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Use of Diethoxymethane as a Solvent for Phase Transfer-Catalyzed *O*-Alkylation of Phenols

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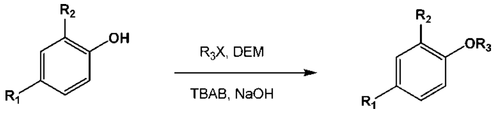
Abstract:

The effectiveness of diethoxymethane (DEM) as a solvent for *O*-alkylation of a variety of phenols under phase transfer conditions has been examined and evaluated. The reaction between 4-methoxy phenol and benzyl chloride was selected to compare reaction rates in various solvents and the efficiency of various PTCs. This reaction was further studied to develop a commercially amenable process complete with recycle streams and efficient product isolation. DEM is a good solvent for these types of phase transfer-catalyzed reactions and can be considered as an alternative solvent for dichloromethane and toluene.

Introduction

The use of phase transfer catalysis in organic synthesis became an area of active research in the mid-1970s.[1] Nucleophilic displacement reactions, strong base condensations, alkylations, dehydrohalogenations as well as oxidations, reductions and polymerizations were all thoroughly investigated. Typical solvents used in these reactions included chloroalkanes such as dichloromethane, aromatic solvents such as toluene and ketones such as methyl isobutyl ketone. Despite its recent commercial availability, very few examples have been reported where diethoxymethane (DEM) is utilized as a solvent for phase transfer catalyzed reactions.[2] The physical properties of DEM make it an excellent candidate for these type of reactions. DEM's boiling point of 88 °C provides a temperature range for the majority of PTC reactions (typically 25−80 °C) while not requiring too high a temperature for solvent recovery. DEM is stable in the presence of strong base, making it amenable to the majority of typical commercial phase-transfer catalysis conditions. Its low water solubility allows for a simplified, single solvent workup strategy. Since DEM has a heterogeneous azeotrope with water, this allows for reaction mixture drying by distillation and direct recycling to subsequent batches. From a safety standpoint, preliminary laboratory data suggests DEM is resistant to the formation of peroxides upon exposure to air.[3] Regulatory issues are limited since DEM is currently not on the SARA 313 list and is considered a non-HAP solvent. With these facts in mind, we report *O*-alkylation reactions amenable to phase transfer catalysis which have been investigated using DEM as the reaction solvent, a comparison to traditional solvents, and a process development example complete with stream recycling.

Scheme 1. **Alkylation of phenols**



***O*-Alkylation of Phenols.** *O*-Alkylation of phenols is a well-known reaction in which PTC excels and was first reported by McKillop[4] using dichloromethane as solvent. A more recent report by Yadav[5] utilizes an engineered three-phase liquid−liquid−liquid PTC system to prepare aromatic ethers in which toluene was selected as the solvent. This engineered system uses a 25% sodium chloride aqueous phase and 100 mol % of the phase transfer catalyst in order to obtain the three-phase system.

Several of the experiments reported in these papers, as well as others, were performed in which the solvents, either dichloromethane or toluene, were replaced with DEM according to Scheme 1. The conditions reported by McKillop[4] are represented by Method A in which the phenol was prepared as a 2.0 M solution in DEM and treated with 2.0 equiv of the electrophile, 1.5 equiv of 25% NaOH, and 10 mol % tetrabutylammonium bromide (TBAB) at 55 °C. Method B consisted of treating a 2.0 M solution of the phenol in DEM with 1.5 equiv of alkyl halide and 10 mol % TBAB. This mixture was exposed to a 25% solution of NaCl containing 1.5 equiv 50% NaOH at 90 °C. It should be noted that the amount of phase transfer catalyst used in Method B was reduced to 10 mol % from 100 mol % as reported in the literature in order to reflect conditions more appropriate for a commercial process. All target compounds were easily prepared in good yields when using DEM as the reaction solvent by either of the previously referenced methods (Table 1). Unreacted phenol was removed as the phenoxide with the aqueous waste streams. Little to no byproduct was detected by gas chromatographic analysis, although some *C*-alkylation most likely occurred. DEM was easily removed by vacuum distillation to isolate the target product. If the product were a solid, in most cases it could be isolated by crystallization from DEM.

