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Synthesis of 2,3,5-substituted pyrrole derivatives

Paula M. T. Ferreira,* Hernâni L. S. Maia and Luís S. Monteiro

Department of Chemistry, University of Minho, Gualtar, P-4700-320 Braga, Portugal

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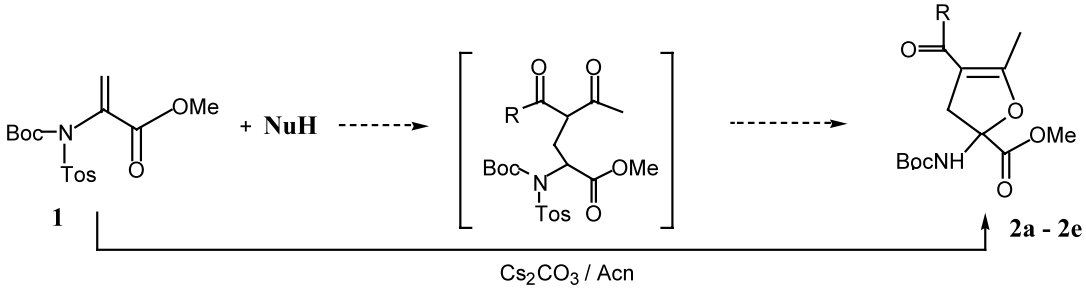
Abstract—2,3,5-Substituted pyrrole derivatives are prepared by treatment of 2,3-dihydrofuran derivatives with trifluoroacetic acid. These in turn are obtained by Michael addition of carbon nucleophiles of the β-dicarbonyl type to *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)-dehydroalanine methyl ester.

1. Introduction

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry. These compounds can have intrinsic biological activity and also constitute the structural feature of many biologically active compounds. The synthetic approaches to pyrrole derivatives are mostly multistep and low yielding.[1–4] Thus, development of new synthetic methods still remains an attractive goal.

2. Results and discussion

We have reported the synthesis of β-substituted alanine derivatives by Michael addition of carbon nucleophiles of the β-dicarbonyl type to *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)-dehydroalanine methyl ester [Tos-ΔAla(*N*-Boc)-OMe].[5] These additional products behaved differently according to the structure of the nucleophile. Thus, the products of the addition of diethyl malonate and cyclohexane-1,3-dione, namely, Tos-Ala[*N*-Boc,β-bis(ethoxycarbonyl)-methyl]-OMe and Tos-Ala[*N*-Boc,β-(2,6-dioxocyclohexyl)]-OMe are stable. However, those of the addition of nucleophiles having at least one alkyl group bonded to one of the carbonyl groups, viz. pentane-2,4-dione and methyl acetocetate, gave cyclic amino acids of the furan type, i.e. 2-(*tert*-butyloxycarbonylamino)-2-methoxycarbonyl-4-(1-oxoethyl)-5-methyl-2,3-dihydrofuran (**2a**)[5] and 2-(*tert*-butyloxycarbonylamino)-2,4-bis(methoxycarbonyl)-5-methyl-2,3-dihydrofuran (**2b**).[5] We believe that these compounds result from rearrangement of the detosylated β-substituted alanine derivative via enolisation with attack of



NuH: pentane-2,4-dione, **a**; methyl acetoacetate, **b**; benzoyl acetone, **c**; benzyloxycarbonyl acetone, **d**; isobutylcarbonyl acetone, **e**.

R: Me, **2a**;[5] OMe, **2b**;[5] Ph, **2c**; OBn, **2d**; *i*-Bu, **2e**.

Scheme 1.

Keywords: dehydroalanine; dihydrofuran; pyrrole; dehydroproline.
* Corresponding author.

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Table 1. Yields obtained in the synthesis of 2,3-dihydrofurans (**2a–e**) and 2,3,5-substituted pyrrole derivatives (**3a–e**)

Entry	NuH	Compound no.	Yield (%)[a]	Compound no.	Yield (%)[a]
1	Pentane-2,4-dione (**a**)	**2a**[5]	88	**3a**	92
2	Methyl acetoacetate (**b**)	**2b**[5]	86	**3b**	90
3	Benzoyl acetone (**c**)	**2c**	80	**3c**	77
4	Benzyloxycarbonyl acetone (**d**)	**2d**	78	**3d**	79
5	Isobutylcarbonyl acetone (**e**)	**2e**	82	**3e**	88

[a] Crude yield of pure material.

the enolic oxygen atom at the amino acid α-carbon atom (Scheme 1, Table 1). Initially the reactions were carried out using an excess of K_2CO_3 as base; however, it was found that the use of 1 equiv. of Cs_2CO_3 leads to less complex reaction mixtures and, thus, higher yields of dihydrofuran derivatives. This method was successfully extended to other β-carbonyl nucleophiles, namely benzoyl acetone (**c**), benzyloxycarbonyl acetone (**d**) and isobutylcarbonyl acetone (**e**) to give new 2,3-dihydrofuran derivatives in good yields.

