4** possessed two stereogenic centres and so two diastereomers were possible. However, only one diastereomer was detected by ¹H and ¹³C NMR spectroscopy. Furthermore, chiral HPLC¹⁰ showed only two peaks of equal intensity corresponding to the two expected enantiomers.

The diastereoselectivity of this reaction is easily explained by considering the geometry of the 'thiolate iminium' species 8 and 9. In this intermediate, the first chiral centre is already present and its stereochemistry can be either R (species 8a,b) or S (species 9a,b). Attack of the thiolate can then occur only on that face of the iminium ion in which steric interactions between the two bulky aromatic rings are minimised. Addition of a thiolate ion 8 with the R configuration thus takes place on the Re face of the iminium ion whereas a thiolate ion 9 with the S configuration adds to the Si face (Scheme 4).

By this mechanism the diastereomer RR-SS ($4b_1,b_2$) is obtained. At this stage the sole evidence for the relative stereochemistry of 4 was based on comparison of the ¹H NMR spectra of compounds 4a and 4b-e. In 4a the proton in position 6 was coupled (⁴J=1.8 Hz) to only one of the protons in position 2



which has been proved to be H_{cis} by an NOE experiment which showed enhancement of H_{cis} when H_6 was irradiated (Scheme 5).



Scheme 5.

For the compounds $4\mathbf{b}-\mathbf{e}$ no coupling constant was observed between H₂ and H₆. Both protons are thus in a *trans* relationship. This observation confirms the stereochemistry expected from the proposed mechanism.

The synthesis was now investigated using a cyclic hydrazine bearing a chiral centre: SAMP¹¹ ((*S*)-1-amino-2-methoxymethylpyrrolidine). The bulky methoxymethyl group will hinder the *Si* face of the intermediate 'thiolate iminium' **10b** so that ring closure of this species will be impossible. The thiadiazine **4f** resulting from the ring closure of the species **10a** was thus obtained as a pure stereoisomer with absolute configuration 4R, 6R, 9S as proved by X-ray structure analysis¹² (Scheme 6).



Scheme 6.

3. Conclusion

Current interest in the 1,3,4-thiadiazines skeleton justifies development of new methods to synthesize compounds with this basic structure. In the novel approach presented here, we show that our method has high diastereoselectivity: the dihydrothiadiazines 4b-e are obtained as the sole diastereomers. The two stereogenic centres created in these compounds have an *exo* relationship. In the presence of SAMP-hydrazone, complete asymmetric induction yields the single enantiomer (4R, 6R, 9S)-4f.

4. Experimental

Melting points are uncorrected (Reichert microscope), optical rotations were obtained using an AA.10 optical activity polarimeter, NMR spectra were recorded using a Bruker AC 200 spectrometer with Me₄Si as internal reference (δ given in ppm, J in hertz), IR spectra (film or KBr pellets) were measured on a Bruker IFS 85 spectrometer, MS spectra were taken on a Hewlett Packard 5989 spectrometer. Flash chromatography was performed on Merck kieselgel 60 Art. 7734 or 9385 silica gel. All reactions were performed under an inert atmosphere (N₂) and all the solvents were freshly distilled using standard procedures.

4.1. Typical procedure for preparation of benzil monohydrazones 3

The *N*,*N*-dialkylhydrazine $(5 \times 10^{-3} \text{ mol})$ [or its hydrochloride salt $(7.5 \times 10^{-3} \text{ mol})$ for **3b**] was added to a solution of benzil $(5 \times 10^{-3} \text{ mol})$ and acetic acid $(5 \times 10^{-3} \text{ mol})$ [or sodium acetate $(7.5 \times 10^{-3} \text{ mol})$ for **3b**] in ethanol (8 mL). The solution was stirred for 20 h under N₂ at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and washed with brine (20 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. The crude compounds were purified by flash chromatography using dichloromethane as eluent. The compounds **3a–e** were crystallised from ethyl acetate.

4.2. Benzil N,N-dimethylmonohydrazone 3a

Pale yellow crystals: mp 99°C; yield 92%; IR (KBr): 2893, 1619, 1532, 1315, 1293, 1204, 1065, 1022, 874, 739, 725, 701, 694, 670 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.59 (s, 3H, CH₃), 2.88 (s, 3H, CH₃), 7.34–7.87 (m, 10H, 2C₆H₅); ¹³C NMR δ : 46.9 (CH₃), 127.3 (CH), 127.6 (CH), 127.9 (CH), 130.2 (CH), 130.3 (CH), 130.5 (CH), 135.5 (C), 138.4 (C), 139.6 (C), 192.5 (CO); MS *m/z*: 252 (M⁺). Anal. calcd for C₁₆H₁₆N₂O: C, 76.17; H, 6.39; N, 11.10. Found: C, 76.44; H, 6.44; N, 11.19.

