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Process Development of the Synthesis of 3,4,5-Trimethoxytoluene

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Abstract:

3,4,5-Trimethoxytoluene (TMT) was synthesized, starting from *p*-cresol, through bromination followed by methylation to give 3,5-dibromo-4-methoxytoluene (DBMT). The methoxylation of the latter with sodium methoxide in methanol was studied under pressure and by continuous distillation of the solvent, methanol. The O-methylation reaction preceding the methoxylation was advantageous from the point of view of separation, purification, and isolation of the desired product and also in reducing the tar formation. The residue obtained was minimized to 0.6−0.7 wt % of the DBMT. The methoxylation reaction with distillative removal of methanol gave a conversion of 98% of DBMT to the mixture of methoxylated products, and the conversion to TMT was 86.5% as compared to 93% and 70.81%, respectively, when the reaction was carried out under pressure in a sealed reactor. However, the overall conversion to TMT based on *p*-cresol is 64.27% for the methoxylation reaction under pressure and 78.46% for the reaction by continuous removal of methanol calculated as isolated yield. The advantages of the methoxylation of the DBMT over the published literature procedures involving direct methoxylation of 3,5-dibromo-*p*-cresol followed by methylation of the dimethoxy-*p*-cresol are the ease of separation, purification, and isolation by vacuum fractionation of the desired product TMT.

Introduction

Fine chemicals based on *p*-cresol have gained significant importance as starting materials in the food and pharmaceutical industry in recent past. One of the industrially important intermediates, 3,4,5-trimethoxytoluene (TMT), obtained from *p*-cresol, on oxidation by air to yield 3,4,5-trimethoxybenzaldehyde, an intermediate for the well-known antibacterial, trimethoprim and on oxidation by peracid to yield 2,3-dimethoxy-5-methyl-2,5-cyclohexadiene-1,4-dione,[1−3] an intermediate for the synthesis of the cardiovascular agent, Coenzyme-Q_{10} (ubiquinone).[4]

The general process scheme for the synthesis of TMT from *p*-cresol involves the unit processes such as bromination, methoxylation, and O-methylation. The bromination of *p*-cresol is usually carried out in a semi-batch mode due to the high exothermicity of the reaction. Since two moles of hydrogen bromide are liberated during the bromination reaction, the recovery of bromine from the liberated hydrogen bromide is an integral part of the process scheme for economic reasons. During the synthesis of 2,6-dibromo-*p*-cresol (DBC), a small amount of 2-bromo-*p*-cresol is formed. Another alternative for the bromination of *p*-cresol is by oxidative bromination with two moles each of hydrobromic acid and hydrogen peroxide respectively in a liquid−liquid two-phase system.[5,6]

The methoxylation of unactivated substituted aryl halides is generally carried out in high boiling solvents such as *N*,*N*-dimethylformamide (DMF) in the presence of copper powder or cuprous halides as catalyst via ipso substitution. The methoxylation reaction is a nucleophilic substitution reaction, and it generally exhibits second-order kinetics. During the methoxylation of aryl halides with sodium methoxide, copper-catalyzed competitive hydrodehalogenation reaction of aryl halide has been reported by Bacon and co-workers.[7−9] The authors found that the amount of reduction increased when methoxy substituents were present ortho to the halogen atom and, further, that the aryl iodides were more responsive to reduction than bromides. The mechanism of the copper-catalyzed nucleophilic substitution of aryl halides was studied extensively by Derek Van Allen[10] et al. The authors reported that the nucleophilic substitution reaction takes place via a four-center mechanism involving interaction between the cuprous methoxide complex and the aryl bromide. The four-center mechanism, σ-bond metathesis, however, does not explain the hydrodehalogenation reaction observed in ortho-substituted aryl halides which according to Bacon et al.[7−9] involved a copper-mediated hydride ion transfer from the methoxide to the aryl halide.