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(1) (a) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis: Principles and Techniques*; Academic Press: New York, 1978. (b) Weber, W. P.; Gokel, G. W. *Phase Transfer Catalysis in Organic Synthesis*; Springer-Verlag: Berlin, 1977.

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(5) Yadav, G. D.; Desai, N. M. *Org. Process Res. Dev.* **2005**, *9*, 749–756.

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Table 1. **Phenolic ethers using DEM as PTC reaction solvent**

entry	method	R_1	R_2	R_3	X	yield (%)
1	A[a]	H	H	Bn	Cl	81
2	A	H	H	Bu	Br	82
3	A	MeO	H	allyl	Cl	91
4	B[b]	MeO	H	Bu	Br	83
5	A	MeO	H	Bn	Cl	85
6	B	*t*-Bu	H	Bu	Br	81
7	A	*t*-Bu	H	allyl	Cl	65
8	B	H	Ac	Bu	Br	86
9	A	MeO	H	Me	OSO_3Me	86
10	A	*t*-Bu	H	Me	OSO_3Me	85
11	A	H	Ac	Me	OSO_3Me	81

[a] Method A - 2.0 M in DEM; 1.5 equiv 25% NaOH; 2.0 equiv electrophile; 10 mol % TBAB; 4 h @ 55 °C. [b] Method B - 2.0 M in DEM; 25% aq NaCl; 1.5 equiv 50% NaOH; 1.5 equiv alkyl halide; 10 mol % TBAB; 2 h @ 90 °C.

Table 2. **Recycle of middle third phase**

exp #	TBAB (mol %)	recycled third phase (g)	yield[a] (%)
1	5.0	0.0	85
2	2.5	4.7	95
3	2.5	5.7	106
4	2.5	6.5	100
5	0.0	7.5	93
6	0.0	5.7	99
7	0.0	4.7	91

[a] A yield of >100% likely reflects the redistribution of product from the middle third phase of the previous run into the product phase.

Of interest was the observation that in some reactions, upon initially settling the reaction mixture, three liquid phases were detected.(6) An NMR analysis of the smaller middle phase revealed the presence of product and phase transfer catalyst. This phenomenon was dependent on the phase transfer catalyst selected as well as the electrophile. This middle third phase was observed with TBAB and tetrabutylammonium hydrogen sulfate, but not with benzytriethylammonium chloride (BTEAC). The middle third phase was not observed with either tetrabutylammonium hydrogen sulfate (TBA salt) when using dimethyl sulfate (DMS) as the electrophile. The lack of a middle phase when using DMS as the electrophile most likely can be attributed to the solubility of the TBA-methyl sulfate salt that results as a byproduct from the desired reaction. Thus, a potential advantage of DEM as a solvent for selected phase transfer-catalyzed reactions is the recovery and reuse of certain phase transfer catalysts.

To investigate the recovery and reuse of the middle third phase, a series of recycle experiments were performed in which either 2.5 mol % or no TBAB was added in addition to the recovered middle phase. This procedure was evaluated on the reaction between 4-methoxy phenol and benzyl chloride using TBAB as the phase transfer catalyst using Method A (Table 2).

The data demonstrate the feasibility of phase transfer catalyst recovery and recycle from the middle third phase when using the combination of selected TBA salts as the phase transfer catalyst and DEM as the reaction solvent. In experiments 2−4, the amount of "virgin" TBAB was reduced by 50% while still obtaining excellent yields. In experiments 5−7, no "virgin" TBAB was added, and yields remained good. This demonstrates that a wide range of "virgin" catalyst can be used while still obtaining high process yields. A cost−benefit analysis would be required to determine the optimum scenario for the process under investigation. The increase in yield between certain experiments can be attributed to recovery of product from the middle third phase. The recycle experiments described in Table 2 demonstrate that an engineered three-phase system as reported by Yadav[5] is not required in order to obtain a phase transfer catalyst system suitable for recycle. These conditions can be obtained by the proper selection of the phase transfer catalyst and solvent system.

