The Effect of Acid Strength on the Mitsunobu Esterification Reaction: Carboxyl vs Hydroxyl Reactivity

David L. Hughes* and Robert A. Reamer

Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065

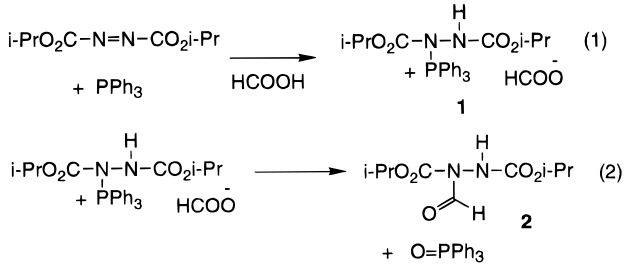
Received December 8, 1995[⊗]

In the presence of carboxylic acids, the adduct formed between triphenylphosphine and diisopropyl azodicarboxylate reacts to form mono- and bis-acylated hydrazides and the carboxylic acid anhydrides. These products are formed via attack of the carboxylate on the triphenylphosphonium group of the adduct, with weaker acids reacting much faster than stronger acids. This provides an explanation for the observation in the literature that acids stronger than acetic acid, such as 4-nitrobenzoic acid and chloroacetic acid, provide better yields in esterification reactions, since reaction of the alcohol with the phosphonium group of the adduct is more rapid than the competing reaction of the carboxylate for the phosphonium group.

Introduction

The Mitsunobu reaction has found widespread use in organic synthesis over the past two decades, especially for the inversion of alcohols via an esterification/hydrolysis procedure.[1] While a variety of carboxylic acids have been used for the esterification reaction, benzoic acid has been the most widely used. In a recent survey that compiled a list of reactions reported during the 1980−1990 period, 374 esterification reactions were listed; 57% employed benzoic acid, 10% acetic acid, 9% formic acid, 8% 4-nitrobenzoic acid or 3,5-dinitrobenzoic acid, 13% other acids, and 3% unspecified.[2] In 1991, Martin and Dodge reported that hindered alcohols gave much improved yields in the Mitsunobu reaction when 4-nitrobenzoic acid was used instead of benzoic acid.[3] In 1992, Bessodes and co-workers demonstrated a similar effect with chloroacetic acid, in that hindered alcohols that reacted in very low yields with benzoic acid or acetic acid gave good yields with chloroacetic acid.[4] Dodge and co-workers followed up these reports by a systematic study of the effect of acidity on the yield of esterification of menthol with various acids. With a series of substituted benzoic acids, they found that the least acidic members (4-MeO, 4-F, H, 4-Me) provided yields of 20−30%, while the most acidic (4-NO_2, 4-CN, 4-$MeSO_2$) furnished yields in the 60−80% range.[5] On the basis of these reports, 4-nitrobenzoic acid has become the acid of choice when inverting carbons bearing a hydroxyl group, as demonstrated by >100 citations to the Martin and Dodge paper. While the authors of the above papers conceded they had no firm explanation for the improved yields with the more acidic carboxylic acids, they rationalized the effect based on a finding of Camp and Jenkins[6] that the oxyphosphonium ion (the reactive intermediate) is favored over the phosphorane (unreactive intermediate) when the acid strength is increased. In this paper we demonstrate that the effect of acidity on the outcome of Mitsunobu reactions is due to the variability in the rates of reaction of the adduct formed between diisopropyl azodicarboxylate (DIAD) and triphenylphosphine with either the carboxyl group of the acid (which leads to decomposition) or the hydroxyl group of the substrate (which leads to esterification).

The first step in the Mitsunobu reaction is formation of the adduct **1** between PPh_3 and DIAD (eq 1). In the



presence of a carboxylic acid, the adduct is protonated, which generates the carboxylate as counterion. With formic acid in dichloromethane solvent, we had previously found that the adduct degrades to form primarily the *N*-formyl derivative (eq 2).[7] This reaction rate is comparable to the esterification reaction; thus, 2.5 equiv of DIAD and PPh_3 was required to complete the esterification reaction. We have now extended this initial observation to include several other acids and other solvents and have found that the acid strength has a profound effect on the stability of adduct **1** and on the pathway by which it reacts with nucleophiles.

Results

Mitsunobu reactions were conducted in the absence of alcohol substrates to determine the fate of triphenylphosphine, diisopropyl azodicarboxylate (DIAD), and the carboxylic acid. The ratios of products and their rate of formation were dependent on choice of solvent and the acidity of the carboxylic acid, as discussed below.

