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One pot synthesis of nitrogen-containing polycyclic δ-lactones by double nucleophilic addition of bis(trimethylsilyl)ketene acetals to pyridines†

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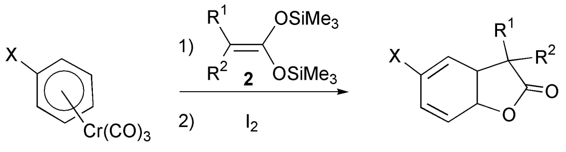
Pyridine and bis(TMS)ketene acetals (TMS = trimethylsilyl) react successively with methylchloroformate and iodine (or peracids) to give, *via* functionalized dihydropyridines, bicyclic nitrogen-containing lactones which have been characterized by X-ray crystallography.

In a series of recent papers,[1–4] we described the direct synthesis of functionalised γ-lactones upon interaction of bis(TMS)ketene acetals with transition metal activated double bonds and involving an original addition–oxidation–addition sequence. This led, in the case of aromatic systems, to a dearomatization reaction with formation of dihydrobenzofuran-2-ones (Scheme 1).



1 **3**

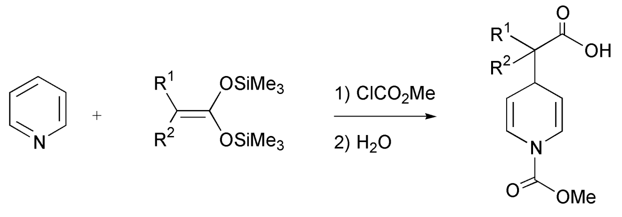
Scheme 1

These results and our current interest in the synthesis and uses of dihydropyridines[5–7] prompted us to extend a similar methodology for the transformation of pyridines. Three reasons guided this choice: first, the double bonds of pyridine, in contrast to those of the above unsaturated systems, are very readily activated towards nucleophilic additions *via* pyridinium derivatives, *e.g.* 1-acylpyridinium salts, reacting with a large variety of nucleophiles among which are silyl enol ethers;[8–10] second, the monoaddition of bis(TMS)ketene acetals to pyridine would lead in one step to new α-dihydropyridinyl carboxylic acids of direct interest as reducing agents for carbene complexes and for their pharmacological properties;[11] and third, the diaddition reaction might be the source of new, bicyclic, nitrogen-containing lactones, as valuable new intermediates for the synthesis of heterocyclic systems.

The purpose of this communication is to describe our successful attempts in the preparation of both types of compound, in the absence of any metal.

Thus, a dichloromethane solution (5 ml) of methylchloroformate (1.55 mmol) was added to a solution of bis(TMS)ketene acetal **2a** (R^1 = R^2 = Me, 2.8 mmol) and pyridine **4** (1.5 mmol), at room temperature. Stirring for 1 h followed by hydrolysis, extraction and evaporation of the solvent *in vacuo* left an oil.

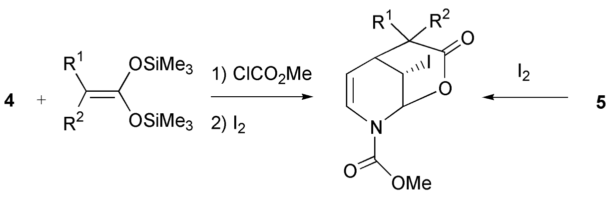
Chromatography on silica gel gave an oil, which, according to TLC, appeared to be a single isomer. Its NMR data‡ agreed with structure **5a**, and indicated the presence of two rotamers at room temperature, giving signals at δ 6.93 and 6.79 as doublets for H-2, and only one signal for H-3, at δ 4.79 as a multiplet, for H-4, at δ 3.36 as a singlet, and for the three methyl groups at δ 3.78 (1Me) and 1.13 (2Me). The ^{13}C NMR spectrum also exhibited separated signals for some of the carbons of the two rotamers, for C-2 at δ 124.9 and 124.6, and for C-3, at δ 106.0 and 105.7. A similar behaviour was observed for various other bis(trimethylsilyl) ketene acetals **2b–f** which gave selectively the expected dihydropyridyl carboxylic acids **5b–f**.



