Reduction of Alkynes by a New Reducing System: Calcium Metal in Amines

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Alkali-metal (Li, Na) reductions of acetylenes in low-molecular-weight amines and ammonia are well documented.[1] Dialkylacetylenes afford the corresponding *trans*-alkenes[1a] while terminal acetylenes are primarily metalated.[1b] However, terminal acetylenes can be reduced quantitatively to the corresponding terminal alkenes[1b] by sodium in liquid ammonia containing ammonium sulfate. By contrast, lithium[2] in ethylenediamine reduces 1-heptyne to *n*-heptane. Reduction of a dialkylacetylene by excess lithium in refluxing ethylamine (17 °C) affords appreciable quantities of saturated product,[1c,3] whereas similar reductions by sodium in ammonia stop cleanly at the alkene.[1a] The reduction of dialkylacetylenes by calcium hexamine [$Ca(NH_3)_6$] in diethyl ether yields the corresponding *trans*-alkenes[4] similar to sodium and lithium reductions.[1] The present work has been undertaken to determine how the new[5] reducing system consisting of calcium in a mixture of methylamine and ethylenediamine (1:1 v/v) reacts with both terminal and internal alkynes.

All the runs depicted in Table I (except 5 and 12) were carried out with a 25% excess of calcium in a mixture of methylamine and ethylenediamine (75 mL of each). These afforded the corresponding *trans*-alkenes in yields of 70–88% with purities of 72–91%. Similar treatment of 2-nonyne and 4-octyne (runs 5 and 12 in Table I) with a solvent of pure ethylenediamine and a 100% excess of calcium afforded products in which the percentage of the corresponding alkene was significantly diminished.

Reduction of 1-heptyne (run 13, Table II) with calcium (25% excess) in the mixed-amine solvents afforded 94% of a mixture containing 47% unreacted alkyne, 6% *n*-heptane, and only 18% 1-heptene, which strongly suggested that metalation had occurred. The 3:1 ratio of 1-heptene to *n*-heptane would seem to indicate that 1-heptene, once formed, was being reduced to *n*-heptane.[6] This was substantiated when treatment of 1-heptyne with a 5-fold excess of calcium afforded 70% of a mixture containing 87% *n*-heptane (run 14, Table II).

No unreacted dialkylacetylenes remained when a 25% excess of calcium was used except in runs 1, 8, and 10, Table I. In these cases the reaction was stopped just prior to consumption of all the calcium. This suggested that a direct reaction between calcium and the amine solvents does not compete as well in alkyne reductions as in the reductions of aromatic hydrocarbons, which required larger excesses of calcium.[5a,c]

Significant amounts of material reported as "unknown" in Table I (runs 4 and 5) resulted in those cases which were carried out in ethylenediamine alone but were not found in reductions of the dialkylacetylenes in the mixed-amine solvent system.

Reduction of 2-, 3-, and 4-nonyne not only afforded the corresponding *trans*-alkene but also, to a much lesser extent, both of the possible isomeric *trans*-alkenes (Table I). Likewise, reduction of 4-octyne resulted in both 2- and 3-octene as minor products (Table I).

In order to establish whether these isomeric *trans*-alkenes were formed by a base-catalyzed[7] isomerization of the double bond in the major product, *trans*-4-nonene was subjected to the conditions of reduction but no *trans*-2- or *trans*-3-nonene could be detected, thus negating this hypothesis.

Another possibility was that the *cis*-alkene formed first and was subsequently isomerized to its trans isomer. However, when *cis*-4-nonene was subjected to the conditions of the reduction, it was found to be stable.

The reduction of 2-nonyne (run 1, Table I) in the mixed-amine solvent system was almost complete at the end of 5 h since only 1% of the unreacted alkyne remained. Extending reaction times to 8 h (run 2, Table I) or even to 20 h (run 3, Table I) did not significantly affect the product composition, again indicating that the products once formed were stable. This was also true for the other dialkylacetylenes in Table I.

Experimental Section

All gas chromatographic analyses were carried out on a Varian Model 3700 capillary instrument equipped with a Hewlett-Packard 3390A integrator. The ^{13}C NMR spectra were obtained on a Varian XL-200 spectrometer operating at 50.3 MHz in 10-mm tubes. All chemical shifts are reported in parts per million relative to tetramethylsilane. The ^{13}C NMR spectra were recorded with spectral widths of 10 000 Hz and 16 000 data points zero-filled to 32K. The calcium shot (99.5% pure) used in all of this work was purchased from Alfa Products.

