An Improved Synthesis of Cyclic Dialkynes

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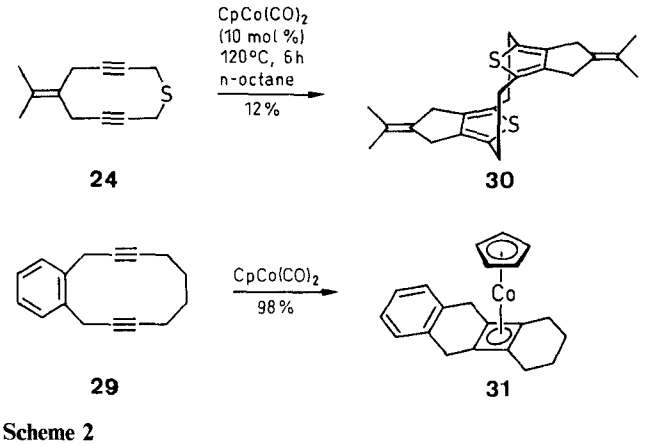
Received 9 November 1992

An improved synthesis of 1,7-cyclododecadiyne **17** (35%), 1,7-cyclotridecadiyne **18** (65%), 1,8-cyclotetradecadiyne **19** (85%), 1,8-cyclopentadecadiyne **20** (65%), 1,9-cyclohexadecadiyne **21** (55%), 1,10-cyclooctadecadiyne **22** (48%) and 1,12-cyclodocosadiyne **23** (27%) is reported. This is achieved by treating the dilithium salts of diterminal dialkynes with α,ω-dihalogenides. As side products, tetraynes are isolated in yields of 1–5%. Furthermore, the synthesis of 6-isopropylidenethiacyclodeca-3,8-diyne **(24)** and [10]orthocyclophane-2,8-diyne **29** is reported. The reaction of **24** with $CpCo(CO)_2$ yields a [2.2](2,5)thiophenophane derivative **30** while **29** gives an intramolecular cyclobutadiene complex **31**.

Cyclic dialkynes are versatile starting materials for the synthesis of metal complexes, superphanes and cage compounds.[1] A straightforward method for their preparation is the cyclization of acyclic diterminal diacetylenes with α,ω-dihalogen compounds. Several methods for this synthetic approach have been developed,[2–5] however, in most cases the somewhat cumbersome use of liquid ammonia[2] or highly carcinogenic hexamethylphosphoric acid triamide[3] is required and the yields leave much to be desired. Recently, we have reported the synthesis of a series of skipped cyclic ene- and dienediynes[6] via the cyclization of dilithium salts of diterminal enediynes with dihalogen compounds in boiling tetrahydrofuran. In this communication we present the results of our investigations concerning the extension of this method for the preparation of known carbocyclic dialkynes of ring size 10 to 22 and of a new heterocyclic diyne and [10]orthocyclophane-2,8-diyne.

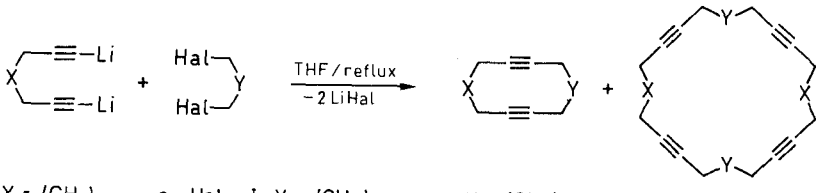
The reaction of the dilithium salts of the diterminal diynes **1–6**,[8] (Scheme 1) with the dihalogenides **9–14** in boiling tetrahydrofuran affords the carbocyclic diynes **16–23**. As side products the macrocyclic tetraynes **25–28** could be isolated in small yields. In the Table, the yields are compared with those reported in the literature. The reaction of the lithium salt of 4-thia-1,6-heptadiyne **(7)**[7] with isopropylidene-1,3-dibromopropane **(15)** leads to the new heterocyclic diyne 6-isopropylidenethiacyclodeca-3,8-diyne **(24)** in 10% yield. Reaction of the dilithium salt of *o*-dipropargylbenzene **(8)**[9] with 1,4-diiodobutane **(10)** affords [10]orthocyclophane-2,8-diyne **29** (Scheme 1) in 4% yield.

