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LETTERS

# Conversions of hydrazones to diazo compounds by *n*-butyllithium and azidotris(diethylamino)phosphonium bromide

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**Abstract**—Lithium hydrazonides, prepared by reactions of hydrazones with *n*-BuLi/hexane in THF at −78°C, are converted by azidotris(diethylamino)phosphonium bromide in THF at ~0°C efficiently, rapidly, and safely to their corresponding diazo compounds along with tris(diethylamino)phosphorimine, nitrogen, and lithium bromide. © 2002 Elsevier Science Ltd. All rights reserved.

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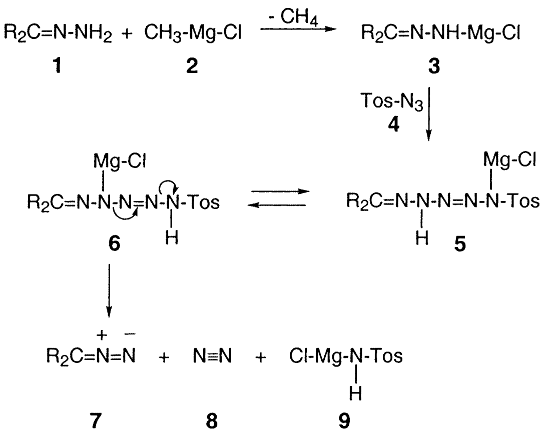
Oxidation of hydrazones is a primary method for synthesis of diazo compounds.[1] Established reagents for such oxidations are mercury(II) oxide, silver(I) oxide, manganese dioxide, and nickel peroxide.[1] Lesser-known oxidants are lead tetraacetate, iodine/triethylamine, phenyliodine(III) diacetate, phenyldipyridinioiodine(III) bis(trifluoromethanesulfonate), barium manganate, mercury(II) acetamide, mercury(II) trifluoroacetate, triphenylbismuth carbonate, sodium and calcium hypochlorites, chlorine dioxide, *N*-bromosuccinimide, potassium ferricyanide, hydrogen peroxide, peracetic acid, oxygen, and *N*,*N*-bis(trifluoromethyl)aminoxyl radicals.[1] The above oxidants are often ineffective for preparing non-stabilized diazo compounds, the procedures usually can only be used safely on a small-scale, separation, isolation, and storage of the diazo products may be difficult, and environmental problems in disposal of the co-products are severe.[1] Improvements in synthesis of unstable diazo compounds have been made by oxidation of hydrazones with lead tetraacetate in tetramethylguanidine/dimethylformamide at −78°C.[1d]

Of significance also with respect to the above preparative methods is that hydrazones (**1**) have been converted by methylmagnesium chloride (**2**, Scheme 1) to chloromagnesium hydrazonides (**3**) which, upon reaction with tosyl azide (**4**) followed by aqueous workup, give stabilized diazo compounds (**7**).[2] Diphenyldiazomethane (50%), 1-diazo-1-phenylethane (35%), and benzoyl(phenyl)diazomethane have been obtained in moderate yields by the above methodology.[2] Further, lithium 9-fluorenone hydrazonide, as prepared from fluorenone hydrazone and methyllithium, and **4** yield 9-diazofluorene (70%).[2] Now reported is that lithium hydrazonides (**11**) react rapidly with azidotris(diethylamino)phosphonium bromide (**12**, Scheme 2)[3] at 0°C to give diazo compounds (**7**) efficiently along with tris(diethylamino)phosphorimine (**15**) and nitrogen (**8**). The overall methodology (Scheme 2) is excellent for converting hydrazones (**11**) of various types[4] to their corresponding diazo compounds (**7**). Azidophosphonium bromide **12** is a readily prepared, safe, diazo transfer reagent known to convert 1,3-dicarbonyl compounds to diazo derivatives (**7**) efficiently.[3]

Hydrazones (**1**) are obtained simply and in high yields from aldehydes and ketones upon use of excess hydrazine and proper methodology.[1d,4] Preparation of hydrazonides **11** by addition of hydrazones **1** in THF to



