77172-47-5; 12-hydroxyoctadecanoic acid polymer, 27924-99-8; 15-hydroxypentadecanoic acid polymer, 37453-68-2; 16-hydroxyhexadecanoic acid polymer, 30792-74-6; 11-bromoundecanoic acid polymer, 77172-42-0; 15-bromopentadecanoic acid polymer, 77172-43-1; 12-hydroxyoctadecanoic acid repeating unit, 27941-02-2; 15-hydroxypentadecanoic acid repeating unit, 73207-55-3; 16-hydroxyhexadecanoic acid repeating unit, 32239-70-6; 11-bromoundecanoic acid repeating unit, 25735-90-4.

Reaction of Halomethyl Ketones with Thiols and Selenols: Substitution vs. Reduction[1,2]

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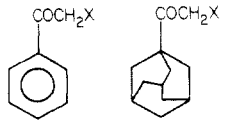
This report describes the novel reduction of iodomethyl ketones to methyl ketones by thiols and selenols in high yield under extremely mild conditions.

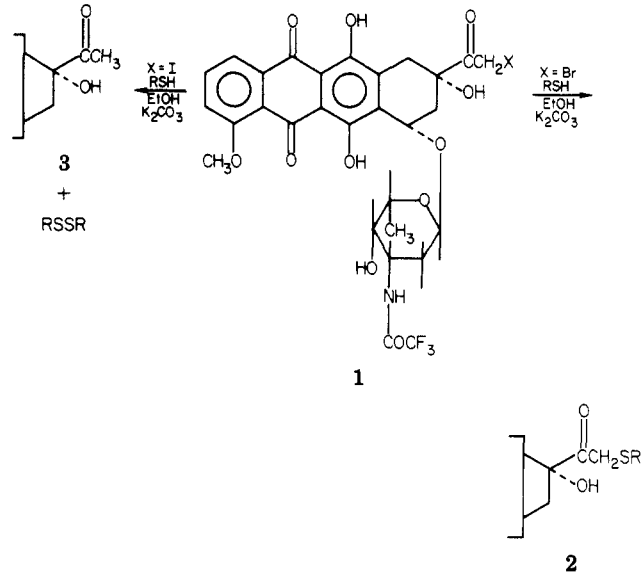
In connection with a major ongoing program on semisynthetic anthracycline analogues, we were interested in preparing some 14-thia analogues of adriamycin and of *N*-(trifluoroacetyl)adriamycin-14-valerate (AD 32), a clinically promising adriamycin analogue,[3,4] for antitumor and structure–activity evaluation. Our initial synthetic approach involved reaction of 14-iodo-*N*-(trifluoroacetyl)-daunorubicin (1, X = I), a readily available intermediate in our laboratory, with alkane- and arenethiols, with the expectation of **2** (Scheme I), from which the corresponding free amino compounds could be achieved by alkaline hydrolysis of the trifluoroacetamide. However, treatment of 1 (X = I) with various short- or long-chain alkanethiols, or with benzenethiol, in anhydrous ethanol at room temperature in the presence of K_2CO_3 in each instance resulted in a rapid reaction and the exclusive formation of *N*-(trifluoroacetyl)daunorubicin (**3**), a known and well-characterized compound; with *n*-dodecanethiol, the concomitant formation of di-*n*-dodecyl disulfide was verified by vapor-phase chromatography. In contrast, when the corresponding 14-bromo compound, 1 (X = Br), was treated with thiols under identical conditions, nucleophilic displacement of the halide occurred, with the formation of the desired 14-thia derivatives, **2**.[2]

Unaware of a precedent for the iodomethyl ketone reduction, we investigated several model compounds to explore the generality of the reaction. Thus, α-chloroacetophenone and α-bromoacetophenone reacted normally with *n*-dodecanethiol and benzenethiol to give the corresponding sulfides **4** (X = $SCH_2(CH_2)_{10}CH_3$, SC_6H_5), whereas α-iodoacetophenone prepared by halide exchange from **4** (X = Cl) under the same conditions afforded exclusively acetophenone and the companion disulfide. Similarly with 1-adamantyl halomethyl ketones **5** (X = Br) gave exclusively substitution, whereas **5** (X = I) underwent reduction.