4.3. Benzil-N-pyrrolidinomonoimine 3b

Pale yellow crystals: mp 114°C; yield 58%; IR (KBr): 3042, 2968, 2870, 1628, 1530, 1288, 1082, 1069, 877, 857, 730, 701, 676 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.76 (m, 4H, 2CH₂), 3.15 (m, 4H, 2NCH₂), 7.34–7.91 (m, 10H, 2C₆H₅); ¹³C NMR δ : 24.2 (2CH₂), 55.1 (2NCH₂), 127.2 (CH), 127.3 (CH), 127.7 (CH), 130.3 (CH), 130.5 (CH), 135.8 (C), 137.9 (C), 139.8 (C), 192.4 (CO); MS *m/z*: 278 (M⁺).

4.4. Benzil-N-piperidinomonoimine 3c

Yellow crystals: mp 71°C; yield 86%; IR (KBr): 3057, 2939, 2819, 1675, 1597, 1470, 1449, 1447, 1316, 1229, 1215, 1036, 940, 786, 776, 729, 699, 641 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.34–1.40 (m, 6H, 3CH₂), 2.73 (m, 4H, 2NCH₂), 7.34–7.89 (m, 10H, 2C₆H₅); ¹³C NMR δ : 23.5 (CH₂), 24.8 (2CH₂), 55.9 (2NCH₂), 127.4 (CH), 128.3 (CH), 128.7 (CH), 129.0 (CH), 130.4 (CH), 130.8 (CH), 133.0 (C), 135.9 (C), 166.3 (CN), 196.4 (CO); MS *m*/*z*: 292 (M⁺). Anal. calcd for C₁₉H₂₀N₂O: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.30; H, 6.88; N, 9.40.

4.5. Benzil-N-morpholinomonoimine 3d

Pale yellow crystals: mp 109°C; yield 90%; IR (KBr): 2973, 2893, 2846, 1673, 1596, 1450, 1446, 1329, 1305, 1269, 1262, 1226, 1108, 1073, 969, 946, 907, 861, 776, 734, 707, 698, 693, 652 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.80 (m, 4H, 2NCH₂), 3.53 (m, 4H, 2OCH₂), 7.31–7.92 (m, 10H, 2C₆H₅); ¹³C NMR δ : 55.1 (2NCH₂), 65.8 (2OCH₂), 127.5 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 131.2 (CH), 133.6 (CH), 132.5 (C), 135.6 (C), 168.0 (CN), 196.3 (CO); MS *m*/*z*: 294 (M⁺). Anal. calcd for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.46; H, 6.14; N, 9.30.

4.6. Benzil-N-homopiperidinomonoimine 3e

Pale yellow crystals: mp 99°C; yield 58%; IR (KBr): 3049, 2937, 2858, 1626, 1550, 1442, 1318, 1312, 1304, 1285, 1077, 1070, 877, 726, 704, 698 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.52 (m, 8H, 4CH₂), 3.30 (m, 4H, 2NCH₂), 7.25–7.87 (m, 10H, 2C₆H₅); ¹³C NMR δ : 27.5 (2CH₂), 27.6 (2CH₂), 57.1 (2NCH₂), 127.1 (CH), 127.6 (CH), 127.7 (CH), 130.0 (CH), 130.1 (CH), 130.2 (CH), 136.1 (C), 136.5 (C), 140.2 (C), 193.5 (CO); MS *m/z*: 306 (M⁺). Anal. calcd for C₂₀H₂₂N₂O: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.62; H, 7.28; N, 9.03.

4.7. Benzil-N-((S)-2-methoxymethylpyrrolidino)monoimine 3f

Yellow oil: $[\alpha]_D^{20}$ +191 (c 1.00, CHCl₃); yield 82%; IR (film): 3056, 3023, 2974, 2925, 2876, 2828, 1636, 1597, 1579, 1543, 1489, 1444, 1283, 1200, 701 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.62–1.95 (m, 4H, 2CH₂), 2.69 and 2.81 (2m, 2H, NCH₂), 3.32 (s, 3H, CH₃), 3.49 (d, J=5.3 Hz, 2H, OCH₂), 3.72 (m, 1H, CH), 7.32–7.87 (m, 10H, 2C₆H₅); ¹³C NMR δ : 23.8 (CH₂), 26.10 (CH₂), 53.9 (NCH₂), 59.3 (CH₃), 65.6 (CH), 73.9 (OCH₂), 127.4 (CH), 127.5 (CH), 127.9 (CH), 130.2 (CH), 130.5 (CH), 130.7 (CH), 135.7 (C), 138.1 (CH), 140.2 (C), 192.9 (CO); MS *m*/*z*: 322 (M⁺). Anal. calcd for C₂₀H₂₂N₂O₂: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.36; H, 6.78; N, 8.43.

