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# Polystyrene-Supported Benzenesulfonyl Azide: A Diazo Transfer Reagent That Is Both Efficient and Safe

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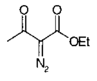
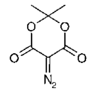
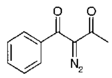
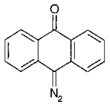
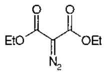
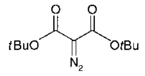
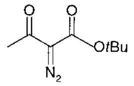
## Introduction

The reaction between an arylsulfonyl azide and a substrate containing an active methylene group is a useful method for the preparation of α-diazo carbonyl compounds.[1] These important intermediates are used in a variety of chemical transformations such as 1,3-dipolar cycloadditions and insertion reactions.[2] Unfortunately, sulfonyl azides are potentially hazardous due to their propensity for explosive decomposition under various reaction conditions. Polymer-supported benzenesulfonyl azide provides a diazo transfer reagent with improved process safety characteristics and thus offers an excellent reactant for laboratory use.

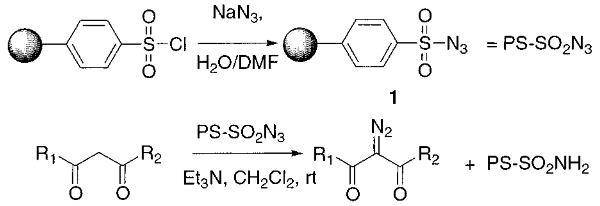
The utilization of polymer-supported reagents, both as delivery and scavenging reagents, is growing in popularity due to the simplicity of use, performance, and ease of product isolation.[3] Although a stable polymer-supported iodine azide has recently been reported for azido-iodination of alkenes,[4] there have been few reports describing a polymer-supported sulfonyl azide for diazo transfer reactions.[5] We reasoned that a polystyrene-supported benzenesulfonyl azide could efficiently deliver a diazo functional group to an activated methylene group with the resulting polystyrene-bound benzenesulfonamide byproduct being removed from the product by filtration with little or no purification necessary. Herein, we report the synthesis of polystyrene-supported benzenesulfonyl azide **1** and its application in the preparation of α-diazo ketones.

**Table 1**

| Entry | Product | PS-SO$_2$N$_3$ % yield[a] | time (h) | p-CBSA % yield[b] | time (h) |
|---|---|---|---|---|---|
| 1 |  | 93.0 | 2.5 | 82.0 | 2.0 |
| 2 |  | 65.0 | 2.5 | 67.0 | 12.0 |
| 3 |  | 98.0 | 4.0 | 93.0 | 16.0 |
| 4 |  | 75.0 | 16.0 | 80.0 | 16.0 |
| 5 |  | 63.0 | 16.0 | 77.0 | 16.0 |
| 6 |  | N.R | 16.0 | N.R | 16.0 |
| 7 |  | 85.3 | 2.5 | 76.0 | 16.0 |

[a] Isolated by flash chromatography. [b] Isolated by RPLC. N.R. = no reaction.[12] Yields are not optimized. PS-SO$_2$N$_3$ = cross-linked polystyrene (1% divinylbenzene) with benzenesulonyl azide attached with a loading of 1.0−1.5 mmol/g. *p*-CBSA = 4-carboxybenzenesulfonyl azide.

**Scheme 1**



## Results and Discussion

The polymer-supported benzenesulfonyl azide resin **1** (Scheme 1) is prepared in one step from commercially available polymer-supported benzenesulfonyl chloride by treatment with sodium azide at room temperature. To compare the efficiency of reagent **1** versus a frequently used solution-phase reagent, comparable diazo transfer reactions were run in solution using 4-carboxybenzenesulfonyl azide (*p*-CBSA).[6] The results of diazo transfer, using **1**, with a variety of substrates, versus that of using *p*-CBSA are presented in Table 1. Polystyrene-supported benzenesulfonyl azide **1** offers the advantage of rapid isolation of the α-diazo product with no aqueous workup and in most cases no need for purification, after filtration from the resin and removal of the solvent. Another advantage of **1** is the comparable and often improved

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(1) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 179−183.

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(4) Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2594−2596.

(5) Previously the Rebek group reported a polymeric tosyl azide prepared on Amberlite XE 305: Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, 1391−1392.

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yields with shorter reaction times versus *p*-CBSA and other reported reagents.[7] It has been noted, with reagents such as *p*-CBSA and 4-acetamidobenzenesulfonyl azide,[7] that the electron-withdrawing effect of the functional group at the 4-position could possibly slow the rate of diazo transfer. The fact that the benzenesulfonyl azide of **1** is attached directly to the carbon backbone of the polystyrene resin circumvents this problem and could explain the shorter reaction times. Products listed in Table 1 using **1** are obtained in a matter of a few hours at room temperature, at which time the starting material is consumed as evidenced by TLC. In most cases where the yields are less than optimum a competing azo coupling of the diazo product and the substrate is observed.[8] Only in the reaction with diethyl and di-*tert*-butyl malonate (entries 5 and 6) was starting material recovered after 16 h.