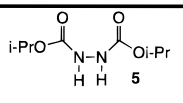
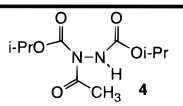
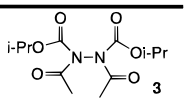
Acetic Acid. The three products isolated by flash chromatography from reaction of DIAD, PPh_3, and HOAc are the mono-*N*-acetylhydrazine **4**, the bis(*N*,*N*′-acetylhydrazine) **3**, and the hydrazide **5**, as shown in Table 1. The product distribution and the rates of formation are

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1996.

(1) Mitsunobu, O. *Synthesis* **1981**, 1−28.
(2) Hughes, D. L. *Org. React.* **1992**, *42*, 335−656.
(3) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.
(4) Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317−4320.
(5) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem.* **1994**, *59*, 234−236.
(6) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045−3049, 3049−3054.
(7) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491.

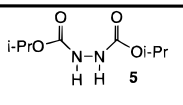
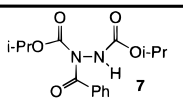
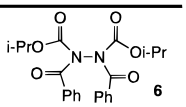
S0022-3263(95)02180-3 CCC: $12.00

Table 1. Products and Reactivity for Decomposition of Adduct 1 with HOAc[a]

Solvent	T_{95} at +2°C[b]	Eq. HOAc	 **5**	 **4**	 **3**
DMF	0.25 h	1.05	7%	82%	4%
Benzene	3 h	1.05	25	49	23
THF	0.7 h	1.05	25	48	22
THF	1 h	2.0	37	48	7
THF	1 h[c]	5.0	79	11	0.3
CH_2Cl_2	0.25 h	1.05	14	77	4
Toluene	8 h	1.05	37	46	17

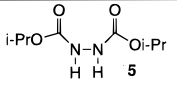
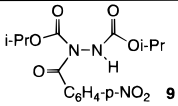
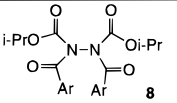
[a]Equimolar DIAD and PPh_3 were used at a concentration of 0.5M. [b]Time required for 95% reaction at +2°. [c] 22°C

Table 2. Products and Reactivity for Decomposition of Adduct 1 with $PhCO_2H$[a]

Solvent	T_{95} at +2°C[b]	Benzoic Anhydride	 **5**	 **7**	 **6**
DMF	1.5h	22%	15%	72%	1%
THF	2 h	31	33	50	12
CH_2Cl_2	0.8 h	35	18	72	2
Toluene	6 h	35	33	48	14

[a]Equimolar DIAD, PPh_3, and PhCOOH were used at a concentration of 0.5M. [b]Time required for 95% reaction at +2°.

Table 3. Products and Reactivity for Decomposition of Adduct 1 with 4-Nitrobenzoic Acid[a]

Solvent	T_{95} at +22°C[b]	 **5**	 **9**	 **8**
DMF	0.5 day	26%	64%	4%
THF	2 days	38	36	19
CH_2Cl_2	0.5 day	21	60	7
Toluene	12 days	60	24	10

[a]Equimolar DIAD, PPh_3, and ArCOOH were used at a concentration of 0.5M. [b]Time required for 95% reaction at +22°.

dependent on the ratios of reactants and the solvent. The fastest reaction occurred in dichloromethane and DMF, where adduct **1** reacted completely within 15 min at 0−5 °C. On the other hand, the decomposition of the adduct required 8 h at 0−5 °C in toluene, in part because the adduct was largely out of solution under these conditions.

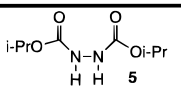
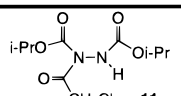
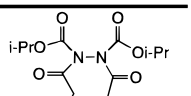
Benzoic Acid. Besides the hydrazide and mono- and bis-acylated products, benzoic anhydride was also observed and isolated from reactions of PPh_3, DIAD, and $PhCO_2H$. The ratios of each product and the reaction times are shown in Table 2. Compared to acetic acid, the phosphonium adduct with benzoate counterion is roughly 3- to 5-fold more stable than with acetate. As with acetate, the slowest reaction occurred in toluene solvent.