4 **2** **5**

a R^1 = Me R^2 = Me, **b** R^1 = Ph R^2 = H, **c** R^1 = *t*Bu R^2 = H,
d R^1 = OPh R^2 = H, **e** R^1 = OMe R^2 = H, **f** R^1 R^2 = C_5H_{10}

An excess of iodine (2 equiv.) was then added to a dichloromethane solution of the acid **5a** together with a saturated aqueous solution of sodium bicarbonate and stirred for 12 h. TLC confirmed the disappearance of the starting material and the formation of a single, less polar compound. Removal of iodine in excess, followed by extraction, evaporation of the solvent, and chromatography gave a single product, as an oil, in 78% yield. Its NMR data§ agreed with structure **6a** and confirmed again the presence of two rotamers giving signals, for the two carbonyl groups at δ 173.8 and 152.6 (152.5 for the second rotamer). The ^{13}C NMR spectrum confirmed the presence of a single double bond, of a deshielded methine group at δ 83.1 (82.7), and of a shielded methine group at δ 13.6 characteristic for a carbon bearing iodine.



2 **6**

The acid **5b** behaved similarly and led to the corresponding lactone **6b** (R^1 = Ph, R^2 = H), which was isolated as a crystalline material, mp 134 °C. Tiny crystals, yet suitable for an X-ray structure analysis, could be grown from dichloromethane–hexane.

A molecular projection of this compound appears in Fig. 1.¶ It confirms the bicyclic nature of the new product and thus the formation of a δ-lactone upon iodination of the enecarbamates of the type **5** probably to give an *N*-acyliminium ion which is trapped intramolecularly by the carboxylate, leading to a *trans*

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† All new compounds described in this paper were fully characterized by 200 and 400 MHz ^{1}H NMR, 50 or 100 MHz ^{13}C NMR, mass spectrometry and/or elemental analyses.

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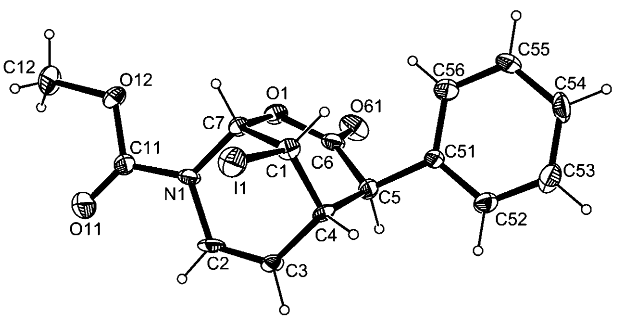
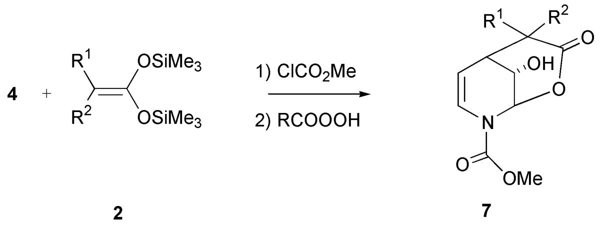


Fig. 1 Molecular view (ORTEP3)[15] with the atom labelling scheme. Ellipsoids are drawn at 50% probability. Selected bond distances (Å) and bond angles (°): C(1)–I(1) 2.148(7), C(1)–C(4) 1.511(10), C(4)–C(3) 1.493(10), C(3)–C(2) 1.317(11), C(2)–N(1) 1.438(9), N(1)–C(7) 1.441(9), C(7)–O(1) 1.457(10), C(7)–C(1) 1.510(10), O(1)–C(6) 1.360(9), C(6)–O(61) 1.181(10), C(6)–C(5) 1.530(9), C(5)–C(4) 1.558(10), N(1)–C(11) 1.370(9), C(11)–O(11) 1.184(9), C(11)–O(12) 1.365(9), O(12)–C(12) 1.439(9); C(4)–C(1)–C(7) 108.4(6), C(4)–C(1)–I(1) 114.1(5), C(7)–C(1)–I(1) 109.3(5), C(1)–C(4)–C(3) 110.2(6), C(4)–C(3)–C(2) 122.4(7), C(3)–C(2)–N(1) 122.1, N(1)–C(11)–O(11) 125.3(7), N(1)–C(11)–O(12) 109.8(6), O(11)–C(11)–O(12) 125.0(7).

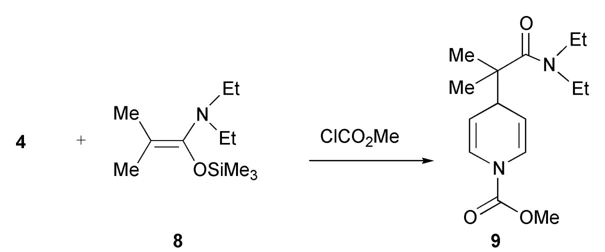
orientation of the carbon–iodine bond with respect to the new carbon-oxygen bond.

This easy two-step diaddition reaction prompted us to attempt the one pot transformation of pyridine into the lactone **6a**. Thus, treatment of the mixture of pyridine and bis(TMS)ketene acetals **2a** first with methylchloroformate, at room temperature for one hour, then with an excess of iodine, followed by stirring overnight, led to the expected lactones **6a** in a 90% yield.

