



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

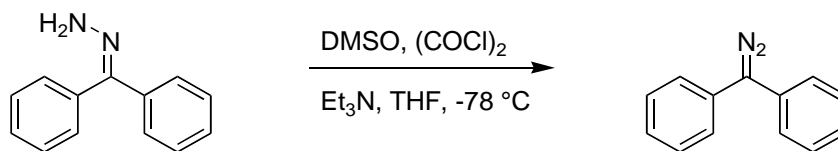
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DIPHENYLDIAZOMETHANE



Submitted by Muhammad I. Javed and Matthias Brewer.¹

Checked by Jonathan A. Ellman and Andy S. Tsai.

1. Procedure

Caution! Diazo compounds are toxic, irritating, and many compounds are explosive. Care should be taken when handling diazo compounds to limit personal exposure. It is prudent to handle diazo compounds behind a blast shield.

A 1-L, three-necked round-bottom flask is equipped with two rubber septa and an overhead mechanical stirrer fitted with a 9.5 x 2 cm rounded Teflon blade (Note 1). The flask is flame dried under a stream of nitrogen which is introduced and vented through the septa *via* 16 gauge needles. The exhaust septum is replaced with a thermometer adapter equipped with a low-temperature alcohol-based thermometer. The flask is charged with dimethyl sulfoxide (3.98 mL, 4.38 g, 56.0 mmol, 1.10 equiv) (Note 2) and anhydrous tetrahydrofuran (450 mL) *via* syringe (Note 3), and the solution is cooled to $-55\text{ }^{\circ}\text{C}$ (Notes 4 and 5) under a positive pressure of nitrogen with stirring. In a separate 100-mL, oven-dried, round-bottom flask is combined oxalyl chloride (4.67 mL, 6.79 g, 53.5 mmol, 1.05 equiv) (Note 6) and tetrahydrofuran (50 mL) *via* syringe. This solution is then added to the mixture over 10 min *via* cannula (Note 7), and the solution is maintained between $-55\text{ }^{\circ}\text{C}$ and $-50\text{ }^{\circ}\text{C}$ for 35 min. The reaction mixture is then cooled to $-78\text{ }^{\circ}\text{C}$ with the aid of a dry-ice acetone bath. To a separate 100-mL, oven-dried, round-bottomed flask is added benzophenone hydrazone (10.00 g, 51.0 mmol, 1.00 equiv) (Note 8) and triethylamine (15.05 mL, 10.84 g, 0.107 mol, 2.10 equiv) (Note 9) and tetrahydrofuran (50 mL). This solution is added to the reaction solution over 10 min *via* cannula (Note 10) to

provide a deep-red solution containing a copious white precipitate. The reaction mixture is maintained at $-78\text{ }^{\circ}\text{C}$ for 30 min, and is then filtered while cold through a medium porosity sintered-glass funnel (Note 11) into a 2-L, round-bottom flask and the solid (Note 12) is rinsed with two 100-mL portions of tetrahydrofuran. The filtrate is concentrated at room temperature by rotary evaporation (15 mmHg) and then at 1.5 mmHg to provide diphenyldiazomethane (9.83 g, 99%) as a red oil that solidifies upon cooling (Note 13). The product is dissolved in pentane (120 mL) (Note 14), the solution is rapidly filtered through activated basic alumina (100 g) (Notes 15 and 16) supported in a medium porosity sintered glass funnel (Note 17) and the solids are rinsed with pentane (~300 mL) until the filtrate is colorless. The filtrate is concentrated at room temperature by rotary evaporation (15 mmHg) and then at 1.5 mmHg to provide diphenyldiazomethane (9.19 g, 93%) as an analytically-pure red crystalline solid (Notes 18 and 19).

2. Notes

1. When this procedure is run on smaller scale a Teflon-coated magnetic stirring bar can be used in place of the overhead mechanical stirrer.

2. Dimethyl sulfoxide was purchased from Acros and was dried over molecular sieves (<50 ppm H_2O).

3. Tetrahydrofuran was purified by passage through activated alumina using a GlassContour solvent purification system.²

4. The temperature was achieved and maintained by adding small pieces of dry-ice to an acetone bath.

5. The dimethyl sulfoxide must be dissolved prior to cooling; it freezes as a nearly insoluble mass on contact with precooled tetrahydrofuran.