General Procedure for Reduction of Dialkylacetylenes with Calcium–Methylamine–Ethylenediamine (See Table I). Methylamine (75 mL, Matheson) was distilled through a potassium hydroxide drying tube into a 500-mL three-neck, round-bottomed flask equipped with a mechanical stirrer, gas inlet tube, and a reflux condenser through which ethylene glycol was circulated (−25 °C).[8] All exits were protected with a U-tube of mercury. The dialkylacetylene (50 mmol) to be reduced, calcium shot (0.0625 mol, 2.51 g), and ethylenediamine (75 mL, Aldrich) freshly distilled from sodium were placed in the reaction flask. The mixture was then stirred for the indicated amount of time (Table I). If the reaction became too vigorous it was controlled with a dry ice–acetone bath or by surrounding the flask with a small amount of dry ice. Prolonged cooling caused the reaction to stop (it resumed when allowed to warm up) and the ethylenediamine to solidify. A gray solid[7] formed during the reaction, which often sparked when dry upon exposure to the atmosphere and reacted vigorously with water. The methylamine was allowed to evaporate by disconnecting the cooling liquid from the condenser. The flask was cooled to 0 °C (ice–water bath) and 200 mL of diethyl ether were added. The mixture was hydrolyzed by the cautious, dropwise addition of 200 mL of 2 M aqueous NH_4Cl. A vigorous reaction accompanied this addition. The layers were separated and the aqueous layer was extracted with two 75-mL portions of diethyl ether. The organic extracts were combined with the organic phase from the reaction mixture and washed with two 75-mL portions of water, two 75-mL portions of 2 N HCl, 75 mL of 5% $NaHCO_3$, and 75 mL of brine, and then dried over anhydrous Na_2SO_4. The solvent was removed by fractional distillation through a 4 in. vacuum-jacketed column.

(1) For some pertinent references, see: (a) Campbell, K. N.; Eby, L. T. *J. Am. Chem. Soc.* **1941**, *63*, 216, 2683. (b) Henne, A. L.; Greenlee, K. W. *Ibid.* **1943**, *65*, 2020. (c) Benkeser, R. A.; Schroll, G.; Sauve, D. M. *Ibid.* **1955**, *77*, 3378.

(2) Reggel, L.; Friedel, R. A.; Wender, I. *J. Org. Chem.* **1957**, *22*, 891.

(3) If reduction is performed at −78 °C with only a small excess of lithium, the *trans*-alkene is obtained in good yield.[1c]

(4) Campbell, K. N.; McDermott, J. P. *J. Am. Chem. Soc.* **1945**, *67*, 282.

(5) (a) Benkeser, R. A.; Belmonte, F. G.; Kang, J. *J. Org. Chem.* **1983**, *48*, 2796. (b) Benkeser, R. A.; Kang, J. *Ibid.* **1979**, *44*, 3737. (c) Benkeser, R. A.; Belmonte, F. G.; Yang, M. *Synth. Commun.* **1983**, *13*, 1103.

(6) Terminal alkenes are reduced with excess calcium in the mixed-amine solvent system to the corresponding alkanes. Benkeser, R. A., Rappa, A., unpublished results.

(7) A calcium–alkyl amide base of unknown structure forms over the course of these reductions. It is a gray solid which, at least partially, precipitates out of solution. See ref 5a for additional information.

(8) A dry ice–acetone condenser works equally well.

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Table I. Reduction of Acetylenes with Calcium-Methylamine-Ethylenediamine

acetylene[b]	reaction time, h	yield, % (bp, °C)[c]	product composition,[a] %				
			trans-2-alkene[d]	*trans*-3-alkene[d]	*trans*-4-alkene[d]	unreacted	unknown
			2-Nonyne				
1[g]	5	87 (146-148)	86	8	4	1	1
2	8	70 (139-146)	91	5	1	0	3
3	20	80 (138-148)	91	6	2	0	1
4[e]	22	82 (144-148)	66	10	8	0	16
5[e,f]	25	82 (148-150)	69	12	11	0	8
			3-Nonyne				
6	4	88 (139-142)	10	79	10	0	1
7	23	85 (138-148)	13	72	14	0	1
			4-Nonyne				
8[g]	7	85 (140-148)	1	5	78	12	4
9	13	75 (144-148)	2	8	90	0	0
			4-Octyne				
10[g]	7	75 (120-124)	1	9	88	1	1
11	23	77 (118-123)	2	11	87	0	0
12[e,f]	26	78 (119-122)	9	17	71	0	3

