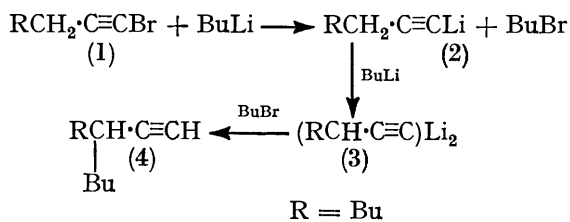


Chain Extension Reactions of Acetylenes. Part 2.† A Comparison of the Reactions of Butyl-lithium with 1-Iodoalk-1-ynes and 1-Bromoalk-1-ynes

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1-Iodohept-1-yne reacts with 2 equiv. of butyl-lithium to form octane and hept-1-yne, whereas 1-bromohept-1-yne undergoes butylation at C-3. In the presence of 1 equiv. of butyl-lithium, metal-halogen exchange gives butyl iodide and lithium hept-1-ynide, which couple to form undec-5-yne on addition of hexamethylphosphoric triamide. The reaction of 2 equiv. of butyl-lithium with either 1-bromo- or 1-iodo-propyne gives largely octane, but chain extension of 1-bromopropyne occurs to give hept-1-yne when 3 equiv. of butyl-lithium are used and butyl bromide is then added. Addition of iodine after butyl bromide gives 1-iodohept-1-yne.

1-HALOGENOALK-1-YNES react with organometallic reagents by metal-halogen exchange¹ [*e.g.* (1) → (2)]. Recently² it has been shown that when at least 2 equiv. of butyl-lithium react with 1-bromoalk-1-ynes (1) a dilithioacetylide (3) is formed, which undergoes butylation with butyl bromide generated *in situ* selectively at C-3, to give 3-butylalk-1-ynes (4) (Scheme 1).



In order to provide more information on the comparative aspects of alkylation of terminal acetylenes at

† Part 1, A. J. G. Sagar and F. Scheinmann, *Synthesis*, 1976, in the press.

¹ S. Y. Delavarene and H. G. Viehe in 'Chemistry of Acetylenes,' ed. H. G. Viehe, Dekker, New York, 1969, p. 109.

² A. J. Quillinan, E. A. Khan, and F. Scheinmann, *J.C.S. Chem. Comm.*, 1974, 1030, and references therein.

C-3, the reactions of 1-iodoalk-1-ynes were examined. The iodo-acetylenes are more stable than their 1-bromo-analogues, especially in the case of 1-iodo-³ and 1-bromo-propynes.⁴

The chain extension reactions of 1-iodohept-1-yne (5)⁵ were studied first. With 1 equiv. of butyl-lithium in hexane-ether at -60 °C, lithium heptynide (6) and butyl iodide are formed by a metal-halogen exchange reaction. The products could be coupled by addition of hexamethylphosphoric triamide at -20 °C to give undec-5-yne (7) in good yields. Undec-5-yne (7) has recently been prepared by Heathcock *et al.*⁶ from lithium hexynide with 1-chloropentane in hexamethylphosphoric triamide. Thus by making use of the metal-halogen exchange reaction¹ and the good alkylation behaviour of a terminal acetylide in dipolar aprotic solvents,⁶ one may use a 1-iodoalk-1-yne as an

³ F. F. Cleveland and M. J. Murray, *J. Chem. Phys.*, 1943, **11**, (10), 450.

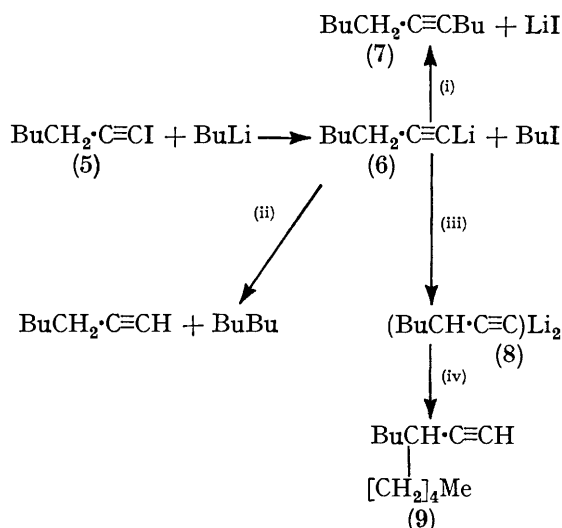
⁴ L. F. Hatch and L. E. Kidwell, jun., *J. Amer. Chem. Soc.*, 1954, **76**, 289.

