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Short Research Article

Synthesis of ($^{14}C_6$-3,4,7,8,11,12)-(1*E*,5*E*,9*E*)-cyclododeca-1,5,9-triene[†]

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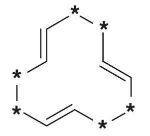
Abstract: Trimerization of butadiene in the presence of Ni(0) affords (1*E*,5*E*,9*E*)-cyclododeca-1,5,9-triene **1** (*ttt*-CDT), (1*E*,5*E*,9*Z*)-cyclododeca-1,5,9-triene **2** (*ttc*-CDT), and other isomers/oligomers. After optimization of reaction conditions, [$^{14}C_6$-3,4,7,8,11,12]-*ttt*-CDT **1** was synthesized efficiently either by homogenous or heterogeneous Ni(0) catalytic trimerization of [1,4-$^{14}C_2$]butadiene **10**, in 60–82% yield. Depending on the exact reaction conditions employed, the yields and ratio of **1/2** ranged from (59–90%) / (41–10%). The all-*trans* isomer was conveniently isolated via Ag$^+$-mediated reversed-phase HPLC. The important intermediate [1,4-$^{14}C_2$]-1,3-butadiene **10** was prepared from potassium [^{14}C]cyanide and 1,2-dibromoethane **3** as starting materials, in seven steps with a 57% yield. The total radioactive yield of [$^{14}C_6$-3,4,7,8,11,12]-*ttt*-CDT **1** is 30% from [^{14}C]KCN. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: *trans,trans,trans*-cyclododecatriene; cyclotrimerization; homogeneous catalysis; butadiene; carbon-14

Introduction

The cyclotrimerization of butadiene is a key reaction in homogeneous catalysis[1] and several transition metal and Ziegler–Natta catalyst systems have been reported.[2] By far, nickel complexes have been found to be the most versatile,[3] and Ni$^{(0)}$-catalyzed reactions have been studied in greatest detail.[4] In such systems, the [Ni^0(butadiene)$_x$] complex has been shown to be the active catalyst, and the all-*trans*-isomer is the predominant product, while the all-*cis*-isomer is not formed.[5]

Susán and Duncan synthesized [$^{14}C_6$]-cyclododecatriene from [$^{14}C_2$-1,4]-1,3-butadiene using a Ziegler-type catalyst system, in 1981.[6] In their report, the overall radiochemical yield was ~15%, the product was 98% *cis,trans,trans*-CDT **2**, and only 2% *trans,trans,trans*-CDT **1**, and separation and isolation of the individual isomers were not addressed. Herein we describe a high conversion, high stereoselectivity synthetic strategy (Scheme 1) that allowed synthesis of all-*trans* [$^{14}C_6$-3,4,7,8,11,12]-*ttt*-CDT **1** as the predominant isomer. Additionally, we accomplished the separation and purification of the *ttt*-CDT isomer using a Ag$^+$-mediated reversed-phase LC method, providing the product as a white crystalline solid with a chemical purity and radiochemical purity of >99%, and at a specific activity of 43 mCi/mmol.



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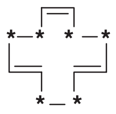

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Results and discussion

The first requirement for this synthetic approach was a high-yield process for the generation of doubly labeled intermediate [$^{14}C_2$-1,4]-1,3-butadiene **10**. As illustrated in Scheme 1, we chose as precursor the quaternary ammonium hydroxide **9** (SA ~15 mCi/mmol), which was prepared via reaction of [^{14}C]KCN (SA ~ 7.5 mCi/mmol) and 1,2-dibromoethane, following published methods, in six steps overall.[3,7]

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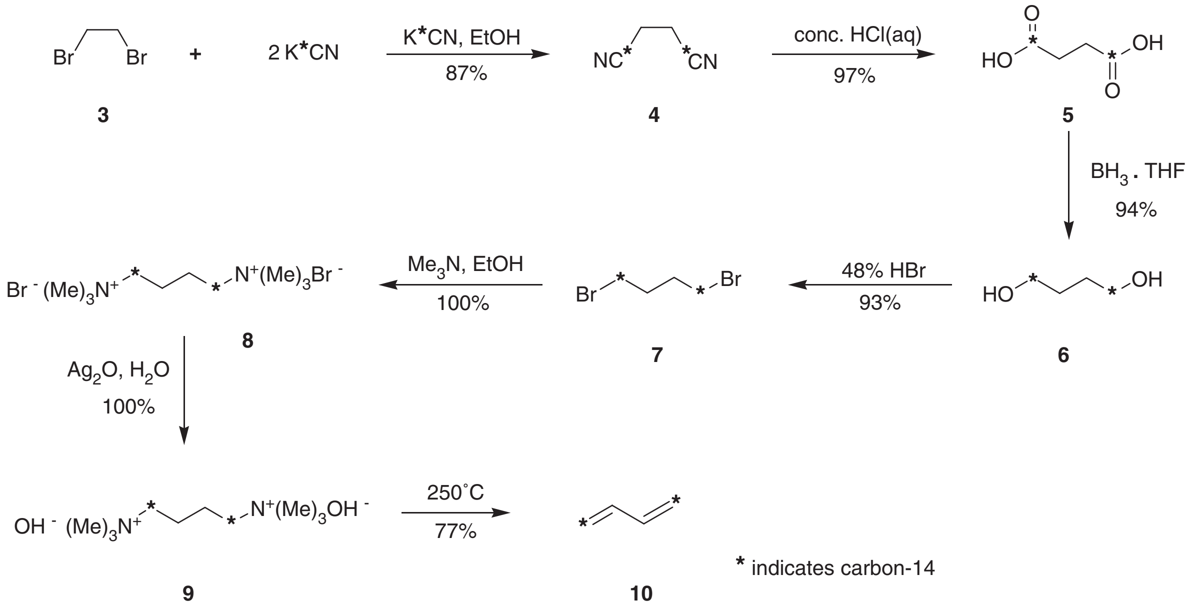
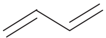


