Tetrahedron Letters, Vol. 34, No. 17, pp. 2737-2740, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

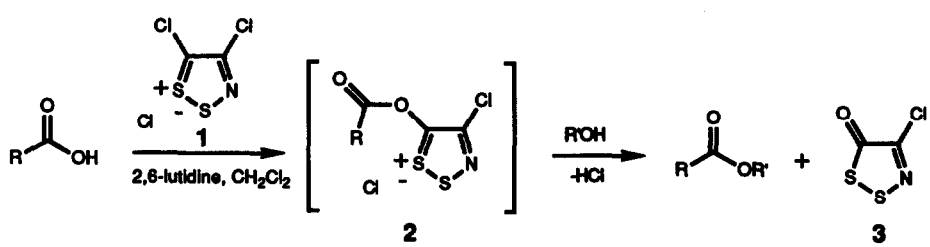
GENERATION OF ESTERS FROM CARBOXYLIC ACIDS USING APPEL'S SALT (4,5-DICHLORO-1,2,3-DITHIAZOLIUM CHLORIDE)

James J. Folmer and Steven M. Weinreb*
Department of Chemistry
The Pennsylvania State University
University Park, PA 16802

Abstract: Esters can be generated directly in good yields under mild conditions from the corresponding carboxylic acid and alcohol using Appel's salt (4,5-dichloro-1,2,3-dithiazolium chloride) and 2,6-lutidine.

The conversion of carboxylic acids into esters is a valuable reaction in organic synthesis and a large number of methods have been developed for this transformation.[1] Nevertheless, there is still great demand for mild, simple procedures to generate esters. Recent work in this area has included the activation of carboxylic acids towards esterification by converting the acid into metal carboxylate salts[2], anhydrides[3], mixed anhydrides[4], and various types of thiol esters.[5] The Mukaiyama group has enjoyed much success in transforming carboxylic acids into esters using 2-halopyridinium salts and related compounds.[6] Their work is based on the consideration that the 2-halo position of the pyridinium salt is susceptible to nucleophilic attack by a carboxylate anion and that the resultant 2-acyloxypyridinium salt can, upon nucleophilic attack by an alcohol at the acyl carbon, be converted into the ester and a pyridone.

We have now developed an *extremely mild* technique for the conversion of carboxylic acids to esters using readily available Appel's salt (1)[7] and equimolar amounts of the carboxylic acid and alcohol (Eq 1). This methodology is mechanistically analogous to the route exploited by Mukaiyama in that it involves the mild *in situ* formation of an activated acid via carboxylate anion attack on the dithiazolium salt 1, followed by nucleophilic attack of the alcohol to give the ester and a stable heterocyclic by-product. Mukaiyama's protocol works best at 40 - 111° C,[6] while our method gives esters under milder conditions (-78° C to rt) and thus is potentially useful for sensitive substrates.

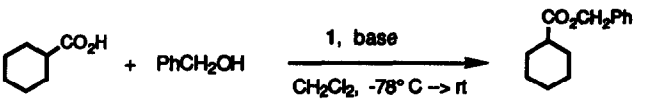


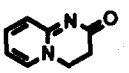
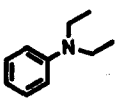
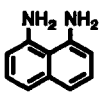
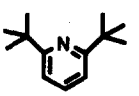
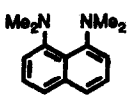
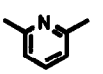
(Eq 1)

The reaction consists of mixing equimolar amounts of a carboxylic acid and alcohol with readily available Appel's salt (1)[7] and 2 equivalents of 2,6-lutidine at -78° C in CH_2Cl_2 and warming to room temperature (Eq 1). We believe the reaction proceeds via the activated species 2 [8,9] which is subsequently attacked by the alcohol to afford the ester and the thione 3. The reaction requires two equivalents of base, one to initially deprotonate the acid and one to scavenge HCl.

A number of different bases were initially screened in order to optimize conditions. Reactions were compared using equimolar amounts of cyclohexanecarboxylic acid and benzyl alcohol, 1.2 equivalents of Appel's salt, and 2.4 equivalents of base under identical conditions.[10] The choice of base is critical to the success of the process, as depicted in Table 1. Bases such as proton sponge[11] or trialkylamines gave poor yields of the ester, while optimum results were obtained using 2,6-lutidine. The reaction was found to work best when the acid, alcohol, base and 1 were mixed at -78° C in CH_2Cl_2 and allowed to slowly warm to room temperature over 5-12 hours.[12] Heating the mixture above room temperature usually resulted in lower yields and more complex product mixtures.

Table 1[a].

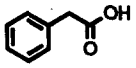
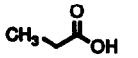
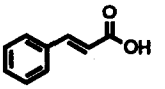
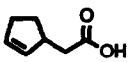
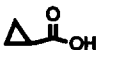
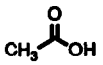
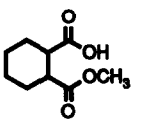
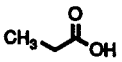
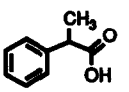


Base	Ester, Isolated Yield (%)	Base	Ester, Isolated Yield (%)
Na_2CO_3	0		46
	0		65
	0		71
	0		81
	24		

[a] All reactions were carried out using 1 equiv.of acid, 1 equiv. of alcohol, 1.2 equiv. of 1, 2.4 equiv. of base.

