was combined with the previously collected solid and refluxed in methanol. Upon re-collection, the solid, the tetraoxide **2**, had mp 266–268 °C and represented an almost quantitative yield: NMR (CF_3CO_2H) δ 7.64–7.28 (m, 6), 7.12 (s, 2), 4.48 (s, 4), 4.12 (s, 2), 3.38–2.82 (t, 4), 2.42–1.58 (m, 2); IR (Nujol) 1603 (w), 1590 (w), 1298 (s), 1149 (s), 1112 (s), 1108 (s), 700 (m) cm^{-1}; MS *m/e* 365 (M^+). Anal. Calcd for $C_{18}H_{20}O_4S_2$: C, 59.33; H, 5.53. Found: C, 58.98; H, 5.43.

Pyrolysis[9] of **2** in gram quantities in high vacuum at 550–600 °C did not yield detectable amounts of [5.1]metacyclophane **10**.

3,3′-Methylenedibenzaldehyde (5). 3,3′-Methylenedi(benzyl alcohol)[1] (**4**) (51.6 g, 0.226 mol) was dissolved in acetone and the solution cooled to × −50 °C. Jones' reagent[10] (125 mL) was added during 1 h with cooling and stirring. The mixture warmed to −30 °C during the subsequent 1.5 h. Following usual workup, the ethereal extract was washed (with brine), dried ($MgSO_4$), and concentrated in vacuo. The residue (50.3 g, 0.225 mol, 99%) was the dialdehyde **5**: NMR δ 9.97 (s, 2), 7.68–7.25 (m, 8), 4.1 (s, 2).

3,3′-Methylenedibenzaldehyde Dithioketal (6). The dialdehyde **5** described above (10.1 g, 0.045 mol) was dissolved in toluene (700 mL). 1,3-Propanedithiol (13.7 g, 0.126 mol) and *p*-toluenesulfonic acid (0.3 g) were added. The mixture was refluxed 16 h with a Dean–Stark trap. The toluene was removed in vacuo. The residue was dissolved in $CHCl_3$, washed (20% aqueous KOH, 1 N HCl, water), and dried ($MgSO_4$), and then the $CHCl_3$ was removed in vacuo. The residue was recrystallized from $MeOH/CH_2Cl_2$ to give the dithiane **6**: mp 157–159 °C (14.6 g, 0.036 mol, 80%); NMR (Me_2SO) δ 7.4–7.0 (m, 8), 5.36 (s, 2), 3.94 (s, 2); IR (Nujol) 1596 (m), 1584 (w), 1270 (m), 746 (s), 710 (s) cm^{-1}. Anal. Calcd for $C_{21}H_{24}S_4$: C, 62.37; H, 5.98. Found: C, 62.56; H, 6.08.

[5.1.5.1]Metacyclophane (8). The dialdehyde **5** (3.3 g, 0.0147 mol) was dissolved in tetrahydrofuran (100 mL) under N_2. The ylide **7** was prepared from 1,3-trimethylenebis(triphenylphosphonium) bromide[7] (10.4 g, 0.0143 mol) and *n*-butyllithium (18.4 mL of a 1.6 N solution, 0.0294 mol) in tetrahydrofuran (150 mL) under N_2. The two solutions were added dropwise with stirring under N_2 to tetrahydrofuran (100 mL) during 2 h. The mixture was refluxed overnight. The tetrahydrofuran was removed in vacuo. The residue was dissolved in water and extracted (ether). The ethereal extracts were washed (brine), dried ($MgSO_4$), and concentrated to dryness. The residue (5.7 g) was dissolved in ethyl acetate and hydrogenated over 10% Pt/C at room temperature and atmospheric pressure. The catalyst and ethyl acetate were removed. The residue was put on to neutral III alumina (100 g). Elution by hexane yielded a crystalline compound **8**: mp 126–127 °C (recrystallized from ether) (0.24 g, 0.508 mmol, 3% yield); NMR δ 7.34–6.98 (m, 12), 6.88 (br, s, 4), 3.94 (s, 4), 2.70–2.30 (t, 8), 1.84–1.00 (m, 12); IR (Nujol) 1604 (m), 1590 (m), 778 (s), 738 (s), 700 (s) cm^{-1}; MS *m/e* 472 (M^+). Anal. Calcd for $C_{36}H_{40}$: C, 91.47; H, 8.53. Found: C, 91.43; H, 8.48.

