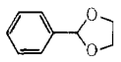
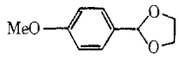
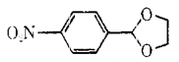
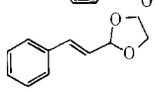
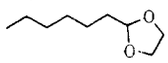
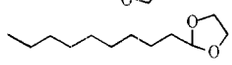
Table I. Conversion of Dioxolanes into Carboxylic Acids

acetal	registry no.	% yield of 2-bromoethyl ester (a)	registry no.	% acid[b,c]	registry no.
	936-51-6	98 (88)	939-54-8	99[d]	65-85-0
	2403-50-1	68 (59)	19263-28-6	96[d]	100-09-4
	2403-53-4	60 (51)	23574-40-5	58[e]	62-23-7
	5660-60-6	91 (75)	39257-72-2	91[e]	621-82-9
	1708-34-5	87 (70)	5454-31-9	91[e]	111-14-8
	4353-06-4	67 (55)	52001-54-4	76[e]	334-48-5

[a] % yield of purified material. [b] Pure by NMR and mp. [c] Based on recovered starting material. [d] Using zinc (5 equiv) and catalytic sodium iodide (2–5 mol %) in refluxing 50% aqueous THF. [e] Using zinc (5 equiv) and zinc chloride (1 equiv) in refluxing dimethyl sulfoxide (Me_2SO).

2-bromoethyl benzoate into benzoic acid (61%) with a 30% recovery of starting material. Cleavage of other 2-bromoethyl esters may require Me_2SO as a solvent in order to maintain synthetically useful yields.

Two recent literature methods for the conversion of 2-haloethyl esters to acids offer excellent alternatives for the second step of eq 3. Ho[12] has shown that thiocarbonate ion gives 75–86% yields of acids and Ugi[13] used cobalt(I)–phthalocyanine to cleave bromoethyl and chloroethyl esters to acids.[14]

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 nuclear magnetic resonance spectrometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected.

The typical experimental procedure for benzaldehyde follows.

2-Bromoethyl Benzoate. 2-Phenyl-1,3-dioxolane (17.8 g, 0.12 mol; prepared from benzaldehyde and 1.2 equiv of ethylene glycol at reflux in benzene containing catalytic *p*-TsOH with water removal (Dean-Stark trap) for 6 h) was dissolved in 150 mL of CCl_4. NBS (21.4 g, 0.12 mol) was added along with a catalytic amount of benzoyl peroxide and the mixture was refluxed overnight. The succinimide was filtered off and the filtrate was washed with aqueous $Na_2S_2O_3$ and then water. The CCl_4 solution was dried ($MgSO_4$) and concentrated to give 26.8 g (98%) of an orange liquid which was distilled to yield 24.1 g (88%) of a colorless liquid: bp 90–92 °C (0.5 mm); NMR (CCl_4) δ 3.7 (t, J = 6 Hz, 2 H), 4.7 (t, J = 6 Hz, 2 H), 7.6 (m, 3 H), 8.2 (m, 2 H).

Benzoic Acid. The ester above (1.00 g, 4.36 mmol) was dissolved in 20 mL each of THF and water. Zinc powder[15] (1.43 g, 21.8 g-atom) and sodium iodide (20 mg) were added. The mixture was refluxed for 24 h, cooled, and filtered. Acidification of the filtrate and extraction with ether gave a solution which was further extracted with aqueous $NaHCO_3$. The remaining ether was dried and concentrated to give 0.13 g (13%) of starting material (as determined by NMR). The bicarbonate layer was acidified and extracted with ether to yield 0.46 g (86%) of white solid (benzoic acid), mp 119–121 °C. Thus, the yield of benzoic acid is 99% based on recovered starting material.

Registry No.—Benzaldehyde, 100-52-7; *p*-anisaldehyde, 123-11-5; *p*-nitrobenzaldehyde, 555-16-8; cinnamaldehyde, 104-55-2; heptanal, 111-71-7; decanal, 112-31-2; ethylene glycol, 107-21-1.

