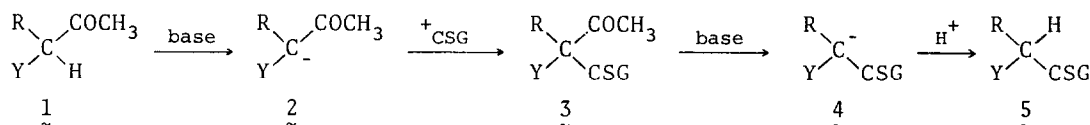


A NOVEL METHOD FOR PREPARATION OF  
 2-(METHYL- OR PHENYLTHIO)ALKANOIC ESTERS

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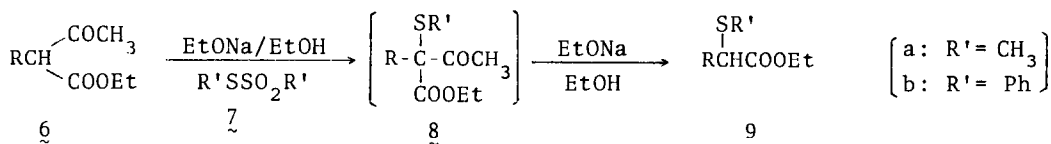
*Abstract: Ethyl 2-acetylalkanoate gave ethyl 2-(methyl- or phenylthio)alkanoate in high yield on treatment with  $\text{CH}_3\text{SSO}_2\text{CH}_3$ ,  $\text{PhSSO}_2\text{Ph}$ , or  $\text{PhSSPh}$  in the presence of small excess of EtONa in EtOH. Application of the present method to synthesis of pellitorine and the queen substance is also described.*

Acetyl group is well known to stabilize an adjacent carbanion and to be easily removable by treating with an alkoxide anion. Hence, a carbanion-stabilizing group (CSG) can be introduced into an acetyl compound (1) *via* the corresponding carbanion (2) and the thus-obtained product (3) is thought to undergo more easily deacetylation than 1. If an alkoxide can be utilized as the common base for the carbanion formation (1 + 2) and the deacetylation (3 + 5), apparently a direct conversion of 1 to 5 will be possible.



In order to realize this possibility, we have investigated thiolation of 2-acetylalkanoic esters (6), and we now wish to report a new and efficient method for preparation of 2-(methyl- or phenylthio)alkanoic esters (9), which have proven to be of considerable value in synthesizing 2-alkenoic acids (or their esters), aldehydes, ketones, and epoxides.<sup>1</sup>

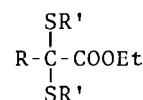
First, we have found that 6<sup>2</sup> affords 9 on treatment with  $\text{CH}_3\text{SSO}_2\text{CH}_3$  (7a) or  $\text{PhSSO}_2\text{Ph}$  (7b) in the presence of excess EtONa in EtOH, as summarized in Table 1. Direct formation of 9 from 6 is attributable to easy deacetylation of a thiolated intermediate (8) with EtONa in EtOH as above mentioned. In fact, treatment of 8a<sup>3</sup> with 0.1 equiv of EtONa in EtOH at room temperature gave 9a in almost quantitative yield. It should be noted that any amount of a dithiolated product, 2,2-bis(methylthio)alkanoic ester (10), was not detected in the reaction mixture.



This may be explained in terms of basicity of EtONa which cannot abstract the 2-proton of 9, but that of 6. A typical procedure is as follows. To a 0.44 M solution of EtONa in EtOH (30 ml), were added successively 6 (R = PhCH<sub>2</sub>) (2.075 g: 9.42 mmol) and 7a (1.325 g: 10.5 mmol), and the resulting mixture was stirred at room temperature for 5 h. After addition of NH<sub>4</sub>Cl aq. solution followed by extraction with Et<sub>2</sub>O, the organic layer was dried and distilled *in vacuo* (bp 94–111 °C/3 mmHg) to give 6a (R = PhCH<sub>2</sub>) (1.892 g: 99.5%).

Table 1. Yield in Transformation of 6 into 9 Using 7<sup>a</sup>

R of <u>6</u>	R' of <u>7</u>	EtONa	Temp./Time	Yield
<i>n</i> -C <sub>10</sub> H <sub>21</sub> -	CH <sub>3</sub>	1.4 equiv	r.t./4 h	98%
PhCH <sub>2</sub> -	CH <sub>3</sub>	1.1 equiv	r.t./4 h	99.5%
PhCH <sub>2</sub> -	Ph	1.9 equiv	r.t./23 h	92%
<i>n</i> -C <sub>5</sub> H <sub>11</sub> CH=CHCH <sub>2</sub> - <sup>b</sup>	CH <sub>3</sub>	1.4 equiv	r.t./48 h	92%

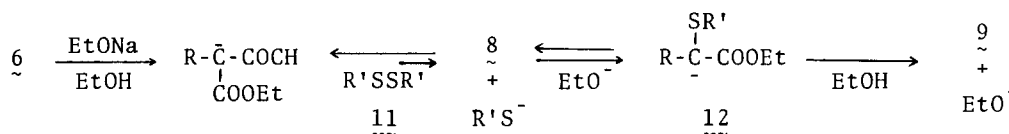


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<sup>a</sup>in EtOH.