4-Nitrobenzoic Acid and Chloroacetic Acid. As with HOAc and $PhCO_2H$, the decomposition products of adduct **1** in the presence of 4-nitrobenzoic acid and chloroacetic acid are the hydrazide and the mono- and bis-acylated products. The results are compiled in Tables 3 and 4. With these acids, the phosphonium adduct is much more stable than with acetate or benzoate, with decomposition occurring over a period of days at room temperature. Thus, the decomposition could be readily monitored by ^{31}P NMR, with adduct **1** having a resonance at 53 ppm and PPh_3=O at 29 ppm. In these cases, no anhydride was isolated by flash chromatography, nor could it be detected by ^{13}C NMR.

Discussion

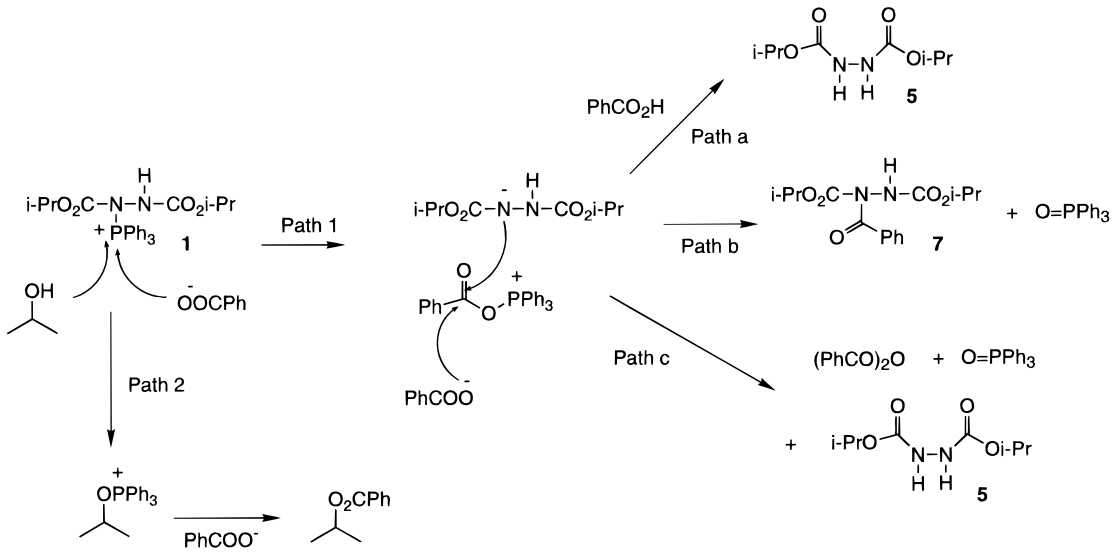
The data in Tables 1−4 demonstrate that the phosphonium adduct **1** is unstable, decomposing to the hydrazide and acylated hydrazides. The identification of benzoic anhydride at the 20−35% level in the reactions involving benzoic acid provides insight on the pathway by which adduct **1** is decomposing. The anhydride and the acylated hydrazides are apparently formed by reaction of benzoate with the phosphonium group of adduct **1** to form the benzoylphosphonium salt (Scheme 1, path 1). This salt then reacts with another mole of benzoate to form benzoic anhydride plus the hydrazide (path c) or can react with the hydrazide anion to produce *N*-benzoylhydrazide (path b). Thus, for a successful Mitsunobu esterification to take place, the alcohol must react faster (path 2) than the carboxylate (path 1) with adduct **1**.

Table 4. Products and Reactivity for Decomposition of Adduct 1 with Chloroacetic Acid[a]

Solvent	T_{90} at +22°C[b]	 5	 11	 10
DMF	10 days	67%	27%	1.5%
THF	3 days	68	17	5
CH_2Cl_2	10 days	69	23	7
Toluene	10 days	57	25	9

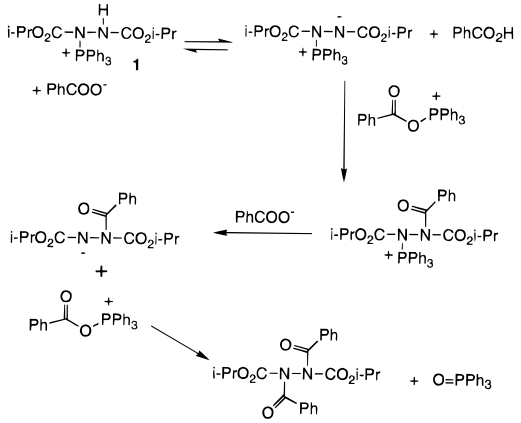
[a]Equimolar DIAD, PPh_3, and $ClCH_2COOH$ were used at a concentration of 0.5M. [b]Time required for 90% reaction at +22°.

