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# Solvent Effects on the Monobromination of α,ω-Diols: A Convenient Preparation of ω-Bromoalkanols

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ω-Bromo alcohols have been used extensively as synthetic intermediates, particularly in the synthesis of pheromones.[1] The classic procedure for preparing such compounds is by heating α,ω-diols with aqueous HBr and petroleum ether (bp 100−120 °C) in a continuous extraction apparatus.[2] This method works reasonably well but can be inconvenient for large-scale syntheses and is not completely selective, with small amounts of diol and dibromide invariably contaminating the desired monobromo alcohol. In 1985, a report appeared which presented a solution to this long-standing problem.[3] Specifically, it was reported that reaction of diols with HBr in benzene with azeotropic removal of water gave highly selectively monobromo alcohols in >99% purity (eq 1).

$$\underset{\mathbf{1}}{\mathrm{HO(CH_2)_nOH}} \xrightarrow[\text{PhH, }\Delta\text{, -H}_2\text{O}]{\text{HBr}} \underset{\mathbf{2}}{\mathrm{HO(CH_2)_nBr}} \qquad (1)$$

**a**: n = 5, **b**: n = 6, **c**: n = 7, **d**: n = 8, **e**: n = 10, **f**: n = 12

The simplicity and purported high selectivity of this method made it very attractive, and it has been used by many other researchers.[4] However, many reports of the use of this method do not detail yields,[5] and there are some reports of good (>80%) yields of bromo alcohols,[6] along with reports of modest yields[7] and/or product purities which do not approach 99%.[8,9] In addition, we have found this reaction to be capricious, with variable yields, and even in the best cases, the product distribution was typically comparable to that observed in the classic continuous extraction procedure. These observations, along with the known health hazards associated with benzene, prompted us to reexamine this problem.

**Table 1. Reaction of 1d with HBr in Different Solvents**[a]

$$\underset{\mathbf{1d}}{\mathrm{HO(CH_2)_8OH}} \xrightarrow{\text{HBr}} \underset{\mathbf{2d}}{\mathrm{HO(CH_2)_8Br}} + \underset{\mathbf{3d}}{\mathrm{Br(CH_2)_8Br}}$$

| | conditions | | | | |
|---|---|---|---|---|---|
| entry | solvent | Dean−Stark | time (h) | ratio[b] **1d**:**2d**:**3d** | yield of **2d**[c] (%) |
| 1 | benzene | yes | 60 | 57:42:1[d] | 32 |
| 2 | | no | 90 | 16:81:3 | 72 |
| 3 | toluene | yes | 72 | 36:62:2 | 55 |
| 4 | | no | 72 | 0:98:2 | 87 |
| 5 | cyclohexane | yes | 68 | 36:62:2 | 59 |
| 6 | | no | 68 | 5:92:3 | 85 |
| 7 | isooctane | yes | 96 | 38:60:2 | 46 |
| 8 | | no | 96 | 25:73:2 | 63 |

[a] All reactions were carried out with 1.1 equiv of aqueous (48%) HBr. [b] Molar ratios based on isolated yields after flash chromatography. [c] Isolated yield of **2d** after flash chromatography. [d] Ratios varied from 71:28:1 to 14:84:2 depending on the rate of heating. See the text.

## Results and Discussion

We decided to replace benzene with solvents which would allow for the azeotropic removal of water since it was suggested that this was important for the formation of pure bromo alcohols.[3] Results for the reaction of a "typical" long-chain diol, 1,8-octanediol (**1d**), with HBr in various solvents, with and without a Dean−Stark trap, are presented in Table 1. In contrast to the previous report, these results suggest that the use of a Dean−Stark trap (entries 1, 3, 5, and 7) is, in fact, detrimental to this reaction. Small amounts of dibromide **3d** were formed under all of the conditions examined, but a Dean−Stark trap led to the recovery of considerable amounts of starting diol **1d**. Reaction in benzene with a Dean−Stark trap proved to be one of the worst reactions. The best conditions found were to simply heat diol **1d** and HBr in toluene at reflux (entry 4).

To better understand the negative effect of a Dean−Stark trap, the aqueous layer was collected and titrated with NaOH. In experiments using benzene as solvent, the amount of acid found in the trap varied from 12% (slow heating, gentle reflux) to 60% (vigorous heating) of the acid originally used. Thus, the lower conversions when using a Dean−Stark trap are likely due to loss of reagent (i.e., acid) from the reaction mixture. Loss of acid is also likely to be the reason other researchers have had to add additional HBr to achieve good conversions.[10] Furthermore, the variable loss of acid (dependent on heating rate) is likely to be at least partially responsible for different conversions under apparently similar conditions; it is a reasonable explanation for the variability in this reaction that we have observed.

