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SYNTHESIS OF ^{13}C AND ^{2}H-LABELLED 2-PHENYLCYCLODODECANONES

V. Pushkara Rao, Jin-Feng Wang, Nicholas J. Turro* and Charles Doubleday Jr.*
Chemistry Department, Columbia University,
New York, N.Y. 10027, USA.

SUMMARY

^{13}C labelled (1,2 and 1,12) and perdeuterated derivatives of 2-phenyl cyclododecanones, as precursors for labelled triplet flexible biradicals to probe magnetic isotope effects at the radical centers on the triplet decay dynamics, were synthesized. Isotopomers of 2-phenylcyclododecanone-$^{13}C_2$-(1,2 and 1,12) were synthesized from cyclododecanone-$^{13}C_2$-(1,2) by dibromination, followed by phenylation with lithiumdiphenylcuprate. Cyclododecanone-$^{13}C_2$-(1,2) was obtained from 1,10-dibromodecane via the following sequence: (1) $K^{13}CN$; (2) hydrolysis; (3) esterification; (4) acyloin condensation. Perdeuterio-2-phenyl cyclododecanone (95% isotopic purity) was prepared from unlabelled 2-phenyl cyclododecanone by a substitution of deuterium for hydrogen by treatment with excess D_2O, catalyzed with D_2-reduced PtO_2 in the presence of D_2O_2.

Key words : 2-phenylcyclododecanone-$^{13}C_2$-(1,2), acyloin condensation, lithiumdiphenylcuprate, perdeuterio-2-phenyl cyclododecanone, deuterium peroxide, platinum-oxide.

INTRODUCTION

The past several years have witnessed an increasing interest in the chemistry of biradicals connected by a flexible chain of methylene groups[1]. Our own research in this area has demonstrated that the triplet lifetimes of acyl-benzyl biradicals derived from the photolysis of large ring phenyl cycloalkanones are dependent on a number of factors including intramolecular parameters such as chain length, local chemical structure near radical centers, and external parameters such as temperature, viscosity and applied magnetic fields[2]. In order to understand the effects of magnetic isotopic substitution at the radical

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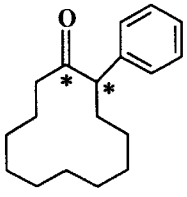
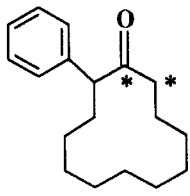
centers on the dynamics of flexible biradicals, we required both ^{13}C and ^{2}H-labelled derivatives of 2-phenylcyclododecanones. In this report we describe a synthesis of commercially unavailable 2-phenylcyclododecanone-$^{13}C_2$ (**1a** and **1b**) and perdeuterio-2-phenylcyclododecanone (**2**).



1a



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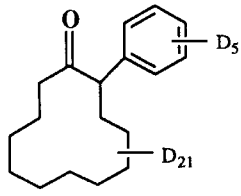

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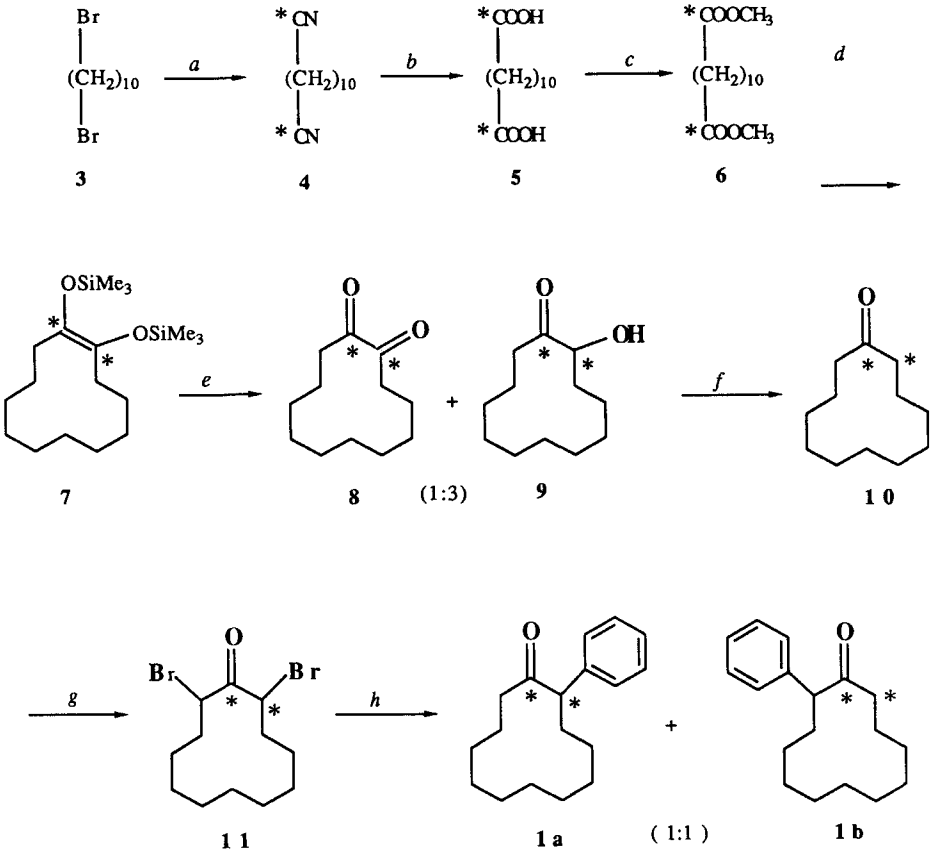
RESULTS AND DISCUSSION