6. Oxalyl chloride (98%) was purchased from Acros and was freshly distilled before use.

7. The internal temperature rose to $-50\text{ }^{\circ}\text{C}$ during this addition.

8. Benzophenone hydrazone was purchased from Acros and was purified by recrystallization from absolute ethanol before use. A 40 g sample of hydrazone was dissolved in 100 mL of boiling absolute ethanol. The solution was allowed to return to room temperature and then was cooled to $-20\text{ }^{\circ}\text{C}$ for 30 min. The precipitate was filtered through a 150-mL, medium-porosity, sintered-glass funnel and was washed with 30 mL of cold ($0\text{ }^{\circ}\text{C}$) absolute ethanol. The recovered solid was dried under 1.5 mmHg vacuum for 12 h to return 34.7 g of pure, crystalline material.

9. Triethylamine was purchased from Acros and was freshly distilled from calcium hydride before use.
10. The internal temperature rose to $-63\text{ }^{\circ}\text{C}$ during this addition.
11. The funnel used was a 600-mL medium-porosity sintered-glass funnel purchased from Chemglass. The glass frit was 9.5 cm in diameter.
12. The white solid is triethylamine hydrochloride.
13. This material is approximately 95% pure based on ^1H NMR spectroscopy. Trace quantities of DMSO, unreacted hydrazone and benzophenone azine are observed.
14. Pentane of 98% or greater purity was purchased from Fisher Scientific and was used as received.
15. The submitters purchased activated Brockman Activity I basic alumina (50–200 micron) from Acros, which was used as received. The checkers purchased activated alumina, Brockman Activity I (60–325 mesh) from Fischer Scientific, which was used as received.
16. The filtration should be done such that the material is on the alumina column for no more than 5 min. When diphenyldiazomethane was allowed to remain in contact with the basic alumina, small quantities of an impurity were noted in the recovered product. GC and proton NMR analysis indicate that this impurity is tetraphenylethylene.
17. The funnel used was a 150-mL medium-porosity sintered-glass funnel purchased from Chemglass. The glass frit was 6 cm in diameter and the alumina bed had a height of 3 cm when contained in the funnel.
18. The product displays the following physicochemical properties: mp $29\text{--}31\text{ }^{\circ}\text{C}$; ^1H NMR (500 MHz, CDCl_3) δ : 7.42 (app t, $J = 7.68\text{ Hz}$, 4H), 7.38–7.31 (m, 4H), 7.22 (app t, $J = 7.33\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 129.53, 129.12, 125.60, 125.16, 62.58; IR (film) cm^{-1} : 2032, 1591, 1491, 1261, 745, 689. Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.25; H, 5.21; N, 14.16.
19. Diphenyldiazomethane decomposes on standing.⁶ To obtain acceptable elemental analysis results, freshly purified diphenyldiazomethane was shipped overnight at dry-ice temperature.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The preparation of diazo compounds is often achieved by the dehydrogenation of hydrazones.³⁻⁵ Reagents that effect this transformation include mercury(II) oxide,⁶ lead(IV) acetate,⁷ manganese dioxide,⁸ chromium(IV) oxide,⁹ silver oxide,⁸ nickel peroxide,¹⁰ bis(acetylacetonato)-copper(II),¹¹ oxone,¹² metal hypochlorites,¹³ barium manganate,¹⁴ peracetic acid,¹⁵ hypervalent organoiodo compounds,^{16,17} and a cobalt Schiff base complex.¹⁸ However, many of these reagents are hazardous and environmentally deleterious, and product yields often suffer due to reaction-byproduct induced decomposition of the diazo species. Additionally, the isolation and purification of the diazo product from the reaction mixture can be problematic and often involves potentially hazardous manipulation of the diazo solution, or substantial product loss during purification.

