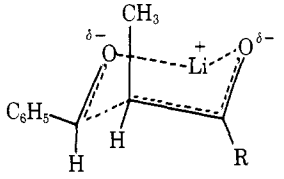
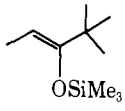
metal cation is chelated by the two oxygens of the reacting array. Kinetic stereoselectivity is maintained even when the condensation is carried out in the presence of large amounts of the highly ionizing solvent HMPT.[7]



I

The tetraalkylammonium enolate[8] derived from ketone **1** gives equally high but *opposite* kinetic stereoselectivity in its reaction with benzaldehyde. Thus, when an equimolar mixture of enol ether **6** and benzaldehyde is treated with a catalytic quantity (3–6 mol %) of benzyltrimethylammonium fluoride in THF at 25 °C for 2 h, the sole reaction product (52% isolated yield) is the silylated aldol **7**.[9]



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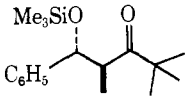
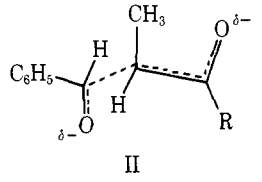


7

In the case of the tetraalkylammonium enolate, in which the cation cannot accept the two partially negative oxygens as ligands, we believe that a transition state such as that depicted in structure II is involved. In this case, to minimize electrostatic repulsion, the oxygens must be directed in generally opposite directions. Consequently, the enolate now attacks the other face of the carbonyl group.



II

Thus, by using a diastereomerically pure lithium enolate derived from a ketone in which one alkyl group is sterically demanding, one may achieve total diastereoselection in the aldol condensation. From a practical standpoint, *erythro* stereoselection is easily achieved with ketones in which one alkyl group is tertiary, such as ethyl *tert*-butyl ketone (**1**) or ethyl 1-adamantyl ketone, since these ketones yield only the (*Z*)-enolate on deprotonation with LDA at −72 °C. In some cases, *threo* stereoselection may be achieved by using tetraalkylammonium enolates derived from these same ketones.[9] *Threo* stereoselection may also be realized by using the lithium (*E*)-enolate. The only acyclic ketone we have studied which meets the two criteria of having a sterically demanding group bound to the carbonyl *and* an easily accessible (*E*)-enolate is ethyl mesityl ketone, which gives a kinetic enolate mixture containing 92% (*E*)-enolate.[10] We are currently exploring ways to extend this discovery to an equivalent of the Reformatsky reaction by creating a ketone such as **1** or **3** in which R is easily convertible to OH.[11]

Acknowledgments. Support for this work was provided by the National Science Foundation (Grant No. GP-31321X), and the United States Public Health Service (Grant No. AI-11607).

References and Notes

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(2) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
(3) Enolate composition is determined in an independent experiment by silylation with trimethylsilyl chloride.[4]
(4) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(5) Enolate diastereomer composition was varied by deprotonating with LDA in the presence of varying amounts of HMPT.[6]
(6) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
(7) The similarity of the hypothetical transition state depicted in structure I to that believed to intervene in pericyclic reactions such as the Diels–Alder reaction, ene reaction, and Cope rearrangement is striking. In fact, it is tempting to attribute the remarkable facility of the lithium enolate reaction to the stability of such an "aromatic" transition state.
(8) I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3257 (1975).
(9) Compound **7** is a true kinetic product. If the reaction is allowed to proceed for 15 h, the product isolated is a 2:3 mixture of **7** and its *erythro* counterpart. Unfortunately, this reaction appears to be of limited generality. In several systems we have examined, the product β-trimethylsilyloxy ketone appears to undergo elimination at a rate comparable to its rate of formation, resulting in the formation of the α,β-unsaturated ketone.
(10) Reaction of this enolate mixture with trimethylsilyl chloride affords a silyl enol ether mixture which may be fractionated through a spinning-band column to yield >98% pure (*E*)-silyl enol ether. Although we have not yet done the experiment, in principle this ether can be converted back to an enolate mixture of comparable purity.
(11) Attempts to perform Baeyer–Villiger oxidations and Beckmann rearrangements on aldols such as **2** and **4** have been unsuccessful.

