

AZIDOTRIS(DIETHYLAMINO)PHOSPHONIUM BROMIDE: A SELF-CATALYZING DIAZO TRANSFER REAGENT

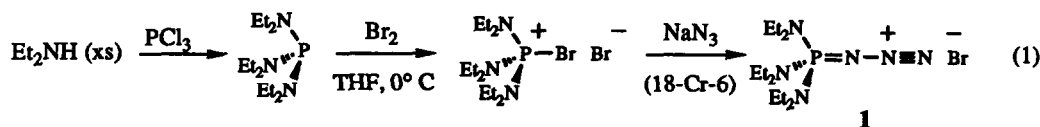
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Abstract: Acidic methylene compounds are conveniently converted to diazo compounds in high yields by azidotris(diethylamino)phosphonium bromide, **1**, in diethyl ether using only a catalytic amount of base. The product diazo compounds are easily separated from the co-product hexaethylphosphorimidic triamide hydrobromide.

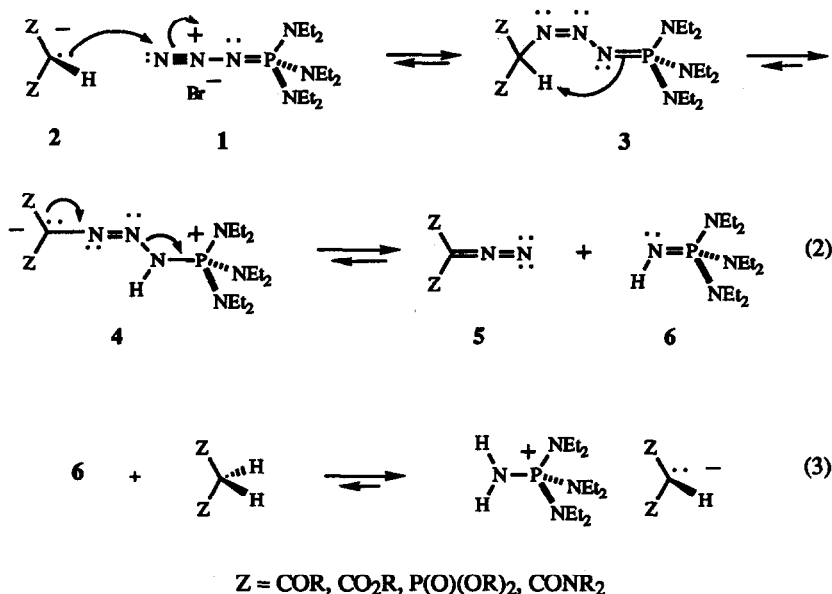
Diazo transfer reactions have almost completely supplanted other methodologies for preparing stable diazo compounds, especially those in which the diazo function is flanked by two electron-withdrawing groups. Reagents such as tosyl azide¹, 2-azido-3-ethylbenzthiazolium tetrafluoroborate (Balli's reagent)^{1c,2}, polymer-bound tosyl azide³, 4-carboxybenzenesulfonyl azide⁴, and N,N-dimethylazidochloromethyleniminium chloride⁵ are now routinely used to prepare diazo compounds from 1,3-dicarbonyl compounds. These established reagents have drawbacks in that undesirable side reactions such as ester amidation,⁶ azo coupling,⁷ or azide formation⁸ can compete with the diazo transfer reaction, a single set of reaction conditions is not generally applicable to all 1,3-dicarbonyls,⁹ some of the reagents are explosive,¹⁰ and most importantly, diazo transfer appears to be ultimately limited by the requirement that the methylene hydrogens of the substrate be sufficiently acidic.

With these considerations in mind, an investigation of the utility of azidophosphonium salts as diazo transfer reagents has been undertaken. Our initial efforts in this area focus on the reactions of azidotris(diethylamino)phosphonium bromide (**1**, Eq. 1) with 1,3-dicarbonyl compounds. Reagent **1** is a hygroscopic, colorless, crystalline solid which is preparable in high yield from inexpensive starting materials (Eq. 1) and stored indefinitely under vacuum. Azide **1** is an exceptionally safe diazo transfer reagent: we have been unable to initiate a detonation of **1** by shock, friction, rapid heating, or even flame.



The overall diazo transfer process proceeds stepwise via three reactions (Eq. 2 and 3): first, attack of the carbanion, **2**, on the terminal nitrogen of **1**; second, proton transfer from the methylene carbon of **3** to the

phosphorimine nitrogen; and finally, elimination of 6 from 4 to give the desired diazo compound, 5. The structural features of 1 as discussed below are conducive to all three steps of the diazo transfer process.



