Some Reactions of Organolithium Compounds with Nitrosamines[1a]

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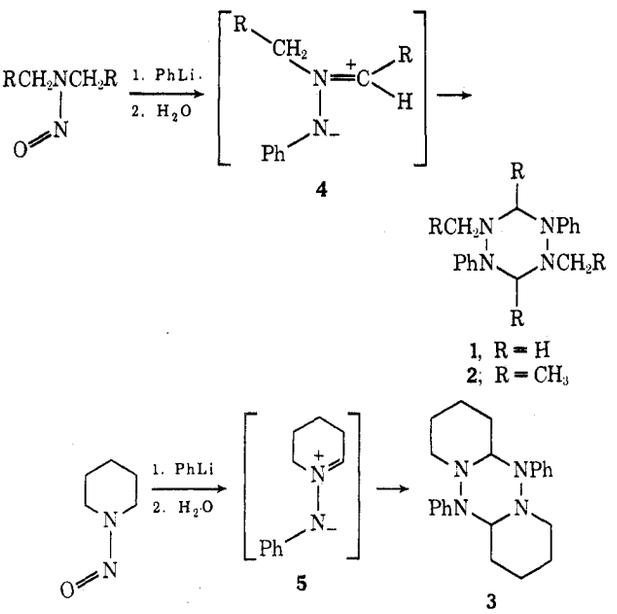
Secondary nitrosamines react with phenyllithium or *tert*-butyllithium to give N'-alkylated lithium salts which undergo elimination to form azomethine imines when treated with water or ethanol. When *N*-methyl-*N*-*tert*-butylnitroamines, *tert*-butyllithium, and ethanol are used, a stable compound, 1,2-di-*tert*-butyl-1-(ethoxymethyl)-hydrazine, can be isolated. The azomethine imines form *sym*-hexahydrotetrazines on standing or can be trapped with *N*-phenylmaleimide or dimethyl acetylenedicarboxylate.

The carcinogenic nature of certain nitrosamines has been well established.[2] These observations and the reported chemotherapeutic activity of other nitrosamines[3] stimulated our interest in the chemistry of these compounds.[4] Although spectroscopic studies are numerous, owing in part to the interest in restricted rotation around N–N bonds,[5] basic chemistry of this functional group remains largely unexplored. It has been, for example, only recently demonstrated that α protons of nitrosamines can undergo base-catalyzed H–D exchange, and α-C-alkylation with methyl iodide,[6] which has thus suggested the existence of an α-nitrosamino carbanion.[6,7] Seebach and Enders[8] have further substantiated this using dimethylnitrosamine (DMNA) and several electrophiles. However, they also observed that nucleophilic attack at the nitroso moiety of dimethylnitrosamine was competitive with metalation at the methyl group when organolithium reagents were employed. *N*-Butyraldehyde oxime was isolated as a by-product when *N*-butyllithium and benzophenone were added sequentially to DMNA in tetrahydrofuran at −80°. Such nucleophilic attack is not surprising, since in our previous communication[4] we reported that some simple alkylnitrosamines reacted with phenyllithium at the N=O moiety, in ether, at −65° to give symmetrical hexahydrotetrazines (**1–3**) in 30–40% yield.

Our results suggested[4] that intermediates such as **4** and **5** are formed and subsequently dimerize head to tail to form the *sym*-hexahydrotetrazines. The present investigation was undertaken to determine if the intermediate azomethine imines (**4**, **5**) might be detected or trapped.



Results

Assuming "normal" addition[9] of phenyllithium to the nitroso moiety, the azomethine imines may have been formed by an elimination reaction either before or after quenching with water. The former pathway was considered unlikely after consideration of the following data. When **4** was generated in the presence of excess phenyllithium (our reaction conditions), it was expected that the highly reactive dipolar species would be phenylated at the methyl group. The reaction of dimethylnitrosamine with phenyllithium did not yield 1-methyl-1-benzyl-2-phenylhydrazine.[10] The reaction of phenyllithium with several akyl nitrosamines gave transient colored species either prior to or after the addition of water.[11] Although the appearance of highly colored intermediates is reminiscent of colored aromatic azomethine imines,[12,13] no further characterization of these species was undertaken.

(1) (a) This investigation was supported in part by U. S. Public Health Service Grant No. CA-02857 and CA-10746 from the National Institutes of Health, National Cancer Institute. (b) Allied Chemical Corp. Fellow, 1970–1971.

(2) (a) P. N. Magee and J. M. Barnes, *Brit. J. Cancer*, **10**, 114 (1956); (b) H. Druckrey, R. Preussmann, S. Ivankovic, and D. Schmahl, *Z. Krebsforsch.*, **69**, 103 (1967).

