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A Safe and Facile Route to Imidazole-1-sulfonyl Azide as a Diazotransfer Reagent

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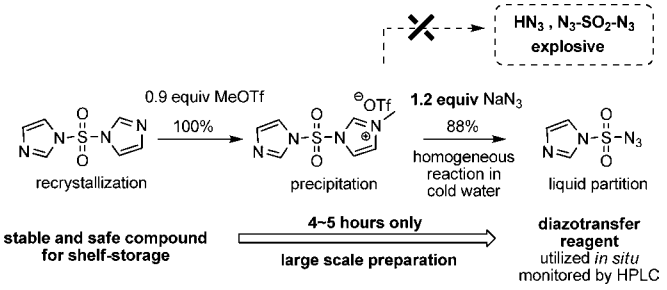
ABSTRACT



A facile approach to the diazotransfer reagent of imidazole-1-sulfonyl azide was reported. The procedure was well optimized to clarify potential explosion risks. A high production yield as well as small batch variation was achieved even without careful pretreatment of reagents and solvents. HPLC and NMR methods to monitor the process were provided. These features made this protocol suitable for large scale preparation in academia and industry as well.

The scientific community has been witnessing a booming era for azide–alkyne Huisgen cycloaddition reactions.[1] Organic azides, which in traditional organic syntheses had mainly been considered as masked amines, became key intermediates for click chemistry in a wealth of recent publications. Accordingly, attention was refocused toward modifying current methodologies to prepare organic azides, including efforts to improve diazotransfer reactions which could convert primary amines into the corresponding azides.[2−7] A key challenge in this area is to develop a safe and facile approach to the synthesis of a highly efficient diazotransfer reagent.

Initially reported in 1972 by Shiner's group[4] and later optimized by Wong's group,[5,6] the TfN_3-driven diazotransfer reaction has been widely applied in academia (Scheme 1).

There are two problems, however, for the preparation of the TfN_3 reagent: a large batch variation in yields[6] and explosive risks.[4] Strategies were proposed to overcome

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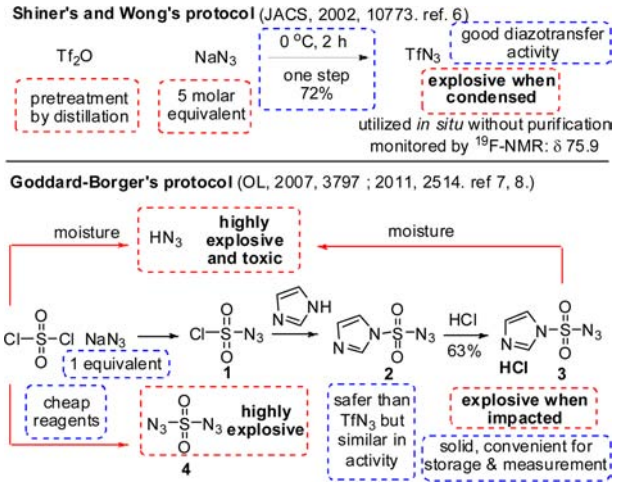
these defects, including fresh distillation of Tf_2O, utilization of greatly excessive NaN_3, and direct employment of the *in situ* generated TfN_3 solution which could be monitored by ^{19}F NMR. Although effective, these inconvenient manipulations actually brought one solution while creating another problem. These inherent defects, particularly the safety concerns, make Wong's protocol rarely employed in scale-up preparations.

Scheme 1. Published Protocols To Prepare Diazotransfer Reagents[a]



[a] Note: the blue and red dashed boxes indicated advantages and disadvantages respectively of the two protocols.

In 2007, Goddard-Borger's group discovered a new diazotransfer reagent, imidazole-1-sulfonyl azide ($Im-SO_2-N_3$, compound **2** in Scheme 1).[7] While maintaining good diazotransfer activity, this new reagent demonstrated a reduced tendency for explosion than TfN_3 and could even be isolated as a solid of the chloride salt. Additionally, structual modifications of compound **2** or its salt have been investigated.[8−10] Listed in Figure 1 are the newly reported

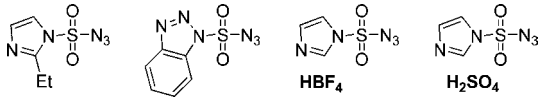
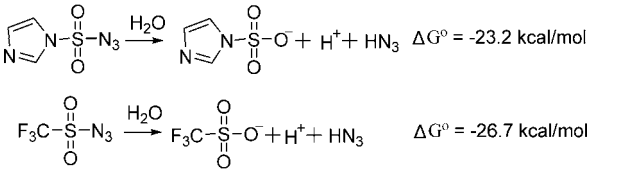