4 5

Scheme I



A similar effect was seen when a selenol was used in place of a thiol. Reaction of 1 (X = Br) with benzeneselenol under the indicated conditions afforded the hitherto unknown 14-(phenylseleno)-*N*-(trifluoroacetyl)daunorubicin, whereas with 1 (X = I) only **3** and diphenyl diselenide were formed.

The formation of methyl ketones from iodomethyl ketones by reaction with thiols is noteworthy for its ease and simplicity, mild reaction conditions, and high, often quantitative, yields. Reactions are easily monitored by thin-layer chromatography, and products, being easily separated by column chromatography from the accompanying disulfide, are obtained in high purity. As indicated by the stoichiometry, complete reaction is obtained at room temperature with a reactant ratio of 2:1 thiol–iodomethyl ketone; a lower ratio of reagents results in mixtures of disulfide, methyl ketone, and unchanged starting material.

It has been previously reported that reactions of chloro- or bromomethyl ketones with thiolate give mixtures of reduction and substitution products (together with unchanged starting material) when equimolar amounts of reactants are used; however, with excess thiolate, reactions gave predominantly reduction products.[5] In the present work, we also can find some substitution product derived from iodomethyl ketone, if the reaction is carried out at −70 °C. These observations suggest that the reactivity of the halogen of the halomethyl ketone function plays a determining role in directing the course of the reaction, reduction vs. substitution. Thus, the significance of the present report lies in the greater reactivity of iodomethyl ketones with thiols at room temperature, a fact which results in almost instantaneous reaction and high yield of reduction product.

The mechanism for the thiol reduction of halomethyl ketones remains somewhat speculative, as is also the situation for the related reduction of benzyl iodides by thiols, recently described by Hevesi.[6] Oki et al.[5] suggest that, in their examples, reduction is brought about by the action of excess thiolate on the initially formed substitution product. However, the rapidity of reaction of iodomethyl ketones, together with the fact that some of the reactions of chloromethyl and bromomethyl ketones require 30 min

(1) This work was supported by Research Grant CA 17263 from the National Cancer Institute, National Institutes of Health, Bethesda, MD.
(2) Presented in part at the 175th National Meeting, American Chemical Society, Anaheim CA, 1978, MEDI 47.
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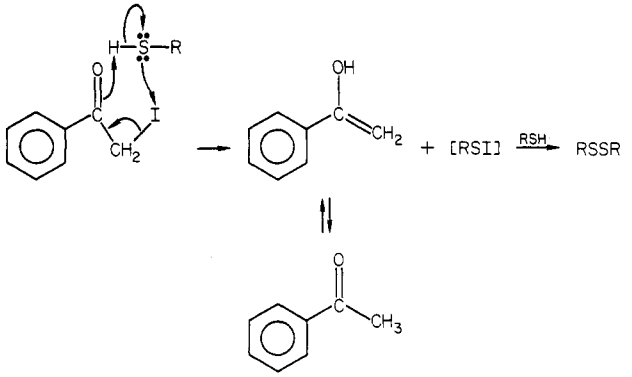
Scheme II



to 10 h for completion, suggests that, for the iodo derivatives, another mechanism, such as that shown in Scheme II, may be involved.

It is unlikely that yet a third mechanistic option, that involving an initial thio substitution, with the accompanying liberation of HI which could then serve as the reducing agent, could be operative, in view of the presence of base used in our reactions (K_2CO_3) and in those of Hevesi (triethylamine).

Experimental Section

Unless otherwise indicated, starting materials were obtained from Aldrich Chemical Company, Metuchen, NJ. Melting points were determined on a Fisher Meltemp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 137B Infracord. The ^1H NMR spectra were determined on a Varian Associates T60-A spectrometer in $CDCl_3$, with tetramethylsilane as internal standard. Biosil-A silicic acid (Bio Rad Laboratories, Rockville Center, NY) was used for all open column chromatographic separations. All reactions were carried out under nitrogen.