A 1:1 mixture of isotopomers of 2-phenylcyclododecanone-$^{13}C_2$ (**1a** and **1b**) were synthesized by following the experimental methods developed for the synthesis of medium-ring cyclic ketones[3,4], with minor modifications. The synthetic scheme adapted is shown in **Scheme 1**.

The synthesis of **1** was initiated from 1,10-dibromodecane **3**, and ^{13}C was incorporated by treating **3** with two equivalents of $K^{13}CN$ (99% ^{13}C). The resultant 1,10-dicyanodecane-$^{13}C_2$ **4** upon hydrolysis followed by esterification with methanol gave dimethyl-1,12-dodecanedicarboxylate-$^{13}C_2$-(1,12) **6** in 65% yield. This diester **6** was subjected to acyloin condensation by following the procedure of Bloomfield in the presence of trimethylchlorosilane in xylene at 110-120°C.[5] Trimethylchlorosilane improves the yield of acyloin condensation and eliminates Dieckmann condensation products; also, the product of the acyloin condensation, disilyl-ether **7**, is easy to isolate from inorganic impurities by filtration. Acidic hydrolysis of **7** gave a mixture of 2-hydroxy cyclododecanone-$^{13}C_2$-(1,2) **9** and cyclododecanedione-$^{13}C_2$-(1,2) **8** in 3:1 ratio (60%). Reduction of this mixture with four equivalents of hydriodic acid in acetic acid resulted in cyclododecanone-$^{13}C_2$-(1,2) **10** in 75% yield.

Scheme 1.[a]



a ^{13}C labelled carbon is represented by (*) ; (*a*) potassium cyanide-^{13}C, 99 atom % ^{13}C, EtOH, reflux; (*b*) KOH/ H_2O, reflux; (*c*) MeOH/HCl, reflux (65% yield from **3**); (*d*) Na/xylene, trimethylchlorosilane, 110-120^0; (*e*) Con. HCl, reflux (yield 60% from **6**); (*f*) 47% HI in H2O/ acetic acid, reflux (75% yield); (*g*) 2 equi. Br_2/acetic acid (81%); (*h*) 2equi. Ph_2CuLi, diethyl ether, -78^0(50%).

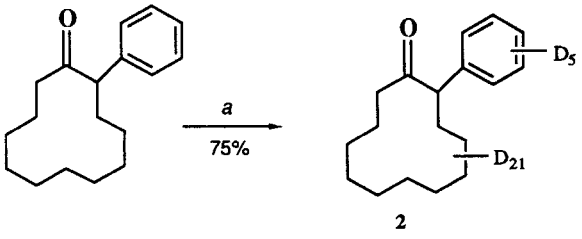
2-Phenylcyclododecanone was synthesized by our published procedure[4]. Dibromination of **10** with bromine in acetic acid, followed by phenylation with lithiumdiphenylcuprate in diethyl ether at -78°C produced the final compound as a 1:1 mixture of isotopomers **1a** and **1b**. Whereas in **1a** the carbonyl carbon and methine carbon (C-2) are labelled with ^{13}C, in **1b** the carbonyl carbon and the methylene carbon (C-12) are labelled. The chemical homogeneity of the final

