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PREPARATION OF ALKENYL SULFIDES AND ENAMINES BY ALKYLIDENATION OF CARBOXYLIC ACID DERIVATIVES

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Abstract: Treatment of S-alkyl thioesters with a reagent prepared from $RCHBr_2$, Zn, $TiCl_4$, and TMEDA in THF at 25°C gives Z-alkenyl sulfides selectively in good to excellent yields. Using the alkylidenation method, ketene dithioacetals and enamines are produced from 1,3-dithian-2-one and amides, respectively.

The Wittig reaction using alkylidenetriphenylphosphorane is a well established method for regioselective construction of a carbon-carbon double bond from a carbonyl compound.[1] Although many good examples of the reagent are seen in the literature, there are still some limitations. One of the notable restrictions is that it does not normally proceed with the carbonyl groups of carboxylic acid derivatives such as esters and amides.[2,3] We have recently reported that the reagent derived from 1,1-dibromoalkane, zinc, $TiCl_4$, and tetramethylethylenediamine (TMEDA) is effective for alkylidenation of carboxylic acid esters.[4a] The reaction provides a route to Z-alkenyl ethers from esters under high stereocontrol. Application to silyl esters has provided fruitful results.[4b] Here, we disclose stereoselective preparation of S-alkenyl sulfides and E-enamines by the alkylidenation approach.

Z-Alkenyl Sulfides Alkenyl sulfides play an important role in organic synthesis, particularly as masked carbonyl compounds.[5] Many methods for their preparation have been reported, however, it is still difficult to prepare the sulfides in a regio- and stereoselective manner, especially in the case of trisubstituted ones.[6] Regio- and stereoselective alkylidenation of S-alkyl thioesters described here provides a solution to this problem.

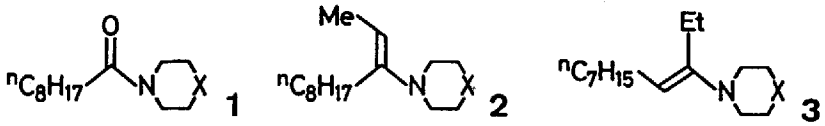
The results are shown in Table 1. Z-Alkenyl sulfides were produced selectively in all cases, as the preparation of alkenyl ethers from esters with the same system.[4] S-Phenyl thioesters also gave the desired alkenyl phenyl sulfides (runs 2, 6, and 10), but the reaction rates were slower and the yields were somewhat lower than those with S-methyl thioesters.

In contrast to alkylidenation of α,β-unsaturated esters which gives oxy-substituted conjugated dienes,[4] treatment of an α,β-unsaturated thioester, S-methyl E-3-phenyl-2-propenethioate, with the reagent resulted in formation of several products which did not contain the desired thio-substituted conjugated dienes.

A carbonyl group bearing two alkylthio-substituents was also subjected

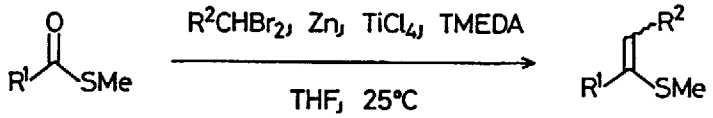
to this transformation. Synthetically useful ketene dithioacetals[7] were produced directly from 1,3-dithian-2-one[8] as shown in Table 2. As the produced dithioacetals are labile to acids and easily polymerized at high temperature, the crude products were purified by distillation under vacuum with a small amount of hydroquinone.[7e]

E-Enamines Amides are also converted to enamines[9] with the reagent as shown in Table 3. In contrast to the case of esters or thioesters, amides gave E-enamines selectively, except for the case of N-(cyclohexylcarbonyl)-piperidine (run 6). The E/Z ratios of products by the alkylidenation reagent are affected by the steric factor of the substituents on carbonyl group.[4] Thus, N-(cyclohexylcarbonyl)piperidine, where both substituents cyclo-C_6H_{11} and $C_5H_{10}N$ are of almost the same size, gave a 1 to 1 mixture of the stereo-isomers. In the case of primary-alkylcarboxamides 1, two regioisomers 2 and 3 (2a/3a=54/46, 2b/3b=53/47) were produced due to isomerization of the initially formed 2 via iminium salts (run 4 and 5).



a: X=CH_2 b: X=O

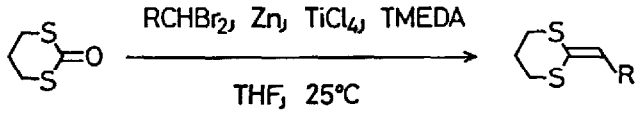
Table 1. Preparation of alkenyl methyl sulfides from S-methyl thioesters[a]



