

Surfactant-mediated solvent-free dealkylative cleavage of ethers and esters and trans-alkylation under neutral conditions

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Abstract—A simple, surfactant-mediated, one-pot, solvent-free dealkylative cleavage of aryl ethers and esters followed by subsequent optional trans-alkylation under essentially neutral conditions has been developed.
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As part of our continued interest in the preparative utility of solvent-free ‘Green Technologies’ we wish to report an environmentally friendly, surfactant-mediated, and solvent-free cleavage of various electron-poor aryl ethers, as well as optional trans-etherification of the resulting phenolate anion under operationally simple, one-pot, neutral conditions utilizing phosphate, thiocyanate, or nitrite ions as nucleophiles.¹ This technology was also successfully applied to the dealkylative cleavage/trans-esterification of various aryl esters utilizing thioacetate as a nucleophile.² The need for such methodology originated from our Industry–University collaborative research program directed toward developing efficient and environmentally friendly pharmaceutical processes.³

Electron-deficient aryl methyl ethers were selected as viable substrates for the nucleophilic cleavage provided these reactions proceed via S_N2 attack on the methyl group.⁴ Furthermore, selective crownether-like complexation of the metal cation with the PEG units in Triton-X should not only solubilize the nucleophilic reagent, but also enhance the nucleophilicity of the counter-ions. In addition, the surfactant properties of Triton-X should improve the reaction kinetics by increasing interfacial area, compensating for the lack of solvation.^{1a} Initial attempts to de-methylate *p*-nitro-

anisole as a representative example with nucleophiles such as KCl, KBr, or KI in the presence of catalytic amount of Triton-X-405 (165 °C, sealed tube) led to unreacted starting material. It occurred to us that success of this methodology would depend on an appropriate choice of the nucleophile, whereby the by-product of the dealkylation could not serve as a potential alkylating agent, which proved to be the case. The solvent-free methoxy cleavage of *p*-nitroanisole was successfully achieved in >95% conversion and selectivity by treating *p*-nitroanisole with KSCN (4 equiv) or KNO₂ (4 equiv) in the presence of catalytic amounts of an appropriate surfactant such as Triton-X-405 over 4 h. Potassium phosphate is also effective in carrying out successful de-methylation, although longer reaction time is required (cf. 24 h for *p*-nitroanisole under otherwise identical conditions). The presence of Triton-X is imperative; the reactions conducted without Triton-X-405 showed only trace amounts of the desired product under otherwise identical conditions. With Triton-X-100, a less efficient complexing agent for K⁺, under otherwise identical conditions, the extent of ether cleavage was only 20%.^{1a} Also, utilizing KNO₂ (amidant nucleophile), nitromethane was detected by GCMS fingerprint, implying that nitrogen was the nucleophilic center.⁵ Addition of allyl bromide or benzyl chloride to the resulting *p*-nitrophenolate anion at this stage directly produced the corresponding allyl or benzyl ether in high yield, thereby adding significant value to this strategy. The efficient, solvent-free, methoxy cleavage/trans-etherification conditions were successfully applied

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through a pad of silica gel and dried over MgSO_4 . Evaporation of the solvent in vacuo produced 0.88 g of allyl-4-nitrophenol ether (75%). The intermediate phenol, if desired, can be isolated as follows: After cooling the reaction to room temperature, MTBE (45 ml) was added and the resulting mixture was acidified to pH 3 using 1 N HCl. The organic layer was washed with brine solution (2×5 ml), dried over magnesium sulfate, and evaporation of the solvent in vacuo produced 0.68 g of phenol (75%). Cleavage of 4-nitroanisole was faster than 3-nitroanisole (entries 1 and 2) presumably due to conjugation. The E_{act} values for the KSCN-mediated ether cleavage for 4-nitroanisole and 3-nitroanisole obtained from kinetic measurements were 32.45 and 39.16 kcal/mol, respectively. The E_{act} difference was exploited to conduct a nontrivial regioselective cleavage of 1-methoxy group in 1,2-dimethoxy-4-nitrobenzene (entry 10).⁷

The surfactant-mediated solvent-free methodology was also extended to the dealkylative cleavage of various aryl esters as well as optional trans-esterification of the resulting carboxylate anion under neutral conditions utilizing thioacetate as nucleophile (Table 2).²

In summary, we have developed a simple, efficient, solvent-free dealkylative cleavage of electron poor aryl ethers/esters and subsequent optional trans-alkylation under essentially neutral conditions. Excellent conversions, selectivity and vessel efficiency achieved renders the process eco-friendly, economically attractive, and illustrates the value of the surfactant mediated solvent-free methodology in organic synthesis.

Acknowledgments

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References and notes

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8. NMR data for all the compounds synthesized are consistent with their expected structures, as for instance: 6,7-Dichloro-2-(3-chloro-but-2-enyl)-5-hydroxy-2-methyl-indan-1-one (entry 11): ¹H NMR (600 MHz, DMSO-*d*₆): δ 11.81 (s, 1H), 7.03 (s, 1H), 2.99–2.77 (d, $J = 17.4$ Hz, 2H), 1.43 (m, 2H), 1.20 (m, 1H), 1.12 (s, 1H), 1.09 (s, 3H), 0.99 (m, 1H), 0.81 (t, $J = 7.2$ Hz, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆): δ 205.2, 159.9, 154.7, 129.9, 123.8, 120.2, 111.5, 49.5, 40.5, 38.5, 23.8, 17.5, 14.4. 6,7-Dichloro-5-hydroxy-2-methyl-2-propyl-indan-1-one (entry 12): ¹H NMR (600 MHz, DMSO-*d*₆): δ 11.87 (s, 1H), 7.05 (s, 1H), 5.47 (t, $J = 7.1$, 1H), 2.90 (m, 2H), 2.40 (dd, $J = 7.1$ Hz, 1H), 2.31 (dd, $J = 7.8$ Hz, 1H), 2.05 (s, 3H), 1.49 (m, 2H), 1.14 (m, 1H), 0.94 (m, 1H), 0.79 (t, $J = 7.2$, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆): δ 204.1, 160.0, 154.9, 132.1, 129.8, 124.4, 121.2, 120.3, 111.4, 52.9, 39.2, 36.0, 35.7, 25.9, 17.1, 14.4. For all the compounds, GCMS analysis (Shimadzu QP5050A) in the EI mode provided similarity index match of >90% compared to the authentic samples in the NIST-98 database.