product was demonstrated by GC and mp. The gross structure and the position of labelled carbons and the relative ratios of isotopomers were inferred from their spectra. The mass spectrum (EI) of **1** showed molecular ion at m/e 260 (vs 258 for unlabelled **1**) indicative of two ^{13}C atoms. Significant EI fragmentation also occurred as shown by ions at 104 and 105 (44:56), 117 and 118 (45:55). The m/e 104 and 105 corresponds to the neutral fragments $PhCH{=}CH_2$ and $Ph^{13}CH{=}CH_2$. Based on the relative intensities of 104 and 105 ions, the relative ratios of **1a** and **1b** were estimated, and the ratio calculated to be ca. 50:50 (after correction for the intensity of the 105 ion observed in the mass spectrum of the unlabelled **1**)[6]. In the ^{13}C-NMR spectrum of **1**, the carbonyl carbon and both α-carbons appeared as doublets with coupling constants ~ 38-40 Hz (J_{C-C}), indicating that all three carbons are labelled. However, the fact that the carbonyl carbon appeared as a simple doublet, not as double doublets or a triplet, clearly suggests that both the labelled α-carbons are not incorporated into a single compound, consistent with the mixture of **1a** and **1b**. The relative ratios of **1a** and **1b** can be inferred from the ^1H-NMR integration pattern of the benzylic methine proton. In the ^1H-NMR spectrum of **1**, two separate signals were observed for $-^{13}CO^{13}CH-$ (**1a**) and $-^{13}COCH-$ (**1b**) as dddd (104 Hz, 8 Hz, 4 Hz, 2 Hz) and ddd (8 Hz, 4 Hz, 2 Hz) respectively, with integration ratio of 1:1.

Perdeuteration of 2-phenylcyclododecanone was carried out by following the method developed by Nguyen-Dinh-Nguyen and Einer A. Stenhagen[7] with minor modifications (**Scheme 2**). Unlabelled **1** was treated in an autoclave at 250°C (1000 psi N_2 pressure) with excess D_2O catalyzed by D_2-reduced PtO_2 in the presence of D_2O_2, for 78 h. Lower reaction temperatures and reaction times yielded partially deuterated **1**. When this reaction was carried out on 2-phenylcyclohexanone, a quantitative amount of biphenyl was obtained. Hence, this method may not be applicable to deuterate six membered cyclic ketones, as aromatization seems to be a dominant process under those reaction conditions.

The chemical homogeneity of **2** was demonstrated by gas-chromatography.[8] Its infrared spectrum showed strong signals corresponding to C-D stretching at 2200 and 2100 cm^{-1} and weak or absent signals corresponding to C-H stretching (3000-2900 cm^{-1}), indicative of quantitative incorporation of deuterium. Its

Scheme 2.



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(a) PtO_2/D_2, Na_2O_2/D_2O, D_2O, 250° C

mass spectrum has ions corresponding to the molecular formulae $C_{18}D_{26}O$ (33%), $C_{18}D_{25}HO$ (39%), $C_{18}D_{24}H_2O$ (22%), $C_{18}D_{23}H_3O$ (6%) (vs $C_{18}H_{26}O$ corresponding to the unlabelled 2-phenylcyclododecanone). Having corrected (18 carbons with 13C natural abundance of 1.1%) and normalized the intensities of the observed molecular-ions, using binomial expansion percentage of protium impuirity in **2** was estimated.[9] The protium impuity thus calculated was found to be ~ 5%.

Transient photochemical studies using these ^{13}C and perdeuterated derivatives of 2-phenylcyclododecanones are currently in progress.

EXPERIMENTAL

Materials and spectra: Potassium cyanide-^{13}C (99 atom % ^{13}C), platinum (IV) oxide were procured from Aldrich. Deuterium C.P. 99.5% atom. min. was obtained from Matheson Gas products. For column chromatographic separations Baker Reagent grade Silica gel (60-200 mesh) was used. NMR spectra were recorded on a Bruker AF 250 MHz or Varian HA-200 instrument. Infrared spectra were recorded on a Perkin-Elmer model 983 and absorption spectra on a Perkin-Elmer model 559A spectrophotometers. Mass spectra (CI and EI) were obtained from a GC-MS system HP-5988A with Gas chromatograph HP-5890).

Dimethyl-1,12-decane-$^{13}C_2$-(1,12)-dicarboxylate (6): In a 500 mL round-bottomed flask fitted with a reflux condenser, were placed 150 mL of 95% ethanol, 10 g. (33 mmol) of 1,10-dibromodecane (**3**) and 2.64 g. (40 mmol) of potassium cyanide -^{13}C (99 atom %). The mixture was refluxed for fifteen hours with stirring in an oil bath at 80°C. At the end of this time, another 2.64 g. of