The effective reducing agents in these reactions comprised primary, secondary, and tertiary alkoxides in which one or more aliphatic-type hydrogen atoms were attached to the carbon, either α or β to the oxygen. Products from tertiary alkoxides included tar. During methoxylation of the aryl halide, competing reduction of the aryl halide takes place via copper-mediated hydride ion transfer from the methoxide

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to the aryl halide to obtain the arene and formaldehyde.[7]

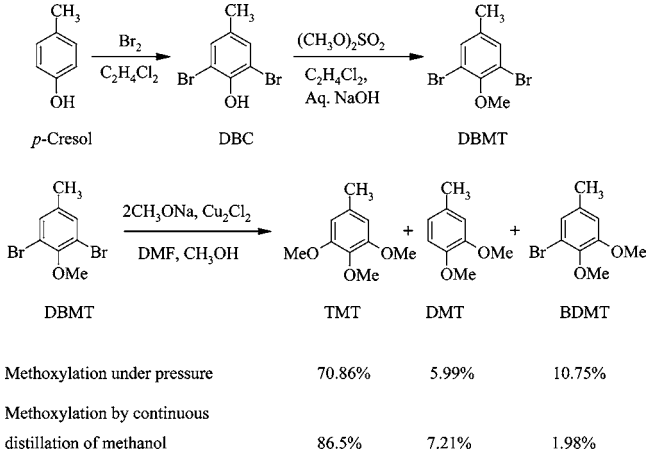
$$Ar{-}Br + CH_3ONa \xrightarrow[CH_3OH]{CuX} Ar{-}H + NaBr + H{-}CHO \quad (1)$$

Formaldehyde could not be isolated in this case due to its loss by volatilization or alkoxide-catalyzed condensation processes.

The process scheme reported in the patented literature[11,12] for the synthesis of TMT involved the use of cuprous iodide as catalyst and DMF as solvent for the methoxylation of DBC, making it an economically unviable process for scale-up. The direct methoxylation of DBC requires at least three moles of sodium methoxide stoichiometrically, of which one mole of the methoxide is consumed by the relatively more acidic phenolic proton, and the remaining two moles, for the substitution reaction. The resulting oxygen-anion charge delocalizes into the aromatic nucleus, thereby deactivating the ring to further substitution reaction. Since bromide is a better leaving group due to its larger atomic radius, a concerted four-center mechanism involving copper methoxide and the carbon−halogen bond can be envisaged. Under these conditions the simultaneous formation of the $C{-}OCH_3$ bond and of NaBr is facilitated.

The formation of excessive amounts of residue probably could be due to the condensation reaction between DBC and the methoxylated cresols (either mono or di) wherein the sodium methoxide acts as base. Further, the separation and purification of 3,5-dimethoxy-*p*-cresol (DMC) by vacuum fractionation is cumbersome. The fractionation step of cresols could be avoided by O-methylating the crude mixture of methoxylated cresols with DMS under alkaline conditions and then separating and purifying the TMT by vacuum fractionation. An alternative to this problem would be to O-methylate the DBC with dimethyl sulfate (DMS) under alkaline conditions and then methoxylate the resulting DBMT with 2.2−2.5 mol of sodium methoxide. Under these conditions the methoxylation takes place in an uncharged aromatic system. The synthesis of TMT starting from *p*-cresol involves bromination and methylation followed by methoxylation as key steps. There is little information available on the byproducts and the intermediates such as the monomethoxylated derivatives formed during direct methoxylation of DBC or DBMT. Therefore, an alternative process scheme with the O-methylation step preceding the methoxylation step was considered. (Scheme 1). The methoxylation of DBMT was studied with methanol as solvent under pressure in a sealed system, as well as by continuous distillation of the solvent methanol at atmospheric pressure. The effect of process parameters such as period of reaction, temperature, and the reactant concentration were studied for the pressure reaction. The reaction carried out by continuous distillation of methanol is superior to the reaction under pressure from the point of view of separation and purification of TMT. The methoxylation of DBMT by continuous distillation of methanol is superior to the direct methoxylation of DBC in terms of conversion, selectivity, isolation, and residue formation.

