ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 5239

Received 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 hazards[4] 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 reagent[5]) has delivered such promising reagents as *p*-acetamidobenzenesulfonyl azide,[6] *p*-dodecylbenzenesulfonyl azide,[7] and imidazole-1-sulfonyl azide hydrogen sulfate[8] as well as polymer-supported[9] and ionic liquid sulfonyl azides.[10] However, all these reagents are nonetheless prone to exothermal decomposition and, therefore, should be handled with care.

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 Hoveyda[11] 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).

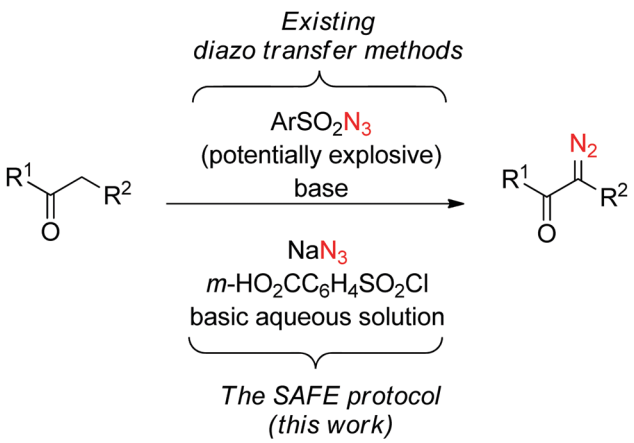
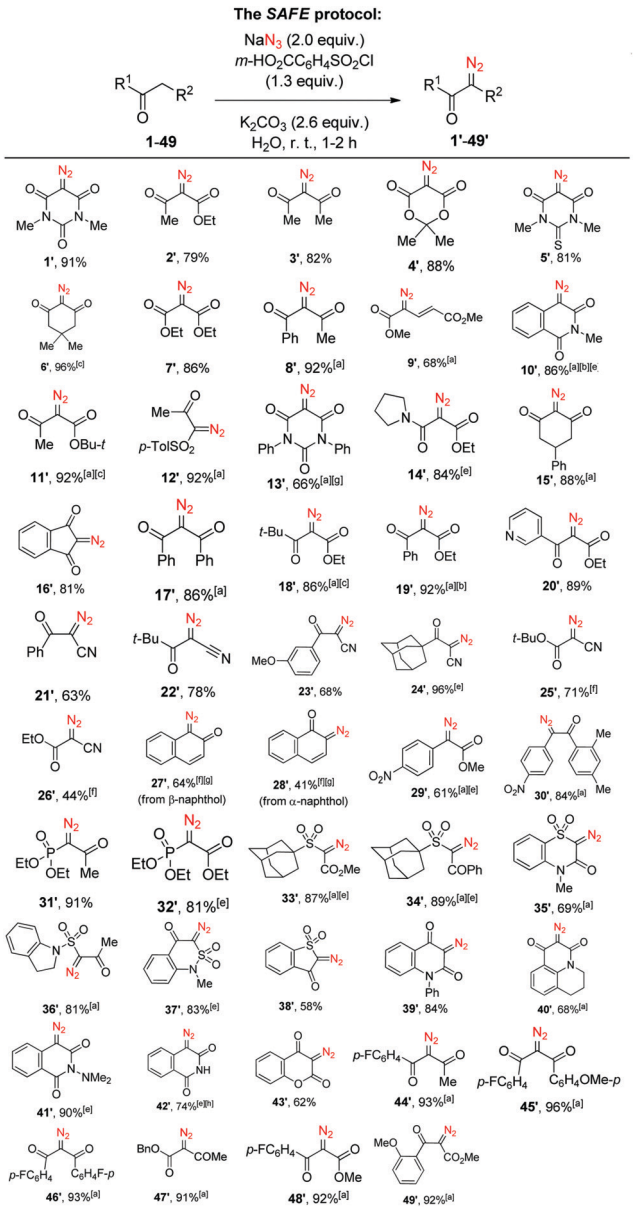


Fig. 1 Comparison of previously employed diazo transfer methods with the SAFE protocol described herein.