Reaction of α-Iodoacetophenone (4, X = I) with Thiols. (a) With Benzenethiol. 4 (X = I; 246 mg, 1.0 mmol; prepared by stirring α-chloroacetophenone with KI in acetone at room temperature) was stirred in absolute ethanol (15 mL) together with anhydrous K_2CO_3 (138 mg), and benzenethiol (216 μL, 2.1 mmol) was added. The reaction, monitored by TLC, was complete within 10 min, as indicated by the complete disappearance of starting material. The reaction mixture was filtered and diluted with $CHCl_3$ (100 mL), and the organic layer was washed with H_2O (4 × 25 mL). The $CHCl_3$ solution was dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator under reduced pressure. Chromatography of the residue on a column of silicic acid (15 g) with petroleum ether (bp 40–60 °C) afforded 209 mg (96% yield) of diphenyl disulfide. Continued elution of the column with petroleum ether containing 1% EtOAc afforded acetophenone [114 mg, 95% yield; ^1H NMR δ 2.57 (s, 3 H, $COCH_3$), 7.32–7.95 (m, 5 H, Ar H)], identical in all respects with an authentic sample.

(b) With *n*-Dodecanethiol. 4 (X = I; 246 mg, 1.0 mmol) and K_2CO_3 (138 mg) were stirred in ethanol (10 mL) at room temperature. *n*-Dodecanethiol (500 μL, 2.1 mmol) was added all at once, and stirring was continued for 10 min, at which time TLC showed the complete absence of starting halide. The reaction mixture was worked up, as above, and chromatographed on silicic acid (15 g). Elution with petroleum ether (bp 40–60 °C) accorded di-*n*-dodecyl disulfide (390 mg, 97% yield, mp 34 °C), identical with an authentic sample. Continued elution with petroleum ether containing 1% EtOAc gave 102 mg (85% yield) of acetophenone.

α-(Phenylthio)acetophenone (4, X = SC_6H_5). α-Chloroacetophenone (154.6 mg, 1.0 mmol) was stirred in ethanol (10 mL) with anhydrous K_2CO_3 (138 mg). Benzenethiol (103 μL, 1.0 mmol) was added, and stirring was continued for 1 h, at which time TLC showed the absence of starting halide. The reaction mixture was worked up, as above, and chromatographed on a column of silicic acid (12 g). Elution with petroleum ether (bp 40–60 °C) containing 2% EtOAc afforded pure product: 208 mg (91% yield); mp 53–54 °C; ^1H NMR δ 4.23 (s, 2 H $COCH_2S$), 7.25–7.97 (m, 10 H, Ar H). Anal. Calcd for $C_{14}H_{12}OS$: C, 73.64; H, 5.31; S, 14.04. Found: C, 73.76; H, 5.39; S, 14.17.

Similarly, reaction of α-bromoacetophenone (199 mg, 1.0 mmol) with benzenethiol afforded, after 30-min reaction time, 221 mg (96% yield) of 4 (X = SC_6H_5).

α-(*n*-Dodecylthio)acetophenone (4, X = $SC_{12}H_{25}$-*n*). Reaction of α-chloroacetophenone (154.6 mg, 1.0 mmol) and *n*-dodecanethiol (240 μL, 1.0 mmol) in 10 mL of ethanol, together with anhydrous K_2CO_3 (138 mg), for 1 h afforded pure product after workup and chromatography (petroleum ether): 279 mg (87% yield); mp 31–32 °C; ^1H NMR δ 0.8 (poorly resolved t, J = 6 Hz, 3 H, CH_3), 2.42 (m, 2 H, SCH_2R), 3.53 (br, 2 H, $COCH_2S$), 7.10–7.72 (m, 5 H, Ar H). Anal. Calcd for $C_{20}H_{32}OS$: C, 74.93; H, 10.08; S, 10.00. Found: C, 74.76; H, 10.16; S, 10.06.