Scheme 1. **Synthesis of 3,4,5-Trimethoxytoluene**



	TMT	DMT	BDMT
Methoxylation under pressure	70.86%	5.99%	10.75%
Methoxylation by continuous distillation of methanol	86.5%	7.21%	1.98%

Experimental Section

Bromination. *Experimental Procedure.* The experiments were carried out in a 1.0-L borosilicate glass reactor equipped with a six-bladed turbine impeller, four baffles, an addition funnel, and a reflux condenser. The outgoing gases were passed through a caustic scrubber. The assembly was kept in a constant-temperature bath. For large-scale industrial bromination reactions the use of a glass-lined reaction vessel can be considered to avoid corrosion.

One mole of *p*-cresol dissolved in 272 mL of 1,2-dichloroethane was cooled to 20 °C. Liquid bromine (2.07 mol) was added continuously over a period of 5.0 h to the reaction mixture. The reaction temperature was maintained at 20−25 °C during the addition of bromine and for an additional 2.0 h to ensure completion of reaction. The reaction mixture was diluted with water and was extracted with 1,2-dichloroethane to recover product. The organic layer was washed with sodium metabisulfite solution to remove the dissolved bromine and then washed with water to remove the dissolved hydrobromic acid. The organic phase was distilled under reduced pressure to remove 1,2-dichloroethane from the crude product mixture. The conversion of *p*-cresol was 100%, and the conversion to DBC was 0.964 mol (96.4%). The conversion to the side product, 2-bromo-*p*-cresol (MBC), was 0.028 mol (2.8%). On commercial scale the organic phase containing the bromo derivatives can be directly taken for the methylation reaction.

Purification of 2,6-Dibromo-p-cresol. The residual product mixture after 1,2-dichloroethane recovery was distilled under reduced pressure to separate the MBC (bp, 109−114 °C at 29−31 mm). The residue was then crystallized from aqueous methanol to obtain DBC (yield: 0.9 mol, 90%; purity: 99.5%).

Analytical Procedure. Five to ten milliliters of the organic layer was evaporated to dryness under vacuum to obtain a solid product. The melting point of the solid was determined to be 46−48 °C. The organic layer was analyzed by gas chromatography on Chemito 8510 equipped with a flame ionization detector and connected to an integrator. The

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quantitation of the isolated DBC was calculated by external calibration against purified industrial standard.

Conditions. Column used was a 2-m long, 0.003-m diameter stainless steel column packed with 10% SE-30 on chromosorb-W; carrier gas, nitrogen; flow rate, 20 mL/min; injector temperature, 300 °C; detector temperature, 300 °C; oven temperature, 150 °C, ramp rate: 10 °C/min, 280 °C.

Methylation. *Experimental Procedure.* The experiments were carried out in a 1.0-L borosilicate glass reactor equipped with a six-bladed turbine impeller, four baffles, an addition funnel, and a reflux condenser. The outgoing gases were passed through a caustic scrubber. The assembly was kept in a constant-temperature bath. The reaction was carried out in a semi-batch mode due to high exothermicity of the reaction.

One mole of DBC (purity: 99.5%) and 1.2 mol of DMS were dissolved in 335 mL of 1,2-dichloroethane, and the temperature of the solution was maintained at 30−35 °C. Sodium hydroxide (1.25 mol, 50%w/w aqueous solution) was added continuously over a period of 4.0 h to the above mixture, maintaining the reaction temperature at 30−35 °C. After complete addition of sodium hydroxide, the reaction mixture was stirred for an additional 1.0 h at the same temperature to ensure completion of reaction. The aqueous and organic layers were separated. The organic phase was washed with water to neutral pH and distilled under reduced pressure to recover the 1,2-dichloroethane. The crude 3,5-dibromo-4-methoxytoluene (DBMT) was distilled under vacuum to obtain the pure compound (yield:0.93 mol, 93%; purity: 99%). The aqueous phase was acidified with 40% sulphuric acid to recover the unreacted DBC, which can be recycled.