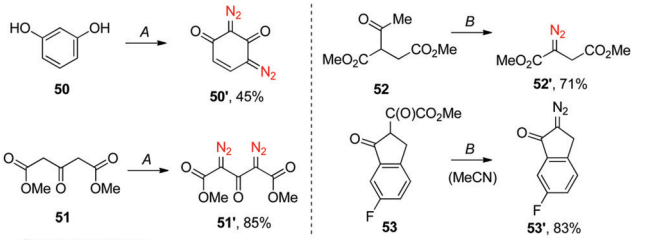
Institute of Chemistry, Saint Petersburg State University, Saint Petersburg 199034, Russian Federation. E-mail: m.krasavin@spbu.ru

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



Scheme 1 Scope of the SAFE diazo transfer reaction. Yields of the isolated products. [a] Acetonitrile (1–2 mL) was added to aid in the formation of a fine suspension or emulsion; [b] 3.0 mmol scale; [c] 6.0 mmol scale; [d] 9.0 mmol scale; [e] increased reaction time (see the ESI,† for details); [f] double amount of NaN_3 and m-$HO_2CC_6H_4SO_2Cl$ was used; [g] purified by chromatography; [h] purified by crystallization.

After relatively brief experimentation involving variations of reagent ratios, solvent volume and reaction time, we realized that a wealth of active-methylene substrates **1–49** can be conveniently transformed into their diazo counterparts **1′–49′** in good to excellent yields *via* a simple 'mix-all' protocol, mostly on 1.5 mmol scale, using *m*-carboxybenzenesulfonyl chloride (commercially available or conveniently prepared in >50 g batches – see the ESI†) and sodium azide in basic aqueous solution (Scheme 1). As it is evident from the substrate scope displayed by the new SAFE method, a diazo group can be transferred from sodium azide to give a wide variety of known as well as hitherto



Reaction conditions:
NaN_3 (4.0 (*A*) or 2.0 (*B*) equiv.), m-$HO_2CC_6H_4SO_2Cl$ (2.6 (*A*) or 1.3 (*B*) equiv.), K_2CO_3 (5.2 (*A*) or 2.6 (*B*) equiv.), H_2O, r. t., 1-2 h

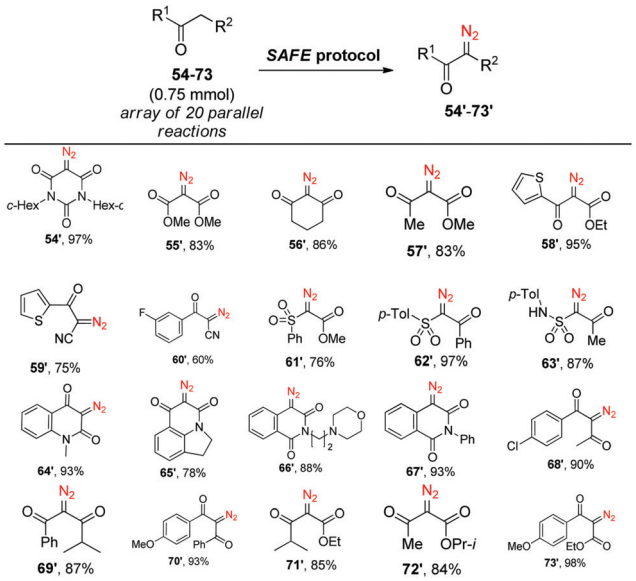
Scheme 2 Double deacylative SAFE diazo transfer.

unreported (**5′**, **13′**, **20′**, **23′–24′**, **30′**, **33′–37′**, **39′**, **40′**, **42′**, **45′**, **49′**) diazo compounds. Only certain substrates required longer reaction time for the diazo transfer; otherwise the reaction was complete in 1–2 h. In addition to the R^2 group being most commonly represented by another carbonyl group, it can include other carbanion-stabilizing moieties such as vinylogous (**9**) and phenylogous (**10**, **41–42**) carbonyls (or variants thereof, *cf.* **27–28**), cyano (**21–26**), sulfone (**33–38**), phosphonate (**31–32**) or electron-deficient aromatic (**29–30**) groups. Some substrates (**25–28**) displayed incomplete conversion and suboptimal product yield under standard reaction conditions; both of these aspects were improved by doubling the amount of NaN_3, the base and the sulfonyl chloride.

Naturally, increasing the amount of these reagents twofold was also needed to achieve double diazo transfer onto substrates **50–51** to produce respective bis-diazo compounds **50′–51′**. Interestingly, the SAFE reaction conditions were found applicable to the variants of the Danheiser deacylative diazo transfer[14] successfully producing hitherto undescribed diazo compounds **52′–53′** with the loss of acetyl and methoxalyl groups, respectively (Scheme 2). Altogether, except for a handful of examples (**13′**, **27′–28′**, **42′**), the crude diazo compounds produced in the course of the initial scope investigation had a purity of at least 95% as determined by ^{1}H NMR. Moreover, the reaction displayed comparable yield on a 3.0–9.0 mmol scale.

