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STUDIES IN THE SYNTHESIS OF A HEXAFLUOROPENICILLAMINE*

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SUMMARY

The known acid $(F_3C)_2C{=}C(NHCOPh)CO_2H$ was more fully characterized (the neutralization equivalent was one-fifth the molecular weight). Thioacetic acid did not react with it. Efforts to effect conjugate addition of α-toluenethiol led with piperidine only to intractable mixtures and with $BF_3{\cdot}Et_2O$ only to the thiol ester. Without catalyst, addition occurred but in the reverse sense to give 2-benzamido-2-benzylthio-3-trifluoromethyl-4,4,4-trifluorobutanoic acid. The latter was reduced by metals in liquid ammonia only to a red non-sulfur polymer but was reductively desulfurized by HBr/AcOH to 2-benzamido-3-trifluoromethyl-4,4,4-trifluorobutanoic acid (two crystalline forms).

INTRODUCTION

Earlier papers have summarized reasons for interest in analogues of penicillamine, $Me_2C(SH)CH(NH_2)COOH$ [2]. Among analogues of potential interest has been the hexafluoro compound (8). Electron withdrawal by fluorine in (8) should make the SH group less subject to oxidation to the symmetrical disulfide and to conversion into an unsymmetrical disulfide with cysteine, respectively major and minor products of normal excretion with penicillamine [3]. It also should change other properties in ways that might permit clarifying mechanisms by which penicillamine exerts a variety of biological actions (cf. reference 1).

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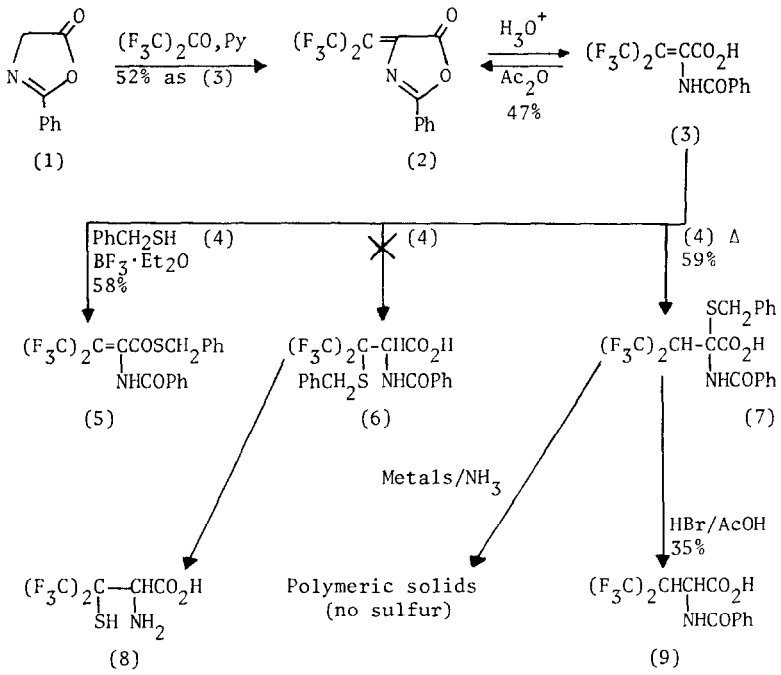

RESULTS AND DISCUSSION

Condensation of the azlactone (1) gave (2), which could be isolated by careful hydrolysis but was readily hydrolyzed further to the unsaturated acid (3); (3) has been reported by Knunyants et al. but with sparse details of synthesis or characterization [4]. Reconversion of (3) to (2) has been achieved with ketene [4], but acetic anhydride proved a more convenient alternative. The conventionally determined neutralization equivalent of (3) proved to be one-fifth the molecular weight. So rapid a hydrolysis to the acid salt produced, i.e. $F_3C(NaO_2C)C{=}C(NHCOPh)CO_2Na$, was astonishing, although hydrolysis to this salt has been reported in aqueous bicarbonate after several days [5].

