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Deacetalisation–bicyclisation routes to novel polycyclic heterocycles using stannous chloride dihydrate

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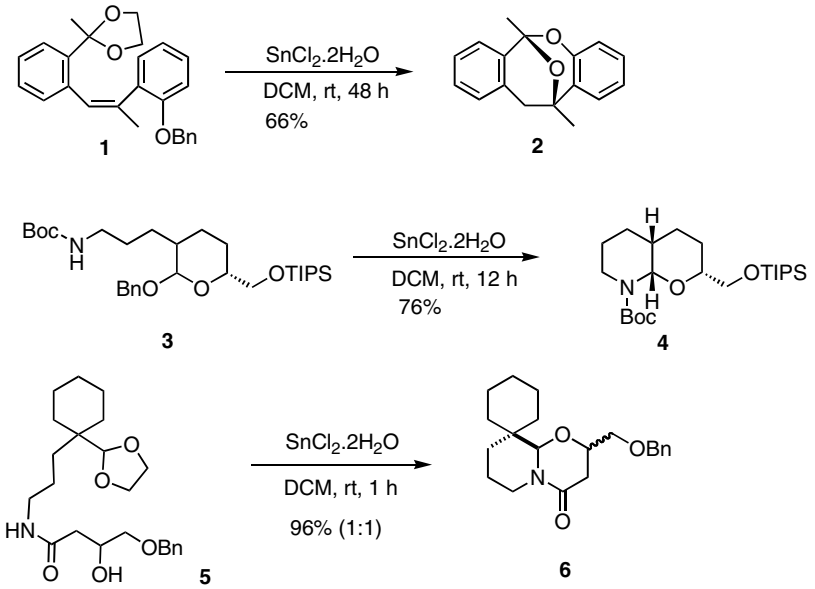
Abstract—The stannous chloride dihydrate-mediated deprotection–bicyclisation of a range of amides possessing a pendant acetal group is reported. These mild reaction conditions have been used to prepare a number of ring-fused heterocyclic compounds, some in enantiomerically pure form, which should be of interest both in their own right and as building blocks for the production of more complex target molecules.

Polycyclic heterocycles are considered to be 'privileged structures' in the pharmaceutical and agrochemical industries.[1] For this reason, methods of producing a diverse range of such compounds with a relatively low molecular weight are invaluable in the search for bioactive lead compounds. Herein we report the preparation of a variety of polycyclic heterocyclic systems using stannous chloride dihydrate in the key step. Stannous



Scheme 1.

Keywords: Heterocycles; Stannous chloride; Deacetalisation; Bicyclisation.
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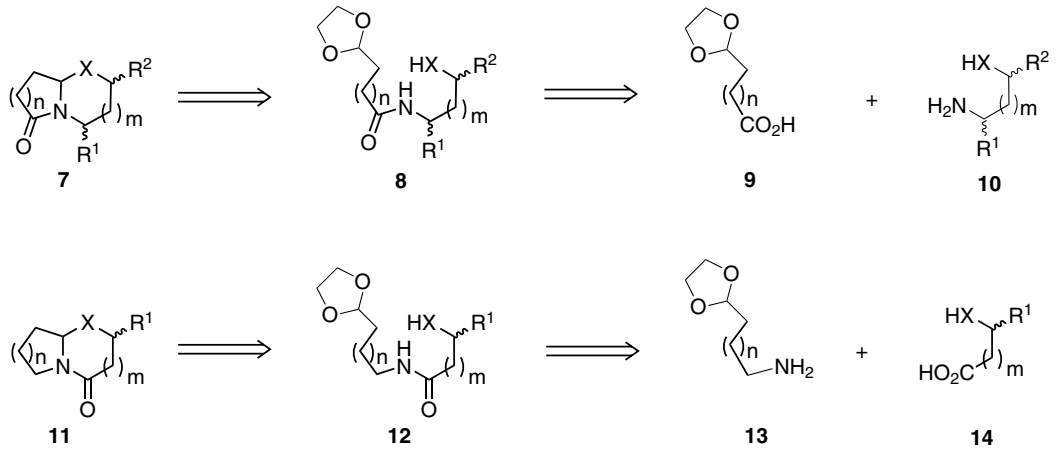