[5.1]Metacyclophane-1,5-dione Bis(trimethylene dithioketal) (9). The dithiane **6** (8.55 g, 0.021 mol) was dissolved in tetrahydrofuran (600 mL). The solution was cooled to −60 °C under N_2, and *n*-butyllithium (20 mL of a 1.6 M solution, 0.032 mol) added dropwise. The mixture was stirred for 1 h, and then 1-bromo-3-chloropropane (3.90 g, 0.025 mol) in tetrahydrofuran (70 mL) was added dropwise. After 2 h the mixture was allowed to warm to room temperature and stirred overnight. The tetrahydrofuran was removed in vacuo. The residue was dissolved in $CHCl_3$. The chloroform solution was washed (1 N HCl, water) and dried ($MgSO_4$), and $CHCl_3$ was removed in vacuo to yield an oil (10.3 g, 101% yield based on product). TLC on silica GF eluted by benzene indicated the presence of a small amount of the dithiane **6** and a single slightly faster moving major component: NMR δ 7.82–7.50 (m, 2), 7.40–6.80 (m, 6), 5.08 (s, 1), 3.96 (s, 2), 3.32 (t, 2), 3.10–2.36 (m, 8), 2.36–1.40 (m, 8).

A portion of the above oil (1 g, 0.002 mol) was dissolved in dry tetrahydrofuran (100 mL). This solution was added, under N_2, dropwise with stirring to LDA (from diisopropylamine (0.424 g, 0.004 mol) and *n*-butyllithium (2 mL of a 1.6 M solution 0.003 mol)) in tetrahydrofuran (400 mL) at −60 °C. After 2 h the reaction mixture was allowed to warm to room temperature and stirred for 2 days. The tetrahydrofuran was removed in vacuo. The residue was dissolved in chloroform. The chloroform solution was washed (1 N HCl, water) and dried ($MgSO_4$), and $CHCl_3$ was removed in vacuo. The residue was chromatographed on neutral III alumina. Elution by pentane/benzene (1:1) yielded the crystalline cyclized dithiane **9** (270 mg, 0.6 mmol, 30% yield). Recrystallization provided the analytical sample (155 mg) of **9**: mp 225–227 °C (recrystallized from $MeOH/CH_2Cl_2$); NMR δ 7.84–7.50 (m, 2), 7.40–7.20 (m, 4), 7.02 (br s, 2), 4.08 (s, 2), 2.88–2.54 (m, 8), 2.14–1.66 (m, 8), 1.36–0.80 (m, 2); IR (Nujol) 1596 (w), 1584 (w), 1420 (s), 904 (m), 782 (s) cm^{-1}; MS *m/e* 444 (M^+). Anal. Calcd for $C_{24}H_{28}S_4$: C, 64.85; H, 6.35. Found: C, 64.61; H, 6.49.

[5.1]Metacyclophane (10). The bridged dithiane **9** (1.3 g, 0.00293 mol) was refluxed in ethanol (250 mL) with Raney nickel (approximately 8 g) for 24 h. The Raney nickel was removed and the filtrate concentrated in vacuo. The residue (294 mg) was purified by preparative GLC on Chromosorb (HP) 60/80 with a Dexsil GC300 coating at 200 °C. The main fraction (t_R 4.7 min) was crystalline (102 mg, 0.43 mmol, 15% yield). It was recrystallized to give [5.1]metacyclophane: mp 53–54 (crystallized from pentane/MeOH); NMR[11] (100 MHz, Varian XL100) δ 7.20–6.84 (m, 6), 6.64 (s, 2), 4.00 (s, 2), 2.54–2.42 (m, 4), 1.60–1.24 (m, 4), 1.12–0.80 (q, 2); IR (Nujol) 1600 (w), 1580 (w), 758 (m), 702 (m) cm^{-1}; MS *m/e* 236 (M^+). Anal. Calcd for $C_{18}H_{20}$ C, 91.47; H, 8.53. Found: C, 91.13; H, 8.83.