(3) (a) F. M. Schabel, T. P. Johnston, G. S. McCaleb, J. A. Montgomery, W. R. Laster, and H. E. Skipper, *Cancer Res.*, **23**, 725 (1963); (b) C. T. Bahner, D. Brotherton, and M. K. Brotherton, *J. Med. Chem.*, **11**, 401 (1968).

(4) For a preliminary report on this work see P. R. Farina, *Tetrahedron Lett.*, 4971 (1970).

(5) (a) C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Amer. Chem. Soc.*, **79**, 6136 (1957); (b) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964); (c) H. W. Brown and D. P. Hollis, *J. Mol. Spectrosc.*, **13**, 305 (1964); (d) J. T. D'Agostino and H. H. Jaffe, *J. Amer. Chem. Soc.*, **92**, 5160 (1970).

(6) L. K. Keefer and C. H. Fodor, *J. Amer. Chem. Soc.*, **92**, 5747 (1970).

(7) R. R. Fraser and Y. Y. Wigfield, *Tetrahedron Lett.*, 2515 (1971).

(8) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **11**, 301 (1972).

(9) P. Buck and G. Köbrich, *Tetrahedron Lett.*, 1563 (1967), have suggested a reverse addition of phenyllithium to nitrosobenzene followed by the displacement of PhOLi with an additional 1 mol of PhLi to account for reaction products.

$$PhN{=}O \xrightarrow{PhLi} PhN(Li^+)OPh \xrightarrow{PhLi} Ph_2NLi + PhOLi$$

By analogy this would presumably give 1,1-dimethyl-2-phenylhydrazine from the reaction of DMNA with phenyllithium if a similar route were applicable and not the observed reaction product.

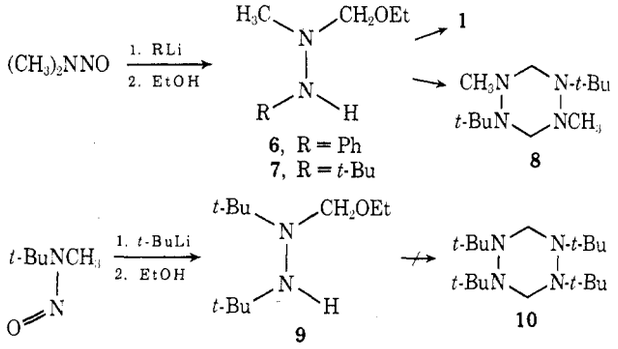
(10) This compound was the major product when PhMgBr was employed and is the subject for a future report.

(11) Orange, purple and blue-black for dimethylnitrosamine, diethylnitrosamine, and *N*-nitrosopiperidine, respectively.

(12) B. Singh, *J. Amer. Chem. Soc.*, **91**, 3670 (1969).

(13) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

Isolation of Ethoxymethylhydrazines.—A dipolar species generated during the water quench could be in equilibrium with its hydrated form.[14] Our attempts to detect such a species after reaction of dimethylnitrosamine with phenyllithium employing nmr spectroscopy were unsuccessful. Some azomethine imines, however, are known to form stable neutral adducts with alcohol.[13] The substitution of absolute ethanol for water in the quench of the reaction of DMNA with *tert*-butyllithium or phenyllithium resulted in the isolation of the corresponding unstable ethoxymethylhydrazines **6** and **7**, which were characterized by nmr.



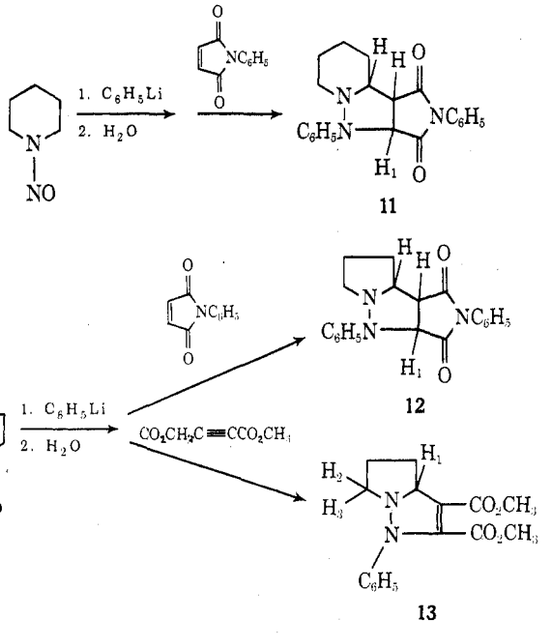
Compound **7** exhibited a singlet at δ 1.03 (9 H, *tert*-butyl) overlapping a triplet at δ 1.15 (3 H, J = 7.0 Hz, CCH_3), a singlet at δ 2.50 (3 H, NCH_3), a quartet at δ 3.52 (2 H, J = 7.0 Hz, OCH_2C), and a singlet at δ 4.02 (2 H, NCH_2O). After a short period of time the nmr spectrum began to change and was replaced in part by a new singlet at δ 2.84 and a peak at δ 3.9. Evaporation of the solvent gave **8**, hexahydro-1,4-dimethyl-2,5-di-*tert*-butyl-*s*-tetrazine, as a colorless liquid. Its nmr showed singlets at δ 1.01 (18 H, *tert*-butyl) and 2.84 (6 H, NCH_3), a mound at δ 3.85 (4 H, NCH_2N) which became a singlet on heating slightly above room temperature, and an AB quartet, J_{AB} = 11.5 Hz, on cooling. (See paragraph at end of paper regarding supplementary material.) Its infrared spectrum did not exhibit any NH absorption. This compound was clearly the product formed from **7** in solution or neat. However, if **7** was dissolved in methanol-d_4 its nmr spectrum remained unchanged even after several days in solution.

