Highly diastereoselective synthesis of 2,3-dihydro-9b*H*- thiazolo[2,3-*a*]isoindolin-5-ones

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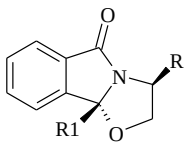
Abstract

Condensation of 2-acetyl benzoic acid with aminothiols proceeds with extremely high diastereoselectivity to produce the desired 2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-one products in good yield. The relative stereochemistry of the major diastereoisomer, formed exclusively when using non-racemic aminothiol substrates, has been determined for the first time by single crystal X-ray analysis.

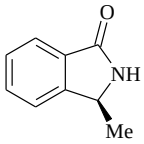
Keywords: Thiazolo[2,3-*a*]isoindolin-5-ones, diastereoselective synthesis

Introduction

The chemistry of the isoindolinone ring system is currently an area of interest for many research groups due to the actual and potential biological activities of many derivatives.[1] We have recently initiated a programme of study aimed at developing the chemistry of isoindolin-1-ones such as (**1**), and we have developed new and stereoselective routes to 3-substituted isoindolinones (**2**) and isoindoloisoquinolines (**3**) from such tricyclic lactam precursors.[2]



(1)



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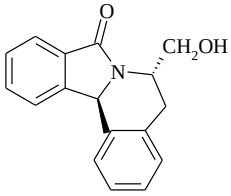

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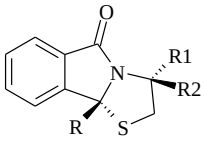


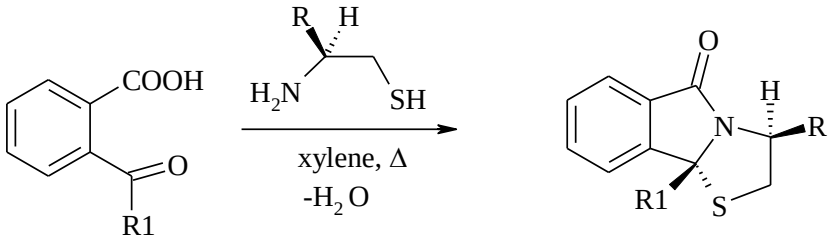
(4)

Due to our general interest in this area of heterocyclic chemistry, we turned our attention to the 2,3-dihydro-9bH-thiazolo[2,3-*a*]isoindolin-5-one ring system (**4**). Chiral compounds of this

type are of interest as non-nucleosidic reverse transcriptase inhibitors.[3] In this communication we present a highly diastereoselective synthesis of the 2,3-dihydro-9bH-thiazolo[2,3-*a*]isoindolin-5-one ring system.

Results and Discussion

In general, equimolar amounts of 2-acylbenzoic acids and the corresponding ˜-aminothiols were heated at reflux under Dean-Stark conditions in xylene solvent for 24 h (Scheme 1). Analysis of the crude product mixture by 250 MHz ^{1}H-NMR spectro-scopy showed clean and efficient conversion to the desired products (**5**) [Table]. With the non-racemic, chiral β-aminothiol substrates, th e product was observed as a single diastereoisomer. Purification was achieved by flash column chromatography. The relative stereochemistry of the non-racemic products derived from L-cysteine ethyl and methyl esters was confirmed by single crystal X-ray analysis; the X-ray of the ethyl ester derivative is presented in the Figure.



Scheme 1

Table 1. Synthesis of 2,3-Dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-ones, (5)

Product	R	R[1]	Yield (%)	diastereoselectivity[a]
5a	H	H	95	N/A
5b	H	Me	88	N/A
5c	H	Et	40	N/A
5d	H	Bn	20	N/A
5e	CO_2Et	H	80	exclusive[b]
5f	CO_2Et	Me	70	exclusive
5g	CO_2Me	H	80	exclusive
5h	CO_2Me	Me	65	exclusive

(a) determined by 250 MHz ^{1}H-NMR spectroscopy (b) minor isomer not visible by 250 MHz ^{1}H-NMR spectroscopy