Our original hope was to add α-toluenethiol (4) conjugatively to (3) to form (6) and then to debenzylate and debenzoylate (6) to (8). Catalysis with a 10% excess of one molar proportion of piperidine gave only intractable mixtures, which contained (3) and (7) by TLC. Addition of (4) to an isolated double bond has been reported with catalysis by $BF_3{\cdot}Et_2O$ [1], but

(4) with the unsaturated acid (3) gave the thiol ester (5) as the only product isolable. The structure of (5) was confirmed by ^{1}H NMR, ^{19}F NMR, IR (shift of -COOH from 1725 cm^{-1} to 1695 cm^{-1} for $-COSCH_2Ph$) and elemental analysis. Moreover, the (5) was insoluble in $NaHCO_3$, reduced $KMnO_4$ more rapidly than did (3), and gave a thiol when heated with aniline, all indicative of a thiol ester; the neutralization equivalent showed an interesting parallel to that of (3) (see EXPERIMENTAL).

Heating in solvent without catalyst can effect addition of an alkanethiol to maleic acid [6], and after prolonged reflux in ethanol, (4) likewise could be induced to add to (3). Although there seemed reason at first to believe that the adduct was (6), the fact that sodium, lithium, or calcium in liquid ammonia led only to red polymeric products that contained no sulfur pointed to (7) as the correct structure. Attempted debenzylation with HBr/AcOH, a procedure successful with aqueous HBr and S-benzylpenicillamine [7] gave (9). Since (7) seemed more likely than (6) to afford (9), our suspicions were enhanced that the adduct in fact had structure (7). Reference to other work of Knunyants et al. then revealed that although normal conjugate addition occurs with $F_3CCH{=}CHCO_2H$, addition in the opposite sense (i.e. to Carbon 3) can occur to $(F_3C)_2C{=}C(CO_2H)-$ with water or ammonia as nucleophiles [8]; hence reverse addition of (4) to (3) is a clean illustration of the latter possibility. The ^{19}F NMR spectrum was of little relevance to the structural question of the adduct (7) since it showed a complex multiplet at δ -18.6 (attributable to the two non-equivalent CF_3 groups; prochiral center present), but coupling constants in the ^{1}H NMR and ^{13}C NMR also supported structure (7) rather than (6). When thioacetic acid was heated with (3) for 24 h in glyme, 78% of the (3) was recovered and no adduct could be isolated.

EXPERIMENTAL

$^{19}Fluorine$ NMR spectra were obtained with a Varian XL-100A spectrometer operating at 94.1 MHz; spectra were calibrated in terms of displacement in ppm from the ^{19}F resonance of CF_3CO_2H used as an external reference, with negative values (i.e. $-\delta$) corresponding to low field. $^{13}Carbon$ NMR spectra were obtained with a JEOL FX90Q spectrometer operating at 22.64 MHz with Me_4Si as a reference. Other general procedures were as described previously [1].

2-Benzamido-3-trifluoromethyl-4,4,4-trifluoro-2-butenoic Acid (3)

In a procedure based on a rather undetailed one [4], hexafluoroacetone (82.3 g, 496 mmol; Matheson Gas Products) was bubbled as a gas (dry ice condenser) during 1 h into a ice-cooled solution of 40.0 g (248 mmol) of 2-phenyl-2-oxazolin-5-one (1) [9] in pyridine (110 mℓ, 1360 mmol). The dark brown solution was stirred for 1.5 h more at 0°C, allowed to warm to ∿25°C (2-3 h) and stirred there for 2 h. The solution then was cooled to 0°C, cold 6 N HCl (250 mℓ) was slowly added (∿30 min), and the solution was vigorously stirred for 4-6 h at ∿25°C; a dark red oil appeared. The mixture was extracted three times with 200-mℓ portions of ether, and the combined extracts were washed with three 100-mℓ portions of H_2O. The ethereal layer was dried ($MgSO_4$), filtered, and concentrated to 47 g (58%) of dark brown solid, mp 150-156°C. Two recrystallizations from ethylene chloride gave 42.2 g (52%) of (3) as white crystals: constant mp 164.5-166°C dec (cited [4] 164-166°C dec); IR (KBr) 3300, 3200-2200, 1725, 1650, 1600, 1500, 1480, 1340, 1260, 1170, 980, 740, 710 and 675 cm^{-1}; NMR (CD_3OD) δ 7.33 (m, 3H, Ph) and 7.64 (m, 2H, Ph). Analysis: Found: F, 35.05 (cited [4], 35.88%). $C_{12}H_7F_6NO_3$ requires F, 34.84%.

