Protected 2-Indoleacetaldehyde Derivatives from 2-Acylindoles

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The conversion of tetracyclic 2-acylindoles **1** to the protected 2-indoleacetaldehydes **4** and **6** is reported. 2-Indoleacetaldehydes **5** undergo oxidation to the corresponding 2-acylindoles **1**.

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In the context of our studies [1] about the synthesis of pentacyclic *Strychnos* indole alkaloids [2] we were interested in developing a procedure for the introduction of an oxidized one-carbon substituent at *C*-6 in tetracyclic hexahydro-1,5-methanoazocino[4,3-*b*]indole systems. This substituent is present at the corresponding position (*C*-16) in pentacyclic *Strychnos* alkaloids of the curan type such as akuammicine (methoxycarbonyl) and strychnofluorine (formyl).

Although the homologation of ketones is a well-known procedure [3], the moderate reactivity of the 2-acylindole carbonyl group implied a difficulty to overcome. In fact, the methoxycarbonylation of ketone **1a** with tosylmethyl isocyanide (TosMIC) or methyl methylthiomethyl sulfoxide was unsuccessful, the starting ketone being recovered unchanged. Since it has been reported that the lithium salt of (methoxymethyl)diphenylphosphine oxide (**2**) reacts with 2-acylindoles [4] we tested this reagent for our purpose.

The Horner-Wittig reaction between deethyldasycarpidone (**1a**) [5] and the lithium salt of **2** afforded the expected vinyl ether **4a** in 80% yield. It is worth noting that the reaction required a prolonged reaction time (24 hours) since after shorter times the intermediate phosphine oxide **3a** was isolated to a considerable extent. A similar Horner-Wittig reaction from the *N*-methyl derivative **1b** [6] led to the corresponding vinyl ether **4b**. All attempts to convert vinyl ethers **4a** and **4b** into the corresponding formyl derivatives **5a** and **5b** under a variety of hydrolytic conditions were unsuccessful, the respective 2-acylindoles **1a** and **1b** being formed in high yields instead. However, a pure sample of aldehyde **5b** could be isolated during the purification of vinyl ether **4b** by column chromatography. This aldehyde showed to be unstable and slowly decomposed to **1b**. On the other hand, reaction of vinyl ether **4a** with pyridinium chlorochromate (PCC) [7] in order to obtain the corresponding ester failed. Deethyldasycarpidone (**1a**) was again obtained (63% yield).

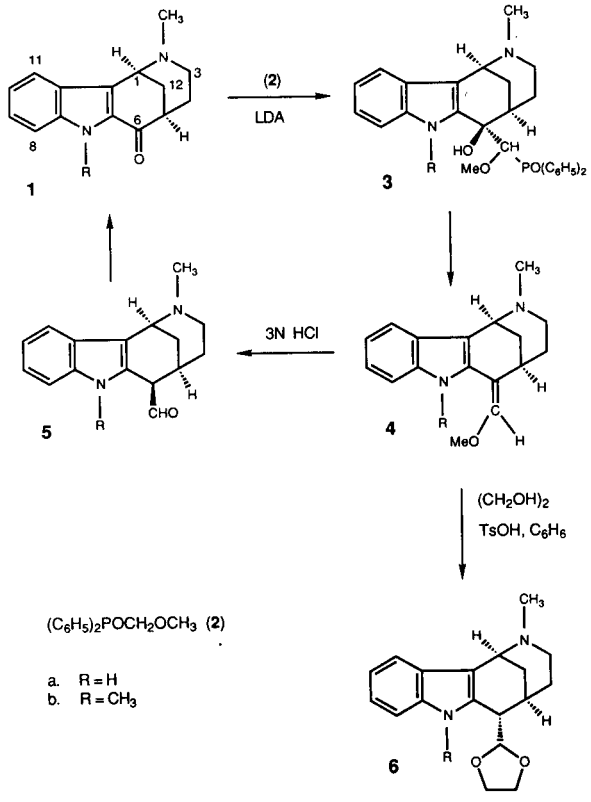
There is some discrepancy about the stability of 2-indoleacetaldehydes. Thus, although some 1,2,3,4-tetrahydrocarbazole-1-carbaldehydes have been obtained as stable materials [8] and compounds having the 2-indoleacetaldehyde moiety have been successfully used as synthetic intermediates [9], an inspection of the literature showed that a few compounds having this moiety have been reported so far [10,11] and that degradative oxidations similar to that of **4** have been previously observed [12], one of them from a tetracyclic aldehyde closely related to **5** [13,14].

Formation of 2-acylindoles **1** from vinyl ethers **4** can be rationalized [13,14] by considering that the initially formed 2-indoleacetaldehyde undergoes oxidation to an α-hydroperoxide which decomposes to formic acid and the isolated 2-acylindole.