An alternative to this mode of carrying out the methylation reaction could be to add DMS in a continuous mode, maintaining a moderately alkaline pH. This mode of addition of both the DMS and alkali could be very useful to optimize the quantity of methylating agent during scale-up.

Analytical Procedure. The organic layer was analyzed by gas chromatography, and the column conditions were the same as those mentioned in the bromination step. The quantitation of the isolated DBMT was calculated by external calibration against purified industrial standard (retention time: 10.5 min.).

Methoxylation. The reaction was carried out in two different modes, (a) under pressure in a sealed reactor and (b) at atmospheric pressure with distillative removal of methanol.

(a) Methoxylation under Pressure. *Experimental Procedure.* Experiments were carried out in a stainless steel autoclave of 600 mL capacity. The autoclave was equipped with a multiple four-bladed, magnetically driven impeller and an internal cooling coil. A solenoid valve controlled the flow of coolant (water) in the coil. The autoclave was heated externally by a heating element, and the temperature of the reaction was maintained within ±1 °C of the desired value.

In a typical reaction, 0.4286 mol of DBMT, 1.072 mol of sodium methoxide (27% w/v solution in methanol), and 0.164 mol of DMF were added to a clean, dry autoclave, and the volume was measured. Freshly distilled dry methanol was added to make up the volume to 400 mL. Before heating the reaction mixture under pressure we ensured that all the sodium metal had reacted completely. The presence of high excess of methanol ensured complete conversion of sodium metal to the methoxide. To the above solution, 0.1212 mol of freshly prepared dry cuprous chloride was added, and the reaction mixture was heated to 140 °C for a period of 8.0 h. After 8.0 h the reaction mixture was cooled to 27−30 °C and distilled under reduced pressure to recover methanol. Five hundred milliliters of water was added to the product mixture and then acidified to pH 3 with 40% sulfuric acid. The solution was filtered under vacuum to remove the insoluble cuprous salts, and the product mixture was extracted into toluene. The toluene layer was washed with water to neutral pH and then was distilled under reduced pressure to remove the solvent toluene. The residual crude mixture was fractionated under vacuum to separate the tar. The fraction collected as distillate was analyzed by gas chromatography to quantitate TMT and other mono- and dimethoxylated toluenes by external calibration against industrial standards. Retention times of the methoxylated toluenes are as follows: 3,4-DMT 4.25 min, BDMT 8.75 min, TMT, 7.25 min.

(b) Methoxylation by Continuous Distillation of Methanol. *Experimental Procedure.* The reactions were carried out in a 2-liter, three-necked, round-bottomed flask fitted with a thermo-well and a 0.16-m long Vigruex column to which a condenser was attached in the downward direction for continuous removal of solvent. The reaction mixture was stirred with a Teflon paddle-type stirrer connected to an overhead motor with a speed regulator. The whole assembly was kept in an oil bath heated with an electric heater.

In a typical reaction, 2.0 mol of DBMT, 5 mol of sodium methoxide (27% w/v solution in methanol), and 0.5198 mol DMF were added to a clean, dry, three-neck flask, and the volume was measured. Freshly distilled dry methanol was added to make up the volume to 1200 mL and was stirred to obtain a homogeneous solution. Freshly prepared dry cuprous chloride (0.3839 mol) was added, and the reaction mixture was heated. The temperature of the reaction mixture was raised progressively from 70 to 105 °C by continuous distillation of methanol over a period of 5.0 h. The final temperature of the reaction mixture, after distillation of most of the methanol, was maintained at 105 °C for an additional 2.0 h. The reaction mixture was cooled to 27−30 °C. Water (1200 mL) was added to the reaction mixture and stirred for 15−20 min. Further purification was carried out as described above for the pressure reaction.

