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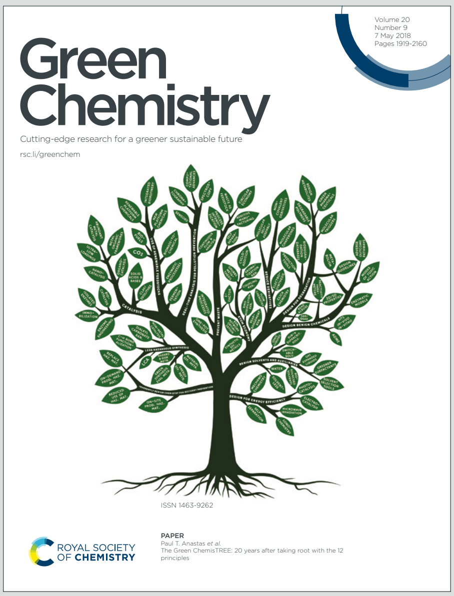

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Aqueous Sodium Tosylate: A Sustainable Medium for Alkylations

Sem Bleus[†], Jeltzlin Zaïnah Semerel[†,‡], Wim Dehaen[†]*

[†] Sustainable Chemistry for Metals and Molecules, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, P.O. box 2404, B-3001 Leuven, Belgium.

[‡] SISSTEM Program, Faculty of Arts and Science, University of Aruba, J. Irausquin Plein 4, Oranjestad, Aruba

*Corresponding author:

Email: wim.dehaen@kuleuven.be

Abstract

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The predominance of typically used alkylation reactions produces significant 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 to prepare alkyl aryl ethers, thioethers and *N*-alkylated tosyl amides in high yields under mild conditions. The generated reaction waste, aqueous NaTos solution, was repurposed as a reaction medium in subsequent steps. This medium was recycled ten times without significant change in 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.

Keywords: Hydrotrope; Phenol; Recycling; Waste repurposing; Water

Introduction

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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 on the starting materials, as various phenols can be bio-sourced.[1] However, the corresponding alkyl phenyl ethers are predominantly prepared *via* Williamson's synthesis-type procedures, which often produce harmful and diverse waste by relying on unbenign 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 (Figure 1), could provide a solution but have received limited attention. Nevertheless, successful organic syntheses in aqueous hydrotrope solutions[9] indicate that the products precipitate during the reaction, facilitating their solventless isolation. Alternatively, dilution can induce phase separation, as the dissolution process is highly hydrotrope-concentration dependent.[10] Unfortunately, few studies thus far systematically investigated the comparison with other solvents.[11] Moreover, hydrotrope recycling has barely been evaluated but would be mandatory considering the high salt loading.[11, 12]

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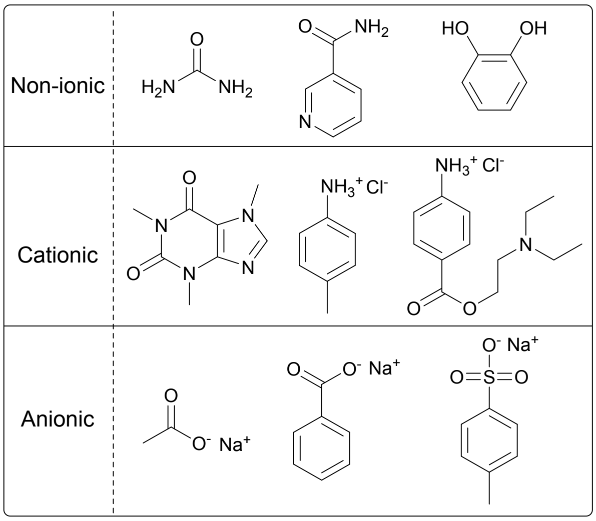
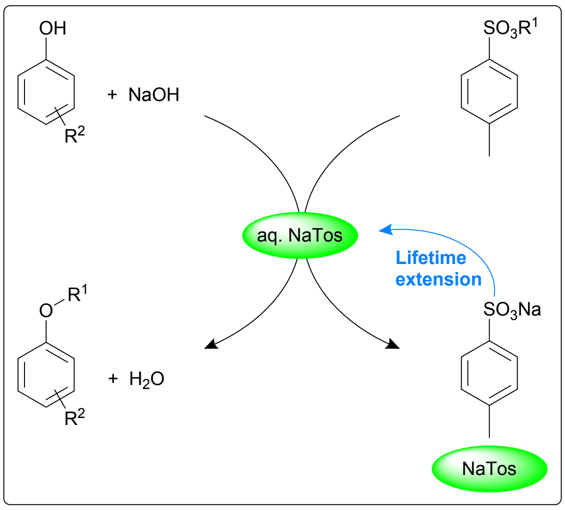


