Organic Process Research & Development **1999**, *3*, 480–484

Studies in Selectivity Aspects in the Synthesis of Aliphatic α-Bromoaldehydes

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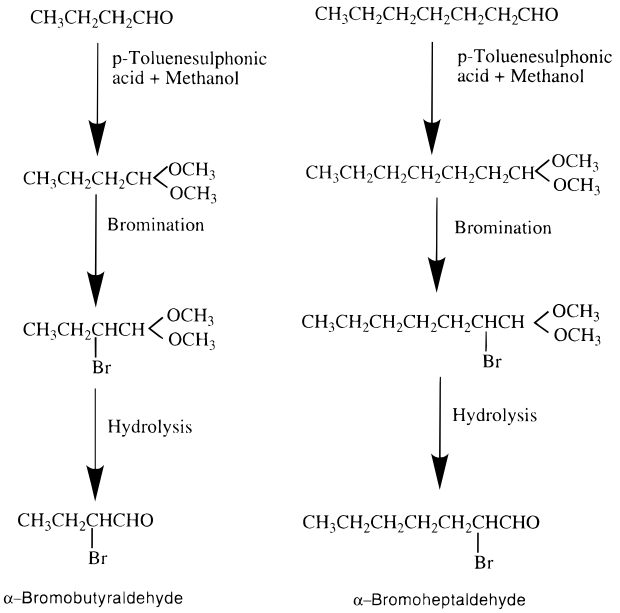
Abstract:

A highly selective process scheme was developed to synthesize α-bromoaldehydes by regulating the important process parameters from a reaction-engineering point of view. Thus, α-bromobutyraldehyde and α-bromoheptaldehyde were synthesized in very high selectivity starting with butyraldehyde and heptaldehyde. In the bromination reaction at 40% conversion ratio, the selectivity was as high as 98% by using liquid bromine as the brominating agent.

Introduction

α-Bromoaldehydes are important organic intermediates in pharmaceutical and fine chemical industries with a significant industrial value. These are usually synthesized[1−6] by direct bromination of aldehydes or by bromination of the dimethylacetal of the aldehyde followed by hydrolysis. In both cases bromination is usually done by liquid bromine. The main drawback of these processes is the low selectivity to the desired product. The hydrobromic acid formed in situ in these reactions causes polymerization of the free aldehyde, which is very difficult to control once started. Hence, the selectivity to the α-bromoaldehydes never exceeds 60%, and the separation of the product from the polymeric reaction mixture is also a difficult task in practice. Calcium carbonate[7] and pyridine[8] may be used to neutralize the hydrobromic acid during the reaction, but the purity of the final product is again a problem. Some selective brominating agent such as *N*-bromosuccinimide[9] or Se(IV) oxyhalides[10] can also be used, but the stoichiometric requirement (mole of bromine/mole of aldehyde or acetal) of such costly reagents for synthesis is not industrially affordable. Some other processes[11−13] have very little industrial significance. Thus, there is an immense scope to modify the selectivity of bromination by manipulating the process parameters from the reaction engineering point of view. In this work, α-bromoaldehydes are synthesized by acetalyzation of butyraldehyde and heptaldehyde, followed by bromination at the α-position using liquid bromine with very high selectivity by controlling the critical reaction parameters (Scheme 1).

Scheme 1. **Production of α-bromoaldehydes**



Results and Discussion

Definition. ***Conversion***. The conversion is defined as the ratio of the moles of reactant reacted to the moles of reactant taken.

Selectivity. The selectivity to a particular product is defined as the ratio of the moles of the reactant reacted for the formation of that particular product to the moles of reactant reacted.

To obtain high selectivity to the α-bromoaldehyde, it was worth considering controlling the important reaction parameters to a certain level. A thorough study of the process parameters for different steps enabled us to get the most suitable process conditions for maximum selectivity to the product.

