Table I. Yields of Thiols from Dithio Esters and Diorganocuprates

substrate	cuprate	product	% yield[a] in ether (THF) cuprate precursor			
			CuCN	$CuBr{\cdot}SMe_2$	CuI	$(CuO_3SCF_3)_2C_6H_6$
1[b]	Me_2CuLi	3[c]	96 (47)	98 (87)	100 (86)	98 (84)
1	Bu_2CuLi	4[d]	93 (88)	92[e] (39)	87[e] (26)	91 (94)
1	Ph_2CuLi	5[f]	91 (44)	85[e] (67)	44 (66)	97[e] (39)
2[g]	Me_2CuLi	6[h]	66 (50)	88 (70)	84 (72)	88 (56)

[a] Yields were determined by GLC calibrated with authentic products and internal standards. Unless noted otherwise (see *e*) the reactants (1.0 mmol) were mixed at 0 °C and stirred at 0 °C for 1 h. All reactions were ~0.1 M. [b] Methyl dithiopropionate. [c] 2-Methyl-2-butanethiol. [d] 5-Ethyl-5-nonanethiol. [e] The reactants were mixed at −78 °C and then stirred at 0 °C for 1 h. [f] 1,1-Diphenyl-1-propanethiol. [g] Methyl dithiobenzoate. [h] α,α-Dimethylbenzyl mercaptan.

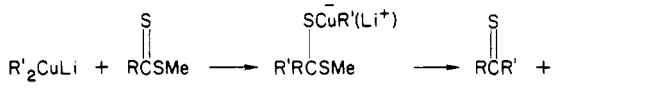
Table II. Yields of Thiols from Dithio Esters and Magnesium Organocuprates

substrate	Grignard	product	% yield[a]	
			stoich.	catalytic
1	MeMgBr	3	85	96
1	BuMgBr	4	16	80
1	PhMgBr	5	77	83
2	MeMgBr	6	71	23

[a] See note *a* of Table I.

transfer mechanism has been proposed for the reaction of organocuprates with α,β-unsaturated ketones,[6] and we note that Cu(I) changes the selectivity of Li and Mg reagents toward dithio esters (from thiophilic to carbophilic attack) just as it changes the selectivity of these reagents toward α-enones (from 1,2- to 1,4-addition). We chose **1** for study because its reduction potential (−1.43 to −1.78V, SCE)[7] is in the range of α-enone reduction potentials (−1.4 to −2.3V) noted by House for the successful conjugate addition of organocuprates.[6] The reduction potential of **2** (−1.11 to −1.34V, SCE)[7] is above that noted for conjugate addition. Clearly, the reduction potential of the substrate is not the only factor determining reactivity. We believe complexation between dithio ester and Cu(I) to be important in this reaction, so that electron transfer, if it does occur, is an "inner sphere" process. Alternatively, complexation of S by Cu could activate the C=S bond to direct nucleophilic attack at C. Thiocarbonyl S–Cu(I) bonding has been well-characterized crystallographically.[8]

Whether it is due to electron transfer or direct nucleophilic attack, the first step involves the carbophilic addition of R′ to the dithio ester followed by the loss of methanethiolate from the tetrahedral intermediate to generate the thioketone and a (methylthio)cuprate (eq 2). Reaction



$$R'_2CuLi + RC(=S)SMe \longrightarrow R'RC(SCuR'(Li^+))SMe \longrightarrow RC(=S)R' + R'C\bar{u}SMe(Li^+) \quad (2)$$

of the thioketone with the (methylthio)cuprate then completes the process, except for the hydrolysis step. Posner and co-workers have shown than (phenylthio)- and (*tert*-butylthio)cuprates are highly reactive,[9] and we find the same is true of (methylthio)cuprates. Thus, 2.0 equiv of MeCu(SMe)Li converts **2** to **6** in virtually quantitative yield (vide supra). In addition, thiobenzophenone (**7**) is converted to **5** by either EtCu(SMe)Li (95%) or Et_2CuLi from any of the precursors studied. These experiments and the observation of "carbophilic–thiophilic" products (vide supra) establish the plausibility of (Cu-bound) thioketones as intermediates.

In summary, the reaction of organocuprates with dithio esters proceeds via a novel sequence of carbophilic additions. Furthermore, considering the high yields obtained and the fact that two C–C bonds are formed in a single step, this new reaction appears synthetically promising as well as mechanistically interesting.

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Supplementary Material Available: Experimental details for 5-ethyl-5-nonanethiol, a representative example (1 page). Ordering information is given on any current masthead page.