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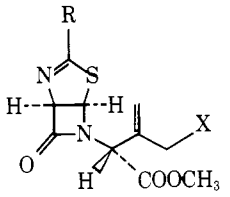
β-Lactam Antibiotics. Novel Synthetic Routes to Cephem-Ring System from β-Lactam Thiazolines via Hydrazinothioazetidinones

Sir:

Acid-catalyzed oxidative ring opening of **1c**[1-3] (X = H) with dimethyl azodicarboxylate (2–3 mol excess) and toluene-*p*-sulfonic acid (1 equiv) in 2% aqueous acetone (20 °C, 4–6 h) afforded **2c** (X = H), 80%: mp 133–135 °C.[4,5] Similarly hydrazinothioazetidinones, **2a, b, d** (X = H), were obtained from **1a, b, d** (X = H).[6] We suggest that this transformation proceeds through a transition state **4**, which undergoes hydrolytic cleavage to **2a–d.** An outstanding property of compounds **2a–d** (X = H)[7] is their tendency to be cleanly converted to deacetoxycephalosporins **3a–d** (80–85% yield) (X = H) by stirring the benzene solution with 30% aqueous KOH or with aluminum oxide at room temperature. This cyclization can be explained by an initial abstraction of the α proton and concomitant attack of the activated double bond on the sulfur atom, resulting in the formation of the C–S bond and of the six-membered ring system, as outlined in **2.** Alternatively, **2a–d** (X = H) were cyclized by treatment with *tert*-butyl hypochlorite (THF, −78 °C) to the corresponding 3-chlorocepham[8] (presumably via an intermediate sulfenyl chloride) which gave, by further dehydrohalogenation, the 3-cephem derivatives **3a–d** (X = H).

Compounds of formula **2a, b** (X = OAc) were obtained with a five-step procedure starting from thiazolines **1a, b** (X = H). Treatment of **1a–d** (X = H) with NBS and aluminum oxide (benzene, 20 °C, 20 h) yielded, almost quantitatively, the monobromides **5** and **6** in 70:30 ratio.[9] Alternatively bromine was quantitatively added to the isopropenyl double bond of **1c** (CH_2Cl_2, 30 min, 20 °C), in the presence of CaO, to give dibromide **28** (as a 1:1 mixture of two diastereoisomers) which was transformed into monobromides **5** and **6** by treatment with triethylamine or simply by passing through a silica gel bed. Monobromides **5** and **6** and dibromide **28** were quantitatively converted to monoacetates **7** and **8** by nucleophilic displacement with potassium acetate (acetone, 40 °C), the resulting mixture of *E*–*Z* isomers being separated either by column



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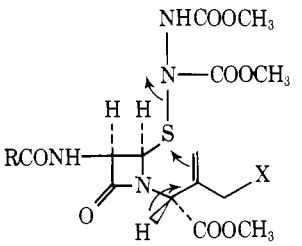

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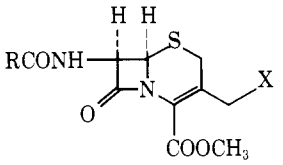

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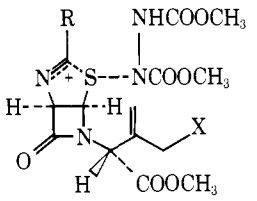