**Scheme 1.**

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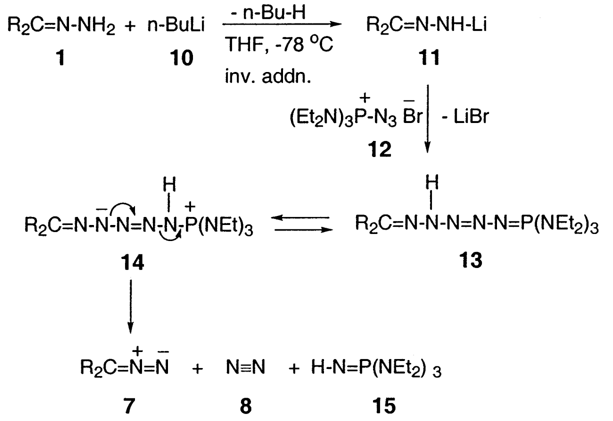
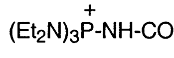


**Scheme 2.**

*n*-BuLi/hexane in THF at −78°C is near-instantaneous and essentially quantitative. To effect the present oxidations of hydrazonides **11** to **7**, an equivalent of azidophosphonium bromide **12** in THF is added to the **11** in THF and hexane at ~0°C. Although not needed for synthesis, the yield and the overall rate of formation of a diazo compound (**7**) can be easily determined upon measuring the nitrogen liberated (Scheme 2). A reaction sequence for the present conversions of **1** to **7** is shown in Scheme 2. In theory the highly basic co-product, tris(diethylamino)phosphorimine (**15**), could make the overall conversions of **1** by **12** catalytic in base.[3b,5] In practice however the base-catalyzed reactions of **1** and **12** by **15** are slow. An important aspect of the present methodology is that the diazo compounds (**7**) produced are protected by **15** (a strong base)[5] which can be easily removed by extraction with aqueous ethylene glycol at −15°C. The traces of **15** remaining in the product are precipitated as phosphorimino carbonate **16** by treatment of the organic extract with $CO_2$ (dry ice).



$$(Et_2N)_3\overset{+}{P}\text{-NH-}CO_2^-$$

**16**

The diazo compounds (**7**) presently prepared (Scheme 2) from their corresponding hydrazones (**1**) are 1-diazo-1-phenylethane, 1-diazotetralin, phenyl(2-propyl)diazomethane, 1-diazoindane, 2-diazo-3,3-dimethylbutane, 1-diazo-2-ethylbutane, 2-diazocamphane, and 1-diazononane as summarized in Table 1. A typical procedure for the present preparations of **7** is given in Ref. 6. Good yields (90–57%) are obtained for all of the diazo compounds (**7**) presently synthesized and the methodology has advantages over traditional oxidation procedures for preparing unstable diazo compounds.[1] Of interest now are whether sodium hydrazonides ($R_2C$=N-NHNa) and azidotris(dimethylamino)phosphonium halides $[N_3P^+(NMe_2)_3X^-$, $X^-=Cl^-$ and $Br^-]$[7] yield diazo compounds (**7**) more cheaply and whether hydrazonide/azidophosphonium halide oxidation–reduction methodologies allow effective syntheses of various *N*-azidimines ($R_2C$=N-$N_3$)[2] and polydiazo compounds.

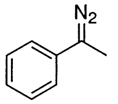
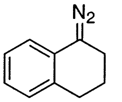
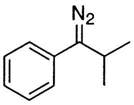
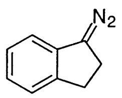
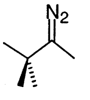
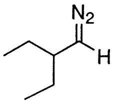
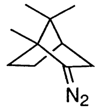
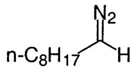
## Acknowledgements

The National Cancer Institute and the Department of Education are thanked for support of this study.

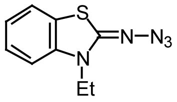
## References

1. (a) For a comprehensive review and references of the above reagents for oxidations of hydrazones (**1**) to diazo compounds (**7**), see: (b) Regitz, M.; Maas, G. *Diazo Compounds*: *Properties and Synthesis*; Academic Press: Orlando, FL, 1986; Chapter 8, pp. 233–256; (c) Bösh, M.; Fink, J.; Heydt, H.; Wagner, O.; Regitz, M. *Methoden Der Organischen Chemie* (*Houben–Weyl*), Vol. E14B; Klaman, D.; Hagemann, H.; Eds.; Georg Thieme Verlag: New York, 1990; pp. 996–1010; and (d) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725.
2. (a) Fischer, W.; Anselme, J.-P. *Tetrahedron Lett.* **1968**, *9*, 877; (b) Anselme, J.-P.; Fischer, W. *Tetrahedron* **1969**, *25*, 855; (c) Of interest also in the experiments in Refs. 2a,b is

