nylpyruvic ester to give pyrimidopyridazine **3c** and with phenylpyruvic acid to give pyrrolopyrimidine **7a**.

Conclusions

We conclude that the simple α-keto acids (pyruvic and phenylglyoxylic) are as useful as their esters for the preparation of pyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones from 6-(1-*alkyl*hydrazino)isocytosines (**1**). Phenyl- and (*p*-hydroxyphenyl)pyruvic acids cyclize with **1** in refluxing water to give 5-aryl-7-alkylpyrrolo[2,3-*d*]pyrimidines in modest, but synthetically useful, yields. However, alkylation of the hydrazino substituent of **1** appears to be necessary for either type of cyclization.

Experimental Section

Melting points were run on a Thomas-Hoover capillary melting point apparatus. NMR spectra were determined with Varian XL-100 of CFT-20 spectrometers with tetramethylsilane as the internal standard; Fourier transform was utilized in cases of poor solubility. The nuclear Overhauser effect (NOE) is expressed as $f_I(S)$ which is the fractional enhancement of nucleus I due to saturation of nucleus S. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF mass spectrometer; an accurate mass was determined by peak matching at 10000 resolution, 10% valley definition. Microanalyses were performed by Atlantic Microlab, Inc. All C, H, and N analyses not reported here were acceptable (±0.3%) and can be found along with other physical data in the supplementary material. Pyruvic acid was obtained from Matheson Coleman & Bell Manufacturing Chemists. (*p*-Hydroxyphenyl)pyruvic and phenylglyoxylic acids were obtained from Aldrich Chemical Co. Phenylpyruvic acid was obtained from Pfaltz and Bauer.

2-Amino-5-(4-hydroxyphenyl)-7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7b). To a solution of 0.82 g (5.0 mmol) of **1a** (as the hemihydrate)[1] in 75 mL of water stirred at reflux was added 1.08 g (6.0 mmol, 98% purity) of (*p*-hydroxyphenyl)pyruvic acid. Under nitrogen, reflux was continued for 2 h, and the resulting mixture was allowed to cool to ambient temperature. The yellow solid was collected by filtration, washed with water, and dried under vacuum at 70 °C; yield 0.35 g. Recrystallization from methanol under a nitrogen atmosphere afforded 0.32 g (22%) of **7b** as yellow crystals: mp >300 °C;[6] ^{1}H NMR (Me_2SO-d_6) δ 3.51 (s, 3 H), 6.19 (br s, 2 H), 6.68 (d, J = 8.7 Hz, 2 H), 6.88 (s, 1 H), 7.71 (d, J = 8.7 Hz, 2 H), 9.15 (s, 1 H), 10.23 (br s, 1 H), and methanol, 3.17 (d, J = 5.3 Hz, 3 H), 4.07 (q, 1 H); NOE $f_{6.88}$(3.51) = 28%; ^{13}C NMR (Me_2SO-d_6) δ 158.9 (C-4), 155.4 (C-7a), 152.2 (C-2), 151.4 (C-4′), 128.5 (d, C-2′ and C-6′), 125.5 (C-1′), 119.1 (C-5), 117.8 (d, $^1J_{CH}$ = 185.6 Hz, C-6), 114.6 (d, $^1J_{CH}$ = 158 Hz, C-3′ and C-5′), 97.0 (d, $^3J_{CH}$ = 5.1 Hz, C-4a), 30.4 (q, $^1J_{CH}$ = 139 Hz, NCH_3);[7] UV (CH_3OH) λ_{max} 250 nm (ϵ 24400), 281 (11900), 299 (13200); mass spectrum (260 °C), *m/e* (relative intensity) 256 (M, 100), accurate mass *m/e* 256.0969 ($C_{13}H_{12}N_4O_2$). Anal. Calcd for $C_{13}H_{12}N_4O_2$·CH_3OH: C, 58.32; H, 5.60; N, 19.43. Found: C, 58.26; H, 5.61; N, 19.44.

Similarly prepared were **3a,b** and **7a,c**. The starting isocytosine, starting α-keto acid, and reaction time are given in brackets, followed by the yield and melting point.

7-Amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,5-(1*H*,6*H*)-dione (3a)[1] [**1a**, pyruvic acid, 1 h]: 48%; mp >300 °C. Anal. $C_8H_9N_5O_2$. Physical parameters were found to be identical with those of the authentic sample.