The procedure presented here¹⁹ is a simple, convenient and high-yielding method to prepare and purify diphenyldiazomethane. This procedure, which uses chlorodimethylsulfonium chloride²⁰ to dehydrogenate benzophenone hydrazone, is advantageous to other routes because it does not rely on the use of environmentally-deleterious heavy-metal salts. The reaction between benzophenone hydrazone and chlorodimethylsulfonium chloride is highly efficient, and the crude product isolated from this procedure contains nearly-pure diphenyldiazomethane contaminated with trace quantities of DMSO, unreacted hydrazone, and benzophenone azine. The product is conveniently purified by simply dissolving the crude mixture in pentane and filtering the solution through a pad of basic alumina to provide analytically pure diphenyldiazomethane in 93% yield. This purification is simpler, and in our hands provides better product recovery, than recrystallization from petroleum ether.⁶

The dehydrogenation of hydrazones with chlorodimethylsulfonium chloride has also been used to prepare solutions of the resonance-stabilized diazo compounds shown in Table 1.¹⁹ Due to the higher reactivity and the potential of these diazo species to explode, no attempts were made to isolate or purify them beyond the initial low-temperature filtration to remove triethylamine hydrochloride; the yields presented Table 1 were determined by nitrogen gas evolution measurements.

Table 1: Preparation of other diazo compounds via chlorodimethylsulfonium chloride mediated hydrazone dehydrogenation.¹⁹

$\text{R}-\text{C}(\text{R}')=\text{N}-\text{NH}_2 \xrightarrow[\text{ii) Filtration}]{\text{i) Me}_2\text{SCl}_2, \text{Et}_3\text{N}, \text{THF}, -78^\circ\text{C}}$		
hydrazone	diazo	N ₂ evolved
		97
		87
		88
		97 *
		51
		5 - 42

* Isolated yield

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Diphenyldiazomethane (883-40-9)

Benzophenone hydrazone (5350-57-2)

Dimethyl sulfoxide: Methyl sulfoxide; Methane, sulfinybis-; (67-68-5)

Oxalyl chloride: HIGHLY TOXIC; Ethanedioyl dichloride; (79-37-8)

Triethylamine; Ethanamine, *N,N*-diethyl-; (121-44-8)



Matthias Brewer was born in 1974 and was raised in Holliston, Massachusetts. He received his undergraduate education at the University of Vermont where he carried out research with Professor A. Paul Krapcho. He received his Ph.D. in 2002 from the University of Wisconsin-Madison where he worked with Professor D. H. Rich on the synthesis of botulinum neurotoxin metalloproteinase inhibitors. Following an NIH Postdoctoral Fellowship with Professor L. E. Overman, he joined the faculty at the University of Vermont in 2005. His research interests include the development of new synthetic methods, the synthesis of natural products, and the synthesis of biologically active compounds.



Muhammad Irfan Javed received a B.S. in Applied Chemistry in 1998 from the University of Engineering & Technology, Lahore, Pakistan under the supervision of Dr. Inam-ul-Haque. He completed his M.S. in Chemistry in 2001 with Dr. T. K. Vinod at Western Illinois University, Illinois before joining Dr. Gregory Friestad's research group at the University of Vermont in 2003. Upon Dr. Friestad's move to the University of Iowa in 2005, Javed opted to remain at the University of Vermont and subsequently joined Dr. Matthias Brewer's research group. His research interests include the development of synthetic methods and green chemistry research.



Andy Tsai was born in Fujian, China in 1984 and immigrated to the United States in 1989. He obtained his undergraduate degree at the University of Michigan where he worked under Professor Richard Laine on functionalized silsesquioxanes. He is currently in the laboratories of Professors Jonathan A. Ellman and Robert G. Bergman pursuing a doctorate in chemistry.


