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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 CF_3SO_2Cl 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 CF_3SO_2Cl followed by an internal cyclization.

Introduction

Trifluoromethanesulfonyl chloride (CF_3SO_2Cl) functions as an effective sulfonating agent for alcohols;[2] it can also act as a chlorinating agent for carbanions. The relative speed is ~10^5 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 CF_3SO_2Cl in Et_3N and CH_2Cl_2.[4] Herein we describe alternative applications of this strategy for constructing heterocycles fused with β-lactams, including O^3-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]

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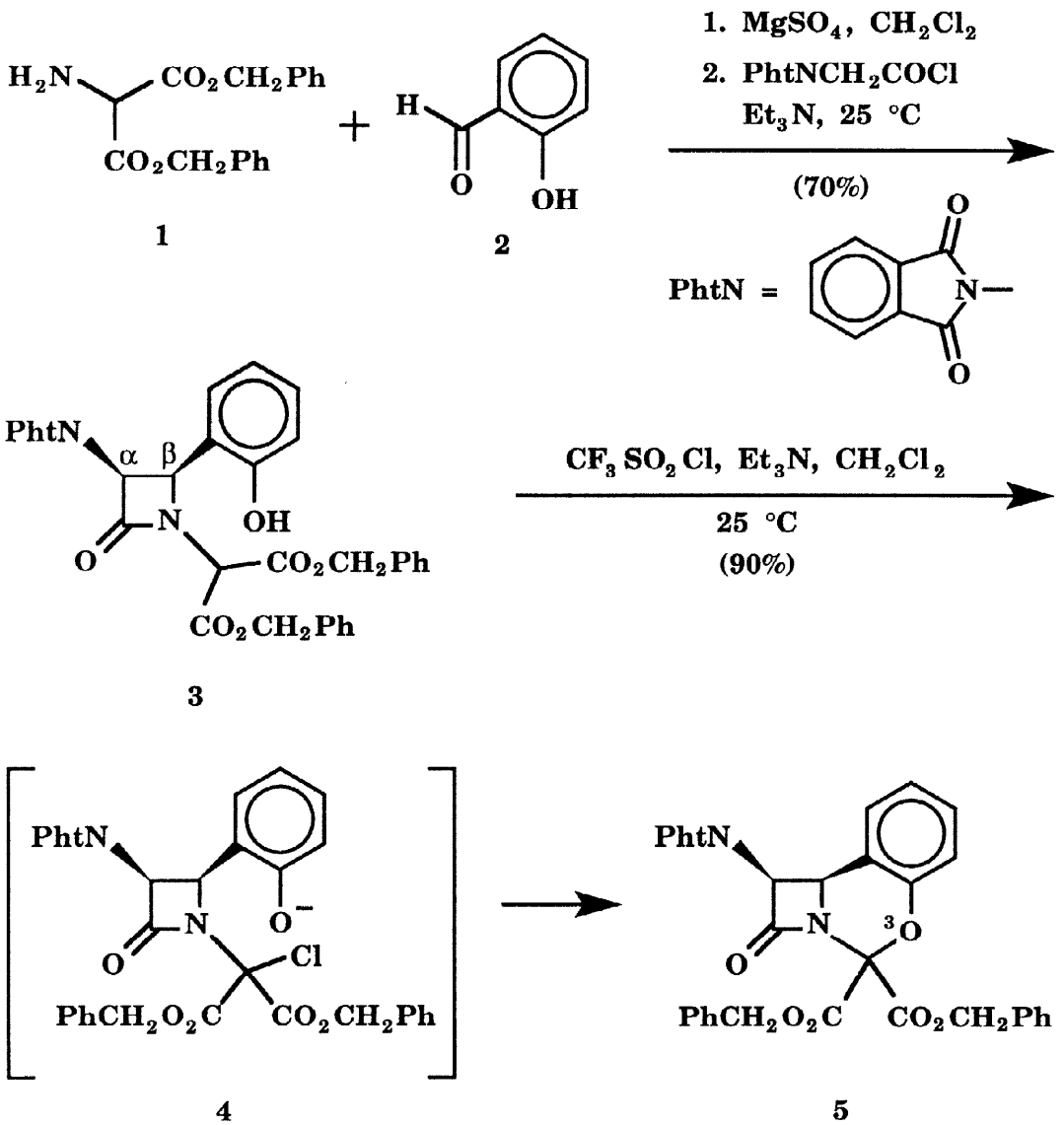
Treatment of hydroxyphenylazetidinone **3** with CF_3SO_2Cl and Et_3N in CH_2Cl_2 at 25 °C gave the desired product **5** in 90% yield.[7] The ^1H NMR spectrum of **5** shows the loss of two hydrogen atoms in the transformation. An absorption at 1798 cm^{-1} in the IR spectrum of **5** indicates the 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 $O{=}C(CO_2CH_2Ph)_2$, which was characterized as its dinitrophenylhydrazone derivative.[8]