Comparison Studies. A model system of 4-methoxy phenol and benzyl chloride to prepare 4-benzyloxy anisole was selected to compare reaction rate and yield in various solvents and the effect of different PTCs in DEM.

Chart 1 compares the relative reaction rate in DEM, dichloromethane and toluene and plots the concentration of product vs the reaction time. The data demonstrates that the studied reaction is much faster (<1 h) in dichloromethane than either DEM or toluene (3 h) while yields were comparable at ∼90%. As would be predicted, the absence of a catalyst in DEM results in a very sluggish reaction with low yield. The fact that the reaction rate in dichloromethane is much faster than DEM and that no middle third phase containing the PTC is present suggests the PTC-phenoxide complex is much more soluble in dichloromethane than either DEM or toluene.

While dichloromethane is an excellent solvent for laboratory PTC reactions at temperatures up to its boiling point, its use in large scale industrial applications is often limited by compliance with environmental regulations. At the same time, while toluene may be used in many large scale commercial PTC applications, DEM offers easier recovery, is not a SARA 313 listed chemical, and is a non-HAP solvent.

The impact on yield with several phase transfer catalysts was evaluated using the aforementioned model system (Table 3). The PTCs were selected across a wide range of "C #"s. The "C #" has been defined as the total number of carbons in a PTC and provides a representation of the solubility of the catalyst in an organic solvent.(7) A higher "C #" generally designates a higher solubility in an organic solvent.

The trend from the study demonstrates that the tetrabutyl cations with either bromide or sulfate anion are most effective in this model system as yields are excellent and the workup is straightforward. The use of tetrabutylammonium iodide resulted in a moderate yield, and the workup was complicated by an early precipitation of solids. The product in this case was isolated by crystallization. The use of Aliquat 336 provided a good yield with a straightforward workup and no middle third phase, which is typical in PTC reactions using this highly organophilic catalyst. Cetylpyridinium chloride (CPC) resulted in a thick emulsion at the end of the 4-h reaction time. CPC is

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(6) (a) Wang, D. H.; Weng, H. S. *J. Chin. Inst. Chem. Eng.* **1996**, *27*, 129–139. (b) Weng, H. S.; Wang, D. H. *J. Chin. Inst. Chem. Eng.* **1996**, *27*, 419–426. (c) Wang, D. H.; Weng, H. S. *J. Chin. Inst. Chem. Eng.* **1995**, *26*, 147–56. (d) Wang, D. H.; Weng, H. S. *J. Eng. Sci.* **1995**, *50*, 3477–86.

(7) The definition of "C #" can be found at www.phasetransfer.com/suppliers/catdir.htm.