Scheme 2. X = O, S, NR[3].

chloride is widely used as a reducing agent and Lewis acid catalyst[2] and, as its dihydrate, it has been employed as a mild reagent for the deprotection of acetals.[3] In recent natural product ventures, we discovered that stannous chloride dihydrate can be employed to mediate several useful deprotection–cyclisation sequences. Thus, as illustrated in Scheme 1, treatment of acetal **1** with $SnCl_2{\cdot}2H_2O$ gave the bicyclic product **2** (the core unit of the novel HIV-1 integrase inhibitors, integrastatins A and B) via a presumed acetal deprotection–debenzylation–hemi-acetal formation–alkene etherification sequence.[4]

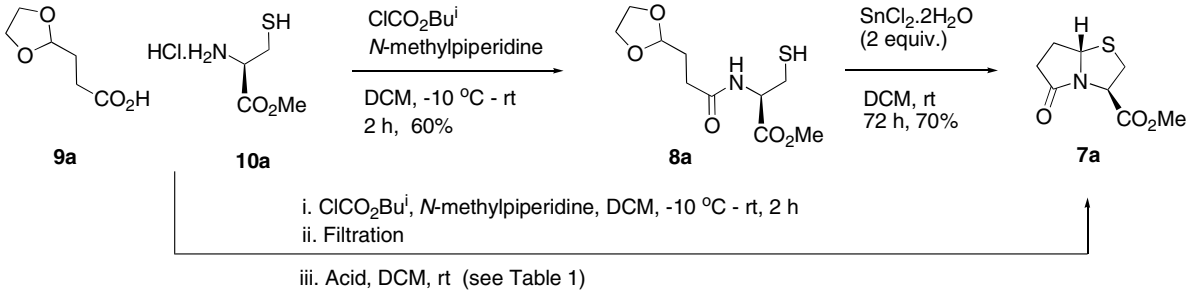
In a related manner, on treatment with $SnCl_2{\cdot}2H_2O$, the acetals **3** and **5** undergo a deacetalisation–cyclisation or deacetalisation–bicyclisation process giving the heterocyclic products **4**[5] and **6**,[6] respectively. The latter $SnCl_2{\cdot}2H_2O$ procedure was subsequently employed by Han and Ong to prepare compounds related to **6** but containing iron tricarbonyl-cyclohexadiene fragments, thus establishing still further its mild nature.[7]

The simplicity of the $SnCl_2{\cdot}2H_2O$ cyclisation procedures, coupled to the novelty of the heterocycles produced, encouraged us to investigate further applications of this methodology. In this Letter, we report the one-pot deprotection–bicyclisation processes outlined retrosynthetically in Scheme 2.

Thus, polycyclic fused heterocycles such as **7**[8] and **11** should be accessible from amides **8** and **12** using the $SnCl_2{\cdot}2H_2O$ cyclisation procedure, with the required amides in turn being produced by the coupling of dioxolanes **9** and **13** with corresponding partners **10** and **14** (Scheme 2).

In order to evaluate the feasibility of these processes, the reaction shown in Scheme 3 was investigated. The readily available acid **9a**[9] was coupled to L-cysteine derivative **10a** using standard conditions giving amide **8a** in 60% isolated yield.[10] On treatment of amide **8a** with $SnCl_2{\cdot}2H_2O$ in dichloromethane (DCM) for 72 h we were delighted to obtain methyl 5-oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate **7a** in 70% yield. This one-pot deprotection–bicyclisation process produced **7a** as a single diastereoisomer $\{[\alpha]_D^{23}\ -250.7\ (c\ 1.25, CHCl_3)\}$ which was tentatively assigned the presumed thermodynamically preferred 3*R*,7a*S*-configuration shown on the basis of NMR studies.