4.8. Typical procedure for preparation of 3,6-dihydro-2H-1,3,4-thiadiazines 4

Lawesson's reagent $(1.5 \times 10^{-3} \text{ mol})$ was added to a solution of the benzil hydrazone **3** $(3 \times 10^{-3} \text{ mol})$ in anhydrous benzene (15 mL). The mixture was refluxed under an inert atmosphere (N_2) for 15 h. Solvents were removed under reduced pressure and the residue was chromatographed using dichloromethane:light petroleum (7:3) as eluent. The compounds **4** were crystallised from diethyl ether.

4.9. 3-Methyl-5,6-diphenyl-3,6-dihydro-2H-1,3,4-thiadiazine 4a

Pale yellow crystals: mp 96°C; yield 89%; IR (KBr): 3052, 3022, 2940, 2864, 1578, 1556, 1492, 1445, 1402, 1336, 1212, 1006, 766, 721, 694, 671 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.27 (s, 3H, CH₃), 3.99 (d, J=13.0 Hz, 1H, CH), 4.09 (dd, J=13.0 Hz and J=1.8 Hz, 1H, CH), 5.01 (d, J=1.8 Hz, 1H, CH), 7.17–7.63 (m, 10H, 2C₆H₅); ¹³C NMR δ : 38.6 (CH), 45.5 (CH₂), 46.1 (CH₃), 124.8 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 137.0 (C), 138.8 (C), 141.6 (C); MS *m/z*: 268 (M⁺). Anal. calcd for C₁₆H₁₆N₂S: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.65; H, 6.05; N, 10.48; S, 11.80.

4.10. 3,4-Diphenyl-5-thia-1,2-diazabicyclo[4.3.0]non-2-ene 4b

White crystals: mp 135°C; yield 85%; IR (KBr): 3055, 2941, 2872, 1592, 1543, 1489, 1441, 1203, 1128, 1102, 1006, 880, 831, 762, 726, 692 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.90 (m, 2H, CH₂), 2.41 (m, 2H, CH₂), 3.56 and 3.94 (2m, 2H, NCH₂), 4.10 (t, J=7.0 Hz, 1H, CH), 5.14 (s, 1H, CH), 7.17–7.64 (m, 10H, 2C₆H₅); ¹³C NMR δ : 21.8 (CH₂), 30.5 (CH₂), 41.6 (CH), 54.3 (CH), 54.4 (CH₂), 124.7 (CH), 127.1 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 136.9 (C), 138.7 (C), 141.0 (C); MS *m*/*z*: 294 (M⁺).

4.11. 3,4-Diphenyl-5-thia-1,2-diazabicyclo[4.4.0]dec-2-ene 4c

White crystals: mp 142°C; yield 83%; IR (KBr): 2936, 2823, 1581, 1559, 1491, 1450, 1366, 1119, 1103, 1074, 978, 961, 828, 767, 722, 695 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.38–1.86 (m, 6H, 3CH₂), 3.08 and 3.93 (ddd, J=12.2, 9.1, 6.3 Hz and ddd, J=12.2, 5.0, 3.4 Hz, 2H, NCH₂), 3.69 (dd, J=11.2 Hz and J=2.9 Hz, 1H, CH), 4.97 (s, 1H, CH), 7.18–7.56 (m, 10H, 2C₆H₅); ¹³C NMR δ : 24.2 (CH₂), 25.9 (CH₂), 30.2 (CH₂), 40.8 (CH), 53.4 (CH), 56.1 (CH₂), 125.4 (CH), 127.3 (CH), 127.6 (CH), 128.0 (CH), 128.2 (CH), 128.7 (CH), 136.7 (C), 138.5 (C), 143.5 (C); MS *m*/*z*: 308 (M⁺). Anal. calcd for C₁₉H₂₀N₂S: C, 73.99; H, 6.54; N, 9.08; S, 10.39. Found: C, 73.73; H, 6.55; N, 8.78; S, 10.24.