⁵ L. Brandsma, 'Preparative Acetylenic Chemistry,' Elsevier, Amsterdam, London, and New York, 1971, p. 99.

⁶ D. N. Brattesani and C. H. Heathcock, *Synth. Comm.*, 1973, **3** (4), 245.

alternative starting compound for the synthesis of internal acetylenes.

The reaction of 1-iodohept-1-yne with 2 equiv. of butyl-lithium under similar conditions gave hept-1-yne and octane in good yields (Scheme 2). This result is in contrast with the reaction of 1-bromohept-1-yne (1), which under similar conditions undergoes alkylation at C-3.² Clearly with 1-iodohept-1-yne (5), after the metal-halogen exchange reaction, the butyl iodide formed reacts rapidly with butyl-lithium to give octane, so that no further base is available to form the dilithium acetylide. In order to form a dilithium acetylide (8) for alkylation at C-3, 1-iodohept-1-yne was treated with 3 equiv. of butyl-lithium followed by 1 equiv. of 1-bromopentane. From this reaction, 3-butyloct-1-yne (9)² was isolated as the main product; octane and hept-1-yne were also detected. Thus, in this case, alkylation at C-3 occurs by addition of external alkyl halide, provided sufficient base has been used to form the dilithium acetylide.

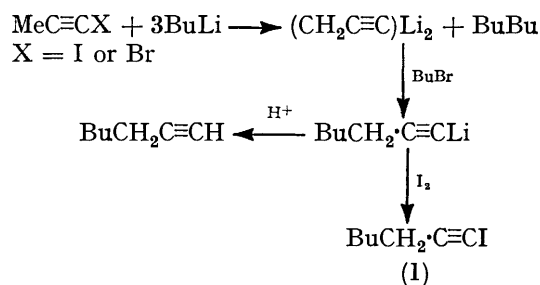


SCHEME 2 Reagents: i, $\text{PO}(\text{NMe}_2)_3$; ii, BuLi-H^+ ; iii, 2BuLi ; iv, $\text{Me}[\text{CH}_2]_4\text{Br}$

In order to investigate the possibility of linear chain extension reactions at C-3 of an alkyne, with preferably, a liquid propyne derivative, the reactions of 1-iodo- and 1-bromo-propyne were studied. Chain extension at both C-3 and C-1 would represent a new approach to the synthesis of substituted and internal acetylenes.

Treatment of 1-bromopropyne with 2 equiv. of butyl-lithium in hexane-ether at -60°C gave octane and varying amounts of hept-1-yne. The reaction of 1-iodopropyne with 2 equiv. of butyl-lithium in ether at -60°C gave largely octane, and butyl iodide was also identified. 1-Bromoprop-1-yne was then treated with 3 equiv. of butyl-lithium followed by butyl bromide in ether at -60°C , to give heptyne and octane. In another reaction, instead of working up by addition of water, addition of ethereal iodine led to 1-iodohept-1-yne (10) (Scheme 3). Thus by consecutive use of two different electrophiles, alkylation at C-3 was followed by

iodination at C-1. Similar results were obtained with the alkylation of 1-iodopropyne; in this case however more octane was formed owing to rapid reaction of the



SCHEME 3

butyl-lithium with the butyl iodide formed *in situ*. The above reactions were carried out with ether as co-solvent with hexane.

This work shows that octane is more readily formed from the reaction of an excess of butyl-lithium with 1-iodoalk-1-yne than in the corresponding reaction with 1-bromoalk-1-yne. Control experiments show that there is virtually no octane formation when butyl bromide is added to butyl-lithium at -60°C in hexane. Even at room temperature, no reaction occurs. In contrast, butyl iodide forms octane in addition to butyl-lithium within 5 min after addition. Addition of ether (in both cases) favours octane formation. Thus in 3 h butyl bromide gives 15% octane whereas butyl iodide gives octane in 85% yield.