<sup>b</sup>The (E) isomer was used in this reaction.

Next, we tried to utilize dimethyl disulfide (11a) or diphenyl disulfide (11b) as a thiolating reagent instead of 7. In thiolation of a stable carbanion such as the carbanion of malonic diester with a disulfide (11), the reaction is always reversible.<sup>4,5</sup> However, in the reaction of 6 with 11 in the presence of excess EtONa in EtOH, it is anticipated that the final irreversible deacetylation (protonation of a carbanion 12 with EtOH) compels the reaction to produce 9.



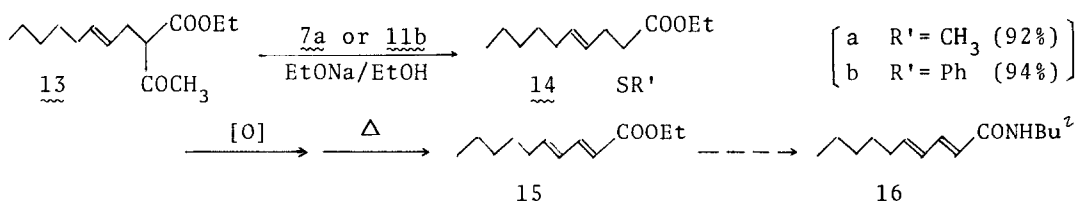
We surveyed the reaction conditions for production of 9 and the results were given in Table 2. As being apparent from a persual of Table 2, 11b can be utilized suitably and 30 °C is preferable for the reaction temperature from standpoints of reaction time and yield. Under these conditions, 9b is obtained in good to high yield. Thus, we recommend 11b as a thiolating reagent for making 9b because of its availability.<sup>6</sup> The following procedure is typical. To a 0.17 M solution of EtONa in EtOH (60 ml), were added 6 (R = PhCH<sub>2</sub>) (203 mg: 0.1921 mmol) and 11b (397 mg: 1.82 mmol), and the resulting mixture was stirred at 30 °C for 96 h. The usual workup and column-chromatography gave 9b (R = PhCH<sub>2</sub>) in 75% yield.

Finally, we would like to describe application of the present methods to synthesis of pellitorine (16; an insecticide)<sup>7</sup> and the queen substance (19; a sex attractant of the queen bee).<sup>1c</sup>

When ethyl 2-acetyl-4-decenoate (13) was subjected to the reaction with 7a or 11b under the conditions given in Table 1 or 2, we obtained ethyl 2-(methyl- or phenylthio)-4-decenoate (14) in high yield. Conversion of 14a to 16 *via* ethyl

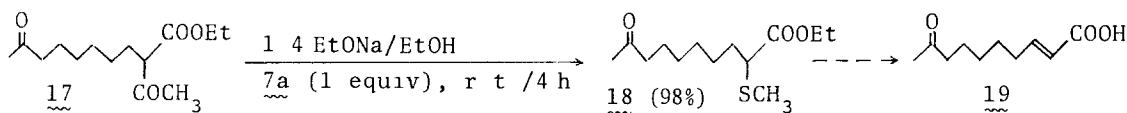
Table 2 Yield in Transformation of 6 into 9 Using 11<sup>a</sup>

R of <u>6</u>	R' of <u>11</u>	EtONa	Temp./Time	Yield	
PhCH <sub>2</sub>	Ph (2 equiv)	1.5 equiv	r.t /120 h	80%	<sup>a</sup> in EtOH. <sup>b</sup> <u>6</u> (R = PhCH <sub>2</sub> ) was recovered in 27% yield. <sup>c</sup> <u>6</u> (R = PhCH <sub>2</sub> ) was recovered in 43% yield. <sup>d</sup> The (E) isomer was used
	Ph (2 equiv)	1.5 equiv	30 °C/90 h	75%	
	Ph (2 equiv)	1.5 equiv	51-55 °C/5 h	54%	
	Ph (1.7 equiv)	2 equiv	reflux/2.5 h	38%	
	CH <sub>3</sub> (3 equiv)	1.5 equiv	r.t /240 h	15% <sup>b</sup>	
	CH <sub>3</sub> (1.4 equiv)	1.5 equiv	52-55 °C/5 h	4% <sup>c</sup>	
	CH <sub>3</sub> (1.4 equiv)	1.5 equiv	reflux/5 h	0%	
n-C <sub>10</sub> H <sub>21</sub> -	Ph (2 equiv)	1.5 equiv	30 °C/96 h	92%	
n-C <sub>5</sub> H <sub>11</sub> CH=CHCH <sub>2</sub> - <sup>d</sup>	Ph (2 equiv)	1.5 equiv	30 °C/96 h	94%	