Scheme 1



The mono- and bis-acylated hydrazides could also potentially be formed by reaction of hydrazide **5** with the benzoic anhydride formed in the reaction. However, extended reaction times did not alter the ratio of products, indicating that the benzoic anhydride was not reacting with hydrazide **5** or mono-acylated product **7** under the reaction conditions. The reaction pathway proposed in Scheme 1 would also suggest that equal amounts of anhydride and hydrazide **5** should be formed via path c if no further reaction of the anhydride occurs.

(8) The reaction pathways depicted in Scheme 1 do not account for the formation of the *N,N′*-diacylated products. We do not believe that the mono-acylated product is converted to the bis-acylated product since the proportion of each stays relatively constant throughout a reaction (instead of mono forming first followed by an increase in bis) and since the ratio remains unchanged once a plateau has been reached. A hypothesis for the formation of the bis adducts is shown below and involves acylation of adduct 1 before loss of the phosphonium group.



This is true in two of the four solvents examined (Table 1). In the other two solvents, the hydrazide is present in greater amounts than the anhydride, but formation of the hydrazide may also arise by protonation of the hydrazide anion formed after displacement of the phosphonium group (path a).[8]

The data in Tables 1 through 4 indicate that the rate of decomposition of adduct **1** is sensitive to the carboxylate counterion. With equimolar HOAc, the reactions are complete at 0−5 °C in 1 h or less in DMF, THF, and dichloromethane. Hence, under these conditions, for an esterification reaction to occur, the reaction of the alcohol with adduct **1** must be very rapid; otherwise, the adduct will completely react with the carboxylate before the alcohol has a chance to react. Thus, with hindered alcohols such as menthol, reaction of adduct **1** with the alcohol is apparently slower than reaction with the carboxylate under many conditions (dependent on solvent, temperature), such that no esterification occurs. This probably accounts for the relatively low number of Mitsunobu esterifications carried out with HOAc. The slow reaction of HOAc with adduct **1** in toluene solution is due in part to the poor solubility of **1** in this solvent, but this result suggests that toluene might be the best solvent for esterifications with HOAc. In fact, esterification of menthol with HOAc and 5 equiv of DIAD/PPh_3 at −15 °C for 12 h and then at 5 °C for 12 h in toluene gave a 67% isolated yield of the inverted acetate, compared to the 0% yield reported by Dodge for reaction in benzene at 5 °C to rt with the same ratio of reactants.[5] In addition, quantitation of the decomposition products **3**−**5** in this reaction indicated that similar ratios of these

products were formed in this esterification reaction as in the reaction reported in Table 1 in the absence of an alcohol substrate.

A comparison of the data in Tables 1 and 2 indicates that reaction of adduct **1** with $PhCO_2H$ is generally three to five times slower than with HOAc. This slower decomposition rate allows more time for the alcohol activation reaction to occur, which presumably accounts for the larger number of successful esterifications with benzoic acid reported in the literature.[2]

The rates of decomposition of adduct **1** in the presence of chloroacetate or 4-nitrobenzoate are on the order of 10^2-10^3-fold slower than with acetate or benzoate, as adduct **1** takes 0.5−10 days to completely react at 22 °C with these acids (Tables 3 and 4). On the other hand, the alcohol activation step is also slower with these less basic counterions, apparently because the carboxylate must act as a base to deprotonate the alcohol for alcohol activation to occur.[7] Thus, alcohol activation is 100-fold faster with acetate than with chloroacetate in dichloromethane.[7] However, decomposition of adduct **1** is about 500- to 1000-fold slower with chloroacetate than with acetate. Therefore, with chloroacetate as counterion, the overall effect is to increase the relative rate of hydroxyl attack over carboxylate attack on adduct **1** by 5−10-fold, leading to improved yields of ester.

