4354 J. Org. Chem. 1986, 51, 4354–4356

Poly(ethylene glycol) Promoted Reactions of Vinylic Dibromides. Dehydrohalogenation and Palladium(0)-Catalyzed Formal Oxidative Homologation

Pei Li and Howard Alper*[1]

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa,
Ontario, Canada K1N 9B4

Received April 10, 1986

Aldehydes are converted to the homologous acids by a simple two-step procedure involving initial generation of a vinylic dibromide followed by Pd(diphos)$_2$ catalyzed, poly(ethylene glycol) induced reaction with base. This reaction is useful for aromatic and α,β-unsaturated aldehydes and is also applicable to cyclic as well as alkyl aryl ketones. 1-Bromoalkynes are formed in good yields when the vinylic dibromide reaction is effected in the absence of the palladium(0) catalyst.

Quaternary ammonium salts are the most commonly used catalysts in phase-transfer reactions.[2-4] Crown ethers have also been employed as phase-transfer agents although they are, in many cases, toxic and expensive. There has been substantial interest in recent years in utilizing poly(ethylene glycols) (PEGs), considered in some instances as acyclic crown ether analogues, as phase-transfer catalysts, and as solvent promoters for various reactions.[5-15] Attractive features of poly(ethylene glycols) include their low cost and apparent lack of significant toxicological properties.

There are reports in the literature where PEG is a useful alternative to other phase-transfer agents. Examples include the manganesecarbonyl bromide (or manganese carbonyl) induced conversion of alkynes to lactones by means of methyl iodide and carbon monoxide, a phase-transfer reaction that proceeds equally well using a quaternary ammonium salt or PEG-400 as the phase-transfer catalyst.[15] There are instances where PEG is clearly superior to a quaternary ammonium salt. For instance, poly(ethylene glycols) are much better than quaternary ammonium salts as catalysts for the dehydrohalogenation of (2-bromoethyl)benzene to styrene in organic–aqueous two-phase media.[6] Another example is the palladium chloride catalyzed oxidation of olefins to carbonyl compounds. The latter reaction is only applicable to terminal olefins when a quaternary ammonium salt containing a long chain alkyl group [e.g., cetyltrimethylammonium bromide] is used as the phase-transfer agent.[16] However, with PEG-400, the reaction is faster using terminal olefins and occurs with internal olefins as well.[14]

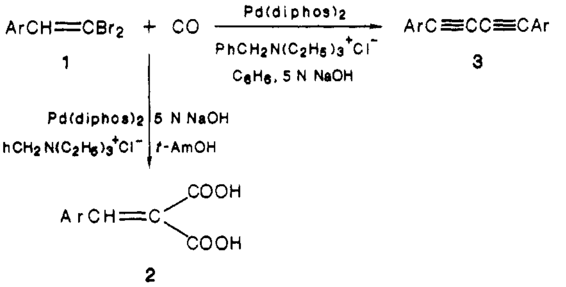
Table I. PEG Promoted Dehydrohalogenation of Vinylic Dibromides[a]

4, R′ = H, R =	concn of NaOH, N	yield of 5, % GC	isolated	IR, $\nu_{C\equiv C}$,[b] cm^{-1}	MS, *m/e*
Ph	5	88	57	2200	182, 180
o-$CH_3C_6H_4$	5	87	72	2190	196, 194
p-$CH_3C_6H_4$	5	86	66	2198	196, 194
p-ClC_6H_4	5	93	46	2200	218, 216, 214
p-$CH_3OC_6H_4$	5	68	51	2200	212, 210
$C_2H_5CH(CH_3)$	10	68	53	2200	162, 160

[a] Reactions conditions: PEG, 15 mL; NaOH, 10 mL; room temperature, 4 h. [b] CH_2Cl_2 solution.

