PAPER

Aqueous sodium tosylate: a sustainable medium for alkylations†

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Typical alkylation reactions produce significant amounts of undesired salt and solvent waste. Herein, we report an efficient alkylation protocol utilising aqueous sodium tosylate (NaTos) solutions as a hydrotrope-containing medium. The methodology represents an inexpensive and straightforward approach for preparing alkyl aryl ethers, thioethers and N-alkylated tosyl amides in high yields under mild conditions. The generated reaction waste, aqueous NaTos salt, was repurposed as a reaction medium in subsequent steps. This medium was recycled ten times without any significant change in the yield, providing an improved environmental factor over various literature examples. Under similar conditions, commonly applied solvents furnished the products with lower yields and more waste.

Introduction

The O-alkylation of phenolic substrates gives access to many relevant compounds (e.g., perfumes, pheromones and pharmaceuticals), but its sustainability requires improvement. Significant advances have already been made in the starting materials, as various phenols can be bio-sourced.[1] However, the corresponding alkyl phenyl ethers have been predominantly prepared via Williamson's synthesis-type procedures, which often produce harmful and diverse waste by relying on non-benign solvents[2] and highly toxic alkylating agents, including alkyl halides[3] or dialkyl sulfates.[4] Furthermore, stoichiometric salt quantities are typically generated as by-products[5] requiring direct disposal due to their limited further use. Dialkyl carbonates are regarded as sustainable alternatives, but their weak alkylating potential necessitates a high energy input[6] and often needs dedicated equipment and catalysts.[7] These factors often favour simpler, unsustainable alkylations, especially within academia, making the development of efficient, straightforward and sustainable methods desirable.

As solvents are the prime source of waste in chemical reactions, considerable attention has been devoted to their substitution with water.[8] Nevertheless, the low solubilisation of organic compounds in aqueous media represents an intrinsic problem. Hydrotropes, non-amphiphilic organic solubilising agents (Fig. 1), can provide a solution but have received limited attention. Nevertheless, successful organic syntheses in aqueous hydrotrope solutions[9] indicate that the products often precipitate during the reaction, facilitating their solvent-less isolation. Alternatively, dilution can induce phase separation, as the dissolution process is highly hydrotrope-concentration dependent.[10] Unfortunately, few studies have thus far systematically investigated comparisons with other solvents.[11] Moreover, hydrotrope recycling has barely been evaluated but would be mandatory considering the high salt loading.[11,12]
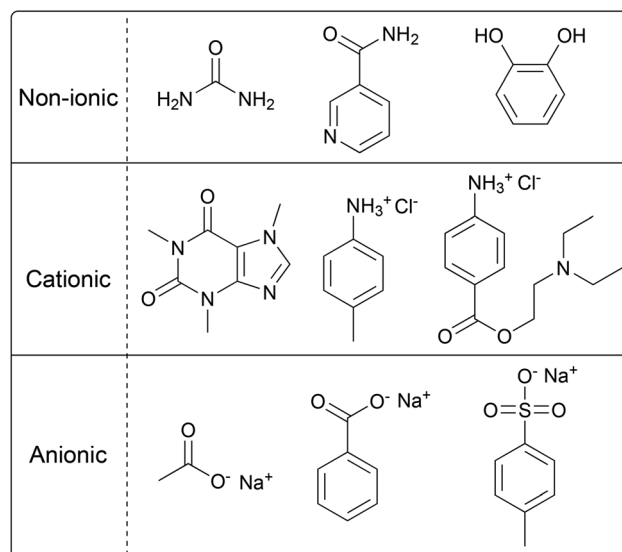

Fig. 1 Representative examples of hydrotropes.

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Based on the successful occurrence of S_N2 reactions in aqueous hydrotrope solutions,[11] we aimed to develop and evaluate a hydrotropic alkylation strategy (Scheme 1) with a solventless work-up. Alkyl tosylates and NaOH were selected as the electrophile and the green base,[13] respectively, since the only side products generated would be water and sodium tosylate (NaTos), a common hydrotrope. As a result, NaTos was preferred as the hydrotrope to minimise waste diversification. The reaction waste was repurposed as a reaction medium in further runs, extending its life cycle. The aqueous hydrotrope solution was benchmarked against several alternative solubilising agents and prior literature examples.