The same product was obtained in 94% yield after 30-min reaction time when α-bromoacetophenone (199 mg, 1.0 mmol) was used in place of the chloro compound.

Reactions of 1-Adamantyl Halomethyl Ketones with Benzenethiol. (a) With Bromomethyl Ketone 5 (X = Br). Reaction of 5 (X = Br; 257 mg, 1.0 mmol) with benzenethiol (103 μL, 1.0 mmol) in ethanol (10 mL) in the presence of anhydrous K_2CO_3 (138 mg) after 30 min afforded 5 (X = SC_6H_5; 270 mg, 94% yield) after chromatography with elution with petroleum ether containing 1% EtOAc: mp 59–60 °C; ^1H NMR δ 3.82 (s, 2 H, $COCH_2S$), 7.15–7.60 (m, 5 H, Ar H). Anal. Calcd for $C_{18}H_{22}OS$: C, 75.47; H, 7.76; S, 11.19. Found: C, 76.05; H, 8.00; S, 11.57.

(b) With Iodomethyl Ketone 5 (X = I). Reaction of 5 (X = I) with 2 equiv of benzenethiol afforded, after chromatography, a quantitative yield of diphenyl disulfide and 1-adamantyl methyl ketone; ^1H NMR δ 2.1 (s, 3 H, $COCH_3$).

Reaction of 14-Iodo-*N*-(trifluoroacetyl)daunorubicin (1, X = I) with Benzenethiol. To a stirred mixture of 1 (X = I;[7] 50 mg, 0.066 mmol) and anhydrous K_2CO_3 (25 mg) in absolute ethanol (10 mL) was added benzenethiol (15 μL, 0.14 mmol). After 10 min, TLC indicated completion of reaction. The reaction mixture was diluted with $CHCl_3$ (50 mL), washed with water (4 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. The crude product was chromatographed on silicic acid. Elution with $CHCl_3$ afforded diphenyl disulfide (13 mg, 90% yield). Further elution with $CHCl_3$ containing 0.2% methanol gave a quantitative yield of *N*-(trifluoroacetyl)daunorubicin (3), which was identical in all respects with authentic compound prepared from daunorubicin and trifluoroacetic anhydride, as described in the patent literature.[7]

14-(Phenylthio)-*N*-(trifluoroacetyl)daunorubicin (2, R = C_6H_5). 1 (X = Br;[2] 250 mg, 0.36 mmol) and benzenethiol (40 μL, 0.40 mmol), together with K_2CO_3 (100 mg), in ethanol (50 mL) afforded, after 30 min, 243 mg of 2 (R = C_6H_5; 93% yield), mp 140–141 °C. The product was purified by precipitation from $CHCl_3$ by the addition of petroleum ether. Anal. Calcd for $C_{35}H_{32}F_3NO_{11}S$: C, 57.45; H, 4.42; F, 7.79; N, 1.92; S, 4.38. Found: C, 57.19; H, 4.61; F, 7.66; N, 1.92; S, 4.13.

α-(Phenylseleno)acetophenone (4, X = SeC_6H_5). Reaction of α-chloroacetophenone (154.6 mg, 1.0 mmol) in ethanol (10 mL) in the presence of K_2CO_3 (138 mg) with benzeneselenol (160 mg, 1.0 mmol), added in small portions over 5 min, afforded product (viscous oil) after 15 min: 179 mg (65% yield); ^1H NMR δ 3.81 (s, 2 H, $COCH_2Se$), 7.25–7.97 (m, 10 H, Ar H). Anal. Calcd for $C_{14}H_{12}OSe$: C, 61.09; H, 4.40; Se, 28.69. Found: C, 61.38; H, 4.63; Se, 29.07.

When α-iodoacetophenone was used in place of the chloro compound, reaction with benzeneselenol afforded only diphenyl diselenide and acetophenone in quantitative yields.

