Tetrahedron Letters, Vol. 33, No. 26, pp. 3737-3740, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Carboxylic Acid Reductions: Insights from Mixed Anhydrides and Thiol Esters

John H. Penn* and Walter H. Owens

Department of Chemistry, West Virginia University
Morgantown, WV 26506 USA

Key Words: Thiol esters; Mixed Anhydrides; Carboxylic Acid Reduction

Abstract: Reduction of thiol esters and mixed anhydrides with lithium has been accomplished. Thiol esters have been found to react exclusively to yield aldehydes. Mixed anhydrides give cleavage in a way that can be rationalized by stability of the incipient anions.

Research in our group has focussed on the selective cleavage of chemical bonds.[1] Interest in pretreatment strategies of fossil fuel[2] substrates has caused us to examine the chemistry of carboxylic acids. Our planned pretreatment was to functionalize the carboxylic acid to another functional group which might be further reacted in a controlled way. We further believed that this strategy could be developed into general synthetic methodology for functional group interconversion. As an initial goal, we chose to reduce the carboxylic acids to aldehyde functional groups.[3] The primary difficulty in this interconversion appears to be controlling the reduction, such that the aldehyde is not further reduced to an alcohol. We report here that thiol esters can be cleaved exclusively to aldehydes while mixed anhydrides are only moderately selective in their bond cleavage pathways.

General Procedure: For all experiments reported here, the indicated compound was dissolved in dry THF and degassed with argon. This mixture was added dropwise over a period of one hour to a solution of near-oxide free lithium wire (from dipping in CH_3OH followed by pentane wash) at -100°C to -78°C under an argon atmosphere. In the case of the mixed anhydrides, the solution was stirred at -78°C until bubbling of CO_2 ceased (*ca.* 3-4 h). In the case of the thiol esters, the solution was stirred vigorously for 4-5 h. After the stirring was completed, an electrophile (*e.g.*, CH_3OH or CH_3I) was added to quench the reaction.

Mixed Anhydrides: Our first efforts for conversion of carboxylic acids into aldehydes utilized mixed anhydrides which were prepared by the general method of Fife.[4] The procedure was modified to allow for the direct

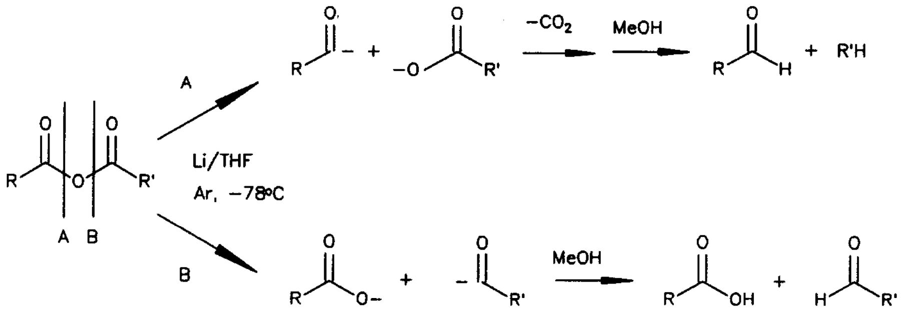

Table I. Product Yields from Lithiation of Mixed Anhydrides.

Compound			Product Yield (mole %)[a]				
			Bond A			Bond B	
	R	R'	RCHO	$R'CO_2H$	R'H	RCO_2H	R'CHO
1	Ph	CPh_3	96.5	–[b]	100.8	–[b]	–[b]
2	$C_{10}H_{21}$	CPh_3	81.3	–[b]	83.6	17.9	19.4
3	C_6H_{11}	CPh_3	73.8	–[b]	71.5	28.3	30.1
4	$C(CH_3)_3$	CPh_3	59.6	–[b]	63.7	41.9	37.1

a) Product yields based on gc analysis using hexadecane as an internal standard. Yield data are estimated to be ±5%.
b) Not observed.

utilization of the carboxylic acid by reacting the acyl pyridinium complex of triphenyl acetic acid with the carboxylic acid to be converted.[5] We reasoned that the difference in bond energies of the two carbonyl carbon to oxygen bonds would be expressed in different bond cleavage rates. Bond A would be the product leading to the desired product, which might then be trapped with an appropriate substrate. Bond B cleavage would represent undesired product and would result in a return to the original carboxylic acid. The results of reductive cleavage of these mixed anhydrides are given in Table I.

For aryl mixed anhydrides (*e.g.*, **1**), selectivity was complete, with only benzaldehyde and triphenylmethane being formed. The triphenylmethane must arise as a product from loss of CO_2 from either the triphenylacetate anion or the triphenylacetyl radical. These species are the expected intermediates from reactions of the anhydride radical anion.[6] With the current data, we are unable to postulate with certainty the exact mechanistic sequence of electron transfers and bond cleavages. Interestingly, the reaction process and yields were not as good when other commonly employed reducing reagents were used. For example, lithium naphthalenide, lithium di-*t*-butylbiphenylide, and sodium naphthalenide gave an orange colored solution with a precipitate which did not result in loss of CO_2 upon warming to room temperature. Quenching with methanol removed both the color and the precipitate with formation of modest amounts of methyl benzoate and benzil in addition to the other products noted here.