The product mixture containing the methoxylated toluenes after separating from the residue was fractionated under vacuum. Pure TMT was collected as a fraction distilling at 117−118 °C at 5 mmHg (yield: 1.62 gmol, 81%; purity: 99%). The residue obtained was 0.6 wt % of DBMT taken initially.

Analytical Procedure. The conversion of DBMT was determined by estimating the amount of sodium bromide formed in the reaction by Volhard's method[13] to get an initial

Table 1. **Bromination of *p*-cresol[a]**

components	gmol	%
p-cresol	1.0	
liquid bromine	2.07	
% overall conversion	1.00	100
% conversion to DBC	0.964	96.40
% conversion to 2-bromo-*p*-cresol	0.028	2.80
% selectivity to DBC	0.964	96.40

[a] Reaction conditions: *p*-cresol, 1.0 mol; mode of addition of bromine, semi-batch; temperature, 20−25 °C; solvent, 1,2-dichloroethane, 272 mL; addition time of bromine, 5.0 h; time for completion of reaction, 2.0 h.

estimate of the progress of the reaction. Since cuprous chloride was used as catalyst in the reaction, the actual amount of sodium bromide formed was calculated by subtracting the number of moles of cuprous chloride from the total moles obtained by titration. The actual conversion of DBMT was calculated based on the GC analysis.

The crude product mixture after separating from the residue was analyzed by gas chromatography, and the column conditions were the same as those mentioned in the bromination step to estimate the amount of TMT and other byproducts formed.

The purity of the isolated product was determined by external calibration against industrial standards.

Results and Discussion

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

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

Conversion to Product. The conversion to any given product is defined as ratio of the moles of the reactant consumed for the formation of that product to the moles of the reactant taken initially.

Bromination. The bromination of *p*-cresol with liquid bromine is an electrophillic substitution reaction. The hydroxyl group, being electron donating in nature, activates the ring, and hence, the reaction does not require a halogen carrier. The continuous addition of bromine prevents its accumulation in the reaction mixture at any given point of time, thereby preventing localized heat generation. The overall conversion of *p*-cresol was 100%, and the selectivity to DBC was 96.4%. The side product, 2-bromo-*p*-cresol was 2.8% (Table 1).

Methylation. At high temperature, the methylation of DBC with dimethyl sulfate under alkaline conditions results in the formation of significant amount of residue of unknown composition. We suspect that the formation of residue at high temperature, could be due to a self-condensation reaction of DBC.[14] To reduce the formation of residue, the reaction was carried out in a semi-batch mode by the continuous addition of aqueous sodium hydroxide to a solution of DBC and dimethyl sulfate in 1,2-dichloroethane. The overall conversion of DBC was 96.21%, and the conversion to DBMT was 94.1%. The residue, calculated based on the weight of DBC, was 1.9% (Table 2).

Table 2. **Methylation of DBC**

components	gmol	%
DBC	1.0	
dimethyl sulfate	1.2	
% conversion of DBC	0.9621	96.21
% converson to DBMT	0.9410	94.10
% residue (by weight of DBC)	0.0190	1.90

[a] Reaction conditions: DBC, 1.0 mole; dimethyl sulfate, 1.2 mol; sodium hydroxide (50% w/w aqueous solution), 1.25 mol; mode of addition of aqueous sodium hydroxide, semi-batch; temperature, 30−35 °C; solvent, 1,2-dichloroethane, 335 mL; addition time of aqueous sodium hydroxide, 4.0 h; time for completion of reaction, 1.0 h.