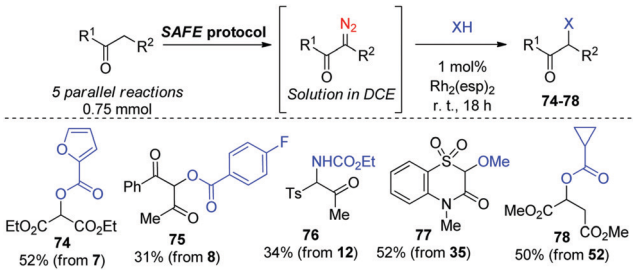
Having established the efficiency of the newly developed SAFE protocol, we sought to apply it to simultaneous generation of different diazo compounds from their active-methylene precursors in an array format. To test this possibility, we prepared an aqueous solution of sodium azide, *m*-carboxybenzenesulfonyl chloride and potassium carbonate and added it in proportionate aliquots to an array of 20 reaction vessels containing different substrates (**54–73**) followed by the addition of 50% v/v of MeCN. After 2 h of stirring at r.t., parallel extraction with chloroform gave, after drying and evaporation of the solvent, diazo compounds **54′–73′** all of which were judged to be at least 95% pure by ^{1}H NMR (Scheme 3). Thus, the SAFE method was found suitable for producing structurally diverse sets of diazo compounds in a parallel fashion.

The established amenability of the SAFE protocol for array diazo compound synthesis motivated us to explore the possibility of modifying compounds **1′–73′** in a combinatorial fashion, so as to obtain the products of subsequent diazo chemistry directly from their active-methylene precursors, without a need to purify the



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

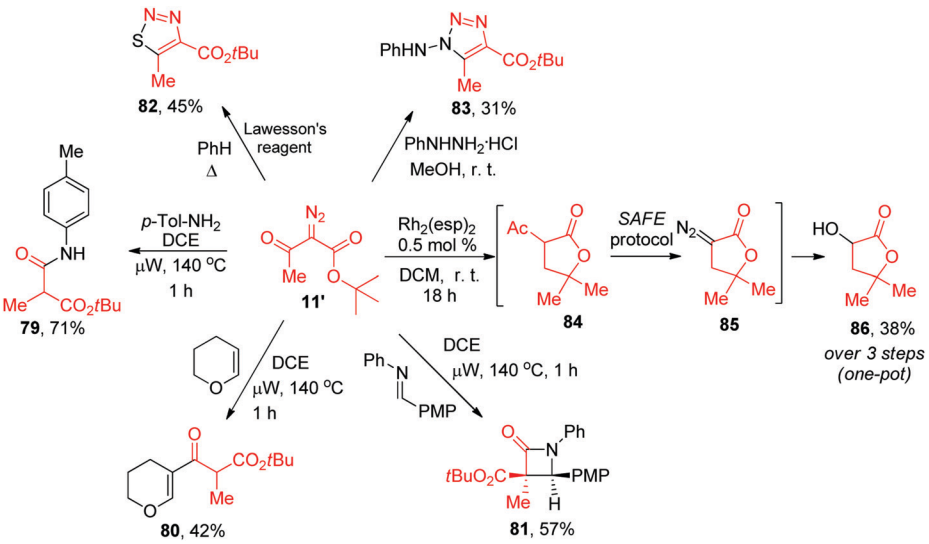
SAFE diazo transfer products in the interim. Such a possibility was indeed realized for a small set of substrates (**7–8**, **12**, **35** and **52**) which were prepared in a parallel fashion and used directly in reactions involving $Rh_2(esp)_2$-catalyzed decomposition[15] and Rh carbene insertion into an O–H or N–H bond of a carboxylic acid, an alcohol or a carboxamide (Scheme 4).



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

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 rearrangement[17] 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 imine[19] to produce β-lactam **81** whose structure was confirmed by single-crystal X-ray analysis (ESI†). Reactions with the Lawesson's reagent[20] and phenyl hydrazine[21] 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 moiety[22] 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 $Rh_2(esp)_2$ 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. McKervey, *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. 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. Rodrigez, *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.