potassium cyanide-^{13}C was added and the mixture was refluxed, with stirring for fifteen hours longer. The flask was allowed to cool, and a solution of 7.0 g. of 90% potassium hydroxide in 50 mL of water was added. After refluxing the solution for another 30 h, the reaction mixture was poured in ice cold water (400 mL) and the solution was neutralized with excess of hydrochloric acid. The resultant cloudy solution was filtered and the crude diacid (**5**) residue thus obtained was treated with 250 mL of dry methanol containing 3 mL of concentrated hydrochloric acid, and the solution was refluxed for 20 h . Evaporation of methanol, followed by extraction with diethyl ether produced the crude diester which was then subjected to column chromatography; elution with 20% ethyl acetate in hexane yielded 5.6 g. (65%) of diester (**6**): m.p: 380C; IR ($CHCl_3$): 2930, 1740, 1250,1160 cm^{-1}; ^{1}H-NMR ($CDCl_3$) d 3.68 (6H, d), 2.30 (4H, q), 1.6 (4H, m), 1.35 (12H, bs); ^{13}C-NMR ($CDCl_3$-enriched carbon only) d 174.5; mass spectrum (EI) m/e 260 (M+), 230, 229.

Cyclododecanone-$^{13}C_2$-(1,2) (10): A mixture of dimethyl-1,12-decane-$^{13}C_2$-dicarboxylate **6** (4.1 g., 16 mmol), and trimethylchlorosilane (10.9 g., 100 mmol) was added dropwise to metallic sodium (64 mmol) dispersed in xylene (100 mL) with vigorous stirring at 110-120°C under an argon atmosphere over a period of 12 h. Stirring was continued at 110-120°C for another 20 h. and then at reflux temperature for 3 h. After cooling and filtration of inorganic substances, the filtrate was concentrated *in vacuo* to give a viscous oil, which was dissolved in ethanol (100 mL). 25 mL of water and concentrated hydrochloric acid (2 mL) were added to the resulting solution and the mixture was heated at reflux for 15 min. under an argon atmosphere. After cooling and diluting with water, the mixture was extracted with ether. The extracts were combined, washed with water, dried over anhydrous sodium sulfate and the crude mixture was found to contain 2-hydroxycyclododecanone (**9**) and 1,2-cyclododecanedione (**8**) in 3:1 ratio (1.85 g.). This mixture, without further purification, was subjected to reduction with excess of hydriodic acid (13 g. of 47 % HI) in acetic acid (35 mL). The red color of free iodine was apparent upon mixing the reactants and became quite deep when the mixture was heated to reflux. After

refluxing for 3 h., the reaction mixture was chilled and quickly poured into 200 mL of sodium hydroxide solution (20%, w/w) containing sufficient sodium bisulfate to reduce all the iodine present. The resultant mixture was extracted with diethyl ether twice and the organic layer was washed with sodium bisulfate solution (5%) and several times with sodium hydroxide solution (20%, w/w) until the wash remained alkaline. A final wash with distilled water and drying over $NaSO_4$ gave the crude reduction product, which upon column chromatography (hexane/ethylacetate) gave 2.8 g. of pure cyclododecanone-$^{13}C_2$ (**10**). This has been unambiguously characterized based on its spectroscopic data and physical characteristics: Mass spectrum (CI) 184 (M+); ^{13}C-NMR (CD_3CN-enriched carbon only) d 209.8 (d, J = 38.2 Hz), 40.2 (d, J = 38.2 Hz) ; ^{1}H-NMR ($CDCl_3$) d 2.45 (m, 4H), 1.72 (m,4H), 1.3 (bs, 14H).

2-Phenylcyclododecanone-$^{13}C_2$ (1a and 1b): 2 equivalents of bromine (1.8 g., 5.5 mmol) in acetic acid was added dropwise to 0.5 g. (2.25 mmol) of cyclododecanone-$^{13}C_2$ (**10**) in 20 mL of acetic acid at room temperature. After stirring the the solution for 4 h. at room temperature, the reaction mixture was poured into ice cold water (150 mL) and extracted three times with chloroform (30 mL). The organic extract was washed several times with 10% sodium bicarbonate solution, washed with water and dried over anhydrous sodium sulfate. The crude reaction mixture was recrystallized with 10% chloroform to give 2,12-dibromocyclododecanone-$^{13}C_2$-(1,2) (0.8 g) . α-Phenylation was carried out by treating **11** (0.8 g.) with Ph_2CuLi. Lithiumdiphenylcuprate was prepared by adding 2 equivalents of phenyllithium (1.18 g., 7 mL of 2.M solution of PhLi) to Cu_2Cl_2 (1.0 g.) in dry ether under an argon atmosphere at 0°C. Stirring was continued at room temperature for 2 h., during which time, formation of lithiumdiphenylcuprate was apparent from the precipitate formation. To the same solution 1,12-dibromocyclododecanone **11** (0.8 g) in ether at -78°C was added, after the addition the temperature was raised to room temperature for 1 h. and stirred at room temperature for 5 h. The reaction was quenched by methanol at -78°C, followed by water at the same temperature and extracted with ether, dried over $NaSO_4$ and repeated chromatography (3% ether