7-Amino-1-methyl-3-phenylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (3b)[1] [**1a**, phenylglyoxylic acid (50% molar excess), 1 h]: 56%; mp >300 °C. Anal. ($C_{13}H_{11}N_5O_2$·$0.5H_2O$). Identified as **3b** by NMR, UV, and TLC comparisons with the original sample.

2-Amino-7-methyl-5-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7a)[8] [**1a**, phenylpyruvic acid, 1 h]: 22% (after recrystallization from methanol); mp > 300 °C. Anal. $C_{13}H_{12}N_4O$·$0.25H_2O$.

2-Amino-7-(2-hydroxyethyl)-5-(4-hydroxyphenyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (7c) [**1b**,[1] (*p*-hydroxyphenyl)pyruvic acid, 1.5 h]: 27%; mp >280 °C dec. Anal. $C_{14}H_{14}N_4O_3$·$0.5H_2O$.

2-[(2-Amino-1,6-dihydro-6-oxo-4-pyrimidinyl)-hydrazono]-3-(4-hydroxyphenyl)propionic acid (8) [**1c**,[1] (*p*-hydroxyphenyl)pyruvic acid, 5 h]: 96%; mp 283-284 °C dec. Anal. $C_{13}H_{13}N_5O_4$.

Acknowledgment. We thank Dr. B. S. Hurlbert, Mr. R. Crouch, and Mr. A. Ragouzeos for NMR spectra, Dr. D. A. Brent, Mr. R. L. Johnson, and Mr. Bernd Soltman for mass spectral data, and Ms. S. Wrenn for UV studies.

Registry No. 1a, 67873-21-6; **1b**, 67873-23-8; **1c**, 6298-85-7; **2** (R^2 = *p*-$HOC_6H_4CH_2$; R^3 = H), 156-39-8; **2** (R^2 = Me; R^3 = H), 127-17-3; **2** (R^2 = Ph; R^3 = H), 611-73-4; **3a**, 67873-29-4; **3b**, 67873-42-1; **7a**, 80042-18-8; **7b**, 80042-19-9; **7c**, 80042-20-2; **8**, 80081-74-9.

Supplementary Material Available: Full data available include the following: Microanalyses for compounds **3a,b,7a,c**, and **8**, NMR and UV data on compounds **7a,c** and **8**, and mass spectral data on compound **7a** (2 pages). Ordering information is given on any current masthead page.

(6) Turned blue above 150 °C but did not melt.

(7) These data correlate well with ^{13}C NMR data for close analogues reported by: Secrist, J. A., III; Liu, P. S. *J. Org. Chem.* **1978**, *43*, 3937.

(8) The crude product was contaminated with a small amount of 7-amino-3-benzyl-1-methylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione,[1] isolated in 2% yield during the recrystallization.

Homogeneous, Palladium(0)-Catalyzed Exchange Deprotection of Allylic Esters, Carbonates, and Carbamates[1]

Paul D. Jeffrey and Stuart W. McCombie*

Anti-Infectives Research, Schering Corporation, Bloomfield, New Jersey 07003

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Soluble palladium complexes are finding increased use in synthesis,[2] and the value of π-allyl complexes in particular has been demonstrated in an elegant series of investigations by Trost.[3] Here, we describe a process for cleavage of the (allyloxy)carbonyl function using catalytic π-allyl activation,[4] designed initially for carboxylate unmasking in β-lactam derivatives and generally applicable to all types of *N*- or *O*-[(allyloxy)carbonyl] structures.

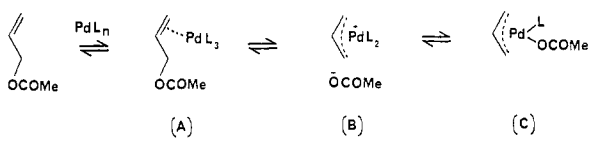
The (allyloxy)carbonyl function, originally introduced as a hydrogenolyzable N-blocking group,[5] is subject to C–O

(1) The process described herein is the subject of European Patent Office Application EP 13-663.

(2) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615-2649.

(3) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393.