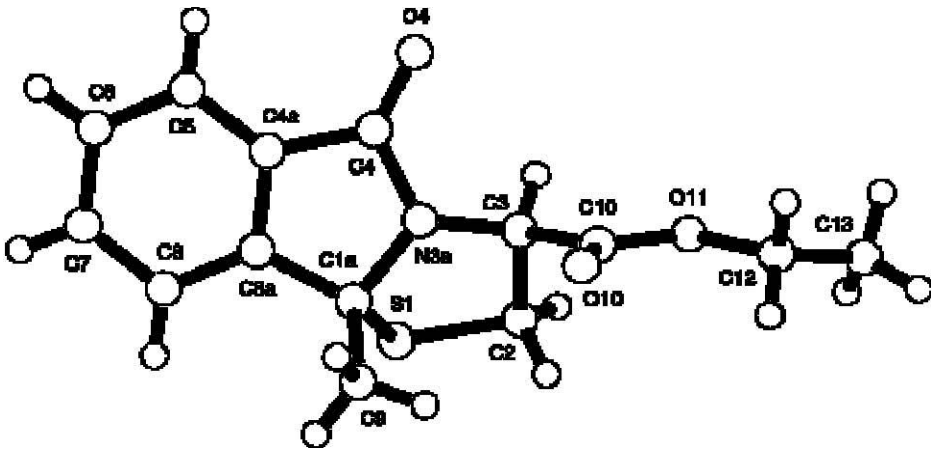
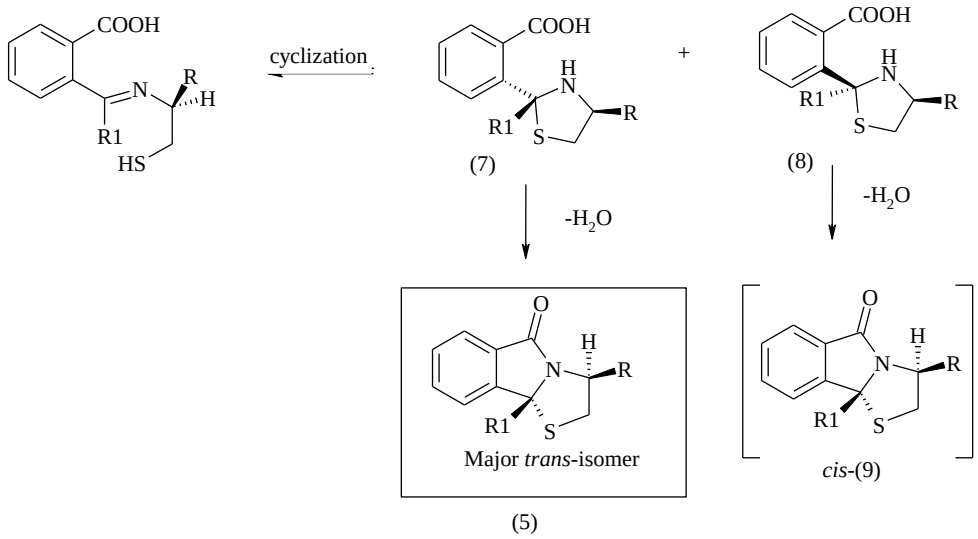


Figure 1

As can be seen from the Figure,the major product diastereoeisomer adopts a "bowl-like" shape, with the ester substituent lying on the outer (convex) face. Based on our earlier work in related areas,[2] we propose a mechanism to explain the stereochemical outcome of the reaction outlined in Scheme 1 which involves initial formation of an iminothiol/thiazolidine intermediate (Scheme 2).



Scheme 2

Reversible cyclization of the iminothiol (**6**) could produce both the *trans* thiazolidine (**7**) and the *cis* thiazolidine (**8**). Ring closure of (**6**) with concomitant loss of water yields the observed *trans* tricyclic product (**5**). In the case of (**8**) however, cyclization to (**9**) appears from simple molecular models to be disfavored due to more remote orientation of the reactive functional groups. Tricyclic compound (**5**) appears to be the thermodynamically more favorable product

isomer. No interconversion from (**5**) to (**9**) is observed by NMR spectroscopy on stirring a solution of (**5**) at room temperature for 7 days.

In summary, we report a highly efficient and direct method for the synthesis of 2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-ones products in good yield. The relative stereochemistry of the major diastereoisomer, formed exclusively when using non-racemic aminothiol substrates, has been determined for the first time by X-ray crystal analysis.