Figure 1: Representative examples of hydrotropes.

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 electrophile and green base,[13] respectively, since the only side products generated would be water and sodium tosylate (NaTos), a common hydrotrope. Resultantly, 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 by comparison to several alternative solubilising agents and prior literature examples.



Scheme 1: Alkylation strategy employed in this work.

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Initially, 3-nitrophenol **1aa** was reacted with an excess 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 process sustainability (Table S1). Under the final conditions (20 wt% NaTos, 1.0 equiv MeTos and 1.2 equiv 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.

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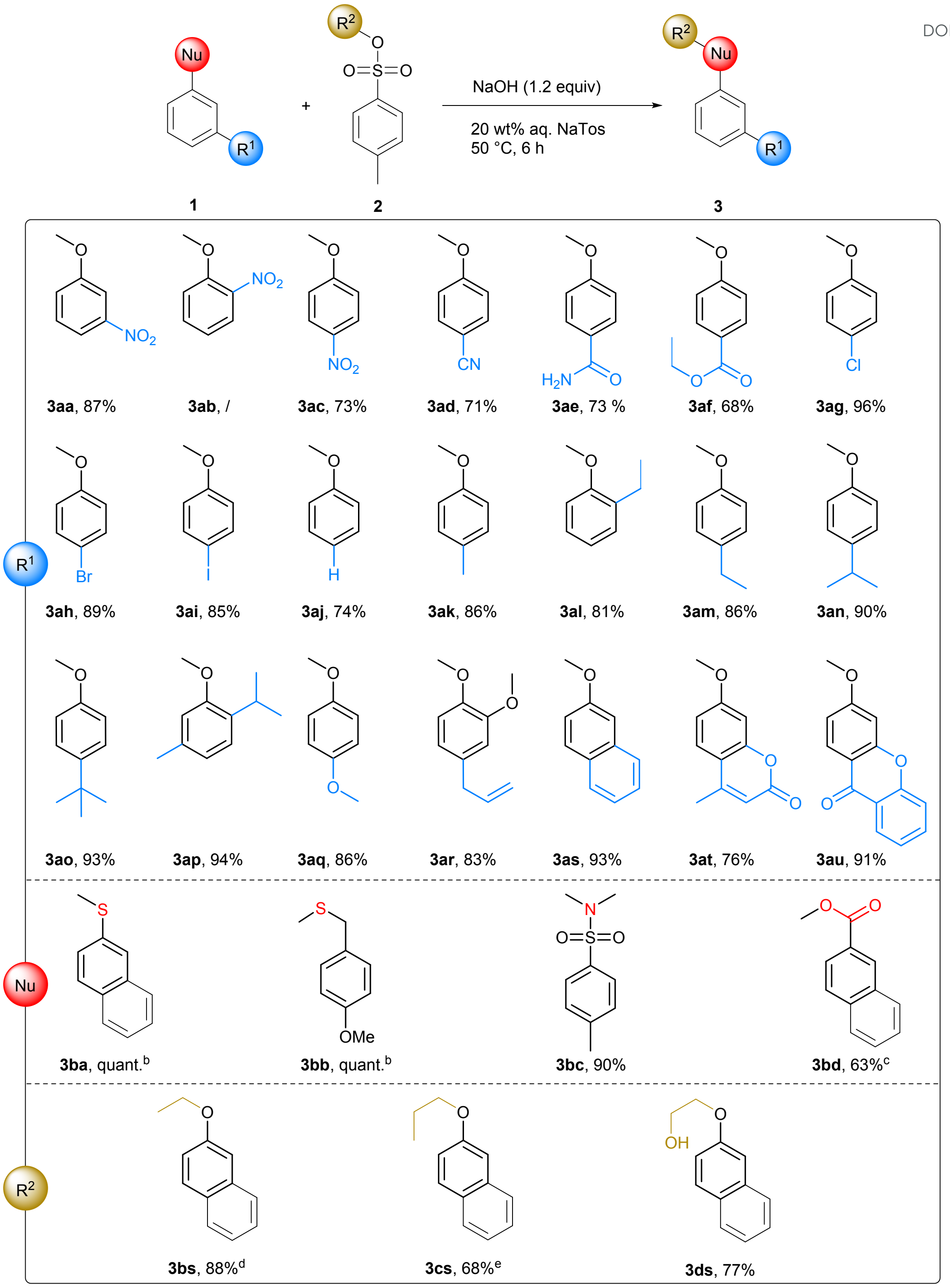