in hexane) to isolate 2-phenylcyclododecanone (250 mg.) as a 1:1 mixture of **1a** and **1b**. Structures of **1a** and **1b** have been unambiguously assigned from their spectral data. While the mass spectrum of the mixture is in support of the gross structure of **1** with two additional ^{13}C-carbons , ^{13}C-NMR and ^{1}H-NMR data (in particular the integration ratio of the benzylic methine proton) are in support of the presence of equal amounts of **1a** and **1b**. The mixture of **1a** and **1b** has the following spectral characteristics: Mass spectrum (EI): 260,132,131,118,117, 105, 104,91,92,55; ^{13}C-NMR (CD_2Cl_2-enriched carbon only) d 211.9 (d, J = 39.5 Hz), 55.8 (d, J = 38.2 Hz), 40.2 (d, J = 40.1 Hz); IR (KBr): 2923, 2864, 1698, 1598, 1489, 1469, 1204, 795 cm^{-1}; ^{1}H-NMR (CD_2Cl_2) d 7.1-7.4 (m, 5H), 4.1 (dddd, J = 104 Hz, 8 Hz, 4 Hz, 2 Hz, 1H), 2.4 (m, 3H), 1.88 (m, 1H), 1.2 - 1.6 (m, 16H).

Perdeuterio-2-phenylcyclodoecanone (2): Perdeuteration of 2-phenylcyclododecanone was carried out by treating unlabelled **1** with an excess of deuterium oxide in the presence of a metallic catalyst and an alkaline catalyst. For the preparation of the metallic catalyst, 44 mg. of PtO_2 and 100 g. of D_2O were placed in a round bottomed flask. Deuterium gas was bubbled through the solution for two hours. During that time, reduction of PtO_2 became apparent from the change in color from brown to black. The alkaline catalyst (D_2O_2 and NaOD) was prepared by adding 30 mg. of Na_2O_2 to 20 mL of deuterium oxide at 0°C over the course of 1h. 100 mg of 2-phenylcyclododecanone was placed in a thick-walled pyrex vessel, followed by the addition of the above prepared alkaline and metallic catalysts. The solution was bubbled with nitrogen for 10 min. and the solution was frozen in an acetone / dry-ice / liquid N2 bath. The vessel was vacuum pumped and then sealed. The vessel was kept in an autoclave at 240-250°C and 1000 psi of nitrogen for 78 h. After the reaction, deuterated water was evaporated and the organic product was extracted with diethyl ether and chromatographed on silica gel (3% ether in hexane) to give perdeuterio-2-phenylcyclododecanone in 75% yield. IR (CCl_4): 2200 and 2100 cm^{-1} (C-D stretching), 1695 cm^{-1} (C=O). Mass Spectrum (EI) m/e 284 (33%), 283 (39%), 282 (22%), 281 (6%) (vs 258 for unlabelled 2-phenylcyclododecanone). This corresponds to the isotopic purity (% of deuterium) of 95%.[8,9]

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6. The intensity of 105 ion in the mass spectrum of **1** was corrected to the intensity of the corresponding ion in the unlabelled 2-phenylcyclododecanone using the following expression. $I^{*}_{105}(corr.) = I^{*}_{105}(obsd.) - I_{105}(obsd.)[I^{*}_{104}(obsd.)/I_{104}(obsd.)]$; * represents labelled **1**.
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8. Gas-chromatographic analysis [25m SE-30 5%, $60^{0}(5')$-10^{0}/min-$220^{0}(20')$] indicates 0.26 min. difference in retention times between **2** and unlabelled **1**.
9. Deuterium and protium contents in **2** were calculated by substituting the corrected (18 carbons with ^{13}C natural abundance of 1.1%) and normalized intensities of the observed molecular-ions corresponding to the molecular formulae $C_{18}D_{26}O$, $C_{18}D_{25}HO$, $C_{18}D_{24}H_2O$ and $C_{18}D_{23}H_3O$, in the binomial expansion $(D+H)^{26} = D^{26} + 26 \times D^{25} \times H + 26 \times 25 \times D^{24} \times H^2/2! + 26 \times 25 \times 24 \times D^{23} \times H^3/3!$. (Remaining terms in the binomial expansion vanishes as the observed molecular-ions correspond only to the first four terms.). The calculated deuterium and protium percentages are 95% and 5%, respectively.