The various products formed by treating 1-bromo- and 1-iodo-alk-1-yne with 2 equiv. of butyl-lithium therefore arise from the differing reactivities of the alkyl halides, formed by rapid metal-halogen exchange, with butyl-lithium.

EXPERIMENTAL

I.r. spectra (for liquid films) were recorded with a Perkin-Elmer 257 grating spectrophotometer and ^1H n.m.r. spectra with a Varian A-60 instrument. Mass spectra were measured with an A.E.I. MS12 spectrometer. G.l.c. analysis was carried out with a Perkin-Elmer 880 gas chromatograph (6 ft \times 0.125 in column packed with 11½% silicone oil MS555 and 11½% Bentone 34 on Chromosorb W; column temp. 102°C ; N_2 carrier gas pressure 16 lb in⁻²). Absolute yields were determined by internal standardisation with n-decane. Preparative g.l.c. was carried out with an Autoprep A-700 instrument, with helium as carrier gas (pressure 60 lb in⁻²). ^{13}C n.m.r. spectra were measured with a Varian CFT 320 spectrometer; assignments of the chemical shifts follow from off-resonance decoupled spectra and from comparison with calculated data. Calculated values are based on $\delta(\text{CH}_4) - 2.3$ p.p.m., with incremental values for α -substituents +8 p.p.m., β -substituents +10 p.p.m., and γ -substituents -2 p.p.m. for saturated carbon atoms; C-3 of an alk-1-yne is additionally influenced by the adjacent acetylene, and *ca.* 12 p.p.m. is subtracted for good agreement with experimental data.⁷

Preparation of Undec-5-yne.—A solution of heptyne
⁷ G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley-Interscience, New York, 1972, p. 71.

(2.6 g, 0.027 mol) in hexane (50 ml) was cooled to -60°C and stirred under nitrogen while *n*-butyl-lithium in hexane (2.7M; 10 ml) was added by syringe. After stirring for 6 h the solution of lithium hept-1-ynide was again cooled to -60°C and butyl bromide (3.75 g, 0.027 mol) in dry hexamethylphosphoric triamide (50 ml) was added dropwise during 0.5 h. The solution was stirred overnight and then diluted with water (100 ml). The aqueous solution was twice extracted with hexane and the combined extracts were washed with water and saturated sodium chloride solution and dried (K_2CO_3). Removal of the solvent and fractional distillation gave (g.l.c. estimates) hept-1-yne (2%), octane (6%), 3-butylhept-1-yne (5%), and undec-5-yne (80%), b.p. 80° at 10 mmHg (lit.,⁸ 113° at 61 mmHg); ν_{max} (film) 2 950 and 2 120 cm^{-1} ($\text{C}\equiv\text{C}$); τ (CDCl_3) 7.9 (m, $2 \times \text{C}\equiv\text{C}\cdot\text{CH}_2$), 8.7 (m, $5 \times \text{CH}_2$), and 9.15 (t, $2 \times \text{CH}_2$), M^+ 152 (Found: C, 86.6; H, 13.0. Calc. for $\text{C}_{11}\text{H}_{20}$: C, 86.8; H, 13.15%); δ_{C} 79.87 (s, C-5 and -6), 31.91 and 31.60br (m, C-3 and -9), 29.48 (t, C-8), 22.75 and 22.34 (t, C-2 and -10), 19.12 and 18.83 (t, C-4 and -7) and 14.19 and 13.80 (q, C-1 and -11). With dimethyl sulphoxide instead of hexamethylphosphoric triamide as solvent the yield of undec-5-yne was only ca. 55%.

Reaction of 1-Iodohept-1-yne with Butyl-lithium in Hexane-ether.—(a) *With one equivalent of butyl-lithium.* To a cooled (-60°C) solution of 1-iodohept-1-yne⁵ (1.11 g, 0.005 mol) in dry ether (20 ml), butyl-lithium in hexane (2.35M; 4 ml) was added, and the solution was stirred under nitrogen for 12 h. A small portion was worked up by adding water, and the hexane layer was examined by g.l.c. Hept-1-yne (43%) and butyl iodide (40%) are the major products.

