Pergamon

Tetrahedron Letters 41 (2000) 2219–2222

TETRAHEDRON LETTERS

Highly diastereoselective synthesis and template manipulation of the thiazolo[2,3-*a*]isoindolin-1-one ring system

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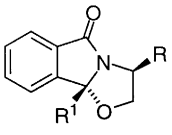
Received 1 November 1999; revised 5 January 2000; accepted 14 January 2000

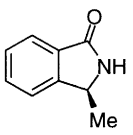
Abstract

Condensation of 2-acetyl benzoic acid with L-cysteine esters proceeds with extremely high diastereoselectivity to produce the desired thiazolo[2,3-*a*]isoindolin-1-one products in good yield. The relative stereochemistry of the major diastereoisomer has been determined by X-ray crystallography. Stereoselective enolate alkylation of this substrate has been investigated as a method to manipulate the ring skeleton, and was found to proceed with up to exclusive levels of stereoselectivity. © 2000 Elsevier Science Ltd. All rights reserved.

The chemistry of the isoindolinone ring system is currently an area of interest 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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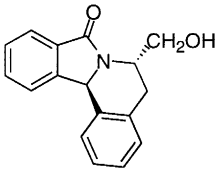

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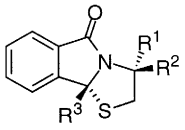

(**4**)

Due to our general interest in this area of heterocyclic chemistry, we turned our attention to the thiazolo[2,3-*a*] isoindolin-1-one ring system (**4**). Chiral compounds of this type are of current interest as non-nucleosidic reverse transcriptase inhibitors.[3] In this communication we present a highly diastereo-

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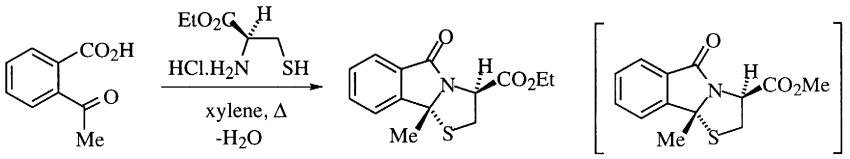
PII: S0040-4039(00)00128-3

selective synthesis of the thiazolo[2,3-*a*]isoindolin-1-one ring system and describe the stereoselective manipulation of the core of the molecule through enolate alkylation to produce novel chiral derivatives.



(**5a**) (**5b**)

Scheme 1.

Equimolar amounts of 2-acetylbenzoic acid and L-cysteine ethyl ester hydrochloride were heated at reflux under Dean–Stark conditions in xylene as solvent for 24 hours (Scheme 1).[3a] Analysis of the crude product mixture by 250 MHz ^{1}H NMR spectroscopy showed clean and efficient conversion to the desired thiazolo[2,3-*a*]isoindolin-1-one product (**5a**), as a single diastereoisomer (and enantiomer).[4] Purification was achieved by flash column chromatography using diethyl ether/petroleum ether (1:1) as eluent to give the target in 70% yield. The thiazolo[2,3-*a*]isoindolin-1-one methyl ester (**5b**) was also prepared in 65% isolated yield as a single diastereoisomer using the corresponding cysteine ester substrate. The relative stereochemistry of both products was confirmed by single crystal X-ray analysis;[5] the X-ray structure of the ethyl ester (**5a**) is presented in Fig. 1.

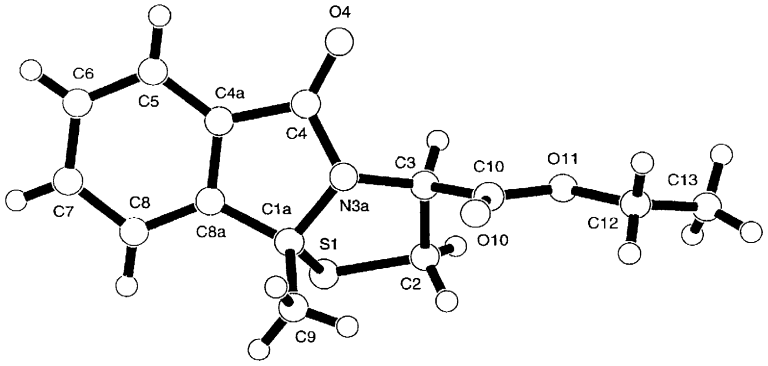
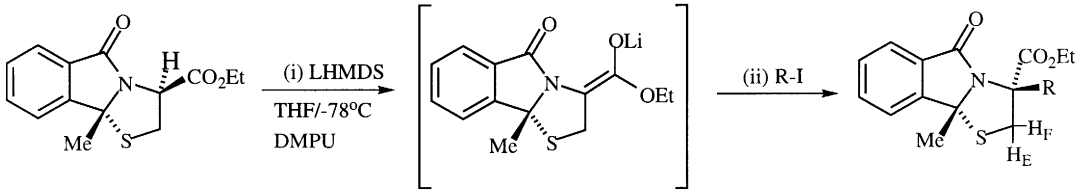


Fig. 1.

As can be seen from Fig. 1, the major product diastereoisomer adopts a 'bowl-like' shape, with the ester substituent lying on the outer (convex) face. The formation of a single product diastereoisomer displaying *trans* relative stereochemistry (with respect to the sulfur atom and ester moiety) using a β-aminothiol as the substrate in the condensation reaction is comparable to our previous work with β-aminoalcohols,[6] and a similar mechanism can be invoked to account for the stereoselectivity observed (see Ref. 6).