Figure 1. Recently published diazotransfer reagents with improved properties.[8−10]

solid diazotransfer reagents with improved chemical properties or an increased safety threshold. Nevertheless, the synthetic procedures were not optimized, which all engaged compound **1** as a key intermediate. While we followed the published protocol to prepare intermediate **1** at 10 g scale, bubbles of hydrochloride were observed which would react with NaN_3 to generate toxic and explosive hydrazoic acid (HN_3). In fact, complete removal of hydrochloride from sulfonyl chloride is hardly accomplished, especially in a scale-up reaction. Even worse, under almost exactly the same conditions, a recent publication indicated that an extremely explosive molecule, sulfuryl diazide ($N_3-SO_2-N_3$, compound **4**, Scheme 1), could also be generated.[11] These concerns were verified by an errant announcement in 2011.[12] Besides, there is another basic argument: is a reagent containing a sulfonyl azide bond really suitable for long-term shelf storage? As anticipated, our computational analysis (Scheme 2) demonstrated that hydrolysis of the sulfonyl azide bond was greatly favored thermodynamically. Although some sulfonyl azides are nonexplosive and nonhydroscopic (e.g., the last two compounds in Figure 1),[10] these kinetically stable compounds are similar to caged tigers which might be released by unpredictable factors over long-term storage. With all these concerns, an updated protocol is desired to meet the following criteria:

(a) It should avoid the coexistence of NaN_3 with strong acid species.

Scheme 2. Computational Studies on Standard Free Energy Change of Sulfonyl Azide Bond Hydrolysis[a]



[a] Note: Calculations were carried out with the B3LYP method using the Gaussian03 program. Detailed descriptions are provided in the Supporting Information.

(b) It must avoid the employment of excessive NaN_3.

(c) It should avoid the formation of $N_3-SO_2-N_3$.

(d) It must utilize a safe and stable reagent, as the storage compound can be conveniently and efficiently converted into a diazotransfer reagent. Similar to Wong's protocol, the generated diazotransfer reagent should be utilized *in situ*, and a bench accessible monitoring method, which can be routinely performed by most laboratories, should be established.

Under these guidelines, a safe and facile protocol to synthesize diazotransfer reagent **2** was described in this paper (eq 1 in Scheme 3).

To avoid the coexistence of a strong acid with NaN_3, we first attempted using sulfuryl diimidazole (compound **5**) as

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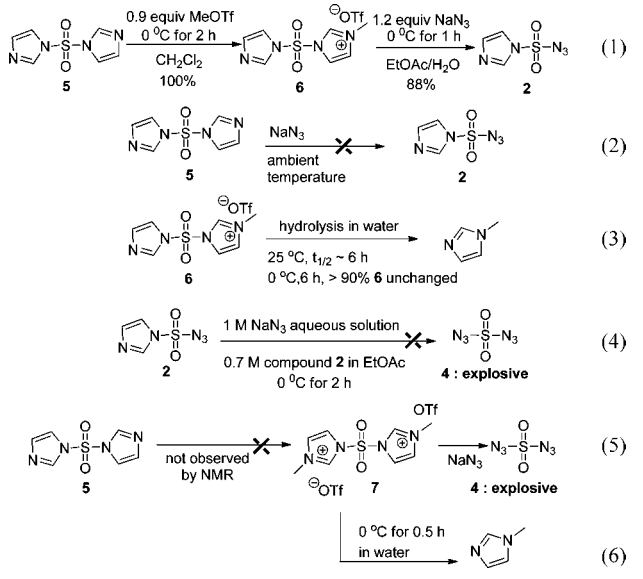
a mild nucleofuge to react with NaN_3 at ambient temperature. However, no reaction was observed under such conditions (eq 2 in Scheme 3). Then, we considered compound **6** as a possibility,[13] as it is a more reactive nucleofuge than **5**. In preliminary experiments, **6** showed high

Scheme 3. Improved Protocol to the Synthesis of Reagent **2**[a]



[a] Note: The second reaction in eq 5 and the reaction in eq 6 were putative results inferred from chemistry knowledge, rather than verified by experiments.

solubility and high stability in cold water (eq 3).[14] We therefore attempted the homogeneous reaction between **6** and NaN_3 in water at 0 °C. Excitingly, the reaction was quickly accomplished within 1 h. During the whole process, the medium is nonacidic, and the employment of largely excessive NaN_3 was unnecessary. Moreover, the product of reagent **2** could almost be completely extracted from the aqueous phase by adding an equal volume of EtOAc solvent. This means, besides providing a high yield via convenient manipulations, this reaction could avoid not only the formation of the explosive HN_3 molecule but also the existence of a large quantity of NaN_3 in reaction waste. Thus, from 0.8 M compound **6** in H_2O, 0.7 M reagent **2** in EtOAc solution was obtained.