The first pertinent structural feature of 1 is the electrophilicity of its diazo group. Diazo transfer reagents, such as Balli's reagent, in which the diazo function is formally a diazonium imine ($\text{N}^+ \equiv \text{N}-\text{N}=\text{R}$) are more electrophilic than those in which the diazo function is part of an azide ($\text{N}=\text{N}=\text{N}-\text{R}$). This confers upon Balli's reagent the ability to react with weaker nucleophiles such as enols, and thus this reagent has the advantage of being a diazo transfer reagent which reacts with 1,3-dicarbonyl compounds in acidic media. Reagent 1 can be represented by resonance structure 1a as a diazonium imine, or by 1b as an azide. Thus the expectation is that 1 will exhibit excellent electrophilic reactivity for the conversion to 3 (Eq. 2). The electrophilicity of 1 should lie between that of Balli's reagent and diazo transfer reagents having the azide structure.

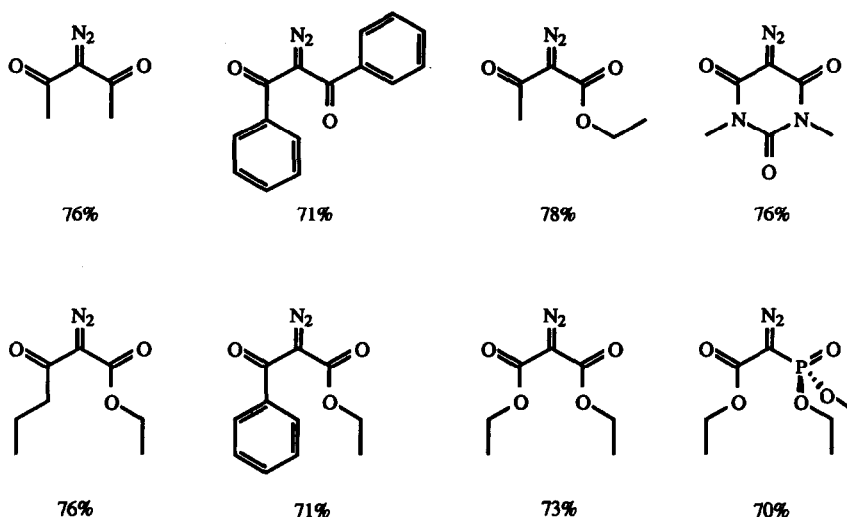


The second pertinent attribute of 1 is the basicity of its phosphorimine nitrogen. Schwesinger and co-workers have demonstrated that phosphorimidic triamides are exceptionally strong neutral nitrogen bases.¹¹ The basicity of the phosphorimine nitrogen in intermediate 3 is thus expected to accelerate the formation of 4 by proton transfer (Eq. 2). With tosyl azide and structurally similar reagents, the basicity of the corresponding nitrogen is greatly attenuated by the adjacent SO₂ group.

Finally, in the elimination step of the diazo transfer reaction ($4 \rightarrow 5 + 6$, Eq. 2), a neutral species, hexaethylphosphorimidic triamide (**6**), is the leaving group. In contrast, most of the established diazo transfer reagents require a negatively charged species to act as the leaving group. Since neutral leaving groups are in general superior to negatively charged leaving groups, the elimination step of the diazo transfer reaction of **1** is expected to be facile. The leaving group **6** is also highly basic and can deprotonate the starting 1,3-dicarbonyl compound (Eq. 3), thus making the overall process catalytic in base. The final co-product from the reaction using a catalytic amount of base is then hexaethylphosphorimidic triamide hydrobromide, **6**•HBr. The elimination step of the reactions of other diazo transfer reagents generally produces a co-product which is too weak a base to be an effective catalyst.

The considerations of **1** discussed above are borne out experimentally in its base-catalyzed reactions with 1,3-dicarbonyl compounds. Reactions of **1** with a variety of 1,3-dicarbonyl compounds proceed rapidly at room temperature to give the desired diazo compounds in uniformly high yield (Table 1). The co-product salt **6**•HBr, is easily separated from the diazo products, **5**.

