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Taking diazo transfer to water: α-diazo carbonyl compounds from *in situ* generated mesyl azide

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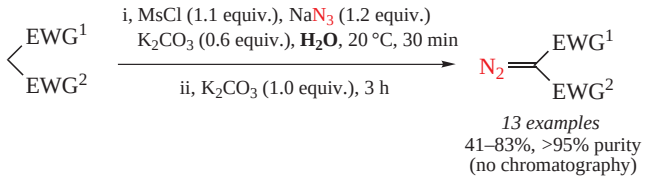
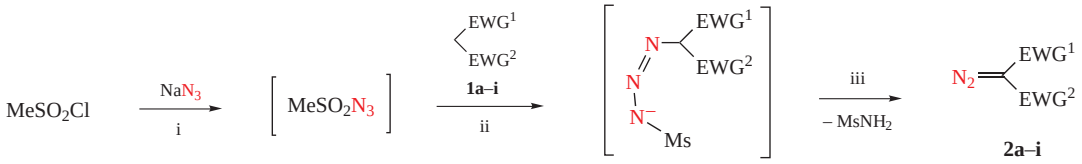
Mesyl azide generated *in situ* in aqueous medium converted a range of active methylene substrates into the corresponding diazo compounds in good yields and high purity with no need for chromatographic purification. The products thus obtained are suitable for the subsequent Rh^{II}-catalyzed O–H insertions with no need for chromatography in the interim.

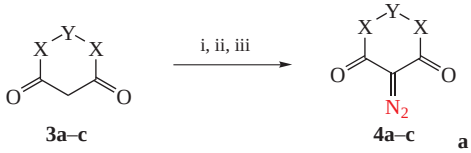


Keywords: diazo transfer, sulfonyl azides, *in situ* generation, mesyl azide, active methylene compounds, aqueous medium.

Over the last few decades, diazo carbonyl compounds have been extensively studied for their wide range of chemical transformations.[1–4] The range of insertion reactions which can be triggered by diazo compounds decomposition into the carbene species with the loss of a nitrogen molecule is quite breathtaking.[1,4] Numerous diazo compounds can be prepared *via* the transfer of diazo function to sufficiently CH-acidic substrates (the process dubbed the Regitz diazo transfer[5]). Despite the practical simplicity of this method, one can be deterred from its frequent use because of the need to initially prepare and handle the potentially explosive[6] sulfonyl azide reagents such as tosyl azide, the most commonly employed reagent in diazo transfer reactions.[4] In principle, the hazards associated with diazo transfer reagents can be almost entirely avoided by preparing them *in situ*, as exemplified by Hoveyda,[8] by the flow reactor diazo transfer synthesis described by Maguire and Collins.[9,10] The recently described 'sulfonyl-azide-free' (SAFE) diazo transfer[11–14] relying on the *in situ* generation of the active reagent from *m*-carboxybenzenesulfonyl chloride and sodium azide in aqueous medium seems promising. The general green character of this transformation and the high purity of the crude products obtained by this method prompted us to investigate if the same approach, *i.e.* the *in situ* preparation of a sulfonyl azide in aqueous medium, could be applied to any of the conventional diazo transfer reagents.

We reasoned that mesyl azide which is less lipophilic compared to tosyl azide (*cLogP* are 0.39 and 2.37, respectively) would be a good choice of a sulfonyl azide reagent suitable for realization of our strategy. Similarly, methanesulfonamide (the by-product of diazo transfer) will be more likely to remain in the aqueous phase (*cLogP* is –0.90) upon completion of diazo transfer, compared to its *p*-toluenesulfonamide counterpart (*cLogP* is 1.08).† After preliminary experimentation with ethyl acetoacetate **1a** as a model substrate, it was established that along with the full conversion, the optimum yield (78%) and purity (>95%) of the obtained ethyl 2-diazoacetoacetate **2a** (Scheme 1) were achieved with the use of 1.1 equiv. of MsCl, 1.2 equiv. of NaN_3 and 0.6 equiv. of K_2CO_3. The unreacted MsN_3