Similarly, **6** rapidly (half-life 1 hr, 30°, CCl_4) lost ethanol to form **1** which was independently synthesized from 1-methyl-2-phenylhydrazine and formaldehyde and therefore establishes structure **1** for a compound reported much earlier by Knorr and Weidel.[15]

When *N*-methyl-*tert*-butylnitrosamine was treated with *tert*-butyllithium and quenched with ethanol, 1,2-di-*tert*-butyl-1-(ethoxymethyl)hydrazine (**9**) was formed in almost quantitative yield. Surprisingly, this compound proved to be stable and was easily distilled at reduced pressure without decomposition. Its nmr spectrum (100 MHz) showed two singlets at δ 1.05 and 1.07 (18 H, *tert*-butyl) overlapping a triplet at δ 1.18 (3 H, J = 7.0 Hz, CH_3), a broad absorption at δ 3.10 (NH) which rapidly underwent exchange with D_2O, a quartet at δ 3.36 (2 H, J = 7.0 Hz, OCH_2C), and a singlet at δ 4.38 (2 H, NCH_2O). Its infrared spectrum showed a weak absorption at 3.05 μ attributed to NH. This compound did not eliminate ethanol to form **10** and was stable at room temperature.

Reactions with Dipolarophiles.—Certain *sym*-hexahydrotetrazines[12,13,16] are known to react with dipolarophiles presumably through dissociation to the 1,3-dipolar form to yield isolable adducts. Neither **1**, **2**, or **3** reacted with dimethyl acetylenedicarboxylate or *N*-phenylmaleimide when refluxed in benzene solution. This was not unexpected, since dissociation is usually favored by appropriate, *i.e.*, aromatic, stabilization adjacent to both the dipolar centers.[12,13,16]

However, if the crude oils obtained from the reaction of phenyllithium with *N*-nitrosopiperidine or *N*-nitrosopyrrolidine followed by quenching with water were stirred with *N*-phenylmaleimide in ether, a white, crystalline solid began to precipitate after 10 min at



room temperature. These compounds were characterized as adducts **11** and **12** from the following data.

Adduct **11** was identified by its 100-MHz spectrum in trifluoroacetic acid which displayed a six-proton multiplet between δ 1.54 and 2.80, a three-proton multiplet between δ 2.88 and 4.12, a one-proton triplet at δ 4.36, a doublet at δ 5.26 (H_1, J = 8.2 Hz), and a ten-proton multiplet between δ 7.16 and 7.68.

The 100-MHz spectrum of adduct **12** in trifluoroacetic acid showed a four-proton multiplet between δ 2.16 and 2.88, a two-proton multiplet centered at δ 3.64, a one-proton doublet of doublets centered at δ 4.24 (J = 7.0 and 2.4 Hz), a one-proton multiplet at δ 5.20, and a doublet (H_1, J = 7.0 Hz) and a ten-proton multiplet between δ 7.12 and 7.60.

Dimethyl acetylenedicarboxylate was also an effective dipolarophile when refluxed in benzene with the oil obtained from the reaction of *N*-nitrosopyrrolidine and phenyllithium. The product, after purification by column chromatography, was characterized as dimethyl 3a,4,5,6-tetrahydro-1-phenyl-1*H*-pyrrolo[1,2-*b*]-pyrazole-2,3-dicarboxylate (**13**) from the following

(14) R. Grashey, R. Huisgen, K. K. Sun, and R. M. Moriarty, *J. Org. Chem.*, **30**, 74 (1965).

