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2,5-DIMETHOXY-2,5-DIHYDROFURAN AS A SYNTHETIC EQUIVALENT OF 3-FORMYL ALKYLPROPIONATE IN PICTET-SPENGLER TYPE REACTIONS

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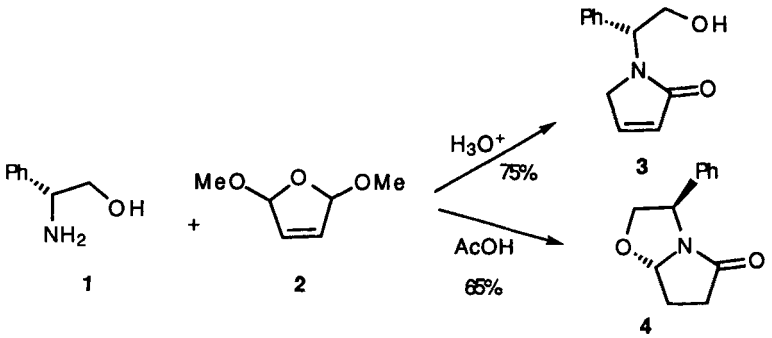
Abstract: 2,5-dimethoxy-2,5-dihydrofuran has been used as a synthetic equivalent of 3-formyl propionate in the Pictet-Spengler type reaction of 2-aryl ethylamines to provide the corresponding arylindolizidinones in moderate yields.

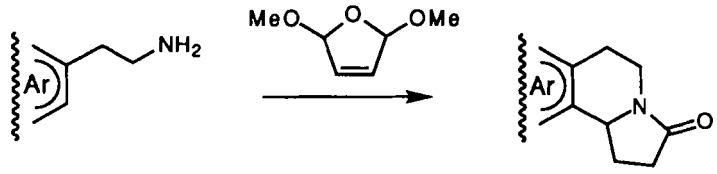
We have recently reported[1] that the reaction of (*R*)-(-)-phenylglycinol (**1**) with 2,5-dimethoxy-2,5-dihydrofuran (**2**) gave the unsaturated lactam **3** or the oxazolidino γ-lactam **4** depending upon the experimental conditions (Scheme 1).



scheme 1

The synthetic utility of lactam **3** has been recently underlined within this laboratory.[1,2] Herein we wish to describe a general exploitation of the preparative technique used to form lactam **4**.

Having realised that in the synthesis of **4**, 2,5-dimethoxy-2,5-dihydrofuran (**2**) acted as a synthetic equivalent of 3-formyl propionate, we planned to apply this reaction to 2-aryl ethylamines **5** in order to prepare arylindolizidinones of type **6**.

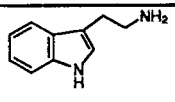
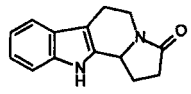
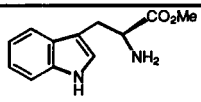
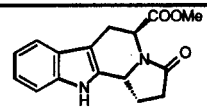
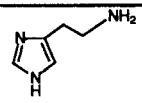
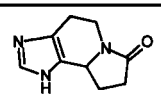
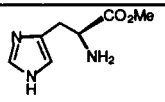
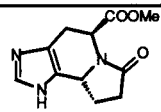
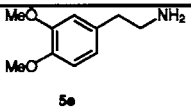
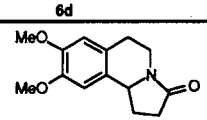


5 **6**

scheme 2

Several compounds of type **6** have already been described in the literature[3-8], and are mainly prepared through the Pictet-Spengler reaction of **5** with 3-formyl propionate or a synthetic equivalent. However, the preparation of 3-formyl propionate[8-13], despite its apparent simplicity, is not so easily feasible. The most rapid procedure involves the alcoholysis of γ-butyrolactone followed by oxidation of the alcohol function.[10] Both of these steps need careful conditions and the overall yield was not, in our hands, as high as published. The use of ketoglutaric acid[5], as a synthetic equivalent, is also a good method for the preparation of compounds **6**, but generally necessitates prolonged heating to undergo the subsequent decarboxylation. The condensation of 3-pyrrolin-2-one with tryptamine has also been reported, giving the expected tetracyclic product in good yield,[4] but 3-pyrrolin-2-one still requires to be prepared (by H_2O_2 oxidation of pyrrole in modest yield[13]). Other methods to prepare compounds **6** have also been described but necessitate several steps.[7,8]