Chart 1. **Relative reaction rate in various solvents**

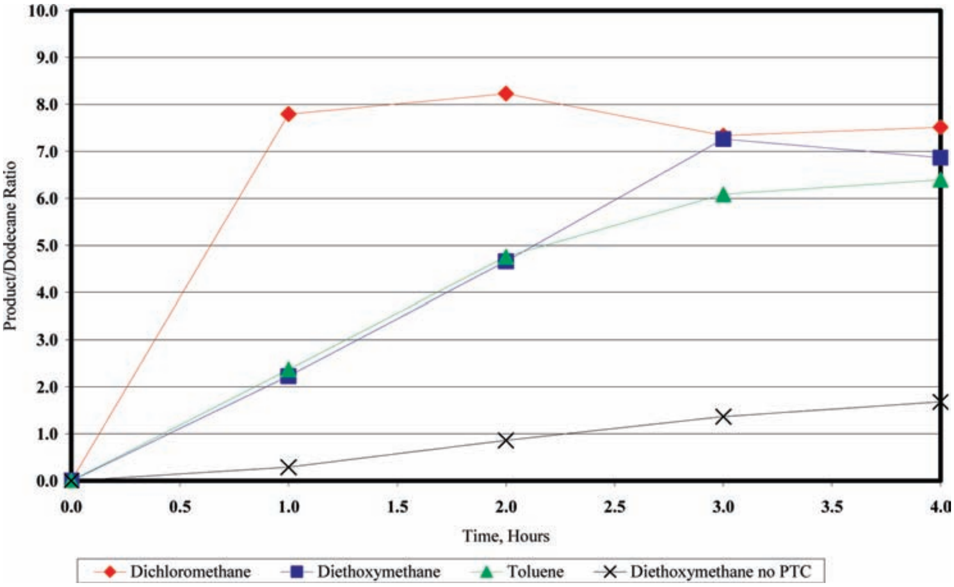

Table 3. **Comparison of various PTCs in the reaction of 4-methoxy phenol and benzyl chloride in DEM**

catalyst	C #	midphase	yield (%)
tetrabutylammonium bromide	16	yes	90
tetrabutylammonium hydrogensulfate	16	yes	93
tetrabutylammonium iodide	16	no	63
Aliquat 336	27	no	83
Aliquat 175	13	yes	88
cetylpyridium chloride	21	emulsion	emulsion
tetraethylammonium chloride	8	no	44
benzyltriethylammonium chloride	13	no	51
butylmethylimidazolium chloride	8	no	76

Table 4. **Raw material and yield data for process development study**

batch	DEM (mL)	BnCl (g)	TBAB (g)	recycled midphase (g)	yield (%)
1	500	126.5	16	–	74
2	100	72.5	8	29	103
3	0	75.0	8	31	100
4	50	90.3	0	40	86
5	50	85.0	4	32.8	80

a well-known surfactant and is not a recommended phase transfer catalyst due to emulsion formation. The reaction mixture using CPC was not evaluated for conversion since the process would not be amenable to commercial production. Benzyltriethylammonium chloride resulted in a moderate yield with no middle third phase, with a reasonable workup. The very hydrophilic phase-transfer catalysts typically do not form a middle third phase since they dissolve readily in water.[6]

The effects observed of catalyst structure on reactivity are consistent with this etherification being an “I-Reaction”[8] (intrinsic reaction rate-controlled reaction) that is commonly enhanced by more organophilic quaternary PTCs (quats) such as Aliquat 336 and is less reactive in the presence of very hydrophilic quats such as tetraethylammonium chloride. When a middle third phase is observed, reaction rates are almost always higher than when the third phase is not observed. That may explain the lower reactivity of Aliquat 336 relative to that of TBAB.

Ionic liquids have been reported to enhance reaction rates due to their ability to support a charged transition state[9] and may be considered as phase transfer catalysts. They are easily recovered due to the fact that they are insoluble in most organic solvents, including DEM. Generally, after water removal and clarification to eliminate the precipitated salts, the ionic liquid is of sufficient purity for recycle. Butyl methylimidazolium chloride ([bmim]Cl) is a commercially available ionic liquid and was evaluated in the model system. The byproduct sodium chloride precipitated, the dense ionic liquid was decanted, and the desired product was easily recovered by crystallization in 76% yield. After removal of water by distillation, the ionic liquid would be ready for recycle. In addition, some additional product could be recovered upon recycling of the ionic liquid. A recycling protocol with the ionic liquid was not pursued.

Application of DEM as an Industrial Process Solvent; Demonstration of a Model. We have demonstrated that DEM may be used as a solvent for the alkylation of phenols utilizing phase transfer catalysis, but a larger-scale trial and the use of recycling would provide more confidence for the use of DEM as a solvent for commercial-scale phase transfer catalyzed reactions. The preparation of 4-benzyloxy anisole at 1 L scale was chosen as a model. The objective of the study was to (a) recycle the middle PTC phase, (b) distill and recycle DEM, (c) crystallize the product from DEM, and (d) recycle the filtrate containing dissolved product, benzyl chloride, and DEM. Five total batches with four batches using recycled streams were executed. The reaction conditions were 1.0 M in DEM, 2.0 mol equiv of benzyl chloride, 1.5 equiv of 25% sodium hydroxide, and TBAB as the PTC at 10 mol % (initial batch) for 4 h at 50−55 °C. Upon completion of the hold time, the layers were allowed to settle to produce three distinct phases. The middle phase was collected and saved for recycling. The upper phase was washed with water, concentrated, and cooled to crystallize