Acknowledgments. We acknowledge the support and encouragement of Dr. Max Wilhelm and helpful discussions with Professor Peter Yates. We thank Ms. N. Cahoon for IR spectra, Ms. R. Behnke for NMR spectra, Mr. S. Brody for GC work, Mrs. B. Warren for mass spectra, and Mr. G. Robertson for microanalyses.

Registry No. **1**, 59054-34-1; **2**, 70445-70-4; **4**, 59054-28-3; **5**, 70445-71-5; **6**, 70445-72-6; **7**, 63591-90-2; **8**, 70445-73-7; **9**, 70445-74-8; **10**, 67638-65-7; 1,3-trimethylenebis(triphenylphosphonium) bromide, 7333-67-7; 1-bromo-3-chloropropane, 109-70-6; 2-(3-chloropropyl)-2-[3-(3-(1,3-dithian-2-yl)benzyl)phenyl]-1,3-dithiane, 70445-75-9.

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Trifluoroacetylation of Amino Acids and Peptides by Ethyl Trifluoroacetate

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Received March 5, 1979

Although the trifluoroacetyl group has not found general use as an N-protecting group in peptide synthesis, it has nevertheless continued to prove useful in certain special circumstances. For example, we recently capitalized on its ready enzymatic removal to develop a new synthesis of azaserine,[1] a compound of interest as an antitumor agent and pancreatic carcinogen. Methods for the introduction of the trifluoroacetyl group into amino acids and peptides include reaction with trifluoroacetic anhydride alone[2] or in trifluoroacetic acid solution,[3] reaction with aqueous *S*-ethyl trifluorothioacetate in mildly alkaline medium,[4] reaction with phenyl trifluoroacetate in phenol,[5] and re-

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0022-3263/79/1944-2805$01.00/0

Table I. *N*-Trifluoroacetylation of Amino Acids and Dipeptides by Ethyl Trifluoroacetate and Triethylamine in Methanol[a]

amino acid or dipeptide	yield, %	reaction time, h	recryst solvent	mp, °C	lit. mp, °C
DL-alanine	87	44	PhH/*i*-Pr_2O	120-121	120-121[b]
DL-alanine[c]	94[d]	23	EtOAc	161-162	
L-alanine	82	25	PhH[e]	70-71	65-67[f]
L-asparagine	77	45	H_2O	162-163	160-162[g]
L-aspartic acid[h]	75	14	EtOAc/PhH	150-151	151-152[i]
L-cystine[j]	83	15	EtOAc/PhH	164-165	165-166[b]
glycylglycine	88	23	EtOAc	186-187	184-185[b]
glycylglycine[c]	89	16	MeOH	236-237 dec	242 dec[k]
L-phenylalanine	96	25	PhH/cyclohexane	121-122	120-121[f]
L-serine[c]	80[d]	96	MeOH	203-204	
L-serine[l]	76[m]	34	CCl_4[m]	73-74[m]	74-75[n]
L-tryptophane	89	23	H_2O	162-164	162-163[b]
L-tryosine	85[o]	17	EtOAc/PhH	194-195	192-193[b]
L-valine	91	45	PhH/cyclohexane	88-89	86-87[f]

[a] Reaction conditions: 10 mmol of amino acid or dipeptide, 10 mmol of triethylamine, 12.5 mmol of ethyl trifluoroacetate, 5 mL of methanol. [b] Reference 3. [c] DCHA in place of triethylamine. [d] Yield of DCHA salt. [e] After sublimation of crude product in high vacuum. [f] Reference 5. [g] F. Weygand and G. Adermann, *Chem. Ber.*, 93, 2334 (1960). [h] Two equivalents of triethylamine. [i] F. Weygand and H. Fritz, *Chem. Ber.*, 98, 72 (1965). [j] 5 mmol of amino acid with 10 mmol of sodium methoxide in place of triethylamine. [k] F. Weygand and M. Reiher, *Chem. Ber.*, 88, 26 (1955). [l] DMF as solvent, *i*-Pr_2NEt as amine. [m] After conversion to benzyl ester. [n] Reference 1. [o] TMG in place of triethylamine.