Summary

In Mitsunobu esterification reactions, unwanted carboxyl activation competes with desired hydroxyl activation. For a successful esterification to occur, a delicate balance must be established such that the carboxylate is a strong enough base to initiate alcohol activation, but not such a strong nucleophile that it reacts with adduct **1** faster than the alcohol. With acetic acid, this balance is difficult to achieve, and esterifications are only successful within a narrow window of experimental conditions. With stronger acids such as chloroacetic and 4-nitrobenzoic acids, this balance is more easily achieved; the rates of both carboxyl and hydroxyl activation are reduced in comparison to acetate, but hydroxyl activation is significantly favored, such that esterifications with these acids can occur with even hindered alcohol substrates.

Experimental Section

General. Triphenylphosphine, diisopropyl azodicarboxylate, chloroacetic acid, chloroacetic anhydride, benzoic acid, benzoic anhydride, (1*S*)-(+)-neomenthol acetate, (−)-menthol, and 4-nitrobenzoic acid were purchased from Aldrich and used without purification. Solvents were dried with molecular sieves to a water level of <40 mg/L. Melting points are uncorrected. ^{1}H NMR spectra were obtained at 250 MHz, ^{13}C at 62.5 MHz. Flash chromatography was performed using E. Merck 230−400 mesh silica gel.

Product Isolation from Reaction with Acetic Acid. Triphenylphosphine (1.31 g, 5.0 mmol), acetic acid (0.32 g, 5.3 mmol), and benzene (8 mL) were combined and cooled to 5 °C. Diisopropyl azodicarboxylate (1.01 g, 5.0 mmol) was added over a 10 min period, keeping the temperature below 8 °C, during which time the reaction became heterogeneous. The mixture was then warmed to 22 °C and became homogeneous within 15 min. After 1 h at 22 °C the solvent was removed *in vacuo* and residue dissolved in dichloromethane (3 mL). This solution was loaded onto 75 g of flash silica, and the products were chromatographed using 4:1 hexane:EtOAc (350 mL), 3:1 hexane:EtOAc (900 mL), and 2:1 hexane:EtOAc (250 mL). Products were visualized on TLC using iodine or polymolybdate (hydrazide **5** could only be observed with iodine visualization). Three products were isolated in the following order of elution:

***N,N′*-Diacetyl-*N,N′*-bis(isopropylcarboxy)hydrazine (3)** (356 mg, 25%): mp 18−19 °C; ^{1}H NMR (C_6D_6) δ 0.90 (12H, d, J = 6.5 Hz), 2.48 (6H, s), 4.83 (2H, septet, J = 6.5 Hz); ^{13}C NMR (C_6D_6) δ 21.0, 21.1, 24.7, 71.7, 151.7, 168.2. Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72. Found: C, 49.72; H, 7.07; N, 9.52.

***N*-Acetyl-*N,N′*-bis(isopropylcarboxy)hydrazine (4)** (573 mg, 47%): mp 59−60 °C (heptane); ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, br d, J = 6.0 Hz), 1.31 (6H, d, J = 6.3 Hz), 2.54 (3H, s), 4.97 (1H, septet, J = 6.3 Hz), 5.03 (1H, septet, J = 6.2 Hz), 6.6 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 21.6, 21.8, 25.3, 70.3, 72.2, 152.6, 155.0, 170.8. Anal. Calcd for $C_{10}H_{18}N_2O_5$: C, 48.77; H, 7.37; N, 11.38. Found: C, 48.87; H, 7.37; N, 11.29.

***N,N′*-Bis(isopropylcarboxy)hydrazine (5)** (296 mg, 29%): mp 107−108 °C (80% water, 20% *i*-PrOH); ^{1}H NMR ($CDCl_3$) δ 1.25 (12 H, d, J = 6.5 Hz), 4.94 (2H, septet, J = 6.5 Hz), 6.55 (2H, br s); ^{13}C NMR ($CDCl_3$) δ 21.9, 70.0, 156.7. Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 47.08; H, 7.85; N, 13.73.

HPLC was used to quantify amounts of these products formed from experiments in other solvents, as reported in Table 1. HPLC conditions were as follows: DuPont C18-RX column, 25 cm × 4.6 mm; detection at 210 nm; 1.5 mL/min flow rate; ambient temperature; gradient elution from 30% MeCN/70% 0.1% aqueous H_3PO_4 to 80% MeCN/20% 0.1% aqueous H_3PO_4 over 25 min; elution times, **5** at 4.0 min; **4** at 6.6 min; **3** at 13.5 min, and triphenylphosphine oxide at 10 min.