The reactions of the diynes **24** and **29** with $CpCo(CO)_2$ in *n*-octane are summarized in Scheme 2. Both, **24** and **29** show a similar behaviour as their respective parent compound thiacyclo-3,8-diyne[10] and 1,7-cyclododeca-



24 **30** **29** **31**

Scheme 2



a. X = $(CH_2)_n$
1 n = 1
2 n = 2
3 n = 3
4 n = 4
5 n = 5
6 n = 7

b. X = S
7

c. X =
8

a. Hal = I, Y = $(CH_2)_m$
9 m = 1
10 m = 2
11 m = 3
12 m = 4
13 m = 5
14 m = 7

b. Hal = Br, Y = C=C(Me)(Me)
15

a. X = $(CH_2)_n$, Y = $(CH_2)_m$
16 m, n = 1
17 m, n = 2
18 m = 3, n = 2
19 m, n = 3
20 m = 4, n = 3
21 m, n = 4
22 m, n = 5
23 m, n = 7

25 m = 3, n = 2
26 m, n = 3
27 m = 4, n = 3
28 m, n = 4

b. X = S, Y = C=C(Me)(Me)
24

c. X = , Y = $(CH_2)_2$
29

Scheme 1

Table. Cyclodiynes **16–23** Prepared

Starting Materials		Product	Yield (%)		mp (°C) or bp (°C)/Torr	
			found	reported[2c]	found	reported
1,6-heptadiyne (**1**)	1,3-diiodopropane (**9**)	1,6-cyclodecadiyne (**16**)	3	–	81	81[12]
1,7-octadiyne (**2**)	1,4-diiodobutane (**10**)	1,7-cyclododecadiyne (**17**)	35	7	36–37	37–38[2c]
1,8-nonadiyne (**3**)	1,4-diiodobutane (**10**)	1,7-cyclotridecadiyne (**18**)	65	40	7	7–8[2c]
1,8-nonadiyne (**3**)	1,5-diiodopentane (**11**)	1,8-cyclotetradecadiyne (**19**)	85	57	98	97–98[2c]
1,8-nonadiyne (**3**)	1,6-diiodohexane (**12**)	1,8-cyclopentadecadiyne (**20**)	65	45	38	38[2c]
1,9-decadiyne (**4**)	1,6-diiodohexane (**12**)	1,9-cyclohexadecadiyne (**21**)	55	23	−3	−3.5[2c]
1,10-undecadiyne (**5**)	1,7-diiodoheptane (**13**)	1,10-cyclooctadecadiyne (**22**)	48	32	97	97[2c]
1,12-tridecadiyne (**6**)	1,9-diiodononane (**14**)	1,11-cyclodocosadiyne (**23**)	27	10	106–107	106.5[2c]

diyne **17**:[11] The reaction of **24** with catalytic amounts of the cobalt complex ($CpCo(CO)_2$) produces the functionalized thiophenophane **30** whereas **29** reacts with one equivalent of $CpCo(CO)_2$ to yield the cyclobutadiene complex **31** in almost quantitative yield.

Cyclic Dialkynes 16–29; General Procedure:

To a solution of the diyne **1–8** (85 mmol) in anhydr. THF (1.5 L) at −20 °C was added 2.5 N BuLi in hexane (68 mL) over a period of 10 min under an Ar atmosphere. A white precipitate was observed, and the color of the solution changed to yellow after all the BuLi had been added. The mixture was allowed to warm to r.t. and the stirring was continued for another 15 min. Finally the dihalogenide **9–15** (90 mmol) was added. The resulting mixture was refluxed for 3–7 d until the precipitate had disappeared. The reaction was terminated as soon as the gas chromatographic analysis showed no starting material. After cooling, the solution was poured into a mixture of petroleum ether (bp 30–75 °C) (300 mL) and 2 N HCl (400 mL). The organic layer was separated and the aqueous layer was extracted with petroleum ether (2 × 100 mL). The combined organic layers were neutralized with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo. The crude products were worked up as follows:

1,6-Cyclodecadiyne **16**: After chromatography (silica gel, CCl_4, 30 cm × 60 mm), the CCl_4 phase was treated with a aqueous solution of $Na_2S_2O_3$ (to remove I_2), dried (Na_2SO_4) and concentrated in vacuo to give a brown crystalline fraction. Further purification was achieved by Kugelrohr distillation (70–80 °C/0.1 Torr); yield: 0.39 g (3%); mp 81 °C (Lit.[12] mp 81 °C).

1,7-Cyclododecadiyne **17**: The crude product was chromatographed as in the case of **16**. All fractions containing more than 70% **17** were concentrated in vacuo and recrystallized from EtOH (−25 °C); yield: 4.75 g (35%); mp 36–37 °C (Lit.[26] mp 37–38 °C).

1,7-Cyclotridecadiyne **18**: The crude product, which should not contain starting material, was chromatographed as in the case of **16**. Treatment with an aqueous solution of $Na_2S_2O_3$, drying (Na_2SO_4), concentration in vacuo and Kugelrohr distillation (80–100 °C/0.1 Torr) afforded **18**; yield: 9.6 g (65%) mp 7 °C (Lit.[20] mp 7–8 °C). From the final fractions of column chromatography 0.15–0.4 g (1–3%) **25** was obtained by recrystallization from EtOH.

18:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.2–2.05 (m, 8 H), 1.85–1.75 (m, 2 H), 1.7–1.65 (m, 4 H), 1.5–1.4 (m, 4 H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 82.2, 80.1, 28.5, 27.3, 25.3, 18.8, 18.2.

25:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.0 (m, 16 H), 1.65–1.4 (m, 20 H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 80.4, 80.0, 28.5, 28.2, 27.7, 18.6, 18.3.

HRMS ($C_{26}H_{36}$) *m/z* ($M^+ - C_3H_7$): calc. 305.2269, found 305.2235.

1,8-Cyclotetradecadiyne **19**: The raw material was filtered through silica gel (10 cm × 60 mm, CCl_4) and recrystallized from EtOH (100 mL) at −15 °C. This gave 10–12 g of white crystals with a characteristic odor. From the mother liquid a further fraction of 1.5–3 g of **19** was obtained by chromatography on silica gel with CCl_4; total yield: 13.5 g (85%) mp 98 °C (Lit.[2c] mp 97–98 °C). The final fractions of column chromatography contained 0.32 g (2%) of **26**.

19:

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.4–2.0 (m, 8 H), 2.0–1.4 (m, 4 H), 1.4–1.2 (m, 8 H).

^{13}C NMR (50.32 MHz, $CDCl_3$): δ = 80.7, 28.0, 26.7, 18.4.

26:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.2–2.05 (m, 16 H), 1.6–1.3 (m, 24 H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 80.2, 28.4, 27.8, 18.6.

HRMS ($C_{28}H_{40}$) *m/z* ($M^+ - C_3H_7$): calc. 333.2582, found 333.2571.

1,8-Cyclopentadecadiyne **20**: The crude product was purified by column chromatography analogous to **16**. After evaporation of the solvents on a rotary evaporator a colorless oil resulted which solidified in the refrigerator. Recrystallization from MeOH afforded **20**; yield: 11.2 g (65%); mp 38 °C (Lit.[2c] mp 38 °C). The tetrayne **27** was obtained from the final fractions of column chromatography. Recrystallization from EtOH gave **27**; yield: 1.0 g (6%).

20:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.1 (m, 8 H), 1.6–1.35 (m, 14 H).

^{13}C NMR (75.47, $CDCl_3$): δ = 80.7, 80.1, 28.3, 28.2, 27.8, 26.9, 18.6, 18.2.

27:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.05 (m, 16 H), 1.6–1.3 (m, 28 H).

^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 80.3, 80.2, 29.0, 28.6, 28.3, 27.9, 18.7, 18.65.

HRMS ($C_{30}H_{44}$) *m/z* ($M^+ - C_3H_7$): calc. 361.2895, found 361.2832.

1,9-Cyclohexadecadiyne **21**, *1,10-Cyclooctadecadiyne* **22** *and 1,12-Cyclodocosadiyne* **23**: When preparing the dilithium salt (see General Procedure) the addition of BuLi to the solution of the α,ω-diyne was carried out dropwise under vigorous stirring to avoid the formation of clumps. The crude reaction mixture of **21** was purified by column chromatography analogous to **16** followed by Kugelrohr distillation (100–120 °C/0.1 Torr) to afford **21**; yield: 10.1 g (55%); mp −3 °C (Lit.[2c] mp −3.5 °C). The tetrayne **27** was obtained from the final fractions of column chromatography by recrystallization from EtOH; yield: 0.51 g (3%).

In the cases of **22** and **23**, the crude product was purified directly by Kugelrohr distillation (130–150 °C/0.1 Torr) to give 9.6 g (48%) of **22** mp 97 °C and 6.9 g (27%) of **23** mp 106–107 °C, respectively.

21:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25–2.1 (m, 8H), 1.6–1.3 (m, 16H).

^{13}C NMR (75.47, $CDCl_3$): δ = 80.5, 28.5, 27.3, 17.9.

28:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.2–2.05 (m, 16H), 1.6–1.25 (m, 32H).

^{13}C NMR (75.47, $CDCl_3$): δ = 80.2, 28.9, 28.4, 18.7.

HRMS ($C_{32}H_{48}$) m/z ($M^+ - C_3H_7$): calc. 389.3208, found 389.3185.

22:

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.2 (m, 8H), 1.5–1.45 (m, 16H), 1.35–1.25 (m, 4H).

^{13}C NMR (50.34, $CDCl_3$): δ = 80.7, 29.0, 28.7 (2 signals), 18.6.

23:

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.15 (m, 8H), 1.45 (m, 16H), 1.30 (m, 12H).

^{13}C NMR (50.34, $CDCl_3$): δ = 80.6, 30.0, 29.3, 28.7, 28.6, 18.5.

