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A Convenient One-Step Synthesis of Methyl 2-Benzamidomethyl-3-oxobutanoate

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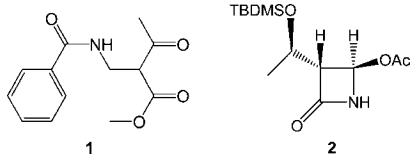
Abstract:

A convenient one-step process for the preparation of methyl 2-benzamidomethyl-3-oxobutanoate (1), a raw material used in the synthesis of (2*R*,3*R*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl)-2,3-dimethyl-4-oxoazetidin-2-yl acetate (2), a key intermediate for carbapenem synthesis is reported. The process is carried out under mild reaction conditions and is amenable to large-scale synthesis.

Introduction

Methyl 2-benzamidomethyl-3-oxobutanoate (**1**) is a raw material used in the synthesis of (2*R*,3*R*)-3-((*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl)-2,3-dimethyl-4-oxoazetidin-2-yl acetate (**2**), which is a key carbapenem intermediate.[1,2] Reported synthetic methods for **1** are complicated and difficult for commercial production.[3−7] In the course of our process optimization for the synthesis of **2**, a simple and practical one-step synthesis of **1** was developed. The improved process is carried out under mild reaction conditions without using hazardous raw materials. Multikilogram scale-up has been successfully completed with a yield of 68%.

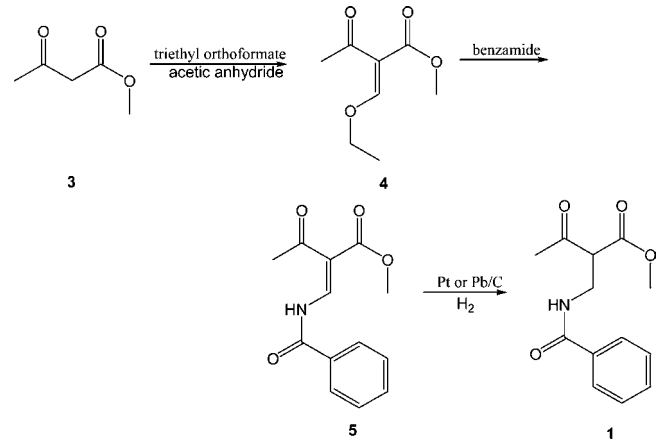


1 2

Results and Discussion

A literature survey revealed two synthetic methods for the preparation of **1**. One method[3−6] involves refluxing a mixture of methyl acetoacetate (**3**), triethyl orthoformate, and acetic anhydride to give methyl 2-(ethoxymethylene)-3-oxobutanoate (**4**), which when heated with benzamide gives methyl 2-(benzamidomethylene)-3-oxobutanoate (**5**); methyl 2-benzamidomethyl-3-oxobutanoate (**1**) is finally obtained by hydrogenation in the presence of Pt or Pd/C catalysts (Scheme 1). This process involves harsh process conditions and three reaction steps. In another method,[7] *N*-(hydroxymethyl)benzamide (**6**) reacts with phosphorus pentachloride to give *N*-(chloromethyl)benzamide (**7**), which reacts with methyl acetoacetate in the presence of sodium hydride or sodium to yield **1** (Scheme 2). Sodium hydride or sodium metal used in this scheme is quite dangerous to work with. Further, this process requires chromatographic purification to give **1**. Thereby, both processes are not suitable for production on a commercial scale.

Scheme 1



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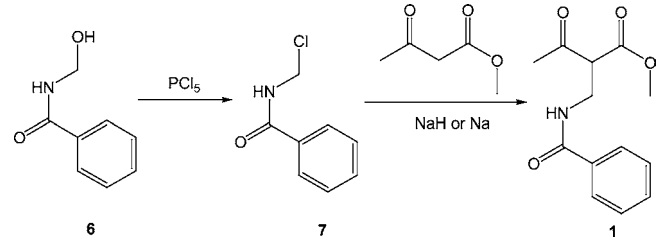
In the course of our efforts to simplify the process from a commercial aspect, we developed an improved process of Scheme 2 to eliminate chlorination step (Scheme 3). In the improved process, methyl 2-benzamidomethyl-3-oxobutanoate (**1**) is prepared in one step by reacting methyl acetoacetate with *N*-(hydroxymethyl)benzamide in the presence of BF_3 etherate. In a typical process, BF_3 etherate is added dropwise to a mixture of methyl acetoacetate (**3**) and *N*-(hydroxymethyl)benzamide (**6**) at 0−5 °C. The reaction mixture is then stirred at room temperature for 2.5 h. After workup, the product is recrystallized in ethyl acetate and *n*-hexane (1:1), giving **1** in a yield of 68%.