We attempted to condense the two-step sequence into a one-pot process but this approach proved to be unsuccessful. However, it was possible to carry out the two-step process with minimal purification of the intermediate amide **8a** prior to treatment with $SnCl_2{\cdot}2H_2O$. Thus, after amide formation using the mixed anhydride method,[11] the reaction was filtered through a pad of silica and the solvent evaporated in vacuo before the addition of new solvent and $SnCl_2{\cdot}2H_2O$. Using this method, product **7a** was obtained in 68% isolated yield (as compared to a 42% overall yield for the two-step process).[12] A number of different acids were then screened in this



Scheme 3.

Table 1. Variation of the acid used in the one-pot process[a]

$SnCl_2{\cdot}2H_2O$ (2 equiv), 72 h	$SnCl_2$ (2 equiv), 72 h	$SnBr_2$ (2 equiv), 72 h	$SnCl_4$ (2 equiv), 72 h	$BF_3{\cdot}Et_2O$ (2 equiv), 24 h	10% aq HCl 72 h	Cat. $TsOH{\cdot}H_2O$ PhMe, Δ, 2 h
68%	57%	35%	5%	26%	39%	29%

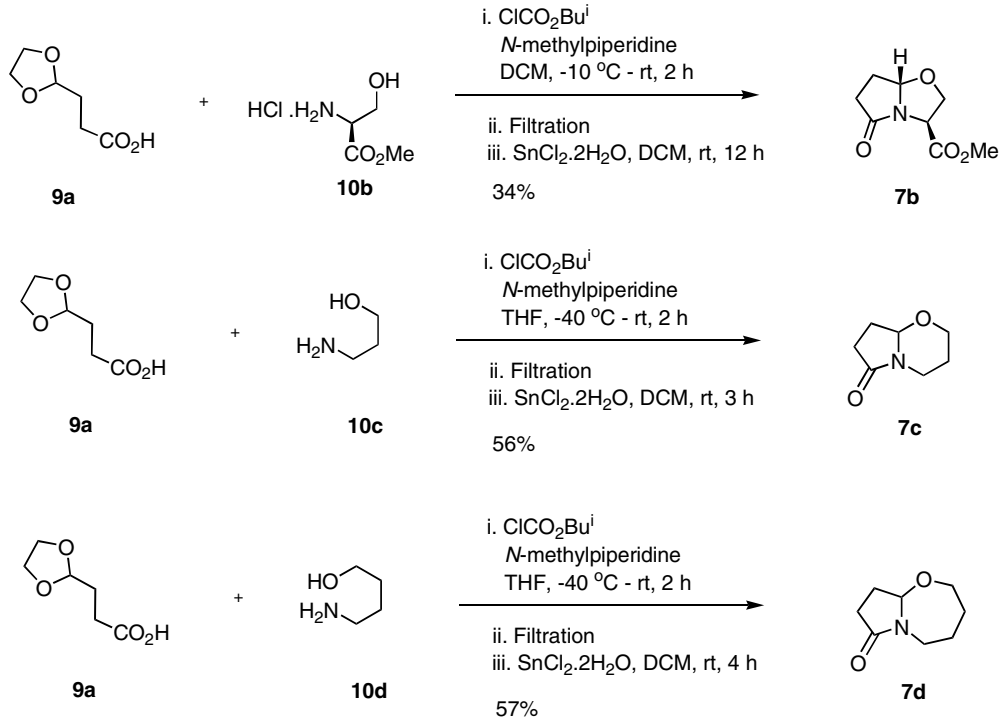
[a] Complete degradation of starting material observed using $TiCl_4$ and $ZnCl_2$.

telescoped process (Table 1) but the original procedure using $SnCl_2{\cdot}2H_2O$ proved to be best. Cyclisation was successful using hydrochloric acid although the 39% yield of heterocycle **7a** was considerably lower than in the stannous chloride procedure (and a number of degradation products were also formed).

