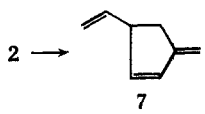

(5)

Comparison of the activation energy reported for the vinylmethylenecyclopropane → 3-methylenecyclopentene rearrangement (25.8 kcal)[9] with that found for 2 → 7 is interesting. If rupture of the cyclopropane bond is the rate-determining step in both cases, then the difference in activation energies (~8.4 kcal) may reflect the difference in stabilization energies of the pentadienyl and allyl radicals, only slightly lower than the value of 9 kcal for another system involving cleavage of a cyclopropane bond.[10]

Acknowledgment. We gratefully acknowledge the Robert A. Welch Foundation (Grant C-490) and The Research Corporation for support of this work.

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(2) Prepared from 1,4-heptadiene and dichlorocarbene ($CHCl_3$, KO-*t*-Bu) in *n*-pentane at 0°.

(3) The isomer with the shorter retention time (**1a**) showed the following spectral properties: nmr (CCl_4) δ 1.07 (m, 1 H), 1.53 (m, 1 H), 2.11 (m, 1 H), 4.7–5.6 (m, 5 H), 6.42 (m, 2 H); ir (neat) 755 (m), 895 (s), 995 (s), 1614 (s), 1634 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 230 nm (ϵ 25,000). The remaining isomer (**1b**) showed nmr (CCl_4) δ 1.07 (m, 1 H), 1.52 (m, 1 H), 2.18 (m), 1 H), 4.7–5.7 (m, 5 H), 6.42 (m, 2 H); ir (neat) 897 (s), 995 (s), 1614 (s), 1634 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 232 nm (ϵ 19,000).

(4) Spectral properties: nmr (CCl_4) δ 1.01 (m, 1 H), 1.45 (m, 1 H), 2.17 (m, 1 HO), 4.60–5.48 (m, 5 H), 5.98 (m, 2 H); ir (neat) 882 (s), 990 (s), 1200 (m), 1428 (m), 1640 (s), 2960 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 237 nm (ϵ 38,000).

(5) Prepared from 1,5-heptadiene and dichlorocarbene ($CHCl_3$, KO-*t*-Bu) in *n*-pentane at 0°.

(6) Spectral properties: nmr (CCl_4) δ 2.32 (t, J = 2.5 Hz, 4 H), 5.1 (s, 2 H), 5.50–6.20 (m, 4 H) (irradiation at δ 2.32 reduces the δ 5.50–6.20 multiplet to an AB quartet with $J_{AB} \simeq$ 11 Hz); ir (neat) 785 (s), 880 (s), 1435 (m), 1445 (m), 1570 (m), 1786 (s), cm^{-1}; uv λ_{max} (C_6H_{12}) 246 mm (ϵ 15,000), 255 (13,000). The spectral data reported here for **5** differ substantially from those reported by earlier workers. See D. S. Matteson, J. J. Drysdale and W. H. Sharkey, *J. Amer. Chem. Soc.*, **82**, 2853 (1960); W. von E. Doering and D. W. Wiley, Tetrahedron, **11**, 183 (1960).

(7) Spectral properties: nmr (CCl_4) δ 1.98–2.87 (m, 2 H), 3.0–3.6 (m, 1 H), 4.60–5.90 (m, 5 H), 5.90–6.40 (m, 2 H); ir (neat) 760 (s), 864 (m), 908 (m) 988 (m), 1071 (m), 1432 (m), 1732 (s) cm^{-1}; uv λ_{max} (C_6H_{12}) 235 nm (ϵ 14,000).

