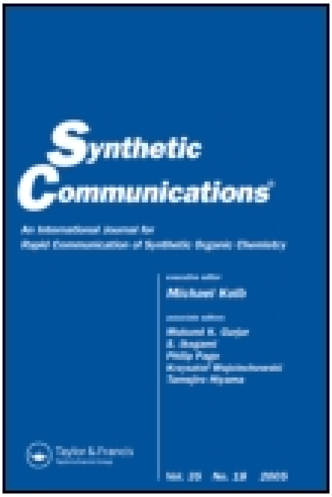


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Thiol Esters in Organic Synthesis XVII.[1] S,S′-Diethyl Dithiomalonate as Masked Ethanol Carbanion and 1,3-Diol Equivalent in the Knoevenagel Condensation

Patricia A. Rose [a] [b] & Hsing-Jang Liu [a]
[a] Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2
[b] Plant Biotechnology Institute, National Research Council of Canada, 110 Gymnasium Place, Saskatoon, Sask., Canada, S7N 0W9

To cite this article: Patricia A. Rose & Hsing-Jang Liu (1991) Thiol Esters in Organic Synthesis XVII.[1] S,S′-Diethyl Dithiomalonate as Masked Ethanol Carbanion and 1,3-Diol Equivalent in the Knoevenagel Condensation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:20, 2089-2095, DOI: 10.1080/00397919108019815

To link to this article: http://dx.doi.org/10.1080/00397919108019815

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [University of Cambridge] at 11:50 08 October 2014

SYNTHETIC COMMUNICATIONS, 21(20), 2089-2095 (1991)

THIOL ESTERS IN ORGANIC SYNTHESIS XVII.[1] *S,S'*-DIETHYL DITHIOMALONATE AS MASKED ETHANOL CARBANION AND 1,3-DIOL EQUIVALENT IN THE KNOEVENAGEL CONDENSATION.

Patricia A. Rose[2] and Hsing-Jang Liu*

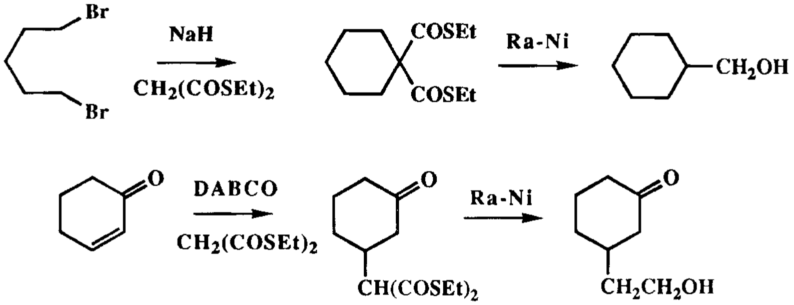
Department of Chemistry, University of Alberta,
Edmonton, Alberta, Canada, T6G 2G2

Abstract: *S,S'*-Diethyl dithiomalonate (**1**) has been shown to be a useful reagent in the Knoevenagel condensation with aldehydes, using DABCO as the base. The resultant products can be reduced either to 1,3-diols by use of sodium borohydride or to ethanol derivatives using Raney Nickel.

S,S'-Diethyl dithiomalonate (**1**) acts as a masked ethanol carbanion equivalent in both alkylation reactions[3] and Michael additions,[4] as the dithiolester unit can be readily reduced by Raney Nickel to the ethanol level, as shown in Scheme 1. In a continuation of our studies in this area, we investigated the utility of **1** in the Knoevenagel condensation and examined the reduction of the products using sodium borohydride and Raney Nickel. We herein report dithiomalonate **1** to be a useful reagent for the formation of 1,3-diols as well as being an ethanol carbanion equivalent (Scheme 2).

---

* To whom correspondence should be addressed.



Scheme 1

$$\mathrm{RCHO} + \underset{\mathbf{1}}{\mathrm{CH_2(COSEt)_2}} \xrightarrow{\mathrm{DABCO}} \mathrm{RCH{=}C(COSEt)_2}$$

$$\mathrm{RCH{=}C(COSEt)_2} \xrightarrow{\mathrm{NaBH_4}} \mathrm{RCH_2CH(COSEt)_2} \xrightarrow{\mathrm{Ra\text{-}Ni}} \mathrm{RCH_2CH_2CH_2OH}$$