[a] Product composition determined by GLPC analysis on an SE-30 capillary column (60 m × 0.25 mm) at 65 °C for 2-, 3-, and 4-nonyne reductions and at 45 °C for 4-octyne reductions. [b] Purchased from Farchan Division, Chemsampco, Inc. [c] At atmospheric pressure. [d] Identified by comparison of gas chromatographic, ^{13}C NMR, and ^{1}H NMR data to that of authentic samples. [e] Reduction in ethylenediamine alone. At the end of these reductions a small amount of unreacted calcium remains, which has a dark coating on its surface. This is in contrast to the mixed-amine solvent system where the calcium is almost always completely consumed. Reductions in methylamine alone were not attempted since reduction of aromatic hydrocarbons proceeds very poorly in this solvent (see ref 2a). [f] Calcium (0.10 mol) was used. [g] Reaction was stopped just prior to consumption of all the calcium.

Table II. Reduction of 1-Heptyne with Calcium-Methylamine-Ethylenediamine

1-heptyne[b]	reaction time, h	yield,[e] %	product composition,[a] %				
			trans-2-heptene[c]	*n*-heptane	1-heptene[d]	unreacted	unknown
13	19	94	21	6	18	47	8
14[f]	18	70	7	87	3	1	2

[a] Product composition determined by GLPC using an SE-30 capillary column (15 m × 0.25 mm) at 45 °C. [b] Purchased from Farchan Division, Chemsampco, Inc. [c] Identified by gas chromatographic retention time, ^{13}C NMR, and ^{1}H NMR data to that of an authentic sample kindly supplied by Professor H. C. Brown. [d] Identified by gas chromatographic retention time, ^{13}C NMR, and ^{1}H NMR data to that of an authentic sample purchased from Aldrich Chemical Co. [e] Yields determined by gas chromatography. [f] Calcium (0.30 mol) used in reduction. Concentrated HCl (50 mL) added dropwise after addition of 2 M NH_4Cl to complete the solution of the calcium salts.

A short-path distillation of the remaining oil yielded the product.

General Procedure for Reduction of Dialkylacetylenes with Calcium in Pure Ethylenediamine (Runs 4, 5, and 12; Table I). The procedure was the same as that used for reductions in the mixed-amine solvent system except that 75 mL of ethylenediamine only was used as the solvent.

Reduction of 1-Heptyne with Calcium–Methylamine–Ethylenediamine (Runs 13 and 14, Table II). The procedure was the same as that for the reduction of the dialkylacetylenes except that an internal standard (*n*-nonane, Phillips, 99%) was used because of the volatility of the products. The internal standard was added at the start along with the reactants. Analysis was performed by gas chromatography. Response factors were determined for all of the identified reduction products by using authentic samples. Unknown products were assumed to be alkenes with response factors similar to that of 1-heptene. Product analysis was performed on material obtained from the dried (Na_2SO_4) ether solution.

Preparation of Authentic Trans Isomers. Authentic samples of *trans*-2-, *trans*-3-, and *trans*-4-nonenes as well as the corresponding *trans*-octenes were synthesized independently by reduction of their respective alkynes using lithium in ethylamine.[1c] All of these *trans*-alkenes were obtained in 99+% purity. Their physical properties (NMR spectra, bp, etc.) agreed well with published values.[9]

Attempted Isomerization of *trans*-4-Nonene. The general procedure for reduction of dialkylacetylenes with calcium–methylamine–ethylenediamine was followed with *trans*-4-nonene (6.31 g, 50 mmol) as the substrate. By the end of 13 h, all of the calcium was consumed and a gray solid[7] had formed. The mixture was stirred for an additional 24 h. The usual workup afforded 5.57 g (44 mmol, 88%) of *trans*-4-nonene (bp 145–148 °C, ~1 atm). Neither isomerization or reduction products could be detected.

Attempted Isomerization of *cis*-4-Nonene. The general procedure for reduction of dialkylacetylenes with calcium–methylamine–ethylenediamine was followed. Calcium (5.02 g, 0.125 mol) and 6.31 g (50 mmol) of a 66:19:15 mixture[10] of *cis*-4-nonene, *n*-nonane, and *trans*-4-nonene, respectively, were used. After 61 h the reaction had not started and all of the calcium remained unchanged. Benzene (1.95 g, 25 mmol) was then added to initiate the reaction.[11] Reaction started within a few minutes and all of the calcium was consumed by the end of 5 h. The mixture was stirred for an additional 19 h. The usual workup afforded 5.55 g (44 mmol, 88%) of a 66:19:15 mixture of *cis*-4-nonene, *n*-nonane, and *trans*-4-nonene, respectively, as a clear oil (bp 116–143 °C, ~1 atm).

