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Different Roles of Trifluoromethanesulfonyl Chloride in the Construction of Heterocycles Fused with β-Lactams

Jih Ru Hwu,^{*,†,‡} Shahram Hakimelahi,^{†,1} Kuang-Lieh Lu,[†] and Shwu-Chen Tsay[†]

[†]Organosilicon and Synthesis Laboratory, Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan 11529, Republic of China; and

> [‡]Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30043, Republic of China

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Abstract: The cis-configurated tricyclic O^3 -isooxacepham 5 and bicyclic isopenam 11 were synthesized. The key step for the preparation of 5 involves chlorination of the corresponding carbanion of 3 with CF₃SO₂Cl followed by an internal alkylation. The biologically active isopenam 11 was synthesized from thio-S-ester 6 via intermediate 9. The key step involves chlorination of the thiol moiety in monocyclic β -lactam 7 by CF₃SO₂Cl followed by an internal cyclization. © 1999 Elsevier Science Ltd. All rights reserved.

Introduction

Trifluoromethanesulfonyl chloride (CF₃SO₂Cl) functions as an effective sulfonating agent for alcohols;² it can also act as a chlorinating agent for carbanions. The relative speed is ~10⁵ faster for chlorination of carbanions than sulfonation of alcohols.^{3,4} These properties have been utilized in the synthesis of 2,2-disubstituted tetrahydropyrans by treatment of the corresponding 5,5-disubstituted pentan-1-ol with CF₃SO₂Cl in Et₃N and CH₂Cl₂.⁴ Herein we describe alternative applications of this strategy for constructing heterocycles fused with β -lactams, including O³-isooxacepham 5 (Scheme 1) and biologically active isopenam 11 (Scheme 2).

Results and Discussion

For the preparation of O^3 -isooxacepham 5, we treated dibenzyl aminomalonate (1) with salicylaldehyde (2) at room temperature to afford the corresponding Schiff base (Scheme 1). Upon reaction with phthalimidoacetyl chloride in situ, this base was led to monocyclic β lactam 3 in 70% overall yield. The free phenoxyl group in the Schiff base did not interfere with formation of the β -lactam ring. The coupling constant 5.0 Hz of the hydrogen atoms on the β -lactam ring indicates the *cis*-relationship of the two substituents at the α - and the β positions.^{5,6} Treatment of hydroxyphenylazetidinone 3 with CF₃SO₂Cl and Et₃N in CH₂Cl₂ at 25 °C gave the desired product 5 in 90% yield.⁷ The ¹H NMR spectrum of 5 shows the loss of two hydrogen atoms in the transformation. An absorption at 1798 cm⁻¹ in the IR spectrum of 5 indicates the presence of a highly strained β -lactam ring. All attempts to remove the benzyl groups from 5 failed and resulted in the destruction of the β -lactam ring. The instability of 5 could result from the susceptibility of the β -lactam moiety therein to the moisture. We found that, upon exposure to water, hemiaminal 5 was hydrolyzed to give keto diester O=C(CO₂CH₂Ph)₂, which was characterized as its dinitrophenylhydrazone derivative.⁸

Scheme 1



A plausible mechanism is shown in Scheme 1 for the cyclization of monocyclic β -lactam 3 to form the [1,3]oxazinane ring in 5. Chlorination of 3 by CF₃SO₂Cl under basic conditions

affords the intermediate 4.7.9 Consequently, an intramolecular cyclization occurred in 4 to produce the target O^3 -isooxacepham 5. The same mechanism was also applied to the cyclization of the aliphatic alcohol derivative of compound 7 to give the corresponding isooxapenam by use of CF₃SO₂Cl.¹⁰

We started our synthesis of biologically active isopenam 11^{11} by deacetylation of thio-Sester 6^{12} with piperidine at room temperature to give the free thiol 7 in 95% yield (Scheme 2). Reaction of mercapto β -lactam 7 with CF₃SO₂Cl in Et₃N and CH₂Cl₂ at room temperature afforded the desired isopenam 10 in 88% yield. Removal of the benzyl groups in 10 by use of 60 psi of H₂ and Pd/C in MeOH at 45 °C followed by decarboxylation in situ gave isopenam 11 in 55% overall yield.



The transformation of monocyclic β -lactam 7 to bicyclic β -lactam 10 may involve chlorination of the thiol functionality in 7 (Scheme 2). Then an intramolecular cyclization could occur in the resultant sulfenyl chloride 9 to produce isopenam 10. In order to obtain evidence to support this proposed mechanism, we carried out the following control experiments.