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(1) Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1992; Vol. 9, pp 1−534.

(2) (a) Pattison, F. L. M.; Stothers, J. B.; Woolford, R. G. *J. Am. Chem. Soc.* **1956**, *78*, 2255−2259. (b) Camps, F.; Casamor, J. M.; Coll, J.; Guerrero, A.; Riba, M. *Org. Prep. Proced. Int.* **1983**, *15*, 63−67.

(3) Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis* **1985**, 1161−1162.

(4) A search of the Science Citation Index showed >50 citations for the years 1987−1996. Significantly, the vast majority of papers citing this article used the method reported to prepare bromo alcohols. During the same period, ~50% of the **1d** → **2d** conversions reported used this method.

(5) See, for example: (a) Nakayama, T.; Mori, K. *Liebigs Ann./Recl.* **1997**, 839−843. (b) Kaiser, A.; Marazano, C.; Maier, M. *J. Org. Chem.* **1999**, *64*, 3778−3782. (c) Sharma, A.; Chattopadhyay, S. *J. Org. Chem.* **1998**, *63*, 6128−6131.

(6) (a) Robertson, J.; Burrows, J. N. *Synthesis* **1998**, 63−66. (b) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48*, 3413−3428.

(7) (a) Percec, V.; Asandei, A. D. *Macromolecules* **1997**, *30*, 7701−7720. (b) Kulkarni, B. A.; Chattopadhyay, S.; Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1993**, *58*, 5964−5966. (c) Börjesson, L.; Csöregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989−2999.

(8) Johansson, G.; Percec, V.; Ungar, G.; Zhou, J. P. *Macromolecules* **1996**, *29*, 646−660.

(9) When toluene was used in place of benzene (with a Dean−Stark trap), good yields of bromo alcohols were obtained but were contaminated with ca. 9% dibromides. (a) Enders, D.; Bartzen, D. *Liebigs Ann. Chem.* **1991**, 569−574. (b) Enders, D.; Finkam, M. *Liebigs Ann. Chem.* **1993**, 551−555.

(10) In the conversion of **1d** to **2d**, an additional 3 × 1 equiv of HBr was needed to achieve good conversion: Nakashima, H.; Hirata, N.; Iwamura, T.; Yamagiwa, Y.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2849−2857.

10.1021/jo000291u CCC: $19.00

**Table 2. Reaction of Diols with HBr in Toluene**[a]

$$\underset{\mathbf{1}}{HO(CH_2)_nOH} \xrightarrow[PhCH_3,\ \Delta]{HBr} \underset{\mathbf{2}}{HO(CH_2)_nBr} + \underset{\mathbf{3}}{Br(CH_2)_nBr}$$

| entry | *n* | time (h) | ratio **1**:**2**:**3**[b] | yield of **2**[c] |
|---|---|---|---|---|
| 1 | 5 | 9 | 5:94:1 | 81 |
| 2 | 6 | 13 | 4:95:1 | 79 |
| 3 | 7 | 72 | 0:99:1 | 94 |
| 4 | 8 | 72 | 1:97:2 | 87 |
| 5 | 10 | 48 | 2:97:1 | 87 |
| 6 | 12 | 72 | 4:94:2 | 80 |

[a] All reactions were carried out with 1.2 equiv of aqueous HBr, no Dean–Stark trap. Additional HBr (0.3–0.5 equiv) was added if significant amounts of diol were present after 36 h. [b] Determined by GC analysis of acetylated crude reaction mixtures. [c] Isolated yield of **2** after flash chromatography.

Since toluene (without a Dean–Stark trap) seemed to be the best solvent for this reaction, we examined diols with other chain lengths under these conditions (Table 2). Reactions did not always proceed to completion when only 1.1 equiv of HBr was used, but excellent results were obtained if the reactions were monitored by TLC and additional HBr was added as required. In all cases, the product distributions were excellent and good yields of bromo alcohols were obtained. It should be noted that the product distributions reported in Table 2 were determined by GC analysis of crude reaction mixtures. This is important since the product distributions could be easily distorted by fractionation. For example, diol **1d** is not very soluble in cold toluene and easily precipitates out; sampling of the supernatant would then give inaccurate compositions. It should also be noted that yields reported are isolated yields of chromatographed bromo alcohols and that isolated yields of dibromides and diols were consistent with GC analyses.

The large polarity difference among dibromides, bromo alcohols, and diols makes chromatographic separations trivial. However, cost considerations, particularly on larger scales, may make it desirable to avoid chromatography. Fortunately, since these reactions are quite clean, reasonably pure bromo alcohols may be obtained by simple Kugelrohr distillation of the crude reaction mixture. For example, with diol **1d**, the desired bromo alcohol **2d** (contaminated with 1% **1d** and 2% **3d**) was obtained in 95% yield using this simple procedure.