(9) "Dictionary of Organic Compounds", 5th ed.; Chapman and Hall: New York, 1982; Sadtler, Standard NMR Spectra Collection.

(10) The method of Campbell and Eby for the preparation of *cis*-alkenes from acetylenes was employed. See ref 1a.

(11) The calcium–alkyl amides formed during the reduction of benzene have been found to catalyze the direct reaction between calcium and the amine solvents. Benkeser, R. A., Rappa, A., unpublished results.

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Registry No. Calcium, 7440-70-2; methylamine, 74-89-5; ethylenediamine, 107-15-3; 2-nonyne, 19447-29-1; 3-nonyne, 20184-89-8; 4-nonyne, 20184-91-2; 4-octyne, 1942-45-6; 1-heptyne, 628-71-7; *trans*-2-nonene, 6434-78-2; *trans*-3-nonene, 20063-92-7; *trans*-4-nonene, 10405-85-3; *cis*-4-nonene, 10405-84-2; *trans*-2-octene, 13389-42-9; *trans*-3-octene, 14919-01-8; *trans*-4-octene, 14850-23-8; *trans*-2-heptene, 14686-13-6; *n*-heptane, 142-82-5; 1-heptene, 592-76-7.

Halogen-Activated Smiles Rearrangement. 2

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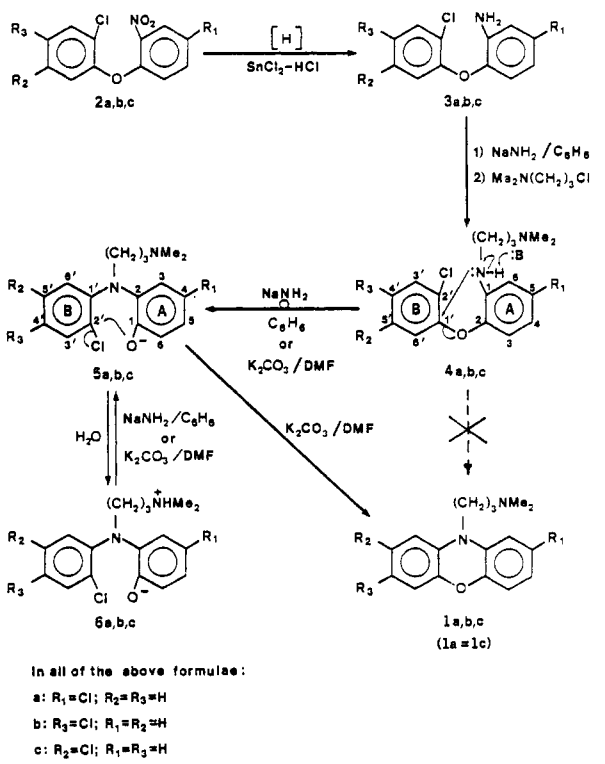
Ring-substituted-10-[3-(dimethylamino)propyl]phenoxazines were previously of interest for pharmacological screening. 2-Chloro-10-[3-(dimethylamino)propyl]phenoxazine (**1a**, $R_1 = R_2 = H$; $R_3 = Cl$) was of special interest since it is isosteric with chloropromazine. The chemistry that developed in the syntheses of **1a** resulted in two papers[1] describing three successful approaches. Two of the routes involved cyclization of an (*o*-halophenoxy)aniline derivative (see **4** → **1**, Scheme I) "directly", and cyclization of a Smiles-rearranged[2] diphenylamine derivative (**6** → **5** → **1**).

The previous experiments did not adequately distinguish the two routes described above. Although we prepared phenoxazine **1a**[1c] "directly" from the *o*-amino-*o'*-bromodiphenyl ether **4a** with K_2CO_3 in DMF, we could not be sure that the diphenylamine **5a**, resulting from Smiles rearrangement of **4a**, was not an intermediate; i.e., **4a** ⟶ [**5a**] → **1a**.[3] All of the previous intermediates (e.g., **4a**)[1c] had substituents on ring A and none on ring B (except for the *o*-bromo group lost on ring closure). Rearrangement occurs on ring B; therefore, evidence for it could only be obtained with the appropriate substituents on ring B.

