Phase-Transfer Catalysis: Mixing Effects in Continuous-Flow Liquid/Liquid O- and S-Alkylation Processes

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Abstract: This article describes detailed studies on the importance of mixing effects in the O- and S-alkylation of selected phenol and thiophenol substrates. Direct comparison between various continuous-flow reactors and a batch microwave reactor demonstrates the excellent mixing properties of the flow devices, which improve the reaction outcome.

Key words: O- and S-alkylation, phase-transfer catalysis, ethers, continuous-flow, mixing

The general concept of using liquid-liquid biphasic conditions for the synthesis of different O- and S-alkylated ethers is a well-established technique in phase-transfer catalysis[1] and one of the most widely used synthetic methods for the alkylation of phenols[2–4] and thiophenols.[5–7] Undoubtedly the main benefits are the use of inexpensive inorganic bases and the ease of purification of the products via simple phase separation and solvent removal.

It is important to emphasize that at least two steps are involved in the catalytic sequence of each phase-transfer reaction. The initial step is the net rate of anion delivery in an active form into the phase of reaction, commonly the organic phase. Subsequently the 'organic phase displacement reaction step' will take place and result in the desired product. A valuable phase-transfer-catalyzed process traditionally requires high reaction rates in both steps and the overall reactivity reaches a steady state level when the 'transfer step' and the 'intrinsic organic reaction step' are equal.[1,8]

Employing microreactor systems for liquid-liquid biphasic reactions in organic synthesis offers attractive benefits, including maximization of both mass transfer rate and reaction rate via a significant increase of interfacial area generated by the intense mixing and segmented flow in continuous-flow (CF) devices. When organic and aqueous phases, with high interfacial tension, are mixed via a T-piece a segmented flow-type pattern is created and thus a large specific interfacial area is formed. Additionally, using the fact that within each formed segment the interaction of the liquid with the channel walls will create a fluid vortex and as a result continuously refreshes the interface between the two phases, efficient liquid-liquid biphasic phase-transfer processes can be performed with high yields and short reaction times.[9] Regardless of aforementioned advantages, there are only a few publications dealing with liquid-liquid biphasic reactions in microreactor devices.[2–6,10–13] In a recent study by Kobayashi's group involving the tetrabutylammonium bromide (TBAB) catalyzed alkylation of a β-ketoester, an increase in yield from 49% (batch) to 75% (glass micromixer) was promoted by using a suitable microreactor.[10]

Herein, we present a study on the mixing efficiency of three different types of continuous-flow devices in the *O*- and *S*-benzyl ether formation employing two model substrates, 4-*tert*-butylphenol and 2,4,6-trimethylthiophenol (see Scheme 1). For the initial optimization and a direct comparison, microwave (MW) batch experiments are also described.

As a good starting point for our studies the phase-transfer-catalyzed benzylation of 4-*tert*-butylphenol was considered as an appropriate model reaction.[2,3] In general, the use of TBAB assures consistently good results in various

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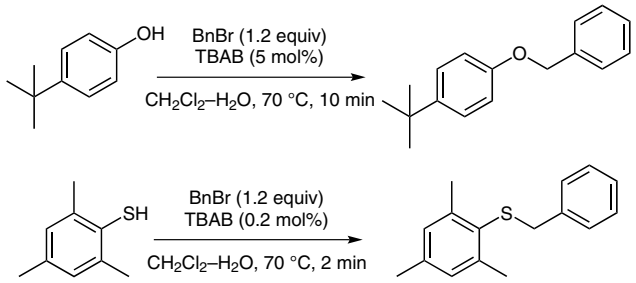

Scheme 1 Formation of *O*- and *S*-benzyl ethers

phase-transfer-catalyzed reactions.[1] Therefore we decided to use TBAB as a standard phase-transfer catalyst (PTC) for the O- and S-alkylation reactions. For the initial batch experiments a small-scale sealed-vessel microwave reactor (Biotage Initiator 8)[14] was used (see Table 1, entries 1–5). In a control experiment, omitting TBAB, benzyl bromide, sodium hydroxide and 4-*tert*-butylphenol were mixed with a water–dichloromethane (1:1, 4 mL) mixture (Table 1, entry 1), leading to only 5% conversion (HPLC, λ = 215 nm) after processing, thereby demonstrating the importance of the PTC for the process. In contrast to the control experiment, using 5 mol% of TBAB led to a 78% conversion to the expected product, while the use of less TBAB (2.5 mol%) led to a decreased conversion of 39% (Table 1, entries 2 and 3). Interestingly, increasing the reaction temperature to 120 °C and concomitantly reducing the amount of PTC to only 0.2 mol%, a 76% conversion of 4-*tert*-butylphenol into the corresponding benzyl ether could still be achieved (Table 1, entry 5). Apparently, increasing the reaction temperature to some extent allows a reduction of the PTC while maintaining good conversion. For our investigations under continuous-flow we decided to use 5 mol% of TBAB, 70 °C reaction temperature and 10 minutes of reaction (residence) time as optimal reaction conditions.