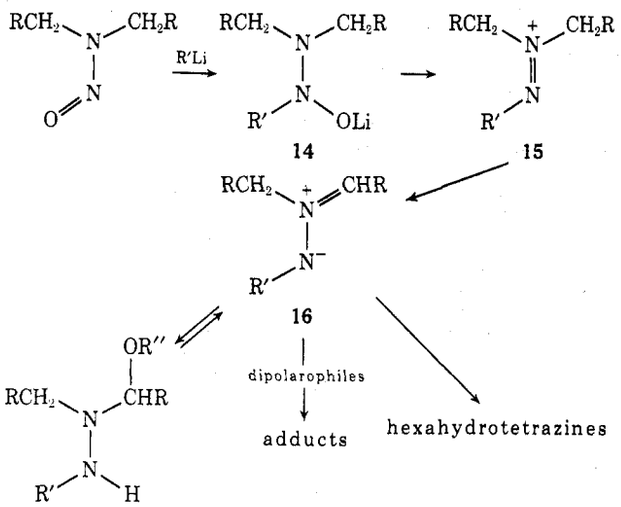
(15) L. Knorr and A. Weidel, *Chem. Ber.*, **42**, 3523 (1909).

(16) (a) R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, *Angew. Chem., Int. Ed. Engl.*, **1**, 406 (1962); (b) R. Grashey and K. Adelsberger, *ibid.*, **1**, 267 (1962).

spectral properties: ir (Nujol) 5.72 and 5.88 (ester C=O), 6.16 and 6.28 μ (unsaturation). The carbonyl values are in good agreement with those found by Singh[12] (5.72 and 5.91 μ) for a similar *N*-phenyl, α,β-unsaturated dimethyl dicarboxylate system. The nmr spectrum exhibited a four-proton multiplet between δ 1.5 and 2.3, a multiplet centered at δ 2.94 (H_2, H_3), two singlets at δ 3.58 and 3.67 (6 H, CH_3), a triplet at δ 4.75 (H_1), and a five-proton aromatic peak at δ 7.08.

Discussion

The reaction of simple alkyl nitrosoamines with phenyl- or *tert*-butyllithium to give *sym*-hexahydrotetrazines can be accommodated by the following scheme, outlined below. The first step involves attack by the organolithium reagent on the nitroso moiety to give **14**, which undergoes elimination to form the azomethine imine **16** (presumably through a diazenium salt **15**[17])



when quenched with a protic solvent such as water or ethanol. The 1,3-dipolar species which is generated is probably in equilibrium to some extent with its hydrate when water is employed. This is supported by the isolation of neutral ethoxymethylhydrazines when ethanol was substituted for water. Two of these hydrazines readily lose ethanol and dimerize to the same *sym*-hexahydrotetrazines which were obtained from the water quench of the reaction.

1,2-Di-*tert*-butyl-1-(ethoxymethyl)hydrazine is of particular interest, since it does not lose ethanol to form hexahydro-1,2,4,5-tetra-*tert*-butyl-*s*-tetrazine[18] on standing or when heated above room temperature. It is difficult to speculate at this time why **9** is so much more stable than **6** or **7**, although steric requirements of the two *tert*-butyl groups are most probably involved.

Cyclic aliphatic nitrosamines, such as *N*-nitrosopyrrolidine or piperidine, apparently form hydrates which are sufficiently long lived to permit reaction with dipolarophiles before dimerization to products. *N*-Nitrosopyrrolidine, however, does not yield an isolable hexahydrotetrazine.

It is noteworthy that nitrosamines can react with organometallics by two major routes: abstraction of an α proton to form an α-nitrosamino carbanion or nucleophilic attack on the NO moiety. The path is probably determined by the nucleophilicity of the reagent, polarity of the solvent, and the nature of the nitrosamine.

(17) G. Buttner and S. Hünig, *Chem. Ber.*, **104**, 1088 (1971).

(18) This product was also not observed when water was used as quenching agent.

Experimental Section

Infrared absorption spectra were determined using a Beckman IR-5A spectrophotometer and ultraviolet absorption spectra were determined using a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. A Varian A-60 or Jeolco 100 nuclear magnetic resonance spectrometer were used to record the nmr spectra. Mass spectra were obtained on a Hitachi Perkin-Elmer RMV. 6D mass spectrometer.

Melting points were determined on a Mel-Temp or Fisher-Johns melting apparatus and are uncorrected. Microanalyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn.

Dimethylnitrosamine, diethylnitrosamine, and *N*-nitrosopyrrolidine were purchased from Eastman Organics, Rochester, N. Y., and were used without further purification.[19a] *N*-Methyl-*tert*-butylnitrosamine was prepared according to a standard procedure.[19b] *tert*-Butyllithium (2 *M* in *n*-pentane) was purchased from Alfa Inorganics, Beverly, Mass.

Phenyllithium Reagent.—Phenyllithium was prepared according to a standard method[20] and titrated prior to use by the method of Gilman.[21] The following modifications were made: lithium wire was cut into pieces 0.5 cm long, argon was substituted for nitrogen, and the solution was allowed to settle overnight before it was siphoned into a container for storage.