For the alkyl mixed anhydrides, the selectivity was not so good. n-Undecyl triphenylacetic anhydride (**2**) gives the maximum amount of selectivity, with *ca.* 80% of the desired bond A cleavage being obtained. Cyclohexylcarboxylic triphenylacetic anhydride (**3**) and pivalic triphenylacetic anhydride (**4**) gave even less selectivity. Since the mixed anhydrides were not sufficiently selective, alternative methods of cleavage using the same strategy were sought.

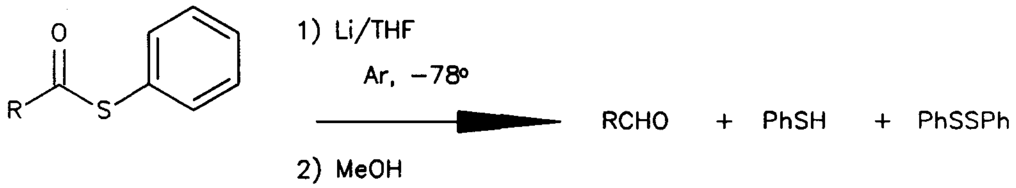

Table II. Product Distribution from Lithiation of Thiol Esters.

Compound		Product Yield (mole %)[a]		
	R	RCHO	PhSH	PhSPh
5	Ph	98.2	101.5	1.3
6	$C_{10}H_{21}$	98.9	99.4	1.4
7	C_6H_{11}	99.7	100.2	1.8
8	$C(CH_3)_3$	98.4	97.9	0.9

a) Product analysis was performed by gc analysis using hexadecane as an internal standard. Yield data are estimated to be ±5%.

Thiol Esters: Given the recent success in other laboratories for converting C-S bonds into carbanions,[7] we reasoned that thiol esters might be cleaved into acyl radicals or anions in a way that would lead to the desired transformation into aldehydes. Thiol esters can be easily formed from the carboxylic acids through the acyl halides.[8] This strategy was indeed realized as seen in Table II. Treatment of lithium with either aryl or alkyl thiol esters, followed by quenching with methanol, resulted in the exclusive formation of the desired aldehydes. Even the tertiary system (*i.e.*, **8**) which showed the least selectivity for the mixed anhydrides gave exclusive conversion to the aldehyde in high yield.

We speculate that the reaction mechanism involves electron transfer from the metal to the thiol ester which undergoes bond cleavage to a radical and an anion. Given the high local concentration of electrons, the radical is further reduced to yield thiophenoxide and an acyl anion which may be subsequently trapped with appropriate electrophiles. In the present case we have trapped the "acyl anion" with protons which result in aldehyde formation. Further support for the formation of an acyl anion is found from the quenching of the benzoyl anion by methyl iodide, where acetophenone (yield, 93.8%) and benzaldehyde (yield, 3.1%) are produced from the benzoyl portion of the molecule. In the worst case, if one assumes that the origin of the benzaldehyde results from formation of the benzoyl radical and subsequent H-atom abstraction, this result indicates a preference for benzoyl anion formation of 94:3. Therefore, we believe that the current strategy for formation of "acyl anions" may be broadly applicable as a synthetic strategy.

In summary, we have determined that cleavage of thiol esters by lithium, followed by treatment with a proton source, results in exclusive formation of aldehydes. This strategy may be generally applicable as a synthetic method for the formation of "acyl anions".

Acknowledgements: Start-up funding was provided by the U.S. Department of Energy, Contract #DE-FC21-87MC24207. We also gratefully acknowledge helpful discussions with Plato Magriotis.

References

1. (a) Penn, J.H.; Lin, Z.; Deng, D.-L., *J. Am. Chem. Soc.*, **1991**, *113*, 1001. (b) Penn, J.H.; Lin, Z., *J. Org. Chem.*, **1990**, *55*, 1554.
2. Freihaut, J.D.; Proscia, W.M., *Energy and Fuels*, **1989**, *3*, 625.
3. The following are general methods for carboxylic acid to aldehyde conversions. (a) Brown, H.C.; Kortnyk, W., *J. Am. Chem. Soc.*, **1960**, *82*, 3866. (b) Brown, H.C.; Stocky, T.P., *J. Am. Chem. Soc.*, **1977**, *99*, 8218. (c) Burgstahler, A.W.; Worden, L.R.; Lewis, T.B., *J. Org. Chem.*, **1963**, *28*, 2918. (d) Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T., *Tetrahedron Lett.*, **1983**, *24*, 1543.
4. Fife, W.K.; Zhang, Z.-D., *Tetrahedron Lett.*, **1986**, *27*, 4933.
5. Smalley, R.K.; Suschitzky, H., *J. Am. Chem. Soc.*, **1964**, *85*, 755.
6. Masnovi, J., *J. Am. Chem. Soc.*, **1989**, *111*, 9081.
7. (a) Cherkauskas, J.R.; Cohen, T., *J. Org. Chem.*, **1992**, *57*, 6. (b) Cohen, T.; Bhupathy, M., *Acc. Chem. Res.*, **1989**, *22*, 152. (c) Cohen, T.; Yu, L.-C., *J. Am. Chem. Soc.*, **1983**, *103*, 2811. (d) Beak, P.; Becker, P.D., *J. Org. Chem.*, **1982**, *47*, 3855. (e) Reitz, D.B.; Beak, P.; Farney, R.F.; Helmick, L.S., *J. Am. Chem. Soc.*, **1978**, *100*, 5428.
8. Satchell, D.P.N., *Q. Rev., Chem. Soc.*, **1963**, *17*, 182.

(Received in USA 5 March 1992)