Product Isolation from Reaction with Benzoic Acid. Triphenylphosphine (2.74 g, 10.5 mmol), benzoic acid (1.40 g, 11.5 mmol), and THF (25 mL) were combined and cooled to 0 °C. Diisopropyl azodicarboxylate (2.07 g, 10.2 mmol) was added over 10 min, keeping the temperature below 5 °C. After 2 h at 5 °C, the mixture was warmed to room temperature, concentrated to an oil *in vacuo*, and dissolved in 5 mL of dichloromethane. This material was chromatographed on 125 g of silica gel using an eluent consisting initially of 1:7 EtOAc:hexane followed by a step gradient to 1:2 EtOAc:hexane. Four products were isolated in the following elution order:

Benzoic anhydride (0.24 g, 19%): ^{1}H and ^{13}C NMR and HPLC retention time match that of an authentic sample.

***N,N′*-Dibenzoyl-*N,N′*-bis(isopropylcarboxy)hydrazine (6)** (0.47 g, 11%): mp 91−92 °C (90:10 EtOH:water); ^{1}H NMR ($CDCl_3$) δ 1.10 (12H, dd, J = 1.8, 6.4 Hz), 4.93 (2H, septet, J = 6.6 Hz), 7.40−7.73 (10H, m); ^{13}C NMR ($CDCl_3$) δ 21.3, 72.8, 128.2, 128.2, 132.0, 134.8, 151.8, 169.3. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.92; H, 5.79; N, 6.75.

***N*-Benzoyl-*N,N′*-bis(isopropylcarboxy)hydrazine (7)** (1.47 g, 47%): mp 120−121 °C (2:1 EtOH:water); ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, J = 6.1 Hz), 1.28 (6H, d, J = 6.2 Hz), 4.87 (1H, septet, J = 6.2 Hz), 5.00 (1H, septet, J = 6.2 Hz), 6.98 (1H, br s), 7.35−7.70 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.3, 21.9, 70.6, 72.4, 128.1, 128.1, 131.9, 135.2, 152.9, 155.3. Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.30; H, 6.51; N, 9.04.

***N,N′*-Bis(isopropylcarboxy)hydrazine (5)** (0.70 g, 33%). Spectral analysis was the same as above.

HPLC was used to quantify amounts of these products formed from experiments in other solvents, as reported in Table 2. HPLC conditions were as follows: DuPont C18-RX column, 25 cm × 4.6 mm; detection at 210 nm; 1.5 mL/min flow rate; ambient temperature; gradient elution from 30% MeCN/70% 0.1% aqueous H_3PO_4 to 70% MeCN/30% 0.1% aqueous H_3PO_4 over 20 min, then to 80% MeCN/20% 0.1% aqueous H_3PO_4 over 4 min; elution times, **5** at 3.8 min, benzoic acid at 4.0 min; triphenylphosphine oxide at 10 min, **7** at 12 min, benzoic anhydride at 16 min, and **6** at 21 min.

Product Isolation from Reaction with 4-Nitrobenzoic Acid. Triphenylphosphine (2.62 g, 10.0 mmol), 4-nitrobenzoic acid (1.70 g, 10.2 mmol), and THF (25 mL) were combined, and diisopropyl azodicarboxylate (2.02 g, 10.0 mmol) was added over 10 min at 23−30 °C. The solution was warmed to

40 °C for 18 h and then concentrated *in vacuo* and dissolved in 5 mL of dichloromethane. This solution was loaded onto 155 g of silica gel and eluted with a step gradient of 1:4 EtOAc:hexane to 1:2 EtOAc:hexane. Three products were isolated in the following elution order:

***N,N′*-Bis(4-nitrobenzoyl)-*N,N′*-bis(isopropylcarboxy)hydrazine (8)** (0.92 g, 19%): mp 150−152 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ 1.15 (12H, d, J = 6.5 Hz), 4.96 (2H, septet, J = 6.6 Hz), 7.89 (4H, d, J = 8.5 Hz), 8.34 (4H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 74.0, 123.5, 128.8, 140.2, 149.6, 150.8, 167.3. Anal. Calcd for $C_{22}H_{22}N_4O_{10}$: C, 52.59; H, 4.41; N, 11.15. Found: C, 52.47; H, 4.35; N, 11.14.