Another advantage of **1** as a diazo transfer reagent is that the polymer-supported benzenesulfonyl azide is thermally stable and is not friction sensitive, providing a reagent with improved safety characteristics over other available reagents. Examination of the differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) trace of **1** reveals that decomposition occurs within a normal range. The DSC trace shows an initiation temperature of 130 °C with an onset temperature of 165.98 °C. The peak exotherm temperature reaches 192.72 °C with a heat of decomposition of 65.6 cal/g. The maximum rate of energy released due to decomposition is approximately 0.27 cal/sec/g. The results of BAM Friction test[9] indicate that the limiting impact energy for **1** is greater than 360 N. These observations and the fact that the parent benzenesulfonyl azide is not observed to be shock sensitive[10] indicates a favorable safety profile at low concentrations. Reagent **1** also compares favorably to safety data reported on other arylsulfonyl azides.[11]

## Conclusions

In summary, we have detailed a new polystyrene-supported benzenesulfonyl azide reagent **1**. The advantages of this polymer-supported reagent are multifold in nature. First, it is simple to prepare from commercially available materials in a single step. Second, it has reactivity capabilities similar to its solution phase counterpart. Third, it provides the advantage of product isolation by resin filtration thus affording α-diazo carbonyl compounds in good to excellent yields without the necessity of an aqueous workup. Finally, our data suggests that polystyrene-supported benzenesulfonyl azide **1** is a relatively safe alternative to existing azide reagents. However, due to the toxicity and potentially explosive nature of diazo alkanes proper caution should be used when using this and any other azide reagents.

## Experimental Section

**General Considerations.** The solution-phase reactions were performed in glassware under an inert atmosphere of dry nitrogen and were magnetically stirred. All reagents, solvents, and anhydrous solvents were used directly as obtained from commercial sources. Radial preparative-layer chromotagraphy (RPLC) was performed on a Chromatotron using coated glass plates with 2 mm or 4 mm thickness of silica gel. Melting points were taken on a capillary melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively. The FTIR spectra of **1** was obtained using a diamond anvil. Reactions using reagent **1** were performed in a 5.0 mL disposable polypropylene/polyethylene syringe fitted with a polyethylene frit (cut to size with a cork borer from linear porous sheets, 70 $\mu$m, 3.2 pore size). Disposal of azide containing material was done in accordance with safe laboratory procedures.[13]

The polymer-supported benzenesulfonyl azide resin **1** was prepared in one step from polymer-supported benzenesulfonyl chloride[14] (100−200 mesh, 1.5−2.0 mmol/g). Typically, 1.5 mmol of resin was swollen in DMF and then treated with 3.0 mmol of $NaN_3$ dissolved in $H_2O$ (1.0 mL) and diluted with DMF (7 mL). After 16 h, the resin was washed with $H_2O$ (5 × 5 mL), DMF (5 × 5 mL), and finally with $CH_2Cl_2$ (3 × 5 mL) and dried under vacuum at 40 °C. The loading of the resin **1** was determined to be 1.0−1.5 mmol/g by combustion analysis between two different batches. The resin was stored at room temperature and appears to be stable at room temperature over an indefinite period of time. FTIR of the resin showed a strong band for the $N_3$ at 2130 cm$^{-1}$.

**General Procedure for Diazo Transfer Using Polystyrene-Supported Benzenesulfonyl Azide 1: 2-Diazo-1-phenyl-butane-1,3-dione (Entry 3).** Polystyrene benzenesulfonyl azide **1** (500 mg, 0.75 mmol) was placed in a 5.0 mL disposable polypropylene/polyethylene syringe and swollen with $CH_2Cl_2$. A mixture of 1-benzoylacetone (81.0 mg, 0.5 mmol) and $Et_3N$ (0.21 mL, 1.5 mmol) in $CH_2Cl_2$ (2.0 mL) was drawn into the syringe containing the resin, placed on a LabQuake shaker, and rotated at room temperature. The reaction progress was monitored by TLC (1:1 $Et_2O$/heptane). After 4 h, the supernatant was collected, and the resin was washed with $CH_2Cl_2$ (3 × 5 mL). The washes were combined with the supernatant and concentrated to give a pale yellow solid that was reasonably pure by NMR. For the purpose of complete characterization, the solid was dissolved in a minimum volume of $CH_2Cl_2$ and passed through a short column of $SiO_2$ eluting with 3:1 heptane/$EtO_2$. Concentration of eluent provided an ivory solid (92.0 mg, 98%): mp 60−61 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.60−7.40 (m, 5H), 2.51 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 191.0, 185.3, 137.7, 132.9, 129.2, 127.6, 29.3; IR (thin film) 3020, 2121, 1648 cm$^{-1}$. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.28; N, 14.89. Found: C, 63.94; H, 4.19; N, 15.00.