(Phenylseleno)methyl 1-Adamantyl Ketone (5, X = SeC_6H_5). Reaction of 5 (X = Br; 257 mg, 1.0 mmol) with benzeneselenol (160 mg, 1.0 mmol) in ethanol (10 mL) in the presence of K_2CO_3 (138 mg) for 15 min afforded, after workup and chromatography, 243 mg of product (73% yield) as a viscous oil; ^1H NMR δ 3.82 (s, 2 H, $COCH_2Se$), 7.2–7.6 (m, 5 H, Ar H). Anal. Calcd for $C_{18}H_{22}OSe$: C, 64.85; H, 6.67; Se, 23.69. Found: C, 64.90; H, 6.80; Se, 23.67.

Reaction of 5 (X = I) with benzeneselenol (2.1 equiv) under identical conditions afforded quantitative yields of diphenyl

(7) British Patent No. 1,217,133 (to Societa Farmaceutici Italia, Milano), Dec 31, 1970.

diselenide and 1-adamantyl methyl ketone.

14-(Phenylseleno)-*N*-(trifluoroacetyl)daunorubicin. Reaction of 1 (X = Br; 250 mg, 0.36 mmol) in ethanol (50 mL) with benzeneselenol (65.5 mg 0.41 mmol) and K_2CO_3 (100 mg) for 15 min, followed by normal workup and chromatography ($CHCl_3$ elution), afforded pure product (175 mg, 63% yield), mp 137–139 °C. Anal. Calcd for $C_{35}H_{32}F_3NO_{11}Se$: C, 53.99; H, 4.15; F, 7.32; N, 1.80; Se, 10.14. Found: C, 53.87; H, 4.17; F, 7.28; N, 1.89; Se, 9.90.

When the 14-iodo compound 1 was substituted for the bromo compound reaction gave diphenyl diselenide and 3 in quantitative yields.

Registry No. 1 (X = I), 26295-55-6; 1 (X = Br), 77270-18-9; 1 (X = SeC_6H_5), 77270-19-0; 2 (R = C_6H_5), 77270-20-3; 3, 26388-52-3; 4 (X = I), 4636-16-2; 4 (X = SC_6H_5), 16222-10-9; 4 (X = $SC_{12}H_{25}$-*n*), 77270-21-4; 4 (X = SeC_6H_5), 35050-01-2; 4 (X = Cl), 532-27-4; 4 (X = Br), 70-11-1; 4 (X = H), 98-86-2; 5 (X = I), 77270-22-5; 5 (X = Br), 5122-82-7; 5 (X = SC_6H_5), 77270-23-6; 5 (X = SeC_6H_5), 77270-24-7; 5 (X = H), 1660-04-4; benzenethiol, 108-98-5; *n*-dodecanethiol, 112-55-0; benzeneselenol, 645-96-5; diphenyl disulfide, 882-33-7; di-*n*-dodecyl disulfide, 2757-37-1; diphenyl diselenide, 1666-13-3.

Diethyl Oxomalonate. An Improved Synthesis

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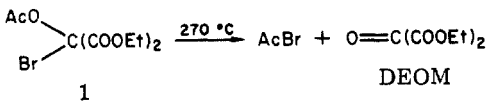
Diethyl oxomalonate (DEOM), a versatile reagent for organic synthesis, is reactive in a wide selection of C–C bond forming processes including Diels–Alder,[1] ene,[2] aldol (especially enamine modification),[3] and Friedel–Crafts[4] reactions. We recently described a synthetic application in which DEOM serves as an eneophilic equivalent of carbon dioxide for elaboration of allylcarboxylic acids from olefins.[5] We now report an improved procedure for preparation of DEOM.[6]

Decomposition of diethyl α-acetoxy-α-bromomalonate (1) at 270 °C is reported to produce DEOM and acetyl bromide.[7] Besides the inconvenience of the metal bath