action with *sym*-trichlorotrifluoroacetone in Me_2SO.[6] The use of high boiling solvents, or odoriferous or strongly electrophilic reagents, can be disadvantageous. Trifluoroacetic anhydride, for example, can cause peptide bond cleavage,[7] while Panetta's Me_2SO procedure requires chromatographic separation of the trifluoroacetyl derivative from the solvent and tends to give poor or mediocre yields.[6] Our finding[1] that serine can be trifluoroacetylated with methyl trifluoroacetate in methanol in the presence of triethylamine prompted us to examine the generality of this method, with the results reported herein.[8]

For these studies, methyl trifluoroacetate was replaced by the more readily available and more readily purified ethyl trifluoroacetate. Stirring a suspension of amino acid in anhydrous methanol containing an equivalent of base and a small excess of ethyl trifluoroacetate leads to a smooth trifluoroacetylation, the progress of which is conveniently indicated by dissolution of the amino acid. The results of these experiments are summarized in Table I. Triethylamine has proven to be the most generally satisfactory base. However, with two of the less soluble amino acids, tyrosine and cystine, it was found necessary to use another base. In the case of tyrosine, 34% of unreacted amino acid was recovered after 4 days of stirring with triethylamine. By using tetramethylguanidine (TMG), only 5% of the unreacted amino acid was recovered after 3 days of reaction. With the highly insoluble cystine, triethylamine returned 90% of unreacted amino acid after 4 days, TMG 31% after 3 days, and sodium methoxide less than 3% after 15 h. Dicyclohexylamine (DCHA), a sterically hindered secondary amine, can also function as a base in this procedure. With this amine, for example, *N*-(trifluoroacetyl)serine (which is an oil[9]) was conveniently prepared and isolated in the form of its crystalline dicyclohexylammonium salt. In one instance, with serine as the amino acid, DMF as the solvent, and ethyldiisopropylamine as the base, reaction was slower than a comparable reaction in methanol but did go essentially to completion. Addition of benzyl bromide then converted the intermediate trifluoroacetamide to *N*-(trifluoroacetyl)-L-serine benzyl ester, resulting in a convenient one-pot synthesis of this compound from the amino acid. It seems likely that other polar aprotic solvents such as Me_2SO and HMPA could be used in place of methanol or DMF, but these have not been investigated.

The single dipeptide examined, glycylglycine, responded well to the procedure, which may then be a general one for peptides sufficiently soluble in the methanolic reaction medium. Finally, it should be noted that the yields quoted in Table I are for recrystallized material and have not been optimized. In most cases, the reactions were conducted only once.[10]

Experimental Section

Melting points, measured in capillary tubes using a Hershberg apparatus with short-range thermometers, are uncorrected. Commercial anhydrous methanol was dried by allowing it to stand several days over 3A molecular sieves. TMG and DMF were purified by fractionation in vacuo from CaH_2. Ethyldiisopropylamine was fractionally distilled from CaH_2 under argon. DCHA was fractionally distilled in vacuo. Triethylamine was fractionally distilled from phthalic anhydride and a center cut was redistilled from NaH under argon. Ethyl trifluoroacetate was distilled from P_4O_{10}. All anhydrous solvents and liquid reagents were stored over 3A molecular sieves. Sodium methoxide (3.6 M) was prepared under argon from sodium and methanol. Amino acids were finely ground and dried in vacuo over P_4O_{10} at 56 °C or (for L-asparagine monohydrate) at 110 °C. Dowex 50W-X8 resin, H+ form, 50–100 mesh, ~5 mequiv/g, was dried in vacuo over P_4O_{10} at 56 °C. Vacuum evaporations were performed on a Buchi rotary evaporator.

