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Preliminary Communication

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One-pot two-step synthesis of 2,5-dihydro-2-oxofuran-3-carboxamides

Abstract: 2,5-Dihydro-2-oxofuran-3-carboxamides were synthesized by a one-pot two-step reaction catalyzed by sodium methoxide. Readily available tertiary α-hydroxyketones were condensed with substituted cyanoacetamides to give 2-imino-2,5-dihydrofuran-3-carboxamides that, without isolation, were hydrolized to the title products.

Keywords: acidic hydrolysis; α-hydroxyketone; cyanoacetamide; 2,5-dihydro-2-oxofuran-3-carboxamide; 2-imino-2,5-dihydrofuran-3-carboxamide.

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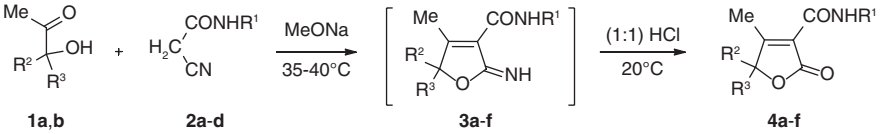
Introduction

2,5-Dihydro-2-oxofuran derivatives are a large family of heterocycles that include synthetically useful compounds, several natural products [1–14], and a number of drugs with diverse biological activities such as antifungal, antibacterial, and anti-inflammatory properties [15–19]. There has been a continuous interest in the development of efficient and convenient methods for the preparation of these heterocycles [10–14, 20–22]. In an extension of our synthetic studies on 2,5-dihydro-2-oxofurans, here we report a convenient and efficient synthesis of the title compounds starting from readily available tertiary α-hydroxyketones **1a,b** (Scheme 1).

The condensation of α-hydroxyketones **1a,b** with cyanoacetamides **2a–d** in the presence of a catalytic amount of sodium methoxide afforded 2-imino-2,5-dihydrofuran-3-carboxamides **3a–f** that, without isolation, were hydrolized to 2,5-dihydro-2-oxofuran-3-carboxamides **4a–f** in good yields. The products **4a–f** are unsubstituted or substituted at the carboxamide nitrogen atom.

Several syntheses of 2,5-dihydro-2-oxofuran-3-carboxamides have been reported in the literature [23–30]. These authors have previously synthesized compounds **4a–f** by related reactions [24–29]. The key step in the current synthesis is the preparation of 2,5-dihydro-2-oxofuran-3-carboxamides **4a–f** by Knoevenagel condensation of compounds **1a,b** with **2a–d**. After hydrolysis of the resultant product **3a–f**, without isolation, the overall yield of this one-pot two-step synthesis is 74–79%. This method is simpler and more convenient than the methods described earlier.



1a: $R^2 = R^3 = Me$
1b: $R^2R^3 = (CH_2)_5$
2a: $R^1 = H$
2b: $R^1 = Me$
2c: $R^1 = Bn$
2d: $R^1 = Ph$

3a, **4a**: $R^1 = H$; $R^2 = R^3 = Me$
3b, **4b**: $R^1 = Me$; $R^2 = R^3 = Me$
3c, **4c**: $R^1 = Bn$; $R^2 = R^3 = Me$
3d, **4d**: $R^1 = Ph$; $R^2 = R^3 = Me$
3e, **4e**: $R^1 = H$; $R^2R^3 = (CH_2)_5$
3f, **4f**: $R^1 = Me$; $R^2R^3 = (CH_2)_5$

Scheme 1

Experimental

General procedure for 4a–f

A mixture of an α-hydroxyketone **1a,b** (10 mmol), a cyanoacetamide **2a–d** (10 mmol), and sodium methoxide (1 mmol) in absolute methanol (15 mL) was heated at 35–40°C for 5 h. After concentration, the residue was acidified with (1:1) aqueous HCl to pH 1–2 and kept at room temperature for 24 h. The solution was extracted with ethyl ether (3 × 20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated. The product **4a–f** was crystallized as indicated below.

4,5,5-Trimethyl-2,5-dihydro-2-oxofuran-3-carboxamide (4a) Yield 77%; mp 125–126°C (from petroleum ether), Refs. [23, 24] mp 125–126°C.

***N*-Methyl-(4,5,5-trimethyl-2,5-dihydro-2-oxofuran)-3-carboxamide (4b)** Yield 79%; mp 65–66°C (from petroleum ether), Refs. [23, 24] mp 65–66°C.

***N*-Benzyl-(4,5,5-trimethyl-2,5-dihydro-2-oxofuran)-3-carboxamide (4c)** Yield 76%; mp 84–85.5°C (from petroleum ether), Ref. [23] mp 86–88°C (from petroleum ether), Ref. [24] mp 84–85°C, Ref. [30] mp 83–84°C.

***N*-Phenyl-(4,5,5-trimethyl-2,5-dihydro-2-oxofuran)-3-carboxamide (4d)** Yield 75%; mp 97–98°C (from petroleum ether), Ref. [23] mp 96.5–98°C.

4-Methyl-5,5-pentamethylene-2,5-dihydro-2-oxofuran-3-carboxamide (4e) Yield 79%; mp 161–163°C (from octane), Ref. [23] mp 161–162.5°C.

***N*-Methyl-(4-methyl-5,5-pentamethylene-2,5-dihydro-2-oxofuran)-3-carboxamide (4f)** Yield 79%; mp 108–109°C (from octane), Ref. [23] mp 108–109°C.

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