Rearrangements of **4** to **5** were the first examples[1b] of a Smiles rearrangement in which only a halogen-atom activated ring B (Scheme I). The diphenylamine **5a** with K_2CO_3 in *N,N*-dimethylformamide (DMF) afforded the phenoxazine **1a**, which was also obtained "directly" from

Scheme I



the diaryl ether **4a**.[1c] The latter reaction could proceed either via the diphenylamine intermediate **5a**[1c] or by direct cyclization of **4a**.[1c] The latter course (with K_2CO_3 in DMF) was favored since carbonate was considered to be a weak base incapable of generating the anilino-nitrogen's conjugate base of **4a**, considered essential for the Smiles rearrangement to occur.

Similar rearrangements, derived from our earlier study,[1b] have appeared in the literature. Since the rearranged isomers were not reported, they apparently were not isolated.[4,5]

We now report that the phenoxazines **1b** and **1c** prepared "directly" from the *o*-aminophenyl phenyl ethers **4b** and **4c** containing chloro substituents on ring B must indeed be formed via the "Smiles-rearranged" diphenylamine isomers **5b** and **5c**, respectively. The substrates chosen in this study were *N,N*-dimethyl-*N'*-[2-(2,4-dichlorophenoxy)phenyl]-1,3-propanediamine (**4b**, $R_3 = Cl$; $R_1 = R_2 = H$) and *N,N*-dimethyl-*N'*-[2-(2,5-dichlorophenoxy)-phenyl]-1,3-propanediamine (**4c**, $R_2 = Cl$; $R_1 = R_3 = H$). They were prepared by transformations analogous to those reported.[1] The preparation of the diphenyl ether intermediates **2** by the Ullmann reaction was greatly improved. Coupling[6] of the appropriate sodium phenolate and aryl halide in Me_2SO at 140 °C eliminated the cumbersome pyrolytic condensations. The products (**2**) were obtained in better than 80% yields. Reduction of **2** as previously described[1] gave the corresponding *o*-phenoxyanilines **3**, isolated as the hydrochlorides.

The key intermediates **4b** and **4c** (Scheme I) were prepared from the appropriate *o*-phenoxyanilines **3b** and **3c**, respectively, as previously described.[1] Intermediates **4b** and **4c** both rearranged in benzene and $NaNH_2$ to the corresponding *o*-anilinophenols (**4** ⟶ **5**), i.e., **4b** rearranged to 2-[2,4-dichloro-*N*-[3-(dimethylamino)-

(1) (a) Bonvicino, G. E.; Yogodzinski, L. H.; Hardy, R. A., Jr. *J. Org. Chem.* **1961**, *26*, 2797. (b) *Ibid.* **1962**, *27*, 4272. (c) A bromine atom was at the 2'-position of ring B of intermediates **2–6**, instead of a chlorine atom as shown in Scheme I.

(2) (a) Smiles, S.; et al. *J. Chem. Soc.* **1931**, 914 and succeeding papers. (b) Bunnett, J. F.; Okamoto, T. *J. Am. Chem. Soc.* **1956**, *78*, 5363. (c) Bunnett, J. F. *Q. Rev. Chem. Soc.* **1958**, *12*, 1. (d) Shine, H. J. "Aromatic Rearrangements"; Elsevier: Amsterdam, 1967; pp 307–316. (e) Truce, W. E.; Kreider, E. M.; Brand, W. W. "Organic Reactions"; Wiley: New York, 1970; Vol. XVIII, Chapter 2. (f) Stevens, T. S.; Watts, D. W. "Selected Molecular Rearrangements"; Van Nostrand Reinhold: New York, 1973; pp 120–124.

(3) The notation **4** ⟶ [**5**] means that **4** rearranges to **5** and that **5** was not isolated; **4** ⟶ **5** means that **4** rearranges to **5** and that **5** was isolated. (b) See: Grundmann, C.; Grunanger, P. "The Nitrile Oxides"; Springer-Verlag: Berlin, Heidelberg, 1971; p 7.

(4) Grundon, M. F.; Matier, W. L. *J. Chem. Soc. B* **1966**, 266.

(5) Nodiff, E. A; Hausman, M. *J. Org. Chem.* **1964**, *29*, 2453.

(6) Schmutz, J.; Kunzle, F.; Hunziker, F.; Burki, A. *Helv. Chim. Acta* **1965**, *48*, 336–347; *Chem. Abstr.* **1967**, *62*, 14681*b*.

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