Kinetics of the Hydrolysis of 1. Buffer solutions for the hydrolysis of 1 contained potassium phosphate (0.05 or 0.10 M); observed rate constants were extrapolated to zero buffer concentration to correct for buffer catalysis. Sufficient potassium chloride was added to achieve an ionic strength of 0.3. The pH of the reaction mixtures was maintained to within ±0.10 pH unit for at least 2 half-lives. Reactions were initiated by combining appropriate volumes of the buffer and an aqueous solution of 1 (final concentration, 0.56 mM). Aliquots (20 μL) of the reaction mixtures (maintained at 37 °C) were removed at timed intervals and injected onto a Partisil SCX column as described above. The column was eluted with 0.08 M ammonium phosphate buffer (pH 3.5), 2.0 mL/min (1500–1800 psi). Under these conditions, the retention times for DL-phenylalanine, adenosine, and 1 were 1.35, 2.25, and 6.90 min, respectively. The amount of unhydrolyzed 1 was measured by electronic integration of the resulting peak. All rate measurements were made in duplicate, and reactions were followed for 3 half-lives (N = 4–10). Apparent first-order rate constants were calculated by a linear least-squares analysis of the resulting data; in all experiments but one, the correlation coefficient was 0.96 or greater.

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Registry No.—1 dihydrochloride, 68867-06-1; 2, 68926-48-7; 3, 68867-07-2; 4, 68867-08-3; 2′,3′-*O*-isopropylideneadenosine, 362-75-4.

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3-(Dimethylamino)-1-propyne: Convenient Precursor for a Versatile Mixed Cuprate Reagent

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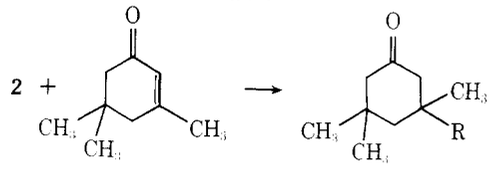
In recent years a number of publications have appeared concerning the use of mixed cuprate reagents in conjugate addition reactions.[1-4] We report here on the mixed cuprate **2** which is prepared as outlined in Scheme I. We believe that **2** has several advantages over the previously reported reagents: (1) the reagent's precursor **1** is commercially available at low cost; (2) any coupling products resulting from oxidation are readily removed via an acid extraction; and (3) one need not employ a complexing agent or a large excess of the mixed cuprate when R = CH_2=CH_2. Isophorone was chosen as the enone for our experiments as this ketone has been extensively studied in conjugate addition reactions with organocuprates.[1] The results of our experiments are contained in Table I.

Scheme I

$$(CH_3)_2NCH_2C{\equiv}CH \xrightarrow[(2)\ CuI\ (3)\ RLi]{(1)\ CH_3Li} R[(CH_3)_2NCH_2C{\equiv}C{-}]CuLi$$

1 **2a**, R = CH_3; **b**, R = $CH{=}CH_2$

Table I

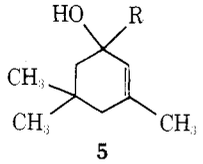


3 **4**

R	registry no.	solvent	temp, °C	yield of **4**[a] %	starting material recovered, %
CH_3	68843-13-0	THF	0	0	not determined
CH_3		THF	−40	0	96
CH_3		Et_2O	0	85–100[c]	0–15
CH_3		Et_2O	−20[b]	100	0
CH_3		Et_2O	−40[b]	84	12
CH_3		Et_2O	−80[b]	17	29
CH_2=CH	68843-14-1	Et_2O	−50	15[d]	60
CH_2=CH		Et_3N	−50	52–58	38–40

[a] All yields were determined via gas chromatography. Compound **3** was the limiting reagent. [b] The reaction which formed the mixed cuprate, i.e., reaction 3, Scheme I, was carried out at this temperature also. [c] Registry no., 14376-79-5. [d] Registry no., 27749-07-1.