(4) Activation involves a series of equilibria:

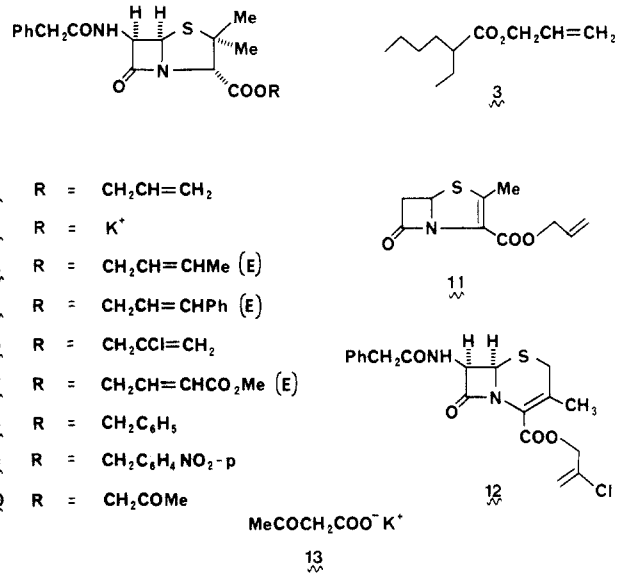


In the case of allylic C–C bond formation with soft nucleophiles, the cationic complex B is involved (ref 3, p 387), whereas for carboxylate nucleophiles, transfer via coordination to the metal as in C has been implicated: Backvall, J. E.; Nordberg, R. E.; Bjorkmanan, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943-944. In support of this latter observation, we have found that, whereas a number of other phosphine–palladium combinations are effective exchange catalysts [e.g., $Pd(OAc)_2$–PPh_3, $Pd(OAc)_2$–$(EtO)_3P$], the presence of strongly chelating phosphine [$Pd(OAc)_2$–$Ph_2PCH_2CH_2PPh_2$] retards the process, presumably by preventing effective complexation of carboxylate ligands onto the metal center.

(5) Stevens, C. M.; Watanabe, R. *J. Am. Chem. Soc.* **1950**, *72*, 725-727.

0022-3263/82/1947-0587$01.25/0

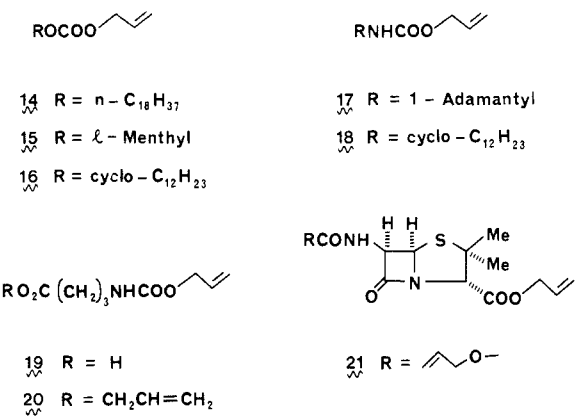
Chart I



scission by organocuprates[6] and nickel carbonyl.[7] More recently, homogeneous, palladium-catalyzed hydrogenolysis has been reported.[8] Seeking a mild process for ester cleavage in sensitive systems, we treated penicillin G allyl ester[9] (1, Chart I) with potassium 2-ethylhexanoate[10] (1.1–1.5 equiv in CH_2Cl_2–EtOAc) in the presence of Pd(PPh_3)$_4$[11] (1–3 mol %) and additional PPh_3[12] (2–5 mol %). Precipitation of the salt (2) was essentially complete in 1 h at 25 °C, and simple filtration gave pure product (85–95%). No β-lactam cleavage products were present in the filtrate, which contained only small amounts of 1 and 2, soluble Pd–phosphine complexes, and the coproduct 3.[13] Several substituted analogues[9] (4–7) behaved similarly, affording excellent yields of the salt 2. As expected, the benzyl esters[9] 8 and 9 were unaffected under these conditions; slow cleavage of the 2-oxopropyl ester[9] 10 was found to occur with 2-ethylhexanoate alone[14] and was not accelerated by palladium complexes.

The sensitive penem ester[15] 11 and the deacetoxycephem[16] 12 were also converted in high yield to the corresponding salts. Simple esters such as allyl benzoate and allyl acetoacetate behaved identically; the latter gave the

Chart II



salt 13 as the major product, in contrast to the decarboxylative rearrangement observed in the absence of alkali metal carboxylate.[17] In certain cases, highly efficient monodeprotection of diallyl symmetrical esters could be carried out; treatment of diallyl malonate with 1 equiv of potassium 2-ethylhexanoate and the Pd(0) catalyst gave the monopotassium salt in near-quantitative yield.