The reaction mixture was again cooled to -20°C , dry hexamethylphosphoric triamide (20 ml) was added, and the mixture was stirred overnight. Work-up in the usual manner and g.l.c. analysis indicated the presence of hept-1-yne (5%) and undec-5-yne (61%). Fractional distillation gave undec-5-yne, b.p. 80° at 10 mmHg (lit.,⁸ 113° at 61 mmHg) in 54% yield, identical with the material described above.

(b) *With two equivalents of butyl-lithium.* 1-Iodohept-1-yne (2.66 g, 0.012 mol) was stirred in dry ether (50 ml) at -60°C , and butyl-lithium in hexane (2.35M; 9.6 ml) was added. After stirring overnight, water was added and the product worked up as usual. G.l.c. showed hept-1-yne and octane as the major products, with a trace of butyl iodide. Careful fractional distillation gave hept-1-yne (45%), b.p. 98.5° (lit.,⁹ 99.78°), and octane (49%), b.p. $126\text{--}128^{\circ}$ (lit.,¹⁰ 125.59°).

(c) *With three equivalents of butyl-lithium and one equivalent of 1-bromopentane.* A solution of butyl-lithium in hexane (2.35M; 10 ml) was added to a cooled (-60°C) solution containing 1-iodohept-1-yne (0.85 g, 0.004 mol) in dry ether (50 ml). The mixture was stirred overnight under nitrogen. Freshly distilled 1-bromopentane (0.45 g, 0.004 mol) in dry ether (10 ml) was then added, and stirring continued overnight. Water (100 ml) was added to the mixture, and the organic layer was separated, washed, and dried. The following products were identified by g.l.c. analysis: hept-1-yne (10%), octane (8%), and 3-butyloct-1-yne (52%), b.p. $110\text{--}115^{\circ}$ at 18 mmHg; ν_{max} (film) 3 320, 2 950, and 2 150 cm^{-1} ($\text{C}\equiv\text{C}$); τ (CDCl_3) 8.95 (t, $2 \times \text{CH}_3$), 8.5 (m, $7 \times \text{CH}_2$), 7.9 (m, $\text{C}\equiv\text{C}\cdot\text{CH}$), and 7.6 (d, $\text{C}\equiv\text{CH}$);

⁸ K. N. Campbell and M. J. O'Connor, *J. Amer. Chem. Soc.*, 1939, **61**, 2897.

δ_{C} 88.32 [d (long-range coupling), C-2], 68.89 (d, C-1), 35.02 (t, C-4 or -1'), 34.77 (t, C-1' or -4), 31.78 (t, C-6), 31.58 (d, C-3), 29.58 (t, C-3'), 26.97 (t, C-5), 22.61 ($2 \times$ t, C-7 and -3'), and 14.10 ($2 \times$ q, C-8 and -4'), *m/e* (M^+ not observed) 109 ($M - \text{C}_4\text{H}_9$) and 95 ($M - \text{C}_5\text{H}_{11}$). The structure of 3-butylhept-1-yne was confirmed by comparison with a sample prepared by treating dilithiohept-1-yne with 1-bromopentane.²

Reaction of Butyl Bromide with One Equivalent of Butyl-lithium in Hexane-Ether.—Freshly distilled butyl bromide (3.23 g, 0.024 mol) in hexane (10 ml) was added to a stirred solution containing butyl-lithium in hexane (2.35M; 12 ml) at -60°C . Samples (0.5 ml) were withdrawn after 5, 10, 15, 20, 30, 40, and 50 min and after 1 h, and in each case the reaction was quenched with water and the product(s) were examined by g.l.c. Unchanged butyl bromide was the only major component and no octane was formed. Even after 12 h stirring, no octane was detected by g.l.c. Dry ether (10 ml) was then added to the reaction mixture and the reaction was monitored after every hour in the same manner. The amount of octane detected after 6 h stirring was 15%. Distillation of the mixture at atmospheric pressure gave octane (12.5%), b.p. $126\text{--}128^{\circ}$ (lit.,¹⁰ 125.5°) and butyl bromide (76%), b.p. $100\text{--}101^{\circ}$ (lit.,¹¹ 101.2°), identical with authentic samples.