A. Acetalyzation. ***Effect of the Mode of Addition on the Selectivity of the Formation of Dimethylacetal of Butyr-***

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 10.1021/op990025m CCC: $18.00
Published on Web 08/26/1999

Table 1. Effect of addition time of butyraldehyde on the selectivity of acetal formed[a]

addition time of butyraldehyde, h	% conversion of aldehyde	% conversion to dimethylacetal	% selectivity to dimethylacetal
0.5	75	60	80
1.0	92	79	86
1.5	100	99	99
2.0	100	93	93

[a] Reaction conditions: butyraldehyde, 40% w/v; methanol, 1.5 L; *p*-toluenesulphonic acid, 1% w/v; temperature, 65 °C.

Table 2. Effect of reaction temperature on the selectivity of dimethylacetal

temperature, °C	% conversion of butyraldehyde	% conversion to acetal	% selectivity to acetal
40	50	49	98
50	78	76	98
65	100	99	99

[a] Reaction conditions: butyraldehyde, 40% w/v; methanol, 1.5 L; *p*-toluenesulphonic acid, 1% w/v; reaction time, 1.5 h.

aldehyde. Butyraldehyde is susceptible to polymerization reactions under acidic conditions. To minimize the side reactions, the effect of the mode of addition of butyraldehyde on the acetalyzation reaction was studied. It was observed that when the aldehyde was added dropwise to the reaction mixture, the selectivity to dimethylacetal was 99% in comparison to 40% in batch-mode reaction. This was due to the accumulation of a higher concentration of butyraldehyde in contact with the acid catalyst, causing the polymerization of the substrate and thus lowering the selectivity.

Effect of Addition Time on the Selectivity of the Formation of Dimethylacetal of Butyraldehyde. When butyraldehyde was added in semibatch manner, with the increase in addition time the overall conversion and selectivity to the product increased significantly (Table 1). This may be due to the lower rate of trimerization of butyraldehyde to *p*-butyraldehyde or polymerization of butyraldehyde under the reaction conditions. A 1.5-h addition time of butyraldehyde was found to be the most suitable under the reaction conditions.

Effect of Reaction Temperature on the Selectivity of the Formation of Dimethylacetal of Butyraldehyde. The reaction temperature was varied from 40 to 65 °C. At lower temperature the reaction was found to be rather slow, and only 50% conversion was achieved in 1.5 h (Table 2). With the increase in temperature to 65 °C, the overall conversion of butyraldehyde increased to 100%, and the selectivity with respect to the product, remained almost 100%. All of the subsequent runs were carried at a temperature of 65 °C.

Effect of Different Catalysts on the Selectivity of the Formation of Dimethylacetal of Butyraldehyde. Different catalysts, both homogeneous (sulphuric acid, *p*-toluenesulphonic acid) and heterogeneous (Amberlite IR-120) were used in the study. In case of ion-exchange resin, the separation of product from the reaction mixture was unconstrained, but the catalyst loading was 5 times in comparison to the homogeneous catalyst like *p*-toluenesulphonic acid (Table 3).

Table 3. Effect of different catalysts on the selectivity of dimethylacetal of butyraldehyde[a]

catalyst	% conversion of butyraldehyde	% selectivity to acetal
sulfuric acid (1% w/v of total reaction volume)	100	86
p-toluenesulfonic acid (1% w/v)	100	99
Amberlite IR-120 (5% w/v)	80	99

[a] Reaction conditions: butyraldehyde, 40% w/v; methanol, 1.5 L; reaction time, 1.5 h; temperature, 65 °C.

Table 4. Effect of *p*-toluenesulphonic acid loading on the selectivity of acetal[a]

p-toluenesulfonic acid loading, % w/v	% conversion of butyraldehyde	% selectivity to acetal
0.5	87	93
1.0	100	99
1.5	100	98

[a] Reaction conditions: butyraldehyde, 40% w/v; methanol, 1.5 L; reaction time, 1.5 h; temperature, 65 °C.