Run	R^1	R^2	Time/min	Yield/%[b]	Z/E[c]
1	Ph	Me	30	77	80/20
2			420	56[d]	82/18
3		^{n}Bu	60	75	84/16
4		$PhCH_2$-	80	80	81/19
5	$^nC_8H_{17}$-	Me	20	94	73/27
6			300	71[d]	68/32
7		$PhCH_2$-	30	87	90/10
8		$^cC_6H_{11}$-	30	95	82/18
9	$^cC_6H_{11}$-	Me	20	88	94/6
10			180	79[d]	91/9
11		$PhCH_2$-	30	95	100/0
12		$^cC_6H_{11}$-	20	97	100/0

a) S-Methyl thioester (1.0 mmol) was treated at 25°C with a reagent derived from 1,1-dibromoalkane (2.2 mmol), zinc (9.0 mmol), $TiCl_4$ (4.0 mmol), and TMEDA (8.0 mmol) in THF. b) Isolated yields. c) The Z/E ratios were determined by ^{1}H NMR analysis. d) S-Phenyl thioesters were used instead of S-methyl ones.

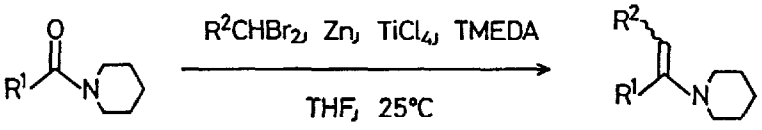
Table 2. Preparation of ketene dithioacetals[a]



Run	R	Time/min	Yield/%[b]	Bp/°C(Torr)[c]
1	Me	20	72	89-91 (4)
2	^{n}Bu	45	76	128-130 (4)
3	$PhCH_2$-	30	87	150-152 (0.2)
4	$^{c}C_6H_{11}$-	75	86	125-127 (0.2)

a) Treatment of 1,3-dithian-2-one (1.0 mmol) with a reagent derived from 1,1-dibromoalkane (2.2 mmol), zinc (9.0 mmol), $TiCl_4$ (4.0 mmol), and TMEDA (8.0 mmol) gave the ketene dithioacetal. b) Isolated yields after distillation. c) Bath temperature.

Table 3. Preparation of enamines from amides[a]



Run	R^1	R^2	Time/h	Yield/%[b]	E/Z[c]
1	Ph	Me	3	70	98/2
2		^{n}Bu	3	80	96/4
3		$PhCH_2$-	3	87	>99/<1
4	$^{n}C_8H_{17}$- (1a)	Me	2	79[d]	>99/<1[e]
5	(1b)		2	72[d]	>99/<1[e]
6	$^{c}C_6H_{11}$-		18	82	53/47

a) The amide (1.0 mmol) was treated at 25°C with a reagent derived from 1,1-dibromoalkane (2.2 mmol), zinc (9.0 mmol), $TiCl_4$ (4.0 mmol), and TMEDA (8.0 mmol) in THF. b) Isolated yields. c) The Z/E ratios were determined by ^1H NMR analysis. d) See text. e) Both regioisomers show high E-selectivities.

Typical Procedure for Alkylidenation: A solution of $TiCl_4$ (1.0 M, 4.0 mmol) in dichloromethane is added at 0°C to THF (10 mL) under an argon atmosphere. To the yellow solution at 25°C is added TMEDA (1.2 mL, 8.0 mmol) and the mixture is stirred at 25°C for 10 min. Zinc dust (0.59 g, 9.0 mmol) is added and the resulting mixture is stirred at 25°C for 30 min. The color of the suspension turns from brownish yellow to dark greenish blue in a slightly exothermic process. A solution of S-methyl thioester (1.0 mmol) and 1,1-dibromoalkane[10] (2.2 mmol) in THF (2 mL) is added to the mixture, and the color gradually turns dark brown. After being stirred at 25°C for 20-80 min, the reaction mixture is cooled to 0°C and sodium methoxide (0.22 g, 4.0 mmol) is added. After being stirred at 0°C for another 15 min, the mixture is

diluted with ether (10 mL) and then passed rapidly through a short column of silica gel. The resulting clear solution is concentrated and the residue is purified by column chromatography on silica gel using hexane-ethyl acetate. Enamines and ketene dithioacetals are prepared as mentioned above and are purified by distillation under reduced pressure after addition of NaOMe (K_2CO_3 in the case of ketene dithioacetals) and filtration of the mixture with Hyflo Super-Cel^R.

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