**General Procedure for Diazo Transfer Using *p*-CBSA: 5-Diazo-2,2-dimethyl[1,3]dioxane-4,6-dione[7] (Entry 2).** To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (144 mg, 1.0 mmol) and $Et_3N$ (0.4 mL, 3.0 mmol) in $CH_2Cl_2$ (10 mL) at room temperature was added 4-carboxybenzenesulfonyl azide (*p*-CBSA, 250 mg, 1.1 mmol). The reaction mixture was stirred at room temperature and monitored by TLC (1:1 $Et_2O$/heptane). After 16 h, the reaction was diluted with $CH_2Cl_2$, washed sequentially with $H_2O$ (2 × 10 mL), saturated aqueous $NaHCO_3$

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[8] Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733.

[9] Friction sensitivity (BAM friction test) was performed by Chilworth Technology, Inc. Princeton, NJ. For comparison of safety friction data see: Balabanov, G. P.; Dergunov, Y. I. *Zh. Prikl. Khim.* (Leningrad), **1968**, *41*, 2578−80 (Russ.).

[10] In *Bretherick's Handbook of Reactive Chemical Hazards*, 5th ed.; Urben, P. G., Ed.; Butterworth-Heinemann Ltd.: Oxford, 1995; Vol. 1, p 752.

[11] Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *Synth. Commun.* **1981**, *11*, 947−956.

[12] Ledon, H. J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 414−417.

[13] In *Prudent Practices for Disposal of Chemicals from Laboratories*; National Research Council, Committee on Hazardous Substances in the Laboratory; National Academy Press: Washington, DC, 1983; pp 87−88.

[14] Personal communication with Mr. Michael McNello, a technical expert at Aldrich. Polystyrene benzenesulfonyl chloride is prepared by the treatment of 1% DVB cross-linked polystyrene resin with fuming sulfuric acid. The resulting benzenesulfonic acid resin is then treated with thionyl chloride in DMF to provide the corresponding sulfonyl chloride resin with a loading of 1.5−2.0 mmol/g. Loading can be determined by reacting the benzenesulfonyl chloride resin with 1,3-propanediamine followed by coupling with Fmoc-gly. Upon treatment with 50% piperidine/DMF, Fmoc release is quantified by measuring absorbance of the combined washes at 302 nm spectrophotometrically.[15]

[15] Zhong, H. M.; Greco, M. N.; Maryanoff, B. E. *J. Org. Chem.* **1997**, *62*, 9326−9330.

(2 × 10 mL), brine (2 × 10 mL), and dried ($MgSO_4$). Filtration and evaporation provided an orange oil (125 mg, 110%). Purification by RPLC ($CH_2Cl_2$) afforded a white solid (114 mg, 67%); mp 92−93 °C; IR (thin film) 3020, 2168, 1724 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.80 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.2, 107.3, 27.0. Anal. Calcd for $C_6H_6NO_4$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.24; H, 3.44; N, 16.50.

**2-Diazo-3-oxobutyric acid ethyl ester[7] (entry 1):** yellow liquid (128 mg, 82%); IR (neat) 3021, 2986, 2142, 1716, 1654 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.31 (q, 2H, $J = 7.0$ Hz), 2.48 (s, 3H), 1.34 (t, 3H, $J = 7.0$ Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 190.4, 161.7, 61.6, 28.4, 14.5. Anal. Calcd for $C_8H_{12}N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.35; H, 5.12; N, 17.72.

**10-Diazo-10*H*-anthracen-9-one[11] (entry 4):** yellow solid (165 mg, 80%); mp 169 °C dec; IR (thin film) 3020, 2059, 1639 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.61 (m, 2H), 7.73 (m, 2H), 7.30−7.12 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCL_3$) $\delta$ 180.2, 133.4, 129.9, 129.2, 128.6, 125.5, 120.9. Anal. Calcd for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.21; H, 3.49; N, 12.60.

**2-Diazomalonic acid diethyl ester (entry 5):** yellow liquid (140 mg, 77%); IR (neat) 3021, 2985, 2142, 1750, 1731, 1686 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 4.31 (q, 4H, $J = 7.0$ Hz), 1.32 (t, 6H, $J = 7.0$ Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 161.3, 61.8, 14.51. Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05. Found: C, 45.21; H, 5.34; N, 15.32.

**2-Diazo-3-oxobutyric acid *tert*-butyl ester[1] (entry 7):** yellow liquid (142 mg, 76%); IR (neat) 3020, 2139, 1708, 1650 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.46 (s, 3H), 1.53 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 191.1, 161.3, 82.7, 28.1. Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 52.30; H, 6.45; N, 15.28.

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**Supporting Information Available:** $^1H$ NMR and $^{13}C$ NMR spectra for compounds **1**−**7**, FTIR, DSC, and TGA traces of the polystyrene-supported benzenesulfonyl azide reagent **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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