

Cite this: *Chem. Commun.*, 2019, 55, 5239Received 13th March 2019,
Accepted 7th April 2019

DOI: 10.1039/c9cc02042j

rsc.li/chemcomm

A 'sulfonyl-azide-free' (SAFE) aqueous-phase diazo transfer reaction for parallel and diversity-oriented synthesis†

Dmitry Dar'in, Grigory Kantin and Mikhail Krasavin *

Diazo transfer reactions are notoriously associated with the use of potentially explosive sulfonyl azides. The first 'sulfonyl-azide-free' (SAFE) protocol for producing diazo compounds from their active-methylene precursors via the Regitz diazo transfer reaction was developed and has displayed a remarkable substrate scope. It can be applied to generating arrays of diazo compounds for further evolution via combinatorial chemistry and a range of scaffold-generating transformations.

Diazo compounds are distinctly versatile reactive building blocks which can be activated, with the loss of a nitrogen molecule, to give rise to carbene or metal carbenoid intermediates.¹ Besides their appeal in synthetic organic chemistry, diazo compounds display a growing significance as tools for chemical biology.² Perhaps the most popular method of preparing diazo compounds is currently the Regitz diazo transfer from a sulfonyl azide to an active methylene substrate.³ Although this process is generally clean and high-yielding, potential explosion hazards⁴ associated with diazo transfer reagents preclude their use on an industrial scale and may even be hindering active exploration of the diazo chemical space. In particular, there have been no examples of diazo compound synthesis in an array format, which would ultimately enable combinatorial library generation based on the vast diazo chemistry.

The continued search for safer alternatives to tosyl azide (the most commonly used diazo transfer reagent⁵) has delivered such promising reagents as *p*-acetamidobenzenesulfonyl azide,⁶ *p*-dodecylbenzenesulfonyl azide,⁷ and imidazole-1-sulfonyl azide hydrogen sulfate⁸ as well as polymer-supported⁹ and ionic liquid sulfonyl azides.¹⁰ However, all these reagents are nonetheless prone to exothermal decomposition and, therefore, should be handled with care.

Institute of Chemistry, Saint Petersburg State University, Saint Petersburg 199034, Russian Federation. E-mail: m.krasavin@spbu.ru

† Electronic supplementary information (ESI) available: Experimental details, full characterization data, crystallographic information, and copies of ¹³C and ¹H NMR spectra. CCDC 1897286. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc02042j

In principle, the risks associated with diazo transfer reagents can be avoided by preparing them *in situ*. Such an approach has not been realized for diazo transfer reactions to-date except for one isolated example reported by Hoveyda¹¹ and the recently reported noteworthy examples of generating diazo compounds in a flow reactor described by Maguire and Collins.¹² Considering this methodology void, we became interested in exploring diazo transfer reactions without a need to prepare, isolate and handle the hazardous reagent which could be instead generated *in situ*.

Any *in situ* protocol is potentially associated with increased by-product formation. It is especially the case with diazo transfer reagents where a large molecular entity (the sulfonyl portion) is already destined to become a by-product and needs to be effectively removed upon completion of the reaction. Our attention was drawn by *m*-carboxybenzenesulfonyl azide which has been successfully employed as a diazo transfer reagent in organic solvents^{13a-f} and in water.^{13g} Although its preparation has never been attempted in an aqueous medium, we saw it as a suitable lead for the development of a 'sulfonyl-azide-free' (SAFE) protocol for the preparation of diazo compounds in water (Fig. 1).