General Procedure for the Preparation of *N*-Trifluoroacetylamino Acids and Peptides. The reaction was conducted in an oven-dried, 25-mL, round-bottomed flask equipped with a Teflon stirring bar and rubber septum. The flask was charged with amino acid or peptide (10 mmol or, for cystine, 5 mmol) and purged with dry argon; dry methanol (5 mL) was added. With stirring, triethylamine (1.4 mL (10 mmol) or, for aspartic acid, 2.8 mL (20 mmol)) was added, followed by ethyl trifluoroacetate (1.5 mL, 12.5 mmol). The mixture was stirred vigorously at room temperature until the amino acid had completely dissolved. At this point methanol (5 mL) was added, the

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(10) Note Added in Proof: Trifluoroacetylation of amino acids by methyl trifluoroacetate/TMG has been reported: W. Steglich and S. Hinze, *Synthesis*, 399 (1976).

flask immersed in cold (10 °C) water, and Dowex 50 resin, H+ form (4 g or, for aspartic acid, 6 g), added. After the mixture was stirred for 10 min, it was filtered, the filtrate was evaporated in vacuo, and the crude derivative was recrystallized from the appropriate solvent (see Table I). In some cases, examination of the crude trifluoroacetyl derivative by NMR spectroscopy showed the presence of methyl ester, undoubtedly formed during treatment with the ion exchange resin. Ester formation can be minimized, as described, by keeping the reaction mixture cold and by using a short reaction time. Alternately, after removal of methanol in vacuo, the reaction with resin may be carried out in water (40 mL) or in 50% aqueous THF (20 mL). In one run with serine as the amino acid, evaporation of methanol gave a crystalline triethylammonium salt, which was treated with an excess of dilute hydrochloric acid and extracted with ethyl acetate to recover the free trifluoroacetyl derivative as an oil.

With tyrosine, TMG (1.25 mL, 10 mmol) was substituted for triethylamine, and the reaction mixture was filtered prior to resin treatment to remove a small amount of unreacted amino acid. With cystine, sodium methoxide in methanol (2.77 mL of 3.6 M, 10 mmol) was used as base, and the reaction mixture was again filtered prior to resin treatment to remove a trace of unreacted amino acid.

When DCHA (2.0 mL, 10 mmol) was used as a base, the reaction mixture was either evaporated in vacuo and the residue recrystallized (DL-alanine) or else the DCHA salt was recrystallized directly from the reaction mixture (serine and glycylglycine). For the latter two compounds, additional methanol (30 mL) had to be added during the reaction with ethyl trifluoroacetate in order to obtain a stirrable slurry.

***N*-(Trifluoroacetyl)-L-serine Benzyl Ester.** L-Serine (1.5 g, 10 mmol) suspended in dry DMF (5 mL) was treated with ethyl trifluoroacetate and ethyldiisopropylamine (1.71 mL, 10 mmol) as described above. After 24 h, most of the amino acid had dissolved. After 34 h, the reaction mixture, which still contained a small amount of undissolved amino acid, was immersed in cold water, and benzyl bromide (1.2 mL, 10 mmol) was added. Further stirring for 17 h at room temperature, followed by workup and purification as previously described,[1] gave 2.20 g (76%) of *N*-(trifluoroacetyl)-L-serine benzyl ester, mp 73–74 °C (lit.[1] mp 74–75 °C).

Acknowledgments. We wish to thank the National Cancer Institute for partial support of this work through contract N01 CP55708.

Registry No. Ethyl trifluoroacetate, 383-63-1; DL-alanine, 302-72-7; L-alanine, 56-41-7; L-asparagine, 70-47-3; L-aspartic acid, 56-84-8; L-cystine, 56-89-3; glycylglycine, 556-50-3; L-phenylalanine, 63-91-2; L-serine, 56-45-1; L-tryptophan, 73-22-3; L-tryosine, 60-18-4; L-valine, 72-18-4; *N*-(trifluoroacetyl)-DL-alanine, 1597-49-5; *N*-(trifluoroacetyl)-DL-alanine DCHA salt, 7609-58-7; *N*-(trifluoroacetyl)-L-alanine, 407-23-8; *N*-(trifluoroacetyl)-L-asparagine, 35146-48-6; *N*-(trifluoroacetyl)-L-aspartic acid, 369-08-4; *N,N'*-bis(trifluoroacetyl)-L-cystine, 402-91-5; *N*-(trifluoroacetyl)glycylglycine, 400-58-8; *N*-(trifluoroacetyl)-L-phenylalanine, 350-09-4; *N*-(trifluoroacetyl)-L-serine DCHA salt, 70333-05-0; *N*-(trifluoroacetyl)-L-serine benzyl ester, 67815-09-2; *N*-(trifluoroacetyl)-L-tryptophan, 363-39-3; *N*-(trifluoroacetyl)-L-tryosine, 350-10-7; *N*-(trifluoroacetyl)-L-valine, 349-00-8.

