appropriate chloride (or mixture of chlorides) was added, and reflux was maintained for an additional 23 h. The cooled mixture was filtered, and the filtrate was concentrated. The residue was poured into cold water. The organic layer was washed with a 10% sodium bisulfite solution and a 5% sodium bicarbonate solution and dried over magnesium sulfate. The conversion was good (>80%) for primary halides and partial for secondary ones. With the above procedure, a mixture of **2** and **3** (1:1) was transformed into a mixture of **4** and **5** (5:1). Product **20** was converted into **21**.

The identity of these iodides with those obtained in the reactions with pyridinium iodide was confirmed by comparison of retention times and spectral data (IR, NMR, and mass).

**General Procedure for Conversion of Iodides into Chlorides.** A mixture of 2 mmol of the appropriate iodide and 4 mmol of dry potassium chloride in 5 mL of acetonitrile (distilled on calcium hydride) was placed in a sealed glass tube and heated at 105 °C for 38 h. The cooled mixture was diluted with water and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate, and the solvent was removed. The amount of conversion ranged between 32 and 50%.

Product **8** was transformed into **7**, **12** into **10**, **17** + **18** into **15** + **16**, **27** into **26**. All chlorides showed retention times as well as spectral data (IR, NMR, and mass) in excellent agreement with those obtained in the reactions with pyridinium chloride.

**4-Chlorocyclohexanone Oxime (29) and 3-(Chloromethyl)cyclopentanone Oxime (30).** **28** (2 mmol) and pyridinium chloride (4 mmol) were refluxed for 27 h in 5 mL of acetonitrile (distilled from calcium hydride). The usual workup afforded **29** and **30** (74%) in a 2:1 ratio; IR ($CCl_4$) 3595, 3260 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 8.6 (m, NOH), 4.25 (m, CHCl of **29**), 3.50 (m, $CH_2Cl$ of **30**), 3.0–1.4 (m); GC–MS *m/e* (relative intensity) (**29**) 149 (isotopic), 147 (parent), 66 (base peak); (**30**) 149 (isotopic), 147 (parent), 55 (base peak).

In addition, these oximes were identified by standard deoximation to the corresponding ketones.[3]

**Acknowledgment.** The National Research Council (CNR) Rome is gratefully acknowledged for partial financial support, Mr. A. Santi for mass spectra recording, and Mr. E. Brancaleoni for high-resolution mass spectra.

**Registry No.** **1**, 4160-49-0; **2**, 66980-41-4; **3**, 21299-26-3; **4**, 71987-94-5; **5**, 31053-10-8; **6**, 5771-58-4; **7**, 57719-96-7; **8**, 72003-75-9; **9**, 16335-43-6; **10**, 67052-06-6; **11**, 7434-01-7; **12**, 71987-95-6; **13**, 29773-67-9; **14**, 71987-96-7; **15**, 71987-97-8; **16**, 71987-98-9; **17**, 71987-99-0; **18**, 71988-00-6; **19**, 2862-90-0; **20**, 66980-42-5; **21**, 71988-01-7; **22**, 765-43-5; **23**, 5891-21-4; **24**, 3695-29-2; **25**, 3481-02-5; **26**, 939-52-6; **27**, 65488-05-3; **28**, 66386-25-2; **29**, 4500-22-5; **30**, 71988-02-8; pyridinium chloride, 628-13-7; pyridinium iodide, 18820-83-2; 1-acetylcyclopentene, 16112-10-0.

## Conjugate Addition of RMgX to Nitroarenes: A Very Useful Method of Alkylation of Aromatic Nitro Compounds

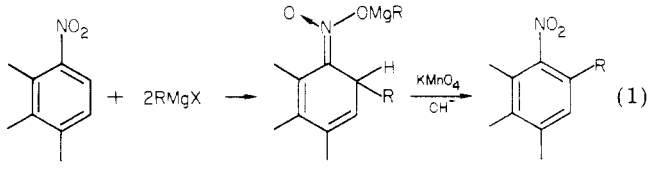
Giuseppe Bartoli,* Marcella Bosco, and Graziano Baccolini