**Table 1.** Diazo compounds (**7**) prepared from hydrazonides **11** and **12**

| Diazo Compound 7 |  |  |  |  |
|---|---|---|---|---|
| % Formed[a] | 85 ± 2 (4)[b] | 86 ± 5 (10)[b] | 78 ± 2 (4)[b] | 60 ± 2 (2)[b] |
| % Isolated[c] | 67 ± 11 (3)[b] | 90 ± 4 (5)[b] | 78 ± 2 (4)[b] | 53 (1)[b] |
| Diazo Compound 7 |  |  |  |  |
| % Formed[a] | 57± 3 (3)[b] | 77 (1)[b] | 74 ± 3 (4)[b] | 81 (1)[b] |
| % Isolated[c] | 46 ± 7 (2)[b] | 77 (1)[b] | 73 ± 4 (4)[b] | 58 (1)[b] |

that *N*-azidimines ($R_2C{=}N\text{-}N_3$) were not detected; (d) Synthesis and the chemistry of *N*-azidimines such as 3-ethyl-2-tetrazobenzothiazoline (**A**) are reported by (e) Balli, H.; Kersting, F. *Ann.* **1963**, 107; (f) Balli, H. *Angew. Chem., Int. Ed. Engl.* **1964**, *43*, 803; and (g) Balli, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 132; (h) Preparation and the behavior of other *N*-azidimines are being studied in this laboratory.



**A**

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3. (a) Azidophosphonium bromide **12** is prepared (80% yield) by reaction of $PCl_3$ and excess $Et_2NH$, bromination ($Br_2$/THF) of the $(Et_2N)_3P$ obtained, and displacement of the resulting $(Et_2N)_3P^+BrBr^-$ with $NaN_3$ in THF/18-Cr-6;[3b,c] (b) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 4987; (c) Azido bromide **12** has been found to be a very safe reagent.[3b]
4. (a) For discussion, details, and references for preparing various hydrazones (**1**), see: (b) Dumic, M.; Koruncev, D.; Koracevic, K.; Polak, L.; Kolbah, D. *Methoden Der Organischen Chemie* (*Houben–Weyl*), Vol. E14B; Klaman, D.; Hagemann, H.; Eds.; Georg Thieme Verlag: New York, 1990; pp. 434–712; and (c) Ref. 1d.
5. (a) Decomposition of diazo compounds is catalyzed by acids. In oxidation of hydrazones by lead tetraacetate the acetic acid formed frequently decomposes the diazo products.[1d] Similar complications usually occur with other oxidants.[1d] Such oxidations are usually greatly improved upon using bases such as pyridine, triethylamine, and, in particular, tetramethylguanidine to neutralize the acidic co-product. Phosphorimine **15** and its analogs $(R_2N)_3P{=}NR$ are much stronger bases than the previous bases cited and thus are expected to protect various sensitive diazo compounds from acid-catalyzed reactions.[5b] (b) Schwesinger, R. *Chimia* **1985**, *39*, 269.
6. *General procedure for conversion of hydrazones (**1**) to diazo compounds (**7**).* A solution of *n*-BuLi (7.5 mmol) in hexane is added to dry THF (50 mL) at −78°C under argon. Hydrazone **1** (7.5 mmol) in dry THF (25 mL) is added dropwise. The resulting mixture is warmed to 0°C. The reaction flask is connected to a gas-measuring cylinder and equilibrated at 0°C. A solution of azidophosphonium bromide **12** (8.0 mmol) in cold, dry THF (25 mL) is added dropwise. When nitrogen evolution ceases, the reaction mixture is diluted with pentane (100 mL) cooled to −78°C. The resulting solution is extracted with 25% aqueous ethylene glycol (5×50 mL) cooled to ca. −15°C. The pentane phase is then poured carefully over dry ice ($CO_2$) and allowed to stand in the dark for 15 min. The cold solution is filtered to remove the small amounts of carbonate **16** giving a solution of the diazo compound (**7**) in pentane/THF (ca. 4:1). The diazo compound (**7**) can be used conveniently in solution or isolated upon removal of the solvents at reduced pressures.
7. Azidotris(dimethylamino)phosphonium bromide $[N_3P^+(NMe_2)_3, Br^-]$ is readily obtained from $(Me_2N)_3P$ by extension of the methodology developed for bromide **12**.[3a,b]