Finally, vinyl ether **4a** was converted into acetal **6**, another protected form of indoleacetaldehyde **5a**. As expected from the above results, attempted hydrolysiis of **6** gave again 2-acylindole **1a**.

In conclusion we have reported the preparation of two forms of protected 2-indoleacetaldehyde derivatives start-

Scheme



ing from 2-acylindoles. The extension of the above transformations to suitably *N*- and *C*-4 substituted tetracyclic 2-acylindoles could provide valuable precursors of *Strychnos* alkaloids of the curan-type.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded in deuteriochloroform on a Varian XL-200 spectrometer or, when indicated, on a Perkin-Elmer R-24B (60 MHz) instrument using TMS as internal standard. The ^{13}C-nmr spectra were recorded on a Varian XL-200 spectrometer (50.3 MHz). The chemical shifts are reported in ppm downfield (δ) from TMS. The ir spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Gravity column chromatography was done with Merck silica gel 60 (0.063-0.200 mm) or Merck neutral grade I alumina. Microanalyses were performed on a Carlo Erba 1106 analyzer by Departmento de Química Orgánica Biológica (CSIC), Barcelona.

(*Z*)-2-Methyl-6-(methoxymethylene)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]-indole (**4a**).

A solution of diisopropylamine (5.5 ml, 37.5 mmoles) in 50 ml of THF at −70° was treated under nitrogen with 24 ml (37.5 mmoles) of *n*-butyllithium (1.6 *M* in hexanes). The mixture was allowed to warm to 0° and phosphine oxide **2** (8.23 g, 33.32 mmoles) in THF (75 ml) was added dropwise. After the addition was completed, the mixture was stirred for 10 minutes, and the flask was chilled to −78°. Ketone **1a** (2 g, 8.33 mmoles) in THF (150 ml) was slowly added to the orange-red solution, the cooling bath was removed, and the mixture was stirred at 40° for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The organic extract was acidified with 2*N* hydrochloric acid and discarded. The acidic aqueous solution was basified with 2*N* aqueous sodium hydroxide solution and extracted with ethyl acetate. The organic portion was dried and concentrated to give 1.9 g (85%) of vinyl ether **4a**, which was reasonably pure by ^{1}H-nmr and tlc (alumina, 95:3:2 ether/acetone/diethylamine, as eluent) and was used directly in the next reaction. A small protion was subjected to column chromatography on alumina (99:1 ethyl acetate/diethylamine) to give analytical sample of **4a**; ir (chloroform): 3440 (NH), 1650 (C=C); ^{1}H-nmr: 1.57 (dm, J = 12 Hz, 1H, 4-Heq), 1.93 (dq, J = 13 and 3 Hz, 1H, 12-H), 2.2-2.7 (m, 6H), 2.36 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 4.37 (dd, J = 3 Hz, 1H, 1-H), 6.15 (s, 1H, =CH), 7.1-7.5 (m, 4H, ArH): ^{13}C-nmr: 29.1 (5-C), 34.0 and 34.4 (4- and 12-C), 43.9 (NCH_3), 46.5 (3-C), 52.8 (1-C), 60.7 (OCH_3), 105.7 (6-C), 110.7 (11b-C), 110.9 (8-C), 118.4 (11-C), 119.9 (10-C), 121.7 (9-C), 127.6 (11a-C), 135.2 and 135.8 (6a- and 7a-C), 143.3 (=CHOMe). The picrate melted at 165-167° (ethanol).

Anal. Calcd. for $C_{23}H_{23}N_5O_8$: C, 55.23; H, 4.66; N, 14.08. Found: C, 55.44; H, 4.91; N, 13.92.

When the reaction was conducted at room temperature for 15 hours, a mixture of vinyl ether **4a** (55%) and 6-(diphenylphosphoryl)methoxymethyl-6-hydroxy-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (**3a**, 32%) was obtained. Both compounds were isolated by column chromatography (silica gel, 99:1 ethyl acetate/diethyamine). A sample of **3a** recrystallized from acetone-methanol melted at 234-236°; ir (potassium bromide): 2500-3500 (OH), 1140 (P=O); ^{1}H-nmr: 1.7 (m, 1H, 12-Hax), 2.05 (tm, J = 13 Hz, 2H, 3- and 4-Hax), 2.20 (s, 3H, NCH_3), 2.2-2.6 (m, 4H), 2.71 (s, 3H, OCH_3), 4.18 (br s, 1H, 1-H), 4.48 (d, J = 7 Hz, 1H, CHPO), 5.5 (br, 1H, OH), 7.0-8.0, (14 H, ArH), 10.4 (br, 1H, NH); ^{13}C-nmr: 26.1 (12-C), 33.0 (4-C), 33.6 (5-C), 44.1 (NCH_3), 46.3 (3-C), 51.9 (1-C), 61.7 (OCH_3), 74.8 (6-C), 87.4 (C-PO), 108.3 (11b-C), 111.7 (8-C), 119.4 (11-C), 119.8 (10-C), 122.2 (9-C), 127.4 (11a-C), 128.6 and 128.8 (m-C), 130.6 and 130.9 (p-Ar), 132.5 and 132.6 (o-Ar), 136.2 (7a-C), 137.5 (6a-C).