***N*-Nitrosopyrrolidine.**—Pyrrolidine (44 g, 0.62 mol) was added slowly to a stirred solution of glacial acetic acid cooled by ice. The yellow solution was then heated to 90° and sodium nitrite (86 g, 1.2 mol) was added, maintaining the temperature between 90 and 95°. The solution was stirred until no more gas was evolved and then evaporated *in vacuo* at 60°. The residue was then extracted with ether. The extract was concentrated and anhydrous sodium carbonate was added to the stirred solution until carbon dioxide evolution was complete. The solution was then filtered and evaporated to a red-brown liquid.

The product was distilled, and the fraction boiling at 66–68° (2.0 mm) was collected, 62 g (80% yield), diluted with a small portion of ether, and stirred with anhydrous sodium carbonate overnight. Filtration and concentration as above, followed by distillation, gave the nitrosamine: bp 69–70° (1.0 mm); ir (film) 6.88 (m), 7.09 (s), 7.66 (s), 8.27, 10.30, 12.38, 13.94 μ; nmr (CCl_4) δ 1.7–2.2 (m, 4 H) and 3.1–3.5 (m, 4 H).

Hexahydro-1,4-dimethyl-2,5-diphenyl-*s*-tetrazine (1). A. From Dimethylnitrosamine.—A solution of dimethylnitrosamine (1.44 g, 19.5 mmol) in 100 ml of anhydrous ether was cooled to −45° with stirring under an argon atmosphere. Phenyllithium (40 ml, 0.96 mmol/ml) was added dropwise over a period of 25 min. After an additional 0.5 hr the solution was warmed to −10° and quenched with water. The ether layer was dried and evaporated *in vacuo*. The pale yellow oil crystallized immediately after trituration with methanol to give 1.0 g (40% yield) of **1**, mp 141–148°. Recrystallization from ligroin (bp 66–75°) gave the analytical sample: mp 151–151.5°; ir (Nujol) 6.24 (s), 8.79 (s), 12.75 (s), 13.41, and 14.51 μ (s); nmr (CCl_4) δ 2.55 (s, 6 H), 4.47 (s, 4 H), and 6.4–7.3 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 268 (26), 135 (45), 134 (72), 120 (17), 105 (86), 91 (18), 77 (100). *Anal.* Calcd for $C_{18}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.53; H, 7.28; N, 20.69.

B. From 1-Methyl-2-phenylhydrazine and Formaldehyde.—The reaction conditions described by Knorr and Weidel[15] were employed using 1-methyl-2-phenylhydrazine[22] and aqueous formaldehyde. The product was recrystallized from hexane and was shown to be identical with **1** obtained from phenyllithium and dimethylnitrosamine.

Hexahydro-1,4-diethyl-3,6-dimethyl-2,5-diphenyl-*s*-tetrazine (2).—A solution of diethylnitrosamine (2.18 g, 21.4 mmol) in

(19) (a) Precautions in handling of nitrosamines should be undertaken owing to the carcinogenic properties of some of these compounds.[2] (b) D. F. Heath and A. R. Mattocks, *J. Chem. Soc.*, 4226 (1961).

(20) R. G. Jones and H. Gilman, *Org. React.*, **6**, 353 (1951).

(21) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Amer. Chem. Soc.*, **45**, 150 (1923).

(22) C. H. Schmidt, *Chem. Ber.*, **103**, 986 (1970).

100 ml of anhydrous ether was cooled to −50° with stirring under an argon atmosphere. Phenyllithium (50 ml, 0.85 mmol/ml) was added dropwise. After 1 hr the reaction mixture was quenched with water, producing an intense purple color which faded and changed to yellow as more water was added. The ether layer was dried and evaporated to a viscous oil. Trituration with methanol gave 2.87 g (30% yield) of the product (**2**), mp 168–171°. Recrystallization from hexane gave white cubic crystals: mp 184–185°; ir (Nujol) 6.28 (s) 7.31 (s), 8.84 (s), 13.50 (s), 14.58 μ (s); nmr (CCl_4) δ 1.04 (t, 6 H), 1.48 (d, 4 H), 2.89 (q, AB of q, 4 H) (J_{AB} = 12, J_{AX} = J_{BX} = 8 Hz), 4.70 (q, 2 H), 6.3–7.3 (m, 10 H); mass spectrum (70 eV) *m/e* (rel intensity) 324 (5), 190, (10), 163 (53), 162 (97), 161 (100), 147 (14), 133 (13), 118 (48), 117 (98), 77 (91). *Anal.* Calcd for $C_{20}H_{28}N_4$: C, 74.03; H 8.70; N, 17.27. Found: C, 74.01; H, 8.66; N, 17.44.

Reaction of *N*-Nitrosopyrrolidine with Phenyllithium.—A stirred solution of *N*-nitrosopyrrolidine (10.9 g, 109 mmol) in 300 ml of anhydrous ether was cooled to −65° under an argon atmosphere. Phenyllithium (218 mmol) in 230 ml of ether was added dropwise to this solution. After 2 hr the reaction was quenched with water and the ether layer was separated and dried. Evaporation of the ether *in vacuo* gave 10.1 g of crude oil. All attempts at purification to give a *sym*-hexahydrotetrazine were unsuccessful.

