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Tetrabromo Hydrogenated Cardanol: Efficient and Renewable Brominating Agent

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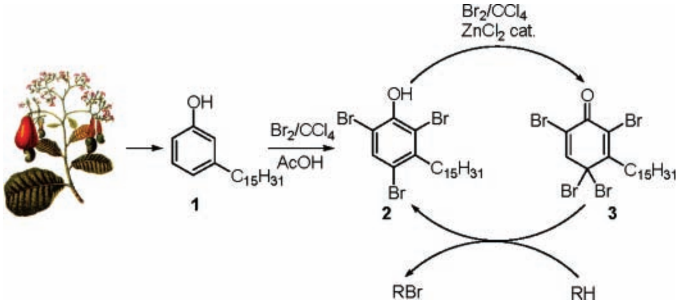
ABSTRACT



2,4,4,6-Tetrabromo-3-*n*-pentadecyl-2,5-cyclohexadienone (TBPCO) has been synthesized and used as a new efficient, convenient, and environmentally friendly brominating agent.

The spongy mesocarp of a cashew nut shell (*Anacardium occidentale* L.) contains, in nearly 25−30% of the total nut weight, an alkyl phenolic oil internationally known as "cashew nut shell liquid" (CNSL). This oil derives as a byproduct from mechanical processing for edible use of the cashew kernel presently in some 350 000 tons per annum worldwide with the expectation to rise up to 600 000 tons per annum soon.[1−3] Therefore, CNSL represents a renewable, widely available, and relatively low-cost organic natural raw material useful for several applications in fine chemistry or for production of varnishes, resins, surfactants, pesticides, etc.[4] Chemically, CNSL is a mixture of anacardic acid, cardanol, and a smaller amount of cardol and 2-methylcardol, with the polyketide long chain being saturated, monoolefinic (8), diolefinic (8,11), and triolefinic (8,11,14) with an average value of two double bonds per molecule (Figure 1).[1−3]

However, anacardic acid undergoes ready thermal decarboxylation. Thus, the distillation of CNSL provides cardanol in high yield and good purity. The subsequent catalytic hydrogenation of distilled cardanol gives rise to 3-*n*-pentadecylphenol (**1**).[5]

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§ Università della Tuscia.

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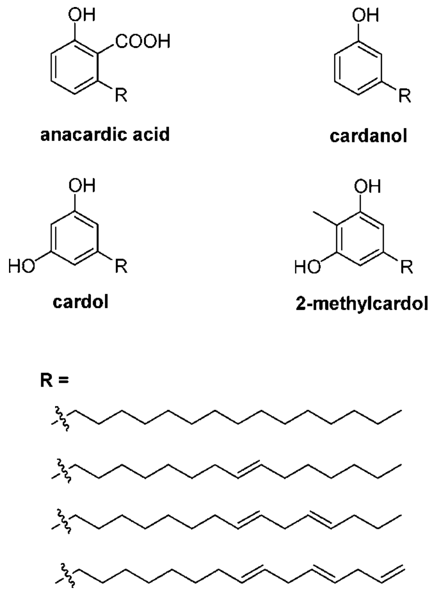


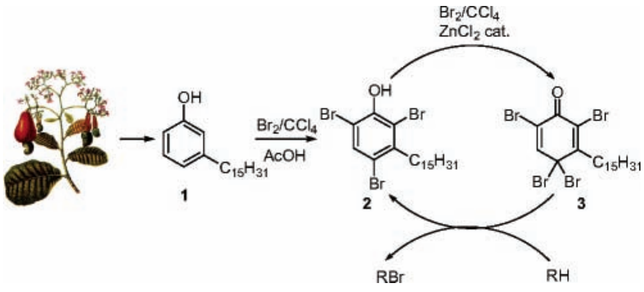
Figure 1. Components of CNSL.

During the past few years, allylation,[6] cyclocarbonylation,[6] and nitration[7] of hydrogenated cardanol, as well as the synthesis of phthalocyanines,[8] porphyrins,[9] and fullerene[10] derivatives of cardanol, have been investigated in our laboratories.

The general importance of halogenation reactions in organic chemistry[11] and, in particular, the role of bromination[12] in the synthesis of organic intermediates or antitumor, antifungal, antibacterial, antineoplastic, and antiviral compounds have drawn our attention.[13] The most commonly used reagents for such a reaction include elemental bromine,[14] organic ammonium tribromides (OATB),[15] copper(II) bromide,[16] *N*-bromosuccinimmide (NBS),[17] and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO).[18] Recently, Patel et al. reported the synthesis of 1,2-dipyridiniumditribromide-ethane (DPTBE) as a new efficient brominating reagent.[19] Despite the variety of reagents available for bromination, low selectivity and formation of undesired side products under mild reaction conditions continue to be problematic.