Table: Condensation of different 2-aryl ethylamines with 2,5-dimethoxy-2,5-dihydrofuran

starting material	product	yield	reference to literature
 5a	 6a	46%	- 58% from ketoglutaric acid (ref. 3) - 45% (ref. 6) - 25% from pyrrole in 2 steps (ref. 4)
 5b	 6b	51% d.e.>95%	- 79% from ketoglutaric acid (ref. 5) - 24% from pyrrole in 2 steps (ref. 4)
 5c	 6c	51%	46% in 3 steps (ref. 8)
 5d	 6d	45% d.e.>95%	not reported(*)
 5e	 6e	53%	≈50% in 3 steps (ref. 7)

(*)Treatment of L-histidine with ketoglutaric acid in aqueous solution has been reported to give a mixture of cyclized and uncyclized Pictet-Spengler condensation products without decarboxylation [14]

A general access to arylindolizidinones of type **6** has been achieved by the use of commercially available and cheap 2,5-dimethoxy-2,5-dihydrofuran as a synthetic equivalent of 3-formyl propionate (table). It is noteworthy that 3-formyl propionate has been synthesized from 2,5-dimethoxy-2,5-dihydrofuran by a ruthenium hydride-catalyzed double bond isomerization followed by hydrolysis.[12]

Different 2-aryl ethylamines **5a-e** were thus condensed with 2,5-dimethoxy-2,5-dihydrofuran in refluxing acetic acid to give arylindolizidinones **6a-e** in moderate yield (45-53%) as reported in Table. In conclusion, this simple one step method appears to be a good alternative to those already published. Furthermore, the reaction displays high diastereoselectivity, towards the histidine and tryptophane methyl esters **5b** and **5d** (products **6b** and **6d** are obtained as single diastereomers).

Experimental:

All the starting materials were commercially available and purified following standard techniques.

Optical rotations were measured on a Perkin-Elmer polarimeter. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR were registrated on a Bruker AC-300 using TMS as internal standard. Mass spectra were recorded on a AEI MS-9 (CI, isobutane) and AEI MS-50 (EI).

General procedure for the condensation with 2,5-dimethoxy-2,5-dihydrofuran: 2,5-Dimethoxy-2,5-dihydrofuran (**2**) (1.2 equiv.) was added to a solution of amine (**5**) (1 equiv.) in glacial acetic acid (10 mL for 10 mmol) and the mixture refluxed for 15-18 h. The acetic acid was distilled off, and the residue was purified by flash chromatography.

1,2,5,6,11,11b-hexahydro-indolizino[8,7-*b*]indol-3-one (6a): from tryptamine (**5a**) (1.2 g; 7.3 mmol) and 2,5-dimethoxy-2,5-dihydrofuran (**2**) (1 mL; 8.2 mmol), yield: 766 mg (46 %); purification by flash-chromatography on silica gel 60 (dichloromethane/methanol 95: 5, Rf-value: 0.5);

mp: 245°C (AcOEt), lit.[6] : 245-247°C; IR (film): ν=1662 cm^{-1} (-C=O), ^{1}H-NMR

($CDCl_3$): δ(ppm): 8.3 (1H, s), 7.5 (1H, d, J=7.6 Hz), 7.35 (1H, d, J=7.6 Hz), 7.2 (1H, dt, J=1.2, 7.6 Hz), 7.15 (1H, dt, J=1.2, 7.6 Hz), 4.9 (1H, t, J=7.5 Hz), 4.5 (1H, m), 3.1-2.9 (1H, m), 2.85 (2H, m), 2.6-2.45 (3H, m), 1.9 (1H, m), ^{13}C NMR ($CDCl_3$): δ(ppm): 174.0, 133.3, 126.9, 122.3, 119.9, 118.6, 111.4, 111.1, 54.4, 37.8, 31.8, 25.8, 21.1; MS (CI, isobutane): m/z=227 [MH^+].

3-oxo-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-5-carboxylic acid methyl ester (6b) : from L-tryptophane methyl ester (**5b**) (1.28 g; 5.9 mmol) and 2,5-dimethoxy-2,5-dihydrofuran (**2**) (856 µL; 7.1 mmol), yield: 858 mg (51%); purification by flash-chromatography on silica gel (dichloromethane / methanol 94: 6, Rf-value: 0.45);
mp: 185°C (CH_2Cl_2/MeOH), lit.[5]: 184-186°C; $[\alpha]_D$=+150 (c=1.5, $CHCl_3$), IR (film): ν=1743 cm^{-1} (-C=O ester), 1675 (-C=O amide), ^1H-NMR ($CDCl_3$): δ(ppm): 9.1 (1H, s), 7.5 (1H, d, J=7.0 Hz), 7.2 (1H, d, J= 7.0 Hz), 7.1 (2H, t, J=7.0 Hz), 5.35 (1H, d, J=7.2 Hz), 5.15 (1H, m), 3.6 (3H, s), 3.4 (1H, m), 3.1 (1H, dd, J=7.2, 15.7 Hz), 2.5 (3H, m), 1.85 (1H, m), ^{13}C NMR ($CDCl_3$): δ(ppm): 174.0, 170.9, 136.2, 132.3, 126.2, 121.8, 119.3, 118.0, 110.9, 104.5, 52.3, 52.2, 49.2, 31.3, 26.0, 23.3; MS (CI, isobutane): m/z=285 [MH^+].