Table 3. **Material balance: methoxylation of DBMT under pressure[a]**

components	mol taken	mol recovered	%
DBMT	0.4286		92.93
DBMT		0.0303	7.07
TMT		0.3035	70.86
DMT		0.0257	5.99
BDMT		0.04606	10.75
% Residue			0.7
Total	0.4286	0.4056	

[a] Reaction conditions: DBMT, 0.4286 mol; sodium methoxide (27% w/v methanol solution), 1.072 mol; DMF, 0.164 mol; CuCl, 0.1212 mol; temperature, 140 °C; solvent, methanol; time of reaction, 8.0 h; speed of agitation, 1000 rpm; volume of reaction mixture, 400 mL.

Methoxylation. Methanol was used as solvent in the reaction due to the easy availability of solution of sodium methoxide in methanol. The rate of the reaction is increased significantly in the presence of cuprous chloride as catalyst and DMF as cosolvent. The formation of dimethylamino derivatives is possible at 140 °C due to the decomposition of DMF and the further competing condensation of dimethylamine with the aryl halide. However, the absence of these derivatives in the final product mixture indicates their loss in the aqueous phase as hydrogen sulfates during acid extraction. Further, there were no uncontrolled reactions with DMF even during scale-up up to 1 kg mol of *p*-cresol, and no exothermicity was observed.

Since the reaction requires higher temperatures, it was carried out in two different modes.

Methoxylation under Pressure. *Material Balance.* In the methoxylation reaction 94.7% of the DBMT has been accounted for. Since the composition of the residue was unknown, it was calculated based on the weight of DBMT taken initially (Table 3).

Effect of Period of Reaction. The time versus conversion data indicates an increase in the conversion of DBMT to 93% with time estimated on the basis of the amount of unconverted DBMT as analysed by GC. The conversion to the side products formed was calculated by gas chromatographic analysis of the crude mixture by external calibration using industrial standards before further purification. The

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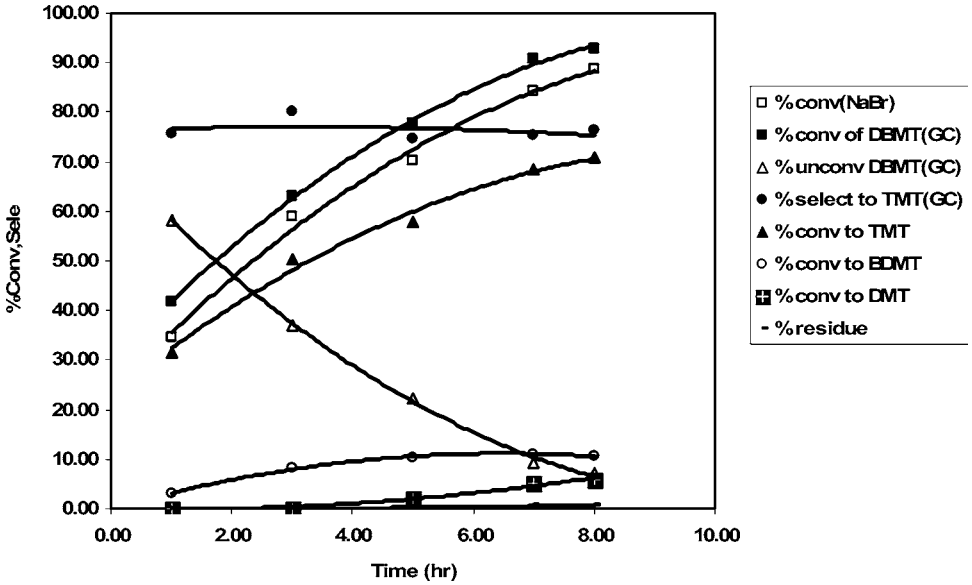