Initial attempts at adding **2** to **3**, which employed THF as solvent, were unsuccessful; however, when ether was used as solvent, the yield of product was excellent. At very low temperatures (−80 °C) yields were low, but a substantial amount of starting material had been consumed. We assume that at this temperature the mixed cuprate did not form completely; thus, when enone was added, unreacted RLi probably added in a 1,2 fashion to form the alcohol **5**. We stress that this is only



5

conjecture as our means of analysis only allowed for the determination of **3** and **4**; we did not pursue the matter further. The fact that cuprate **2** will not form at low temperature precludes the application of our method to the formation of mixed cuprates from highly unstable lithium reagents. We had initially hoped that **2** could be formed at low temperature with relatively unstable α-halolithium intermediates.

A reliable procedure for effecting the conjugate addition of a vinyl group from a mixed cuprate to an enone in high yield without employing a large excess of the copper reagent or a complexing agent, which is oftentimes difficult to remove, has not been reported to date.[1-4] We have found that when triethylamine is employed as solvent, cuprate **2b** will add to isophorone in good yield (52–58%). If ether is used instead of triethylamine, the yields are reduced drastically. We attribute the success of the amine solvent to its ability to better solubilize the intermediate copper(I) acetylide and thus accelerate the reaction of acetylide with RLi at the low temperature required to keep the vinyl cuprate from decomposing.

Experimental Section[5]

Starting Materials and Reagents. Methyllithium in ether (Ventron Corp.) and vinyllithium in THF (Organometallics, Inc.) were standardized by the usual double titration method. Commercial samples of CuI were obtained from Fisher Scientific Co. and purified

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according to the procedure of Posner.[2] Commercial 3-(dimethylamino)-1-propyne was obtained from Story Chemical Corp. (Farchan Division) and used without further purification. Isophorone was purchased from the Aldrich Chemical Co.

Preparation of $CH_3[(CH_3)_2NCH_2C{\equiv}C-]CuLi$ (2a). To a solution of 0.5 g (6.02 mmol) of 3-(dimethylamino)-1-propyne in 30 mL of ether cooled to 0 °C was added dropwise and with stirring 4.23 mL of 1.42 M methyllithium (6.02 mmol). The resulting mixture (a white precipitate had formed) was stirred for 45 min and then added dropwise with stirring via a syringe with a wide bore needle to a slurry of 1.15 g (6.02 mmol) of CuI in 2 mL of ether cooled to 0 °C. After stirring at 0 °C for 30 min, 4.23 mL of 1.42 M methyllithium (6.02 mmol) was added. The resulting mixture was then stirred for an additional 30 min at 0 °C.

Preparation of $[CH_2{=}CH-][(CH_3)_2NCH_2C{\equiv}C-]CuLi$ (2b). The reagent was prepared in exactly the same manner as **2a** with the following exceptions: (1) triethylamine was employed as the solvent; (2) the final step in which the mixed copper lithium reagent was formed was carried out at −50 °C, and vinyllithium was used instead of methyllithium.

Reaction of 2a with Isophorone. To a solution of **2a** (prepared above) cooled to 0 °C was added dropwise with stirring a solution of isophorone (0.67 g, 4.8 mmol) and an internal standard dissolved in an equal volume of ether. The resulting mixture, which progressively became darker, was then stirred for 1 h at room temperature. At this time an aliquot was removed and quenched with a saturated solution of ammonium chloride. The organic layer was extracted with HCl and then analyzed via gas chromatography. The reaction was repeated with THF as solvent and also at various temperatures. For results, see Table I. The product obtained in the reaction had an infrared spectrum identical with that of an authentic sample.

Reaction of 2b with Isophorone. The reaction was carried out in exactly the same manner as described for **2a** with the following exceptions: (1) the solution of **2b** (prepared above) was cooled to −50 °C before the isophorone and internal standard were added; (2) after the isophorone was added, the reaction mixture was stirred for 90 min at 0 °C. For results, see Table I. The product obtained in the reaction had IR and NMR spectra identical in every respect with those of an authentic sample.[6]

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Registry No.—1, 7223-38-3; 3, 78-59-1; CH_3Li, 917-54-4; CuI, 7681-65-4; $CH_2{=}CHLi$, 917-57-7.