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Department of Chemistry
Rice University
Houston, Texas 77001

W. E. Billups*[11]
W. Y. Chow
K. H. Leavell
E. S. Lewis

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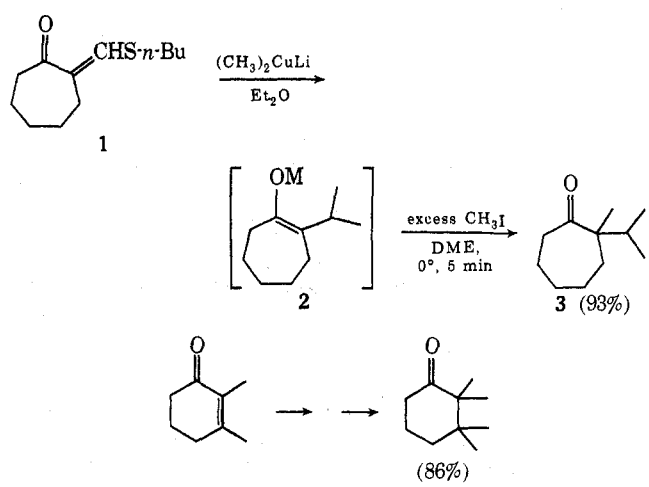
Conjugate-Addition Alkylation of α,β-Unsaturated Ketones

Summary: The copper–lithium enolates formed in the conjugate addition of organocopper lithium reagents to α,β-unsaturated ketones may be alkylated with generally high regioselectivity and efficiency in 1,2-dimethoxyethane as solvent.

Sir: The combination of dissolving metal reduction of α,β-unsaturated ketones (and analogous functions) with direct alkylation of the enolate anion so formed provides a simple and efficient method for regioselective alkylation.[1] Although it would clearly be a useful extension of this method to couple similarly the conjugate addition of organocopper reagents to α,β-unsaturated ketones[2] with alkylation,[3] attempts to alkylate the copper–lithium enolate intermediates have been either unsuccessful[4] or unsatisfactorily slow.[5,6] The ostensible unreactivity of these enolates was presumed to be the consequence of increased covalency of the copper–oxygen, as opposed to the lithium–oxygen, bond.[4]

We have discovered that the copper–lithium enolates formed in the conjugate addition of organo- (methyl- and vinyl-) copper lithium reagents to α,β-unsaturated ketones, while quite unreactive in ether (normally the solvent of choice for maximum yield of 1,4 addition),[2,7] become receptive to alkylation in 1,2-dimethoxyethane (DME). Thus, the half-life for methylation of the enolate produced in the double conjugate addition[4] to 2-*n*-butylthiomethylene ketone **1** is reduced from ~5 hr at room temperature in ether to ≪30 sec at 0° in DME, a reactivity difference of $\sim 10^5$.[8,9]



It is interesting that neither DME or tetramethylethylenediamine[10] in ether in stoichiometric proportions (3 equiv/1 equiv of Cu) nor 1:1 DME–ether was nearly so effective as pure DME in enhancing the rate of methylation of **2**, although all reactions were considerably faster than in pure ether. Accordingly, it seems to be necessary to remove essentially all of the ether prior to the addition of DME. Both tetrahydrofuran and hexamethylphosphoramide had a rate-accelerating effect comparable to, but apparently slightly less than, DME. The results of a survey upon the scope of this procedure for conjugate-addition alkylation are collected in Table I.

Some enolate ⇄ ketone equilibration is obviously occurring in certain cases (particularly the slower alkylation reactions) with concomitant formation of unalkylated, isomeric, and dialkylated products. However, we judge the yields of the desired conjugate-addition alkylation product to be comparable to those expected in the alkylation of the corresponding pure lithium enolate, considering the relatively hindered environment of the reaction site.[1b] It is noteworthy that the methylation of the lithium enolate **2**

Table I
Conjugate-Addition Alkylation of α,β-Unsaturated Ketones[a]