Dimethyl 3a,4,5,6-Tetrahydro-1-phenyl-1*H*-pyrrolo[1,2-*b*] pyrazole-2,3-dicarboxylate (13).—A solution of 80 ml of benzene containing 4.8 g of crude oil from the previous experiment and 4.3 g of dimethyl acetylenedicarboxylate was refluxed overnight. The brown residue was chromatographed on 450 g of deactivated neutral alumina[23] using carbon tetrachloride followed by 1:4 (volume) chloroform–carbon tetrachloride. The yellow band was collected to give 2.85 g of a pale yellow oil. Thin layer chromatography on silica gel (Eastman) with chloroform as eluent showed a spot having R_f 0.71 and two contaminants which were visualized using iodine. Further purification by thick layer on silica gel H gave the product as a single spot by tlc.

Trituration of the oil with several drops of hexane and cooling in the refrigerator for several days gave a low-melting solid, mp 54–55°. Recrystallization from 1:1 (volume) ethanol–water gave an analytical sample: mp 61–61.5°; ir (Nujol) 5.72 (s), 5.88 (s), 6.16 (s), 6.28 (s), 13.09 (s), 13.70 (m), 14.30 μ (s); uv (ethanol) λ_{max} 356 mμ (ε 13,600); nmr (CCl_4) spectral designations given in text; mass spectrum *m/e* (rel intensity) 312 (26, P), 273 (39), 243 (63), 229 (10), 215 (100), 211 (14), 198 (12), 144 (10), 77 (79), 72 (12). *Anal.* Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 6.05; N, 9.14.

Hexahydro-*N*,1-diphenyl-1*H*-pyrrolo[1,2-*b*]pyrazole-2,3-dicarboximide (12).—*N*-Phenylmaleimide (1.2 g, 7.0 mmol) was added to a stirred solution of crude oil obtained from *N*-nitrosopyrrolidine (1.0 g, 0.6 mmol) and phenyllithium in 100 ml of ether. After 10 min of stirring at room temperature, a white, crystalline precipitate began to form. The reaction mixture was stirred overnight and then filtered to give 0.30 g of the adduct: mp 216–218° dec; ir (Nujol) 5.85 (s), 6.24 (m), 8.36 (s), 13.37 (s), 14.24 (w), 14.49 μ (m); nmr (CF_3COOH) spectral designations given in text; mass spectrum *m/e* (rel intensity) 333 (81, P), 172 (86), 158 (23), 157 (19), 129 (18), 117 (11), 93 (17), 91 (21), 81 (78), 78 (78), 77 (43), 69 (100). *Anal.* Calcd for $C_{20}H_{19}N_3O_2$: C, 72.10; H, 5.74; N, 12.60. Found: C, 72.29; H, 5.82; N, 12.55.

Dodecahydro-5,11-diphenyldipyrido[1,2-*b*:1′,2′-*e*]-*s*-tetrazine (3).—A solution of *N*-nitrosopiperidine (1.70 g, 15.0 mmol) in 150 ml of anhydrous ether was cooled to −65° with stirring under an argon atmosphere. To this solution was added 30 ml of phenyllithium (1.0 mmol/1 ml) over a 15-min period. The solution changed color from yellow to green to light blue to dark blue during the addition. After an additional 1 hr the solution was quenched with water which reversed the color changes. The ether layer was separated, dried, and evaporated to a viscous yellow oil. Trituration with hexane and cooling overnight gave 0.77 g (30%) of the hexahydrotetrazine **3** as white crystals, mp 135–140°. Recrystallization from hexane gave an analytical sample: mp 151–151.5°; ir (Nujol) 6.23 (s), 7.95 (m), 9.65 (m), 13.26 (s), 14.39 μ (s); nmr (CCl_4) δ 1.1–2.1 (m, 12 H), 2.83–3.21 (m, 4 H), 3.57 (d, 1 H), 4.03 (s, 1 H), 6.37–7.20 (m, 10 H); mass spectrum *m/e* (rel intensity) 348 (17, P), 173 (78, P/2), 174 (60), 172 (34), 135 (64), 130 (23), 122 (47), 117 (60), 105 (43), 93 (100), 77 (100), 66 (100). *Anal.* Calcd for $C_{22}H_{28}N_4$: C, 75.82; H, 8.10; N, 16.10. Found: C, 76.03; H, 8.06; N, 16.15.