*Istituto di Chimica Organica, 40136 Bologna, Italy*

*Received June 5, 1979*

We recently reported[1a] that conjugate addition of alkyl Grignard compounds to nitroarenic systems in THF yields *o*- or *p*-alkylnitronate adducts. This reaction provides a series of general methods of synthesizing aromatic alkyl compounds containing different nitrogen functional groups. When the reactions were carried out with a 2:1 RMgX/substrate molar ratio and the adducts were decomposed with Lewis acids ($BF_3$ or concentrated HCl) alkylnitroso compounds were obtained in fair to good yields.[1b] Conversely, the use of a large excess of RMgX, in the presence of catalytic amounts of CuI, yielded amino derivatives.[2] More recently, other authors[3] reported a method of alkylation of nitrobenzenes and -naphthalenes by treatment of an equimolar solution of RLi or RMgX in THF for 1 h at 0 °C to give nitronate adducts, which were converted in situ to aromatic alkylnitro derivatives with DDQ or bromine and triethylamine. However, in our opinion, the use of a 1:1 RMgX/substrate molar ratio can be disadvantageous in most instances. We have found, for example, that the alkylation of 6-nitrobenzothiazole under the aforementioned experimental conditions leads to a crude product which contains large amounts of unreacted material. As a consequence of this there are considerable difficulties in purification with a decrease in the yields of the pure 6-nitro-7-alkylbenzothiazoles.

In previous work[1b] we discovered that an excess of metalloorganic reagent is required for the adduct formation to proceed to completion, since part of the RMgX is displaced from the reaction, being bound to the nitro or nitronate function. A 2:1 RMgX/substrate molar ratio ensures that reaction will proceed to completion in a short time for any given substrate. There are a few exceptions. Nitroindole, for instance, contains an acidic hydrogen, which can protonate RMgX. In this case a larger excess (3:1) is necessary. Since the presence of a large excess of RMgX in the reaction mixture prevents the use of oxidizing agents like DDQ or bromine in dry THF, we devised a method compatible with these experimental restrictions. In addition, the present method utilizes a procedure which has proven to be more advantageous in the time of reaction as well as in the choice of reagents. A 1 M solution of a nitroarene in THF was treated with a 2 M solution of RMgX in the same solvent at 0 °C for few minutes. The subsequent addition of an acetone–water solution of 0.67 mol of $KMnO_4$ immediately leads to the formation of alkynitroarenes (eq 1). The wide range of applicability



(1)

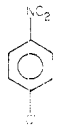
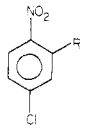
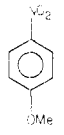
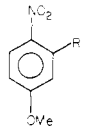
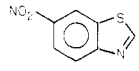
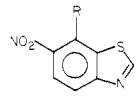
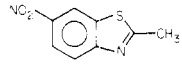
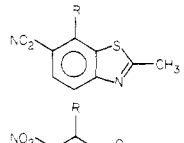
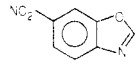
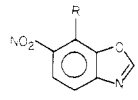
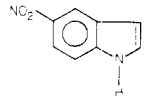
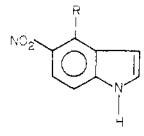
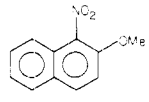
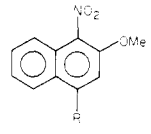
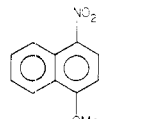
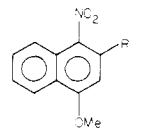
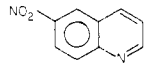
of this method is substantiated by good yields obtained for a large number of mono- and bicyclic aromatic systems. Investigated reactions, products, and yields are reported in Table I. Unsatisfactory results were exclusively obtained with 6-nitroquinoline. It is worth remembering, however, that the quinoline system gave analogous results during the synthesis of nitroso compounds.[1b] Chloro, methoxy, and methyl substituents as well as thiazole, pyrrole, and oxazole heterocondensed rings do not interfere with the reaction. In all cases alkylnitroarenes isolated after work up of the reaction mixture are chromatographically pure: particularly, only 7-alkylnitro derivatives from 6-nitrobenzothiazoles and 6-nitrobenzoxazole and the 4-alkyl derivative from 5-nitroindole are obtained, as expected from high regioselectivity previously observed in alkylation orientation of these substrates.[1a,b] These methods of in situ conversion of nitro to alkylnitro derivatives are of great utility, since a two-step procedure, involving the synthesis of nitroso compounds[4] and subse-

(1) (a) G. Bartoli, R. Leardini, M. Lelli, and G. Rosini, *J. Chem. Soc., Perkin Trans. 1*, 884 (1977); (b) G. Bartoli, R. Leardini, A. Medici, and G. Rosini, *ibid.*, 692 (1978).

