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SYNTHESIS AND STRUCTURE OF LARGE RING 2-PHENYLCYCLOALKANONES AND 2,n-DIPHENYLCYCLOALKANONES

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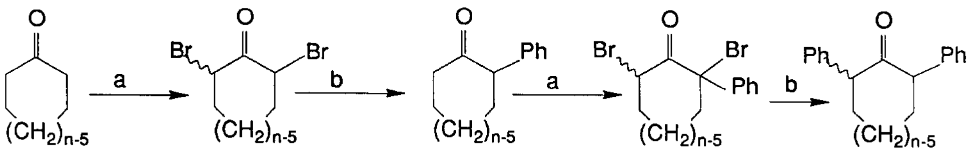
Summary. The title compounds have been prepared in good yield by treating the corresponding 2,n-dibromocycloalkanone with $LiCuPh_2$. Single-crystal X-ray structures are reported for cis- and trans-2,12-diphenylcyclododecanone.

In connection with our photochemical studies on large ring cycloalkanones,[1,2] we required a series of novel 2,n-diphenylcycloalkanones (n = number of ring carbons). Compared to alkylation, there are relatively few methods of phenylation,[3] and none seemed directly applicable to symmetrical disubstitution. We report here that Posner's monoalkylation of 2,n-dibromocycloalkanones with organocuprates[4] is readily adapted to mono- and diphenylation of cycloalkanones, as shown below.



$\mathbf{1}_n$ $\mathbf{2}_n$ $\mathbf{3}_n$

n=10,11,12,15
a: 2eq. Br_2 /AcOH, b: 3-6 eq. Ph_2CuLi / ether

In a typical procedure, 1.5 mmol dibromoketone or phenyldibromoketone in 25 mL anhydrous ether was added rapidly to 4.5 mmol lithium diphenylcuprate[5] in 15 mL ether/hexane at -78°C. After addition the cooling bath was removed and the solution was allowed to warm spontaneously to 25° (0.5 h). The mixture was then quenched at -78° with MeOH, and worked up by dilution with water and ether extraction. GC analysis of the crude product mixture gave the yields shown in Table 1. The cis isomer of 3 always predominates. A lower yield was obtained if less than 3 equivalents of cuprate were used, if the MeOH quenching was done at 25°, or if unreacted PhLi was present during addition of the dibromide. Flash chromatography on silica gel with 3% ether in hexane followed by recrystalization in hexane gave 99% pure product by GC.

Table 1. Percent yields of **2** and **3**.[a]

n	2_n	3_n	cis-3/trans-3
10	81	83	95/5
11	61	67	83/17
12	82	71	93/7
15	82	75	83/17

a) From GC analysis of crude mixture. Yields of **2** and **3** are based on **1** and **2**, respectively.

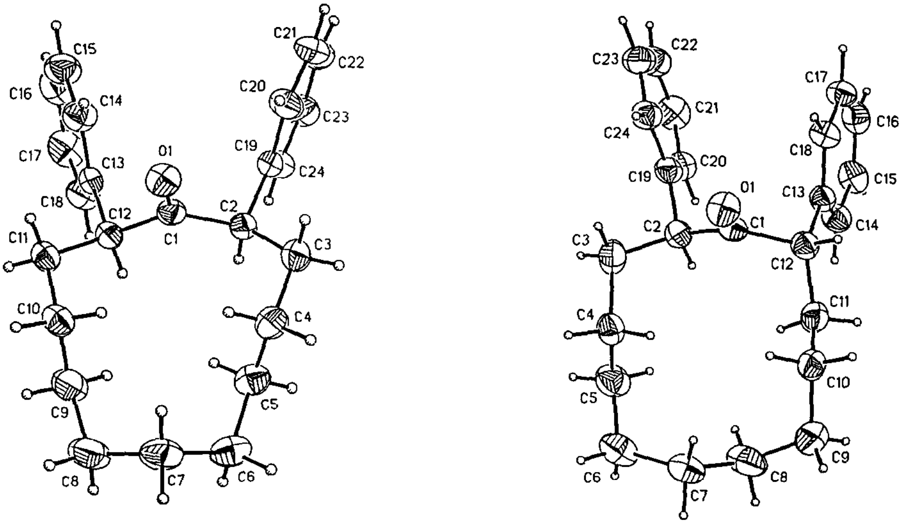


Figure 1. Single-crystal X-ray crystallographic structures for cis (left) and trans (right) 2,12-diphenylcyclododecanone.