Table I. Diazo- α,α' -dicarbonyl Compounds (**5**) Prepared from **1**



Preparation of 1: Hexaethylphosphorustriamide¹² (1.05 equiv.) is added dropwise to a stirred solution of bromine (1.0 equiv.) in dry THF (ca. 10 mL solvent/ mL of bromine) at 0° C. After the addition is complete, sodium azide (1.2 equiv.) is added along with a catalytic amount of 18-crown-6. The mixture is stirred under argon for 2 days, filtered, and the solvent removed on a rotary evaporator. The crude product is recrystallized from THF to give colorless, hygroscopic crystals (80%): ¹H NMR (CDCl₃): δ 1.31(t, 18 H, $J = 7.13$ Hz, CH₃CH₂N), 3.32(d of q, 12 H, $J_{H/P} = 12.5$ Hz, $J_{H/H} = 7.13$ Hz, CH₃CH₂N); ¹³C NMR: δ 13.52 (d, $J = 1.9$ Hz, CH₃CH₂N), 40.63 (d, $J = 4.4$ Hz, CH₃CH₂N); ³¹P NMR: δ 36.15; IR (KBr wafer): 2162 cm⁻¹.

General Procedure for Diazo Transfer to 1,3-Dicarbonyls: The active methylene compound is added to a stirred suspension of **1** (1.1 equiv.) in dry ether (ca. 20 mL of solvent/ g of **1**). Small amounts of potassium *t*-

butoxide or other alkoxide bases are added slowly until a color change is noted, after which the mixture is stirred for 16 to 24 h. The co-product $(\text{Et}_2\text{N})_3\text{P}=\text{NH}_2^+ \text{Br}^-$ ($6\cdot\text{HBr}$) separates as a solid or an oil. If an oil forms, sodium sulfate is added to crystallize the co-product. A small amount of ammonium sulfate is added to neutralize the catalytic amount of $(\text{Et}_2\text{N})_3\text{P}=\text{NH}$ present, and the reaction mixture is filtered. The filtrate is passed rapidly through a 10 cm x 1.5 cm column of Florisil or silica gel (60 to 100 mesh) using an additional volume of ether as eluent. The total eluent is dried over MgSO_4 and rotary evaporated, giving the desired diazo compound in approximately 60 to 80% yield. The product may contain trace (<2 mol %) amounts of unreacted dicarbonyl compound. All diazo compounds synthesized by this procedure have satisfactory ^1H and ^{13}C NMR and IR spectra.

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- ¹ The literature on tosyl azide is reviewed in: (a) M. Regitz, *Angew. Chem.*, **1967**, *79*, 786 (*Angew. Chem. Int. Ed. Engl.*, **1967**, *6*, 733); (b) M. Regitz, *Synthesis*, **1972**, 351; (c) M. Regitz and G. Mass, *Diazo Compounds: Properties and Synthesis*, Academic Press: Orlando, Fla., 1986, Ch. 13 .
- ² (a) H. Balli and F. Kersting, *Justus Liebigs Ann. Chem.*, **1961**, *647*, 1; (b) H. Balli, *ibid.*, p. 11; (c) H. Balli and R. Löw, *Tetrahedron Lett.*, **1966**, 5821.
- ³ (a) W. R. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, **1974**, 1391; (b) H. Dürr, G. Hauck, W. Brück and H. Kober, *Z. Naturforsch. B: Anorg. Chem., Org. Chem.*, **1981**, *36B*, 1149.
- ⁴ J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **1968**, *33*, 3610.
- ⁵ (a) B. Kokel and H. G. Viehe, *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 716; (b) B. Kokel and N. Boussouira, *J. Heterocyclic Chem.*, **1987**, *24*, 1493.
- ⁶ (a) A. M. van Leusen, P. M. Smid, and J. Strating, *Tetrahedron Lett.*, **1965**, 337; (b) M. Regitz, *Chem. Ber.*, **1966**, *99*, 3128.
- ⁷ (a) M. Regitz, *Ann. Chem.*, **1964**, *676*, 101; (b) M. Regitz and D. Stadler, *Justus Liebigs Ann. Chem.*, **1965**, *687*, 214; (c) M. Regitz, *Chem. Ber.*, **1965**, *98*, 36.
- ⁸ K. Kühlein and H. Jensen, *Liebigs Ann. Chem.*, **1974**, 369.
- ⁹ Refer to Table 13.3 in Ref. 1c.
- ¹⁰ G. G. Hazen, L. M. Weinstock, R. Connell, and F. W. Bollinger, *Synthetic Communications*, **1981**, *11*, 947.
- ¹¹ R. Schwesinger, *Chimia*, **1985**, *39*, 269.

¹² Hexaethylphosphorotriamide, available commercially from Aldrich Chemical Co. and Lancaster Synthesis, is preparable in bulk by reaction of PCl_3 with excess dry diethylamine at 0° to 25° C for 2-3 days. Most of the excess diethylamine is distilled off, and the residue is neutralized with 3 M NaOH. The aqueous phase is removed and extracted with ether. The combined organic phases are washed with water and then satd. NaCl, dried, and evaporated to give hexaethylphosphorotriamide in over 80% yield.

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