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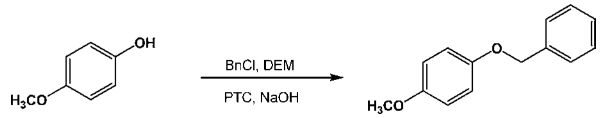
(8) Starks, C.; Liotta, C.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*; Chapman and Hall: New York, 1994.

Scheme 2. **Model system 4-benzyloxy anisole**



the product. The product was filtered, washed with heptane, and vacuum-dried (Table 4). Batches 2−5 were performed by recycling the DEM distillate, product filtrate, and fresh DEM to equal the volume of DEM used in the initial batch. Additional benzyl chloride was charged in order to equal 2.0 equiv. The PTC was introduced by addition of the recycled middle third phase, and fresh TBAB. The amount of fresh TBAB was varied to in order observe the effect on the conversion and yield of the process.

Several trends can be observed from the data collected during the process of recycling streams. The increased yield in the recycled batches can be attributed to recovering product from the recycled filtrate. The highest yields and best benzyl chloride usage factors were obtained in Batches 2 and 3 when 5 mol % of TBAB was added to the recycled middle third phase. A reduction in the amount of TBAB added in the recycled middle third phase in Batches 4 and 5 resulted in a rather large drop in the isolated yield and increases in the amount of benzyl chloride added to the next batch. Further experiments would be required to determine if the observed yield loss was due to the reduction in TBAB addition amount or other process parameters such as catalyst decomposition or impurity buildup in the filtrate. Experiments would also need to be designed to investigate a purge level for both the middle third phase and the product filtrate. However, the unoptimized results from this short recycle study demonstrate the feasibility of recycling the DEM distillate, the DEM filtrate, and the middle third phase streams. A starting point for future process development efforts reguarding reactions of this type has been established.

Conclusions

DEM has proven to be a good solvent for *O*-alkylation phenols under PTC conditions. Yields are good to excellent, and product workup is straightforward. Selected combinations of DEM and catalyst provided a reaction system in which the catalyst can be easily recovered and recycled. Recovery and recycle of DEM and the phase transfer catalyst were demonstrated in a model example that should be applicable to scale up. The physical properties of DEM and the lack of current regulatory restrictions make DEM an excellent candidate to replace dichloromethane or aromatic solvents in commercial phase transfer catalyzed reactions. Application of DEM in other classifications of PTC reactions are currently under investigation.

Experimental Section

Diethoxymethane (DEM) was obtained and used without further purification from FutureFuel Chemical Company. All reactions were performed using a mechanical stirrer with a banana-shaped blade. The agitation speed was set at 250 ± 25 rpm. Liquid products were purified by Kugelrohr distillation at <1 mmHg at 125−150 °C and analyzed using a Varian 300 MHz NMR. Weight percent assays were determined using either benzyl benzoate or dimethoxybenzene as an internal standard.

Alkylation of Phenols (Method A). The phenol (0.1 mol) was dissolved in DEM (50 mL). The alkyl halide or DMS (0.2 mol) was added followed by tetrabutylammonium bromide (3.2 g, 0.01 mol). Water (15 mL) and 50% caustic (12 g, 0.15 mol) were thoroughly mixed and added to the DEM solution. The temperature increased to 30−35 °C. The temperature was adjusted to 50−55 °C and held for 4 h. The layers were allowed to settle, and the lower aqueous phase, and the middle third phase (if present) were removed. The organic phase was washed with a saturated $NaHCO_3$ solution (25 mL) followed by a saturated NaCl solution (25 mL). The organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude sample was purified by short-path distillation and analyzed by NMR.

