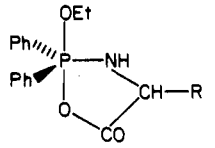
Gly-DL-Phe-Gly-OEt was isolated under specified conditions; instead, the pure L tripeptide was isolated in 70% yield. A carbodiimide coupling carried out in parallel provided an 8% yield of racemate. The test is said to be sensitive to as little as 1% racemization. This further suggests the proposed mechanism and is very encouraging as regards future applicability of our new method.

On the surface, our new coupling method is reminiscent of another amide-bond-forming process—the "phosphazo method"[17]—which employs trivalent P–N compounds (formed from the amine component and PCl_3) and unactivated carboxylic acids; however, this reaction suffers considerable racemization due to the apparent intermediacy of mixed anhydrides.[18] The phosphazo compounds therefore appear to function simply as dehydrating agents, in marked contrast to our method. Another unusual amide-forming reaction, possibly of greater relevance to the present work, is one reported by Mukaiyama, employing a sulfenamide, a phosphine, and a carboxylic acid.[19]

The sensitivity of the coupling to steric effects was tested as follows: a competition experiment was carried out by using the iminophosphorane derived from Ph_2POEt and ethyl azidoacetate, carrying out the coupling as usual but using 1 equiv each of Z-Gly and Z-L-Val. The resulting product mixture was found by NMR to contain 20.5% valine dipeptide and 79.5% glycine dipeptide. This gives a rate ratio of about 1:4 for valine vs. glycine. In comparable couplings using the *p*-nitrophenyl ester method the rate ratio is about 1:20 for these residues.[9] Thus, the present method exhibits about one-fifth the steric sensitivity of a traditional ester aminolysis, supporting the proposed intramolecular acyl transfer as the rate-determining step. It should be noted as well that the isolated yield obtained in a Z-Val coupling using this method was comparable (70%) to those obtained in other couplings (Table I).

Further strong support for our proposed mechanism was obtained by the successful synthesis and characterization of a stable amino(acyloxy)phosphorane in which the acyl transfer step is inhibited by incorporation of the reactive groups into a five-membered ring. Upon mixing equimolar amounts of ethyl diphenylphosphinite and DL-2-azido-3-methylbutanoic acid in ether solution, nitrogen was evolved and crystals of the adduct separated and were removed by filtration. The product **5a** (mp 100–120 °C dec) exhibited a ^{31}P chemical shift of −35.2 ppm (upfield from H_3PO_4); this is typical of pentacoordinate phosphorus compounds which generally exhibit large negative ^{31}P chemical shifts, and the value agrees well with that reported by Chaus and co-workers[20] for a similar amino(acyloxy)phosphorane.



5a, R = *i*-Pr
b, R = Me

The compound rearranged over a period of several weeks to a compound with a ^{31}P NMR singlet at +26.2 ppm. A similar adduct (**5b**) prepared by using DL-2-azidopropanoic acid (^{31}P NMR −39.6 ppm) rearranged with a half-life of approximately 4 h (product ^{31}P NMR +23.0 ppm). The reaction is probably ethylation of the carboxylate anion such as has been observed for adducts of trialkyl phosphites by Gusar' and co-workers.[21]

The above observations demonstrate that this new coupling reaction is a significant departure from previous methods in terms of the chemistry involved and consequently may represent a strategically useful alternative method of peptide coupling. The demonstration of such usefulness would in particular require the successful application to the coupling of large and/or sterically hindered peptide segments. A significant problem which remains is that nonpolar solvents such as toluene, which work well for the reaction, are generally not suitable for peptide work. The potential value of the new method justifies further investigations of this interesting reaction.

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(Phenylthio)nitromethane: A Convenient Reagent for the Construction of Bicyclic β-Lactams

Summary: 2-[(Phenylthio)carbonyl]-1-azabicyclo[4.2.0]-octan-8-one (**10**), 2-[(phenylthio)carbonyl]-1-azabicyclo-[3.2.0]heptan-7-one (**12**), and 3,3-dimethyl-2-[(phenylthio)carbonyl]-4-oxa-1-azabicyclo[3.2.0]heptan-7-one were prepared in high overall yields from monocyclic β-lactams **7**, **11a**, and **13** by using (phenylthio)nitromethane (**1**) as the key reagent for cyclization.