(2) G. Bartoli, A. Medici, and G. Rosini, *Synthesis*, 436 (1978).
(3) F. Kienzle, *Helv. Chim. Acta*, 61, 449 (1978).

0022-3263/80/1945-0522$01.00/0 

Table I. Preparation of Alkylnitroarenes

| substrate | product | R | % yield | mp, °C |
|---|---|---|---|---|
|  |  | $CH_3$ | 40 | oil |
| | | $PhCH_2CH_2$ | 36 | oil |
|  |  | $CH_3$ | 56 | 54-55[a] |
| | | $PhCH_2CH_2$ | 62 | oil |
|  |  | $CH_3$ | 75 | 126-127 |
| | | $n$-$C_4H_9$ | 68 | 52-54 |
|  |  | $CH_3$ | 75 | 141-143 |
|  |  | $CH_3$ | 60 | 125-126 |
| | | $PhCH_2CH_2$ | 72 | 128-130 |
|  |  | $PhCH_2CH_2$ | 68 | 173-175 |
| | | $n$-$C_4H_9$ | 66 | 108-110 |
|  |  | $CH_3$ | 62 | 83-85 |
| | | $n$-$C_4H_9$ | 75 | 98-100[a] |
|  |  | $CH_3$ | 71 | 103-104 |
| | | $n$-$C_4H_9$ | 73 | 40-41 |
|  | tars | | | |

[a] These products are identical with samples obtained by oxidation of 1-nitro-4-methoxy-6-methyl-1,3-cyclohexadiene and 1-nitro-2-methoxy-4-*n*-butyl-3,4-dihydronaphthalene with DDQ.[5]

quent oxidation to nitro derivatives, can lead to unsatisfactory results. For instance, 6-nitroso-7-methylbenzothiazole can be prepared from the 6-nitro derivative in very good yields (>80%). However, it did not react with $KMnO_4$ in acetone–water, $H_2O_2$ in acetic acid, or diluted nitric acid at room temperature. Warming the mixture gave mainly tars.

## Experimental Section

Spectroscopic and physical methods were used to identify reaction products.

IR and $^1H$ NMR spectra were recorded with Perkin-Elmer 257 and JEOL-60 60-MHz instruments, respectively.

Infrared spectra of purified alkylnitro compounds (KBr disks for solids, neat for liquids) showed the presence of the two nitro group characteristic stretching bands in the 1500–1300-$cm^{-1}$ region.

Alkyl groups were evidenced by their proton chemical shifts from tetramethylsilane, used as an internal standard, in NMR spectra.

The presence of an AB system and the value of the coupling constants for the two aromatic hydrogen atoms of benzo-condensed heterocyclic compounds indicated the alkyl substitution position.

Elemental analysis data closely agreed with that expected from molecular formulas (C, ±0.20; H, ±0.09; N, ±0.12).

Melting points of solid compounds are reported in Table I.

**Starting Materials.** *p*-Chloronitrobenzene, p-methoxynitrobenzene, 5-nitroindole, and 6-nitroquinoline were commercial products (EGA). 6-Nitrobenzothiazole,[6] 6-nitro-2-methylbenzothiazole,[6] 1-nitro-2-methoxynaphthalene,[7] 1-nitro-4-methoxynaphthalene,[8] and 6-nitrobenzooxazole[9] were prepared according to the cited literature procedures. THF was purified as previously described.[1a]

