Communications

One-Pot Synthesis of Amides and Esters from 2,2,2-Trihaloethyl Esters Using Phosphorus(III) Reagents

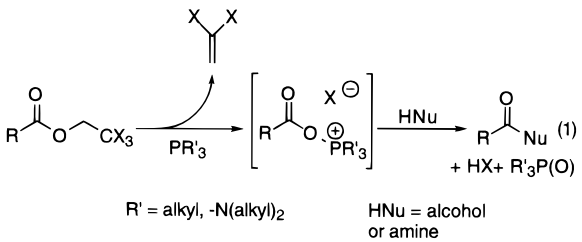
Jeremy J. Hans, Russell W. Driver, and Steven D. Burke*

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1369

Received December 3, 1998

The synthesis of amides and esters from carboxylic acid derivatives is a transformation of general synthetic interest. Preparation of complex amides and esters from protected carboxylic acids is generally achieved by carboxylic acid deprotection followed by formation of an activated acyl species and treatment with an amine or alcohol nucleophile. Such a deprotection/condensation protocol requires two or more steps and can be attended by difficulties in working with the free carboxylic acid intermediate.

The 2,2,2-trichloroethyl group is a useful protecting group for carboxylic acids,[1] and the 2,2,2-tribromoethyl group has also been used in this capacity.[2] The removal of trihaloethyl esters has been accomplished with a variety of reductive methods, the most popular being treatment with zinc. The use of phosphorus(III) compounds for the reductive cleavage of trichloroethyl-protected phosphotriesters has also been reported,[3] presumably involving formation of an electrophilic phosphonium species in addition to liberation of the dialkyl phosphate anion and 1,1-dichloroethylene. Although phosphonium salts have long been used to activate carboxylate functional groups in condensation reactions,[4,5] in situ formation of these species by reduction of trihaloethyl esters to effect condensation reactions has not been exploited. Herein we report amidation or transesterification of trihaloethyl esters using phosphorus(III) compounds, as generalized in eq 1. This one-pot deprotection, activation, and condensation sequence provides an operationally simple method for the title transformations.



The conversion of 2,2,2-tribromoethyl benzoate (**1a**) to *N*-butylbenzamide (**2**) using hexamethylphosphorous triamide (HMPT) was selected to determine the optimal reaction conditions (Table 1). The tribromoethyl ester provides a softer, more reactive halogen electrophile than its trichloroethyl ester counterpart, and HMPT was chosen for its high nucleophilicity.[6] Treatment of **1a** with 1.2 equiv of HMPT, 1 equiv of butylamine, and 2.5 equiv of triethylamine in THF at 0 °C provided **2** in 36% yield (entry 1). Use of benzene as a nonpolar solvent gave a similar yield (entry 2), while more polar solvents such as acetonitrile (entry 3) or dimethylformamide (DMF, entry 4) facilitated the reaction, with DMF providing the best yield. Lowering the reaction temperature improved the yield of **2** to 83% (entry 5). Small amounts of 2,2-dibromoethyl benzoate and *N*,*N*-dimethylbenzamide were isolated byproducts in these reactions.

Investigation of the choice of reductant and electrophile revealed the combination of HMPT and tribromoethyl protecting group to be the most effective for amide synthesis (Table 2). The reaction of HMPT with **1a** proceeded rapidly at −55 °C (entry 1). The use of tributylphosphine slowed the reaction and provided **2** in reduced yield (entry 2). Decreasing the nucleophilicity of the phosphorus reagent by using triphenylphosphine markedly slowed the reaction at room temperature (entry 3), resulting in a 24% yield of **2** after 48 h. This yield is similar to that of the corresponding control experiment conducted in the absence of phosphine (entry 4). Heating the triphenylphosphine reactions produced yields only marginally higher than controls. Use of the trichloroethyl ester necessitated the use of higher temperatures to afford complete consumption of starting material, and lower yields were obtained (entries 5 and 6). Using the optimized conditions, secondary and tertiary amides of aromatic and aliphatic acids as well as a protected alanylalanine dipeptide have been synthesized from the corresponding tribromoethyl esters (Table 3).

Modification of the amide synthesis conditions allowed for the synthesis of esters using this strategy. Initial attempts to effect the transesterification of trihaloethyl esters by addition of HMPT to tribromoethyl esters failed to produce the desired products. The use of PBu_3 as phosphine reagent gave the ester products, albeit in low yield (Table 4, entry 1). Addition of 2 equiv of the acylation catalyst 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[7] markedly improved yields in both HMPT- and tributylphosphine-induced reactions. In contrast to the amidation reactions, tributylphosphine provided yields of ester products superior to those obtained with HMPT. Substantial amounts of *N*,*N*-dimethylamide products were observed when HMPT was used as reductant, presumably resulting from attack on activated acyl intermediates by dimethylamine liberated by the alcoholysis of HMPT.[8] In support of this theory, HMPT underwent methanolysis

* To whom correspondence should be addressed. Tel: (608) 262-4941. Fax: (608) 265-4534. E-mail: burke@chem.wisc.edu.