Next, we focused our attention toward transferring the MW reaction conditions into a flow process, aiming to further enhance the reaction profile. Compared to conventional batch reactors, lab-scale flow equipment with small-diameter channels or capillaries offers enhanced heat and mass transfer and allows safer operation of reactions in an extended range of temperatures and/or pressures.[15] Rapid mixing and excellent heat transfer performance can be easily maintained at higher production scale as well.[15a,16] Three different types of continuous-flow reactor setups were tested: a stainless steel coil reactor, a packed bed reactor (filled with stainless steel beads) and a glass chip microreactor (see Figure 1). All of them were connected with a lab-scale continuous-flow system (Syrris ASIA)[17] equipped with two syringe pumps, two sample loops (5 mL volume each) and a back pressure regulator (for a detailed description of the reactor setup and experimental details see the Supporting Information). Following the 'microwave-to-flow' paradigm,[18] the already optimized MW conditions were directly translated into a continuous-flow protocol, assuring identical reaction conditions. To our satisfaction, all three different flow setups performed excellently, resulting in more than 93% conversion (Table 1, entries 6–8) as compared to the 77% conversion in the MW experiments, thus confirming the superior mixing properties of the continuous-flow equipment. For ease of experimentation, the stainless steel beads (60–125 μm) filled reactor was used in several further experiments. Unfortunately, all attempts to decrease the amount of TBAB resulted in a decreased conversion similar to the batch MW experiments. Nevertheless, the benzyl ether formation while using only 2.5 mol% or 1 mol% of PTC was considerably higher as compared to the identical batch MW reaction (Table 1, entry 3 vs. entry 9 and entry 4 vs. entry 10). Higher temperatures resulted in increased amounts of unidentified side products in both MW and CF experiments.

Table 1 Phase-Transfer O-Alkylation of 4-*tert*-Butylphenol

Entry[a]	Method[b]	Temp (°C)	Time (min)	TBAB (mol%)	Product (%)[c]	Side products (%)[c]
1	MW	70	10	0	5	1
2	MW	70	10	5	78	1
3	MW	70	10	2.5	39	1
4	MW	90	5	1	19	1
5	MW	120	10	0.2	76	9
6	coil	70	10	5	94	1
7	chip	70	10	5	94	1
8	packed bed microreactor	70	10	5	93	1
9	packed bed microreactor	70	10	2.5	58	1
10	packed bed microreactor	90	5	1	50	5

[a] All results are mean values of at least triplicate experiments.
[b] For detailed information see the Supporting Information.
[c] HPLC conversions measured at λ = 215 nm.

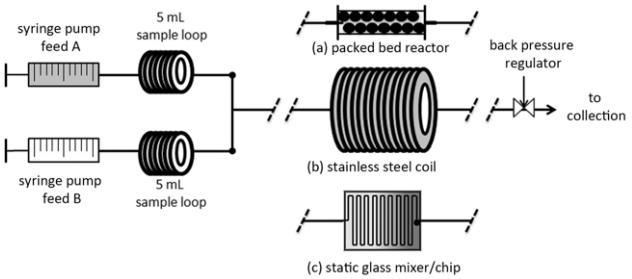

Figure 1 Different continuous-flow setups, using (a) packed bed microreactor (filled with stainless steel beads), (b) stainless steel coil or (c) static glass mixer