Scheme 1

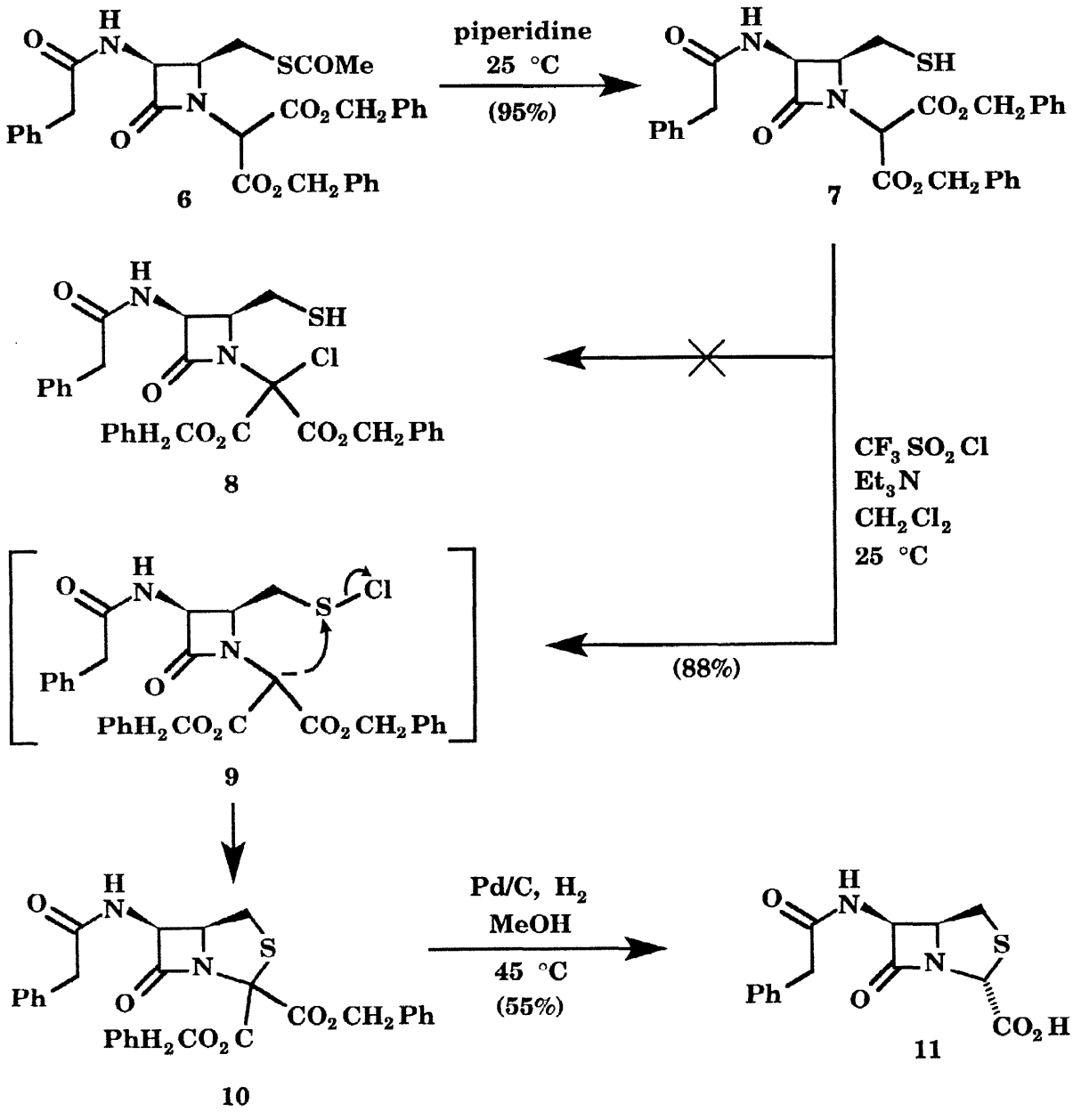


A plausible mechanism is shown in Scheme 1 for the cyclization of monocyclic β-lactam **3** to form the [1,3]oxazinane ring in **5**. Chlorination of **3** by CF_3SO_2Cl under basic conditions