Substrate	Alkyln reagent[b]	Alkyln conditions: Time, min (hr)	Alkyln conditions: Temp, deg	Addn alkyln, % yield[c]	Other products (% yield)[c,d]
2-*n*-Butylthiomethylene-cycloheptanone	CH_3I	5	0	93[e]	
	$(CH_3)_2CHCH_2I$	(18)	25	64	2-Isopropyl (15) 2,7-Dialkyl-2-isopropyl (8)
	$CH_2{=}CHCH_2CH_2Br$	(50)	25	53	2-Isopropyl (31) 2-Isopropyl-7-alkyl (3) Alkyl enol ether (5)
	$(CH_3)_2CHI$	(50)	25	19	2-Isopropyl (20) 2,7-Diisopropyl (10) Alkyl enol ether (40)
2-*n*-Butylthiomethylene-cyclohexanone	CH_3I	5	0	86[e]	
2-Cyclohexenone	CH_3I	10	0	64[f]	3-Methyl (4) Trimethyl (10)
	$CH_2{=}CHCH_2Br$	10	0	74[g]	3-Methyl (10) 2,2- and 2,6-diallyl-3-methyl (6)
2-Cyclohexenone[h]	CH_3I	10	0	48[i]	3-Vinyl (2) Dimethyl-3-vinyl (11)
2,3-Dimethylcyclohexenone	CH_3I	10	0	86	2,3,3-Trimethyl (4)
2-Methyl-5-isopropenyl-2-cyclohexenone (carvone)	CH_3I	5	0	86[j]	
	CH_3CH_2I	(4)	25	63[k]	2,3-Dimethyl-5-isopropenyl (22) Diethyl-2,3-dimethyl-5-isopropenyl (16)
3-Penten-2-one	CH_3I	5	0	46	4-Methyl (2) 4,5-Dimethyl-3-hexanone (3)
3-Methyl-3-pentene-2-one	CH_3I	10	0	64	3,4-Dimethyl (2) 4,4,5-Trimethyl-3-hexanone (4)
4-Methyl-3-pentene-2-one	CH_3I	10	0	54	4,4-Dimethyl (11) 4,5,5-Trimethyl-3-hexanone (5)

[a] Ketone in ether was added to ~0.25 *M* ethereal $(CH_3)_2CuLi$ (3 equiv for *n*-butylthiomethylene ketones, 1.5 equiv for other substrates) at 0° and allowed to react for 30–45 min. The ether was evaporated and DME (~2.5–5 ml/mmol of ketone) was added. [b] Tenfold excess. [c] Yield by glc unless indicated otherwise. All nine previously unknown addition alkylation products gave satisfactory elemental analysis (eight by combustion, one by high resolution mass spectrometry). All products gave ir and nmr spectra consistent with the indicated structures. [d] Parent name for ketone by-products from enones, if not indicated, is the saturated ketone. [e] Isolated yield after distillation. [f] Trans–cis, 4:1, separated by preparative glc and identified by nmr spectral data comparison,[11] $NaOCH_3$–CH_3OH equilibration [cis–trans, 84:16 → 15:85 (lit.[12] 12:88)], and conversion of the trans isomer to its semicarbazone [mp 202° (lit.[13] mp 202°)]. [g] 8:1 mixture of two isomers, major isomer presumably trans. [h] $(CH_2{=}CH)_2CuLi$ in place of $(CH_3)_2CuLi$. [i] ~3:1 mixture of two isomers, major isomer presumably trans. [j] Only one isomer detected, presumably trans. [k] Only one isomer detected, presumably having secondary methyl and ethyl groups trans.

(M = Li), generated by cleavage of the corresponding enol acetate with methyllithium, proceeded with $t_{1/2} \sim 5$ hr in ether at room temperature, *i.e.*, at essentially the same rate as the copper–lithium enolate produced by conjugate addition (see above).

A typical procedure is as follows. 2-*n*-butylthiomethylenecycloheptanone (**1**, 13.4 g, 63.2 mmol) prepared in the usual manner[14] from the hydroxymethylene precursor,[15,16] in 60 ml of ether was added dropwise with stirring to ethereal dimethylcopper lithium (189 mmol, 0.25 *M*)[17] over 15 min at 0° under a nitrogen atmosphere. After 30 min at 0°, the solvent was removed by gentle heating under reduced pressure. (CAUTION—Since isolation of RCu compounds in the absence of zinc or magnesium salts is reported to give "a colored, explosive solid,"[2] the residue was never allowed to become dry. In this work, no special sensitivity or instability of the intermediate mixture was observed.) The remaining moist, yellow precipitate (under nitrogen) dissolved exothermically upon addition of DME (150 ml) giving a green-black mixture which was cooled to 0°. Methyl iodide (40 ml, 640 mmol) was added quickly and the reaction terminated after 5 min at 0° by pouring the mixture into saturated sodium bicarbonate (~500 ml). After addition of sufficient aqueous ammonia (~100 ml) to solubilize the precipitated copper salts, the product was extracted into pentane (three portions) and the pentane solution was washed with dilute ammonium hydroxide and water, dried ($MgSO_4$), and evaporated. Distillation of the resulting oil afforded 9.8 g (93%) of the known[18] 2-isopropyl-2-methylcycloheptanone (**3**) as a colorless liquid [bp 111° (17 mm)].