Initially, 3-nitrophenol **1aa** was reacted with an excess of MeTos and NaOH in 30 wt% aq. NaTos. The promising 94% NMR yield of 3-nitroanisole **3aa** prompted us to optimise the reaction conditions regarding the process sustainability (Table S1†). Under the final conditions (20 wt% NaTos, 1.0 equiv. of MeTos and 1.2 equiv. of NaOH stirred at 50 °C for 6 h), significantly less waste and a slightly decreased 87% isolated yield resulted (Scheme 2; entry 14, Table S1†). No excess alkylating agent was required and **3aa** conveniently precipitated out of the reaction mixture, facilitating a solventless work-up by simple filtration. A control experiment in pure water (entry 15, Table S1†) afforded a significantly lower 50% NMR yield. Here, **3aa** could not be isolated without solvents due to unconverted **1aa** being present. Direct alkylation with tosyl chloride and excess methanol according to the reduce derivates principle was unsuccessful, as it selectively resulted in the tosylated phenol.
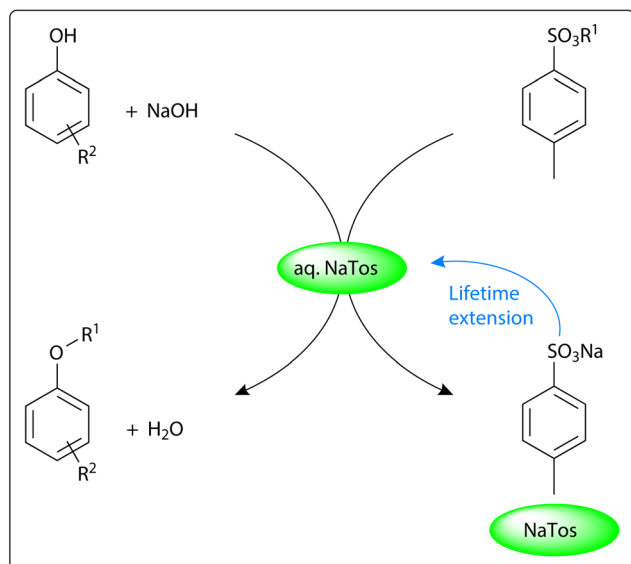
The optimised conditions were subjected to a phenol scope to assess their generality, as summarised in Scheme 2. Both electron-rich and electron-poor phenols were evaluated, generally furnishing the products in high yields with spontaneous

phase separation from the aqueous mixture in each case. The reaction towards 2-nitroanisole **3ab** only proceeded with 48% conversion, which may be attributed to the encumbered oxygen reactivity resulting from the intramolecular hydrogen bonding of 2-nitrophenol.[14] From the data, two characteristics regarding the hydrotrope-containing medium became apparent. First, the interference by the aqueous medium seems low as no or limited hydrolysis occurred for the amide **3ae** and the esters **3af** and **3at**, respectively. Second, the results indicate a correlation between the solubilisation and yield. Polar substrates with hydrogen-accepting capabilities generally resulted in lower yields (**3aa–3af**) due to the significant solubilisation of the products in the aqueous hydrotrope solution, as corroborated by ^{1}H-NMR analysis of the aqueous phase. The results for compounds **3aj–3ap** indicate that the medium partially dissolves the products with smaller alkyl chains (**3aj–3am**), whereas phase separation is near-quantitative when several or larger aliphatic groups are present (**3an–3ap**). More polarisable halide substituents (**3ag–3ai**) and even larger fused ring systems (**3as–3au**) were tolerated well, portraying the high solubilisation of the phenolate salts in the aqueous medium.