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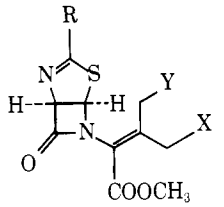
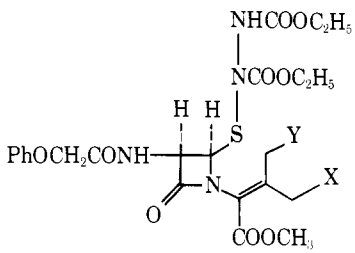
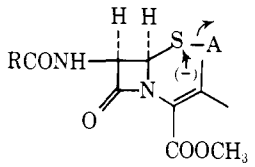


5, X = Br; Y = H
6, X = H; Y = Br
7, X = OAc; Y = H
8, X = H; Y = OAc
9, X = OAc; Y = Br
10, X = Br; Y = OAc
11, X = Y = H
12, X = OCH_3; Y = H
13, X = $OC(CH_3)_3$; Y = H

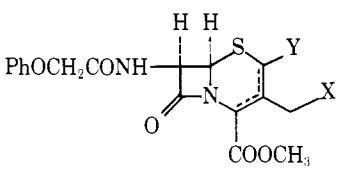
a, R = CH_3
b, R = $C(CH_3)_3$
c, R = CH_2OPh
d, R = CH_2Ph



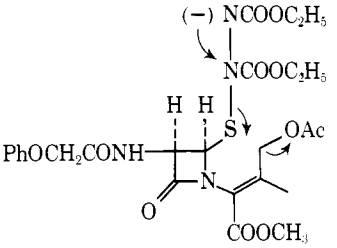
14, X = Y = H
15, X = OAc; Y = H
16, X = H; Y = OAc
17, X = OCH_3; Y = H
18, X = $OC(CH_3)_3$; Y = H



19



20, X = OAc; Y = H
21, X = H; Y = OAc
22, X = OCH_3; Y = H
23, X = H; Y = OCH_3
24, X = $OC(CH_3)_3$; Y = H



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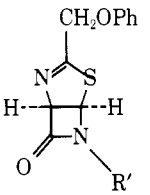
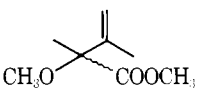
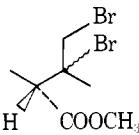


26, R′ = 

27, R′ = H

28, R′ = 

chromatography or by fractional crystallization. NBS bromination of **7a**,[10] **b** in refluxing benzene (10 min, 500-W tungsten lamp) afforded the bromoacetates **9a, b** (40-60% yield). Analogously **8a, b** gave **10a, b.** Reductive dehalogenation of both **9a, b** and **10a, b** with zinc-acetic acid (THF, 20 min, 0 °C) yielded the acetates **1a, b** (X = OAc) as a mixture of epimers having both natural and unnatural configuration at the carbon α to the carbomethoxy group.[3] The acid catalyzed ring opening of **1a, b** (X = OAc) with dimethyl azodicarboxylate afforded **2a, b** (X = OAc) (55% yield) as a mixture of epimers. Cyclization of **2a, b** (X = OAc) with potassium *tert*-butoxide (THF, 15 min, −78 °C) afforded **3a, b** (X = OAc) (30-40% yield) in mixture with their 2-cephem analogues.