A further possibility existed for the transformation of the acids **5** into lactones: the oxidative cyclization *via* the epoxidation of one of the double bonds of the dihydropyridines **5**.[4,5]



Thus, when the same mixture originating from the monoaddition of the ketene acetals **2a** to pyridine was subjected to a *m*-chloroperbenzoic acid oxidation, at room temperature, a new compounds **7a** was isolated after silica gel chromatography in 75% yield, as a solid, mp 130° C. Its NMR spectra‖ confirmed the presence of two rotamers, the ^{13}C NMR spectrum of **7a** differing from the spectrum of **6a** by the shift of one signal from δ 13.6 (C-I) to δ 45.6, confirming the formation, upon cyclization, of a secondary alcohol.



Finally it is worthy to note that the *O*-silyl ketene *N,O* acetal **8** reacted under the same conditions as **2a–f** to give in 75% yield the corresponding homodihydronicotinamide **9**. However, in contrast to **5a**, no lactonisation took place upon its treatment with iodine.

This new method is being applied to the synthesis of chiral dihydropyridines for the enantioselective reduction of carbene complexes and further functionalizations of the lactones are in progress.

Notes and references

‡ *Spectral data* for **5a**; δ_H (200 MHz) 10.65 (s, br, 1H), 6.93 and 6.79 (d, *J* 7.4, 2H), 4.79 (s, br, 2H), 3.78 (s, 3H), 3.36 (s, br, 1H), 1.13 (s, 6H); δ_C (50 MHz) 183.62 (CO_2H), 151.92 (COOMe), 124.94, 124.62, 106.00, 105.70 (C=C), 53.56 (OMe), 47.17 (CMe_2), 40.18 (CH), 21.33 (2 Me).

§ For **6a**; δ_H (400 MHz) 7.28, 6.92 (d, *J* 6, 1H), 6.40, 6.25 (s, 1H), 5.16 (t, *J* 6.8, 1H), 5.06, 5.04 (s, 1H), 3.85 (s, 3H), 2.41, 2.39 (s, 1H), 1.45 (s, 3H), 1.35 (s, 3H), δ_C (100 MHz) 173.88 (CO), 152.67, 152.50 (CO), 121.79 (C=C), 105.42, 104.99 (C=C), 83.18, 82.69 (C(N)O), 54.08 (OCH_3), 46.66 (C_q), 44.51, 44.37 (CH), 27.26, 26.12 (Me), 13.64 (C-I).

¶ *Crystal data for* **6b**: [$C_{15}H_{14}INO_4$]; M_r = 399.17; monoclinic; space group $P2_1/n$; a = 6.1448(5), b = 12.505(1), c = 18.965(1) Å, β = 92.97(1)°, V = 1455.3(2) Å^3, Z = 4, $\rho_{\text{calcd.}}$ = 1.822 Mg m^{-3}, μ = 2.216 mm^{-1}, numerical absorption correction applied, T_{min} = 0.5938, T_{max} = 0.6860; MoKα radiation; T = 180 K; ω/φ scans (Oxford-Diffraction Xcalibur);[12] 2θmax = 50.04°; reflections collected/unique used, 7143/2514 (R_{int} = 0.0889) 2119 [$I > 2\sigma(I)$]; parameters refined, 191; $R/wR2[(I > 2\sigma(I)]$ = 0.0660/0.1593; GOF = 1.123; $\Delta/\sigma_{\text{max}}$ = 0.006; $[\Delta\rho]_{\text{min}}/[\Delta\rho]_{\text{max}}$, −1.31/1.72. Structure solution and refinement with the programs SIR97[13] and SHELXL97.[14] CCDC 178733. See http://www.rsc.org/suppdata/cc/b2/b201780f/ for electronic files in .cif or other electronic format.

‖ For **7a**; δ_H 6.94 (d, *J* 8.2, 1H), 6.81 (d, *J* 8.2, 1H), 6.34, 6.18 (s, br, 1H), 5.10, 5.02 (d, *J* 8.2), 4.79 (s, br, 1H), 3.84 (s, 3H), 2.36, 2.38 (s, 1H), 1.42 (s, 3H), 1.37 (s, 3H); δ_C 152.83, 152.70 (CO), 121.84 (C=C), 103.93, 103.52 (C=C), 81.21, 80.83 (C(N)O), 51.04 (OCH_3), 46.17 (CMe_2), 45.60 (COH), 42.60, 42.52 (CH), 27.17 (Me), 26.02(Me).

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