It is not obvious why these reactions give product distributions which deviate significantly from the statistical 25:50:25 mixture of **1**:**2**:**3** that one might expect. In the classical continuous extraction chemistry,[2] selective extraction of the bromo alcohol (leaving the more polar diol to react) effectively protects it from further reaction. Similarly, other monoprotection/functionalization schemes for diols are accompanied by reasonable explanations for the observed selectivities.[11] In this case, it can be reasoned that, for the high yields of **2** that are observed, the bromo alcohols must be much less reactive than the diols. And, in fact, treatment of bromo alcohol **2d** with 1.1 equiv of HBr in toluene at reflux for 48 h resulted in only 11% conversion to the dibromide. Thus, we can superficially explain the nonstatistical mixtures as being due to the relatively lower reactivity of bromo alcohols (compared to diols) under the reaction conditions. The fundamental reason(s) for this lower reactivity is not obvious,[12] but if one considers that (long-chain) bromo alcohols might behave like surfactants, then one may speculate that the bromo alcohols are less reactive due to the formation of aggregates such as reverse micelles or water/oil microemulsions. Such aggregates might be expected to shield the polar hydroxyl groups from reagents in the bulk solvent. We have no direct evidence for aggregation, but it is consistent with observations that azeotropic removal of water decreases selectivities[9] (since water is sometimes required for nonionic surfactants to form aggregates[13]) and that the selectivities are somewhat concentration dependent (at higher concentrations, slightly lower selectivities are obtained). Whatever the real reason(s) may be, this method should be very useful to chemists interested in preparing $\omega$-bromo alcohols as synthetic intermediates.

## Experimental Section

**General Information.** Diols were obtained from Aldrich Chemical Co.; hydrobromic acid (47–49%, BDH, AnalaR) and reagent grade solvents were used without further purification. Thin-layer chromatography was carried out using Merck 5715 silica gel F254 plates, while flash chromatography employed EM Science 35–75 $\mu$m silica gel 60. Ratios of products (Table 2) were determined by GC–MS analysis of acetylated (xs $Ac_2O$, pyr, cat. DMAP) crude reaction mixtures and are not corrected for response factors; the order of elution using an HP5 column was dibromide, bromoacetate, and diacetate. All bromo alcohols prepared are known compounds and showed spectral data consistent with literature values.[3]

**Typical Procedure.** To a mixture of diol **1d** (30 g, 0.205 mol) and toluene (600 mL) was added concentrated HBr [27 mL of a 48% (9 M) aqueous solution, 0.24 mol]. The heterogeneous mixture was stirred and heated at reflux for 36 h. TLC analysis (silica, ether as eluent, $R_f$ = (diol **1d**) 0.05, (bromo alcohol **2d**) 0.55, and (dibromide **3d**) 0.95) indicated substantial amounts of diol **1d** still remained. Thus, a further quantity of HBr (10 mL, 0.09 mol) was added, and the mixture was heated at reflux for a further 36 h, at which time TLC analysis showed no diol remaining. The reaction mixture was allowed to cool to rt, and the phases were separated. The organic layer was diluted with ether and washed with 1 M NaOH, brine, and phosphate buffer (3 M, pH 7). Drying ($Na_2SO_4$) and concentration of the organic layer gave a yellow oil which was distilled (Kugelrohr, bath temp 110–120 °C, 0.2 Torr) to provide bromo alcohol **2d** as a colorless liquid (42.0 g). GC analysis of this material (after acetylation) showed a purity of 97% (1% diol, 2% dibromide). Alternatively, flash chromatography of the crude reaction mixture (500 g of silica, hexanes–ether, 1:1) provided 37.4 g (87%) of **2d** free of diol or dibromide.

Essentially identical results were obtained when 1200 mL of toluene (40 mL/g of diol) was used, but use of 10 mL/g of diol resulted in formation of considerably more dibromide (6%).

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(11) See, for example: (a) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388–3390. (b) Houille, O.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1996**, *37*, 625–628.

(12) It was suggested by a reviewer that differences in reactivity might be due to lower aqueous solubility of bromo alcohols compared to diols and that experiments with a PTC might provide some insights. Addition of 10 wt % $BnEt_3NCl$ or Aliquat 336 to these reactions did not affect product distributions, suggesting that aqueous solubility is not a significant issue here.

(13) *Organized Assemblies in Chemical Analysis: Reversed Micelles*; Hinze, W. L., Ed.; JAI Press: Greenwich, CT, 1994.