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Carbene and Silicon Routes toward a Simple Nitrile Ylide. Spectroscopic, Kinetic, and Chemical Characterization

Summary: The generation and characterization of methyl nitrile ylide photochemically by addition of singlet methylene to acetonitrile and chemically from a silylthioimidate and subsequent dipolar cycloaddition are carried out.

Sir: One of the more interesting members of the 1,3-dipole family is the nitrile ylides.[1-5] Although a variety of methods are available for the preparation of aryl-substituted nitrile ylides,[6-9] these techniques are not generally suitable for the synthesis of simple alkyl-substituted systems. In searching for alternate ways to form these dipoles, we have discovered two new and potentially general routes for nitrile ylide formation. Generation of an intermediate

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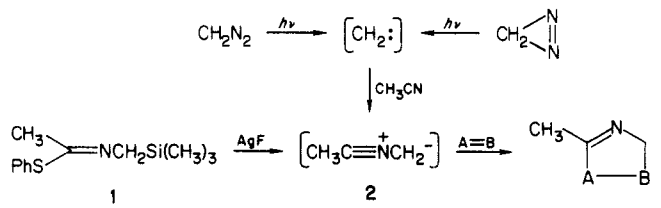
Table I. Relative Rates for Cycloaddition Reactions of Methyl Nitrile Ylide (2)

quencher	k_q (M^{-1} s^{-1})	k_{rel} (time resolved)[a]	k_{rel} (product analysis)[b]
fumaronitrile	$(2.2 \pm 0.1) \times 10^9$	$(3.9 \pm 0.3) \times 10^2$	$(4.3 \pm 0.6) \times 10^2$
dimethyl acetylenedicarboxylate	$(1.5 \pm 0.1) \times 10^8$	27 ± 2	42 ± 10
acrylonitrile	$(5.6 \pm 0.2) \times 10^6$	1.0	1.0
methyl acrylate	$(3.3 \pm 0.1) \times 10^6$	0.6 ± 0.1	0.7 ± 0.1
methyl propiolate	$(4.4 \pm 0.3) \times 10^5$	0.08 ± 0.01	0.10 ± 0.01

[a] Relative rate constants from time-resolved laser flash analysis of quenching of 2 in air-saturated acetonitrile at 25 °C. [b] Relative rates from product ratios produced in steady state photolysis in air-saturated acetonitrile solutions at 0 °C.

Scheme I



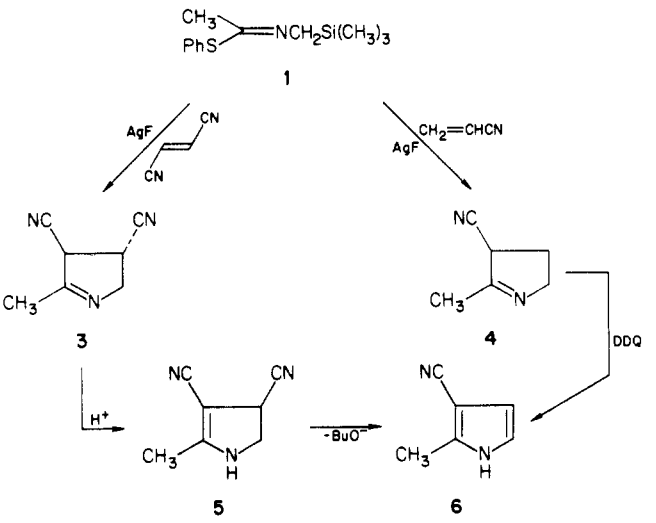
having nitrile ylide reactivity was achieved from the photolysis of diazomethane or diazirine in acetonitrile.[10,11] The 1,3-dipole formed in this manner has been trapped by a variety of dipolarophiles and has also been characterized by time-resolved laser spectroscopy. An alternate route to the same dipole involves desilylation of an appropriately substituted nitrilium cation. Thus, phenyl thiosilylimidate 1 serves as a convenient nitrile ylide precursor and undergoes smooth dipolar cycloaddition with a variety of dipolarophiles in the presence of silver fluoride according to Scheme I.

Pulsed excimer laser photolysis of diazomethane or diazirine (308 nm, ca. 10 MJ, 10^{-8} s HWFM) produces a transient absorption with λ_{max} at 280 nm. This transient is assigned as methyl nitrile ylide (2) on the basis of (1) analogy to the absorption spectra of related dipoles,[10] (2) isolation of dipolar cycloadducts when the steady state photolysis is conducted in the presence of a dipolarophile, and (3) the excellent agreement of the relative magnitude of the absolute rate constants for quenching of the 280-nm transient and the relative ratio of cycloaddition products produced by trapping experiments (Table I).