Scheme 2: Substrate scope of the alkylation reaction in hydrotrope-containing water.[a]
[a] Conditions: 2.5 mmol scale, 20 wt% NaTos (6 ml), NaOH (1.2 equiv), MeTos (1.0 equiv), 50 °C, 6 h; [b] 3 h, N_2 atmosphere; [c] NaOH (1.0 equiv), 65 h; [d] 18 h; [e] 40 wt% NaTos (6 ml), 18 h

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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 to 48% conversion, which may be attributed to the encumbered oxygen reactivity resulting from 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 solubilisation and yield. Polar substrates with hydrogen-accepting capabilities generally resulted in lower yields (**3aa**-**3af**) due to significant solubilisation of the products in the aqueous hydrotrope solution, as corroborated by ^{1}H-NMR analysis of the aqueous phase. The results for the compounds **3aj**-**3ap** indicate that the medium partially dissolves 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 seem well tolerated, given a 90% yield for the *N*-methyl-*p*-toluenesulfonamide **2bc** methylation to **3bc**. Methyl ester **3bd** could be obtained from the corresponding carboxylate **2bd** using 1.0 equiv NaOH in a moderate 63% yield. The low nucleophilicity of **2bd** increased the reaction time and made (tosylate) ester hydrolysis by the base a prominent side reaction, as indicated by crude NMR. Moreover, an additional base wash was required to remove residual acid, rendering carboxylic acids less suitable substrates.

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The tosylate esters were varied next, using 2-naphthol as 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 in 20 wt% NaTos with 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 MeTos and 1.2 equiv 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 nine additional cycles (Figure 2) with a 93% average yield, using 1.0 equiv of base per run and a total volume of 60 mL hydrotrope-containing water. As NaTos is generated *in situ*, the medium is gradually enriched in hydrotrope. Nevertheless, the consistently high yields indicate the product remains sparingly soluble at high hydrotrope loading. Saturation occurred after six runs at a theoretical NaTos concentration of 62 wt%, which correlates with 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 precipitation.

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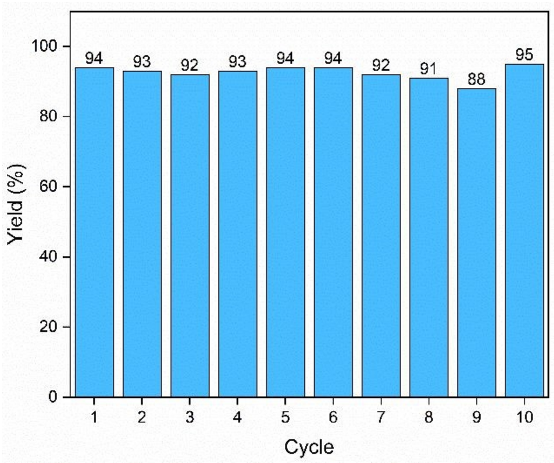

Figure 2: Recyclability study for the methylation of **2as**.[a]
[a] Conditions: Cycle 1: 25 mmol scale, 20 wt% NaTos, 1.2 equiv NaOH, 1.0 equiv MeTos, 16 h, 50 °C; Cycle 2-10: 25 mmol scale, recycled medium, 1.0 equiv NaOH, 1.0 equiv MeTos, 16 h, 50 °C

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 in hydrotrope-containing water. Although pure water and solventless conditions generate less salt waste than the hydrotrope, their low conversions necessitate chromatography or energy-intensive distillation. Moreover, the E factors without purification are 57-220% higher than for the sixfold used aqueous hydrotrope solution. 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, aqueous NaTos solution provided a significantly higher yield, making it a valuable alkylation medium, especially in routine syntheses.