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(19) A. P. Sloan Foundation Fellow, 1971–1973.

Department of Chemistry
University of Illinois
Urbana, Illinois 61801

Robert M. Coates*[19]
Louise Ofenshain Sandefur

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The Removal and Displacement of the Thiazolidine Ring in Penicillin.[1] IV. Formation of a Biologically Active Cephem System

Summary: The thiazolidine ring of penicillin V (1) has been removed and replaced by a cephem system.

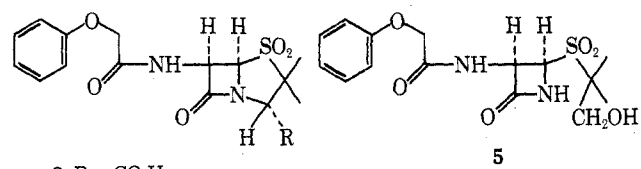
Sir: The thiazolidine ring of penicillins has been displaced for the case of 6-[2-methyl-2-(*o*-nitrophenoxy)propionamido]penicillanic acid[2] and phthalimidopenicillanic acid.[1] We now wish to report the extension of this displacement reaction to 6-phenoxyacetylaminopenicillanic acid (penicillin V, 1).

Penicillin V (1) was oxidized to the sulfone 2[3] using neutral aqueous permanganate: mp 149–151°; 94%; ir (KBr) 3450, 1800, 1735, 1675, 1600, 1530, 1325, 1240 cm^{-1}; nmr (acetone-d_6) δ 8.0 (d, 1, NH), 7.1 (m, 5, phenyl), 6.1 (dd, 1, J_1 = 5, J_2 = 11 Hz, H-6), 5.1 (d, 1, J = 5 Hz, H-5), 4.55 (s, 2, CH_2), 4.4 (s, 1, CH), 1.5, 1.3 (s, 6, CH_3). The sulfone 2 was converted to the isocyanate 3 *via* the mixed anhydride using ethyl chloroformate and pyridine, followed by treatment with sodium azide and thermal rearrangement. The use of triethylamine with the penicillin V side chain resulted in reduced yields of the isocyanate owing to loss of the β-lactam. Hydrolysis of the isocyanate afforded the "aldehyde" 4: 47%; mp 118–119°; $[\alpha]^{25}D$ 72.7° (*c* 0.5, $CHCl_3$); ir (KBr) 3400, 1805, 1675, 1600, 1530, 1315, 1245 cm^{-1}; nmr ($CDCl_3$) δ 8.6 (d, 1, NH), m at 7.1 (aromatic and benzene solvate), 6.05 (dd, 1, J_1 = 5, J_2 = 11 Hz, H-6), 5.3 (s, 1, H-3), 4.85 (d, 1, J = 5 Hz, H-5), 4.5 (s, 2, CH_2), 1.4, 1.45 (s, 6, CH_3). This compound seems to exist entirely in the ring-closed form since no aldehyde absorption is detectable by nmr.[1,2,4]

"Aldehyde" 4 was reduced to alcohol 5 with sodium borohydride: 56%; mp 142–144°; $[\alpha]^{25}D$ 28.6 (*c* 1, $CHCl_3$); mass spectrum (70 eV) *m/e* 219 [$M^+ - SO_2C(CH_3)_2CH_2OH$]; ir (KBr) 3300–3500, 1780, 1660, 1600, 1530, 1300, 1250 cm^{-1}; nmr ($CDCl_3$) δ 8.2 (d, 1, NH), 7.8 (s, 1, NH), m at 7.2 (5, phenyl), 5.95 (dd, 1, J_1 = 5, J_2 = 10 Hz, H-6), 5.25 (d, 1, J = 5 Hz, H-5), 4.55 (s, 2, CH_2), 3.75, 3.95 (overlapping s, 3, CH_2,OH), 1.4, 1.3 (s, 6, CH_3).

