Organic Process Research & Development **2007**, *11*, 739–741

One-Pot Process for the Amination of Oxazolidinyl-methyl Mesylate by Sodium Diformylamide

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Abstract:

An efficient one-pot process for the preparation of pure (*R*)-*N*-[3-(4-iodophenyl)-2-oxo-5-oxazolidinyl]methylacetamide 1 from the mesylate 2b in 91% yield has been developed. The one-pot process makes use of commercially available sodium diformylamide 3 and avoids the use of highly hazardous reagents, simplifies workup procedures, and precludes detrimental impurity issues.

Introduction

N-Aryloxazolidinone derivatives are an important class of biologically active compounds that exhibit antibacterial activity.[1,2] Our interest in this field required the development of a practical and scalable process for the preparation of (*R*)-*N*-[3-(4-iodophenyl)-2-oxo-5-oxazolidinyl]-methylacetamide **1** (Figure 1).

Typical reagents employed for the amination of alkyl sulfonates, such as NaN_3 (followed by reduction of the alkyl azide), sodium or potassium phthalimide (followed by cleavage of the imide with hydrazine), or ammonia were unsuitable for our purposes because of associated low productivity, highly hazardous reagents and problematic impurity generation. To overcome these issues we sought to make use of an efficient modified Gabriel reagent, sodium diformylamide, which has been reported to require less harsh cleavage conditions than those used to cleave the commonly employed phthalimides,[3] is commercially available, and also could be prepared in kilogram quantities in excellent yield[4] (Scheme 1).

We now wish to report our results in developing a productive scalable process for the preparation of **1**.

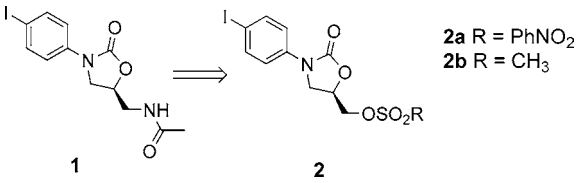
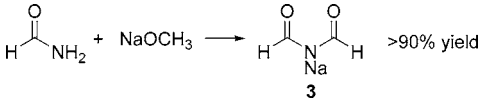


Figure 1. **Structures of required acetamide and its precursor.**

Scheme 1. **Preparation of sodium diformylamide[4]**



Results and Discussion

Our initial experiments focused on the reaction between the nosylate **2a** and sodium diformylamide **3** (Scheme 2). In some solvents such as acetonitrile or tetrahydrofuran, <90% conversion of **2a** to **4** (a mixture of mono- and diformylamides **4a** and **4b**) was observed even after 24 h at reflux temperature with a 3 mol equiv excess of **3**. A more efficient reaction was found in DMF at 80 °C with a 20 mol% excess of **3**, and formylamide **4** was isolated in 90% yield by simply cooling the reaction mixture, adding water, and then filtering. Acid hydrolysis followed by *in situ* liberation of free amine **5** by the addition of base and subsequent reaction with acetic anhydride afforded **1** in 80–85% yield from **2**. The product, however, was found to be contaminated with **4a**. Since complete hydrolysis of **4a** and **4b** was observed,[5] it was assumed the regeneration of **4a** occurred *via* reaction of **5** with the mixed anhydride formed from formic acid, generated in the hydrolysis of **4**, and acetic anhydride. This problem was solved by removing the formic acid by vacuum distillation prior to the addition of acetic anhydride. After this procedure change, the LC area percent purity (LCAP) of product **1** was better than 99% (Scheme 2).

Encouraged by these results, we sought to make use of less expensive, but relatively less reactive, mesylate **2b** in our development of a one-pot process. Besides being a cheaper building block, the mesylate **2b** has greater solubility in aprotic solvents than **2a** thus permitting the reaction to be conducted at higher concentration for improved productivity. Consequently, a satisfactory reaction time,[6] 4 h at 85

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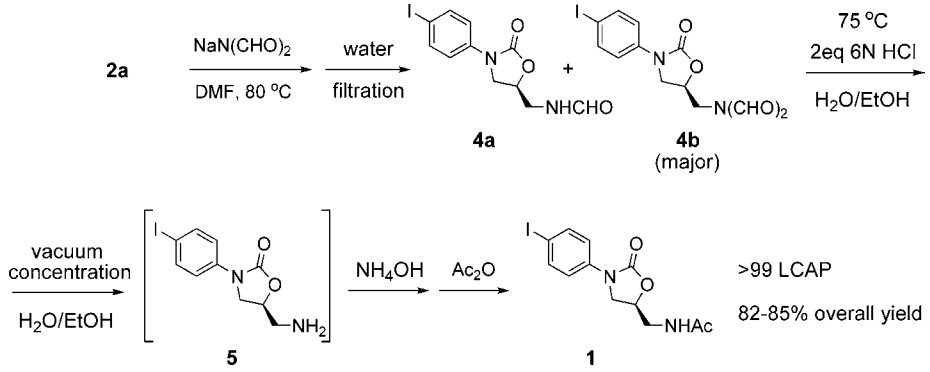
(5) Complete hydrolysis was confirmed by HPLC before the addition of acetic anhydride.