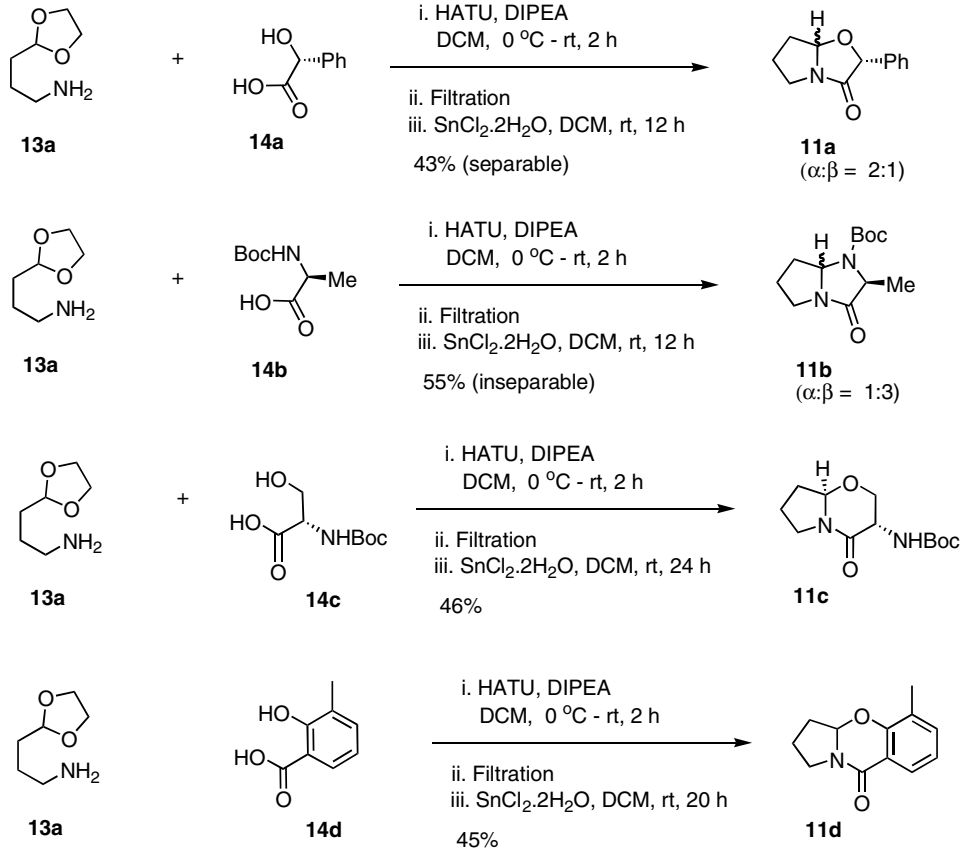
Next, three further examples were explored to indicate the generality of the procedure (Scheme 4). Thus, amide formation between acid **9a** and L-serine derivative **10b** followed by treatment with $SnCl_2{\cdot}2H_2O$ induced the desired deacetalisation–bicyclisation reaction to give the novel heterocycle **7b** $\{[\alpha]_D^{23}$ −124 (*c* 1.0, $CHCl_3)\}$ in moderate yield over the two-step process. In a similar manner, amide formation between acid **9a** and the amino alcohols **10c** and **10d** followed by deacetalisation–bicyclisation gave the known[13] heterocyclic system **7c** {hemi-aminal proton: δ_H 4.94 ppm, 1H, dd, $J = 6.5$, 2.8 Hz; IR 1690 cm^{-1}. Lit.[13] δ_H 4.94 ppm, 1H, m; IR 1690 cm^{-1}} and the novel homologue **7d** in reasonable yields over the two steps.

Our attention turned next to the second combination of coupling partners outlined in Scheme 2, in particular the use of amine **13a**[14] with a range of acids **14a–d**. This approach, in which HATU was shown to be preferable to the mixed anhydride method for amide formation, proved to be more general (Scheme 5). Thus, deacetalisation–bicyclisation produced the novel[15] heterocyclic products **11a–d** in moderate to good yields over the two-step sequence. In the case of the bicyclo[3.3.0]-octane adducts **11a** and **11b**, mixtures of diastereomeric products were obtained (ratio established by NMR spectroscopy), and the major diastereomer was tentatively assigned by inspection of molecular models (NOE studies were uninformative). The bicyclo[4.3.0]nonane adduct **11c** was obtained as a single diastereoisomer. The formation of the benz-annellated product **11d** is noteworthy as all attempts to use aromatic coupling partners in the first approach (Scheme 4) were unsuccessful.