Another safety concern for Goddard-Borger's protocol is the generation of explosive compound **4**. Considering the inertness of **5** toward NaN_3 (eq 2), we presumed that reagent **2** should also be reluctant to react with NaN_3. (eq 4) Indeed, under similar conditions used to convert **6** to **2**, NMR analysis indicated that the content of **2** in EtOAc solution did not change after it was stirred with 1 M aqueous NaN_3 solution at 0 °C for 2 h.[15] Then, the only chance to form **4** in our synthetic route is through the formation of a possible dimethylated side product, compound **7** (eq 5). Consistent with previous studies,[13] this possible side product was not detected by NMR in our experiment either. In case a trace amount of intermediate **7** did form, an extra precaution was designed in the second step of eq 1. That is, prior to the addition of NaN_3, the intermediate **6** alone was stirred in cold water for 0.5 h. We already proved that the majority of **6** could survive such a manipulation. We presumed that **7**, if it existed, should have quickly decomposed in cold water due to its high reactivity.

Finally, an HPLC method, utilizing UV detection, was established to quantify the *in situ* generated diazotransfer

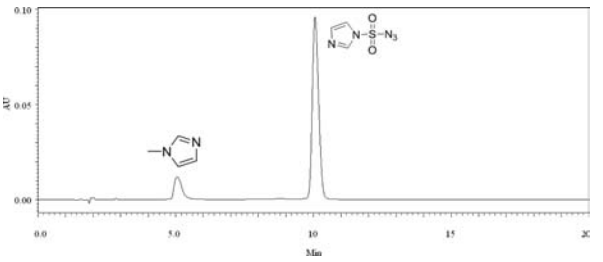
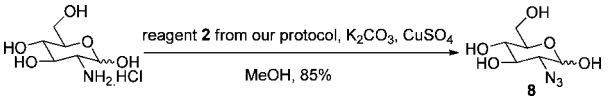


Figure 2. HPLC analysis of in situ generated diazotransfer reagent **2** and the byproduct *N*-methyl imidazole. Detection: UV absorption at 220 nm. Column: Agela Venusil MP C18 (4.6 mm × 250 mm, 5 μm) . Mobile phase: MeOH/H_2O = 37/63. Flow rate: 1 mL/min.

reagent **2** in EtOAc solution (Figure 2). This method was verified by NMR analysis by using isopropyl benzoate as an inert and nonvolatile internal standard.[16] For our two-step protocol (eq 1 in Scheme 3), the yield of reagent **2**, by using compound **5** as the limiting reagent, was consistently around 88% in multiple batches. Unlike Wong's protocol, purification of the key reagent MeOTf proved to be unnecessary to maintian the consistency of yield. When the protocol was scaled up to over the 100 g level, the yield did not dramatically change if the solution in step b was thoroughly stirred. HPLC analysis, as well as the NMR data, indicated the existence of side product *N*-methyl imidazole as a sole impurity in the final EtOAc solution of reagent **2**. We proved that this impurity did not affect the diazotransfer reaction of the glucosamine (Scheme 4) reactant.

Scheme 4. Diazotransfer Reaction of D-Glucosamine Hydrochloride by Utilizing *in Situ* Generated Reagent **2**



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(14) The hydrolysis process was monitored by NMR, and the experimental data were summarized in the Supporting Information. Caution: The final pH value for the second reaction in eq 1 was between 7 to 8, implying unlikely probability for HN_3 formation. Additionally, compound **2** was not detected in the aqueous phase by NMR analysis at the end of the conversion. *Nevertheless, careful disposal of the aqueous waste with NaClO solution, as well as the strict compliance with our optimized protocol, is necessary to avoid the occurrence of an explosion.*

In summary, a facile and safe protocol (eq 1 in Scheme 3) to prepare diazotransfer reagent **2** was introduced. The stable compound sulfuryl diimidazole (**5**), which could be prepared from cheap reagents and purified by crystallization in good yield, was employed as a shelf-storage compound. From this compound, *via* a two-step process, the diazotransfer reagent **2** could be prepared in less than 5 h with a consistently high yield. During the whole process, there was no chromatography purificaiton, no need to carefully purify involved reagents, and little chance to generate explosive HN_3 and $N_3{-}SO_2{-}N_3$ molecules. To the best of our knowledge, it was the first safe preparation of a sulfonyl azide derivative as a diazotransfer reagent at over the 100 g level. It demonstrated the feasibility of our ptotocol to be applied to large scale preparation in both academia and industry.

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Supporting Information Available. Full experimental details, NMR spectra, and HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) For detail experimental procedures, please refer to the Supporting Information.

(16) The NMR method for measuring the yield of reagent 2 was summarized in Supporting Information.

(17) Caution: sulfonyl azides are potentially explosive compounds, and therefore full compliance with our optimized protocol should be strictly held, especially for scale up preparation.

The authors declare no competing financial interest.