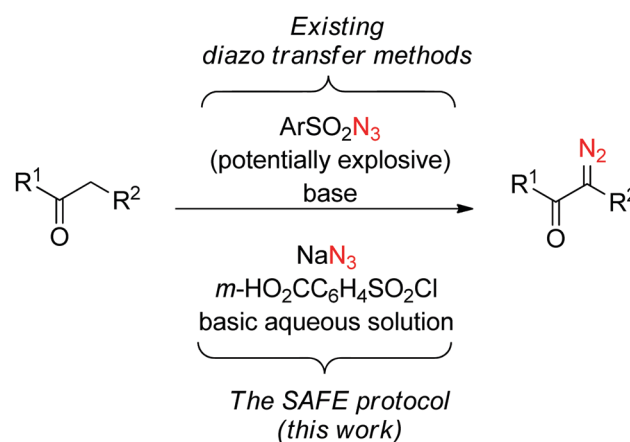
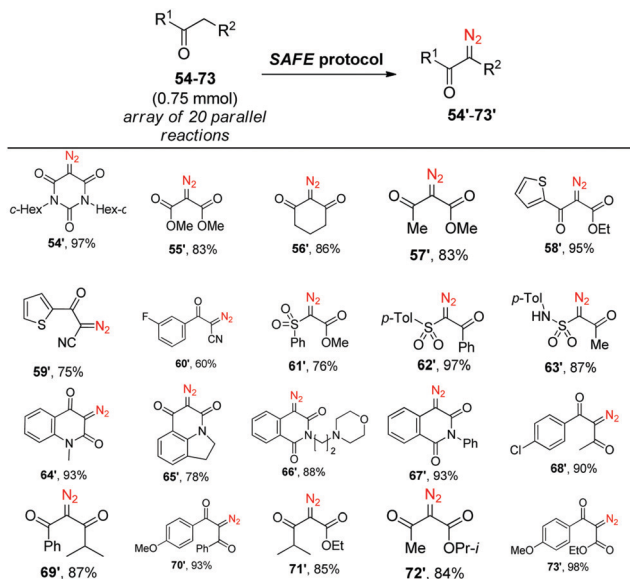
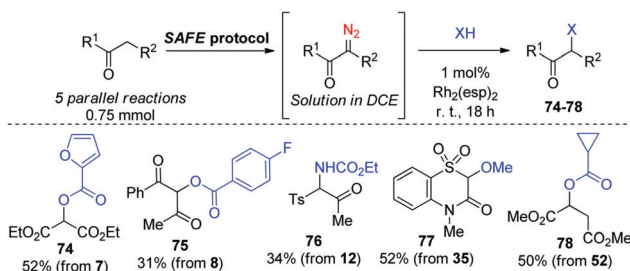


Fig. 1 Comparison of previously employed diazo transfer methods with the SAFE protocol described herein.



Scheme 3 SAFE array synthesis of diazo compounds 54'–73'.

SAFE diazo transfer products in the interim. Such a possibility was indeed realized for a small set of substrates (7–8, 12, 35 and 52) which were prepared in a parallel fashion and used directly in

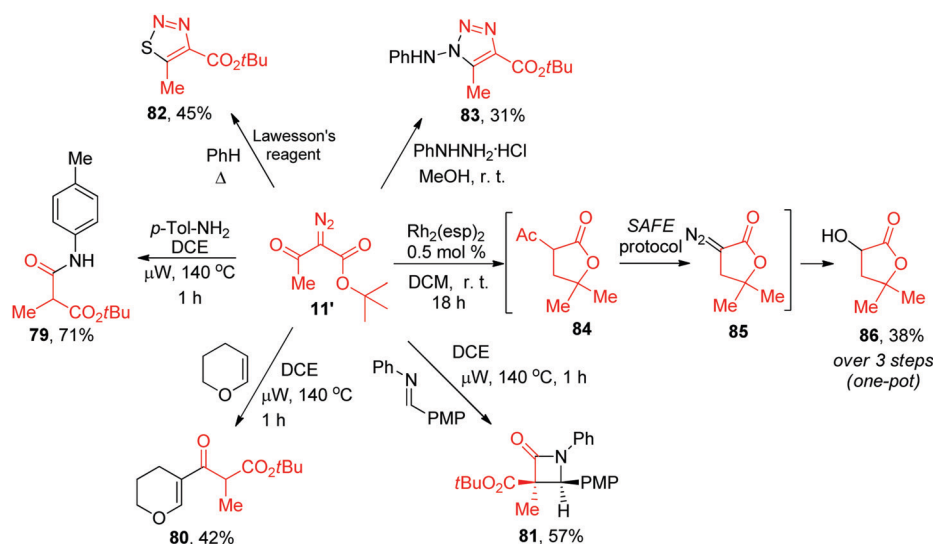


Scheme 4 Combinatorial format for the SAFE diazo transfer and subsequent Rh carbene X–H insertion reactions.