Since treatment of the dibromoketone derived from **1** with LiCuPh$_2$ apparently produces the kinetic enolate of **2**,[4] we attempted to prepare **3**$_{12}$ in one step from 2,12-dibromocyclododecanone by trapping the enolate with electrophilic phenyl. However, addition of dibromoketone to LiCuPh$_2$ followed by BiPh$_3$CO$_3$[3c] gave only low yields of 2$_{12}$ and 2-phenyl-12-bromocyclododecanone.

The structures of cis- and trans-3$_{12}$ (Figure 1), separated by preparative silica gel TLC, were determined by single crystal X-ray analysis.[6] All ketones **2** and **3** prepared in this study were characterized by NMR, IR, GC/MS, and UV spectroscopy. 200 MHz NMR data are shown in Table 2.

Table 2. ^{1}H nmr chemical shifts for **3**$_n$ (δ, ppm, CDCl$_3$).

n		phenyl	alpha	beta[a]	ring
10	cis	7.04 (m,10H)	4.15 (dd,2H)	2.27 (m,2H)	1.4-1.85 (m,12H)
	trans	6.91 (m,10H)	4.04 (dd,2H	2.48 (m,2H)	1.4-1.9 (m,12H)
11	cis	7.06 (m,6H)	4.06 (dd,2H)	2.38 (m,2H)	1.3-1.8 (m,14H)
		6.96 (m,4H)			
	trans	7.04 (m,6H)	4.02 (dd,2H)	2.18 (m,2H)	1.3-1.8 (m,12H)
		6.92 (m,4H)		2.00 (m,2H)	
12	cis	7.07 (m,10H)	4.09 (dd,2H)	2.30 (m,2H)	1.3-1.7 (m,16H)
	trans	6.91 (m,10H)	3.85 (dd,2H)	2.40 (m,2H)	1.2-1.7 (m,16H)
15	cis	7.12 (m,6H)	3.82 (dd,2H)	2.22 (m,2H)	1.2-1.7 (m,22H)
		6.94 (m,4H)			
	trans	7.05 (m,6H)	3.78 (dd,2H)	2.12 (m,2H)	1.2-1.65 (m,20H)
		6.90 (m,4H)		1.77 (m,2H)	
6[b]	cis	7.2 (m,10H)	3.75 (m,2H)	2.0 - 2.5 (m,6H)	

a) In most cases two of the beta-hydrogens are hidden in the ring multiplet.
b) From Ref. 3d.

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5. $LiCuPh_2$ was formed by room temperature addition of 5.2 mL of 1.7M PhLi in hexane to 0.65g (4.5 mmol) CuBr suspended in 10 mL ether, followed by 10 m stirring.

6. Analysis performed on a Nicolet R3m diffractometer with Cu ($\bar{\lambda}$=1.54178 Å). Both isomers form monoclinic crystals, space group C2/c, 8 molecules per unit cell. **Cis isomer** cell parameters: a=25.419(4)Å, b=5.677(1) Å, c=31.132(4) Å, α=90°, β=119.11(1)°, γ=90°, V=3925(1) Å^3. Final agreement factors: R=0.065, R_w=0.092. **Trans isomer** cell parameters: a=26.312(6) Å, b=11.298(3) Å, c=15.154(3) Å, α=90°, β=119.81(2)°, γ=90°, V=3909(1) Å^3. Final agreement factors: R=0.0706, R_w=0.0978. Complete structural data have been submitted to the Cambridge University Crystallographic Data Centre.

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