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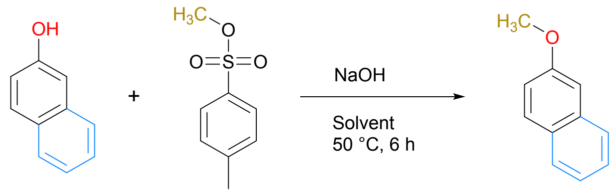
Table 1: Yield and E factor comparison for **2as** methylation in different solvents.[a]



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 NaOH, 1.0 equiv MeTos, 6 h, 50 °C; [b]After 1 run at 25 mmol scale; [c]After 6 runs at 25 mmol scale; [d]After 10 runs at 25 mmol scale; [e] Precipitated by water, succeeded by filtration; [f] Excluding work-up

The developed methodology was compared to literature methylations of **2as**. Upon saturation (run 6), the E Factor is significantly lower than for 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 work-up as only GC yields are reported.[19,20] These methods are more energy intensive due to high reaction temperatures and distillation to remove solvents, purify products and recover catalysts. Additionally, these reactions need 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.

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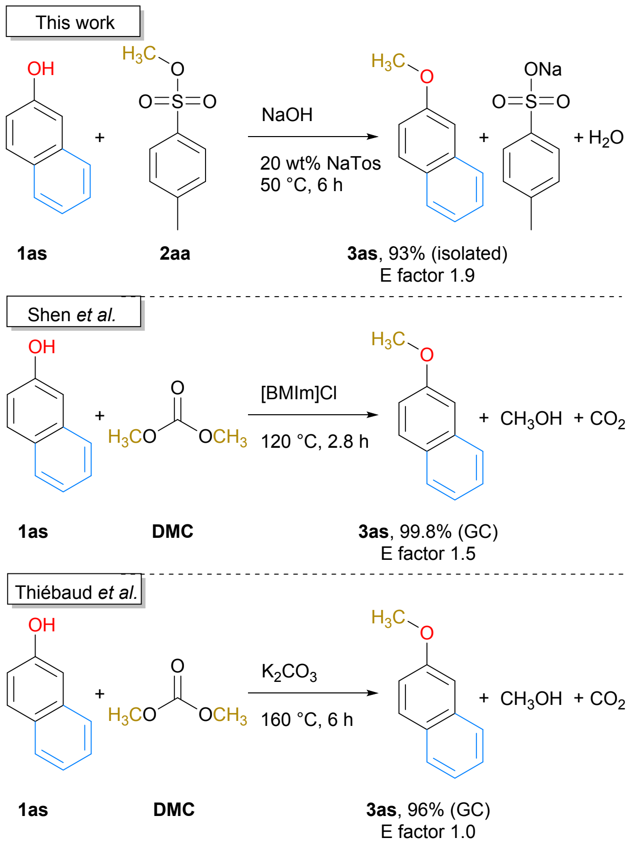

Scheme 3: Comparison of the developed method to other **2as** methylations with an E factor < 2.

Similarly 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 current green preparations of alkyl tosylates regularly involving reagent excesses and producing stoichiometric halogenated waste.[23] Nevertheless, alkylation of the green tosylic acid[16] with water as sole by-product seems viable,[24] potentially providing a suitable, greener alternative.

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Conclusion

Summarised, 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 in E factor and is among the better alkylation methods in terms of waste generation and energy consumption in 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.

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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 & editing W.D., S.B. and J.Z.S.

Supporting Information

Experimental details and characterisation data are available in the Supporting Information.

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Conflict of interest

There are no conflicts of interest to declare.