Several other nucleophiles were evaluated (Scheme 2). Under nitrogen atmosphere, aromatic and aliphatic thiols could be methylated quantitatively within 3 h (**3ba–3bb**). Tosyl amides also seemed to be well tolerated, given a 90% yield resulted for the methylation of *N*-methyl-*p*-toluenesulfonamide **2bc** to **3bc**. Methyl ester **3bd** could be obtained from the corresponding carboxylate **2bd** using 1.0 equiv. of NaOH in a moderate 63% yield. The low nucleophilicity of **2bd** increased the reaction time and led to significant (tosylate) ester hydrolysis by the base, as indicated by crude NMR. Moreover, washing with NaOH was required to remove the residual acid, rendering carboxylic acids less suitable substrates.
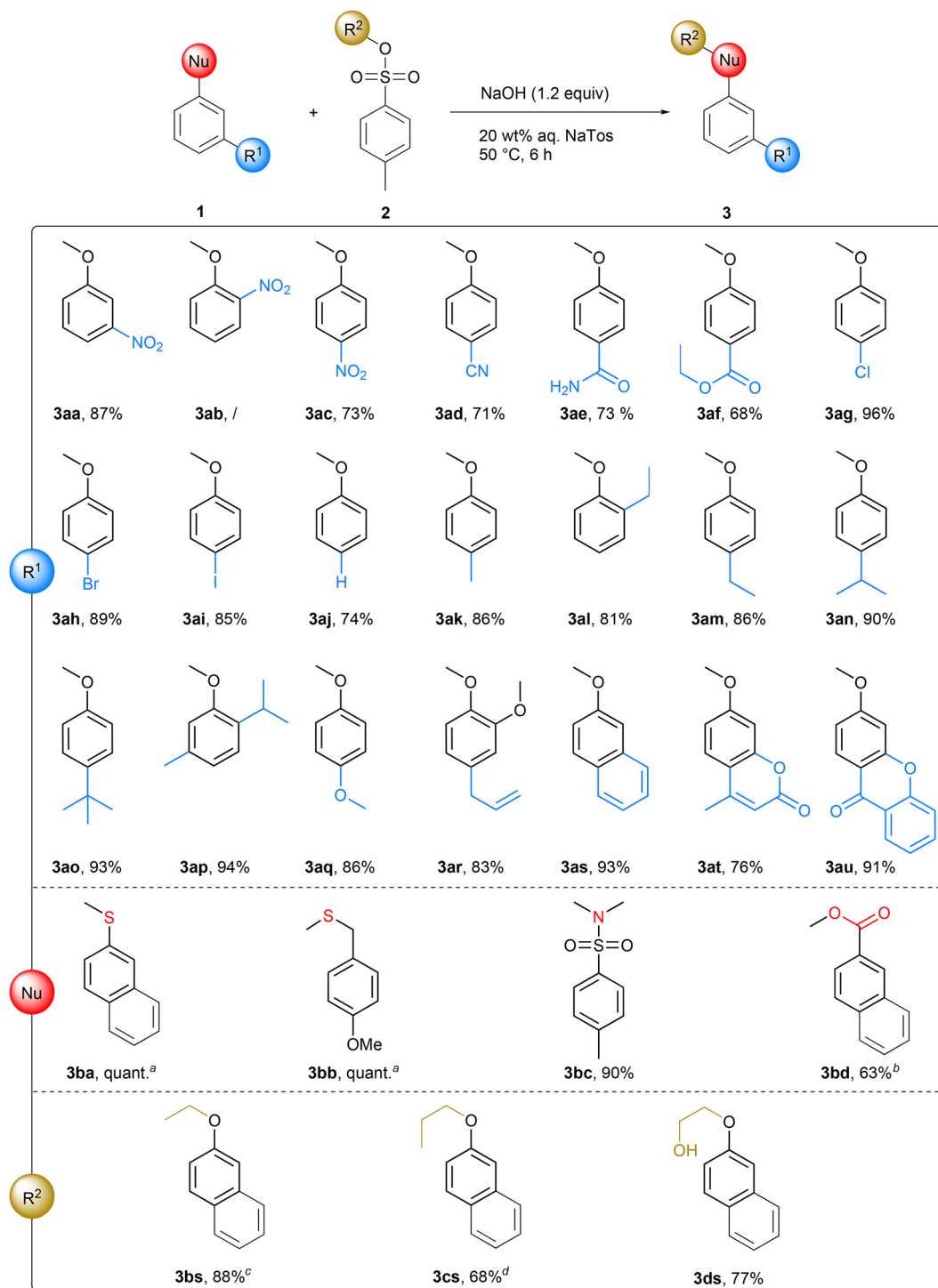
The tosylate esters were varied next, using 2-naphthol as a nucleophile (Scheme 2). Whereas the methylation of **2as** furnished the product in a 94% yield within 6 h, the ethylation towards **3cb** required a threefold increased reaction time to attain a slightly lower yield. The effect was even more pronounced for **3cs** since the limited conversion of propyl tosylate **2cs** in 30 wt% NaTos led to an inseparable mixture. Complete conversion was achieved using 40 wt% NaTos, yielding **2cs** in 68%, mainly because it tended to liquefy when filtered. The alkylation using 2-hydroxyethyl tosylate **2ds** was completed in 6 h with 20 wt% NaTos in good yield, indicating that solubility is the decisive factor. The developed methodology thus mainly suits methylations or the introduction of relatively polar groups. Other cases require additional optimisation.