References and Notes

(1) H. J. E. Loewenthal in "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., Plenum Press, London, 1973, p 323.
(2) Reference 1, p 330.
(3) Esters are isolated from the ozonolysis of dioxolanes: P. Deslongchamps, C. Moreau, D. Frehel, and P. Chenevert, *Can. J. Chem.*, **53**, 1204 (1975), and references cited therein.
(4) J. D. Prugh and W. C. McCarthy, *Tetrahedron Lett.*, 1351 (1966).
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(7) (a) 2-Acetoxy-3-bromobutane and zinc in aqueous ethanol give 2-butene: H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 182 (1958). (b) 2-Iodoethyl carbamates yield amines when treated with zinc in refluxing methanol: J. Grimshaw, *J. Chem. Soc.*, 7136 (1965). (c) Reductive elimination of a 2-bromoethyl ester derived from a sugar was carried out recently with zinc in hot acetic acid: K. Block and C. Pederson, *Acta Chem. Scand., Ser. B*, **31**, 248 (1977). (d) In addition, 2-haloethyl esters have been electrolytically reduced: E. Kasafirek, *Tetrahedron Lett.*, 2021 (1972); M. F. Semmelhack and G. E. Heinsohn, *J. Am. Chem. Soc.*, **94**, 5139 (1972).
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(10) Zinc promoted elimination of a 2-bromoethyl ether is catalyzed by zinc chloride: O. Grummitt, E. P. Budewitz, and C. C. Chudd, "Organic Syntheses", Collect Vol. IV, Wiley, New York, N.Y., 1963, p 748.
(11) 2-Methoxyethoxymethyl ethers are cleaved with zinc bromide: E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976).
(12) T.-L. Ho, *Synthesis*, 715 (1974).
(13) H. Eckert and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **15**, 681 (1976).
(14) This paper is dedicated to the memory of Lawrence C., Anderson, deceased February 17, 1978.
(15) Several bottles of zinc gave equal results, for example, zinc metal dust (Fisher Scientific Co.) and purified zinc powder (J. T. Baker Chemical Co.).

(3-Methyl-3-methoxy-1-butynyl)copper, a Useful Reagent for the Generation of Mixed Cuprates

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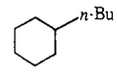
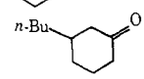
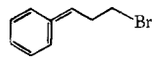
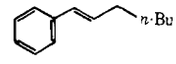
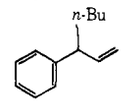
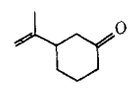
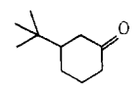
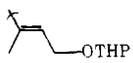
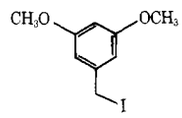
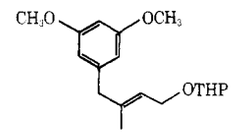
Received March 30, 1978

The use of mixed cuprate (Gilman) reagents derived from terminal alkynes, $RC{\equiv}CCuR_T$, for the selective transfer of alkyl or alkenyl groups (R_T) was introduced several years ago[1] for the purpose of conserving valuable R_T groups in synthetic processes such as cross coupling or enone conjugate addition. These cuprates are generally formed by reaction of a cuprous

0022-3263/78/1943-3418$01.00/0

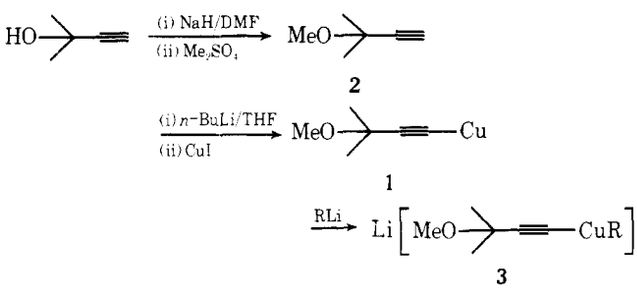
Table I.