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DOI: 10.1039/D3GC04206E

References

1. J. Yan, Q. Meng, X. Shen, B. Chen, Y. Sun, J. Xiang, H. Liu and B. Han, *Science Adv.*, 2020, **6**, eabd1951
2. Y. Zhong, I. Douair, T. Wang, C. Wu, L. Maron and D. Cui, *Angew. Chem., Int. Ed.*, 2019, **59**, 4947; P. S. Hellwig, A. M. Barcellos, R. Cargnelutti, T. Barcellos and G. Perin, *J. Org. Chem.*, 2022, **87**, 15050; N. V. Tzouras, L. P. Zorba, E. Kaplanai, N. Tsoureas, D. J. Nelson, S. P. Nolan and G. C. Vougioukalakis, *ACS Catal.*, 2023, **13**, 8845
3. W. H. Gardiner, M. Camilleri, L. A. Martinez-Lozano, S. P. Bew and G. R. Stephenson, *Chem. - Eur. J.*, 2018, **24**, 19089; I. Medina-Mercado, A. Colin-Molina, J. E. Barquera-Lozada, B. Rodríguez-Molina and S. Porcel, *ACS Catal.*, 2021, **11**, 8968; A. Senior, K. Ruffell and L. T. Ball, *Nat. Chem.*, 2022, **15**, 386
4. J. Alan, M. Schade, M. Wagener, F. Christian, S. Nordhoff, B. Merla, T. R. Dunkern, G. Bahrenberg and P. Ratcliffe, *J. Med. Chem.*, 2019, **62**, 6391; G. H. M. de Kruijff, T. Goschler, N. Beiser, A. Stenglein, O. M. Türk and S. R. Walgvogel, *Green Chem.*, 2019, **21**, 4815
5. F. Chang, C. Wang, Q. Chen, Y. Zhang and G. Liu, *Angew. Chem., Int. Ed.*, 2021, **61**, e202114809; C. A. Franco, T. I. da Silva, M. G. Dias, B. W. Ferreira, B. L. de Sousa, G. M. Bousada, R. W. Barreto, B. G. Vaz, G. da S. Lima, M. H. dos Santos, J. A. S. Grossi and E. V. Vieira Varejão, *J. Agric. Food Chem.*, 2022, **70**, 2806
6. J. A. Barrett, Y. Gao, C. M. Bernt, M. Chui, A. T. Tran, M. B. Foston and P. C. Ford, *ACS Sustain. Chem. Eng.*, 2016, **4**, 6877; Y. W. Lui, B. Chan and M. Y. Lui, *ChemSusChem*, 2022, 15, e202102538

View Article Online
DOI: 10.1039/D3GC04206E

7. T. N. Glasnov, J. D. Holbrey, C. O. Kappe, K. R. Seddon and T. Yan, *Green Chem.*, 2012, **14**, 3071; U. Tilstam, *Org. Process Res. Dev.*, 2012, **16**, 1150; A. Dhakshinamoorthy, A. Sharmila and K. Pitchumani, *Chem. – Eur. J.*, 2010, **16**, 1128

8. M.-O. Simon and C.-J. Li, *Chem. Soc. Rev.*, 2012, **41**, 1415; B. H. Lipshutz, F. Gallou and S. Handa, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5838; T. Kitanosono, K. Masuda, P. Xu and S. Kobayashi, *Chem. Rev.*, 2018, **118**, 679; M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237

9. T. Sela and A. Vigalok, *Adv. Synth. Catal.*, 2012, **354**, 2407; S. N. Jadhav, A. S. Kumbhar, C. V. Rode and R. S. Salunkhe, *Green Chem.*, 2016, **18**, 1898; C.-X. Shi, Y.-T. Guo, Y.-H. Wu, Z.-Y. Li, Y-Z. Wang, F.-S. Du and Z.-C. Li, *Macromolecules*, 2019, **52**, 4260

10. M. R. Thakker, J. K. Parikh and M. A. Desai, ACS *Sustainable Chem. Eng.*, 2018, **6**, 3215; A. Mazaud, R. Lebeuf, M. Lageurre and V. Nardello-Rataj, *ACS Sustainable Chem. Eng*. 2020, **8**, 15268