Given the high hydrotrope content, the medium recyclability was evaluated for the synthesis of **3as**. The first cycle was performed with 1.0 equiv. of MeTos and 1.2 equiv. of NaOH in 94% yield. The undiluted medium was readily recovered during filtration and reused without intermediate purification. The reaction was repeated with this filtrate after loading with stoichiometric MeTos, 2-naphthol and base, considering the excess NaOH present to facilitate product isolation would be recoverable. This process could be repeated for nine additional

Scheme 1 Alkylation strategy employed in this work.

Scheme 2 Substrate scope of the alkylation reaction in hydrotrope-containing water. Conditions: 2.5 mmol scale, 20 wt% NaTos (6 ml), NaOH (1.2 equiv.), MeTos (1.0 equiv.), 50 °C, 6 h; [a] 3 h, N_2 atmosphere; [b] NaOH (1.0 equiv.), 65 h; [c] 18 h; [d] 40 wt% NaTos (6 ml), 18 h.

cycles (Fig. 2) in a 93% average yield, using 1.0 equiv. of the base per run and a total hydrotrope-containing water volume of 60 mL. As NaTos is generated *in situ*, the medium becomes gradually enriched in hydrotrope. Nevertheless, the consistently high yields indicate that the product remains sparingly soluble at a high hydrotrope loading. Saturation occurred after six runs at a theoretical NaTos concentration of 62 wt%, which correlates with the available solubility data.[15] The precipitated salt could readily be removed from the product by washing with water, although increasing overall water consumption. Alternatively, lowering the reactant concentrations or diluting the reaction medium could delay the precipitation.
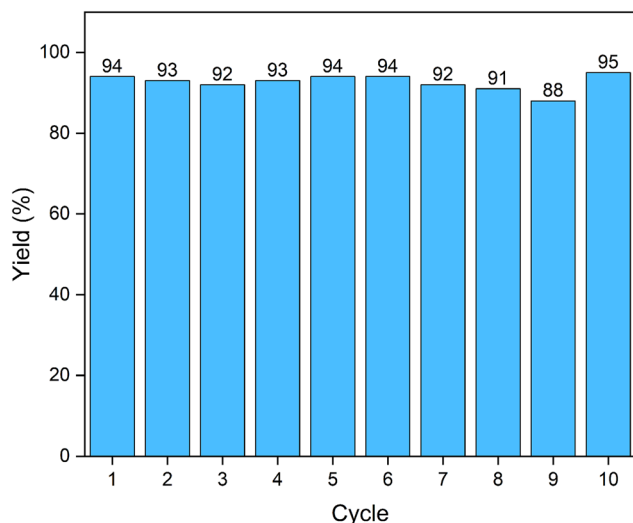
Fig. 2 Recyclability study for the methylation of **2as**. Conditions: cycle 1: 25 mmol scale, 20 wt% NaTos, 1.2 equiv. of NaOH, 1.0 equiv. of MeTos, 16 h, 50 °C; cycle 2–10: 25 mmol scale, recycled medium, 1.0 equiv. of NaOH, 1.0 equiv. of MeTos, 16 h, 50 °C.

The E factors after one, six and ten cycles were determined to be 5.0, 2.1 and 1.9, showing the pronounced effect of medium recycling on the overall waste generation. In comparison (Table 1), the relatively green solvents[16] acetonitrile and DMSO, commonly employed for alkylations,[17] produce over four times the waste of a single run in NaTos solution. For ethylene glycol, the value was sixfold higher than that in hydrotrope-containing water. Although pure water and solvent-less conditions generate less salt waste than the hydrotrope,
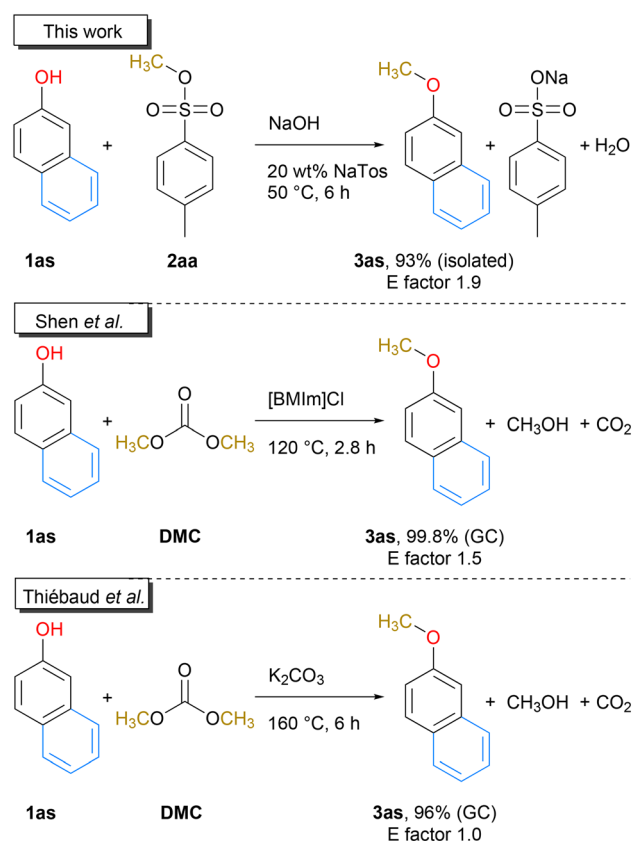
Table 1 Yield and E factor comparison for **2as** methylation in different solvents[a]