This successful result prompted us to investigate the possibility of the cyclization of compounds **14–18** easily available from the corresponding azetidinonethiazolines **7, 8, 11, 12,** and **13.** Thus, treatment of **11c** with diethyl azodicarboxylate as described before afforded **14** (70% yield). Ring closure of **14** (THF, −78 °C) with **5** equiv of a strong base such as potassium *tert*-butoxide or lithium diisopropylamide, gave deacetoxycephalosporin **3c** (X = H)[11] as a mixture of Δ^2 and Δ^3 isomers in 40% yield. This reaction confirmed our views and represents to our best knowledge the first example of transformation of an azetidinone of general formula **19** into cephalosporins.[12] Additionally, **7** and **8** were separately transformed into the corresponding hydrazinothioazetidinones **15** and **16** (80% yield) which were cyclized affording a complex mixture of products[13] among which were cephalosporin, **20** (10% yield), 2-acetoxy-3-methylcephem, **21**[14] (15% yield), and deacetoxycephalosporin, **3c** (X = H). The proposed mechanism for the reductive closure to **3c** (X = H) is outlined in **25.** Moreover, compounds **5c** and **6c,** dissolved in the desired alcohol containing 2,6-lutidine (1 equiv) were treated with a solution of silver trifluoromethanesulfonate in diethyl ether (30 min, 0-20 °C) to give the corresponding alkoxymethyl ethers (*E* isomer only). When methanol was used, the expected compound **12c** (50% yield) and **26** (30% yield, probably arising from an allylic rearrangement of the intermediate carbocation) were obtained. Treatment of **5c** and **6c** with *tert*-butyl alcohol under the above conditions afforded **13c** (70% yield) and the azetidinone **27**[15] (10% yield) apparently arising from an unstable analogue of

26. Compounds **12c** and **13c** were then transformed into the corresponding hydrazinothioazetidinones **17** and **18.** Cyclization of **17** under the conditions described before, afforded **22**[16] (Δ^2 and Δ^3 mixture) in 20% yield and **23**[17] (Δ^3 isomer) in a very small amount. Instead, ring closure of **18** gave only the expected **24** (10% yield) with the corresponding Δ^2 isomer (20% yield). Synthesis of 3-thiomethyl-3-cephem derivatives from the bromides **5c** and **6c** is currently being investigated in our laboratories.

References and Notes

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(2) S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, **97**, 5008 (1975).
(3) In a parallel study, **1c** (X = H) gave deacetoxycephalosporin, **3c** (X = H), on treatment with iodine in THF containing 1% H_2O in the presence of mercuric oxide and α,α'-azoisobutyronitrile. M. Foglio, G. Franceschi, P. Masi, A. Suarato, German Offenlegungsschrift 2 534 811. See also R. G. Micetich and R. B. Morin, *Tetrahedron Lett.*, 279 (1976).
(4) Proofs of the assigned structures were obtained by mass spectral fragmentation and IR and NMR spectroscopy.
(5) The corresponding 3-methylcepham, apparently arising from a not oxidative side reaction involving an addition of the thiol intermediate to the isopropenyl double bond, was also isolated, 5% yield: mp 120–121 °C.
(6) Compound **1** (R = Ph, X = H) appeared not to undergo the ring opening reaction.
(7) Compounds **2** can be deacylated to the corresponding aminohydrazinothioazetidinones and reacylated to the desired acylamino analogues of **2,** thus extending the synthetic usefulness of these intermediates. M. Foglio, G. Franceschi, P. Masi, and A. Suarato, German Offenlegungsschrift 2 525 510.
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(9) Attributions according to: G. J. Martin and M. L. Martin, *Prog. NMR Spectrosc.*, **8,** 228 (1972).
(10) **7a** and **8a** were also prepared from **7c** and **8c** by hydrogenolysis (Zinc 90% acetic acid, 0°, 1.5 hr) of the phenoxymethyl side chain. M. Foglio, U. Scarponi, and F. Arcamone, German Offenlegungsschrift 2 540 309.
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(12) Very recently a similar cyclization affording the 3-methoxycephem nucleus has been reported: J. Gosteli, *Chimia*, **30,** 13 (1976).
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Free Radical Participation in the Reaction of Metalate Anions with Alkyl Halides[1]

Sir:

The displacement of halides and other groups from alkyl substrates by metalate anions represents one of the most important routes for the formation of metal-carbon σ bonds. The generally high stereoselectivity of these reactions has been widely interpreted as evidence against the intermediacy of free alkyl radicals and in favor of an S_N2 pathway.[2] Other studies, particularly those of Traylor[3] and Kuivila,[4] have suggested the possibility that certain carbon-metal bond-forming reactions, considered to take place by nucleophilic substitution, may proceed by other pathways. Here we wish to describe spectroscopic and chemical evidence establishing that the reaction of certain metalate anions with the more reactive alkyl halides proceeds in substantial part through the intermediacy of free alkyl radicals produced by electron transfer.[5,6]