Sir: Recently we described that (phenylthio)nitromethane (**1**)[1] is a versatile reagent for the conversion of aldehydes into α-substituted *S*-phenyl thio esters.[2] For example, sequential reaction of acetaldehyde with **1** and KOH and MsCl–Et_3N according to the Miyashita procedure[3] gave **2**[4] (60%). This nitroalkene **2** reacted smoothly with potassium phthalimide in DMF followed by direct ozonolysis of the intermediate **3** in situ to produce **4** (68%). In ad-

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(4) Since our original publication, we have optimized the preparation of **2**. The reaction of MeCHO with **1** in the presence of KO-*t*-Bu (0.1 equiv) in THF: *t*-BuOH (1:1) at 0 °C followed by MsCl (3 equiv) and Et_3N (3 equiv) in CH_2Cl_2 at −78 °C gave **2** (≥89%).

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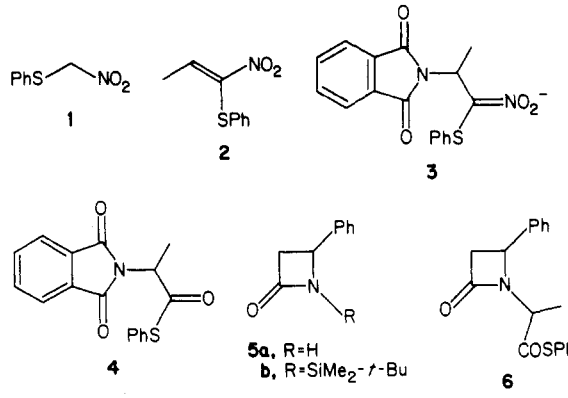
dition and in the same way **2** reacted smoothly with several nitrogen, oxygen, sulfur, and carbon centered nucleophiles to produce the corresponding α-substituted S-phenyl thio esters. In light of these observations and following the elegant Shibuya precedent,[5] we anticipated that **2** should be ideally suitable for the N-derivatization of β-lactams. Herein we report that (phenylthio)nitromethane (**1**) is indeed a useful reagent in β-lactam synthetic chemistry.

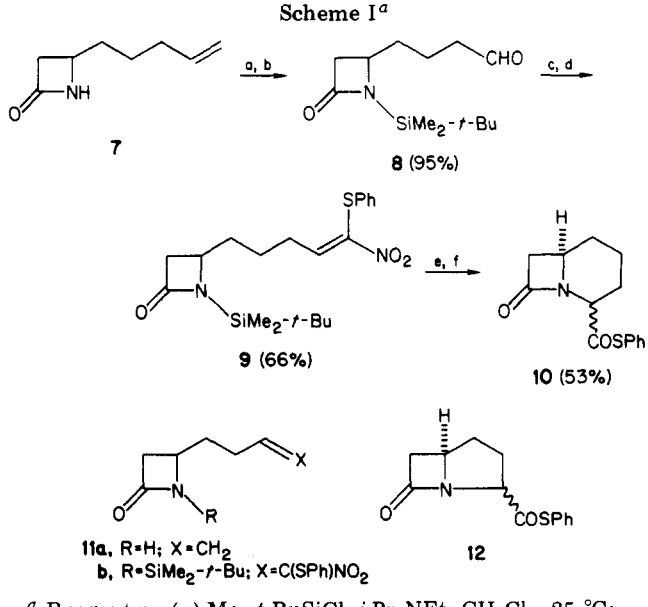
4-Phenyl-2-azetidinone[6] (**5a**) reacted smoothly with **2** (KO*t*-Bu–*t*-BuOH, THF) followed by ozonolysis in situ to produce **6**[7] (41%) as a mixture of diastereoisomers (1:1.3).



As an alternative procedure **5b** also reacted with **2** (*n*-$Bu_4N^+F^-$, THF) and ozone to produce the same diastereoisomeric mixture **6** (71%). The stability of the β-lactam ring on these model transformations was auspicious for extension to bicyclic β-lactam synthesis.