Entry	Solvent	Yield (%)	E factor
1	20 wt% NaTos	93[b]	5.0
2	Recycled NaTos	93[c]	2.1
3	Recycled NaTos	93[d]	1.9
4	Acetonitrile	65	21.0
5	DMSO	86	21.1[e]
6	Ethylene glycol	62	30.1
7	Water	56	3.3[f]
8	Neat	31	6.8[f]
9	1 wt% SDS	80	2.2

[a] Conditions: 2.5 mmol scale, 20 wt% NaTos, 1.2 equiv. of NaOH, 1.0 equiv. of MeTos, 6 h, 50 °C. [b] After 1 run at the 25 mmol scale. [c] After 6 runs at the 25 mmol scale. [d] After 10 runs at the 25 mmol scale. [e] Precipitated by water, followed by filtration. [f] Excluding work-up.

their low conversions necessitate chromatography or energy-intensive distillation. Moreover, the E factors without purification are 57–220% higher than that for the aqueous hydrotrope solution used six times. After ten cycles, the hydrotrope-containing medium even provided an 18% improvement over 1 wt% aqueous sodium dodecyl sulfate (SDS). Moreover, the complete E factor[18] of a single run was 11% lower. In each case, the aqueous NaTos solution provided a significantly higher yield, making it a valuable alkylation medium, especially in routine syntheses.

The developed methodology was compared to literature methylations of **2as**. Upon saturation (run 6), the E factor is significantly lower than these reported in various literature protocols (Table S2†). In particular, our method provides one of the few examples with an E factor < 2.0. DMC-based catalytic strategies producing less waste exist (Scheme 3) but do not consider product degradation or solvent usage during the work-up as only GC yields are reported.[19,20] These methods are more energy intensive due to the high reaction temperatures and distillation to remove solvents, purify products and recover catalysts. Additionally, these reactions need a protective nitrogen atmosphere[19] or flow equipment.[20] Our method represents an energetically favourable alternative with a more straightforward reaction set-up, product isolation and recycling.

Scheme 3 Comparison of the developed method to other **2as** methylations with an E factor < 2.

Similar to DMC, the formed side products in our approach (NaTos and water) are reusable, non-toxic, have a low potential towards bioaccumulation and are readily biodegradable.[21] MeTos, despite being more toxic than DMC, has a lower toxicity than other common alkylating agents[22] and is less volatile, limiting exposure through inhalation. The main disadvantage is that current green preparations of alkyl tosylates regularly involve reagent excesses and produce stoichiometric halogenated waste.[23] Nevertheless, alkylation of the green tosylic acid[16] with water as a sole by-product seems viable,[24] potentially providing a suitable and greener alternative.

Conclusion

In summary, we successfully developed an aqueous alkylation method relying on sodium tosylate as the solubilising agent, with the only by-products being water and the hydrotrope itself. The optimised conditions tolerated a broad phenol scope and could be extended to other nucleophiles and alkyl groups. The reaction proved scalable and recyclable for at least ten consecutive cycles. In addition, the aqueous hydrotrope solution outperformed several alternative green solubilisation methods with respect to the E factor and is among the better alkylation methods in terms of waste generation and energy consumption in the literature. Our research represents one of the few examples in which hydrotropes have been evaluated in-depth regarding their recyclability and performance compared to other media.

Author contributions

Conceptualisation: W. D. and S. B.; formal analysis: S. B. and J. Z. S.; funding acquisition: W. D.; investigation: S. B. and J. Z. S.; methodology: W. D. and S. B.; resources: W. D.; supervision: W. D.; visualisation: S. B.; writing – original draft: S. B.; writing – review and editing W. D., S. B. and J. Z. S.

Conflicts of interest

There are no conflicts of interest to declare.

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