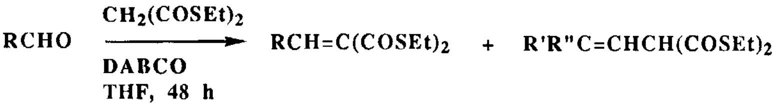
$$\mathrm{RCH{=}C(COSEt)_2} \xrightarrow{\mathrm{XS\ NaBH_4}} \mathrm{RCH_2CH(CH_2OH)_2}$$

Scheme 2

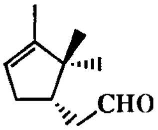
S,S'-Diethyl dithiomalonate (**1**) is a readily available reagent whose preparation has been described previously.[3] The Knoevenagel condensation reaction was carried out with a series of aldehydes under mild conditions utilizing diazabicyclo[2.2.2]octane (DABCO) as the base. The results are listed in Table 1. In a typical experiment, *S,S'*-diethyl dithiomalonate (1.2 eq) was added to THF (10 mL/mmol) in a dry, argon flushed flask and the solution cooled to 0°C. DABCO (1 eq) and sodium sulfate (~0.3 g/mmol of aldehyde) were added and the mixture stirred for 10 minutes. Freshly distilled aldehyde (1 eq) was then added, the solution slowly warmed to room temperature and left to stir under argon for 48 hours. The reaction was then quenched with 1M HCl, extracted into

Table 1

Knoevenagel Condensation of *S,S'*-Diethyl Dithiomalonate with Aldehydes



$$\mathrm{RCHO} \xrightarrow[\mathrm{DABCO} \\ \mathrm{THF,\ 48\ h}]{\mathrm{CH_2(COSEt)_2}} \mathrm{RCH{=}C(COSEt)_2} + \mathrm{R'R''C{=}CHCH(COSEt)_2}$$

Entry	Aldehyde	Yield (%)	Ratio of α,β:β,γ isomers
1	furfural	84	
2	isovaleraldehyde	71	4:1
3	isobutyraldehyde	72	1:3
4	dihydrocinnamaldehyde	63	5:3
5	heptanal	64	2:1
6		65	10:1
7	$CH_3(CH_2)_{16}CHO$	38	2:1

dichloromethane, washed with saturated brine and dried over magnesium sulfate. The non-polar products could be easily purified by flash chromatography on silica gel, typically using 5% ethyl acetate in petroleum ether as an eluant.

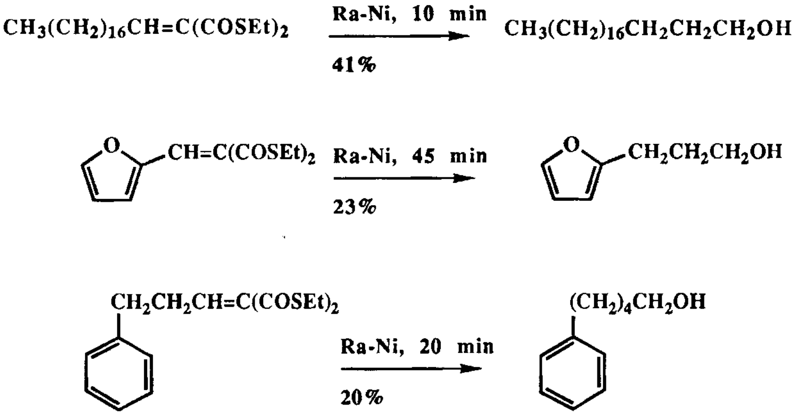
An interesting result of the condensation was the formation of a mixture of two products in the cases of Entries 2-7, namely the α,β- and the β,γ-double bond isomers. Apparently, conjugation to two thiolester groups does not completely override the steric strain due to the large *cis*-related substituents of the double bond.

The most dramatic example of this is seen in Entry 3. Fortunately, during sodium borohydride reduction, there appears to be sufficient isomerization of the double bond to reduce both isomers to the desired 1,3-diol. Alternatively, the α,β-isomer could be purified by washing the mixture through a silica gel column adsorbed with 10 % silver nitrate.

In an attempt to improve the yields of the condensation reaction we tried several different reaction conditions, without success. Increasing the reaction temperature to reflux led to the partial decomposition of the *S,S'*-diethyl dithiomalonate, along with lower yields. Bases such as sodium hydride or potassium carbonate were investigated, however very little product formation was observed in either case. A series of catalysts were also examined. Titanium tetrachloride,[5] cesium carbonate[6] and alumina[7] were applied, however only trace amounts of product were formed in each case.