The presence of an enolisable H-atom within the substructure of such tricyclic products led us to investigate the stereoselective enolate alkylation of the thiazolo[2,3-*a*]isoindolin-1-one ring system. As outlined in Scheme 2, deprotonation using a non-nucleophilic base would generate an enolate intermediate. The absolute stereochemistry of the precursor amino acid moiety would obviously be destroyed, but the newly created chiral centre within the isoindolinone ring system might be expected to control the approach of an electrophile. In effect, a chiral relay would be established, with the stereochemical information ultimately being transferred from the initial amino acid substrate in order to generate the new quaternary centre in target (**6**) with high levels of stereocontrol. This represents a

new example of Seebach's concept of 'self-reproduction' of chirality[7] within this heterocyclic system. A similar asymmetric alkylation of thiazolines has been reported by Pattenden and co-workers.[8]



(**5a**) (**6**)

Scheme 2.

Compound (**5a**) was treated with 1.1 equivalents of LHMDS at −78°C in dry THF. After 30 minutes, the enolate was quenched with 1.1 equivalents of the electrophile (Table 1) in the presence of 1.1 equivalents of DMPU, before warming to room temperature for dilute acidic work-up. Analysis of the crude product was carried out by 250 MHz ^{1}H NMR spectroscopy. Purification was achieved by flash column chromatography on silica gel using ethyl acetate/light petroleum mixtures as eluent. Yields quoted in Table 1 are of isolated materials.

Table 1
Stereoselective enolate alkylation of thiazolo[2,3-*a*]isoindolin-1-one, (**5a**)

Electrophile	**R**	**Yield (%)**	**Diastereoselectivity**[a]
MeI	Me	45	exclusive[b]
$PhCH_2Br$	Bn	38	≥23:1
Allyl-Br	$CH_2CH{=}CH_2$	25	exclusive[b]
EtI	Et	15	≥17:1
Pr	Pr	10	5:1
i-PrI	*No reaction*		
$BrCH_2CO_2Me$	*No reaction*		

[a]determined by 250MHz ^{1}H-NMR spectroscopy

[b]minor isomer not visible by 250MHz ^{1}H-NMR spectroscopy

As can be appreciated from Table 1, extremely high levels of asymmetric induction were achieved with a range of typical electrophiles, albeit in moderate to low yields. Variation of the counter-ion (using KHMDS, NHMDS) did not lead to an improvement in yield in a representative case (enolate benzylation), nor did addition of catalytic NaI to the electrophile.

The relative stereochemistry of the product derived from alkylation with methyl iodide (**6**, R=Me) was investigated by NOE techniques, and was found to be as indicated in Scheme 2 (i.e. methyl groups *cis* with respect to one another). The protons assigned as H_E and H_F at δ 6.52 and 6.15 ppm were irradiated in the quantitative NOE experiments. When irradiated at δ 6.52 ppm there was no positive NOE observed for either of the methyl groups. When irradiated at δ 6.15 ppm, a small (ca. 2%) NOE was observed for both methyl groups (an NOE of 25% was observed between the geminal protons H_E and H_F in the experiment). That there is no NOE observed between the proton on one face of the molecule and the methyl groups; and that a small NOE was observed to both methyl groups when the other proton was irradiated, indicates that the methyl groups lie *cis* with respect to one another. The approach of

the electrophile during enolate alkylation therefore occurs from the (outer) convex face of the bicyclic substrate.

In summary, we report a facile and highly diastereoselective synthesis of the thiazolo[2,3-*a*]isoindolin-1-one ring system. Stereoselective enolate alkylation can be achieved with up to exclusive levels of diastereoselectivity, generating novel thiazolo[2,3-*a*]isoindolin-1-one derivatives containing a chiral quaternary carbon centre.

Acknowledgements

We thank the Universities of Loughborough and Huddersfield for facilities and financial support of this research.

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4. (3*R*, 9*bR*)-Ethyl-9b-methyl-5-oxo-2,3,5,9b-tetrahydro[1,3]thiazolo[2,3-*a*]isoindole-3-carboxylate (**5a**): 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 46–48°C (ether/hexanes); $[\alpha]_D$=−273.10 [c=1.1, $CHCl_3$]; ν_{max} (Nujol)/cm^{-1} 1731.6 (COOEt), 1710.1 (N–C=O), 1468.2 (Ar); δ_H ($CDCl_3$, 250 MHz) 1.33 (3H, t, *J* 7.1, $COOCH_2CH_3$), 1.96 (3H, s, Phth-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, -NC*H*COOEt), 7.47–7.64 (3H, m, Ph-H), 7.78–7.82 (1H, m, Ph-H); δ_C ($CDCl_3$, 250 MHz) 14.5, 28.5, 40.6, 58.4, 62.3, 122.4, 124.9, 126.4, 129.5, 129.5, 135.0, 149.5, 170.8, 170.9; *m/z* (EI) M^+ 277 (100%), 262 (23), 204 (80), 146 (88), 86 (37), 84 (56), 49 (53); found 277.07749; $C_{14}H_{15}NO_3S$ requires 277.07727. The enantiomeric diastereoisomer prepared from D-cysteine ethyl ester was prepared and had an optical rotation of +261.80.
5. X-Ray data deposited at the Cambridge Crystallographic Data Centre, Cambridge, UK, (CCDC 140138).
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