Once the reaction conditions were optimized, we probed the scope and generality of the reaction. A number of different acids and alcohols were studied and a representative sample is shown in Table 2. The reaction gave modest to good yields of esters, depending on the alcohol used. Primary alcohols gave the best yields of esters, followed by secondary and then tertiary, probably due to the steric interactions in the attack of the alcohol on the activated intermediate **2**. However, even *t*-butanol gave a 39% yield of the ester of phenylacetic acid. It is of interest to note that the reaction of phenylacetic acid with phenol did not yield any ester. One explanation for this result is that the phenol may be deprotonated by the base and the resultant aryloxy anion may compete with the carboxylate anion for the dithiazolium salt **1**, resulting in complex mixtures.

Table 2. Preparation of esters from carboxylic acids and alcohols using Appel's salt.[a]

Acid	Nucleophile	Ester, Isolated Yield (%)	Acid	Nucleophile	Ester, Isolated Yield (%)
	$PhCH_2OH$	75		$PhCHCHCH_2OH$[b]	64
	CH_3CH_2OH	77		$PhCH_2OH$	74
	$PhCHCHCH_2OH$[b]	81			
	$PhCH(CH_3)OH$	59		CH_3CH_2OH	55
	$(CH_3)_3COH$	39			
	PhOH	0		$PhCH_2OH$	76
	$PhCH_2CH_2OH$	63		$PhCH(CH_3)OH$	40
	$PhCHCHCH_2OH$[b]	70		CH_3CH_2OH	73
	$PhCH_2OH$	84			
	$PhCH_2CH_2OH$	76		CH_3CH_2OH	63

[a] All reactions were carried out using the general procedure. [b] *trans*-cinnamyl alcohol was used.

General Procedure for the Esterification of Carboxylic Acids. To a stirred slurry of the dithiazolium salt **1**[7] (0.207 g, 1.0 mmol) in 3 mL of dry CH_2Cl_2 under an Ar atmosphere at -78° C was added a solution of the acid (0.87 mmol), alcohol (0.87 mmol) and 2,6-lutidine (0.233 mL, 2.0 mmol) in 1 mL of dry CH_2Cl_2 over a period of 1 min. The mixture was stirred at -78° C for 2 h and warmed to rt overnight (12 h). The reaction was quenched with 5 g of ice and was poured into 5 mL of CH_2Cl_2. The organic layer was washed with brine (2 x 10 mL), dried over $MgSO_4$, filtered through a plug of

silica gel (CH_2Cl_2) and concentrated in vacuo. The residue was purified by silica gel chromatography. Yields of isolated products are given in Table 2.

Acknowledgment. This work was supported by the National Institutes of Health (GM-32299). We are grateful to Professor Charles Rees for bringing Appel's salt to our attention.

References and Notes

(1) Haslam, E. *Tetrahedron* **1980**, *36*, 2409. LaRock, R.C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations.* VCH Publishers: New York, 1989; p 966. Hofle, G.; Steglich, W. *Synthesis* **1972**, 619. Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. Tedder, J. M. *Chem. Rev.* **1955**, *55*, 787. Greene, T. W.; Wuts, P. G.; Hassner, A.; Krepski, L.; Alexanian, V. *Tetrahedron* **1978**, 2069. Rehn, D.; Ugi, I. *J. Chem. Res., Synop.* **1977**, 119. Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277.

(2) Shaw, J. E.; Kunerth, D. C.; Sherry, J. J. *Tetrahedron Lett.* **1973**, 689. Shaw, J. E.; Kunerth, D. C. *J. Org. Chem.* **1974**, *39*, 1968. Johnstone, A. W. ; Rose, M. E. *Tetrahedron* **1979**, *35*, 2169. Mehta, G. *Synthesis* **1972**, 262. Wang, S. S.; Gisin, B. F.; Winter, D. P.; Makofse, R.; Kulesha, I. D.; Tzougraki, C.; Meinhofer, J. *J. Org. Chem.* **1977**, *42*, 1286.

(3) Routes which require initially converting the carboxylic acid to the anhydride are generally inefficient if the acid is valuable. For an exception, see: Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(4) Inanaga, J.; Kirata, K.; Saeki, H.; Katsaki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(5) Corey, E. J.; Nicolau, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409.

(6) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 707, and references cited therein.

(7) This compound is easily prepared in one step from sulfur monochloride and chloroacetonitrile by the procedure of: Appel, R.; Janssen, H.; Siray, M.; Knock, F. *Chem Ber.* **1985**, *118*, 1632. It is very sensitive to water and other nucleophiles.

(8) A similar intermediate has been proposed for the halopyridinium salts used by Mukaiyama. See: Mukaiyama, T.; Usui, M.; Shimada, E. *Chemistry Lett.* **1975**, 1045 and reference 6.

(9) It is also possible that the reactive intermediate is a ketene, generated by elimination of an α-H in the intermediate **2**. See: Funk, R. L.; Abelman, M.M.; Jellison, K. M. *Synlett.* **1989**, 36. Kohl-Mines, E.; Hansen, H. J. *Helv. Chim. Acta.* **1985**, *68*, 2244.

(10) The mixture was stirred in 4.0 mL of dry (distilled from CaH_2) CH_2Cl_2 at -78° C for 2 h and then warmed to rt over 12 h.

(11) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *J. Chem. Soc., Chem. Commun.* **1968**, 723.

(12) It did not make any difference in yields of esters if the solution of acid, alcohol, and base was added to a slurry of the dithiazolium salt or if the addition was reversed.

(Received in USA 1 February 1993)