Table 5. Product distribution with material balance under the best suitable acetalyzation reaction conditions[a]

material	moles of butyraldehyde accounted for	% butyraldehyde accounted for	% overall material balance on the basis of butyraldehyde
butyraldehyde (input)	8.33	100	100
dimethylacetal (output)	8.24	99	100
p-butyraldehyde	0.05	0.6	100
residue	0.04	0.48	100

[a] Reaction conditions: butyraldehyde, 40% w/v; methanol, 1.5 L; *p*-toluenesulphonic acid, 1% w/v; temperature, 65 °C; reaction time, 1.5 h.

Effect of* p-*Toluene Sulphonic Acid Loading on the Selectivity of the Formation of Dimethylacetal of Butyraldehyde. The rate of acetalyzation of butyraldehyde increased with the increase in catalyst loading, whereas the selectivity remained almost the same. A 1% catalyst loading was found to be most suitable to achieve maximum selectivity under the reaction conditions (Table 4).

Material Balance. A 100% overall material balance was achieved on the basis of butyraldehyde (Table 5).

B. Bromination. ***Effect of Addition Time of Bromine on the Selectivity of the Formation of* α-*Bromodimethylacetal of Butyraldehyde.*** It was observed that with an increase in addition time of bromine, the selectivity with respect to the product formed increased significantly. This may be due to the lower rate of polymerization or dibromination reaction under the reaction conditions. An addition time of 2 h was found to be most suitable for this reaction (Table 6).

Effect of Molar Ratio of Dimethylacetal of Butyraldehyde to Bromine on the Selectivity of the Formation of* α-*Bromodimethylacetal of Butyraldehyde. The molar ratio

Table 6. **Effect of addition time of bromine on the selectivity of α-bromodimethylacetal of butyraldehyde[a]**

addition time of bromine, h	% overall conversion of dimethylacetal of butyraldehyde	% selectivity to α-bromodimethylacetal of butyraldehyde
0.5	40	75
1.0	40	82
2.0	40	98

[a] Reaction conditions: acetal, 2 mol/L; bromine, 0.8 mol/L; solvent, dichloromethane, temperature, 10 °C; reaction volume, 1 L.

Table 7. **Effect of mole ratio of acetal to bromine on the selectivity of α-bromodimethylacetal of butyraldehyde[a]**

acetal:bromine	% conversion of acetal	% selectivity to α-bromodimethylacetal
1:0.4	40	98
1:0.7	70	81
1:1.1	100	45

[a] Reaction conditions: acetal, 2 mol/L; bromine, 0.8 mol/L; solvent, dichloromethane; temperature, 10 °C; reaction volume, 1 L; reaction time, 3 h.

Table 8. **Effect of temperature on the selectivity of α-bromodimethylacetal of butyraldehyde[a]**

temperature, °C	% conversion of acetal	% selectivity to α-bromodimethylacetal
10	40	98
30	40	53
40	40	39

[a] Reaction conditions: acetal, 2 mol/L; bromine, 0.8 mol/L; solvent, dichloromethane; reaction volume, 1 L; reaction time, 3 h.

of acetal to bromine was varied from 1:0.4 to 1:1.1. It was observed that at the ratio of 1:0.4, the selectivity was 98% (Table 7). This is because the concentration of hydrobromic acid, which causes the polymerization of acetal, never exceeds the threshold concentration for polymerization reaction at this conversion level.

Effect of Temperature on the Selectivity of the Formation of α-Bromodimethylacetal of Butyraldehyde. The reaction temperature was varied from 10 to 40 °C (Table 8). At higher temperature, the rate of reaction was very fast, but the selectivity to the product decreased due to the faster rate of polymerization reaction under the reaction conditions. A temperature of 10 °C was found to be most suitable under the reaction conditions.