6-Isopropylidenethiacyclodeca-3,8-diyne **24**: The dilithium salt of 4-thia-1,6-heptadiyne (**7**); 22.0 g, 0.2 mol) was treated with isopropylidene-1,3-dibromopropane (**15**; 48.4 g, 0.2 mol) (see General Procedure) and refluxed in THF for 14 h. After chromatography (silica gel, petroleum ether (bp 30–75 °C)/EtOAc, 5:1), **24** was obtained as colorless crystals; yield: 3.5 g (10%), (**WARNING**: The compound exploded on attempted Kugelrohr distillation!).

24; mp 153 °C (decomp.):

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45 (t, 4H), 3.0 (s, 4H), 1.75 (s, 6H).

^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 128.8 and 122.2 (s, C=C), 85.2 and 77.3 (s, C≡C), 23.7 and 22.7 (t, CH_2), 20.8 (q, CH_3).

IR (KBr): ν = 2281, 2251, 2204 cm^{-1}.

HRMS (EI) ($C_{12}H_{14}S$): m/z = calc. 190.0686, found 190.0751.

[10]Orthocyclophane-2,8-diyne **29**: The dilithium salt of *o*-dipropargylbenzene (**8**) (2.8 g, 18 mmol) was treated with 1,4-diiodobutane (**10**; 5.6 g, 18 mmol) (see General Procedure) and refluxed in THF for 40 h. The crude product was purified by Kugelrohr distillation; yield: 0.95 g (4%).

29:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (s, 4H), 3.54 (t, J = 2.2 Hz, 4H), 2.1 (m, 4H), 1.6 (m, 4H).

^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 136.6 (s), 130.3 (d), 127.4 (d), 82.5 (s), 78.9 (s), 27.3 (t), 24.1 (t), 19.7 (t).

IR ($CDCl_3$): ν = 3058, 3016, 2930, 1432, 1328 cm^{-1}.

HRMS (EI) ($C_{16}H_{16}$): calc. 208.1252, found 208.1210.

8,18-Diisopropylidene[2.2](2,5)-5,6-dihydro-4*H*-cyclopenta[*c*]thiophenophane (30):

A solution of **24** (380 mg, 2 mmol) and $CpCo(CO)_2$ (40 mg, 0.2 mmol) in degassed *n*-octane (30 mL) was refluxed for 6 h. After cooling, the solvent was removed in vacuo, the residue dissolved in CH_2Cl_2 and purified by column chromatography (silica gel, petroleum ether (bp 30–75 °C)/Et_2O, 5:1). After removal of the solvent colorless crystals of **30** were obtained; yield: 45 mg (12%).

30:

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.35 (d, ^2J = 21 Hz, 4H) and 3.25 (d, ^2J = 21 Hz, 4H, CH_2), 3.0–3.1 and 2.75–2.85 (AA'BB', 8H, CH_2), 1.7 (s, 12H, CH_3).

^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 147.0 and 138.7 (s, $C_{thiophene}$), 136.7 and 124.7 [s, $(CH_3)_2C=C$], 32.0 and 27.5 (t, CH_2), 20.9 (q, CH_3).

HRMS (EI): ($C_{24}H_{28}S_2$): calc. 380.1633, found 380.1647.

Reaction of $CpCo(CO)_2$ with 29:

A solution of **29** (80 mg, 0.39 mmol) and $CpCo(CO)_2$ (72 mg, 0.4 mmol) in degassed *n*-octane (10 mL) was refluxed under an Ar atmosphere until **29** had disappeared. After cooling the solvent was removed in vacuo. The residue was dissolved in a small amount of CH_2Cl_2 and filtered through alumina (grade III) using petroleum ether (bp 30–75 °C) as eluent to afford **31**; yield: 130 mg (98%); yellow crystals; mp 143 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (s, 4H, H_{arom}), 4.4 (s, 5H, H_{Cp}), 3.4 (d, ^2J = 18 Hz, 2H) and 3.25 (d, ^2J = 18 Hz, 2H, C_{arom}–$CH_2C_{cyclobutadiene}$), 2.30–2.40 (m, 2H) and 1.95–2.05 (m, 2H, $CH_2CH_2CH_2CH_2$), 1.75–1.9 (m, 2H) and 1.45–1.6 (m, 2H) ($CH_2CH_2CH_2CH_2$).

^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 135.2 (s, C_{arom}), 129.6 and 125.6 (d, C_{arom}), 80.4 (d, C_{Cp}), 74.8 and 72.2 (s, $C_{cyclobutadiene}$), 28.6, 23.5 and 23.3 (t, CH_2).

HRMS (EI) ($C_{21}H_{21}Co$): m/z calc. 332.0975, found 332.0947.

We thank the Deutsche Forschungsgemeinschaft (SFB 247), the Fonds der Chemischen Industrie and the BASF Aktiengesellschaft, Ludwigshafen, for financial support. R.M. is grateful to the Studienstiftung des Deutschen Volkes for a graduate fellowship.

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