Anal. Calcd. for $C_{29}H_{31}N_2O_3P$: C, 71.58; H, 6.42; N, 5.75. Found: C, 71.60; H, 6.38; N, 5.84.

2,7-Dimethyl-6-(methoxymethylene)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (**4b**).

Operating as above according to the second protocol, 2-acylindole **1b** (0.5 g, 1.97 mmoles) was transformed into the vinyl ether **4b**, which was isolated (230 mg, 42%) by column chromatography (silica gel, 95:5 chloroform/methanol); ir (chloroform): 1645 (C=C); ^{1}H-nmr: (60 MHz) 2.12 (s, 3H, NCH_3), 3.6 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 4.05 (br t, 1H, 1-H), 5.8 (s, 1H, =CH), 6.8-7.4 (m, 4H, ArH). In one run, a fraction of aldehyde **5b** was obtained: ir (chloroform): 1730 (CO); ^{13}C-nmr: 26.7 (4-C), 31.1 (N_a-CH_3), 32.8 (12-C), 33.9 (5-C), 43.6 (N_b-CH_3), 45.3 (3-C), 51.9 (1-C), 52.6 (6-C), 105.8 (11b-C), 109.5 (8-C), 119.4 (11-C), 120.0 (10-C), 122.8 (9-C), 128.9 (11a-C), 132.6 (6a-C), 138.0 (7a-C), 199.7 (CHO).

Hydrolysis of Vinyl Ether **4a**.

A solution of vinyl ether **4a** (280 mg, 1.05 mmoles) in THF (10 ml) and 3*N* hydrochloric acid (10 ml) was stirred at 80° for 8 hours. Water was added to the mixture, and the resulting aqueous solution was basified with 10% aqueous potassium carbonate and extracted with methylene chloride. The organic extracts were washed with brine, dried, and evaporated. The crude material was chromatographed (silica gel 99:1 chloroform/diethylamine) to give 180 mg (72%) of ketone **1a**.

(1*RS*, 5*SR*, 6*RS*)-2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carbaldehyde Ethylene Acetal (**6a**).

A solution of vinyl ether **4a** (1.16 g, 4.33 mmoles), ethylene glycol (2.5 ml, 43.3 mmoles), and *p*-toluenesulfonic acid monohydrate (1.23 g, 6.5 mmoles) in 30 ml of benzene was refluxed under a Dean-Stark trap for 2 hours. The benzene was removed and the residue was taken up in 10% aqueous potassium carbonate and extracted with methylene chloride. The organic extracts were washed with brine, dried, and evaporated. The residue was purified by column chromatography (alumina, 99:1 ethyl acetate/diethylamine) to give 100 mg of a mixture of acetal **6a** and its *C*-6 epimer and 400 mg of pure acetal **6a** (38% overall yield); ir (chloroform): 3420 (NH); ^{1}H-nmr: 1.68 (dm, 1H), 2.0-2.3 (m, 4H), 2.34 (s, 3H, NCH_3), 2.36 (br, 1H), 2.58 (d, J = 6 Hz, 1H), 2.85 (d, J = 6.5 Hz, 1H, 6-H), 3.9 (m, 4H, OCH_2), 4.24 (dd, J = 3 Hz, 1H, 1-H), 4.87 (d, J = 6 Hz, 1H, HCO), 7.1-7.5 (m, 4H, ArH), 8.7 (br, 1H, NH); ^{13}C-nmr: 26.5 (5-C), 30.3 (12-C), 32.3 (4-C), 43.5 (NCH_3), 43.6 (6-C), 46.4 (3-C), 52.3 (1-C), 64.7 and 65.3 (OCH_2), 105.1 (ketal C), 106.6 (11b-C), 111.1 (8-C), 118.4 (11-C), 119.9 (10-C), 121.6 (9-C), 128.4 (11a-C), 135.8 (7a-C), 136.0 (6a-C). The picrate melted at 122-124° (ethanol).

Anal. Calcd. for $C_{24}H_{25}N_5O_9$: C, 54.65; H, 4.78. Found: C, 54.22; H, 4.41.

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