11. T. Sela, X. Lin and A. Vigalok, *J. Org. Chem.*, 2017, **82**, 11609

12. A. Kumbhar, S. Kamble, M. Barge, G. Rashinkar and R. Salunkhe, *Tetrahedron Lett.* 2012, **22**, 2756

13. R. K. Henderson, A. P. Hill, A. M. Redman and H. F Sneddon, *Green Chem.*, 2015, **17**, 945

14. S. R. Thawarkar, B. Thombare, B. S. Munde and N. D. Khupse, *RSC Adv.*, 2018, 8, 38384

15. K.-K. Pei, R.-X. Zhao, G.-L. Zhang, Q. Xia and F.-B. Zhang, *J. Chem. Eng. Data*, 2018, **63**, 1556.

16. D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288

View Article Online
DOI: 10.1039/D3GC04206E

17. For reactions in acetonitrile see: R. R. Milburn and V. Snieckus, *Angew. Chem. Int. Ed.*, 2004, **43**, 888; M. Y. Lui, A. K. L. Yuen, A. F. Masters and T. Maschmeyer, *ChemSusChem*, 2016, **9**, 2312; Q. Zheng, H. Xu, H. Wang, W.-G. H. Du, N. Wang, H. Xiong, Y. Gu, L. Noodleman, K. B. Sharpless, G. Yang and P. Wu, *J. Am. Chem. Soc.*, 2021, **143**, 3753; For reactions in dimethylsulfoxide see: X. Shen, M. Zhou, C. Ni, W. Zhang and J. Hu, *Chem. Sci.*, 2014, **5**, 117; J. B. Washington, M. Assante, C. Yan, D. McKinney, V. Juba, A. G. Leach, S. E. Baillie and M. Reid, *Chem. Sci.*, 2021, **12**, 6949; X. Dong, Q. Y. Li and T. P. Yoon, *Org. Lett.*, 2021, **23**, 5703

18. R. A. Sheldon, *Green Chem.*, 2023, **25**, 1704

19. Z. L. Shen, X. Z. Jiang, W. M. Mo, B. X. Hu, N. Sun, *Green Chem.*, 2005, **7**, 97

20. S. Ouk, S. Thiébaud, E. Borredon and P. Le Gars, *Green Chem.*, 2002, **4**, 431

21. J. Dreyfuss, J. M. Shekosky and J. J. Ross Jr., *Toxicol. Appl. Pharmacol.*, 1971, **20**, 548; W. F. Bergfeld, D. V. Belsito, C. D. Klaassen, R. Hill, D. Liebler, J. G. Marks Jr., R. C. Shank, T. J. Slaga, P. W. Snyder and F. A. Andersen, *Int. J. Toxicol.*, 2011, **30**, 270S; K. Stanton, C. Tibazarwa, H. Certa, W. Greggs, D. Hildebold, L. Jovanovich, D. Woltering and R. Sedlak, *Integr. Environ. Assess. Manag.*, 2009, **6**, 155

22. J. McCann, E. Choi, E. Yamasaki and B. N. Ames, *Proc. Nat. Acad. Sci.*, 1975, **72**, 5135

23. J. Morita, H. Nakatsuji, T. Misaki and Y. Tanabe, *Green Chem.*, 2005**, 7,** 711; F. Kazemi, A. R. Massah and M. Javaherian, *Tetrahedron*, 2007, **63**, 5083; K. Asano and S. Matsubara, *Org. Lett.*, 2009, **11**, 8, 1757

24. X. Dong, R. Sang, Q. Wang, X.-Y. Tang and M. Shi, *Chem. - Eur. J.,* 2013, **19**, 16910; B. M. Choudary, N. S. Chowdari and M. L. Kantam, *Tetrahedron*, 2000, **56**, 7291; S. Velusamy, J. S. Kiran Kumar and T. Punniyamurthy, *Tetrahedron Lett.*, 2004, **45**, 203; B. Das, B. V. Saidi Reddy and M. Ravinder Reddy, *Tetrahedron Lett.*, 2004, **45**, 6717;

View Article Online
DOI: 10.1039/D3GC04206E

J. Chandra, R. Chaudhuri, S. R. Manne, S. Mondal, and B. Mandal, *ChemistrySelect*, 2017, **2**, 8471