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A CONVENIENT SYNTHESIS OF O-ALKYL THIOESTERS FROM ESTERS

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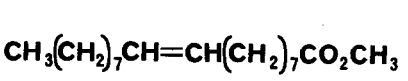
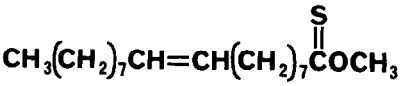
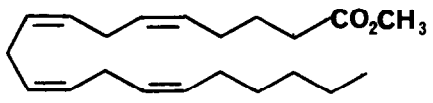
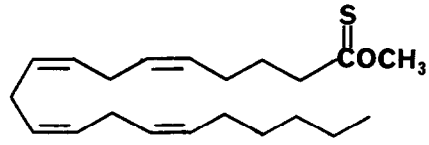
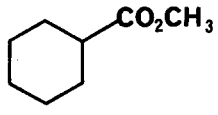
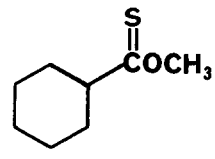
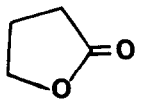
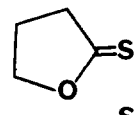
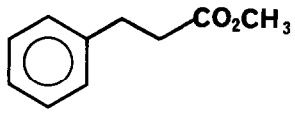
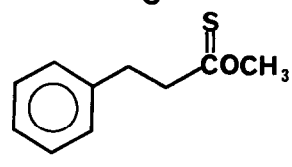
Summary: O-Alkyl thioesters may be prepared from the corresponding carboxylic esters by successive treatment with lithium diisopropylamide, chlorotrimethylsilane, and hydrogen sulfide.

Few methods exist for the preparation of thioesters that do not involve carbon chain homologation.[1] During the course of recent synthetic work, it was desired to prepare a series of polyunsaturated thioesters from the corresponding carboxylic esters and in consequence a method for the direct conversion of esters to thioesters was developed as reported herein.

In a typical small scale experiment, the appropriate ester (3 mmol) was dissolved in 15 ml of tetrahydrofuran and treated at -78° with 1.1 equiv of lithium diisopropylamide with stirring under argon. After 5 min the mixture was quenched with 1.2 equiv of chlorotrimethylsilane. After 10 min at -78° the solution was allowed to warm to 0° and was maintained at 0° while dry hydrogen sulfide[2] was gently passed through the mixture until it was saturated with the gas. The sealed flask was then stirred at 25° until the reaction was complete, as determined by tlc analysis. The product was isolated by evaporation of the tetrahydrofuran followed by treatment of the residue with ether and water, extraction of the ether with additional water, drying, evaporation of the ether and chromatography. The results of representative experiments are summarized in the Table.

Thiono esters are useful intermediates for a number of synthetic purposes. In connection with the development of inhibitors of leukotriene biosynthesis we wished to study arachidonic acid thiohydroxamate as a potential inhibitor. The required hydroxamate derivative was readily prepared in high yield from methyl thionoarachidonate by reaction with 2 equiv of hydroxylamine hydrochloride and 2 equiv of sodium methoxide in methanol at 23° for 3 hr.[3] The arachidonic acid thiohydroxamate forms a tight complex with ferric ion (deep indigo color in ethanol) and also is a strong competitive inhibitor of the arachidonate 5-lipoxygenase from rat basophilic leukemic cells (EC_{50} 2.0 μM at 7 μM arachidonate).[4]

TABLE

Ester	Product[a]	Yield[b]
		89%
		83%
		73%
		48%[5]
		75%

[a] All products gave satisfactory spectral data on purified and homogeneous samples.

[b] All yields refer to isolated product.

References and Notes

1. J. Meijer, P. Vermeer, L. Brandsma, Rec. Trav., 92, 601 (1973).
2. Hydrogen sulfide was dried by passage through a drying tube filled with phosphorus pentoxide.
3. W. Walter and E. Schamann, Synthesis, 111 (1971).
4. This work was assisted financially by a grant from the National Institutes of Health.
5. This compound has been prepared previously in excellent yield by a two-step process from γ-butyrolactone. See M. K. Kaloustian and F. Khouri, Tetrahedron Letters, 22, 413 (1981).

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