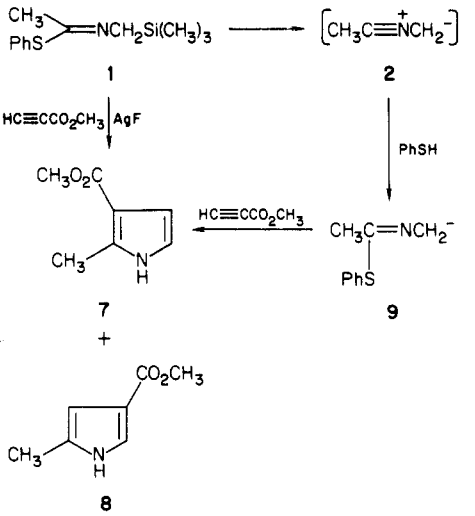
We conclude that methyl nitrile ylide (2) is formed by the addition of singlet methylene to acetonitrile.[11]

It was of interest to compare the results for the preparation of nitrile ylide 2 by the "carbene" route to those of production of 2 by an alternate method. We found that silylthioimidate 1 could be prepared in multigram quantities by heating equimolar quantities of acetonitrile and (trimethylsilyl)methyl triflate at 70 °C followed by quenching with thiophenol. Treatment of acetonitrile solutions of 1 with acrylonitrile, fumaronitrile, dimethyl fumarate, benzaldehyde, or dimethyl acetylenedicarboxylate with a slight excess of silver fluoride at 25 °C results in cycloadducts of identical structure with those produced by the carbene route. The structures of the cycloadducts were characterized by their conversion to pyrroles which were prepared by independent syntheses (Scheme II).

Scheme II



Scheme III



Although these results suggest the commonality of methyl nitrile ylide (2) as an intermediate via the carbene or silicon route, the ratio of the regioisomeric cycloadducts (i.e., 7 and 8) derived from methyl propiolate via the two methods differed. For example, the ratio of pyrroles produced from the carbene route (1:1) was slightly different from that obtained from silylimidate 1 (7:8 = 2:3). Most importantly, the ratio of the cycloadducts was found to be strikingly dependent on the purity of silylthioimidate 1. Thus, the ratio of pyrroles 7 and 8 (Scheme III) changed from 2:3 to 9:1 when an aged sample of 1 was used.[12] We propose that the different product ratios result from the operation of an alternate mechanism which involves the thiophenol that is released in the decomposition of silylthioimidate 1 to nitrile ylide 2. Most likely, the initially

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(12) Aged samples of silythioimidate 1 undergo hydrolysis to give the corresponding amide and thiophenol.

generated dipole **2** reacts with excess thiophenol to give carbanion **9** which then undergoes conjugate addition to the activated acetylene. Further support for this proposal will be presented in our full manuscript.

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Registry No. 1, 92925-16-1; 2, 98587-57-6; 7, 3168-85-2; 8, 40611-76-5; CH_2N_2, 334-88-3; MeOC(O)C≡CC(O)OMe, 762-42-5; PhCHO, 100-52-7; CH_3CN, 75-05-8; $Me_3SiCH_2OSO_2CF_3$, 64035-64-9; PhSH, 108-98-5; (*E*)-PhSCH=CHC(O)OMe, 49833-37-6; (*Z*)-PhSCH=CHC(O)OMe, 49833-38-7; (*Z*)-MeOC(O)CH=C(SPh)C(O)OMe, 59790-38-4; (*E*)-MeOC(O)CH=C(SPh)C(O)OMe, 59790-39-5; $CH_3C(O)NHCH_2CH(OH)Ph$, 3306-05-6; $NH_2CH_2CH(Ph)OH$, 7568-93-6; $CH_3C(OEt)_3$, 78-39-7; HCHO, 50-00-0; 3*H*-diazirine, 157-22-2; fumaronitrile, 764-42-1; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; methyl propiolate, 922-67-8; dimethyl fumarate, 624-49-7; *N*-[(trimethylsilyl)methyl]acetonitrilium triflate, 98587-59-8; *N*-benzyl-3-carbomethoxy-2-methyl-1*H*-pyrrole, 87281-49-0; 2-methyl-4-carbethoxy-1*H*-pyrrole, 2199-50-0; 2-methyl-3,4-dicarbomethoxy-1*H*-pyrrole, 90610-59-6; 4,5-dihydro-2-methyl-5-phenyloxazole, 66614-71-9; 2,5-dihydro-4-methyl-5-phenyloxazole, 98587-60-1; 4-methyl-5-phenyloxazolidine, 42794-92-3; (±)-norephedrine, 14838-15-4.

Supplementary Material Available: Experimental details of preparation and reaction of silylthioimidate **1** (8 pages). Ordering information is given on any current masthead page.

