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Synthesis of novel tricyclic isoindole derivatives

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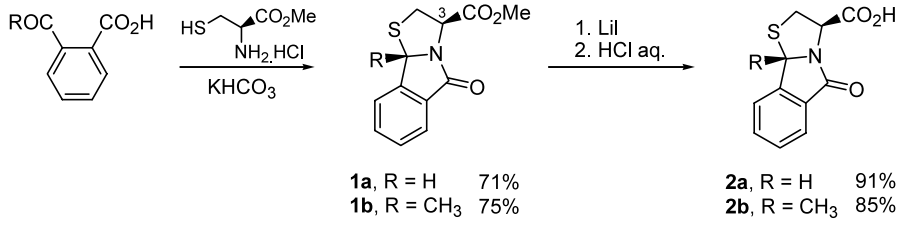
Abstract—Novel 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles were prepared from the thermolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids in acetic anhydride. The structure of 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6a** was determined by X-ray crystallography.

In relation with our ongoing research[1] we became interested in exploring the possibility of preparing 1,3-thiazolidine-4-carboxylic acid fused to five-membered ring systems which could be used as potential münchnone precursors. Our target was the synthesis of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids in order to study their reactivity.

The reaction of *L*-cysteine methyl ester with 2-carboxybenzaldehyde was carried out following the general procedure reported earlier for the synthesis of thiazolidines.[2] The product was purified simply by recrystallisation. This resulted in the direct diastereoselective synthesis of methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydro-thiazolo[2,3-*a*]isoindole-3-carboxylate **1a** in 71% yield. Compound **1a** has been reported with the incorrect stereochemistry, as being the (3*S*,9b*R*) stereoisomer.[3] It derives from *L*-cysteine thus the configuration of C3 must be *R*.[4,5] Methyl (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **1a** was converted into the corresponding acid **2a** in 91% yield ($[\alpha]_D^{25} = -343$, *c* 0.1, EtOH) by the reaction with lithium iodide in ethyl acetate and treatment with aqueous HCl, following a known synthetic procedure previously reported[1a,1c] (Scheme 1).

Oliver et al. reported the synthesis of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** directly from the reaction of 2-carboxybenzaldehyde with cysteine hydrochloride in the presence of pyridine.[6] However, the stereochemistry of the product was not mentioned. We repeated this synthetic procedure which led to compound **2a** (58%), $[\alpha]_D^{25} = -343$ (*c* 0.1, EtOH). This value for the optical rotation indicates that the diastereoselectivity of this process was the same as the one observed for the route described above.

The reactivity of compound **2a** as a münchnone precursor was studied. Attempts were made to promote cyclodehydration by heating at reflux a solution of



1a, R = H 71%
1b, R = CH_3 75%

2a, R = H 91%
2b, R = CH_3 85%

Scheme 1.

Keywords: diastereoselectivity; thiazolo[2,3-*a*]isoindoles; 3-methylene-2,5-oxazolo[2,3-*a*]isoindoles.
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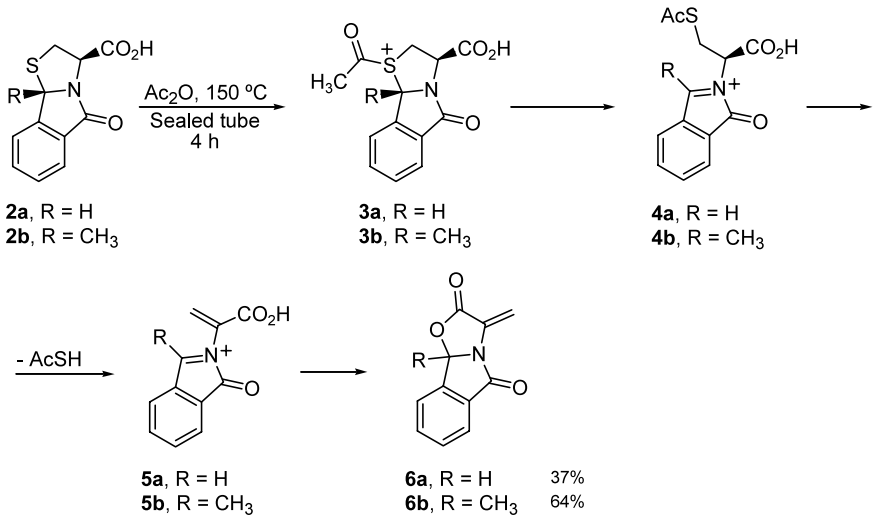

Scheme 2.

compound **2a** in acetic anhydride in the presence of dimethyl acetylenedicarboxylate. However, the expected 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole was not obtained even when prolonged heating was used.

Nevertheless, we carried out the reaction of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** with acetic anhydride and dimethyl acetylenedicarboxylate in a sealed tube. The solution was heated at 150°C for 4 h. Although no 1,3-dipolar cycloadduct was obtained, this study led to an interesting result. We isolated one product in 37% yield which was identified as 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6a**[7] (Scheme 2). The structure of **6a** was determined by X-ray crystallography as illustrated in Figure 1.

The mechanism proposed for the formation of compound **6a** is outlined in Scheme 2. The first step is the acetylation of the sulfur atom with acetic anhydride giving **3a** followed by a ring-opening reaction. The elimination of thioacetic acid from compound **4a** leads to *N*-acyliminium ion **5a**. This intermediate undergoes a 5-*endo*-trig cyclisation reaction with formation of 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6a**.