3, R =	Registry no.	Substrate	Registry no.	Products[a]	Registry no.	Yield, %
n-Bu	66777-74-0		626-62-0		1678-93-9	40[b]
n-Bu			930-68-7		39178-69-3	100[b]
n-Bu			4392-24-9		829-99-2	62[b]
					40395-23-1	32[b]
i-C_3H_5	66777-75-1				6611-97-8	95[b]
t-Bu	66777-76-2				936-99-2	95[b]
	66777-77-3		66769-61-7		66769-62-8	92[c]

[a] Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for each product. [b] Yield by VPC analysis. [c] Isolated yield.

acetylide (RC≡CCu) with an organolithium compound (R_TLi). Although such mixed Gilman reagents have proved to be of considerable value in synthesis, there have been certain practical problems connected with their use. Simple *n*-alkynylcopper compounds such as 1-pentynylcopper are only sparingly soluble in the ususal solvents (tetrahydrofuran (THF) or ether) for cuprate reactions, which can cause mixed cuprate formation to be slow or variable in rate. The use of the more soluble cuprous *tert*-butylacetylide[1b] is not very satisfactory because of the high cost of *tert*-butylacetylene (ca. $1/g).

We have recently described the use of a mixed cuprate system derived from the soluble cuprous acetylide **1** in the preparation of a key intermediate for maytansine synthesis.[2] This readily available and inexpensive reagent is an effective and practical alternative to cuprous *tert*-butylacetylide. We describe here the details for the preparation of the precursor acetylene **2** as well as the general applicability of **1** to the formation of highly reactive cuprates **3**.



The requisite acetylene, 3-methyl-3-methoxy-1-butyne (**2**), is easily prepared in 84% yield by treatment of commercially available 2-methyl-3-butyn-2-ol[3] with 1.5 equiv of sodium hydride followed by the addition of 1.5 equiv of dimethyl sulfate, without prior purification of the reagents or solvent; bp of **2**, 77–80 °C (lit.[4] bp 80 °C).

The addition of a THF solution of the lithio derivative of **2** to a suspension of CuI in THF at 0 °C produces a red-orange solution of **1**. Upon concentration under reduced pressure, **1** is obtained as a red oil which solidifies upon trituration with hexane. **1** is very soluble in THF, moderately soluble in ether (ca. 0.1 M at 0 °C), and insoluble in hexane. Mixed cuprates **3** were prepared by the addition of **1** to the desired lithio reagent at −78 °C. The results of several representative reactions as shown in Table I indicate the general utility of **1** as a precursor for mixed Gilman reagents.[5]

Experimental Section

3-Methoxy-3-methyl-1-butyne (2). A slurry of sodium hydride (7.2 g, 150 mmol; 50% in mineral oil) in 150 mL of DMF was cooled to 0 °C, and 8.4 g (100 mmol) of 2-methyl-3-butyn-2-ol[3] dissolved in 100 mL of DMF was added dropwise over 30 min. The reaction mixture was stirred for an additional 30 min, and dimethyl sulfate (19 g, 14.3 mL, 150 mmol) was slowly added over a 20-min period. After stirring for an additional 5 min at 0 °C, the flask was allowed to warm to room temperature and stirring was continued for 45 min. Excess sodium hydride was then destroyed by the dropwise addition of glacial acetic acid to the cooled (0 °C) reaction mixture. Direct distillation through a 30 cm Vigreux column afforded 8.2 g (84%) of pure material: bp 77–80 °C (lit.[4] bp 80 °C); IR (liquid film) 3290, 1080 cm^{-1}; NMR ($CDCl_3$) δ 3.35 (s, 3 H), 2.38 (s, 1 H), 1.46 (s, 6 H).