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(6) We are greatly indebted to Professor H. O. House for supplying us with spectra of the ketone **4b**. Both compounds **4a** and **4b** have been thoroughly characterized by Professor House. See ref 1 for published spectral data.

Telluroamino Acids: Synthesis of Telluromethionine[1]

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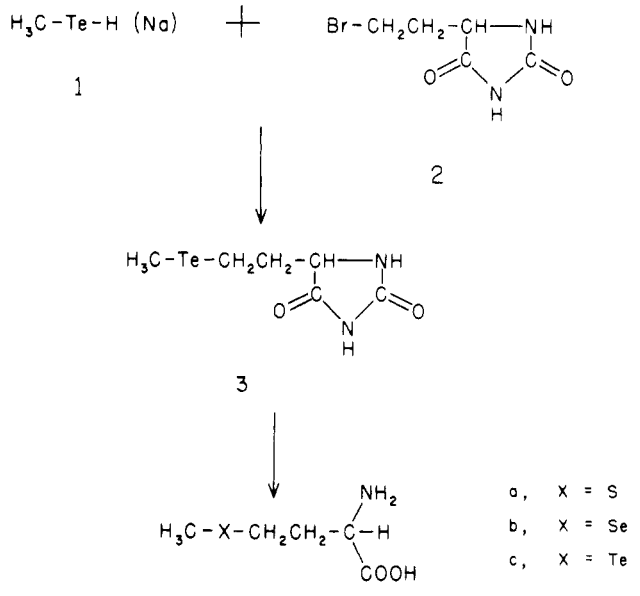
The general field of organoselenium chemistry is well documented because many of these compounds are of biological importance.[2] In addition, selenium reagents have been used in preparative organic chemistry for many years. In contrast, the chemistry of organotellurium compounds has not been well established as a result of both a lack of interest in this area and also the problems associated with the preparation and handling of many of these substances.[3] We have been interested in the preparation of telluroamino acids because of the potential clinical use of the ^{123m}Te-labeled compounds as pancreatic imaging agents. Reported attempts to prepare ^{123m}Te-labeled telluroamino acids by microbiological approaches have been unsuccessful.[4] Previous reports from this laboratory have described the preparation of aryltelluro-substituted α-amino acids.[5] We now report the synthesis of the first known alkyltelluro-substituted α-amino acid, DL-α-amino-γ-(methyltelluro)butyric acid (**4c**, "telluromethionine").



Selenomethionine (**4b**) has been prepared by both microbiological methods[6] and a variety of chemical methods.[7] Many of the latter approaches involved the generation of benzylselenol, but our early attempts to prepare telluroamino acids by similar methods were unsuccessful because of the extreme instability of benzyltellurol.[8] In the present investigation we had hoped to use benzyltellurol to prepare a derivatized form of **4c**. Our inability to use benzyltellurol precluded the preparation of the requisite benzyltelluro-substituted intermediates that were envisioned as substrates for DuVigneaud reduction[9] and subsequent transformation to the desired methyltelluro-substituted product. An alternate method involving the direct introduction of the methyltelluro moiety was therefore considered, and we have now prepared **4c** by a method involving the initial reaction of methyltellurol (**1**) with 5-(β-bromoethyl)hydantoin (**2**).

Results and Discussion

Sodium ditelluride (Na_2Te_2) was generated by reaction of tellurium powder with metallic sodium in liquid ammonia.[10] Alkylation with CH_3I gave dimethyl ditelluride (CH_3–Te–Te–CH_3),[11] which was subsequently reduced with $NaBH_4$ in MeOH–C_6H_6 to yield methyltellurol (**1**). The tellurol **1** readily reacted with 5-(β-bromoethyl)hydantoin (**2**) at room temperature in MeOH–C_6H_6 to yield 5-[(methyltelluro)ethyl]-hydantoin (**3**). It was necessary to control carefully the reaction conditions in order to isolate **3** in reasonable yield, and the generation of the intermediate **3** was found to be a critical step in the overall synthesis of **4c**. Because of the strongly basic reductive conditions, the subsequent coupling of **1** with

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