In determination of the neutralization equivalent (neut. equiv.) of (3), 0.2038 g (0.62 mmol) in ∿40 mℓ of EtOH containing phenolphthalein was titrated in quite the usual way with 0.0489 N NaOH; 65.8 mℓ (3.22 mmol) of NaOH was required for the usual end point. The equivalent weight calcd for $C_{12}H_7F_6NO_3$ with five potential acid equivalents is 65.4 (found, 63.3). With R = $F_3C\text{-}\dot{C}\text{=}\dot{C}\text{-}NHCOPh$, the stoichiometry of (3) with five equivalents of OH^- can be envisioned as follows:

$$F_3CRCO_2H \xrightarrow{OH^-} HOCF_2RCO_2H \xrightarrow[(-NaF,H_2O)]{OH^-} FC(O)RCO_2H \xrightarrow{OH^-} HO_2CRCO_2H \xrightarrow{2HO^-} NaO_2CRCO_2Na$$

Mechanistic speculation has been offered for similar reactions of allylic fluorides [10]. Acidification, chilling, and scratching of the neutralized solution gave 74 mg (39%) of HO_2CRCO_2H, neut. equiv. 146 (calcd 152); the mp of 70-85°C presumably differs from that obtained by treating (3) with $NaHCO_3$ (cited [5] 167-168°C) because of a different composition of geometrical isomers.

The azlactone (2), 2-phenyl-4-hexafluoroisopropylidene-2-oxazolin-5-one, could be isolated after a condensation like that described [using

4.03 g of (1)] by adding enough HCl (3 N) to neutralize the pyridine, stirring for 30 min, and extracting the resulting oil with ether. Drying (Na_2SO_4) and concentration gave 2.5 g (32%) of dark oil which, triturated with hexane several times, gave 1.32 g (17%) of (2), mp 77-80°C (cited [4] 82-84°C). However, to confirm the identity of (3) by conversion to (2), 0.200 g (0.61 mmol) of (3) was heated at ∿85°C with 0.720 g (7.05 mmol) of acetic anhydride for 3 h under N_2. The solution was cooled and concentrated (reduced pressure) to an oil, which was rubbed with hexane (∿10 mℓ). After ∿3 days at 0°C, crystals were separated and recrystallized from hexane; yield of (2), 0.088 g (47%), mp 79-81°C (cited [4] 82-84°C; reference 4 mentions conversion of (3) to (2) with acetic anhydride but gives details only for use of ketene).

S-Benzyl 2-Benzamido-3-trifluoromethyl-4,4,4-trifluoro-2-butenethioate (5) (nc)

Freshly distilled $BF_3 \cdot Et_2O$ (5.23 g, 36.8 mmol) was added to (3) (3.00 g, 9.2 mmol) with protection from moisture ($CaCl_2$), and the mixture was stirred for 20 min to effect solution. α-Toluenethiol (4) (1.14 g, 9.2 mmol) was added during 30 min with stirring, which was continued for 2 h at ∿25°C and for 2 h at 65°C. The solution was cooled (solid precipitated) and poured onto 25 g of ice. Three 30-mℓ ether extracts were combined, washed four times with 20-mℓ portions of H_2O and dried (Na_2SO_4). Removal of ether gave 2.67 g (67%) of light brown solid, mp 115-125°C. This solid was washed twice with 10-mℓ portions of hexane and recrystallized three times from $CHCl_3$-hexane to give 2.30 g (58%) of (5) as long white needles: constant mp 143-145°C; IR (KBr) 3300, 1695, 1670, 1640, 1600, 1500, 1480, 1420, 1350, 1230, 1150, 1010, 920, 770, 710 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.36 (s, 2H, CH_2), 7.26-7.84 (m, 10H in two sets, Ph) and 8.48 (s, 1H, NH); ^{19}F NMR showed a quartet at δ -20.6 [J(FF), 8 Hz] further split into a doublet [J(FH) = 2.0 Hz, trans coupling of CF_3 to NH] and a second unsplit quartet area at δ -23.7 [J(FF), 8 Hz]. Analysis: Found: C, 52.79; H, 3.24; F, 26.38%. $C_{19}H_{13}F_6NO_2S$ requires C, 52.65; H, 3.03; F, 26.30%.