Experimental Section

General Procedures. All solvents, where necessary, were dried, distilled and stored over 4Å molecular sieves prior to use. Reagent chemicals were purchased from Lancaster Synthesis Ltd. and the Aldrich Chemical Co. Ltd, and were purified before use as required. Flash-column chromatography was carried out using Merck silica gel (70 – 230 Mesh ASTM). Pressure was applied at the column head using hand bellows. Analytical thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under UV light (at 254 nm) or by staining with either potassium permanganate solution or iodine. Infra-red spectra were recorded in the range 4000□600 cm^{-1}, using Perkin Elmer Paragon 100 FT-IR Spectrometer, with internal calibration. Solid samples were run as Nujol mulls, and liquids as thin films. ^{1}H Nuclear magnetic resonance spectra were recorded using either a Bruker Avance 400 MHz Spectrometer or a Bruker AC 250 MHz Spectrometer. Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q), double doublets (dd) and multiplets (m) etc. ^{13}C Nuclear magnetic resonance spectra were recorded using either a Bruker Avance DPX-400 MHz Spectrometer (run at 100 MHz) or a Bruker AC 250 MHz Spectrometer (run at 67.5 MHz). Mass spectra were recorded using a Fisons VG Quattro II SQ instrument and Accurate-Mass mass spectra were recorded using a Kratos MS80 instrument. X-Ray crystallography was carried out using a Rigaku AFC7S diffractometer with graphite monochromated Cu-Kα radiation. Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre (ref: CCDC140138). Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Melting points were determined on a 9100 Thermal Apparatus melting point block and are uncorrected Yields are for isolated pure products. Optical rotations were performed using an Optical Activity AA – 10 Automatic Polarimeter.

General procedure for synthesis of 2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-ones

To a stirred solution of the keto acid in xylene (mixture of isomers, 150 mL) was added an equimolar amount of the aminothiol along with a three-fold molar excess of sodium acetate portion-wise over 5 h under reflux. The mixture was heated for a further 24 h under Dean-Stark conditions. The resultant solution was filtered and the xylene removed under reduced pressure. Purification was achieved by flash column chromatography with ether/petrol mixtures as eluent.

250 MHz ^{1}H NMR analysis of crude non-racemic products confirmed the formation of a single diastereoisomer. Recrystallisation was achieved from ether/hexanes mixtures.

2,3-Dihydro-9b*H*-thiazolo[2,3-a]isoindolin-5-one (5a). [4]Off white crystals; 3.019 g, 95%; mp 99 □101 ºC (ether/hexanes) lit.[4] 98□100.5 ºC; ν_{max} (Nujol)/cm^{-1} 1701 (N-C==O), 1468 (Ar); δ_H ($CDCl_3$, 400MHz) 3.33 - □3.42 (3H, m, -NCH_2CH_2S-), 4.38 - □4.57 (1H, m, -NCH_2CH_2MS-), 5.85 (1H, s, N-CH-S), 7.46 - □7.59 (3H, m, Ar-H), 7.78□ - 7.80 (1H, m, Ar-H); δ_C ($CDCl_3$, 400MHz) 36.9, 44.8, 66.4, 123.6, 125.2, 129.6, 131.5, 133.0, 145.5, 171.2; *m/z* (EI) M^+ 191 (100%), 158 (42), 145 (90), 132 (28), 117 (23), 104 (11), 90 (15), 77 (10); (Found 191.0404. $C_{10}H_9NOS$ requires 191.0404).

9b-Methyl-2,3-dihydro-9b*H*-thiazolo[2,3-a]isoindolin-5-one (5b). Orange oil; 1.40 g, 88%; ν_{max} (thin film)/cm^{-1} 1701 (N-C==O), 1466 (Ar); δ_H ($CDCl_3$, 250MHz) 1.91 (3H, s, CH_3), 3.33□ - 3.47 (3H, m, -NCH_2CH_2S-), 4.52 - 4.60 (1H, m, -NCH_2CH_2S-), 7.43□ - 7.62 (3H, m, Ar-H), 7.77 (1H, d, *J* 7.3, Ar-H); δ_C ($CDCl_3$, 400MHz) 28.9, 38.0, 43.4, 76.0, 122.1, 124.5, 129.5, 129.9, 133.3, 150.9, 170.8; *m/z* (EI) 205 (100%), 190 (15), 158 (60), 146 (55), 130 (19), 103 (10); (Found 205.0564. $C_{11}H_{11}NOS$ requires 205.0561).