Scheme 2



6 7 1

During the optimization studies, we have carried out the reaction using different equivalents of BF_3 etherate. The results are tabulated in Table 1. The preparation of **1** with 2.0 equiv of BF_3 etherate (entry 5) gives maximum yield. Less than 2.0 equiv of BF_3 etherate results in lower yields (entries 1−3 and

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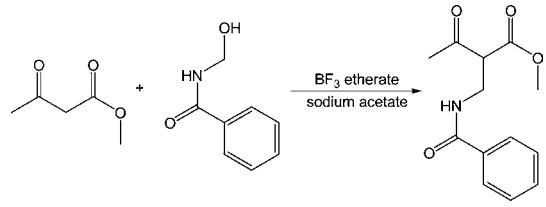
Scheme 3



3 6 1

4). More than 2.0 equiv of BF_3 etherate causes more side reactions and does not increase the yields (entries 6 and 7).

Table 1. **Preparation of methyl 2-benzamidomethyl-3-oxobutanoate (1) using different equivalents of BF_3 etherate**

entry	HMB/MAA[a] (mol/mol)	BF_3 etherate/ MAA (mol/mol)	reaction time (h)	purity (%)	yields (%)
1	1:1	1.2/1	6.0	96.8	36
2	1:1	1.4/1	5.0	97.6	41
3	1:1	1.6/1	5.0	98.1	50
4	1:1	1.8/1	3.0	98.5	63
5	1:1	2.0/1	2.0	98.2	68
6	1:1	2.2/1	2.0	97.3	64
7	1:1	2.4/1	2.0	94.4	57

[a] HMB: *N*-(hydroxymethyl)benzamide; MMA: methyl acetoacetate.

The reaction between **3** and **6** is moderately exothermic; on a commercial scale, the addition of BF_3 etherate should be carried out under brine coolant blanketing. The rate of addition of BF_3 etherate should be such that the temperature of the reaction mixture does not rise above 5 °C. The total addition time is about 1 h; extended addition time is tolerated; faster addition causes more side reactions.

The present method has the following advantages over the reported literature methods. The reaction is carried out in one step without involving hazardous raw materials, chromatographic purification, or harsh reaction conditions; thus, the process is amenable to large-scale synthesis. Solvents used in the process are easily recyclable, and the consumption of solvents is minimized, thereby making the process more cost-effective and environmentally friendly.

In conclusion, a single-step, cost-effective, and scalable process for the preparation of methyl 2-benzamidomethyl-3-oxobutanoate (**1**) with improved yield is reported.

Experimental Section

General. Reagents are used as such without purification. Melting point is measured using a capillary melting point apparatus without correction. HPLC is performed with a Waters instrument using a Hypersil ODS2 (150 mm × 4.6 mm, 5 μ) column with a UV detector (240 nm) and mobile phase of phosphate buffer (pH 6.5)/acetonitrile (5:1) with flow rate 1.0 mL/min. ^{13}C and ^{1}H NMR spectra are recorded using a Bruker AVANCE instrument at 150 MHz and 600 MHz, respectively. The chemical shift data are reported as δ (ppm) downfield from tetramethylsilane which is used as an internal standard. Infrared spectra are recorded using a Thermo Scientific Nicolet iS10 instrument. Mass spectra are recorded using an API 4000 (ABI) instrument.

Preparation of Methyl 2-Benzamidomethyl-3-oxobutanoate (1). To a mixture of methyl acetoacetate (**3**) (1.16 kg, 10 mol) and *N*-(hydroxymethyl)benzamide (**6**) (1.51 kg, 10 mol) cooled to 0 °C is slowly added BF_3 etherate solution (2.5 L, 20 mol) with stirring. The rate of addition of BF_3 etherate solution is maintained in such a way that the reaction temperature does not exceed 5 °C and the addition time is about 1 h. Upon complete addition, the reaction temperature is raised to 25 ± 3 °C and reacted for 2.5 h with stirring. The reaction mixture is added to a solution of sodium acetate in water (3.0 kg sodium bicarbonate in 6 L water), mixed well, and then allowed to separate. The aqueous layer is extracted twice with methylene chloride, each time with 3 L. The organic layers are combined and dried with anhydrous magnesium sulfate. After removal of solvents under vacuum, the residue is recrystallized in ethyl acetate and *n*-hexane (1:1) and dried to yield **1** (1.69 kg, 68%). Mp 79.8−79.9 °C. Chromatographic purity by HPLC > 98%. ^{1}H NMR ($CDCl_3$): δ 7.72 (d, 2H, 2 × Ar−H), 7.49 (m, 1H, Ar−H), 7.41 (dd, 2H, 2 × Ar−H), 6.82 (s, 1H, NH), 3.95 and 3.93 (m, 2H, CH2), 3.92 (m, 1H, −COCH), 3.76 (s, 3H, $-OCH_3$), 2.32 (s, 3H, $-COCH_3$). ^{13}C NMR ($CDCl_3$): δ 202.6, 169.2, 167.7, 134.1, 131.8, 128.7, 127.1, 58.3, 52.8, 37.8, 30.1. IR (ν cm^{-1}, KBr) 3312 (NH) 1746 (CO), 1710 (CO), 1638 (CO), 1534−1449 ($CH{=}CH_{Ar}$), 692 (CH_{Ar}). MS (*m*/*e*): 250.3 $[M + H]^+$.

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