$$\text{1- or 2-butene} \xrightarrow[\text{PEG-400, H}_2\text{O}]{\text{O}_2,\ \text{PdCl}_2,\ \text{CuCl}_2} \text{butanone}$$

In 1983, one of us described palladium(0)- and phase-transfer-catalyzed carbonylation reactions of vinylic dibromides.[17] While vinylic dibromides 1 derived from aromatic aldehydes are carbonylated to unsaturated diacids 2 when reacted with a catalytic amount of Pd(diphos)$_2$ [diphos = 1,2-bis(diphenylphosphino)ethane], benzyltriethylammonium chloride as the phase-transfer agent, 5 N sodium hydroxide, and *tert*-amyl alcohol as the organic phase, diynes 3 are formed when the same process is effected using benzene as the organic solvent. Monoacids were obtained, using benzene as the organic phase, when the reactant dibromide was that derived from an aliphatic aldehyde or from a ketone.



Diynes 3 are not formed from 1 in the absence of the palladium catalyst or in the presence of the metal complex but as a one-phase reaction (in tetrahydrofuran). The fact that bromophenylacetylene reacts with Pd(diphos)$_2$, $PhCH_2N(C_2H_5)_3{}^+Cl^-$, 5 N NaOH, and C_6H_6 to give 3 (Ar

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0022-3263/86/1951-4354$01.50/0

Table II. Pd(diphos)$_2$ Catalyzed Conversion of 4 to 6[a]

		yield of 6, %		pertinent spectral data		
4, R =, R′ =	base, concn (N)	GC	isolated	IR,[b] ν_{CO}, cm^{-1}	MS, *m/e*	^{1}H NMR,[c] δ
Ph, H	NaOH, 5	100	95	1710	136	3.55 (s, 2 H, CH_2), 7.18 (s, 5 H, Ph), 10.62 (s, 1 H, COOH)
o-$CH_3C_6H_4$, H	NaOH, 5	52	51	1710	150	2.32 (s, 3 H, CH_3), 3.60 (s, 2 H, CH_2), 7.11 (s, 4 H, aromatic), 9.80 (s[br], 1 H, COOH)
p-$CH_3C_6H_4$, H	NaOH, 10	77	68[d]	1711	150	2.30 (s, 3 H, CH_3), 3.67 (s, 2 H, CH_2), 7.10 (m, 4 H, aromatic), 10.45 (s[br], 1 H, COOH)
p-ClC_6H_4, H	NaOH, 5		35	1720	172 170	3.41 (s, 2 H, CH_2), 7.22 (s, 4 H, aromatic), 9.78 (s[br], 1 H, COOH)
	KOH, 5		56			
p-$CH_3OC_6H_4$, H	NaOH, 10	96	85	1713	166	3.68 (s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 6.60–7.50 (m, 4 H, aromatic), 10.2 (s[br], 1 H, COOH)
PhCH=CH, H	NaOH, 10		58	1700	162	3.25 (d, 2 H, CH_2), 6.40 (d, 1 H, J = 16 Hz, PhCH), 7.24 (m, 6 H, Ph and CH=), 10.4 (s, [br], 1 H, COOH)
Ph,CH_3	NaOH, 10		18	1710	150	1.55 (d, 3H, CH_3), 3.72 (q, 1 H, CH), 7.28 (s, 5 H, Ph), 11.80 (s[br], 1 H, COOH)
	KOH, 10		23			
$(CH_2)_2CH(CH_3)(CH_2)_2$	NaOH, 10	89	42	1721	142	0.98 (d, 3 H, CH_3), 1.20–2.70 (m, 10 H, ring protons), 10.95 (s, 1 H, COOH)