Effect of an Alternative Different Brominating Agent on the Selectivity of the Formation of α-Bromodimethylacetal of Butyraldehyde. Liquid bromine and dioxane−dibromide were used to brominate acetal. Dioxane−dibromide was prepared in the laboratory by adding equimolar proportion of bromine into dioxane in a semibatch mode fashion at 15 °C. Under the reaction conditions, 100% selectivity to the product was obtained with dioxane−dibromide, whereas 98% with bromine at 40% conversion of acetal.

Effect of Different Solvents on the Selectivity of the Formation of α-Bromodimethylacetal of Butyraldehyde.

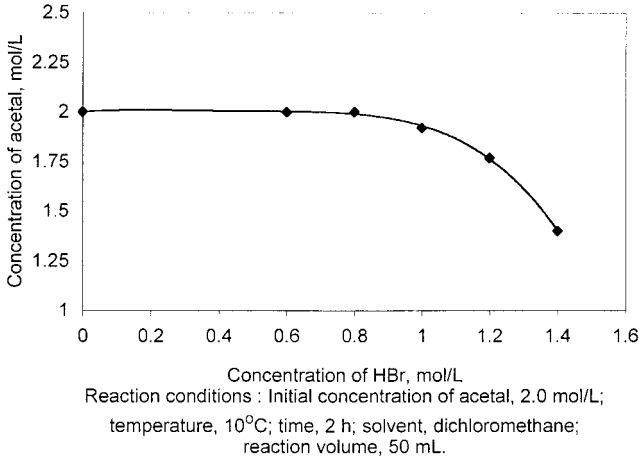

Figure 1. **Effect of HBr concentration on the stability of dimethylacetal of butyraldehyde under the reaction conditions.**

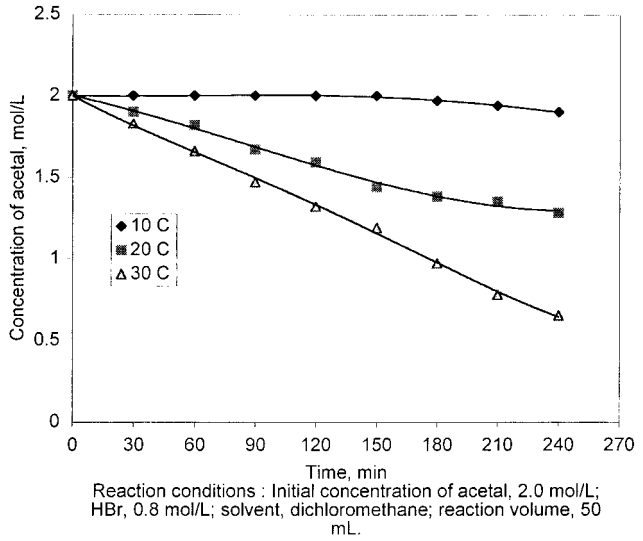

Figure 2. **Effect of temperature on the stability of acetal.**

Ethylenedichloride, methylenedichloride, and carbontetrachloride were used as solvents for this reaction. At 40% conversion ratio of acetal, 98% selectivity, was achieved with each solvent. In a view to remove the solvent at a minimum temperature to avoid the polymerization reaction, methylenedichloride was preferred under the reaction conditions. However, as the vapor pressure of methylenedichloride is very high at room temperature, it is worth considering using any one of the other solvents for industrial production.

Effect of HBr Concentration on the Stability of Acetal. The stability studies on solutions of the acetal had been carried out at various concentrations of dissolved HBr (Figure 1) and at different temperatures (Figure 2) for a specific HBr concentration. It was found that, the critical level at which the stability of the acetal would be affected was higher than would produced by carrying out the reaction to 40% conversion level at 10 °C even if all the HBr remained in solution.

Material Balance. A complete product distribution of this bromination reaction under the best suitable conditions is given in Table 9. A 100% material balance was accounted for on the basis of dimethylacetal of butyraldehyde.