Figure 1. **Methoxylation under pressure: effect of period of reaction. Reaction conditions: DBMT, 0.4286 mol; sodium methoxide (27% w/v methanol solution), 1.072 mol; DMF, 0.164 mol; CuCl, 0.1212 mol; temperature, 140 °C; solvent, methanol; time of reaction, 8.0 h; speed of agitation, 1000 rpm; volume of reaction mixture, 400 mL.**

selectivity to TMT showed a marginal decrease from 3 to 8 h due to formation of side products such as 3,4-dimethoxytoluene (DMT) and 3-bromo-4,5-dimethoxytoluene (BDMT). The plausible mechanism for the formation of the DMT is due to the hydrodehalogenation reaction. The simplest representation of this process would be displacement of the bromide ion from the aromatic nucleus by the hydride ion, the transfer of which would convert the methoxide ion into formaldehyde. The role of copper in the reduction process might be envisaged as promoting the halide ion detachment and possibly also providing a temporary site for hydride ion during its transfer.[8] Since the formation of DMT showed an increasing trend, a further increase in the time of reaction could result in an increased formation of DMT in the reaction mixture (Figure 1).

Effect of Temperature. The effect of temperature on the rate of reaction was studied for a period of 5.0 h in the range 100−140°C. When the temperature was increased from 100 to 140 °C, the conversion of DBMT increased from 45% to 78%, and the conversion to TMT increased from 34% to 58%. The rates of substitution and hydrodehalogenation reactions increased with increasing temperature as can be seen from the amount of DMT and the BDMT formed (Table 4). The amounts of various products formed were determined by GC analysis by external calibration against industrial standards.

Effect of DBMT Concentration. The effect of substrate concentration on the rate of reaction was studied for a period of 5.0 h. The concentration of the DBMT was increased from 0.1428 mol to 0.4284 mol, keeping the concentration of sodium methoxide constant. With increase in concentration of the DBMT, the conversion of DBMT increased from 28% to 78% with concomitant increase in the conversion to TMT from 20% to 58%. Under these conditions the conversion to BDMT increased significantly, but the conversion to DMT was marginal, indicating the low rate of hydrodehalogenation reaction. The increase in the rate of the substitution reaction was dependent on the increase in the concentration of the substrate (Table 5). This could mean that the reaction is first order with respect to DBMT and second-order overall.

Kinetic studies of the reaction under pressure indicate that the rate of methoxylation is very high as compared to that of the hydrodehalogenation reaction. Since the volume of the reaction mixture and the temperature are constant, methoxylation and hydrodehalogenation reactions compete when the DBMT concentration is low, resulting in an increased formation of DMT and BDMT. To minimize the

Table 4. **Methoxylation under pressure: effect of temperature[a]**

temperature (°C)	100	120	140
% conversion of DBMT (GC)	45.09	66.46	77.60
% conversion to TMT	34.05	50.60	57.84
% unconverted DBMT (recovered)	54.91	33.54	22.40
% conversion to DMT	0.00	1.30	2.18
% Conversion to BDMT	3.29	6.71	10.35
% residue (based on DBMT taken initially)	0.00	0.10	0.21

[a] Reaction conditions: DBMT, 0.4286 mol; sodium methoxide (27% w/v methanol solution), 1.072 mol; DMF, 0.164 mol; CuCl, 0.1212 mol; solvent, methanol; time of reaction, 5.0 h; speed of agitation, 1000 rpm; volume of reaction mixture, 400 mL.

Table 5. **Methoxylation under pressure: effect of DBMT concentration[a]**

Reactant concentration (moles)	0.1428	0.2856	0.4284
% Conversion of DBMT (GC)	28.31	40.83	77.60
% Conversion to TMT	19.95	28.75	57.86
% Unconverted DBMT (Recovered)	71.69	59.17	22.40
% Conversion to DMT	0.00	1.67	2.18
% Conversion to BDMT	1.38	2.55	10.35
% Residue (based on DBMT taken initially)	0.00	0.10	0.21

[a] Reaction conditions: sodium methoxide (27% w/v methanol solution), 1.072 mol; DMF, 0.164 mol; CuCl, 0.1212 mol; solvent, methanol; temperature, 140 °C, time of reaction, 5.0 h; speed of agitation, 1000 rpm; volume of reaction mixture, 400 mL.