Octahydro-*N*,1-diphenylpyrazolo[1,5-*a*]pyridine-2,3-dicarboximide (11).—*N*-Phenylmaleimide (1.7 g, 9.8 mmol) in 50 ml of ether was added to a stirred solution of crude oil from the above reaction (1.5 g, 7.9 mmol). After 45 min a white precipitate began to form. The reaction mixture was stirred overnight and then filtered, giving 0.7 g (25%) of the adduct, mp 225–227° dec. Recrystallization from acetonitrile gave an analytical sample: mp 228–229.5° dec; ir (Nujol) 5.84 (s), 6.25 (w), 7.23 (m), 8.38 (m), 13.71 (w), 14.47 μ (m); nmr (CF_3COOH) spectral designations given in text; mass spectrum *m/e* (rel intensity) 347 (78, P), 231 (13), 181 (55), 173 (39), 158 (11), 131 (78), 119 (14), 100 (21), 93 (16), 77 (24) 69 (100). *Anal.* Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.10; N, 12.10. Found: C, 72.74; H, 6.18; N, 12.18.

1-Methyl-1-ethoxymethyl-2-phenylhydrazine (6).—Dimethylnitrosamine (4.25 g, 0.575 mol) dissolved in 150 ml of anhydrous ether was cooled to −65° under an argon atmosphere. Over a period of 1 hr, 100 ml of 0.115 *M* phenyllithium was added to the well-stirred solution. After an additional 10 min, 25 ml of absolute ethanol (dried over 3A molecular sieves) was added to the white suspension. The solution color changed from orange to deep yellow to pale yellow during the addition of ethanol. When the addition was completed, water was added until the solution separated into two distinct layers. The ether layer was separated, dried over anhydrous potassium carbonate, and evaporated *in vacuo* at room temperature to a pale yellow oil: nmr (CCl_4) δ 1.13 (t, CCH_3), 2.57 (s, NCH_3), 3.40 (q, OCH_2C), 4.12 (s, NCH_2O), 5.1 (br s, NH). This compound rapidly loses ethanol on standing to form **1**.

1-Methyl-1-ethoxymethyl-2-*tert*-butylhydrazine (7).—Dimethylnitrosamine (7.4 g, 0.1 mol) was dissolved in 300 ml of anhydrous ether and cooled to −70° under an argon atmosphere. Over a period of 1 hr 47 ml of 2.34 *M tert*-butyllithium was added to the well-stirred solution. After an additional 1 hr the yellow solution was quenched with 25 ml of absolute ethanol and the temperature was brought to 0°. Water (50 ml) was then added to dissolve precipitated salts and the ether layer was separated and dried. The ether was evaporated *in vacuo* at room temperature to give the product (16 g, 84% yield): ir (film) 3.07 (w, NH), 7.25 (m) and 7.38 (s), 8.88 (m), 9.00 (m), 9.30 (s), 10.10 (m), 11.35 (s), 12.92 μ (w); nmr (CCl_4) spectral designations given in text.

Hexahydro-1,4-dimethyl-2,5-di-*tert*-butyl-*s*-tetrazine (8). A.—A solution of 2.50 g (0.0156 mol) of 1-methyl-1-ethoxymethyl-2-*tert*-butylhydrazine was stirred overnight in 25 ml of carbon tetrachloride. Evaporation of the solvent and distillation gave 1.24 g (71%) of **8** which was collected at 59° (0.05 mm).

B.—The same conditions employed for **7** were used, except that water was substituted for ethanol. This permitted the direct isolation of **8**: ir (film) 7.22 (m), 7.38 (s), 8.26 (s) 9.28 (s) 11.09 (m), and 13.80μ (s); nmr (CCl_4) spectral designations appear in text; mass spectrum *m/e* (rel intensity) 228 (10, P), 171 (7), 115 (11), 114 (17), 99 (31), 71 (58), 70 (10), 58 (50), 57 (100), 41 (38), 39 (10). *Anal.* Calcd for $C_{12}H_{28}N_4$: C, 63.11; H, 12.36; N, 24.53. Found: C, 63.20; H, 12.53; H, 24.45.

1,2-Di-*tert*-butyl-1-(ethoxymethyl)hydrazine (9).—*N*-Methyl-*N*-*tert*-butylnitrosamine (4.64 g, 0.040 mol) was dissolved in 300 ml of anhydrous ether and cooled to −70° under an argon atmosphere. Over a period of 1 hr 19 ml of 2.34 *M tert*-butyllithium was added with stirring. After an additional 1 hr 10 ml of absolute ethanol was added and the temperature was brought to 0°. Water (50 ml) was added and the ether layer was separated, dried, and evaporated *in vacuo* to a pale yellow liquid, 6.2 g (77% yield). This material was distilled and the fraction boiling at 52–54° (2.0 mm) was collected: ir (film) 3.05 (w), 7.22 (m), 7.37 (s), 9.32 (s), 10.20 (m), 11.84 (m), 12.60 (m), and 13.80 μ (m); nmr (CCl_4) spectral designations appear in text; mass spectrum *m/e* (rel intensity) 176 (2), 129 (59), 85 (26), 73 (83), 71 (27), 57 (100), 46 (28), 45 (65), 41 (98), 39 (22), 31 (100). *Anal.* Calcd for $C_{11}H_{26}N_2O$: C, 65.30; H, 12.95; N, 13.84. Found: C, 65.08; H, 12.78; N, 13.61.