**Reaction Procedure.** A solution of RMgX (0.02 mol) in tetrahydrofuran is added dropwise at 0 °C under nitrogen to a stirred solution of the nitroarene (0.01 mol) in the same solvent. The reaction is stirred for a few minutes (1–5 min) and an acetone–water solution (1:1 (v/v)) of $KMnO_4$ (0.0067 mol) is added dropwise at 0 °C with vigorous stirring. The freezing bath is removed and the reaction is stirred for a few minutes. The mixture is extracted with $CH_2Cl_2$. The organic layer is filtered, washed with water, dried with magnesium sulfate, and evaporated at reduced pressure. The crude nitroalkylarene can be purified by chromatography on a short column of $SiO_2$, using an appropriate mixture of cyclohexane–ethyl acetate as eluent. In the reactions

(4) G. Bartoli and G. Rosini, *Synthesis*, 270 (1976).
(5) G. Bartoli, M. Bosco, A. Melandri, and A. C. Boicelli, *J. Org. Chem.*, **44**, 2087 (1979).
(6) E. R. Ward and W. H. Poesche, *J. Chem. Soc.*, 2825 (1961).
(7) E. Baltazzi, *C. R. Hebd. Seances Acad Sci.*, **230**, 2207, (1950).
(8) F. G. Baaddar, L. S. El-Assal, and V. B. Bagos, *J. Chem. Soc.*, 986 (1958).
(9) M. Roussos and J. Lecomte, German Patent 1 124 499 (1962); French Patent Appl. (1960); *Chem. Abstr.*, **57**, 9858 (1962).

of nitroindole, 0.03 mol of RMgX is used.

**Registry No.** 1-Chloro-4-nitrobenzene, 100-00-5; 1-methoxy-4-nitrobenzene, 100-17-4; 6-nitrobenzothiazole, 2942-06-5; 2-methyl-6-nitrobenzothiazole, 2941-63-1; 6-nitrobenzoxazole, 17200-30-5; 5-nitro-1*H*-indole, 6146-52-7; 2-methoxy-1-nitronaphthalene, 4900-66-7; 1-methoxy-4-nitronaphthalene, 4900-63-4; 6-nitroquinoline, 613-50-3; 4-chloro-2-methyl-1-nitrobenzene, 5367-28-2; 4-chloro-2-(2-phenylethyl)-1-nitrobenzene, 72206-90-7; 4-methoxy-2-methyl-1-nitrobenzene, 5367-32-8; 4-methoxy-1-nitro-2-(2-phenylethyl)-benzene, 72206-91-8; 7-methyl-6-nitrobenzothiazole, 72206-92-9; 7-butyl-6-nitrobenzothiazole, 72206-93-0; 2,7-dimethyl-6-nitrobenzothiazole, 72206-94-1; 7-methyl-6-nitrobenzoxazole, 72206-95-2; 6-nitro-7-(2-phenylethyl)benzoxazole, 72206-96-3; 5-nitro-4-(2-phenylethyl)-1*H*-indole, 72206-97-4; 4-butyl-5-nitro-1*H*-indole, 72206-98-5; 2-methoxy-4-methyl-1-nitronaphthalene, 72206-99-6; 4-butyl-2-methoxy-1-nitronaphthalene, 69745-40-0; 4-methoxy-2-methyl-1-nitronaphthalene, 72207-00-2; 2-butyl-4-methoxy-1-nitronaphthalene, 72207-01-3.

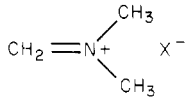
## Preformed Mannich Salts: A Facile Preparation of Dimethyl(methylene)ammonium Iodide

Thomas A. Bryson,* Gordon H. Bonitz, Curtis J. Reichel, and Richard E. Dardis

*Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208*

*Received May 17, 1979*

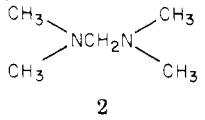
Preformed Mannich salts of the type **1a–c**, have recently



1a, X = $I^-$
b, X = $Cl^-$
c, X = $^-OOCCF_3$

found increased and varied usage[1] as electrophiles in a wide range of reactions, and dimethyl(methylene)ammonium iodide (**1a**) has been of particular interest due to its reactivity and stability. We have used the elegant but somewhat time-consuming procedure of Eschenmoser et al.[2] to prepare **1a**, but extensive use of this salt has required an alternate and more convenient source of this reagent which is disclosed herein.