Next, we turned our attention to the S-alkylation of 2,4,6-trimethylthiophenol. As thiophenols tend to be more reactive compared to phenols, we also expected to find a higher sensitivity to the changes in the reaction conditions, related to the amount of PTC as well as to the mixing profiles in MW batch and CF reactions. Starting traditionally with the MW batch optimization, several control experiments in the absence of a PTC were performed (Table 2, entries 1 and 2). Working at 70 °C and after 10 minutes reaction time, only 7% of the corresponding thioether was observed (HPLC, λ = 215 nm). At 100 °C, however, the reaction proceeded further to 23% conversion, even in the absence of TBAB. Applying the previously optimized conditions for the O-alkylation and just altering the base from sodium hydroxide to potassium carbonate resulted in a quantitative transformation (Table 2, entry 3).[19] Interestingly, no side product formation was observed in this case. Reducing both the reaction time (2 min) and the amount of PTC (0.2 mol%) resulted in only 26% conversion in the MW batch experiment (Table 1, entry 4). To our surprise, transferring the conditions into the CF equipment resulted in >82% of benzyl thioether. Notably, the specific mixing characteristics in the three different microreactors did influence the outcome of S-alkylation in contrast to the previously performed O-alkylation. At this point the packed bed microreactor flow experiment performed superior (100% conversion; Table 2, entry 7) compared to the stainless steel coil and glass chip reactors (82% and 91%, respectively; Table 2, entries 5 and 6) under otherwise identical conditions. Reducing the amount of TBAB to 0.1 mol%, while keeping the temperature constant, produced a slight drop to 97% of conversion. This could be avoided by increasing the temperature to 90 °C (Table 2, entries 8 and 9). The 'soft' 1,3,5-trimethylthiophenoxide anions seem to be more reactive and were able to cross the liquid-liquid interfacial barrier into the organic phase more easily as compared to the 'hard' 4-*tert*-butylphenoxide anions. We strongly believe that this, in conjunction with the intense mixing and high interfacial areas created by the stainless steel bead filled CF reactor, caused the gain in efficiency and reaction rate. This effect can also be utilized to run the S-alkylation completely without the addition of any TBAB (Table 2, entries 10–12).

Table 2 Phase-Transfer S-Alkylation of 2,4,6-Trimethylbenzenethiol

Entry[a]	Method[b,c]	Temp (°C)	Time (min)	TBAB (mol%)	Product (%)[d]
1	MW	70	10	0	7
2	MW	100	10	0	23
3	MW	70	10	5	100
4	MW	70	2	0.2	26
5	coil	70	2	0.2	82
6	chip	70	2	0.2	91
7	packed bed microreactor	70	2	0.2	100
8	packed bed microreactor	70	2	0.1	96
9	packed bed microreactor	90	2	0.1	100
10	packed bed microreactor	70	2	0	20
11	packed bed microreactor	70	10	0	57
12	packed bed microreactor	100	10	0	84

[a] All results are mean values of at least triplicate experiments.
[b] CAUTION: malodorous smell can cause nausea and unconsciousness.
[c] For detailed information see the Supporting Information.
[d] HPLC conversions measured at λ = 215 nm.

In conclusion, we have demonstrated the advantages of using continuous-flow technology in the O- and S-alkylations of phenols and thiphenols. The simple concept of using efficient mixing and high interfacial areas in phase-transfer-catalyzed liquid-liquid reactions resulted in significant rate enhancements with drastic decrease in the amount of used PTC under continuous-flow conditions.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **Synthesis of 1,3,5-Trimethyl-2-[(phenylmethyl)thio]-benzene**:
A: Batch Microwave Conditions: Into a 5-mL microwave Pyrex process vial equipped with a magnetic stir bar organic stock solution A (2 mL; 0.2 M 2,4,6-trimethylthiophenol and 0.24 M benzyl bromide in CH_2Cl_2) and aq stock solution D [2 mL; 0.6 M K_2CO_3 and 0–2 mM (0–1 mol%) TBAB] were placed. The vial was sealed with a Teflon septum fitted in an aluminum crimp top and heated in the microwave reactor for 1–10 min (fixed hold time) at 70–100 °C (3–18 bar). After cooling to 45 °C, the reaction mixture was immediately quenched with 2 M aq HCl to reach pH <2. After 2 min of vigorous stirring the aqueous phase was separated via syringe and 10 μL aliquots of the organic phase were subjected to HPLC analysis (λ = 215 nm). 1,3,5-Trimethyl-2-[(phenylmethyl)thio]benzene was isolated by phase separation from the basic aqueous phase, followed by H_2O extraction (3 ×). The obtained organic phases were combined, dried over $MgSO_4$, filtrated and concentrated under vacuum to provide the *S*-benzyl ether (88 mg, 91% yield, yellowish plates); mp 35–36 °C (lit.[3]: mp 36 °C). MS (APCI, –): *m*/*z* = 242.1 [M^+], 241.1 [M^+ – 1], 151.1 [M^+ – 91]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3 H), 2.37 (s, 6 H), 3.78 (s, 2 H), 6.92 (s, 2 H), 7.08–7.11 (m, 2 H), 7.22–7.25 (m, 3 H).
B: Continuous Flow Conditions: For details please see the provided Supporting Information.