reactions involving Rh₂(esp)₂-catalyzed decomposition¹⁵ and Rh carbene insertion into an O–H or N–H bond of a carboxylic acid, an alcohol or a carboxamide (Scheme 4).

The latter finding demonstrated that the purity of diazo compounds obtained *via* the SAFE protocol was adequate for Rh^{II}-catalyzed X–H insertion chemistry. Considering the versatility of diazo compounds in generating diverse molecular skeletons,¹⁶ we aimed to confirm that 11' (an exemplary compound prepared, without purification, on a 9 mmol scale, *vide supra*) can be considered a starting point for generating skeletally diverse compounds thereby validating the SAFE protocol for future use in diversity-oriented synthesis. This compound was split into six 1.38 mmol batches which were individually subjected to a range of reactions hallmark for diazo compounds. In particular, microwave-assisted Wolff rearrangement¹⁷ of compound 11' generated the respective ketene which was subsequently trapped with an aniline (to give 79), or enol ether (to give 80)¹⁸ or underwent a [2+2] Staudinger cycloaddition with an imine¹⁹ to produce β-lactam 81 whose structure was confirmed by single-crystal X-ray analysis (ESI†). Reactions with the Lawesson's reagent²⁰ and phenyl hydrazine²¹ delivered 1,2,3-thiadiazole 82 and 1,2,3-triazole 83, respectively. Finally, the Rh^{II} carbene insertion into the C–H bond of the *tert*-butyl moiety²² produced γ-lactone 84 which was, without isolation, subjected to the deacetylative SAFE diazo transfer (realized in a two-phase format by adding the alkaline aqueous diazo transfer cocktail to the crude DCM solution of 84). However, instead of diazo compound 85, we obtained α-hydroxy γ-lactone 86 formed, presumably, *via* the metal carbene insertion into the HO–H bond catalyzed by the leftover Rh₂(esp)₂ present in the biphasic mixture (Scheme 5).

To conclude, we developed the first 'sulfonyl-azide-free' (SAFE) protocol for diazo transfer in an aqueous medium.²³ It has been found workable for 73 structurally diverse, active-methylene substrates and produced the respective diazo compounds (22 of them new) in high product yields and purities. The SAFE method was found to be applicable to producing diazo compounds in an



Scheme 5 Diversity-oriented synthetic exploration of 11'.

array format and the products thus obtained can be conveniently used in subsequent chemistry conducted in a combinatorial fashion. Moreover, the range of chemistries applied to the evolution of the diazo compound scaffold can be expanded so as to enable diversity-oriented synthesis of skeletally unique compounds. Efforts are underway in our laboratories to adapt the SAFE protocol to a continuous flow format. The results of these studies will be reported in due course.

We are grateful to the Russian Foundation for Basic Research for financial support (grant #19-03-00775). We thank the Research Centre for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and the Centre for X-ray Diffraction Methods of Saint Petersburg State University Research Park for obtaining the analytical data.

Conflicts of interest

The authors declare no conflict of interest.