Deprotection of allylic carbonates and carbamates took place on treatment with 2-ethylhexanoic acid or an equivalent carboxylic acid (1.1–1.5 equiv for carbonates and 2.2–3 equiv for carbamates) in the presence of the palladium/triphenylphosphine catalyst system (1–5 mol %) at room temperature for several hours. Decarboxylation of the intermediate carbonic or carbamic acid afforded the product. In the examples 14–18 (Chart II) the reactions were monitored (TLC) to completion, and the products were isolated by extraction, by chromatography, or by precipitation from the reaction as an appropriate salt in the case of aliphatic amines. Aromatic amines gave erratic results owing to competing N-allylation; treatment of *N*-[(allyloxy)carbonyl]-*p*-anisidine under the standard conditions gave a mixture of *p*-anisidine and its mono- and di-*N*-allyl derivatives.

In those cases where the final product is zwitterionic, it is frequently possible to find a solvent in which only the fully deprotected material is sparingly soluble. Thus, cleavage of 19–22 [2-ethylhexanoic acid with the Pd(0) complex in CH_2Cl_2–Et_2O] gave good yields of amino acid product as a direct precipitate from the reaction mixture.[18]

The mild conditions used in these reactions leave most of the commonly employed[19] N or O protecting groups unchanged; even allylic ethers cleave only under more forcing conditions.[20] At the same time, the general stability of the (allyloxy)carbonyl group allows a number of other protecting groups (e.g., Boc, Tcec[21] and TBDMS[22]) to be removed in its presence. The reactivity of the double

(6) Anderson, R. J.; Hendrick, C. A.; Siddall, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 735–737. Ho, T. *Synth. Commun.* **1978**, *8*, 15–17.

(7) Corey, E. J.; Suggs, W. J. *J. Org. Chem.* **1973**, *38*, 3223–3224.

(8) Two alternative processes have been described, both of which involve production of a π-allylpalladium hydride species: Tsuji, J.; Yanakawa, T. *Tetrahedron Lett.* **1979**, 613–616. Hutchins, R. O.; Learn, K.; Fulton, R. P. *Ibid.* **1980**, 27–30.

(9) These esters were prepared by reaction of the appropriate halogeno compound with the salt 2 in DMF at 25 °C.

(10) Displacement of the exchange equilibrium over to the desired product is assured by employing the alkali metal salts of 2-ethylhexanoic acid, which are soluble in most common solvents, excepting hydrocarbons.

(11) Commercially available (Alfa Division, Ventron Corp.) or prepared according to: Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121–124.

(12) Use of additional phosphine, although not essential, is advisable in small-scale experiments, as aerial oxidation to the phosphine oxide (ineffective as an activating ligand) is catalyzed by the palladium complex: Stern, E. W., *J. Chem. Soc., Chem. Commun.* **1970**, 736.

(13) Isolated by chromatography and identified by comparison with an authentic sample prepared by standard esterification of the acid with allyl alcohol.

(14) 2-Oxopropyl (acetonyl) esters are readily cleaved by nucleophiles: Cheney, L. C.; Godfrey, J. C.; Crast, L. B.; Luttinger, J. R. U.S. Patent 3 284 451, 1966.

(15) Prepared by intramolecular Wittig cyclization by use of the route described for the corresponding *p*-nitrobenzyl ester: Lang, M.; Prasad, K.; Holick, W.; Gosteli, J.; Ernest, I.; Woodward, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 6296–6301.

(16) Prepared by acid-catalyzed rearrangement of 6 sulfoxide.

(17) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.

(18) Precipitated products were generally 95+% pure; small amounts of occluded impurities could be removed by reverse-phase or ion-exchange chromatography or recrystallization.

(19) McOmie, J. F. W. "Protective Groups in Organic Chemistry"; Plenum: London, 1973.

(20) Such exchange processes have been carried out in concentrated solutions at elevated temperatures: Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821–3824. Hata, G.; Takahashi, H.; Miyake, A. *J. Chem. Soc. Chem. Commun.* **1970**, 1392–1393. Experiments under the conditions of the present paper established that allyl 1-octyl ether is not cleaved appreciably over a 6-h period at 25 °C, that allyl phenyl ether reacts slowly, and that *N*-allyl amides are unaffected.

(21) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555–2557.

(22) Corey, E. J.; Ventakeswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

bond toward electrophiles can be modified by substituents (examples 6 and 7) to allow selective synthetic transformations on other, more reactive residues within a molecule. Examples of such processes in the synthesis of β-lactam antibiotics will be found in forthcoming publications from these laboratories.

Experimental Section

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were determined on 5–10% solutions in the indicated solvent by using a Varian T-60 or EM-390 instrument, and IR spectra were determined on solutions or in Nujol suspensions by using a Perkin-Elmer 727B instrument. Baker silica gel (60–200 mesh) was used for column chromatography. All reactions were run in an atmosphere of nitrogen or argon, with subsequent workup under aerobic conditions.

Preparation of Allylic Derivatives. 2-Chloro-2-propenyl (3*S*,5*R*,6*R*)-2,2-Dimethyl-6-(phenylacetamido)-7-oxopenam-3-carboxylate (6). Penicillin G potassium salt (50 g), sodium iodide (10 g), and 1,2-dichloro-2-propene (20 mL) were stirred in DMF (300 mL) at 25 °C for 20 h. The mixture was added to water (500 mL) containing Na_2SO_3 (10 g) and extracted with CH_2Cl_2–Et_2O (1:5 v/v, 500 mL). The solution was washed with water (2 × 200 mL), dried, and evaporated, and the product was crystallized with ether–hexanes to afford small, white needles: 51.9 g (94%); mp 73–75 °C; $[\alpha]^{26}_D$ +157.0° (*c* 0.4, $CHCl_3$); ^{1}NMR ($CDCl_3$) δ 1.43 (s, 6), 3.60 (s, 2), 4.40 (s, 1), 4.69 (s, 2), 5.3–5.7 (m, 4), 6.28 (d, 1, exch by D_2O), 7.24 (s, 5). Anal. Calcd for $C_{19}H_{21}N_2O_4ClS$: C, 55.8; H, 5.2; N, 6.85; Cl, 8.7; S, 7.8. Found: C, 55.8; H, 5.1; N, 6.7; Cl, 8.7; S, 7.5.

2-Propenyl (3*S*,5*R*,6*R*)-2,2-dimethyl-6-(phenylacetamido)-7-oxopenam-3-carboxylate (1) was similarly prepared from the salt **2** and excess allyl bromide in DMF and was obtained as a thick, colorless oil: IR (CH_2Cl_2) 3450, 1775, 1730, 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 6), 3.63 (s, 2), 4.37 (s, 1), 4.64 (br d, 2), 5.1–6.0 (m, 5), 6.32 (br d, 1, exch by D_2O), 7.31 (s, 5).

(*E*)-2-Butenyl (3*S*,5*R*,6*R*)-2,2-dimethyl-6-(phenylacetamido)-7-oxopenam-3-carboxylate (4) was similarly obtained as a pale yellow oil: IR (CH_2Cl_2) 3, 350, 1775, 1730, 168 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 6), 1.71 (d, 3), 3.64 (s, 2), 4.37 (s, 1), 4.62 (s, 2), 5.4–6.1 (m, 4), 6.37 (br d, 2, exch by D_2O), 7.40 (s, 5).

(*E*)-2-Phenyl-2-propenyl (3*S*,5*R*,6*R*)-2,2-dimethyl-6-(phenylacetamido)-7-oxopenam-3-carboxylate (5) was obtained from the salt **2** and an equivalent amount of cinnamyl bromide in DMF. Workup afforded a yellowish foam: IR (CH_2Cl_2) 3400, 1780, 1730, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 6), 3.63 (s, 2), 4.42 (s, 1), 4.83 (d, 2), 5.4–5.8 (m, 2), 6.0–6.5 (m, 3), 6.71 (d, 1), 7.34 (s, 10).

(*E*)-3-(Methoxycarbonyl)-2-propenyl (3*S*,5*R*,6*R*)-2,2-dimethyl-6-(phenylacetamido)-7-oxopenam-3-carboxylate (7) was similarly prepared by using an equimolar proportion of methyl γ-bromocrotonate and was a thick oil which slowly decomposed at ambient temperature: ^{1}NMR ($CDCl_3$) δ 1.45 (s, 6), 3.63 (S, 2), 3.75 (s, 3), 4.41 (s, 1), 4.77 (dd, 2), 5.4–5.8 (m, 2), 6.03 (m, 1), 6.31 (br d, 1, exch by D_2O), 6.90 (dt, 1), 7.28 (s, 5).

2-Chloro-2-propenyl (6*R*,7*R*)-3-Methyl-7-(phenylacetamido)-8-oxo-3-cephem-4-carboxylate (12). Method A. The sulfoxide of **6** was prepared by oxidation with 1 equiv of MCPBA in dichloromethane and was crystallized from ether as white prisms: mp 105–106.5 °C; $[\alpha]^{26}_D$ +198.5° (*c* 0.39, $CHCl_3$); ^{1}NMR ($CDCl_3$) δ 1.24 (s, 3), 1.73 (s, 3), 3.63 (s, 2), 4.68 (s, 1), 4.80 (AB, 2), 5.03 (d, 2), 5.51 (br s, 1), 5.60 (br s, 1), 6.04 (dd, 1), 7.17 (br d, 1, exch by D_2O), 7.30 (s, 5). Anal. Calcd for $C_{19}H_{21}N_2O_5ClS$: C, 53.6; H, 4.9; N, 6.6; Cl, 8.35; S, 7.5. Found: C, 53.5; H, 5.0; N, 6.5; Cl, 8.1; S, 7.6.

Method B. A solution of the foregoing sulfoxide (1.50 g) in dioxane (50 mL) containing phosphoric acid (85%; 120 mg) and pyridine (100 mg) was refluxed for 5 h, and the mixture was then evaporated. The residue was passed through a short silica gel column by eluting with 10:1 v/v CH_2Cl_2–Et_2O. Evaporation and cystallization from ether gave the product as cream needles: 0.78 g (54%); mp 166–170 °C; $[\alpha]^{26}_D$ +60.5 (*c* $CHCl_3$); 0.54, IR (Nujol) 3300, 1765, 1720, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3), 3.30 (AB, 2), 3.61 (s, 2), 4.77 (s, 2), 4.93 (d, 1), 5.38 (m, 1), 5.55 (m, 1), 5.73 (dd, 1), 6.60 (d, 1, exch by D_2O), 7.30 (s, 5). Anal. Calcd for $C_{19}H_{19}N_2O_4ClS$: C, 56.0; H, 4.7; N, 6.9; S, 7.9. Found: C, 55.7; H, 4.5; N, 6.8; S, 7.6.

4-[[(Allyloxy)carbonyl]amino]butyric Acid (19). 4-Aminobutyric acid (10 g) in water (100 mL) containing NaOH (10 g) and THF (25 mL) was stirred at 0.5 °C and allyl chloroformate (12 mL) added dropwise. After 0.5 h, the solution was acidified with 12 N HCl (30 mL) and extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and evaporated, and the residue was pumped at high vacuum to give the product (19 g, 100%) as a white solid. A sample recrystallized from Et_2O–hexanes had a melting point of 42–44 °C. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.3; H, 6.95; N, 7.5. Found: C, 51.0; H, 6.8; N, 7.7.

1-[[(Allyloxy)carbonyl]amino]adamantane (17). 1-Aminoadamantane (3.05 g) was stirred at 0–5 °C in CH_2Cl_2 (30 mL), and aqueous 1 N NaOH (25 mL) and allyl chloroformate (2.8 mL) in CH_2Cl_2 (10 mL) was added dropwise. After 0.5 h, the organic phase was washed with 1 N HCl(aq), dried, and evaporated to give the product (4.8 g) as a white solid. A portion was recrystallized from hexanes as white plates, mp 56.5–58 °C. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.5; H, 8.9; N, 5.95. Found: C, 71.5; H, 8.95; N, 5.8.

[[(Allyloxy)carbonyl]amino]cyclododecane (18) was prepared in an analogous fashion from cyclododecylamine; mp 97–99 °C. Anal. Calcd for $C_{16}H_{29}NO_2$: C, 71.9; H, 10.9; N, 5.2. Found: C, 72:1; H, 10.7; N, 5.1. The carbonate esters 14–16 were prepared from the alcohol with allyl chloroformate and pyridine in dry THF essentially as described in the literature.[7]

Palladium(0)-Catalyzed Cleavage Reactions. The following examples illustrate conditions for cleavage of the various types of *O*-allyl substrates. It should be noted that the use of aged, brown samples of tetrakis(triphenylphosphine)palladium frequently gives inferior results (slower reaction rates) when compared with those of fresh samples. The complex should be stored under nitrogen and protected from light.

Penicillin-9 Potassium Salt (2) from the Allyl Ester. A solution of the ester **1** (0.38 g) in dichloromethane (3 mL) and potassium 2-ethylhexanoate (0.5 M in EtOAc, 3 mL) was stirred with PPh_3 (25 mg) and $Pd(PPh_3)_4$ (25 mg) for 0.5 h at 25 °C. The mixture was diluted with acetone (20 mL), and the product was filtered, washed with ether, and dried in vacuo to afford pure **2** (0.325 g, 84%) as a white powder, identical in all respects (^{1}H NMR, IR, antibacterial activity) with a commercial sample.

Larger-scale preparations using ethyl acetate as the reaction solvent, 1.1 equiv of potassium 2-ethylhexanoate, and a 2-h reaction period afforded the following isolated yields of the salt **2** from the indicated ester: **1**, 94%; **4**, 91%; **5**, 92%; **6**, 94%; **7**, 85%.

(6*R*,7*R*)-3-Methyl-7-(phenylacetamido)-8-oxo-3-cephem-4-carboxylic Acid from 12. A solution of the chloroallyl ester **12** (0.407 g) in CH_2Cl_2 (5 mL) and EtOAc (2.2 mL), PPh_3 (25 mg), and Pd (PPh_3)$_4$ (25 mg) was stirred at ambient temperature for 1 h. The gelatinous precipitate was collected and washed with ethyl acetate. The resulting potassium salt was stirred in water (15 mL) and gradually treated with 1 M phosphoric acid (2 mL). The crystalline *acid* was collected, washed with water and a small quantity of ether, and dried in vacuo to afford a cream solid, 0.195 g (54%). (Additional material was present in the filtrate and washings.) This was identical (IR, ^{1}H NMR) with an authentic sample.[23]

1-Ammonioadamantane 2-Ethylhexanoate from 17. A solution of the carbamate **17** (2.35 g), 2-ethylhexanoic acid (3.6 g), PPh_3 (0.25 g), and $Pd(PPh_3)_4$ (0.25 g) in CH_2Cl_2 (40 mL) was stirred at 25 °C for 2 h; crystallization commenced after ca. 0.5 h. Ether (70 mL) was added, and the product was collected, washed with ether, and dried in vacuo to yield 1-ammonioadamantane 2-ethylhexanoate: 2.65 g (89%); white plates; mp 150–155 °C dec (varies with rate of heating). Anal. Calcd for $C_{18}H_{33}NO_2$: C, 73.2; H, 11.2; N, 4.75. Found: C, 73.2; H, 11.0; N, 4.7.

4-Aminobutyric Acid from 19. A solution of the carbamate **19** (1.87 g), 2-ethylhexanoic acid (1.65 g), PPh_3 (0.2 g), and $Pd(PPh_3)_4$ (0.22 g) in CH_2Cl_2 (25 mL) and ether (15 mL) was stirred at 25 °C for 18 h. The precipitate was collected, washed with

(23) Green, G. F. H.; Page, J. E.; Staniforth, S. E. *J. Chem. Soc.* **1965**, 1595–1605.

CH_2Cl_2, and dried to afford 4-aminobutyric acid (0.95 g, 92%) identical (IR, ^1H NMR in D_2O solution) with an authentic sample.

1-Octadecanol from Carbonate 14. A solution containing **14** (1.72 g), HOAc (0.6 mL), PPh_3 (0.2 g), and $Pd(PPh_3)_4$ (0.2 g) in CH_2Cl_2 (15 mL) was stirred at 25 °C for 18 h, washed with $NaHCO_3$ solution, dried, and evaporated to yield fairly pure 1-octadecanol containing a small amount of Ph_3P. Recrystallization from methanol gave the pure alcohol: 1.12 g (83%); mp and mmp 58–60 °C.

Registry No. 1, 80127-23-7; 2, 113-98-4; 4, 80127-24-8; 5, 80225-13-4; 6, 76627-82-2; 6 sulfoxide, 80127-25-9; 7, 80183-95-5; 12, 80127-26-0; 14, 76627-81-1; 15, 76648-56-1; 16, 80127-27-1; 17, 76627-80-0; 18, 80127-28-2; 19, 80127-29-3; 1,2-dichloro-2-propene, 78-88-6; allyl bromide, 106-95-6; (*E*)-cinnamyl bromide, 26146-77-0; methyl (*E*)-γ-bromocrotonate, 6000-00-6; 4-aminobutyric acid, 56-12-2; allyl chloroformate, 2937-50-0; 1-aminoadamantane, 768-94-5; cyclododecylamine, 1502-03-0; (6*R*,7*R*)-3-methyl-7-(phenylacetamido)-8-oxo-3-cephem-4-carboxylic acid, 27255-72-7; potassium (6*R*,7*R*)-3-methyl-7-(phenylacetamido)-8-oxo-3-cephem-4-carboxylate, 34708-38-8; 2-ethylhexanoic acid, 149-57-5; 1-adamantamine 2-ethylhexanoate, 80127-30-6; 1-octadecanol, 112-92-5; $Pd(PPh_3)_4$, 14221-01-3.

Stable Thiiranium and Thiirenium Chlorides. Ionization of β-Thioalkyl and β-Thiovinyl Chlorides in Sulfur Dioxide

Vittorio Lucchini,* Giorgio Modena, and Tiziano Zaupa

Centro Meccanismi di Reazioni Organiche del CNR, Istituto di Chimica Organica, Universitã, 35100 Padova, Italy

Giuseppe Capozzi

Istituto di Chimica Organica, Universitã di Messina, 98100 Messina, Italy

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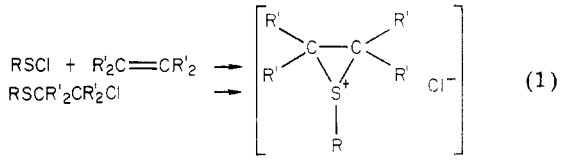
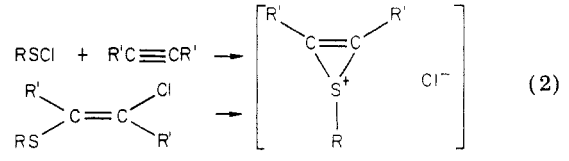
Thiiranium **1** and thiirenium ions **2** have been proposed as intermediates both in the addition of sulfenyl chlorides to double and triple bonds and in the solvolysis of β-thioalkyl and β-thiovinyl chlorides[1] (eq 1 and 2).



(1)

1



(2)

2

Compelling evidence for the presence of these intermediates along the reaction paths of addition[2] and solvolysis[3,4] reactions has been provided by stereochemical[2,3] and kinetic studies.[4] Furthermore we have shown that, in the addition of methanesulfenyl chloride to dialkylacetylenes in sulfur dioxide at low temperature, the corresponding thiirenium chlorides are rapidly formed and may easily be detected by ^1H NMR spectroscopy.[5,6] Stable thiiranium[7,8] and thiirenium salts,[6,9] with the proper counterion, have been isolated: addition of chloride ion to them gives products sterically identical with those obtained from the direct addition of sulfenyl chloride to the corresponding ethylenes or acetylenes.[5,10]

No intermediates, in the form of thiiranium or thiirenium halides, have been detected in the solvolysis reactions, so that the presence of cyclic intermediates is based upon indirect evidence only.

We have already reported that, contrary to the behavior of less heavily substituted thiirenium ions, 1-methyl-2,3-di-*tert*-butylthiirenium chloride (**6**) is stable in sulfur dioxide at room temperature.[6] It may therefore be expected that the corresponding adduct, (*E*)-2,2,5,5-tetramethyl-3-(methylthio)-4-chloro-3-hexene (**4**), might spontaneously ionize in this solvent. We report herein kinetic results for this ionization study, which has been extended, for the sake of comparison, to the reaction of the saturated analogue 2,3-dimethyl-3-(methylthio)-2-chlorobutane (**3**).

Results

The reactions of the adducts **3** and **4** in sulfur dioxide were followed by ^1H NMR spectroscopy. In agreement with expectation, vinyl chloride **4** ionizes to 1-methyl-2,3-di-*tert*-butylthiirenium chloride (**6**) at a measurable rate at room temperature ($t_{1/2}$ at 25 °C ≃ 90 min). The conversion of alkyl chloride **3** to pentamethylthiiranium chloride **5** is much faster and was to be followed at lower temperature ($t_{1/2}$ at −60 °C ≃ 5 min). The signals of thiiranium chloride **5** (δ 2.39, methyl bound to sulfur; δ 1.97 and 1.93, ring carbon methyls) and thiirenium chloride **6** (δ 2.61, methyl bound to sulfur; δ 1.53, *tert*-butyls) were identified through comparison with those of the hexachloroantimonate salts of the same cations.[6,8] The ionization of **3** was followed by measuring the integrated intensities of the α-Cl methyls in **3** and the sulfur methyl in **5**, which are relatively isolated. For the ionization of **4** the *tert*-butyl resonances of **4** and **6** have been monitored.

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