Application of Dithioester Reactions with Grignard Reagents to Carbon–Carbon Bond Formation: Synthesis of Egomaketone and *ar*-Turmerone

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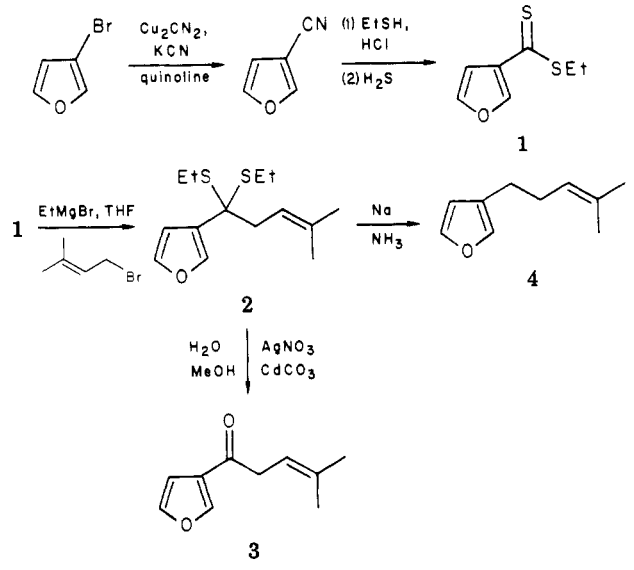
Received February 1, 1979

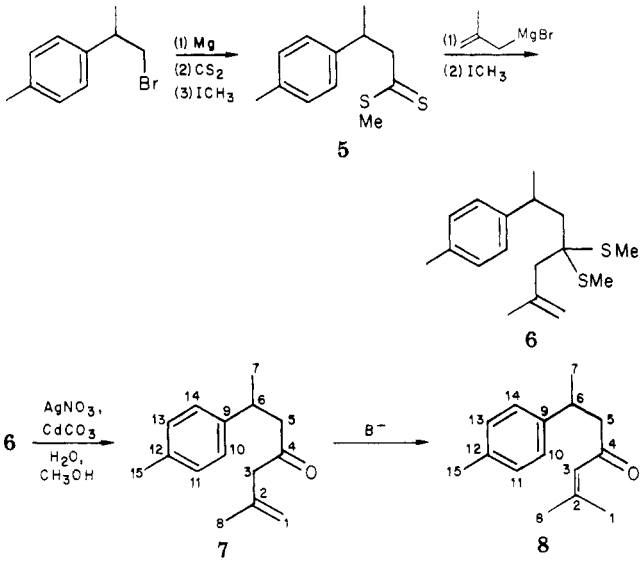
The addition of alkyl- and allylmagnesium halides to dithioesters can occur respectively in a thiophilic and carbophilic manner.[1,2] We have shown previously that these two regioselective reactions occur, under appropriate experimental conditions, in nearly quantitative yields and can be usefully applied in organic synthesis. In particular, we developed various paths for the preparation of β-unsaturated ketones[2] and achieved a convenient synthesis of isoartemisia and artemisia ketones from a β-unsaturated dithioester.[3] Herein we describe a convenient synthesis of egomaketone (**3**),[4] perillene (**4**),[6] iso-*ar*-turmerone (**7**), and *ar*-turmerone (**8**).[7,8]

Egomaketone (**3**) and perillene (**4**) were synthesized by utilizing a thiophilic addition reaction as depicted in Scheme I. Ethyl 3-furandithiocarboxylate (**1**) was pre-

Scheme I



Scheme II



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(9) The reaction of carbon disulfide with 3-furylmagnesium bromide was also investigated as a route to this dithioester, but attempted synthesis of the Grignard reagent failed.

0022-3263/79/1944-2807$01.00/0