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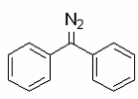
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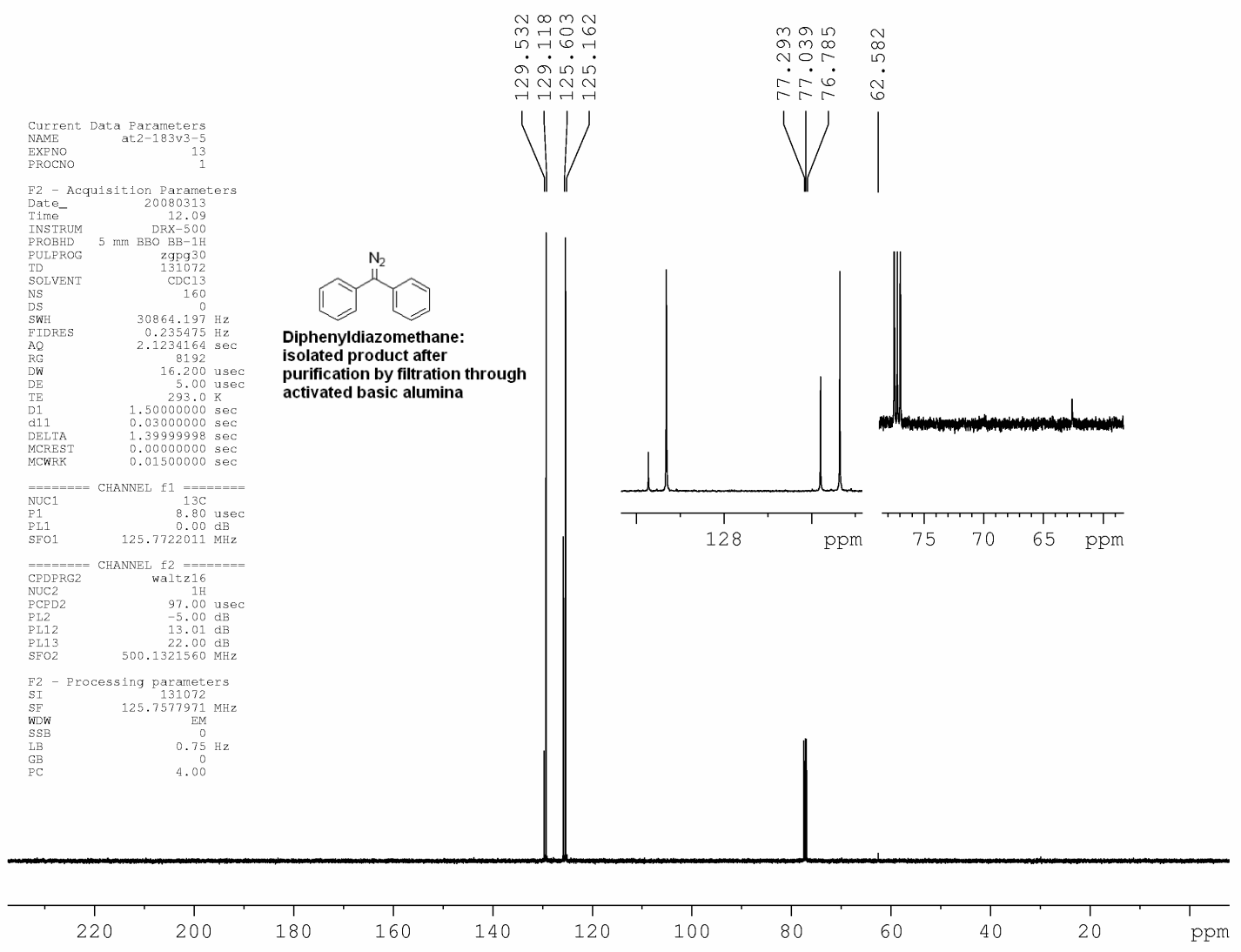
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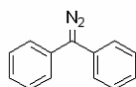


**Diphenyldiazomethane:
isolated product after
purification by filtration through
activated basic alumina**



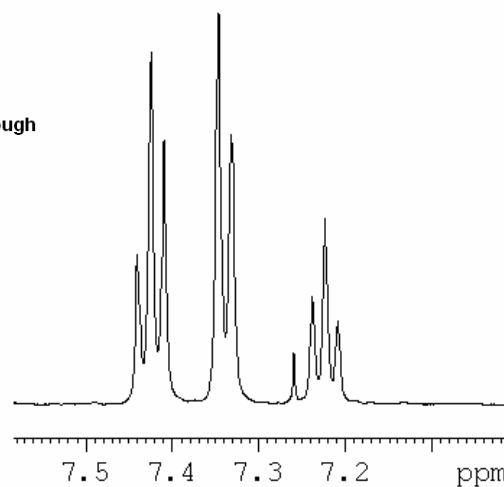
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DRX-500 zBBO probe

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7.347
7.332
7.260
7.239
7.224
7.209



Diphenyldiazomethane:
isolated product after
purification by filtration through
activated basic alumina

7.441
7.424
7.410
7.347
7.332
7.260
7.239
7.224
7.209



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