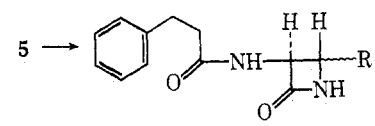
In a model reaction, compound 4 reacted with thiophenol in the presence of triethylamine to give a mixture of cis and trans (1:1) 3-(phenoxyacetamido)-4-phenylthio-2-azetidinone (6): 80%; ir (KBr) 3380, 1763, 1655, 1600, 1540; nmr (acetone-d_6) δ 8.1 (br s, 1, NH), m at 7.2 (11, aromatic and solvate), 5.65 (dd, ½, J_1 = 5, J_2 = 10 Hz, H-3 cis), 5.4 (d, ½, J = 5 Hz, H-4 cis), 5.2 (d, ½, J = 2 Hz, H-4 trans), 4.8 (m, ½, H-3 trans), 4.6 (2s, 2, CH_2).

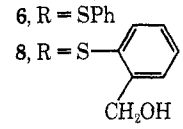
Azetidinones in which the nitrogen is substituted (7) do not react with mercaptans under these conditions. Also, if the mercaptan is sterically bulky the reaction is slow and the competing epimerization of H-4 becomes the dominant reaction route. Compound 5 reacted with isobutylmercaptan only very slowly (4 days) to give 3-(phenoxyacetamido)-4-*trans*-isobutylthio-2-azetidinone. *tert*-Butylmercaptan did not give the desired product at all; instead *trans*-5 was isolated.

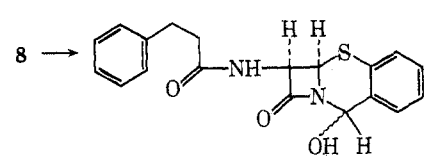


5

2, R = CO_2H
3, R = NCO
4, R = ~OH
7, R = $CO_2CH_2CH(CH_3)_2$



6, R = SPh
8, R = S– 



9

Reaction of 5 with *o*-mercaptobenzyl alcohol in the presence of triethylamine gave cis and trans (1:1) 3-(phenoxyacetamido)-4-(2-hydroxymethylphenylthio)-2-azetidinone (8): 78%; ir (CH_2Cl_2) 3300, 1755, 1690, 1540, 1500 cm^{-1}; nmr (acetone-d_6) δ 8.7-6.9 (m, NH and aromatic, 11), 5.75 (dd, ½, J_1 = 5, J_2 = 8 Hz, H-3 cis), 5.4 (d, ½, J = 5, H-4 cis), 5.2 (d, ½, J = 2, H_4 trans), 4.9 (2s, 2, CH_2), 4.7 (2s, 2, CH_2), 4.4 (dd, ½, J_1 = 2, J_2 = 7 Hz, H_3 trans), 3.7 (s, 1, OH); mp 140–142°; mass spectrum (70 eV) *m/e* 358 (M^+).

Oxidation of 8 with dimethyl sulfoxide and dicyclohexylcarbodiimide[5] gave, after column chromatography, compound 9: 20%; mp 148–150°; ir ($CHCl_3$) 3400, 1775, 1690, 1600, 1495 cm^{-1}; nmr ($CDCl_3$, cephem numbering) δ 8.0–6.9 (m, aromatic and NH), 6.0 (s, 1, H-4), 5.7 (dd, 1, J_1 = 5, J_2 = 8.5 Hz, H-7), 5.25 (d, 1, J = 5 Hz, H-6), 5.05 (s, 1, OH), 4.5 (s, 2, CH_2).

Compound 9 was tested for biological activity[6] and was shown to be active against *Diplococcus pneumoniae*, 0.4;