The neutralization equivalent of (5) was 143, pointing to a sequence like that with (3) for the first two equivalents of alkali, followed by cyclization involving the -C(O)F and PhC(O)NH- moieties, with neutralization of the HF by the third equivalent (neut. equiv. calcd 144); reference 5 reports oxazinones from reaction of carboxylate analogues of (5) with $NaHCO_3$.

2-Benzamido-2-benzylthio-3-trifluoromethyl-4,4,4-trifluorobutanoic Acid (7) (nc)

α-Toluenethiol (4) (0.38 g, 3.06 mmol) was added dropwise to a solution of (3) (1.00 g, 3.06 mmol) in EtOH (~4 mℓ) during 30 min. The mixture then was heated at 60-65°C for 38 h. Removal of EtOH gave viscous yellow oil, which was rubbed continuously with hexane at -78°C until it solidified. This solid, washed ten times with hexane to remove all traces of thiol, gave 0.81 g (59%) of (7) as white powder, mp 124-126°C. One recrystallization from CCl_4 gave 0.40 g (29%) of (7): mp 125.5-127°C; IR (KBr) 3375, 3050, 2950, 2900-2200, 1730, 1660, 1640, 1570, 1510, 1480, 1420, 1280, 1240, 1160, 1100, 1040, 940, 770 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (doublet of doublets, 2H, CH_2), 5.14 (septet, 1H, CH), 7.20-7.90 (m, 10H in two sets, Ph) and 10.26 (broad singlet, 1H, NH?); ^{19}F NMR showed a complex multiplet (two overlapping quartets with further splitting) at δ -18.6; ^{13}C NMR with H decoupled gave a septet for F_6C_2CH at 53.6 ppm (reference TMS) with J(F-C-C) = 27.5 Hz. Analysis: Found: C, 50.42; H, 3.22; F, 24.93%; neut. equiv. 456. $C_{19}H_{15}F_6NO_3S$ requires C, 50.55; H, 3.36; F, 25.25%; neut. equiv. 451.

2-Benzamido-3-trifluoromethyl-4,4,4-trifluorobutanoic Acid (9)

Dry HBr (1.75 g, 21.6 mmol) was passed into glacial acetic acid (9 mℓ) in a 3-necked flask equipped with a gas inlet tube, condenser, and drying tube ($CaCl_2$). The adduct (7) (0.908 g, 2.0 mmol) was added and the solution stirred at ~25°C under N_2. After 96 h, TLC showed no change. The solution was heated under reflux for 24 h, after which TLC (EtOH) showed only one major component; the R_f (0.60) was different from that of starting material (R_f 0.55). Removal of solvent left dark oil, which solidified under vacuum (1 torr) during 2 h (102% yield, mp 120-140°C). Three recrystallizations from EtOH-H_2O gave 0.232 g (35%) of (9) as white crystals: constant mp, 152-154°C (cited [11] 149-150°C). However, when this (9) was dried at 80°C (1 torr) for 18 h, the mp changed to 172-173°C. Elemental analysis was performed on this material (mp 172-173°C) is such a way as to permit hydration; it was exposed to the air (but protected from dust) for 5 days and then was dried at 60°C (1 torr) for 12 h. Elemental analysis performed immediately after drying was in excellent agreement for structure (9); only 0.08% H_2O was present, ruling out any possibility of a hydrate for the lower melting material. Presumably, the difference in melting

points resulted from a change in crystalline form, but insufficient (9) remained for further study of this point. Spectra were determined with (9) of mp 152-154°C: IR(KBr) 3280, 3100-2500, 1715, 1650, 1600, 1530, 1430, 1320, 1300, 1260, 1220, 1160, 1100, 960, 900, 800 and 700 cm^{-1}; ^{1}H NMR (CD_3OD) δ 4.38 [m, 1H, $(CF_3)_2CH$], 5.68 (d, 1H, $CHCO_2$), 7.42-7.84 (m, 5H, Ph). Analysis: Found: C, 43.76; H, 2.82; F, 34.50; H_2O, 0.08%. $C_{12}H_9F_6NO_3$ requires C, 43.78; H, 2.76; F, 34.63; H_2O, 0.00%.

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