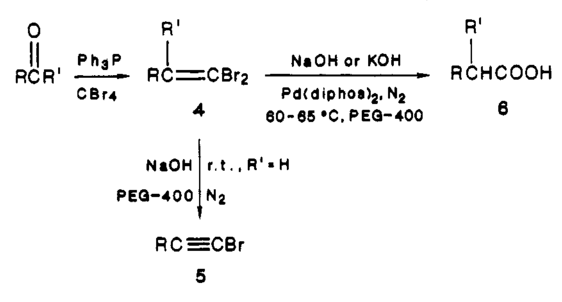
[a] Reaction conditions: PEG, 15 mL; NaOH or KOH, 10 mL; CH_2Cl_2, 2 mL; 60–65 °C, 17 h. [b] CH_2Cl_2 solution. [c] $CDCl_3$ with Me_4Si as internal standard. [d] 5.5% acid was obtained when the reaction was run in the absence of PEG-400.

= Ph) provided some evidence for the intermediacy of bromoarylacetylenes in the conversion of 1 to 3. However, bromoarylacetylenes were not isolated as byproducts in any of the reactions of 1 using a quaternary ammonium salt as the phase-transfer agent, with or without the palladium catalyst.

It was of interest to determine whether poly(ethylene glycols) could promote the dehydrohalogenation of vinylic dibromides under basic conditions. We now wish to report the realization of that transformation. Furthermore, the use of a palladium catalyst and PEG-400 enables one to produce saturated monoacids in acceptable yields.

Results and Discussion

Vinylic dibromides 4 are readily prepared by reacting an aldehyde[18] or ketone[19] with carbon tetrabromide and triphenylphosphine. Treatment of a vinylic dibromide, derived from an aromatic aldehyde [i.e., 4, R = aryl, R′ = H], with PEG-400 (15 mL) and 5 N NaOH (10 mL) at room temperature for 4 h (N_2 atmosphere), affords bromoarylacetylenes 5 in 46–72% isolated yields [gas chromatographic yields were higher—see Table I for results]. The reaction also takes place with a vinylic dibromide prepared from an aliphatic aldehyde, provided a higher concentration of base [i.e., 10 N NaOH] is used. No reaction occurs in the absence, or in the presence of a catalytic amount, of PEG-400. Potassium hydroxide is of no advantage when compared with sodium hydroxide for the conversion of 4 to 5. For example, repetition of the dihydrobromination reaction of 4 (R = *o*-$CH_3C_6H_4$, R′ = H) with KOH gave 66% of 5 R = *p*-$CH_3C_6H_4$), 31% of *p*-tolualdehyde, and 1% of *p*-methylbenzyl alcohol [gas chromatographic yields].



This synthetic route to 1-bromoalkynes is a simple and mild one and is superior to the known sluggish, phase-transfer reaction of benzyl bromides with bromoform, aqueous base, and benzyltriethylammonium chloride.[20] The latter method cannot be used for the preparation of (1-bromoalkyl)acetylenes. The PEG-induced dehydrobromination of vinylic dibromides may, in some cases, be a satisfactory alternative to the synthesis of bromoalkynes from terminal alkynes.[21] The results of this PEG reaction, together with that for the elimination of 1,2-dibromoalkanes to alkynes,[22] as well as others noted previously,[6,12] clearly demonstrate the genuine utility of poly(ethylene glycols) for effecting dehydrohalogenation processes.

When the vinylic dibromide reaction is repeated in the presence of a catalytic amount of Pd(diphos)$_2$ for 17 h at 60–65 °C, then carboxylic acids 6 are formed in 18–95% isolated yields. The acids were identified by comparison of physical data with those for authentic samples. The ratio of substrate to metal catalyst used was 18:1, and the base concentration was either 5 N or 10 N (see Table II for data). Potassium hydroxide can, in some instances, be more effective than sodium hydroxide in reactions involving poly(ethylene glycols) and in the two cases examined here, KOH gave acids in higher yields than NaOH. Diynes 3 were formed as low yield byproducts in several of these reactions. Tetrakis(triphenylphosphine)palladium and bis(dibenzylideneacetone)palladium also catalyze acid formation from vinylic dibromides, but yields are poor.