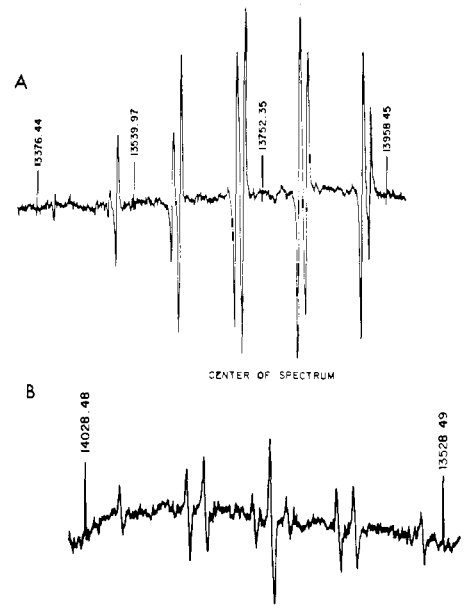

Figure 1. (A) ESR spectrum of the $(CH_3)_2CH$ radical (septet of doublets) obtained by reacting $CpFe(CO)_2Na$ with isopropyl iodide in THF. (B) ESR spectrum of the $CH_2{=}CHCH_2\dot{C}H_2$ radical (triplet of triplets) obtained by reacting $CpFe(CO)_2Na$ with cyclopropylcarbinyl iodide in THF. The proton NMR field markers are in kilohertz.

An intense ESR spectrum of isopropyl radicals (Figure 1a) can be detected by mixing at room temperature 0.1 M THF solutions of sodium cyclopentadienyl(dicarbonyl)iron, **2,** and isopropyl iodide in a flat mixing cell of simple design inserted into the ESR cavity so as to minimize the time between mixing and observation. The solutions were contained in 50–100-ml syringes and were driven by a dual syringe pump at a flow rate of about 9 ml/min. Radical concentration increased with increasing flow rates and concentrations of the starting solutions. Similar quality ESR spectra of ethyl, *n*-butyl, *sec*-butyl, and *tert*-butyl radicals were detected in reactions of **2** with the corresponding iodides under similar conditions. While the corresponding bromides and chlorides did not yield detectable concentrations of alkyl radicals, the more stable allyl and benzyl radicals were observed in the reactions of **2** with allyl and benzyl bromides, respectively.[7] Significantly, reaction of **2** with tropylium tetrafluoroborate in THF/acetonitrile gave rise to an intense spectrum of the tropyl radical. No ESR signals attributable to organometallic radical species were observed in the above reactions, presumably because of the combined effects of short lifetimes, low steady-state concentrations, and the broad line widths expected for such species.

The foregoing results are insufficient to establish the extent to which alkyl radicals participate in the principal product-forming reaction, although the high rates of generation required to produce detectable concentrations of such short-lived radicals argue against an insignificant role. Consequently, we have sought chemical evidence which would more quantitatively define the role of radical intermediates in these processes. Thus, the reaction of cyclopropylcarbinyl iodide, **1** (X = I), with sodium cyclopentadienyl(dicarbonyl)iron in THF at 0 °C, followed by an unexceptional workup, produces a 70:30 mixture of cyclopropyl- and allylcarbinyl(cyclopentadienyl)(dicarbonyl)iron, **3** and **4,** respectively, as ascertained by their characteristic H^1 NMR spectra.[8] If this reaction is carried out in the ESR cavity, the spectrum of the allylcarbinyl radical is observed (Figure 1b).[9] By contrast, the reaction of cyclopropylcarbinyl bromide with **2** yields, within the limits of detection (>3%), only **3.**[12]