9b-Ethyl-2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-one (5c). Yellow oil; 0.44 g, 40%; ν_{max} (thin film)/cm^{-1} 1705 (N-C==O), 1466 (Ar): δ_H ($CDCl_3$, 250MHz) 0.72 (3H, t, *J* 7.3, -CH_2CH_3), 2.27 (2H, q, *J* 7.8, -CH_2CH_3), 3.31 - □3.43 (3H, m, -NCH_2CH_2S-), 4.49 - 4.61 (1H, m, -NCH_2CH_2S-), 7.41 - □7.46 (2H, m, Ar-H), 7.55 - □7.61 (1H, m, Ar-H), 7.75 - 7.78 (1H, m, Ar-H); δ_C ($CDCl_3$, 400MHz) 9.3, 34.1, 37.2, 43.2, 79.4, 121.9, 123.9, 127.7, 130.2, 132.8, 148.8, 171.0; *m/z* (EI) M^+ 219 (82%), 204 (14), 190 (100), 172 (67), 160 (23), 130 (14), 119 (13), 91 (8), 77 (9); (Found 219.0718. $C_{12}H_{13}NOS$ requires 219.0717).

9b-(Phenylmethyl)-2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-one (5d). Colourless crystals; 0.094 g, 20% (Found: C, 72.09; H, 5.30; N, 4.97%. $C_{17}H_{15}NOS$ requires C, 72.60; H, 5.34; N, 4.98%). mp 108 - □110 ºC (ether/hexanes); ν_{max} (Nujol)/cm^{-1} 1701 (N-C==O), 1465 (Ph-H);δ_H ($CDCl_3$, 250MHz); 3.16 - □3.33 (3H, m, -NCH_2CH_2S-), 3.46 (2H, q, *J* 8.8, CH_2Ph), 4.45 - □4.51 (1H, m, -NCH_2CH_2S-), 7.06 - □7.10 (2H, m, Ar-H), 7.12 - 7.17 (3H, m, Ar-H), 7.37 - □7.46 (2H, m, Ar-H), 7.52 - □7.59 (1H, m, *J* 1.2 7.6, Ar-H), 7.65 (1H, dt, *J* 0.9 6.45, Ar-H); δ_C ($CDCl_3$, 400MHz) 37.9, 44.3, 47.4, 79.6, 122.6, 122.7, 125.5, 127.1, 127.4, 128.3, 129.2, 130.2, 130.7, 132.9, 137.8, 149.5, 171.3; *m/z* (EI) M^+ 281 (4%), 234 (38), 220 (18), 204 (14), 191 (100), 178 (30), 163 (20), 130 (61), 102 (32), 91 (51), 77 (17); Found 281.0870. $C_{17}H_{15}NOS$ requires 281.0874).

(3*S*, 9b*R*)-Ethyl-2,3-dihydro-9b*H*-thiazolo[2,3-*a*]isoindolin-5-on-3-carboxylate(5e). White crystals; 2.69 g, 80% (Found C, 59.21; H, 4.84; N, 5.39%. $C_{13}H_{13}NO3S$ requires C, 59.32; H, 4.94; N, 5.32%); mp 77 - □80 ºC (ether/hexanes); $[\alpha]_D$ = □225.2º [c = 1.84, $CHCl_3$]; ν_{max} (Nujol)/cm^{-1}1731 (COOEt), 1710 (N-C==O), 1468 (Ar); δ_H($CDCl_3$, 250MHz) 1.31 (3H, t, *J* 7.2, $COOCH_2CH_3$) 3.55□ - 3.68 (2H, m, -S-CH_2-), 4.29 (2H, q, *J* 7.2, $COOCH_2CH_3$), 5.24 (1H, dd, *J* 5.0 7.2, -NCHCOOEt), 6.08 (1H, s, N-CH-S-), 7.45-□7.61 (3H, m, Ar-H), 7.80 (1H, d, *J* 7, Ar-H); δ_C ($CDCl_3$, 400MHz) 15.4, 40.1, 58.1, 62.4, 66.6, 123.7, 124.9, 129.7, 130.2, 133.4, 145.3,

170.3, 170.6; *m/z* (EI) M^+ 263 (78%), 190 (80), 132 (33), 91 (39); (Found 263.0618. $C_{13}H_{13}O_3NS$ requires 263.0616).