Alkylation of Phenols (Method B). Sodium chloride (87.5 g, 1.50 mol) and 50% caustic (12 g, 0.15 mol) were dissolved in water (200 mL). Tetrabutylammonium bromide (3.2 g, 0.01 mol) was added to the solution. The phenol (0.1 mol) was dissolved in DEM (50 mL) and added to the solution. The alkyl halide (0.15 mol) was added and the mixture heated to reflux (85−90 °C) and held for 2 h. The reaction mixture was cooled to <50 °C, and the phases were allowed to settle. The organic phase was washed with a saturated $NaHCO_3$ solution (25 mL) followed by a saturated NaCl solution (25 mL). The organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation. The crude sample was purified by short-path distillation and analyzed by NMR.

4-Benzyloxy Anisole - Recycling of DEM, Middle Phase, and Filtrate Streams - Initial Batch. 4-Methoxy phenol (62 g, 0.5 mol), benzyl chloride (126.5 g, 1.0 mol), and TBAB (16 g, 0.05 mol) were dissolved in DEM (500 mL). Water (60 mL) and 50% caustic (60 g, 0.75 mol) were thoroughly mixed and added over 30 min to the reaction mixture. The contents were then heated to 50−55 °C and held for 4 h. The layers were allowed to settle, and the middle third phase was removed, weighed, and saved for recycle. The organic phase was washed with water (100 mL) and then heated to 105 °C to remove residual amounts of water and DEM. The amount of distillate collected was approximately 250 mL. The distillate was saved for future recycle. The pot contents were cooled to 30 °C and seeded with a small amount of 4-benzyloxy anisole to crystallize the product. The slurry was further cooled to 0−5 °C, filtered, and washed with heptanes (100 mL). The filtrate was saved, weighed, and analyzed for benzyl chloride. The product was vacuum-dried at 50 °C and assayed by NMR.

4-Benzyloxy Anisole - Recycling of DEM, Middle Phase, and Filtrate Streams - Recycle Batch. The analysis of the filtrate was used to calculate the amount of virgin benzyl chloride. The amount of benzyl chloride in the filtrate was subtracted from 126.5 g and charged to the reaction flask. The filtrate from the previous batch was added followed by the

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(9) (a) Sharma, Y. O.; Degani, M. S. *J. Mol. Cat. A: Chem.* **2007**, *277*, 215–220. (b) Jorapur, Y. R.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 345–354. (c) Man, B. Y. W.; Hook, J. M.; Harper, J. B. *Tetrahedron Lett.* **2005**, *46*, 7641–7645. (d) Kim, D. W.; Hong, D. J.; Seo, J. W.; Kim, H. S.; Kim, H. K.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3186–3189. (e) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281–4285. (f) Li, Y. X.; Bao, W. L.; Wang, Z. M. *Chin. Chem. Lett.* **2003**, *14*, 239–242. (g) Judeh, Z. M. A.; Shen, H.; Chi, B. C.; Feng, L.; Selvasothi, S. *Tetrahedron Lett.* **2002**, *43*, 9381–9384.

distillate from the previous batch. TBAB (0−8 g, 0−0.025 mol) was added followed by the middle third phase from the previous batch. 4-Methoxy phenol (62 g, 0.5 mol) was dissolved in the reaction mixture. Water (60 mL) and 50% caustic (60 g, 0.75 mol) were thoroughly mixed and added over 30 min to the reaction mixture. The contents were heated to 50−55 °C and held for 4 h. The layers were allowed to settle, and the middle third phase was removed, weighed, and saved for recycle. The organic phase was washed with water (100 mL) and then heated to 105 °C to remove residual amounts of water and DEM. The amount of distillate collected was approximately 250 mL. The distillate was saved for future recycle. The pot contents were cooled to 30 °C and seeded with a small amount of 4-benzyloxy anisole to crystallize the product. The slurry was further cooled to 0−5 °C, filtered, and washed with heptanes (100 mL). The filtrate was saved, weighed, and analyzed for benzyl chloride. The product is vacuum-dried at 50 °C and assayed by NMR.

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