The above 2,3-dihydrofurans showed to be excellent starting materials for the synthesis of the corresponding pyrrole derivatives, by treatment at room temperature with 10% trifluoroacetic acid (TFA) in dichloromethane (Scheme 2, Table 1). This reaction seems to proceed via cleavage of the Boc group with ring opening and subsequent attack of the nitrogen atom of the amine function on the enolic carbon atom.

The pyrrole derivatives described above are dehydroprolines, which may have intrinsic biological activity, making them suitable for the synthesis of modified peptides to which they would certainly impose high conformational constraints. Thus, we believe this method to be excellent for the synthesis of furanic amino acids and dehydroprolines derivatives.

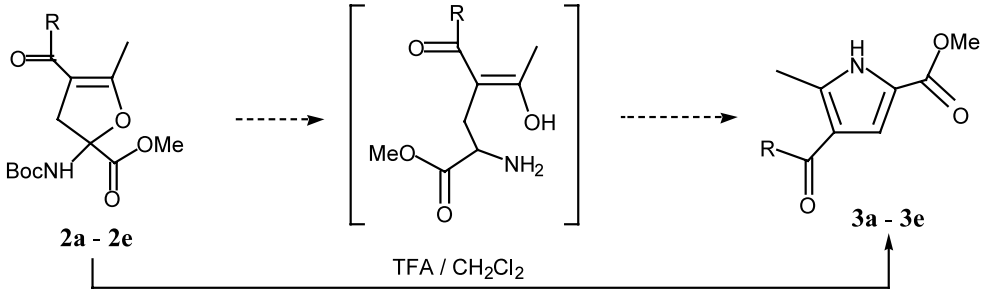
3. General experimental procedure (example)

3.1. Preparation of the 2,3-dihydrofuran derivative 2d

To a solution of Tos-ΔAla(*N*-Boc)-OMe (1 mmol) in acetonitrile (0.1 mol dm^{-3}), Cs_2CO_3 (1 equiv.) was added at room temperature with rapid stirring, followed by benzyloxycarbonyl acetone (1 equiv.), The reaction was monitored by TLC and when no starting material was detected, the solution was filtered and the solvent evaporated at reduced pressure to give **2d** (78%) as an oil, δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.44 (9H, s, CH_3 Boc), 2.27 (3H, s, CH_3), 3.20 (2H, q, $J=15.9$ Hz, CH_2), 3.84 (3H, s, CH_3 OMe), 5.16 (2H, s, CH_2), 5.89 (1H, s, αNH), 7.36–7.61 (5H, m, ArH); δ_C (75.4 MHz; $CDCl_3$) 28.02, 39.75, 53.42, 67.07, 81.34, 91.15, 100.60, 127.99, 128.30, 128.44, 128.54, 129.75, 136.18, 153.23, 164.65, 166.99, 168.74.

3.2. Preparation of the 2,3,5-substituted pyrrole derivative 3d

To a solution of **2d** (1 mmol) in dichloromethane (0.1 mol dm^{-3}), TFA (10%) was added at room temperature with rapid stirring. The reaction was monitored by TLC and when no starting material was detected, 30 cm^3 of dichloromethane were added and the solution was washed with $NaHCO_3$ 1 mol dm^{-3} and saturated brine (3×10 cm^3 each) and dried over $MgSO_4$. Removal of the solvent at reduced pressure afforded **3d** (79%), mp 129.5–130.5°C (from diethyl ether/*n*-hexane), (found: C, 65.92; H, 5.51; N, 5.15. Calcd for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.13%); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.58 (3H, s, CH_3), 3.86 (3H, s, CH_3 OMe), 5.29 (2H, s, CH_2), 7.28 (1H, d, $J=2.7$ Hz, CH), 7.33–7.44 (5H, m, ArH), 9.21 (1H, s, αNH); δ_C (75.4 MHz; $CDCl_3$) 13.51, 51.69, 65.58, 113.83, 117.40, 120.43, 128.01, 128.51, 129.76, 136.45, 139.72, 161.29, 164.31.



R: Me, **3a**; OMe, **3b**; Ph, **3c**; OBn, **3d**; *i*-Bu, **3e**.

Scheme 2.

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