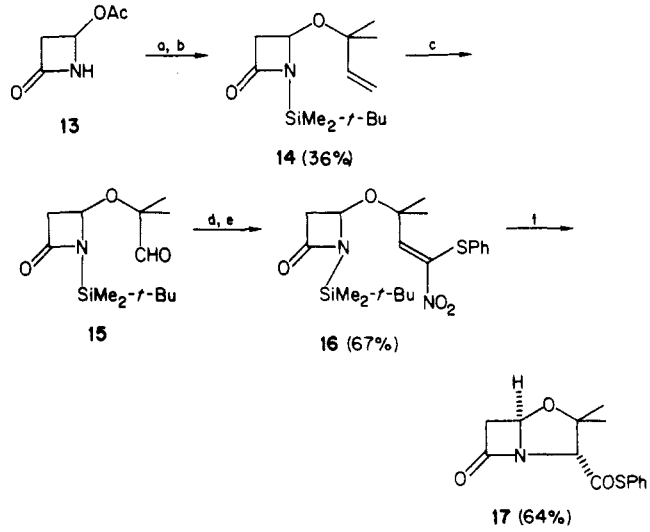
4-(4-Pentenyl)-2-azetidinone (**7**), which was prepared from 1,6-heptadiene and chlorosulfonyl isocyanate,[7] was converted into the nitroalkene **9** (Scheme I). This compound as with all other (phenylthio)nitroalkenes that we

Scheme I[a]



[a] Reagents: (a) Me_2-*t*-BuSiCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C; (b) O_3, CH_2Cl_2, −78 °C; Me_2S;[13] (c) $PhSCH_2NO_2$, *t*-BuOH, THF, *t*-BuOK (0.1 equiv), 0 °C; (d) Et_3N, $MeSO_2Cl$, −78 °C to 0 °C; (e) HF, C_5H_5N, CH_2Cl_2, −78 °C to 0 °C;[8] (f) *t*-BuOH, THF, *t*-BuOK (1 equiv), −30 °C; O_3, −78 °C, CH_2Cl_2.

Scheme II[a]



[a] Reagents: (a) $Me_2C(OH)CH{=}CH_2$, $Zn(OAc)_2 \cdot 2H_2O$, PhMe, 80 °C; (b) Me_2-*t*-BuSiCl, EtN-*i*-Pr_2, CH_2Cl_2, 25 °C; (c) O_3, CH_2Cl_2, −78 °C; Me_2S; (d) $PhSCH_2NO_2$, *t*-BuOH, THF, *t*-BuOK (0.1 equiv), 0 °C; (e) MsCl, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (f) Bu_4NF, THF, −55 °C; O_3, THF-CH_2Cl_2, −78 °C.

have prepared was obtained geometrically pure. Reaction of **9** with HF–pyridine in dichloromethane (N-desilylation[8]) followed by KO-*t*-Bu and ozone gave the corresponding bicyclic β-lactam **10**[10] (53%) as a mixture of diastereoisomers (1:1.1). This new β-lactam synthetic methodology was equally effective in the construction of the corresponding azabicyclo[3.2.0]heptane and oxadethiapenam ring systems. Thus, using an identical protocol, the known[8] β-lactam **11a** was converted into the (*Z*)-nitroalkene **11b** (72% overall). In THF solution **11b** was reacted with $Bu_4N^+F^-$ at −55 °C[10] followed by direct ozonolysis in situ (THF, CH_2Cl_2, −78 °C) to produce **12**[12] (83%) (β:α = 2.5:1 diastereoisomeric mixture). Under these conditions, desilylation, cyclization, and the oxidative Nef process were all taking place in the same reaction vessel. Since the

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undesirable β-epimers of both **10** and **12** were the kinetically preferred products we sought to establish conditions for epimerization. Thus warming of chromatographically pure β-**10** in THF containing *N,N*-diisopropylethylamine gave pure α-**10** (>95%). Finally 4-acetoxy-2-azetidinone (**13**)[14] was reacted with 2-methyl-3-buten-2-ol in the presence of zinc acetate in refluxing benzene[15] followed by *tert*-butyldimethylsilylation to produce **14** (36%). This was converted into **15** and subsequently **16** (67%) in the usual way. Cyclization of **16** proceeded smoothly in the presence of tetrabutylammonium fluoride and ozone to stereoselectively provide the oxadethiapenam **17**[15,16] (64%) accompanied by the C-2 epimer (14%).

The concise syntheses of **10**, **12**, and **17** using (phenylthio)nitromethane (**1**) are noteworthy in that the method is potentially of general utility in the construction of diverse bicyclic β-lactams containing the carboxylic acid moiety.[17] Both a detailed study of the stereochemistry of reaction and its extension to highly functionalized systems of biological interest are current objectives.

Acknowledgment. We thank the Atlantic Richfield Foundation, Northwestern University, and Pfizer Central Research for generous support.