Upon treatment with CF₃SO₂Cl in Et₃N and CH₂Cl₂ at room temperature, benzyl malonate gave benzyl dichloromalonate in 90% yield after 1.0 h;⁷ yet *n*-butylthiol reacted instantly with a stoichiometric amount of CF₃SO₂Cl to produce *n*-butylsulfenyl chloride quantitatively.⁹ When a mixture of benzyl malonate and *n*-butylthiol in an equimolar ratio was allowed to react with one equivalent of CF₃SO₂Cl in Et₃N and CH₂Cl₂ for 5.0 min, *n*-butylsulfenyl chloride was generated as the exclusive product. In this reaction, dibenzyl malonate remained intact. Thus, we conclude that the conversion of mercapto β -lactam 7 to isopenam 10 went through sulfenyl chloride 9 rather than the alkyl chloride 8.

Conclusions

Two types of the reaction mechanisms could be responsible for the construction of the heterocyclic B-rings fused with a β -lactam nucleus by use of CF₃SO₂Cl. Formation of the [1,3]oxazinane ring in O³-isooxacepham 5 from the corresponding (hydroxyphenyl)-azetidinone 3 and CF₃SO₂Cl involves chloromalonate 4, as shown in Scheme 1.

On the other hand, synthesis of biologically active 11 from mercapto β -lactam 7 could involve sulfenyl chloride 9 as shown in Scheme 2. Therefore, the reaction likely went through a chlorination of the thiol moiety by CF₃SO₂Cl followed by an intramolecular cyclization.

Experimental Section

General Procedure. Chemicals were purchased from Fluka Chemical Co. Reagentgrade solvents were distilled and then stored over molecular sieves 4A. Products were isolated by use of column chromatography (Merck silica gel 60, particle size 230-400 mesh ASTM), packed in glass column (20 g of silica gel/gram of crude material). Analytical thinlayer chromatography (TLC) analyses were performed on precoated plates (silica gel 60 F_{254}), purchased from Merck. Melting points were measured by means of Büchi 510. Proton NMR spectra were obtained on a Varian-XL-200 spectrometer. Infrared spectra were measured on a Beckman IR-8 spectrophotometer. Microanalysis data were obtained by use of a Perkin-Elmer 240B microanalyzer.

(±)-Dibenzyl 2-[cis-4-(2-Hydroxyphenyl)-2-oxo-3-phthalimido-1-azetidinyl]malonate (3). To a solution of dibenzyl aminomalonate (1, 2.99 g, 9.99 mmol) in CH_2Cl_2 (45 mL) was added salicylaldehyde (2, 1.22 g, 9.99 mmol) and anhydrous MgSO₄ (s, 20 g). After the mixture was stirred at room temperature for 24 h, it was filtered. Then Et_3N (2.22 g, 21.9 mmol) and phthalimidoacetyl chloride (2.90 g, 13.0 mmol) in CH_2Cl_2 (15 mL) were added into the solution

in sequence at room temperature. After 5.0 h, the solution was washed with water $(2 \times 50 \text{ mL})$, dried over MgSO₄ (s), and concentrated under reduced pressure. The crude product was purified by use of column chromatography (silica gel, CHCl₃ as eluant) to give 3 (4.13 g, 6.99 mmol) in 70% yield: mp 158–160 °C; ¹H NMR (CDCl₃) δ 3.99 (d, J = 5.0 Hz, 1 H), 4.41 (s, 4 H), 4.71 (s, 1 H), 4.77 (d, J = 5.0 Hz, 1 H), 6.71–7.72 (m, 19 H); IR (CH₂Cl₂) 3300, 1775, 1750, 1730, 1720 cm⁻¹. Anal. Calcd for C₃₄H₂₆N₂O₈: C, 69.15; H, 4.44; N, 4.74%. Found: C, 69.20; H, 4.50; N, 4.81.

Dibenzyl (6RS,7SR)-8-Oxo-7-(phthalimido)-3-oxa-4,5-benzo-1-azabicyclo[4.2.0]octane-2,2dicarboxylate (5). To a solution of 3 (2.95 g, 5.00 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (0.610 g, 6.03 mmol). Trifluoromethanesulfonyl chloride (0.86 g, 5.1 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise to the reaction mixture at 0 °C over a period of 5.0 min. After the mixture was warmed up to room temperature, it was concentrated under reduced pressure to dryness and then Et_2O was added. The ethereal solution was washed with H_2O , dried over MgSO₄ (s), and treated with charcoal. After filtration, evaporation, and purification by use of column chromatography (silica gel, CHCl₃ as eluant), compound 5 (2.65 g, 4.50 mmol) was isolated in 90% yield as a foam: ¹H NMR (CDCl₃) δ 4.12 (d, J = 5.0 Hz, 1 H), 4.44 (d, J = 5.0 Hz, 1 H), 4.65 (br s, 4 H), 6.91–7.86 (m, 18 H); IR (CH₂Cl₂) 1798, 1740, 1730, 1710 cm⁻¹. Anal. Calcd for $C_{34}H_{24}N_2O_8$: C, 69.38; H, 4.11; N, 4.76%. Found: C, 69.59; H, 4.28; N, 4.89.