A possible mechanism for the conversion of dibromides to acids is illustrated in Scheme I. Initial interaction of PEG with NaOH (or KOH) would give a complex[6,10] which could then add to the palladium catalyst affording 7. The latter is then converted to 8 by reaction with the organic substrate, either by electron transfer or by an ionic pathway. Reductive elimination would then give the enol 9 [the palladium catalyst would be regenerated in this step]. Tautomerism of 9 to the acid bromide 10 and subsequent hydrolysis would afford the product. Bromoacetylenes are not intermediates in the conversion of vinylic dibromides to acids. For example, carboxylic acid was not detected

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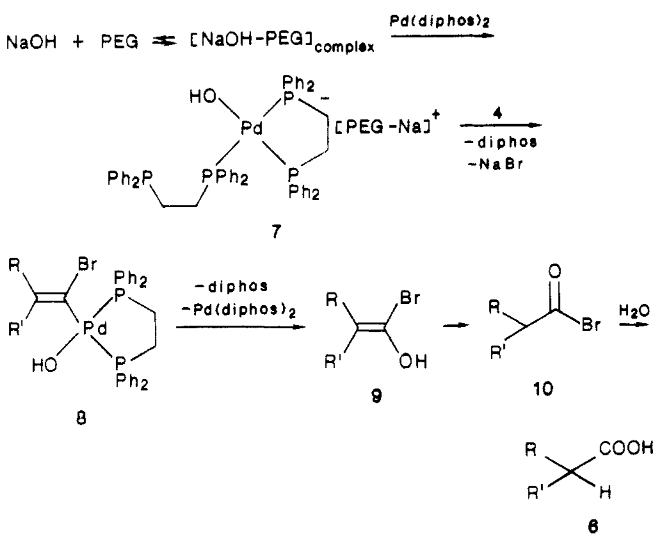
Scheme I



when **5** (R = p-$CH_3C_6H_4$) was exposed to $Pd(diphos)_2$, 5 N NaOH, and PEG-400 at 60 °C.

The conversion of aldehydes, via **4**, to carboxylic acids **6**, can be considered overall as an oxidative homologation reaction. This process has considerable scope, being applicable to aromatic aldehydes containing chloro, alkyl, or alkoxy substituents, α,β-unsaturated aldehydes (e.g., cinnamaldehyde), and cyclic (4-methylcyclohexanone) as well as alkyl aryl ketones (e.g., acetophenone). The two-step reaction is simple in execution and workup and compares favorably with other methods for effecting the same transformation [e.g., reduction of an aldehyde to an alcohol, conversion to the chloride and then to a Grignard reagent, followed by reaction with carbon dioxide to give the carboxylic acid]. This new process is of considerable practical value as, for example, it is superior to existing commercial methods for the conversion of p-anisaldehyde to p-methoxyphenylacetic acid.

Experimental Section

Proton magnetic resonance spectral determinations were made on a Varian EM-360 or XL-300 spectrometer. Carbon magnetic resonance spectra were recorded on a Varian FT-80 instrument. A Perkin-Elmer 783 spectrometer was used for recording infrared spectra, and mass spectral determinations were made on a VG-7070E spectrometer. Melting point determinations were made on a Fisher-Johns apparatus.

Vinylic dibromides were prepared from aldehydes or ketones following literature procedures.[18,19] Poly(ethylene glycol) (PEG-400) and $Pd(diphos)_2$ were purchased from Aldrich Chemical Co. and were used as received. Distilled water was used to prepare the base solutions. All reactions were run under a nitrogen atmosphere.