Registry No. **1**, 60595-16-6; **2**, 69477-87-8; **3**, 96746-22-4; **4**, 92339-69-0; **5a**, 5661-55-2; **5b**, 96746-23-5; **6** (isomer 1), 96746-24-6; **6** (isomer 2), 96746-25-7; **7**, 96746-26-8; **8**, 96746-27-9; **9**, 96746-28-0; **10** (isomer 1), 96746-29-1; **10** (isomer 2), 96746-30-4; **11a**, 74373-13-0; **11b**, 96746-31-5; **12** (isomer 1), 96746-32-6; **12** (isomer 2), 96746-33-7; **13**, 28562-53-0; **14**, 96746-34-8; **15**, 96746-35-9; **16**, 96746-36-0; **17** (isomer 1), 96746-37-1; **17** (isomer 2), 96746-38-2; potassium phthalimide, 1074-82-4; acetaldehyde, 75-07-0; 1,6-heptadiene, 3070-53-9; 2-methyl-3-buten-2-ol, 115-18-4.

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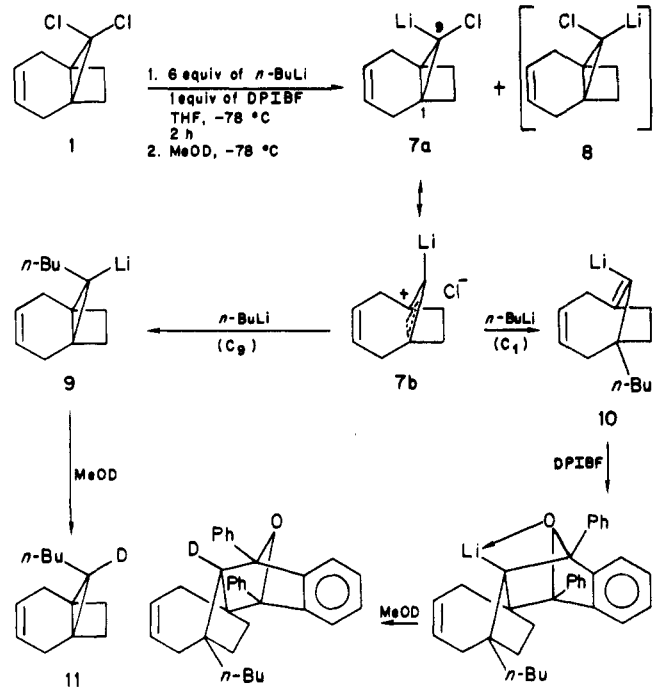
Electrophilic Carbenoids. Formation and Trapping of an Anti-Bredt Vinyllithium

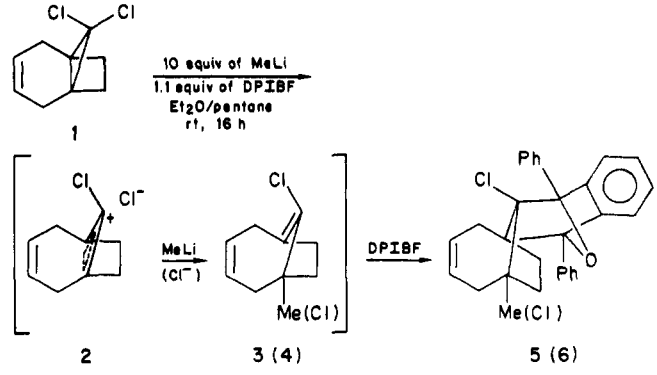
Summary: The reaction of 9,9-dichloro[4.3.1]propell-3-ene (**1**) with excess *n*-BuLi produces a lithium carbenoid which shows exceptional electrophilic reactivity, which includes reaction via cationic ring-opening to afford an anti-Bredt vinyllithium intermediate, **10**.

Sir: We[1] and others[2] have been intensely interested in the properties of bridgehead alkenes. The twisted π-bond structure thereby demanded might be stabilized by the polarizing effect of a lithium substituent. Calculationally,[3] two geminal lithiums lead to energetic equality between the planar and perpendicular olefin structural alternatives, while one lithium leads to a substantial decrease in the π-bond rotation barrier.[3b] Our studies[4] of the electrophilic behavior[5,6] of lithium cyclopropylidenoids has led to a particularly poignant example, which we now report.

When **1**[1i] was treated with excess MeLi in the presence of diphenylisobenzofuran (DPIBF) at room temperature, a slow reaction occurred. Apart from dimers,[1i] the only

Scheme I





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