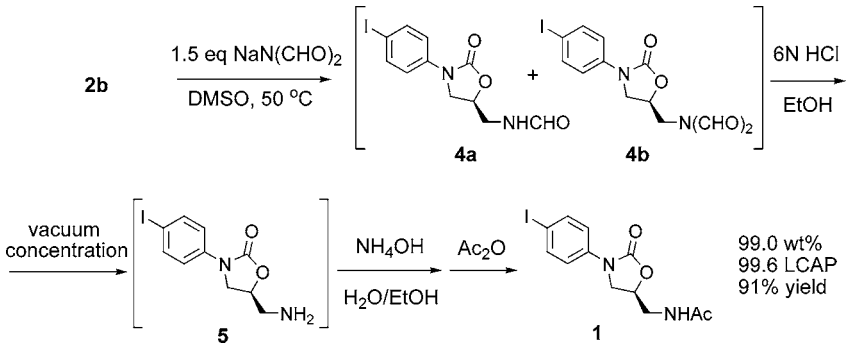
(6) Three volumes of DMF (vs the weight of substrate) were needed to dissolve nosylate **2a**. For mesylate **2b**, two volumes of solvent were enough and were employed to accelerate the first reaction (with three volumes of solvent, starting material **2b** was still detected after 10 h at 80 °C).

10.1021/op700062c CCC: $37.00
Published on Web 05/31/2007

Scheme 2. **Preparation of acetamide 1 with isolation of intermediates 4a and 4b**



Scheme 3. **One-pot process for the preparation of acetamide 1 from mesylate 2b**



°C, could be achieved by employing **2b**. However, *in situ* hydrolysis of **4a** and **4b** was inefficient and incomplete in DMF even with large volumes of acid. By switching to DMSO, this step became highly efficient and a one-pot process was realized (Scheme 3).

When the amination step was performed at 80 °C, it was found that a considerable amount of **7** (8%) was formed, and this compound was subsequently converted to **6** at the hydrolysis stage (Figure 2). Although **6** was readily rejected at the final isolation stage and had no impact on the purity of **1**, the formation of **6** did represent considerable yield loss. The formation of compound **7** could be traced to the reaction of the ambident nucleophile, represented by the resonance forms **3a** (Figure 3), at oxygen rather than nitrogen in the amination step. By lowering the reaction temperature to 50 °C, albeit with an increase in reaction time to 14 h, the reaction at oxygen was apparently suppressed and the formation of **7** could be reduced to <2%. This optimization condition resulted in the increase of overall yield from 84 to 91%.

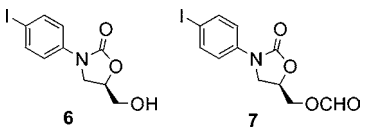


Figure 2. **Structures of impurities in the process.**

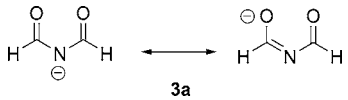


Figure 3. **Diformylamide anion resonance forms.**

Conclusion

An efficient one-pot process for the preparation of (*R*)-*N*-[3-(4-iodophenyl)-2-oxo-5-oxazolidinyl]methylacetamide **1** from mesylate **2b** in excellent overall yield (91%) and purity (99.6 LC area% pure) has been developed. Keys to the efficiency of this preparation were the use of sodium diformylamide **3** as the amination reagent and DMSO as the solvent.

Experimental Section

Compounds **2a** and **2b** were provided by our colleagues at Merck & Co., and their preparation will be reported separately. All other reagents and solvents were commercially available and were used as received. NMR spectra were recorded with a Bruker DPX-400 spectrometer. The HPLC assay was performed on a Zorbax RX-C8 4.6 mm × 250 mm column at 25 °C, and compounds were detected at 210 nm. A gradient elution (35/65 to 90/10 CH_3CN/0.25% $HClO_4$ over 9 min) was employed at a flow rate of 1.0 mL/min.

One-pot Preparation of (*R*)-*N*-[3-(4-Iodophenyl)-2-oxo-5-oxazolidinyl]-methylacetamide (1). The mesylate **2b** (51.63 g, 130 mmol) was dissolved in DMSO (104 mL) at 30 °C, and sodium diformylamide (18.55 g, 195 mmol) was charged. The mixture was aged at 50−60 °C for 14 h. HCl (6 N, 65 mL, 390 mmol) and ethanol (200 proof, 416 mL) were added, and the mixture was vigorously stirred at 75 °C for 4 h. The mixture was then concentrated to 260 mL by a vacuum distillation at 60−75 °C. After the mixture was cooled to 50 °C, water (52 mL) and 27−30% NH_3−H_2O (28 mL, 390 mmol) were added to dissolve all solids. To the resulting clear solution was added acetic anhydride (37 mL, 390 mmol), and the reaction was aged at 70−75 °C for 10 min. Water (312 mL) was added slowly to the solution

over 30 min at 70−75 °C, and the resulting slurry was cooled to ambient temperature over 2−3 h and was aged overnight. Product acetamide **1** was isolated by filtration; the cake was washed with water (2 × 130 mL) and was dried in a vacuum oven at 50 °C to afford acetamide **1** as a white crystalline solid (43.31 g, 99.0 wt %, 99.6 LCAP, (0.4 LCAP DMSO)) in 91% yield. The loss to mother liquor and cake wash liquor was 2.6%. ^{1}H NMR (400 MHz, d_6-DMSO): δ 1.83 (3H, s), 3.32−3.43 (2H, m), 3.70−3.74 (1H, dd, J = 8.9, 8.9 Hz), 4.06−4.11 (1H, dd, J = 8.9, 8.9 Hz), 4.70−4.74 (1H, m), 7.36−7.38 (2H, d, J = 8.5 Hz), 7.70−7.73 (2H, d, J = 8.5 Hz), 8.21−8.24 (1H, t, J = 4.7 Hz). ^{13}C NMR: (100 MHz, d_6-DMSO): δ 22.5, 41.4, 47.0, 71.6, 87.2, 120.0, 137.4, 138.3, 154.0, 170.0.

Received for review March 12, 2007.

OP700062C