To find an alternative, environmentally friendly, mild, clean, efficient, regioselective, simple workup, and cost-effective procedure, we investigated the use of hydrogenated cardanol as starting material for the preparation of such a brominating reagent, as part of our ongoing program for the utilization of this compound in fine chemistry. First, 2,4,6-tribromo-3-*n*-pentadecylphenol **2** was easily obtained in 4 h by reaction of 3-*n*-pentadecylphenol **1** in carbon tetrachloride under reflux with 3 equiv of bromine (1.0 M solution in CH_3COOH). The fourth bromine atom in position 4 of the phenolic ring of **2** was introduced by treatment of this latter compound in carbon tetrachloride with a fourth bromine equivalent (1.0 M solution in CCl_4) in the presence of $ZnCl_2$ in a catalytic amount producing 2,4,4,6-tetrabromo-3-*n*-pentadecyl-2,5-cyclohexadienone **3** (TBPCO) in nearly quantitative yield (Scheme 1).[4b]

Scheme 1. Preparation of TBPCO and Bromination of Organic Substrates



This brominating agent easily and inexpensively made in multigram quantity is a crystalline solid, facile to handle, and stable for extended periods when stored in a refrigerator.

The presence of the long alkyl chain in the meta position of the phenole ring gives to TBPCO a lower melting point and a higher solubility in apolar organic solvents than those of similar products lacking a long alkyl side chain (i.e.,

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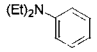
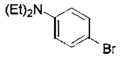
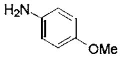
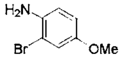
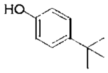
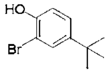
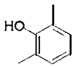
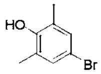
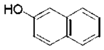
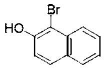
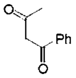
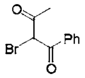
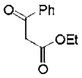
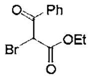
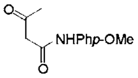
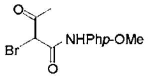
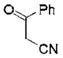
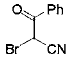
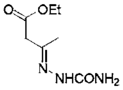
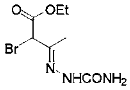
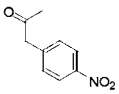
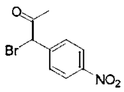
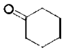
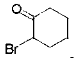
TBCO). For the same reason, its precursor 2,4,6-tribromo-3-*n*-pentadecylphenol **2** is soluble in most organic solvents but is highly insoluble in water, methanol, and acetonitrile thus facilitating its recovery by separation from brominated products at the end of the reaction.[20] These properties represent a further advantage of this reagent in respect to other known organic tetrabromides together with the smooth regeneration of TBPCO and the natural origin of these reagents.

The results of bromination at room temperature of activated aromatic amines and phenols, β-naphthol, and sensitive substrates such as carbonyl compounds are summarized in Table 1. TBPCO works well with both aromatic (entries 1−5) and aliphatic (entries 6−12) substrates as well as with different polarity solvents.

Table 1. Bromination of Organic Substrates with TBPCO

entry	RH	RBr(a)	solvent	time (h)	yield (%)(b)
1			C_6H_{12}	0.1	97
2			Et_2O	0.1	95
3			Et_2O	0.1	89
4			C_6H_{12}	24	96
5			Et_2O	0.5	98
6			C_6H_{12}	15	95
7			C_6H_{12}	15	92
8			CH_2Cl_2	6	89
9			Et_2O	10	96
10			CH_2Cl_2	1	97
11			CH_2Cl_2	4(c)	87
12			C_6H_{12}	24	93

[a] All the bromo derivatives are known compounds reported in the literature. Their identities and purities were confirmed by ^1H NMR spectra. [b] Yields of isolated product by crystallization with methanol of the 2,4,6-tribromo-3-*n*-pentadecylphenol **2**. [c] Reaction performed under reflux.

2,4,4,6-Tetrabromo-3-*n*-pentadecyl-2,5-cyclohexadienone **3** (TBPCO) seems to be an electrophilic brominating agent in which "positive" bromine is transferred to release aromatic phenolate anions.

In conclusion, this paper reports the synthesis of new tetrabromide reagent TBPCO obtained from natural and largely available CNSL. [TBPCO demonstrates an excellent bromine carrier that is able to brominate different organic substrates.] The reaction generally occurs under mild conditions, requires a simple workup procedure, and permits both the recovery and the regeneration of the brominating reagent. Therefore, the whole reaction may be considered environmentally friendly. On the basis of preliminary findings, the regioselective monobromination of TBPCO seems more favored than that of TBCO. Moreover, investigations are in progress by computational calculations able to quantify the effect of the steric hindrance of an alkyl side chain on the *ortho*-bromine atoms of TBPCO. Kinetics measurements will be made also to exactly determine the peculiar properties of TBPCO in respect to the other similar brominating agents.

At present, further investigations are in progress to find additional applications of this reagent in organic synthesis.

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Supporting Information Available: Experimental procedures including characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267.

(20) **General Experimental Procedure for Bromination of Organic Substrates.** To a stirred solution of organic substrate (0.5 mmol) dissolved in the appropriate solvent (10 mL) (Table 1) was added in small portions 2,4,4,6-tetrabromo-3-*n*-pentadecyl-2,5-cyclohexadienone (0.55 mmol). The reaction mixture was magnetically stirred until the disappearance of the starting organic substrate (monitored by TLC). After completion of the reaction, the reaction mixture was concentrated under reduced pressure and was purified by crystallization of 2,4,6-tribromo-3-*n*-pentadecylphenol from CH_3OH. The brominated organic substrate was obtained in satisfactory yield and purity.