A Novel Dieckmann-Type Cyclization, the Final Step of the Synthesis of a Carbacephem Derivative

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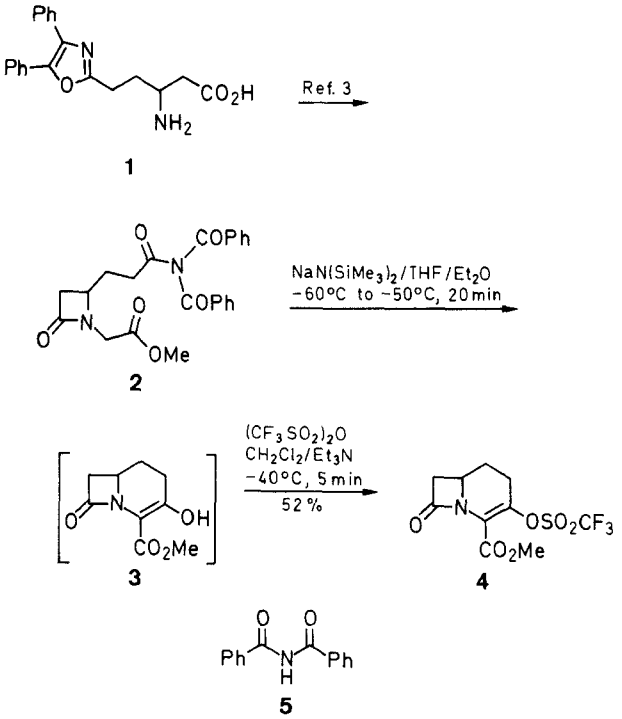
Dedicated to Prof. C. H. Krauch on the occasion of his 60th birthday

The treatment of the triacylamine, methyl 4-(dibenzoylaminocarbonylethyl)-2-oxoazetidine-1-acetate (**2**), with sodium bis(trimethylsilyl)amide leads to an unprecedented Dieckmann-type ring closure to form the anion of the carbacephem derivative, methyl 3-hydroxy-1-carbacephem-4-carboxylate, (**3**).

The four component condensation (4CC)[1] is one of the convenient methods for the synthesis of β-lactam antibiotics and related compounds.[2] The racemic β-amino acid **1** readily yields the *N,N*-dibenzoyl carbonamide **2**[3] by a 4CC with allyl isocyanide, followed by a conversion of the *N*-allyl carbonamide group into a methoxycarbonyl group and photooxidation of the 4,5-diphenyl-2-oxazolyl moiety by Wasserman's method.[4]

The *N,N*-dibenzoyl carbonamide **2** is smoothly cyclized to form the enolate of **3** by treatment with sodium bis(trimethylsilyl)amide at −60 °C in tetrahydrofuran. Protonation of the enolate yields **3**, a relatively stable compound that can be isolated and subjected to chromatography. Its ^{1}H-NMR spectrum (broad resonance at $\delta = 11.5$) indicates that it largely exists in the enolic form. While one expects a 1:1 formation of the *N,N*-dibenzoylimide **5** and the desired enol **3**, this is only observed conducting the reaction as described above. In contrast, when potassium *tert*-butoxide at 0 °C in toluene is used, **5** can be isolated in nearly quantitative yield accompanied by only a minor amount of **3**.



To our best knowledge, the aforementioned cyclization is the first example for the use of triacylamines in such Dieckmann-type condensations.[5]

The (±)-carbacephem derivative **4**, an analogue of well-known intermediates[6-8] in the synthesis of other carbacephem derivatives, is obtained by treating crude **3** with triflic anhydride in the presence of triethylamine. The title compound **4** decomposes slowly within three months at ambient temperature. At −15 °C under nitrogen, however, **4** can be stored for at least six months.