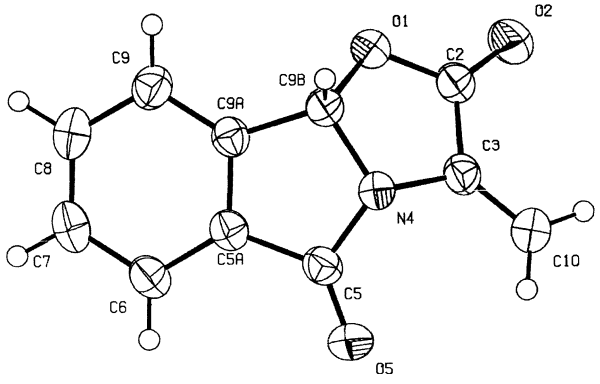

Figure 1. ORTEPII plot of 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindole **6a** with anisotropic displacement ellipsoids calculated at the 50% probability level.

The process can be regarded as involving the formal elimination of the elements of SH from (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2a** followed by cyclisation. It represents the synthesis of isoindole derivative (**6a**), a new member to a class of compounds having a significant number of applications.[2,8]

In order to determine the scope of this route to 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles we prepared (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2b** (Scheme 1). When the reaction of *L*-cysteine methyl ester with 2-acetylbenzoic acid was carried out at room temperature with a reaction time of 30 min (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]-isoindole-3-carboxylate **1b** was obtained in 18% yield. Changing the reaction time to 12 h led to compound **1b** in 28% yield. The best result was obtained performing the reaction in the presence of sodium acetate in refluxing toluene for 5 h (75%). The reported value for the optical rotation of compound **1b** is $[\alpha]_D^{25} = -289.6$[3] (*c* 1.75, $CHCl_3$) in contrast with the value of $[\alpha]_D^{25} = -328.7$ (*c* 1.75, CH_2Cl_2) obtained for the same compound prepared by our synthetic procedure. Compound **2b** was obtained from **1b** in 85% yield.

We carried out the reaction of (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid **2b** with acetic anhydride in a sealed tube (Scheme 2). The solution was heated at 150°C for 4 h. In a process analogous to that described for the synthesis of oxazolo[2,3-*a*]isoindole derivative **6a**, compound **2b** was converted into the new tricyclic isoindole derivative 9b-methyl-3-methylene-2,5-dioxo-3*H*,9b*H*-

oxazolo[2,3-*a*]isoindole **6b**[7] in 64% yield. When the reaction of **2b** with acetic anhydride was performed in the presence of dimethyl acetylenedicarboxylate (sealed tube, 150°C, 4 h) compound **6b** was isolated but in lower yield (40%) but no 1,3-dipolar cycloadduct was formed.

In conclusion, we report a synthetic methodology to new tricyclic isoindole derivatives, 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles through the thermolysis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acids in acetic anhydride. Work is in progress to further investigate the scope of this and other related reactions as a route to new tricyclic ring systems.

Acknowledgements

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4. The reported value for the optical rotation of compound **1a** is $[\alpha]_D^{25} = -233.6$[3] (*c* 2.31, $CHCl_3$) in contrast with the value of $[\alpha]_D^{25} - 400.5$ (*c* 2.3, CH_2Cl_2) obtained for the same compound prepared by our synthetic procedure. This result suggests that **1a** was obtained in a much higher diastereoisomeric excess since a positive value for the optical rotation of *N*-acyl-2-substituted-thiazolidine-4-carboxylates is usually associated with (2*R*,4*R*) stereochemistry whereas a negative value is associated with (2*S*,4*R*) stereochemistry.[1,5a,b] The structure of **1a** was established by X-ray crystallography, a result to be disclosed in a specific paper.
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7. *General procedure for the synthesis of 3-methylene-2,5-dioxo-3H,9bH-oxazolo[2,3-a]isoindoles* ***6a*** *and* ***6b***. A solution of 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylic acid (**2a** or **2b**) (1.28 mmol) in Ac_2O (2.6 ml) was heated, in a sealed tube, at 150°C for 4 h. The reaction was cooled to room temperature and was diluted with dichloromethane (50 ml). The organic phase was washed with a saturated aqueous solution of $NaHCO_3$ and with water, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography [hexane–ethyl acetate (2:1)].
3-Methylene-2,5-dioxo-3H,9bH-oxazolo[2,3-a]isoindole **6a**: obtained as a solid (37%). Mp 174.2–176.0°C (from ethyl ether). δ_H ($CDCl_3$, 300 MHz) 5.93 (1H, d, $J = 1.4$ Hz), 5.96 (1H, d, $J = 1.4$ Hz), 6.51 (1H, s), 7.68–7.79 (3H, m, Ar-H), 7.95–7.97 (1H, Ar-H); δ_C ($CDCl_3$, 75.5 MHz) 87.0, 107.9, 125.1, 125.5, 130.1, 131.7, 131.9, 134.4, 141.1, 165.2 and 169.3; *m*/*z* 201 (M^+, 33%), 172 (4), 157 (41) and 133 (100). The crystal structure of **6a** has been deposited at the CCDC with the deposition number CCDC 218858.
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