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991. (b) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.

(2) (a) Stark, W. M.; Hawker, C. J.; Hart, G. J.; Philippides, A.; Petersen, P. M.; Lewis, J. D.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, *23*, 2875. (b) Weiguny, J.; Schafer, H. J. *Liebigs Ann. Chem.* **1994**, 225.

(3) (a) Letsinger, R. L.; Groody, E. P.; Tanaka, T. *J. Am. Chem. Soc.* **1982**, *104*, 6805. (b) Letsinger, R. L.; Groody, E. P.; Lander, N.; Tanaka, T. *Tetrahedron* **1984**, *40*, 137.

(4) (a) Hruby, V. J.; Barstow, L. E. *J. Org. Chem.* **1971**, *36*, 1305. (b) Yamada, S.; Takeuchi, Y. *Tetrahedron Lett.* **1971,** 3595. (c) Castro, B.; Dormoy, J.-R. *Bull. Soc. Chim. Fr.* **1971**, 3034. (d) Castro, B.; Dormoy J. R. *Tetrahedron Lett.* **1972**, 4747. (e) Castro, B.; Dormoy, J.-R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219. (f) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205. (g) Coste, J.; Frérot, E.; Jouin P. *J. Org. Chem.* **1994**, *59*, 2437.

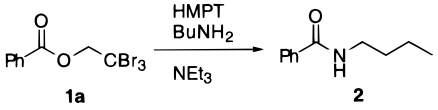
(5) (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801. (b) Kim, M. H.; Patel, D. V. *Tetrahedron Lett.* **1994**, *35*, 5603. (c) Coste, J.; Campagne, J.-M. *Tetrahedron Lett.* **1995**, *36*, 4253.

(6) Castro, B. R. *Org. React.* **1983**, *29*, 1.

(7) (a) Höfle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (c) Hassner, A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; p 2022.

10.1021/jo9823700 CCC: $18.00
Published on Web 02/17/1999

Table 1. Initial Studies of Amide Formation

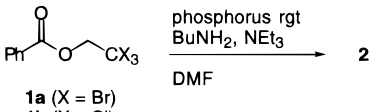


1a 2

entry	solvent	*T* (°C)	% yield of **2**[a]
1	THF	0	36
2	benzene	0	35
3	CH_3CN	0	70
4	DMF	0	75
5	DMF	−55	83

[a] Isolated yields.

Table 2. Effect of Phosphorus Nucleophile and Halogen on the Synthesis of 2

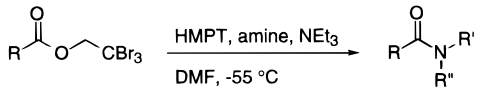


1a (X = Br)
1b (X = Cl)

entry	X	phosphorus rgt	*T* (°C)	time (h)	% yield of **2**[a]
1	Br	HMPT	−55	0.5	83
2	Br	PBu_3	−55 → 0	1.2	25
3	Br	PPh_3	rt	48	24[b]
4	Br	none	rt	48	17[c]
5	Cl	HMPT	rt	4.5	18
6	Cl	PBu_3	90	3.5	39

[a] Isolated yields. [b] 42% of **1a** was recovered. [c] 66% of **1a** was recovered.

Table 3. Optimized Conversion of Tribromoethyl Esters to Amides



1a (R=Ph)
3 (R=*c*-Hex)
4 (R=(*S*)-BOCNHCH(CH_3))

5a (R=Ph, R'=R"=Et)
5b (R=Ph, R'=CH_2CO_2Et, R"=H)
6a (R=*c*-Hex, R'=Bu, R"=H)
6b (R=*c*-Hex, R'=R"=Et)
7 (R=(*S*)-BOCNHCH(CH_3), R'=(*S*)-CH(CH_3)CO_2Et, R"=H)

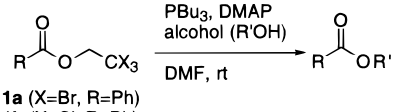
entry	trihaloethyl ester	amine	product	% yield[a]
1	**1a**	$HNEt_2$	**5a**	76
2	**1a**	HCl·GlyOEt	**5b**	77
3	**3**	$BuNH_2$	**6a**	88
4	**3**	$HNEt_2$	**6b**	57
5	**4**	HCl·AlaOEt	**7**	70

[a] Isolated yields.

when subjected to similar reaction conditions in the absence of tribromoethyl ester.[9] The reduced nucleophilicity of alcohols relative to amines allows attack by dimethylamine to become a competitive reaction pathway in the HMPT-mediated transesterifications.