Scheme 1

Table 1 Optimization of butadiene cyclotrimerization[a]

Entry	Method	 (mmol/ml)	Ni(acac)$_2$ (mg/mmol)	AlEt$_3$ (μl/mmol)	Solvent/(ml)	Yield (%)	*ttt*:*ttc*	Color
1	A	11.5/1	119/0.04	100/0.2	toluene/2.0	14	90:10	Light brown
2	B	11.5/1	110/0.4	1.0/2	toluene/5.0	22	N/A	Black
3	B	13.8/1.2	27/0.1	220/0.4	toluene/2.0	78	66:34	Black
4	A	30/2.6	27/0.1	220/0.4	toluene/5.0	82	67:33	Brown
5	A	11.4/1	27/0.1	220/0.4	toluene/5.0	60	79:21	Brown
6	A	11.4/1	27/0.1	220/0.4	1,5-COD/5.0	34	59:41	Yellow
7[b]	A	28.8/2.7	34/0.12	277/0.5	toluene/5.0	78	67:13	Brown

[a] Reaction conditions: sealed glass vessel, 80°C, 20 h under He.
[b] 'Hot run,' using labeled butadiene; yield is total mCi isolated.
Method A: AlEt$_3$ to a mixture of Ni(acac)$_2$/butadiene in solution.
Method B: Butadiene condensed into preformed Ni(acac)$_2$/AlEt$_3$ catalyst solution.

Refluxing of 1,2-dibromoethane **3** (1 equiv.) with [^{14}C]KCN (1 equiv.) in 70% EtOH(aq.) gave [$^{14}C_2$-1, 4]succinonitrile **4** in 87% yield (based on KCN). Acidic hydrolysis of **4** with conc. HCl under refluxing conditions afforded [$^{14}C_2$-1,4]succinic acid **5** in quantitative yield. The reduction of **5** with borane–THF at 0°C provided diol **6** (94%), which was easily converted into the dibromide **7** by refluxing the diol **6** with 48% HBr. Reaction of [$^{14}C_2$-1,4]-1,4-dibromobutane **7** with trimethylamine gas in ethyl alcohol provided the ammonium bromide **8**. Compound **8** was converted to the corresponding ammonium hydroxide in quantitative yield using freshly prepared silver(I) oxide, generated *in situ*. Finally, the generation of [$^{14}C_2$-1,3]butadiene **10** was accomplished by pyrolysis of **9**, passing the evolved gases first through a 2 N H_2SO_4 gas scrubber to remove Me_3N(g), followed by passage over Drierite™ to remove water.

A limited number of cyclotrimerization experiments were conducted to optimize the reaction conditions, with the intent of maximizing total conversion and isomer-selectivity. (Table 1) Consideration was given to (i) the reduction of Ni(II) in the presence of the butadiene (Method A) *versus* addition of butadiene to a zerovalent 'bare' nickel complex (Method B), (ii) the ratio of Ni:butadiene, and (iii) the ratio of AlEt$_3$:butadiene. Based on the results of these experiments, the conditions used for Entry 4 were employed for execution of the 'hot run,' using the [$^{14}C_2$-1,4]-1,3-butadiene **10**; these results are shown as Entry 7, and the ratio of *ttt*-CDT:*ttc*-CDT is the actual total isolated activity (mCi) for each isomer (Table 1).

Separation and purification of the *ttt*-CDT and *ttc*-CDT isomers were accomplished using Ag^+-mediated complexation-based chromatography. Complexation-based chromatography (GC, LC), involving electron-rich metal salts such as $AgNO_3$, $Rh(OAc)_2$, etc. has been studied extensively and there are two basic approaches for LC separation: (i) π-complex formation between the analyte and metal ions dissolved in the mobile phase,[8] and (ii) π-complexing metal ions immobilized on the stationary phase.[9]

The mixture of isomers **1** and **2** separated successfully by reversed-phase flash chromatography (VersaPack™ C18 Cartridge, 40 × 75 mm), eluting with Ag^+ salt) gave high pure compound **1**.

Conclusion

A new synthesis has been developed and the reaction conditions optimized to provide high purity [$^{14}C_6$-3,4,7,8,11,12]-(1*E*,5*E*,9*E*)-cyclododeca-1,5,9-triene in 30% overall radioactive yield from [^{14}C]-KCN.

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