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 CF_3SO_2Cl.[10]

We started our synthesis of biologically active isopenam **11**[11] by deacetylation of thio-*S*-ester **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 CF_3SO_2Cl in Et_3N and CH_2Cl_2 at room temperature afforded the desired isopenam **10** in 88% yield. Removal of the benzyl groups in **10** by use of 60 psi of H_2 and Pd/C in MeOH at 45 °C followed by decarboxylation in situ gave isopenam **11** in 55% overall yield.

Scheme 2



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 CF_3SO_2Cl in Et_3N and CH_2Cl_2 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 CF_3SO_2Cl 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 CF_3SO_2Cl in Et_3N and CH_2Cl_2 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 CF_3SO_2Cl. Formation of the [1,3]oxazinane ring in O^3-isooxacepham **5** from the corresponding (hydroxyphenyl)-azetidinone **3** and CF_3SO_2Cl 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 CF_3SO_2Cl followed by an intramolecular cyclization.

Experimental Section

General Procedure. Chemicals were purchased from Fluka Chemical Co. Reagent-grade 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 thin-layer 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 $MgSO_4$ (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 × 50 mL), dried over $MgSO_4$ (s), and concentrated under reduced pressure. The crude product was purified by use of column chromatography (silica gel, $CHCl_3$ as eluant) to give **3** (4.13 g, 6.99 mmol) in 70% yield: mp 158–160 °C; ^1H NMR ($CDCl_3$) 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 (CH_2Cl_2) 3300, 1775, 1750, 1730, 1720 cm^{-1}. Anal. Calcd for $C_{34}H_{26}N_2O_8$: C, 69.15; H, 4.44; N, 4.74%. Found: C, 69.20; H, 4.50; N, 4.81.

Dibenzyl (6*RS*,7*SR*)-8-Oxo-7-(phthalimido)-3-oxa-4,5-benzo-1-azabicyclo[4.2.0]octane-2,2-dicarboxylate (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 $MgSO_4$ (s), and treated with charcoal. After filtration, evaporation, and purification by use of column chromatography (silica gel, $CHCl_3$ as eluant), compound **5** (2.65 g, 4.50 mmol) was isolated in 90% yield as a foam: ^1H NMR ($CDCl_3$) 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 (CH_2Cl_2) 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 N_2 for 10 h. The reaction mixture was quenched by addition of EtOAc (80 mL) and washed with water (4 × 80 mL), dried over $MgSO_4$ (s), and concentrated under reduced pressure. The residue was purified by use of column chromatography ($CHCl_3$ as eluant) to give **7** (2.53 g, 4.74 mmol) as a foam in 95% yield: ^1H NMR ($CDCl_3/D_2O$) 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 (CH_2Cl_2) 3480–3260, 1769, 1739, 1683 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$: 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 (5*RS*,6*RS*)-7-Oxo-6-(phenylacetamido)-3-thia-1-azabicyclo[3.2.0]heptane-2,2-dicarboxylate (10). To a solution containing **7** (2.66 g, 4.99 mmol) and Et_3N (1.21 g, 12.0 mmol) in CH_2Cl_2 (50 mL) was added CF_3SO_2Cl (0.86 g, 5.1 mmol) in CH_2Cl_2 (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 Et_2O (50 mL) was added. The ethereal solution was washed with water (2 × 50 mL), dried over $MgSO_4$ (s), and treated with charcoal. After filtration, concentration under reduced pressure, and then purification by use of column chromatography ($CHCl_3$ as eluant), compound **10** (2.33 g, 4.40 mmol) was isolated in 88% yield: ^1H NMR ($CDCl_3$) 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 (CH_2Cl_2) 3410, 1785, 1745, 1670 cm^{-1}. Anal. Calcd for $C_{29}H_{26}N_2O_6S$: 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.

(2*RS*,5*SR*,6*SR*)-7-Oxo-6-(phenylacetamido)-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid (11). A solution of **10** (2.65 g, 4.99 mmol) in MeOH (100 mL) containing 1% aqueous $NaHCO_3$ (15 mL) was hydrogenated over Pd/C (10%, 1.50 g, 1.41 mmol) and 60 psi of H_2 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-d_6) 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 $C_{14}H_{14}N_2O_4S$: 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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