Representative Cuprate Reaction Employing Cuprous Acetylide 1. A 1 M solution of 3-methoxy-3-methyl-1-butyne (**2**) in THF was treated at 0 °C with 1 equiv of *n*-butyllithium. The clear, colorless solution was stirred for 5–10 min and transferred into a slurry of cuprous iodide in THF (1 mmol/mL), precooled to 0 °C. The resulting red-orange solution of **1** was then stirred at this temperature for 30 min and subsequently transferred either by syringe or canula to a −78 °C solution of the desired lithio reagent (0.5–1 M). Under the above conditions, a virtually instantaneous reaction occurred, yielding a pale yellow to colorless solution of the mixed cuprate **3**. The use of the more concentrated conditions led to the appearance of a white precipitate during cuprate formation (presumably lithium iodide) which readily dissolved at around −30 °C to give homogeneous solutions of **3**. A typical reaction then involved adding the substrate neat or as a solution in THF at −78 °C followed by warming to −20 °C and stirring for several hours. Standard extractive workup employing pH 8 aqueous ammonia in saturated ammonium chloride gave products which were either virtually pure (by GLC and NMR) or, in a few cases, contaminated by small quantities of the conjugated diyne, resulting from oxidative coupling of the acetylenic ligand.

The formation of the mixed Gilman reagents **3** can also be accomplished satisfactorily by the addition of the organolithium reagent to a solution of the cuprous acetylide **1**.

Registry No.—1, 66769-63-9; **2**, 13994-57-5; 2-methoxy-3-butyn-2-ol, 115-19-5.

References and Notes

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(2) E. J. Corey, M. G. Bock, A. P. Kozikowski, A. V. Rama Rao, D. Floyd, and B. H. Lipshutz, *Tetrahedron Lett.*, 1051 (1978).
(3) Available from the Aldrich Chemical Co.
(4) V. I. Nibitin, E. M. Gazunova, S. S. Sabirov, and I. N. Grigina, *Zh. Org. Khim.*, **2**, 1969 (1966); *Chem. Abstr.*, **66**, 85403u (1967).

(5) This work was assisted financially by a grant from the National Institutes of Health.

Electrochemical Reduction of 1-Benzyl-3-carbamoylpyridinium Chloride, a Nicotinamide Adenine Dinucleotide Model Compound

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Received February 27, 1978

The electrochemical reduction of pyridine nucleotides, e.g., nicotinamide adenine dinucleotide (NAD^+), and related model compounds has been the subject of active investigation, extensively reviewed.[2-4] It has been consistently found that one- or two-electron reduction products are formed, i.e., respectively tetrahydrobipyridine derivatives and dihydropyridines.

Only in a few cases has the detailed structure of the tetrahydrobipyridines been determined,[5] while generally the structure has been postulated exclusively on the grounds of UV spectroscopic evidence. It appears that further research on the structure of these dimeric compounds is highly desirable, also in view of their possible biological role; for example, a dimer from the NAD^+ has been reported[6] to be involved in the plant phenol oxidase activity.

In this paper we report the results obtained in the electrochemical one-electron reduction of 1-benzyl-3-carbamoylpyridinium chloride (1), a model compound strictly related to the natural coenzyme. The previously reported[7,8] polarographic behavior of 1-benzyl-3-carbamoylpyridinium ion has been confirmed by our experiments. It is essentially characterized by two reduction waves, the first one (wave A) pH independent and the second (wave B) appearing only at alkaline pH values. The first step implies the reversible transfer of one electron to the pyridinium cation to give a radical which irreversibly dimerizes, as shown by fast-scan cyclic voltammetry tests.[9]

Electrolyses of **1** have been performed at different potential values within the wave A plateau, in about 0.1 M solution buffered in the pH range 8 to 10. Under these conditions, a precipitate is invariably formed and adsorption effects, already noted by other workers,[9] were pronounced enough to block the electrode surface and reduce to zero value the current within a short time after the beginning of the electrolysis. This difficulty has been overcome using a 1:1 (v/v) mixture of benzene and aqueous solution under vigorous stirring. In such a way, the precipitate is washed away from the electrode and transferred into the interphase aqueous solution–benzene, ensuring successful completion of the electrolysis. Under these conditions, a faradaic n value of 1 ± 0.1 has been measured.