The condensation products could be reduced in a series of different manners. As we had previously shown that 1,3-dithiolesters could be reductively cleaved by Raney Nickel in high yields to generate an ethanol group, we decided to investigate the reaction of the unsaturated compounds under similar conditions, in hopes of forming the same type of product. As shown in Scheme 3, several of the condensation products were treated with acid washed W2 Raney Nickel[4] (1 mL Raney Nickel/100 mg of compound, in benzene). The desired alcohols were formed, however in dismal yields, no doubt due to the large number of operations which the reducing agent was required to carry out.

This problem could be circumvented if we could show that the selective reduction of the double bond was possible, as our earlier work[3,4] had already proven the utility of Raney Nickel reductions on the saturated dithiolester system. Indeed, reduction of the condensation product of **1** and heptanal (Table 1, Entry 5)



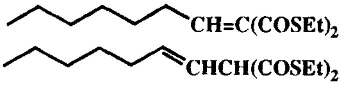
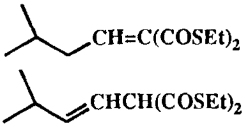
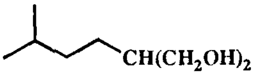
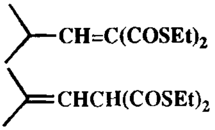
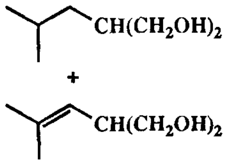
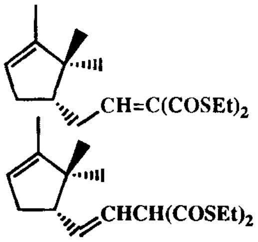
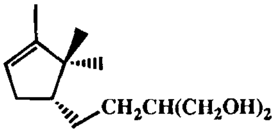
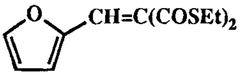
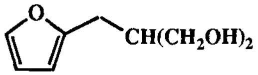
Scheme 3

with 1 molar equivalent of sodium borohydride at 0°C in methanol was found to give the desired saturated system in 90 % yield.

Complete reduction to the 1,3-diol stage could also be carried out, requiring only a large excess of sodium borohydride and longer reaction times. The diols were produced in good yields as shown in Table 2. In a typical reaction the dithiolester was dissolved in 98% ethanol (5 mL/100 mg) and 2 molar equivalents of sodium borohydride were added. The mixture was stirred at room temperature for 48 hours, with periodical addition of sodium borohydride (~2 molar equivalents every 12 hours). The reaction was worked up avoiding contact with water as the products were often highly water soluble. Therefore, the crude reaction mixture was concentrated, dissolved in ether and the borate salts filtered off. After reconcentrating, the residue was subjected to flash chromatography using a short column of silica gel and unreacted starting material removed using 10% ether / petroleum ether. The product was then washed off the column with pure ether.

Table 2

Sodium Borohydride Reduction to 1,3-Diols

Entry	Thiol Ester	Product	Yield (%)
1		$CH_3(CH_2)_6CH(CH_2OH)_2$	73
2			70
3			60
4	$PhCH_2CH_2CH{=}C(COSEt)_2$ $PhCH_2CH{=}CHCH(COSEt)_2$	$PhCH_2CH_2CH_2CH(CH_2OH)_2$	55
5			74
6			84

S,S'-Diethyl dithiomalonate (**1**) has been shown to be a useful reagent as either an ethanol carbanion equivalent or for introducing a 1,3-propanediol unit into aldehydic positions.

Acknowledgements

We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support, and to the Province of Alberta for a Fellowship for P.A.R.

References and Notes

1. For Part XVI of this series, see Liu, H.J.; Rose, P.A.; Sasaki, D.J., *Can. J. Chem.*, in press.
2. Present address: Plant Biotechnology Institute , National Research Council of Canada, 110 Gymnasium Place, Saskatoon, Sask., Canada, S7N 0W9.
3. Liu, H. J.; Lai, H. K., *Can. J. Chem.*, **1979**, *57*, 2522.
4. Liu, H. J.; Oppong, I.V., *Can. J. Chem.*, **1982**, *60*, 94.
5. (a) Lehnert, W., *Tetrahedron*, **1974**, *30*, 301; (b) Lange, J.; Kanabus-Kaminska, J. M. ; Kral, A., *Synth. Commun.*, **1980**, *10*, 473.
6. Lavallee, J. F.; Deslongchamps, P., *Tetrahedron Lett.*, **1988**, *29*, 6033.
7. Texier-Boullet, F.; Foucaud, A., *Tetrahedron Lett.*, **1982**, *23*, 4927.

(Received in USA 7 June, 1991)