***N*-(4-Nitrobenzoyl)-*N,N′*-bis(isopropylcarboxy)hydrazine (9)** (1.26 g, 36%): mp 109−111 °C (80:20 EtOH:water); ^{1}H NMR ($CDCl_3$) δ 1.14 (6H, d, J = 6.1 Hz), 1.31 (6H, d, J = 6.2 Hz), 4.92 (1H, septet, J = 6.2 Hz), 5.02 (1H, septet, J = 6.2 Hz), 6.86 (1H, br s), 7.81 (2H, d, J = 7.5 Hz), 8.28 (2H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 21.9, 71.1, 73.2, 123.4, 128.6, 141.1, 149.3, 152.3, 155.1, 169.5. Anal. Calcd for $C_{15}H_{19}N_3O_7$: C, 50.99; H, 5.42; N, 11.89. Found: C, 51.01; H, 5.36; N, 11.89.

***N,N′*-Bis(isopropylcarboxy)hydrazine (5)** (0.77 g, 38%). Spectral analysis was the same as above.

HPLC conditions were the same as above for reactions with benzoic acid; retention times, 4-nitrobenzoic acid at 4.5 min, **9** at 13.5 min, and **8** at 22.6 min.

Product Isolation from Reaction with Chloroacetic Acid. Triphenylphosphine (2.62 g, 10.0 mmol), chloroacetic acid (0.983 g, 10.4 mmol), and THF (25 mL) were combined, and diisopropyl azodicarboxylate (2.02 g, 10.0 mmol) was added over 10 min at ambient temperature. The reaction was warmed to 40 °C for 21 h, concentrated, and chromatographed on 150 g of silica gel, using a step gradient from 1:7 EtOAc:hexane to 1:2 EtOAc:hexane. Three products were isolated in the following elution order:

***N,N′*-Bis(chloroacetyl)-*N,N′*-bis(isopropylcarboxy)hydrazine (10)** (0.18 g, 5%): mp 52−53 °C (heptane); ^{1}H NMR ($CDCl_3$) δ 1.28 (12 H, dd, J = 3.2, 6.2 Hz), 4.78 (4H, q, J = 16.1 Hz), 5.06 (2H, septet, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 21.6, 44.6, 73.3, 150.6, 165.2. Anal. Calcd for $C_{12}H_{18}Cl_2N_2O_6$: C, 40.35; H, 5.08; N, 7.84, Cl, 19.85. Found: C, 40.32; H, 5.17; N, 7.69, Cl, 19.91.

***N*-(Chloroacetyl)-*N,N′*-bis(isopropylcarboxy)hydrazine (11)** (0.48, 17%): mp 59−61 °C (heptane); ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, br m), 1.33 (6H, d, J = 6.2 Hz), 4.74 (2H, s), 4.98 (1H, septet, J = 6.3 Hz), 5.06 (1H, septet, J = 6.3 Hz), 6.66 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 21.6, 21.8, 45.3, 70.9, 73.1, 152.4, 154.8, 167.4. Anal. Calcd for $C_{10}H_{17}ClN_2O_5$: C, 42.79; H, 6.10; N, 9.98, Cl, 12.63. Found: C, 43.02; H, 6.17; N, 10.22, Cl, 12.26.

***N,N′*-Bis(isopropylcarboxy)hydrazine (5)** (1.39 g, 68%). Spectral analysis was the same as above.

Compound **11** could not be separated from triphenylphosphine oxide by HPLC, so the ratios listed in Table 4 were obtained by flash chromatographic isolation of products of reactions conducted at ambient temperature.

Preparation of (1*S*)-(+)-Neomenthol Acetate. (−)-Menthol (477 mg, 3.05 mmol), acetic acid (0.99 g, 16.5 mmol), triphenylphosphine (3.93 g, 15.0 mmol), and toluene (30 mL) were combined and cooled to −20 °C with stirring. Diisopropyl azodicarboxylate (3.09 g of 97% purity, 14.8 mmol) was added over 10 min, keeping the temperature below −10 °C. The batch became heterogeneous after the addition. The reaction was held at −14 to −18 °C for 12 h and then at 5 °C for 12 h. The mixture was then warmed to room temperature and concentrated to a solid *in vacuo*. The solid was dissolved in dichloromethane (10 mL) and loaded onto 205 g of silica gel. Elution was done with 500 mL each of 5%, 7%, 8%, 10%, and 15% EtOAc in hexanes. (1*S*)-(+)-Neomenthol acetate (408 mg, 67% yield) was obtained along with 26 mg (5.5%) of unreacted menthol. The neomenthol acetate identity was confirmed by comparison of the ^{1}H NMR with an authentic sample.

JO952180E