General Procedure for the PEG-400 Promoted Conversion of Vinylic Dibromides to Bromoacetylenes. A mixture of PEG-400 (12 mL) and 5 N or 10 N NaOH (10 mL) was stirred for 30 min. The vinylic dibromide **4** (2.0 mmol) dissolved in PEG-400 (3 mL) was added drop-by-drop to the stirred solution. The reaction mixture was stirred for 4 h at room temperature and then transferred to a separatory funnel and neutralized with 5 N HCl. A saturated solution of NaCl was added and the bromoacetylene (**5**) was extracted with ether [4 × 60 mL], the ether extract was washed with distilled water [3 × 200 mL], and then dried over $MgSO_4$. After removing the solvent on a rotary evaporator, the residue was purified by silica gel thin-layer chromatography (hexane as developer) affording pure **5**.

General Procedure for the $Pd(diphos)_2$ Catalyzed Conversion of Vinylic Dibromides 4 to Monoacids 6. A mixture of PEG-400 (10 mL) and 5 N or 10 N NaOH or KOH (10 mL) was stirred for 30 min. The palladium catalyst, $Pd(diphos)_2$ [0.10 g, 0.11 mmol], dissolved in 2 mL of methylene chloride and then diluted with 3 mL of PEG-400, was added to the base–PEG mixture, and stirring was continued for 4 h at room temperature. The vinylic dibromide **4** (2.0 mmol), dissolved in 2 mL of PEG-400 was added drop-by-drop (over a 30-min period) to the stirred solution and the resulting reaction mixture was heated at 60–65 °C for 17 h. After cooling to room temperature, the layers were separated and saturated sodium chloride (10 mL) was added to the PEG phase. Ether was added, and the ether extract was washed with distilled water [3 × 150 mL], dried ($MgSO_4$), and concentrated to give traces, if any, of diyne as byproduct.

The PEG–aqueous layer was neutralized with 5 N hydrochloric acid and then extracted with ether (3 × 80 mL). The ether extract was dried ($MgSO_4$) and concentrated to give the acid **6**. Further purification, if necessary, could be effected by distillation or by silica gel thin-layer chromatography.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for support of this research. We are indebted to Professor Yoel Sasson for providing us with preprints of research relevant to the subject matter of this paper.

Registry No. 4 (R = Ph, R′ = H), 7436-90-0; 4 (R = o-$CH_3C_6H_4$, R′ = H), 104464-03-1; 4 (R = p-$CH_3C_6H_4$, R′ = H), 60512-56-3; 4 (R = p-Cl C_6H_4, R′ = H), 77295-59-1; 4 (R = p-$CH_3OC_6H_4$, R′ = H), 60512-57-4; 4 (R = $C_2H_5CH(CH_3)$, R′ = H), 85066-83-7; 4 (nR = PhCH = CH, R′ = H), 90766-67-9; 4 (R = Ph, R′ = CH_3), 60014-86-0; 4 (R = $(CH_3)_2CH(CH_3)$, R′ = $(CH_2)_2$), 64285-83-2; 5 (R = Ph), 932-87-6; 5 (R = o-$CH_3C_6H_4$), 72591-20-9; 5 (R = p-$CH_3C_6H_4$), 33491-05-3; 5 (R = p-ClC_6H_4), 33491-03-1; 5 (R = p-$CH_3OC_6H_4$), 33675-41-1; 5 (R = $C_2H_5CH(CH_3)$), 30689-73-7; 6 (R = Ph, R′ = CH_3), 492-37-5; 6 (R = $(CH_2)_2CH(CH_3)$, R′ = $(CH_2)_2$), 4331-54-8; 6 (R = Ph, R′ = H), 103-82-2; 6 (R = o-$CH_3C_6H_4$, R′ = H), 644-36-0; 6 (R = p-$CH_3C_6H_4$, R′ = H), 622-47-9; 6 (R = p-CLC_6H_4, R′ = H), 1878-66-6; 6 (R = p-$CH_3OC_6H_4$, R′ = H), 104-01-8; 6 (R = PhCH=CH_2, R′ = H), 621-82-9; PEG, 25322-68-3; $Pd(diphos)_2$, 31277-98-2.