Table I. ^{1}H NMR Data for Dimers 2 and 3

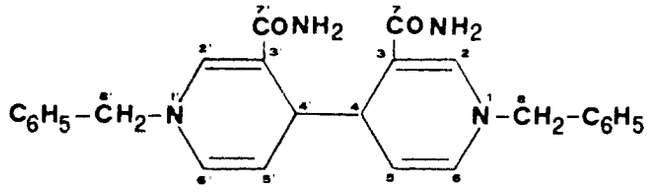
2			3	
δ, ppm	J, Hz	Protons	δ, ppm	J, Hz
7.5–7.1		aromatic	7.5–7.1	
7.24 (d)	1.2	$H_2 + H_{2'}$	7.13 (d)	1.4
6.97		amide	6.33	
6.02 (dd)	1.2	$H_6 + H_{6'}$	5.89 (dd)	1.4
	7.9			7.8
4.36 (dd)	4.7	$H_5 + H_{5'}$	4.47 (dd)	4.6
	7.9			7.8
4.35		benzyl	4.30	
3.24 (d)	4.7	$H_4 + H_{4'}$	3.35 (d)	4.6

Table II. ^{13}C NMR Data for Compounds 2, 3, 4, and 5

2 δ, ppm	carbon atoms	3 δ, pm	4 δ, ppm	carbon atoms	5 δ, ppm
169.3	$C_7 + C_{7'}$	170.3	169.0	C_7	167.5
138.1	$C_2 + C_{2'}$	138.5	137.8	C_2	144.9
130.2	$C_6 + C_{6'}$	129.7	129.5	C_6	47.0
102.2	$C_5 + C_{5'}$	102.2	101.8	C_5	109.1
101.6	$C_3 + C_{3'}$	102.0	100.3	C_3	99.2
56.2	$C_8 + C_{8'}$	56.3	55.9	C_8	58.5
38.9	$C_4 + C_{4'}$	39.2	22.3	C_4	122.5
		benzene rings			
138.2	C_1	138.0			
128.3	$C_3 + C_5$	128.2			
127.1	$C_2 + C_6$	127.2			
127.1	C_4	127.0			

From the crude reduction product the dimers **2** and **3** have been isolated and purified following the procedure described in the Experimental Section. The UV spectra of both **2** and **3** are closely similar and will be discussed in detail below.

However, a feature must be immediately emphasized,



2 and 3

namely the absence of any 1,2-dihydropyridine long-wavelength (above 400 nm) absorption, which excludes structures involving dimerization at position 2, and thus restricts the possible structure of these products to 4,4′-, 6,6′- or 4,6′-linked dimers.

In the ^{1}H NMR spectra of both **2** and **3** (Table I) only 13 protons are detectable, namely 5 aromatic, 3 vinyl, 2 methylene, 1 methine, and 2 amide protons, showing the symmetry of the structure and disproving the occurrence of mixed dimers. The following additional ^{1}H NMR data are relevant to the assignment of the structure: (i) the chemical shifts of the methine protons in both **2** and **3** are clearly indicative of 1,4- rather than 1,6-dihydropyridine moieties, by comparison with ^{1}H NMR spectra of the dihydropyridine monomers **4** and **5**;[10] (ii) the value of the coupling constant ($J \approx 8$ Hz) between the two hydrogens on the unsubstituted double bond indicates that its position is α with respect to the ring nitrogen atom, as it is known that this value is greater (about 10 Hz)[5a,10-12] for double bonds in position β with respect to the nitrogen atom. Therefore, these data provide reasonable evidence for a symmetric dimeric 4,4′-linked structure for both **2** and **3**.

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