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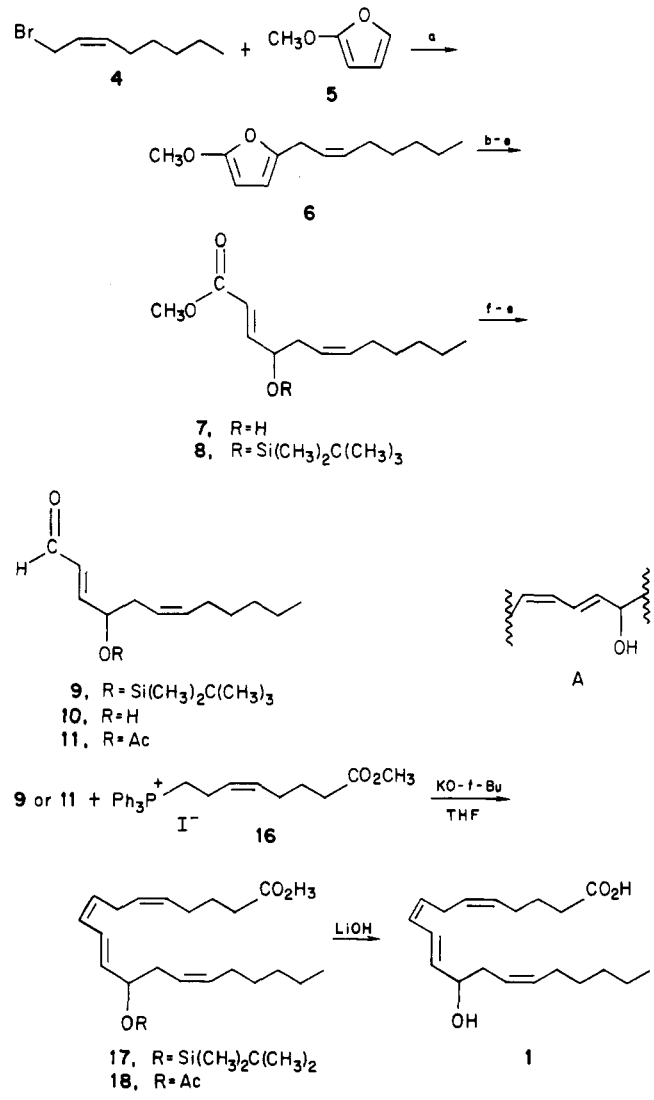
Total Synthesis of (±)-12-Hydroxy-5(*Z*),8(*Z*),-10(*E*),14(*Z*)-eicosatetraenoic Acid (12-HETE)

Summary: A total synthesis of 12-HETE is reported which incorporates an oxidative cleavage of an appropriately substituted furan to provide a functionalized *trans*-allylhydroxy fragment which is subsequently elaborated in an operationally simple manner affording a practical preparation of 12-HETE.

Sir: The monohydroxyeicosatetraenoic acids (HETEs) have been the focus of intense investigation due to the interesting and varied biological activities they exhibit. In particular, 12-HETE (**1**) is the major lipoxygenase product found in human platelets[1] and has been demonstrated to be present in high levels in epidermal tissue of patients with psoriasis.[2] In connection with an ongoing effort in our laboratories to study the lipoxygenase enzymes, a ready supply to the various HETEs was required. Synthetic studies of the various HETEs have been reported.[3] An efficient practical synthesis of 5-HETE[4] and an enzymatic preparation of 15-HETE[5] provide convenient access to these important natural products. Our interest in securing significant quantities of 12-HETE led us to explore alternative synthetic approaches. The total synthesis of 12-HETE (**1**), reported herein, illustrates a general and

Scheme I[a]



[a] (a) *t*-BuLi (1.1 equiv), THF, **4** (1 equiv), −50 °C, 1 h, 73%; (b) bipyridinium chlorochromate (5 equiv), CH_2Cl_2, room temperature, 2.5 h; (c) I_2 (0.15 equiv), ether, room temperature, 4 h; (d) $NaBH_4$ (1 equiv), MeOH, 0 °C, 15 min; (e) TBDMSCl (1.1 equiv), imidazole (2.2 equiv), DMF, 50 °C, 2.5 h, 42% (over four steps); (f) DIBAL (2 equiv), CH_2Cl_2, −78 °C, 5 min; (g) pyridinium chlorochromate (2 equiv), CH_2Cl_2, room temperature, 2.5 h, 57% (over two steps); (h) 48% HF, CH_3CN, 2 h, room temperature, 83%; (i) Ac_2O (2 equiv), pyridine, room temperature, 4 h, 85%.

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