Table 6. **Material balance: methoxylation of DBMT by continuous distillation of methanol[a]**

components	mol taken	mol recovered	%
DBMT	2.000		
DBMT		0.0420	2.10
TMT		1.7300	86.5
DMT		0.1440	7.20
BDMT		0.0396	1.98
residue			0.63
total	2.000	1.9556	
TMT (isolated yield)		1.62	81.0

[a] Reaction conditions: DBMT, 2 mol; sodium methoxide, 5 mol; DMF, 0.52 mol; CuCl, 0.38 mol; solvent, methanol; speed of agitation, 200 rpm; volume of reaction mixture, 1200 mL; final temperature, 105 °C; period of reaction, 5.0 h to distill off methanol and raise the temperature to 105 °C, 2.0 h to complete the reaction.

formation of these two side products, it is essential to maintain a rate of methoxylation higher than that of the hydrodehalogenation reaction. Since most of the nucleophilic substitution reactions are second order in nature, high concentrations of the reactants generally increase the rate of substitution reaction. Thus, carrying out the methoxylation reaction by continuous distillation of methanol at atmospheric pressure could be another approach. Under these conditions the concentrations of the reactants progressively increase, and the temperature can be raised to the desired value. To increase the rate of methoxylation reaction at low concentration of DBMT, we carried out this reaction with the continuous distillation of methanol at atmospheric pressure.

Methoxylation by Continuous Distillation of Methanol. *Material Balance.* In the methoxylation reaction 97.78% of the DBMT has been accounted for. Since the composition of the residue was unknown, it was calculated on the basis of the weight of DBMT taken initially (Table 6). Five trials were carried out, maintaining the same reaction conditions to ensure reproducibility. Under the above conditions, the conversion of DBMT was 97.9 ± 2%, and the conversion to TMT was 86.50 ± 2%.

Under these conditions the conversion to BDMT is only 2% as compared to 10% formed when the reaction was carried out under pressure. Similarly the conversion to DMT was increased to 7.21% as compared to 6.0% when the reaction was carried out under pressure due to increased rate of the hydrodehalogenation reaction. During the continuous distillation of methanol the viscosity of the reaction mixture increased progressively due to the formation of insoluble sodium bromide. The increase in the viscosity could lead to increased mass transfer resistance in the scale-up of this process. This increase in viscosity can be overcome by increasing the amount of the cosolvent such as DMF in the reaction mixture (Table 6). Use of large amounts of DMF could cause unexpected problems such as decomposition of DMF and side reactions involving the formation of dimethylamino-substituted products. Solvents such as diglyme could be used as cosolvent, but the economics of the process may be compromised.

Comparison of the Efficiency of the Methoxylation Process over Existing Methoxylation Processes. The direct methoxylation of DBC with sodium methoxide results in the formation of substantial amounts of residue. Also the use of solvents such as DMF raises the overall cost of the process. Methoxylation under pressure results in a 5-fold increase in the formation of BDMT. Since TMT and BDMT form a very close boiling mixture, separation by vacuum fractionation is extremely difficult. In the alternative process, methoxylation by continuous distillation of methanol, the separation problem was not encountered due to the formation of BDMT in very low levels (Tables 3 and 6). A cheaper solvent, methanol, was used in the process. The ease of scale-up of this process makes this an attractive alternative in comparison to scale-up of the existing processes.

Conclusion

We have shown that the methoxylation of DBMT carried out by continuous removal of methanol is superior that of DBC due to the enhanced yield and purity of isolated TMT. The overall yield of both of these processes based on *p*-cresol (78.46% and 83.72%, respectively) is comparable. We have been able to minimize the formation of residue to 0.6−0.7 wt % of the DBMT. The O-methylation reaction preceding the methoxylation has several advantages from the point of view of separation, purification, and isolation of TMT over the existing processes.

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