Esters of both primary and secondary alcohols were produced in good yields using the tributylphosphine−DMAP procedure (Table 4, entries 2−11). Acylation of *tert*-butyl alcohol proved difficult, giving only 11% of the *tert*-butyl benzoate ester when *tert*-butyl alcohol was used as cosolvent (entry 12). As a control, treatment of **1a** with 2-methoxyethanol and DMAP in the absence of phosphine for 24 h at room temperature produced no product by TLC analysis. As with the amidation reactions, the use of the trichloroethyl ester derivatives required higher temperatures for starting material consumption and provided lower yields (entry 13).

Table 4. Synthesis of Esters from Trihaloethyl Esters



1a (X=Br, R=Ph)
1b (X=Cl, R=Ph)
3 (X=Br, R=*c*-Hex)

entry	trihaloethyl ester	alcohol (R′OH)	product	% yield[a]
1	**1a**	$CH_3O(CH_2)_2OH$	**8a**	21[b]
2	**1a**	$CH_3O(CH_2)_2OH$	**8a**	69
3	**1a**	BuOH	**8b**	81
4	**1a**	BnOH	**8c**	77
5	**1a**	2-pentanol	**8d**	62
6	**1a**	(−)-menthol	**8e**	61
7	**3**	$CH_3O(CH_2)_2OH$	**9a**	74
8	**3**	BuOH	**9b**	65
9	**3**	BnOH	**9c**	70
10	**3**	2-pentanol	**9d**	63
11	**3**	(−)-menthol	**9e**	65
12	**1a**	*t*-BuOH[c]	**8f**	11
13	**1b**	$CH_3O(CH_2)_2OH$	**8a**	44[d]

[a] Isolated yields. [b] Reaction conducted in the absence of DMAP. [c] 1:1 DMF/*t*-BuOH was used as solvent. [d] Reaction temperature = 100 °C.

The mechanism implied in eq 1, involving an acyloxyphosphonium intermediate,[4b−d,g,5] is supported by the observation of 1,1-dibromoethylene by proton and carbon NMR analysis of the crude distillates from reaction mixtures in the conversion of **1a** to **2** and **1a** to **8a**. Furthermore, ^1H NMR coupling constants for menthol-derived esters **8e** and **9e** revealed a retention of configuration at the carbinol carbon. Thus, esterification does not proceed by a Mitsunobu-type inversion in which the alcohol is activated by a phosphonium species and then displaced by a carboxylate anion.[10] The beneficial effect of catalytic DMAP in transesterification reflects the lower nucleophilicity of alcohols, relative to amines.

In summary, secondary and tertiary amides have been synthesized in moderate to good yields from tribromoethyl esters in one step by treatment with HMPT and amine. Similarly, esters of primary and secondary alcohols have been prepared from tribromoethyl esters by treatment with tributylphosphine in the presence of DMAP. Trichloroethyl carboxylates gave lower yields of ester and amide products when subjected to these reaction conditions. This method conveniently bypasses the free acid form of the substrate and provides a direct and efficient method for the conversion of protected carboxylic acids to esters or amides.

Acknowledgment. This research was supported by NIH Grant Nos. GM 28321 and CA74394. Additional support from Merck and Pfizer is gratefully acknowledged. The University of Wisconsin NMR facility receives financial support from NSF (CHE-9208463) and NIH (1S10 RR0 8389-D1).

Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **1**−**9**.

JO9823700

(8) (a) Petrov, K. A.; Nifant'ev, É. E.; Lysenko, T. P.; Evdakov, V. P. *Zh. Obshch. Khim.* **1961**, *31*, 2377. (b) Nifant'ev, É. E.; Ivanova, N. L.; Fursenko, I. V. *Zh. Obshch. Khim.* **1969**, *39*, 854. (c) Houalla, D.; Sanchez, M.; Wolf, R. *Bull. Soc. Chim. Fr.* **1965**, 2368.

(9) A solution of HMPT in DMF was treated with methanol (1.4 equiv), DMAP (1 equiv), and 4-(*N*,*N*-dimethylamino)pyridinium trifluoroacetate (DMAP·TFA, 0.4 equiv). Phosphorus NMR analysis of an aliquot of this reaction mixture after 10 min showed no HMPT resonance (122.7 ppm) and two downfield resonances that correspond to $MeOP(NMe_2)_2$ (137.9 ppm) and $(MeO)_2PNMe_2$ (147.6 ppm). This spectrum is similar to the ^{31}P spectrum obtained in the ethanolysis of HMPT (ref 8c).

(10) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. *Org. React.* **1992**, *43*, 335.