The reactions were performed under a blanket of nitrogen. The solvents were purified and dried according to standard procedures and stored over 4 Å molecular sieves. All reagents were of commercial quality and used without further purification. The NMR spectra were measured on a Bruker AM 360 spectrometer (360.13 MHz for ^{1}H-NMR, 90.56 MHz for ^{13}C-NMR, 337.3 MHz for ^{19}F-NMR) with TMS as internal standard and TFA (in the case of ^{19}F-NMR) as external standard. The IR spectra were recorded on a Perkin-Elmer Model 177 infrared spectrophotometer. The mass spectra were measured on the Atlas CH5 spectrometer (70 eV, EI-mode).

(±)-Methyl 3-[(Trifluoromethyl)sulfonyloxy]-1-carbacephem-4-carboxylate (4):

A solution of methyl 4-(dibenzoylaminocarbonylethyl)-2-oxo-azetidine-7-acetate[3] (**2**, 1.35 g, 3.2 mmol) in THF (20 mL) is added to sodium (bistrimethylsilyl)amide (7.3 mL of a 1 M THF solution, 7.3 mmol) in Et_2O (10 mL) at −60 °C within 10 minutes. After 10 minutes at −50 °C, the mixture is quenched with dil H_2SO_4 (2.05 mL of 1.8 N H_2SO_4, 3.69 mmol) and poured into a mixture of water (15 mL) and EtOAc (10 mL). The organic layer is decanted, (it contains a small amount of **3**, which can be extracted as described later), the water layer is saturated with NaCl and thoroughly extracted with EtOAc (5 × 20 mL). Compound **3** is re-extracted from the ethyl acetate layer with sat. $NaHCO_3$ solution (2 × 20 mL). The combined $NaHCO_3$ extracts are rapidly acidified to pH 6 with phosphoric acid (4.15 mL, 85 %), saturated with NaCl and subsequently extracted with EtOAc (6 × 30 mL). The organic layer is dried ($MgSO_4$), and the solvent is removed *in vacuo* at 25 °C.

The resulting oily product **3**, R_f = 0.29 (EtOAc/hexane/MeOH, 3:7:1), is dissolved in CH_2Cl_2 (20 mL) together with Et_3N (0.48 mL, 3.5 mmol) and cooled to −40 °C. Triflic anhydride (0.49 mL, 3.0 mmol) is added in one portion. After 5 min. the mixture is poured into a sat. $NaHCO_3$ solution (20 mL) and the layers are separated. The aqueous phase is extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers are washed with water, dried ($MgSO_4$) and filtered through a thin layer of silica gel (0.063–0.2 mm). The solvent is evaporated *in vacuo*. The resulting light yellow oil crystallizes on scratching; yield: 0.55 g (50 % from **2**); mp 83–84 °C (Et_2O).

$C_{10}H_{10}F_3NO_6S$	calc.	C 36.47	H 3.03	N 4.25
(329)	found	36.70	3.12	4.03

^{1}H-NMR ($CDCl_3$): δ = 1.68–1.80 (m, 1 H, CH_2), 2.36–2.43 (m, 1 H, CH_2), 2.60–2.65 (m, 2 H, CH_2C=), 2.73 (dd, 1 H, ^2J = 15.8 Hz, ^3J = 2.3 Hz, CH_2CON), 3.38 (dd, 1 H, ^2J = 15.8 Hz, ^3J = 5.3 Hz, CH_2CON), 3.68–3.74 (m, 1 H, CH), 3.90 (s, 3 H, OCH_3).

^{13}C-NMR ($CDCl_3$): δ = 26.4 (CH_2), 43.5 (CH_2), 46.2 (CH_2), 53.0 (CH + OCH_3), 118.3 (q, J_{C-F} + 320.3 Hz, CF_3), 123.0 (C=C), 142.3 (C=C), 159.7 (CON), 165.4 (CO_2).

^{19}F-NMR ($CDCl_3$): δ = 7.17 (s, CF_3).

MS: *m/z* (%) = 329 (6), 298 (4), 196 (100), 165 (11), 126 (16), 67 (13).

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