Hexahydro-1,4-dimethyl-2,5-diphenyl-*s*-tetrazine (1) from Halogen-Free Phenyllithium.—Dimethylnitrosamine was sim-

(23) Neutral alumina activity I (450 g) and 22.5 g of water were shaken until the powder appeared homogenous.

ilarly treated with phenyllithium which was halogen free.[24] The product isolated was identical with that obtained using phenyllithium prepared from bromobenzene and lithium metal.

Registry No.—1, 27377-48-6; 2, 30514-23-9; 3, 30514-22-8; 6, 42297-06-3; 7, 42297-07-4; 8, 42297-08-5; 9, 42297-09-6; 11, 42297-10-9; 12, 42297-11-0; 13, 42297-12-1; *N*-nitrosopyrrolidine, 930-55-2; pyrrolidine, 123-75-1; dimethylnitrosamine, 62-75-9; diethylnitrosamine, 55-18-5; dimethyl acetylenedicarboxylate, 762-42-5; *N*-phenylmaleimide, 941-69-5; *N*-nitrosopiperidine, 100-75-4; *N*-methyl-*N*-*tert*-butylnitrosamine, 7068-83-9.

Supplementary Material Available.—Nmr data for compound 7 freshly dissolved in CCl_4 and after standing for 3 hr and 4 days and for compound 8 in CCl_4 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4259.

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Reactions of Lithium Diorganocuprates(I) with Oxiranes

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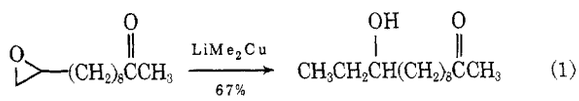
Lithium diorganocuprates have been shown to be highly effective reagents for the nucleophilic ring opening of oxiranes in the trans manner. These reactions occur more rapidly in diethyl ether than in tetrahydrofuran. Evidence and precedent for a mechanism involving the formation of a triorganocopper(III) intermediate is discussed. The selectivity of lithium diorganocuprates in reactions with substrates containing epoxide along with other electrophilic sites is discussed in terms of the hard and soft acid–base theory.

The nucleophilic ring opening of oxiranes by organometallic reagents is a frequently used method for the generation of new carbon–carbon σ bonds;[1] in many cases the utility of the reaction is curtailed owing to competing reactions arising from the Lewis acidity or the basicity of the organometallic reagent. We have observed that lithium diorganocuprates(I) are capable of ring opening of oxiranes under very mild conditions. In a series of preliminary communications,[2-4] we have demonstrated the ability of these reagents to circumvent many of the troublesome side reactions frequently encountered in the reactions of other organometallic reagents with oxiranes. In order to conserve journal space our published results will be summarized in a brief manner in the following paragraphs. The main body of this paper is largely concerned with extensions of our earlier results and mechanistic discussion. The Experimental Section of this paper includes details of certain key experiments described in the earlier communications.

In the introductory communication[2] the reactions of cyclohexene oxide with methyl- and phenyllithium were compared with the corresponding lithium diorganocuprates(I). The results indicated that the cuprates were more reactive toward oxiranes and were somewhat superior in terms of yields of trans nucleophilic addition products. Polymeric methylcopper and methylcopper complexes with trimethyl phosphite or tri-*n*-butylphosphine were unreactive toward cyclohexene oxide, whereas lithium methylcyanobis(triethyl phosphite)copper(I) reacted only slightly. In these ring-opening reactions of oxiranes the lithium ion is undoubtedly lending an electrophilic assist by coordination with the oxirane oxygen. In contrast to the coupling reactions of organocuprates and alkyl halides,[5] these oxirane reactions proceed more rapidly in diethyl ether than in THF. The latter solvates the lithium ion more effectively to the detriment of the lithium ion–oxirane complex. Perhaps the most significant observation was that lithium diorganocuprates could selectively ring open oxiranes in the presence of unprotected carbonyl functions (ester or ketone), *e.g.*, eq 1.



(1)

In the second communication[3] we compared the reactions of methylmagnesium, methyllithium, and methylcopper reagents with 1,2-epoxybutane and 1,2-epoxy-3-butene.[6] With the latter substrate methylmagnesium reagents gave 16–68% conjugate addition (mixture of *cis*- and *trans*-2-penten-1-ol), methyllithiums gave 20–55%, and lithium dimethylcopper gave 94%. The conjugate mode of addition of lithium dialkylcuprates to α,β-unsaturated carbonyl compounds,[7,8] allylic acetates,[9] and propargylic acetates[10] had already been documented. More recently we reported on the regio- and stereoselectivity of the reactions of methyl-

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