Table 9. **Product distribution with material balance in the bromination of dimethylacetal of butyraldehyde[a]**

material	% dimethylacetal accounted for, mol	% dimethylacetal accounted for	% overall material balance on the basis of dimethylacetal of butyraldehyde
Dimethylacetal of butyraldehyde (input)	2	100	100
α-bromodimethylacetal (output)	1.96	98	100
butyraldehyde	0.005	0.25	100
p-butyraldehyde	0.02	1.0	100
residue	0.015	0.75	100

[a] Reaction conditions: acetal, 2 mol/L; bromine, 0.8 mol/L; reaction temperature, 10 °C; solvent, dichloromethane; reaction volume, 1 L; reaction time, 3 h.

Table 10. **Effect of different acids on the selectivity of α-bromobutyraldehyde in the hydrolysis of α-bromodimethylacetal of butyraldehyde[a]**

acid	% conversion of α-bromodimethylacetal of butyraldehyde	% selectivity to α-bromobutyraldehyde
hydrochloric acid	100	60
hydrochloric−acetic acid (3:2)	100	85
p-toluenesulfonic acid	100	75
Amberlite IR-120	100	98

[a] Reaction conditions: temperature, 70 °C; acid used, 5% w/v of α-bromodimethylacetal; time, 2 h; reaction volume, 500 mL.

Table 11. **Effect of different amberlite IR-120 concentration on the conversion and selectivity to α-bromobutyraldehyde[a]**

Amberlite IR-120 concentration, % w/v	% conversion of α-bromodimethylacetal	% selectivity to α-bromobutyraldehyde
1	41	92
3	72	97
5	100	98
7	100	80

[a] Reaction conditions: temperature, 70 °C; acid used, 5% w/v of α-bromodimethylacetal of butyraldehyde; time, 2 h; reaction volume, 500 mL.

C. Hydrolysis. The α-bromodimethylacetal was hydrolyzed under reflux conditions, and the methanol formed in situ in the reaction mixture was distilled out simultaneously from the reaction mixture to shift the equilibrium to the product side. Different acids such as hydrochloric acid, *p*-toluenesulphonic acid, hydrochloric acid−acetic acid, and Amberlite IR-120 were used for the hydrolysis (Table 10). Amberlite IR-120 was found to be the best under the reaction conditions to achieve maximum selectivity at 100% conversion ratio. The reaction was studied for different acid concentrations, and 5% w/v of Amberlite IR-120 concentration was found to be the most suitable to obtain maximum conversion and selectivity under the reaction conditions (Table 11).

Summary

Optimum Conditions. ***Acetalyzation:*** butyraldehyde concentration 40% w/v; *p*-toluenesulphonic acid concentration, 1% w/v; temperature, 65 °C; reaction time, 1.5 h; conversion, 100%; selectivity, 99%.

For heptaldehyde, at a conversion ratio of 100%, the selectivity obtained was 98%.

Bromination: dimethylacetal of butyraldehyde, 2 mol/L; bromine, 0.8 mol/L; solvent, dichloromethane; reaction temperature, 10 °C; reaction volume, 1 L; conversion of dimethylacetal of butyraldehyde, 40%; selectivity to α-bromodimethylacetal of butyraldehyde, 98%.

For heptaldehyde, at a conversion ratio of 40%, the selectivity obtained was 99%.

Hydrolysis: reaction temperature, 70 °C; Amberlite IR-120, 5% w/v of bromoacetal; reaction volume, 500 mL; conversion, 100%; selectivity to α-bromoaldehyde, 98%.

For heptaldehyde, 97% selectivity was obtained at a conversion ratio of 100%.

Comparison of this Process with the Existing Processes. α-Bromoaldehydes are prepared, either by selective brominating agents or by using bases such as pyridine to hinder the effect of hydrobromic acid on the polymerization reaction of bromoacetal.