(±)-Dibenzyl 2-(*cis*-4-Mercaptomethyl-2-oxo-3-phenylacetamido-1-azetidinyl)malonate (7). A solution containing 6 (2.87 g, 4.99 mmol) and piperidine (4.25 g, 49.9 mmol) in DMF (25 mL) was stirred at room temperature under N₂ for 10 h. The reaction mixture was quenched by addition of EtOAc (80 mL) and washed with water (4 × 80 mL), dried over MgSO₄ (s), and concentrated under reduced pressure. The residue was purified by use of column chromatography (CHCl₃ as eluant) to give 7 (2.53 g, 4.74 mmol) as a foam in 95% yield: ¹H NMR (CDCl₃/D₂O) δ 2.22–2.51 (br, 2 H), 3.59 (s, 2 H), 4.09–4.27 (m, 1 H), 5.24 (s, 4 H), 5.34 (s, 1 H), 5.37 (d, J = 5.0 Hz, 1 H), 7.20–7.41 (m, 15 H); IR (CH₂Cl₂) 3480–3260, 1769, 1739, 1683 cm⁻¹. Anal. Calcd for C₂₉H₂₈N₂O₆S: C, 65.40; H, 5.30; N, 5.26; S, 6.02%. Found: C, 65.43; H, 5.28; N, 5.27; S, 6.12.

Dibenzyl (5RS,6RS)-7-Oxo-6-(phenylacetamido)-3-thia-1-azabicyclo[3.2.0]heptane-2,2dicarboxylate (10). To a solution containing 7 (2.66 g, 4.99 mmol) and Et₃N (1.21 g, 12.0 mmol) in CH₂Cl₂ (50 mL) was added CF₃SO₂Cl (0.86 g, 5.1 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C over a period of 5.0 min. The stirred mixture was allowed to warm up to room temperature for 1.0 h. The solution was concentrated under reduced pressure to dryness and then Et₂O (50 mL) was added. The ethereal solution was washed with water (2 × 50 mL), dried over MgSO₄ (s), and treated with charcoal. After filtration, concentration under reduced pressure, and then purification by use of column chromatography (CHCl₃ as eluant), compound 10 (2.33 g, 4.40 mmol) was isolated in 88% yield: ¹H NMR (CDCl₃) δ 2.71-3.10 (m, 2 H), 3.52 (s, 2 H), 4.31-4.57 (m, 1 H), 5.08 (s, 2 H), 5.12 (s, 2 H), 5.23 (dd, J = 8.0, 4.5 Hz, 1 H), 6.81-7.01 (br, 1 H), 7.30-7.51 (m, 15 H); IR (CH₂Cl₂) 3410, 1785, 1745, 1670 cm⁻¹. Anal. Calcd for C₂₉H₂₆N₂O₆S: C, 65.65; H, 4.94; N, 5.28; S, 6.04%. Found: C, 65.59; H, 4.88; N, 5.30; S, 6.14. Acid (11). A solution of 10 (2.65 g, 4.99 mmol) in MeOH (100 mL) containing 1% aqueous NaHCO₃ (15 mL) was hydrogenated over Pd/C (10%, 1.50 g, 1.41 mmol) and 60 psi of H₂ at 45 °C for 5.0 h. The mixture was filtered and then AcOH (20 mL) was added to the residue. After the solvent was removed under reduced pressure, the residue was then purified by use of column chromatography (EtOAc as eluant) to give 11 (0.84 g, 2.7 mmol) in 55% yield: mp 141–143 °C; ¹H NMR (DMSO-d₆) δ 2.72–3.12 (m, 2 H), 3.50 (s, 2 H), 4.21–4.28 (m, 1 H), 4.88 (s, 1 H), 5.17 (dd, J = 9.0, 4.5 Hz, 1 H), 6.91 (br s, 1 H), 7.38 (s, 5 H), 7.80-8.50 (br, 1 H); IR (nujol) 3500-3300, 1779, 1705, 1669 cm⁻¹. Anal. Calcd for C₁₄H₁₄N₂O₄S: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.81; H, 4.50; N, 9.20; S, 10.50.

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References and Notes

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(2RS,5SR,6SR)-7-Oxo-6-(phenylacetamido)-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic