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REACTION OF 4-ACETOXY-2-AZETIDINONE WITH TERTIARY CARBANIONS: PREPARATION OF 4-ALKYL- AND 4-ALKYLIDENE-2-AZETIDINONES

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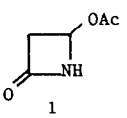
ABSTRACT. Reaction of 4-acetoxy-2-azetidinone with tertiary stabilised carbanions gives carbon-substituted 2-azetidinones which have been transformed into 4-alkylidene-2-azetidinones.

The discovery of naturally occuring carbapenem antibiotics has prompted a search for analogue synthesis. Although many 2-azetidinones bearing carbon substituents at C(4) are known[1] there are few reports of carbon-carbon bond formation at C(4)[2] and no high-yielding transformations of this type using N-unsubstituted 2-azetidinones have been described.† The methods described below introduce either singly - or doubly-bonded groups at C(4) starting from 4-acetoxy-2-azetidinone.[3] Attention is drawn to the use of a tertiary stabilised carbanion which avoids the problem of product instability during the reaction, a problem which has reduced yields in related earlier work.[2b,c]

4-Acetoxy-2-azetidinone 1 reacted in tetrahydrofuran (-20 to +20°) with the sodium salts of phenylthiophosphonoacetates 2a,b[4] to give carbon-substituted 2-azetidinones 3a,b[5] in yields of 96% and 80% respectively. Similarly reaction of 1 with diethyl phenylthiomalonate 4[6] gave 5[7] (96%). Long-range couplings between NH and C(3)-H's are in accord with the expected values[8] and are shown in the Table.



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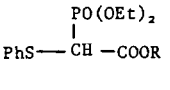
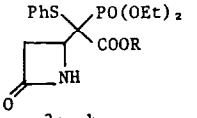
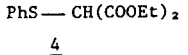


2a R=Bz
2b R=tBu



3a, b



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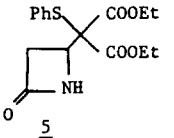

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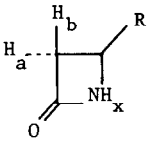
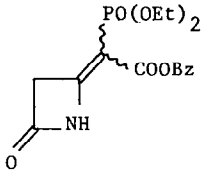
TABLE Long-Range Coupling Constants

Compound	Jax (Hz)	Jbx (Hz)
3b	2.5	1
5	2.0	1.3



2-Azetidinones having sp^2 hybridisation at C(4) have been the subject of several recent reports.[9] Sulphoxidation of 3a or 5 with m-chloroperbenzoic acid followed by thermal elimination of benzenesulphenic acid gave olefins 6[10] (75%) (olefin geometry not assigned) and 7[11] (70%). The thermal elimination yielding 6 was unusually facile being readily completed at 45° (toluene) whilst the thermolysis yielding 7 required 2 hours in refluxing toluene. Compounds 6 and 7 showed β-lactam carbonyl absorptions at 1840 cm^{-1}, in accord with values recently reported by Bachi[9a] for related compounds prepared by another method.

Further carbanion reactions leading to the synthesis of fused 2-azetidinones will be reported in due course.



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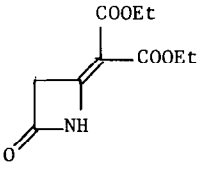

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EXPERIMENTAL (typical procedures)

4-[(Benzyloxycarbonyl)(diethylphosphono)(phenylthio)]methyl-2-azetidinone, 3a. 2a (2.0 g) In tetrahydrofuran (10 ml) was added to 50% sodium hydride (0.27 g) in tetrahydrofuran (15 ml) at 0°. After hydrogen evolution had ceased the solution was cooled to -70° and 4-acetoxy-2-azetidinone (0.65 g) added. The mixture was stirred at room temperature for 2 hours then acidified with acetic acid. Water was added and the product extracted with chloroform. Silicagel chromatography of the dried chloroform layer gave homogenous 3a (2.26 g) eluted with 5% methanol in chloroform.

4-[(Benzyloxycarbonyl)(diethylphosphono)]methylene-2-azetidinone, 6.

3a (3.0 g) In methylene chloride (30 ml) at 0° was oxidised using m-chloroperbenzoic acid (1.4 g) in methylene chloride (30 ml). After 30 minutes the solution was washed with aq. sodium bicarbonate, dried and evaporated to give the crude sulphoxide which was dissolved in toluene (50 ml) and warmed at 45° for 2 hours. Removal of the solvent followed by silicagel chromatography gave 6 (1.7 g) eluted with 5% ethyl acetate in chloroform. White needles MP 109-111° were obtained from diethyl ether.

4-[(Bis[ethoxycarbonyl])(phenylthio)]methyl-2-azetidinone, 5.

Diethyl phenylthiomalonate 4 (600 mg) was added to a stirred suspension of sodium hydride (100 mg of 50%) in tetrahydrofuran (15 ml) at 0°. When hydrogen evolution had ceased 4-acetoxy-2-azetidinone (260 mg) was added and the mixture warmed to room temperature. After 2 hours the mixture was diluted with ethyl acetate, washed with saturated brine and dried (Na_2SO_4). Removal of the solvent *in vacuo* followed by silicagel chromatography gave homogeneous 5 (650 mg), eluted using 20% ethyl acetate in methylene chloride. Crystallisation from diethyl ether gave white cubes MP 69-71° (300 mg).

4-[Bis(ethoxycarbonyl)]methylene-2-azetidinone, 7.

m-Chloroperbenzoic acid (100 mg) was added to 5 (170mg) in methylene chloride (5 ml) at 0°. After 30 minutes the solution was diluted with methylene chloride and washed successively with aqueous sodium sulphite and aqueous sodium carbonate then dried (Na_2SO_4). The solvent was replaced with toluene and the solution refluxed for 2 hours. Removal of the solvent followed by chromatography gave homogeneous crystalline 7 (80 mg) eluted with 10% ethyl acetate in methyl chloride. White needles MP 139-144° were obtained by recrystallisation from diethyl ether.

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References and Footnotes

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3. K. Clauss, D. Grimm, G. Prossel, Annalen, 1974, 539.

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5. 3a. Yield 96% (chromatographed). ν_{max} (CH_2Cl_2) 1770, 1730 cm^{-1}. δ($CDCl_3$, 60MHz) 1.28 (6H,m), 2.78-3.65 (2H,m), 3.91-4.57 (5H,m,-OCH_2 and C(4)-H), 4.85 (centre of system 2H,AB,J=12); 6.26 (NH); 7.08-7.83 (10H,m). m^+ 463.120 ($C_{22}H_{26}NO_6PS$ requires 463.121).
3b. Yield 80% (chromatographed). MP 140-141° (petroleum ether). νmax (CH_2Cl_2) 1765, 1735 cm^{-1}. δ($CDCl_3$, 220MHz) 1.21 (9H, s); 1.35 (3H, t, J=7); 1.39 (3H, t, J=7); 3.05 (H, ddd, J=15, 5, 2.5); 3.41 (H, ddd, J=15, 2, 1); 4.35 (centre of 5H, m, -OCH_2 and C(4)-H); 6.09 (NH); 7.3-7.75 (5H, aromatic H's). Found C, 52.9; H, 6.3; N, 3.2%. $C_{19}H_{28}NO_6PS$ requires C, 53.1; H, 6.5; N, 3.2%.

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7. 5 Yield 96% (chromatographed). MP 69-71°(Et_2O). ν_{max} (CH_2Cl_2) 1775, 1730cm^{-1}. δ(100MHz, $CHCl_3$) 1.28 (3H,t,J=7); 1.31 (3H,t,J=7); 2.86-3.35 (2H,m); 4.1-4.4 (5H,m); 6.08 (NH); 7.25-7.7 (5H,m). Found C,56.93; H,5.63; N,4.11%. $C_{16}H_{19}NO_5S$ requires C,56.95; H,5.67; N,4.15%.

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10. 6 Yield 75% (chromatographed). MP 109-111° (Et_2O). λ_{max} (EtOH) 252nm (ε 24,400). ν_{max} (CH_2Cl_2) 1840, 1720 cm^{-1}. ($CDCl_3$, 60MHz) 1.28 (6H,t,J=7); 3.81-4.45 (6H,m,2 x OCH_2 and C(3)-H's), 5.22 (2H, S); 7.38 (5H, S); 9.48 (NH). Found C,54.6; H,5.7; N,3.7%. $C_{16}H_{20}NO_6P$ requires C,54.4; H,5.7; N,3.9%.

11. 7 Yield 70% (chromatographed). MP 139-144° (Et_2O). λ_{max} (EtOH) 260nm (ε 22,000). ν_{max} (CH_2Cl_2) 1839, 1725 cm^{-1}. δ($CDCl_3$, 60MHz) 1.29 (3H,t,J=7); 1.33 (3H,t,J=7); 3.88 (2H,S); 4.21 (2H,q,J=7); 4.29 (2H,q,J=7); 9.0 (NH). Found C,52.64; H,5.80; N,6.05%. $C_{10}H_{13}NO_5$ requires C,52.86; H,5.76; N,6.17%.

† Note added in proof. A recent report describes the first efficient transformation of this type.
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