(3*S*,9b*R*)-3-Ethyl-9b-methyl-2,3-dihydro-9b*H*-thiazolo[2,3-a]isoindolin-5-on-3-carboxylate(5f). White crystals; 2.07 g, 70% (Found: C, 60.56; H, 5.49; N, 5.38%. $C_{14}H_{15}NO_3S$ requires C, 60.65; H, 5.42; N, 5.05%); mp 110□ - 113 ºC (ether/hexanes); $[\alpha]_D$ = □273.10º [c = 1.1, $CHCl_3$]; ν_{max} (Nujol)/cm^1 1731 (COOEt), 1710 (N-C==O), 1468 (Ar); δ_H ($CDCl_3$, 250MHz) 1.33 (3H, t, *J* 7.1, $COOCH_2CH_3$), 1.96 (3H, s, CH_3), 3.77 -□3.98 (2H, m, -S-CH_2-), 4.24 - □4.34 (2H, m, $COOCH_2CH_3$), 5.14 (1H, dd, *J* 6.3 8.7, -NCHCOOEt), 7.47 - □7.64 (3H, m, Ar-H), 7.78 - □7.82 (1H, m, Ar-H); δ_C ($CDCl_3$, 250MHz) 14.5, 28.5, 40.6, 58.4, 62.3, 122.3, 124.9, 126.3, 129.4, 129.5, 135.0, 149.4, 170.7, 170.9; *m/z* (EI) M^+ 277 (100%), 262 (23), 204 (80), 146 (88); (Found 277.0774. $C_{14}H_{15}NO_3S$ requires 277.0772).

(3*S*,9b*R*)-3-Methyl-2,3-dihydro-9b*H*-thiazolo[2,3-a]isoindolin-5-on-3-carboxylate (5g). White needles; 2.69 g, 80% (Found C, 57.62; H, 4.49; N, 5.67%. $C_{12}H_{11}NO_3S$ requires C, 57.83; H, 4.42; N, 5.62%); mp 83 - □86 ºC (ether/hexanes); $[\alpha]_D$ = □233.6º [c = 2.31, $CHCl_3$]; ν_{max} (Nujol)/cm□^{1} 1731 (COOEt), 1710 (N-C==O), 1468 (Ar); δ_H ($CDCl_3$, 400MHz) 3.60 - □3.69 (2H, m, -SCH_2) 3.82 (3H, s, $COOCH_3$), 5.25 (1H, dd, *J* 4.8 7.6, -NCHCOOMe), 6.08 (1H, s, -N-CH-S), 7.47 - □7.52 (2H, m, Ar-H), 7.57 - 7.59 (1H, m, Ar-H), 7.80 - □7.82 (1H, m, Ar-H); δ_C ($CDCl_3$, 400MHz) 40.0, 53.3, 57.9, 66.7, 123.8, 125.0, 129.8, 130.8, 133.4, 145.1, 170.8, 170.9; *m/z* (EI) M^+ 249 (15%), 227 (4), 209 (36), 190 (14), 135 (100), 119 (7), 107 (59), 93 (50); (Found 249.0455. $C_{12}H_{11}O_3NS$ requires 249.0459).

(3*S*,9b*R*)-3-Methyl-9b-methyl-2,3-dihydro-9b*H*-thiazolo[2,3-a]isoindolin-5-on-3-carboxylate (5h). White needles; 2.07 g, 70%; mp 113 - 116 ºC (ether/hexanes); $[\alpha]_D$ = □289.6º [c = 1.75, $CHCl_3$]; ν_{max} (Nujol)/cm□^{1} 1750 (COOEt), 1693 (N-C==O), 1466 (Ar); δ_H ($CDCl_3$, 400MHz) 1.94 (3H, s, $COOCH_3$), 3.79 - □3.94 (2H, m, -SCH_2), 3.81 (3H, s, CH_3), 5.14 (1H, dd, *J* 6.4 8.8, -NHCHCOOMe), 7.47 - □7.50(2H, m, Ar-H), 7.57 - □7.59 (1H, m, Ar-H), 7.77□ - 7.79 (1H, m, Ar-H); δ_C ($CDCl_3$, 400MHz) 27.9, 40.1, 52.8, 57.7, 77.3, 121.8, 125.3, 128.9, 129.3, 137.2, 148.9, 170.2, 170.9; *m/z* (EI) M^+ 263 (5%), 163 (26), 160 (100), 119 (20), 100 (33), 87 (11); (Found 263.0619. $C_{13}H_{13}NO_3S$ requires 263.0616).

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