4.12. 3,4-Diphenyl-8-oxa-5-thia-1,2-diazabicyclo[4.4.0]dec-2-ene 4d

White crystals: mp 177°C; yield 61%; IR (KBr): 3062, 2966, 2852, 1583, 1560, 1493, 1445, 1143, 1114, 1070, 1007, 982, 762, 717, 693 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.35 and 3.73 (ddd, J=12.4, 10.9, 3.9 Hz and dt, J=12.4, 2.1 Hz, 2H, NCH₂), 3.56 (dd, J=10.4, 9.6 Hz, 1H, CH), 3.84–4.05 (m, 4H, 2CH₂), 5.06 (s, 1H, CH), 7.20–7.58 (m, 10H, 2C₆H₅); ¹³C NMR δ : 40.1 (CH), 53.0 (CH), 54.6 (CH₂), 67.7 (CH₂), 68.4 (CH₂), 125.5 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 128.9 (CH), 138.0 (C), 138.2 (C), 142.6 (C); MS *m*/*z*: 310 (M⁺). Anal. calcd for C₁₈H₁₈N₂OS: C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.53; H, 5.83; N, 8.97; S, 10.15.

4.13. 9,10-Diphenyl-8-thia-1,11-diazabicyclo[5.4.0]undec-10-ene 4e

White crystals: mp 116°C; yield 57%; IR (KBr): 3057, 3020, 2932, 2918, 2848, 1580, 1545, 1492, 1364, 1223, 1123, 956, 914, 762, 722, 692 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.51–2.20 (m, 8H, 4CH₂), 3.86 (d, J=7.8 Hz, 1H, CH), 3.86 and 4.24 (d, J=7.8 Hz and t, J=5.2 Hz, 2H, CH₂), 5.17 (s, 1H, CH), 7.12–7.60 (m, 10H, 2C₆H₅); ¹³C NMR δ : 26.6 (CH₂), 29.3 (CH₂), 30.2 (CH₂), 31.6 (CH₂), 42.6 (CH), 57.6 (CH₂ and CH), 124.5 (CH), 126.5 (CH), 127.1 (CH), 128.2 (CH), 128.3 (CH), 128.5 (CH), 132.1 (C), 139.1

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(C), 143.2 (C); MS *m/z*: 322 (M⁺). Anal. calcd for C₂₀H₂₂N₂S: C, 74.49; H, 6.88; N, 8.69; S, 9.94. Found: C, 74.64; H, 6.80; N, 8.80; S, 9.92.

4.14. (4R,6R,9S)-9-Methoxymethyl-3,4-diphenyl-5-thia-1,2-diazabicyclo[4.3.0]non-2-ene 4f

White crystals: mp 116°C; $[\alpha]_D^{20}$ –461 (c 1.00, CHCl₃); yield 70%; IR (KBr): 3013, 2913, 2895, 2824, 1577, 1544, 1494, 1449, 1281, 1194, 1130, 1089, 712, 694 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.85–2.19 and 2.31–2.52 (2m, 4H, 2CH₂), 3.47 (s, 3H, CH₃), 3.74–3.81 and 3.95 (m and dd, J=12.7, 6.3 Hz, 3H, CH and CH₂), 4.20 (t, J=7.2 Hz, 1H, CH), 5.12 (s, 1H, CH), 7.11–7.72 (m, 10H, 2C₆H₅); ¹³C NMR δ : 25.9 (CH₂), 29.0 (CH₂), 40.8 (CH), 55.0 (CH), 59.4 (CH₃), 64.0 (CH), 74.0 (CH₂), 124.5 (CH), 127.0 (CH), 127.1 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 135.8 (C), 138.6 (C), 140.8 (C); MS *m*/z: 338 (M⁺). Anal. calcd for C₂₀H₂₂N₂OS: C, 70.97; H, 6.55; N, 8.28; S, 9.47. Found: C, 70.78; H, 6.41; N, 8.00; S, 9.18.

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- 10. Column: ODH; eluent: hexane:isopropanol (95:5); pressure: 0.7 torr.
- 11. SAMP is commercially available, but can also be prepared in six steps from (S)-proline: D. Enders, P. Fey, H. Kipphardt, Org. Synth. 1987, 65, 173–182 and references cited therein.
- Crystals of 4f (1.2×0.53×0.13 mm) grown from CHCl₃. C₂₀H₂₂N₂OS, *M*=338.47, orthorhombic; *a*=8.217 Å, *b*=12.595 Å, *c*=17.300 Å, *Z*=4, space group: P2₁2₁2₁, ρ_{calc}=1.255 g cm⁻³. Mo-Kα radiation λ=0.7107 Å, 6425 reflections were measured of which 2496 were unique with *I*>2σ(*I*). Crystallographic calculations were carried out using the Siemens SHELXTL-PLUS program. The final *Rw*² and *R* parameters were 0.1379 and 0.054.