3a–c

4a–c

a X = O, Y = CMe_2, 69%
b X = CH, Y = CMe_2, 72%
c X = NMe, Y = C(O), 56%

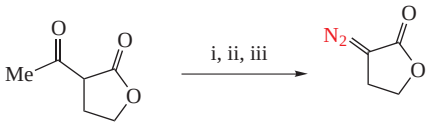
a EWG^1 = C(O)Me, EWG^2 = CO_2Et, 78%
b EWG^1 = EWG^2 = C(O)Me, 77%
c EWG^1 = EWG^2 = CO_2Me, 54%
d EWG^1 = C(O)Bu^t, EWG^2 = CN, 41%
e EWG^1 = 3-pyridylcarbonyl, EWG^2 = CO_2Et, 70%
f EWG^1 = 2-thienylcarbonyl, EWG^2 = CO_2Et, 71%
g EWG^1 = C(O)Ph, EWG^2 = C(O)Me, 83%
h EWG^1 = 4-$ClC_6H_4C(O)$, EWG^2 = CO_2Me, 80%
i EWG^1 = 4-$MeC_6H_4SO_2$, EWG^2 = CO_2Me, 73%

Scheme 1 *Reagents and conditions*: i, MsCl (1.1–1.25 equiv.), NaN_3 (1.2–1.5 equiv.), H_2O, room temperature, 10 min; ii, K_2CO_3 (0.6 equiv.), H_2O, MeCN (when needed), room temperature, 30–60 min; iii, K_2CO_3 (1.0 equiv.), H_2O, room temperature, 3 h.

(~0.1 equiv.) was hydrolyzed over 3 h into water-soluble methanesulfonamide (which remained in the water phase after extractive workup) by adding an additional equivalent of K_2CO_3. Notably, addition of 25% MeCN to the reaction mixture did not affect the outcome of the reaction thus demonstrating the suitability of water as the solvent of choice. This protocol was extended to a range of other linear (**1b–i)** and cyclic (**3a–c)** active-methylene substrates to produce the corresponding diazo compounds **2b–i, 4a–c** in generally good yields and high purity without a need for chromatographic purification (see Scheme 1). In some cases, reaction time for the diazo transfer step (synthesis of **2i**) or the amount of MsCl/NaN_3 (synthesis of **2f–h**) had to be increased in order to achieve full conversion.

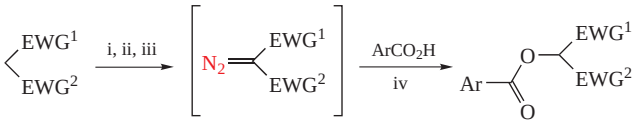
The utility of this approach was successfully demonstrated by deacylative diazo transfer to α-acetobutyrolactone **5**, which gave α-diazobutyrolactone **6** (Scheme 2).

Encouraged by these findings, we were keen to demonstrate that the purity of the diazo compounds thus obtained would make them suitable for the immediate use in subsequent transformations (as was demonstrated previously for the SAFE diazo transfer procedure[11]). To this end, to the dichloromethane extracts of diazo compounds **2b** and **2g** (see Scheme 1), benzoic acids were added followed by the addition of 1 mol% of $Rh_2(esp)_2$ catalyst (Scheme 3). The reactions carried over 18 h afforded, after aqueous workup and chromatographic purification, the anticipated O–H insertion products **7a**,**b** in moderate yields.



5 **6**, 59%

Scheme 2 *Reagents and conditions*: i, MsCl (1.1 equiv.), NaN_3 (1.2 equiv.), H_2O, room temperature, 10 min; ii, K_2CO_3 (0.6 equiv.), H_2O, room temperature, 60 min; iii, K_2CO_3 (1.0 equiv.), H_2O, room temperature, 3 h.



1b,**g** **2b**,**g** **7a**,**b**

a $EWG^1 = EWG^2$ = Ac, Ar = Ph, 38%
b EWG^1 = Bz, EWG^2 = Ac, Ar = 4-FC_6H_4, 22%

Scheme 3 *Reagents and conditions*: i, MsCl (1.1 equiv.), NaN_3 (1.2 equiv.), H_2O, room temperature, 10 min; ii, K_2CO_3 (0.6 equiv.), H_2O, room temperature, 30 min; iii, K_2CO_3 (1.0 equiv.), H_2O, room temperature, 3 h; iv, $Rh_2(esp)_2$ (1 mol%), DCM, room temperature, 18 h.

† *cLogP* values were calculated using Molinspiration property engine v2018.10 at www.molinspiration.com.

In summary, we have modified the known diazo transfer protocol so that potentially explosive mesyl azide is prepared and used *in situ*. Conducting the reaction in aqueous medium will likely reduce the environmental impact of these syntheses, particularly on industrial scale (the volume of the organic solvent employed for product extraction is a less critical factor, compared to the volume of the reaction mixture, and can be substantially limited). The high purities of diazo compounds thus obtained make them suitable for subsequent transformations, with no need for interim chromatographic purification.

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Online Supplementary Materials

Supplementary data associated with this article (experimental procedures, analytical data and copies of ^1H NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2020.05.037.

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