In conclusion, a mild, cheap and simple method of producing a diverse range of polycyclic heterocycles from commercially available or easily accessible starting materials using a stannous chloride-mediated deacetalisation–bicyclisation procedure has been developed. The products, several of which were obtained in diastereoselective processes, should be of interest both in their own right and as building blocks for the production of more complex target molecules. We are currently carrying out further optimisation and mechanistic studies[16] as



Scheme 4.



Scheme 5.

well as extending the range of the procedure and investigating its application to complex natural product targets.

Acknowledgements

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10. All novel compounds were fully characterised by their $^{1}H/^{13}C$ NMR, IR and HRMS or elemental analysis.
11. Other coupling agents were also investigated: with propane phosphonic acid anhydride (T3P®) a 41% overall yield was obtained; when HATU was employed the amide coupling step was unsuccessful.
12. *Representative procedure*: Methyl 3*R*,7a*S*-5-oxohexahydropyrrolo[2,1-*b*]thiazole-3-carboxylate (**7a**). (a) Isobutyl chloroformate (44 μL, 0.34 mmol) was added dropwise to a solution of acid **9a**[9] (50 mg, 0.34 mmol) and *N*-methylpiperidine (41 μL, 0.34 mmol) in DCM (4 mL) at −10 °C. After 2 min, an ice cold solution of L-cysteine methyl ester hydrochloride **10a** (62 mg, 0.36 mmol) and *N*-methylpiperidine (44 μL, 0.36 mmol) in DCM (1 mL) was added dropwise and stirring continued at −10 °C for 1 h and then at rt for a further 1 h. The solution was then filtered through a short pad of silica gel, washing through with EtOAc (3 × 5 mL) and the volatiles removed from the filtrate in vacuo to give the crude amide **8a**, which was used immediately without further purification; (b) Unpurified amide **8a** was re-dissolved in DCM (5 mL). Stannous chloride dihydrate (Aldrich 20803-5, 0.17 g, 0.75 mmol)

was added to this solution and the reaction mixture stirred at rt for 72 h whereupon it was diluted with $CHCl_3$ (5 mL) and then treated with K_2CO_3 (0.25 g, 1.8 mmol) and stirring continued for a further 0.5 h. The mixture was filtered through a short pad of a mixture of Celite® and silica gel (1:1), washing through with EtOAc (3×10 mL). The filtrate was concentrated in vacuo and the crude product purified by flash column chromatography, eluting with a solvent system of petroleum ether–EtOAc (1:1), to give the title compound **7a** (46 mg, 0.23 mmol, 68%) as a clear colourless oil; R_f (petroleum ether–EtOAc, 1:1) 0.33; $[\alpha]_D^{23}$ −250.7 (*c* 1.25, $CHCl_3$); IR ν_{max} (neat) 2954, 1743, 1709, 1437, 1388, 1285, 1218, 1177 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.19 (1H, dd, *J* 7.0, 4.0 Hz, NCHS), 5.08 (1H, dd, *J* 7.5, 4.5 Hz, $CHCO_2Me$), 3.73 (3H, s, CO_2Me), 3.38 (1H, dd, *J* 11.5, 7.5 Hz, C*H*HS), 3.33 (1H, dd, *J* 11.5, 4.5 Hz, CH*H*S), 2.73–2.60 (1H, m, C*H*HC=O), 2.59–2.48 (2H, m, CH*H*C=O, C*H*H), 2.19–2.09 (1H, m, CH*H*); δ_C (100 MHz, $CDCl_3$) 176.3, 170.2, 66.3, 57.6, 52.7, 36.1, 31.0, 24.6; *m*/*z* (ESI) 202 (100, MH^+), 142 (10%, $M-CO_2Me$); HRMS (ESI) MH^+, found 202.0539. $C_8H_{12}NO_3S$ requires 202.0532.

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16. In addition to Lewis acid activation provided by Sn(II), it is likely that HCl generated during the reaction plays a vital role (attempts to carry out the reactions in the presence of potassium carbonate were unsuccessful).