(E,E)-2,4-decadienoate (15) was established in the literatures,<sup>9</sup> and similarly 14b could be transformed into 15 in 89% yield by oxidation with NaIO<sub>4</sub> in MeOH-H<sub>2</sub>O, followed by pyrolysis in refluxing benzene

Ethyl 2-methylthio-9-oxodecanoate (18), an important precursor for synthesis of 19,<sup>1c</sup> was also yielded by treatment of ethyl 2-acetyl-9-oxodecanoate (17)<sup>10</sup> with 7a and EtONa in EtOH. It is noteworthy that the present route to 18 does not require protection of the keto group of 17, in a sharp contrast with the known method, *z* *e* methylthiolation of methyl 9-oxodecanoate with 11a and lithium cyclohexyl(isopropyl)amide<sup>1c</sup>. When the latter method was performed without protection of the keto group, methyl 2,8-bis(methylthio)-9-oxodecanoate was accompanied and the yield of methyl 2-methyl-9-oxodecanoate was less than 30%<sup>1c</sup>



Thus we established a convenient method for production of 2-(methyl- or phenylthio)alkanoic esters (9). Compared with the traditional methods such as sulfenylation of alkanolic acid (or its ester)<sup>1c,1d,11</sup> and alkylation of (methylthio)acetic acid,<sup>1e</sup> the present method possesses some advantages in efficiency and convenience since inexpensive EtONa (small excess), which is easier to handle than the usually used BuLi or LDA, is employed as a base, the reaction proceeds in ethanol under simple and mild conditions, and the yield

is very high.<sup>12</sup>

# References and Notes

1. (a) For a review, B. M. Trost, *Chem. Rev.*, 78, 363 (1978); (b) D. Seebach and M. Teschner, *Chem. Ber.*, 109, 1601 (1976) and the references cited therein; (c) B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, 98, 4887 (1976); (d) J. Nogami, M. Kawada, R. Okawara, S. Torii, and H. Tanaka, *Tetrahedron Lett.*, 1979, 1045; (e) B. M. Trost and Y. Tamaru, *J. Am. Chem. Soc.*, 99, 3101 (1977); (f) E. Vedejs and G. R. Martinez, *J. Am. Chem. Soc.*, 101, 6452 (1979).
2. 6 was easily prepared by the reaction of the corresponding alkyl or 2-alkenyl halide with ethyl acetoacetate in the presence of EtONa in EtOH.
3. 8a was prepared by the reaction of 6 with 7a in the presence of NaH (1.4 equiv) in THF (r.t./5 h; 96% yield) or EtONa (0.8 equiv) in EtOH (r.t./4 h; 74% yield).
4. M. Ōki, W. Funakoshi, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, 44, 828 (1971); T. Fujisawa, K. Hata, and T. Kojima, *Chem. Lett.*, 1973, 287.
5. This is the case in thiolation of the carbanion of 6 with 11. When the carbanion of 6 (R = PhCH<sub>2</sub>), produced by the action of NaH in THF, was treated with 11b at from room temperature to boiling temperature, the thiolation did not take place and 6 (R = PhCH<sub>2</sub>) was recovered unchanged.
6. 7 was prepared by oxidation of 11 with H<sub>2</sub>O<sub>2</sub> (2 mol-equiv) in AcOH.
7. M. Jacobson, *J. Am. Chem. Soc.*, 75, 2584 (1953); L. Crombie, *J. Chem. Soc.*, 1955, 999 and 1007.
8. 13 was prepared in 74% yield by the reaction of 2-octenyl chloride with ethyl acetoacetate in the presence of EtONa in EtON.
9. K. Tanaka, M. Terauchi, and A. Kaji, *Chem. Lett.*, 1981, 315; J. Tsuji, H. Nagashima, T. Takahashi, and K. Masaoka, *Tetrahedron Lett.*, 1977, 1917.
10. 12 was given by the reaction of 5-bromo-1-pentanol with acetylacetone in the presence of K<sub>2</sub>CO<sub>3</sub>-KI in EtOH (reflux/4 d) to give 8-hydroxy-2-octanone (37%), followed by mesylation with methanesulfonyl chloride-pyridine (90%) and the subsequent treatment with ethyl acetoacetate and EtONa in EtOH (40%). These yields were not optimized and exploring the best conditions for these reactions is the subject of an on-going study.
11. D. A. R. Happer, J. W. Mitchell, and G. J. Wright, *Aust. J. Chem.*, 26, 121 (1973).
12. The present method is also preferable to the synthetic method using the carbanion of substituted malonic diester: K. Ogura, H. Itoh, T. Morita, K. Sanada, and H. Iida, *Bull. Chem. Soc. Jpn.*, 55, 1216 (1976).

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