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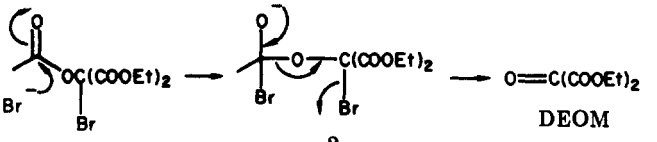
required for this pyrolysis, the published procedure calls for treatment of the crude product with water and $NaHCO_3$. The crude DEOM hydrate, obtained after rotary evaporation, must then be dehydrated. We discovered that *impure* 1 eliminates acetyl bromide under considerably milder conditions. Thus, impure 1 is obtained by bromination of diethyl malonate followed by reaction of the crude dibromide with potassium acetate in ethanol, filtration to remove precipitated potassium bromide, and rotary evaporation of the solvent.[7] The impure diethyl α-acetoxy-α-bromomalonate is transformed to DEOM during slow distillation under reduced pressure. Acetyl bromide collects in a suitable trap cooled to −78 °C, and the distillate collected at 98–110 °C (11 mm) consists of nearly pure DEOM.

We suspect that the elimination of acetyl bromide is catalyzed by traces of KBr which converts 1 to 2 since 1



1 2

can be distilled without decomposition if the crude product is partitioned between ether and water, the ether layer is dried, and solvent removed prior to distillation to remove the last traces of KBr. Powdered anhydrous reagent KBr does *not* catalyze decomposition of 1, probably owing to insolubility. However, the presumed bromide ion catalyst is soluble in impure 1. Therefore, we examined distillation of 1 in the presence of tetrabutylammonium bromide. As expected, this soluble bromide salt catalyzes complete conversion of 1 to DEOM and acetyl bromide.

Experimental Section

Diethyl Oxomalonate. Since HBr gas is evolved, the bromination of diethyl malonate is conducted in an efficient fume hood. A dry 5-L three-necked round-bottom flask is fitted with a mechanical stirrer, a condenser topped with a nitrogen inlet connected to a nitrogen source and a pressure-releasing oil bubbler, and a 500-mL pressure-equalizing addition funnel. Diethyl malonate (400 g, 2.5 mol) is placed in the flask. Diethyl malonate purchased from Fisher Scientific Co. is used as received. The addition funnel is charged with bromine (850 g, 5.5 mol) of which 10 mL are added to the flask, and the resulting mixture is stirred until HBr gas evolution is observed and the red color of bromine fades. The remainder of the bromine is added dropwise at a rate which maintains a steady evolution of HBr gas. After the addition is complete, the mixture is heated with an oil bath at 60 °C for 1 h and then at 90 °C for an additional 1 h. The reaction mixture is cooled to 50 °C and after removal of the addition funnel a stream of nitrogen is bubbled through the mixture until only a slight turbidity is observed when the effluent gas stream is bubbled through 0.05 N $AgNO_3$. It is crucial that HBr is thoroughly removed in this manner prior to addition of KOAc to the reaction mixture. The reaction mixture is diluted with 500 mL of absolute ethanol and warmed to 50 °C. Anhydrous KOAc (52 g) in a minimum volume of boiling hot ethanol (about 150 mL) is added to the reaction mixture. Over a period of 4 h four additional portions (50 g each) of KOAc, each *partially* dissolved in 100 mL of boiling hot ethanol, are added (2.5 mol total of KOAc). After addition of the last portion the reaction mixture is stirred for 2 h at 50 °C and then boiled under reflux overnight. The precipitated KBr is removed by filtration with suction and washed with 100 mL of absolute ethanol. Solvent is removed from the combined filtrate and washings by rotary evaporation. The crude residual oily product is slowly distilled under reduced pressure. In order to collect the liberated acetyl bromide, a 250-mL trap is inserted between the distillation gas outlet and the vacuum pump and maintained at −78 °C. The fraction with bp 89–110 °C (11 mm) is nearly pure DEOM. Redistillation of this fraction through a 50-cm adiabatic column packed with glass helicies gives

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