We have found that **2** reacts cleanly and efficiently with



2

trimethylsilyl iodide[3] (TMSI) to form **1a** (96% yield) which is in all respects identical with **1a** formed by the Eschenmoser procedure.[2] The mechanism of this process can be rationalized by molding together the analogy of the Jung conversion of ketals to ketones using trimethylsilyl iodide[4]

Scheme I

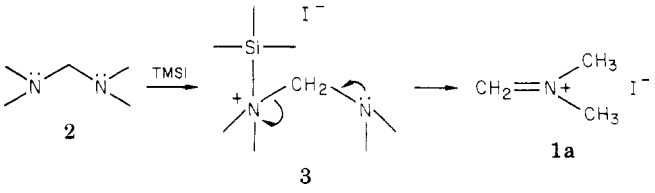
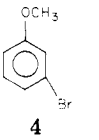
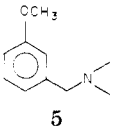
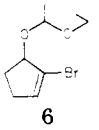
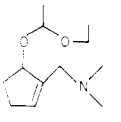
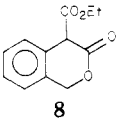
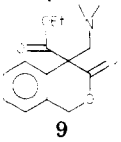
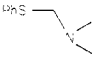


Table I

| | solvent | base or metal | $t$, °C | product | % yield |
|---|---|---|---|---|---|
|  4 | $Et_2O$ | Mg | 25 (2 h) |  5 | 86[1d] |
|  6 | THF | *n*-BuLi | 25 |  7[a] | 30[9] |
|  8 | THF | NaH | 25 |  9 | 62 |
| HSPh (**10**) | $Et_2O$ | NaH | 25 |  11 | 80[8] |

[a] Isolated as the methiodide salt.

and the preparation of **1b** using acetyl chloride,[1e] leading to the assumption that **2** and TMSI form **3** which subsequently cleaves to give Mannich salt **1a** (Scheme I).[10]

Addition of salt **1a** (formed by this procedure) to nucleophiles such as Grignard reagents, vinyllithium reagents, sodium thiophenoxide, and stabilized carbanions gives the expected results, some of which are summarized in Table I.

Further studies show that cleavage of tetraalkyl aminals (i.e., **12**) with TMSI gives the desired Mannich salts cleanly and efficiently. These salts (**13a,b**) were further characterized by addition of organolithium reagents generating amines (**14**).

12a, R = Et; R',R' = $(CH_2)_5$
b, R = $CH(CH_3)_2$; R' = *n*-Bu

13a, R = Et; R' = $(CH_2)_5$
b, R = $CH(CH_3)_2$; R' = *n*-Bu

These studies indicate that TMSI cleavage of tertiary geminal diamines is generally applicable to afford preformed Mannich salts and perhaps the corresponding neutral enamine structures. We are currently investigating other aspects of the TMSI cleavage of symmetrical and unsymmetrical aminals.

### Experimental Section

**Preparation of Dimethyl(methylene)ammonium Iodide (1a).** A 250-mL three-necked, round-bottomed flask, equipped with a magnetic stirring bar, rubber septum, and $N_2$ inlet, was

(1) (a) S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976); (b) S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *ibid.*, **99**, 6066 (1977); (c) J. Hooz and J. N. Bridson, *ibid.*, **95**, 602 (1973); (d) C. D. Poulter, J. L. Roberts, and P. S. Borromeo, *Tetrahedron Lett.*, 1299 (1977); J. L. Roberts and C. D. Poulter, *ibid.*, 1621 (1977); (e) G. Kunst and L.-F. Tietze, *Angew. Chem., Int. Ed. Engl.*, **15**, 239 (1976); (f) N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.*, **99**, 944 (1977).

(2) J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenemoser, *Angew. Chem., Int. Ed. Engl.*, **10**, 330 (1971).

(3) We realized optimum yields when the TMSI was prepared fresh according to Jung's procedure [M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977)]; however, salt **1a** was produced in 94% yield when commercially available TMSI was used.

(4) M. E. Jung, W. A. Andrus, and P. L. Ordstein, *Tetrahedron Lett.*, 4175 (1977).

0022-3263/80/1945-0524$01.00/0 