1,2,3,5,6,9b-hexahydro-7*H*-3-oxoimidazo[4,5-*c*]pyrrolo[1,2-*a*]pyridine (6c) : from histamine (**5c**) (764 mg; 6.9 mmol) and 2,5-dimethoxy-2,5-dihydrofuran (**2**) (1.25 mL; 10.3 mmol), yield: 624 mg (51%); purification by flash-chromatography on silica gel (dichloromethane/methanol 90: 10, Rf-value: 0.2);
mp: 107-109°C (CH_2Cl_2/MeOH), lit.[8]: 108-110°C; IR (film): ν=1682 cm^{-1} (-C=O), ^1H-NMR ($CDCl_3$): δ(ppm): 7.55 (1H, s), 4.8 (1H, t, J=7.0 Hz), 4.45 (1H, dd, J=5.8, 12.5 Hz), 3.05 (1H, dt, J=5.1, 12.5 Hz), 2.8 (1H, m), 2.7 (1H, m), 2.6-2.4 (3H, m), 1.9 (1H, m), ^{13}C NMR ($CDCl_3$): δ(ppm): 173.9, 134.6, 134, 123.6, 55.3, 36.9, 31.6, 25.3, 21.8; MS (EI): m/z=177 [M^+].

1,2,3,5,6,9b-hexahydro-7*H*-3-oxoimidazo[4,5-*c*]pyrrolo[1,2-*a*] pyridine -5-carboxylic acid methyl ester 6d : from L-histidine methyl ester (**5d**) (28 g; 160 mmol) and 2,5-dimethoxy-2,5-dihydrofuran (**2**) (24 ml; 200 mmol), yield: 17.5 g (45%); purification by flash-chromatography on silica gel (dichloromethane / methanol 92: 8, Rf-value: 0.3);

mp: 72°C (CH_2Cl_2/MeOH); $[\alpha]_D$=+24 (c=1, $CHCl_3$), IR (film): ν=1735 cm^{-1} (-C=O ester), 1682 (-C=O amide), ^{1}H-NMR ($CDCl_3$): δ(ppm): 7.55 (1H, s), 5.3 (1H, d, J=7.0 Hz), 4.9 (1H, dd, J=7.0, 8.5 Hz), 3.7 (3H, s), 3.2 (1H, d, J=15.8 Hz), 3.05 (1H, ddd, J=2.0, 7.0, 15.8Hz), 2.7 (2H, m), 2.5 (1H, m), 1.9 (1H, m), ^{13}C NMR ($CDCl_3$): δ(ppm): 174.4, 170.6, 135.2, 133.2, 121.9, 53.4 , 52.9, 49.1, 31.6, 26.2, 24.2; MS (CI, isobutane): m/z=236 [MH^+]; Anal. calcd. for $C_{11}H_{13}N_3O_3$, 0.5 H_2O: C, 54,10; H, 5,73; N, 17,21; found: C, 54,11; H, 5,42; N, 16,98

8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one (6e) : from 3.4-dimethoxy-phenylalanine (**5e**) (500 mg; 2 mmol) and 2,5-dimethoxy-2,5-dihydrofuran **2** (287 µl; 2.4 mmol), yield: 262 mg (53%); purification by flash-chromatography on silica gel (ether/methanol 95: 5, Rf-value: 0.3);

mp: 104°C (Et_2O-MeOH); IR (film): ν=1674 cm^{-1} (-C=O), ^{1}H-NMR ($CDCl_3$): δ(ppm): 6.65 (1H, s), 6.6 (1H, s), 4.75 (1H, t, J=7.7 Hz), 4.3 (1H, ddd, J=1,9, 5,6, 12.5 Hz), 3.9 (6H, s), 3.05 (1H, dt, J=4,5, 12.5 Hz), 2.9 (1H, dt, J=5.6, 12,5 Hz), 2.75-2.6 (2H, m), 2.6-2.4 (2H, m), 1.85 (1H, m), ^{13}C NMR ($CDCl_3$): δ(ppm): 172.5, 147.6, 147.3, 128.9, 125.0, 111.2, 107.2, 56.0, 55.5, 55.4, 36.5, 31.2, 27.5, 27.2; MS (CI, isobutane): m/z=248 [MH^+]; Anal. calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6,93; N, 5,66; found: C, 67,81; H, 6,99; N, 5,56.

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