Reaction of Butyl Iodide with One Equivalent of Butyl-lithium in Hexane-Ether.—Butyl iodide (4.30 g, 0.024 mol) in hexane (10 ml) was added to a cooled (-60°C), stirred solution of butyl-lithium (2.35M; 12 ml) in hexane. Small samples were withdrawn after 5, 10, 15, 20, 30, 40, and 50 min and after 1 h; the reaction was quenched in each case with water and the product(s) were examined by g.l.c. Octane had been formed even after 5 min, and after 1 h the yield was ca. 40%. Dry ether (10 ml) was then added to the same solution and the samples were analysed after every hour. After 3 h the mixture was worked up as in the previous experiment and distillation yielded octane (85%).

Reactions of 1-Bromo- and 1-Iodo-prop-1-yne with Two Equivalents of Butyl-lithium in Hexane-Ether.—Butyl-lithium in hexane (2.7M; 10 ml) was added to a stirred solution of 1-bromoprop-1-yne⁴ (1.25 g, 0.01 mol) in dry ether (10 ml) at -60°C under nitrogen. An initial white precipitate slowly turned yellow. After stirring overnight (16–20 h), the reaction was worked up in the usual manner and the products were examined by g.l.c. Octane, the major product, was obtained in 53% yield (also isolated by preparative g.l.c.). The amount of hept-1-yne formed was variable; the highest yield was 30%.

Similarly, 1-iodoprop-1-yne³ gave octane (63%) and butyl iodide, which was identified by g.l.c. peak enhancement with an authentic sample. In this case, no hept-1-yne was detected by g.l.c.

Reactions of 1-Bromo- and 1-Iodo-prop-1-ynes with Three Equivalents of Butyl-lithium and One Equivalent of Butyl Bromide.—1-Bromoprop-1-yne (0.8 g, 0.066 mol), was stirred at -60°C in dry ether (10 ml). A solution of butyl-lithium in hexane (2.7M; 7 ml) was added and the solution stirred under nitrogen for 12 h. It was again

⁹ A. L. Henne and K. W. Greenlee, *J. Amer. Chem. Soc.*, 1945, **67**, 484.

¹⁰ A. F. Shepard, A. L. Henne, and T. Midgley, jun., *J. Amer. Chem. Soc.*, 1931, **53**, 1949.

¹¹ E. L. Skau and R. McCullough, *J. Amer. Chem. Soc.*, 1935, **57**, 2440.

cooled to -60°C , freshly distilled butyl bromide (1.0 g, 0.066 mol) was added, and the stirring was continued overnight. Work-up in the usual manner (with g.l.c. estimation) gave octane (49%), hept-1-yne (40.5%), and butyl bromide (trace). Preparative g.l.c. gave the pure products, which were identical with authentic samples.

With 1-iodoprop-1-yne as the starting material, the yields of octane and hept-1-yne were 65 and 25%, respectively.

1-Iodohept-1-yne.—1-Bromoprop-1-yne was treated with 3 equiv. of butyl-lithium and 1 equiv. of butyl bromide as in the previous experiment. Instead of adding water, a solution of iodine (1.75 g, 0.066 mol) in ether was added at 0°C . Octane (45%), 1-iodohept-1-yne (32%), and hept-1-yne (6.5%) were isolated by preparative g.l.c.

Use of 1-iodoprop-1-yne instead of 1-bromoprop-1-yne gave octane (68.5%) and 1-iodohept-1-yne (30%), b.p. $78-80^{\circ}$ at 12 mmHg (lit.,⁵ 78° at 10 mmHg); ν_{max} (film) 2 950 and 2 200 cm^{-1} ($\text{C}\equiv\text{C}$); τ (CDCl_3) 7.5 (t, $\text{CH}_2\cdot\text{C}\equiv\text{C}$), 8.5 (m, $3 \times \text{CH}_2$), and 9.0 (m, CH_3); M^+ 222; δ_{C} 94.25 (s, C-2), 31.06 (t, C-5), 28.41 (t, C-4), 22.34 (t, C-3 or -6), 20.90 (t, C-3 or -6), 14.06 (q, C-7), and -6.34 (s, C-1).

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