However, in the first case, uses of costly specific reagents are not of industrial choice, and in the second case, the purity of the isolated final product is a problem.

In this study, bromination is done by using liquid bromine only. Here, the stoichiometric amount of bromine was kept only at 40% of the exact requirement, by which conversion was controlled at 40% level. Up to 40% conversion of dimethylacetal of butyraldehyde whatever amount of HBr acid formed does not affect the polymerization reaction under the reaction conditions. Thus, selectivity as high as 98% could be achieved. The unreacted dimethylacetal of butyraldehyde after bromination reaction was recycled back successfully without a trace of residue or tarry material formation in the first recycle, only 0.6% in the second recycle and 0.8% in the third recycle.

Conclusion

It was possible to obtain very high selectivity in all three steps. By fixing the conversion of dimethylacetal of butyraldehyde at 40%, the rate of polymerization of acetal to polyacetal type resins was minimized to get 98% selectivity under the best suitable reaction conditions.

Experimental Section

A. Acetalyzation of Aldehydes. The experiments were carried out in a 2-L borosilicate glass reactor equipped with a six-blade turbine impeller, four baffles, a dropping funnel, and a reflux condenser. The assembly was kept in a constant-

temperature bath. A predetermined quantity of catalyst, dissolved in methanol, was taken in the reactor, and the reaction mixture was heated to the desired temperature. A known quantity of the aldehyde was added in a semibatch fashion to the reaction mixture over a predetermined period of time, maintaining the desired temperature within the specified range. After the stipulated period of reaction, the reaction mixture was neutralized, after cooling, with 5% sodium carbonate solution, and methanol was removed by vacuum distillation. After removal of methanol and water, the residual solution was fractionated under reduced pressure to obtain pure acetal. The reaction mixture was analyzed by gas chromatography (Chemito 8510) equipped with a flame-ionization detector (FID) and connected to an integrator. The details are as follows: column, SS (2 m, 10% OV-17 on chromosorb W); carrier, nitrogen; flow rate, 30 mL/min; oven temperature, 60 °C, 5 °C/min, 120 °C, 1 min, 20 °C/min, 5 min; injector temperature, 300 °C; detector temperature 300 °C.

B. Bromination of Dimethylacetal. The bromination experiments were carried out in a 2-L borosilicate glass reactor equipped with a six-blade turbine impeller, four baffles, a dropping funnel, and a water condenser. The outgoing gases were passed through a caustic scrubber. The assembly was kept in a constant-temperature ice bath. Predetermined quantities of acetal dissolved in solvent were kept at the desired temperature. A known quantity of bromine, diluted with the same solvent, was added in a semibatch mode to the reaction mixture over a specified period of time, maintaining the desired temperature within the specified range. After bromination, the reaction mixture was washed 2−3 times with water and finally with 10% sodium carbonate solution to remove free hydrobromic acid. The solution was dried overnight over anhydrous sodium sulfate. The solvent was distilled out at atmospheric pressure and then under vacuum to obtain first the unreacted acetal (37−39 °C, 39−41 mm), which was recycled back, and then bromoacetal (95−98 °C, 30−31 mm) with 99% purity. The reaction mixture was analyzed by gas chromatography as was used in the acetalyzation reaction. The temperature programming is as follows: oven temperature, 100 °C, 5 °C/min, 150 °C, 1 min, 20 °C/min; injector temperature, 300 °C; detector temperature, 300 °C.

C. Hydrolysis of α-Bromoacetals. The experiments were carried out in the same reactor used in the acetalyzation and bromination reactions. The bromoacetal and the acid were charged into the reactor, and methanol was distilled out simultaneously from the reaction mixture to shift the reaction to the right side. After the stipulated reaction period, α-bromoaldehyde was isolated by fractionating the residual mixture under vacuum by using a 2-m wiremesh packed column. Samples were analyzed by GC under the same conditions as used in the bromination reactions.

Received for review March 30, 1999.

OP990025M