Notes and references

- 1 A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKerverey, *Chem. Rev.*, 2015, **115**, 9981.
- 2 K. A. Mix, M. R. Aronoff and R. T. Raines, *ACS Chem. Biol.*, 2016, **11**, 3233.
- 3 W. Regitz, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 733.
- 4 F. W. Bollinger and L. D. Tuma, *Synlett*, 1996, 407.
- 5 T. J. Curphey, *Org. Prep. Proced. Int.*, 1981, **13**, 112.
- 6 J. S. Baum, D. A. Shook, H. M. L. Davies and H. D. Smith, *Synth. Commun.*, 1987, **17**, 1709.
- 7 F. W. B. G. Hazen, F. E. Roberts, W. K. Russ, J. J. Seman and S. Staskiewicz, *Org. Synth.*, 1996, **73**, 144.
- 8 G. T. Potter, G. C. Jayson, G. J. Miller and J. M. Gardiner, *J. Org. Chem.*, 2016, **81**, 3443.
- 9 E. Tarrant, C. V. O'Brien and S. G. Collins, *RSC Adv.*, 2016, **6**, 31202.
- 10 M. K. Muthyala, S. Choudhary and A. Kumar, *J. Org. Chem.*, 2012, **77**, 8787.
- 11 E. S. Sattely, S. J. Meek, S. J. Malcolmson, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 943.
- 12 (a) R. M. O'Mahony, D. Lynch, H. L. D. Hayes, E. N. Thuama, P. Donnellan, R. C. Jones, B. Glennon, S. G. Collins and A. R. Maguire, *Eur. J. Org. Chem.*, 2017, 6533; (b) B. J. Deadman, R. M. O'Mahony, D. Lynch, D. C. Crowley, S. G. Collins and A. R. Maguire, *Org. Biomol. Chem.*, 2016, **14**, 3423.
- 13 (a) R. J. Moreau and E. J. Sorensen, *Tetrahedron*, 2007, **63**, 6446; (b) D. Morton, A. Dick, D. Ghosh and H. M. L. Davies, *Chem. Commun.*, 2012, **48**, 5838; (c) I. Rodríguez, M. I. Calaza, A. I. Jimenez and C. Cativiela, *Tetrahedron*, 2012, **68**, 9578; (d) D. Ghosh, J. Lo, D. I. Morton, D. Valette, J. Xi, J. Griswold, S. Hubbell, C. Egbuta, W. Jiang, J. An and H. M. L. Davies, *J. Med. Chem.*, 2012, **55**, 8464-8476; (e) C. Qin and H. M. L. Davies, *Org. Lett.*, 2013, **15**, 6152; (f) C. Doebelin, Y. He and T. M. Kamenecka, *Tetrahedron Lett.*, 2016, **57**, 5658; (g) R. M. O'Mahony, C. M. Broderick, D. Lynch, S. G. Collins and A. R. Maguire, *Tetrahedron Lett.*, 2019, **60**, 35.
- 14 R. L. Danheiser, R. F. Miller, R. G. Brisbois and S. Z. Park, *J. Org. Chem.*, 1990, **55**, 1959.
- 15 C. Hunter, K. Chinthapally and I. Sharma, *Eur. J. Org. Chem.*, 2016, 2260.
- 16 M. Ibbeson, L. Laraia, E. Alza, C. J. O'Connor, Y. S. Tan, H. M. L. Davies, G. McKenzie, A. R. Venkitaraman and D. R. Spring, *Nat. Commun.*, 2014, **5**, 3155.
- 17 M. Presset, Y. Coquerel and J. Rodriguez, *J. Org. Chem.*, 2009, **74**, 415.
- 18 R. P. Pandit and Y. R. Lee, *Org. Biomol. Chem.*, 2014, **12**, 4407.
- 19 Y. Wang, Y. Liang, L. Jiao, D.-M. Du and J. Xu, *J. Org. Chem.*, 2006, **71**, 6983.
- 20 M. Caron, *J. Org. Chem.*, 1986, **51**, 4075.
- 21 Z. Wang, X. Bi, P. Liao, R. Zhang, Y. Liang and D. Dong, *Chem. Commun.*, 2012, **48**, 7076.
- 22 M. P. Doyle, V. Bagheri, M. M. Pearson and J. D. Edwards, *Tetrahedron Lett.*, 1989, **30**, 7001.
- 23 *The aqueous-phase waste should be disposed of according to the general guidelines for aqueous solutions containing inorganic azides: Bretherick's handbook of reactive chemical hazards*, ed. P. G. Urben, Butterworth-Heinemann, Oxford, 6th edn, 1999.