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Purposeful regioselectivity control of the Birch reductive alkylation of biphenyl-4-carbonitrile

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ABSTRACT

Birch's reductive alkylation of biphenyl-4-carbonitrile (**1**) provides alkylated 1,4-dihydroderivatives of various structural types: 4-alkyl-4-phenylcyclohexa-2,5-dienone, 1,4-dialkyl-4-phenylcyclohexa-2,5-dienecarbonitrile (with the same or different alkyl fragments), and 4-(1-alkylcyclohexa-2,5-dienyl) benzonitrile. Each of these products become dominant depending on the nature of long-living anionic form generated from **1**, namely, the stable product of two-electrons reduction – dianion ($\mathbf{1}^{2-}$); 1-alkyl-4-cyano-1-phenylcyclohexa-2,5-dien-4-yl anion ($\mathbf{1\text{-}Alk}_{\mathbf{1}}^{-}$), originated due to the alkylation of dianion $\mathbf{1}^{2-}$ at the position 1 of biphenyl moiety; or 1-(4-cyanophenyl)cyclohexa-2,5-dien-1-yl anion ($\mathbf{1\text{-}H}_{\mathbf{4'}}^{-}$), being the product of dianion $\mathbf{1}^{2-}$ protonation at position 4′ by protonating reagent (MeOH or NH_4Cl). The orientation of alkyl fragment incorporation into biphenyl-4-carbonitrile scaffold is in agreement with calculated electronic structure of the anionic species under investigation. The dominating type of their reactivity towards alkyl halides proved to be nucleophilic (S_N2 mechanism).

1. Introduction

The shortest and most convenient approach to compounds with cyclohexa-1,4-dienylic structural motif, valuable in synthesis of natural, bioactive compounds[1] and new materials, is based on Birch's reduction or reductive alkylation of aromatic compounds.[2] Despite the fact that most of the substrates studied in Birch's reaction were unsubstituted arenes or ones bearing electron donating groups, the electron-deficient substrates are particularly attractive for the following reason. Their reduction by alkali metal in liquid ammonia provides quite stable anionic forms (AFs), *viz*., radical anions (RAs), dianions (DAs) or (after subsequent protonation) cyclohexadienyl anions (CHDAs). In turn, stability of these AFs opens the possibility of their preparative generation and the investigation of their identity, electronic structure and reactivity towards electrophilic reagents (S_N/*ET*-mechanism competition). The data thus obtained can serve as the basis for construction of a general synthetic approach utilizing electron-deficient arene's AFs as effective anionic synthons.[3] Unlike AFs of nitro- and carbonyl-bearing arenes undergoing predominantly transformations of functional group, AFs of aromatic carboxylic acids and their derivatives (esters, amides, nitriles) provide dihydroproducts of aromatic ring modification at positions *ipso*-and *para*- to functional group.[2d,e,m,n,4–7]

Our research interest concerns arenecarbonitrile AFs. It has been shown that AFs of benzo- and tolunitriles, 1-naphthonitrile, 9-anthracenecarbonitrile, phthalo- and terephthalonitrile, 9,10-anthracenedicarbonitrile react with alkyl halides exclusively at aromatic moiety and provide the products – subsequent alkylated cyanoarenes and cyanoalkyl-1,4-dihydroarenes – in good to high yields.[7] The presence of the readily and variably modifiable cyano group[8] in product's structure provides wide possibilities for further preparing practically important substances and materials.

In this work, we concentrated on study of biphenyl-4-carbonitrile (**1**) as the most affordable isomer among biphenylcarbonitriles, which reductive alkylation has not been explored until now. According to literature data, a fairly stable radical anion and dianion can be generated from nitrile **1** under chemical,[9]

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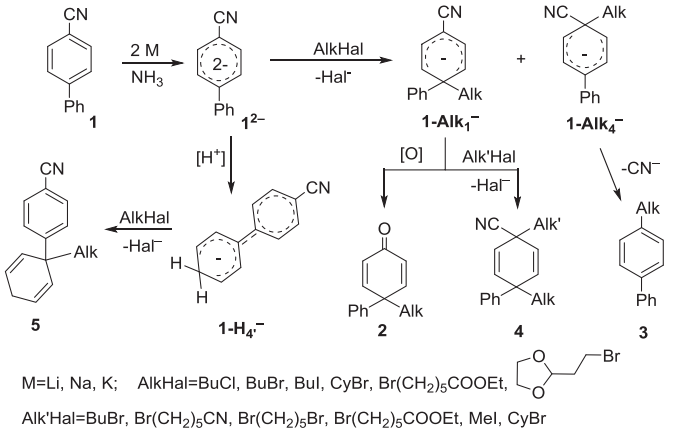
electrochemical,[10] pulse radiolysis[11] reduction. These data together with our previous results describing identity, electronic structure and reactivity of cyanoarene AFs in liquid ammonia[3,7] allowed us to anticipate the formation of quite stable dianion or cyclohexadienyl anion under the two-electron reduction of **1** by alkali metal in liquid ammonia in preparative amounts. Subsequent interaction of these AFs with alkyl halides would lead to the formation of alkylated products, comprising in their structure dihydrobiphenylic moiety and cyano group, which makes them valuable structural blocks in organic synthesis. Preparation of products with given alkyl fragment location in cyanobiphenyl scaffold requires the study of the dependence of alkylation orientation upon the type of AF generated from nitrile **1** and its reactivity toward different alkyl halides, that was the subject of our present paper.

2. Results and discussion

Reduction of nitrile **1** was performed by the action of alkali metal (Li, Na, K ~2.1 equiv. per **1**) in liquid ammonia. At first, we observed the formation of a dark green solution obviously pertinent to the RA $\mathbf{1}^{\bullet-}$, which in 2–5 min turned into a dark-brown suspension of obviously being DA $\mathbf{1}^{2-}$ alkali salt (Scheme 1).[12] Unfortunately, the low solubility of this salt in ammonia prevented to get its NMR spectra that's why the conclusion about the identity (DA or CHDA) and stability of nitrile **1** two electron reduction product in liquid ammonia was made on the basis of the following experimental data. Stirring of the obtained suspension for an hour in atmosphere of evaporating ammonia with subsequent quenching by bringing into contact with air led to a return of nitrile **1** (≥90%) and the appearance of a small amount (≤5%) of biphenyl. Also this suspension remained unchanged in sealed NMR ampoule at room temperature during a week; subsequent alkylation by the excess of butyl bromide led to the product mixture identical to the one obtained by the alkylation of this AF just after generation (see Table 1, Entry 6); the main product was 1,4-dibutyl-4-phenylcyclohexa-2,5-dienecarbonitrile. These results in total allowed us to suggest that two electron reduction of nitrile **1** in liquid ammonia provides the long living DA $\mathbf{1}^{2-}$, which is quite stable with the respect to fragmentation as well as to protonation by the solvent.

In order to reveal the reactivity and synthetic productivity of DA $\mathbf{1}^{2-}$, we used alkylating reagents differing in alkyl fragment structure, the additional ω-functions, and on the nature of the halogen atom (Scheme 1). The structure of the main alkylated product was found out to depend substantially on the nature of alkylating reagent. On the contrary, the nature of the alkali metal used to reduce **1** had no significant effect on the results of reductive alkylation,



Scheme 1. The routes of products formation proposed for DA $\mathbf{1}^{2-}$ alkylation.

sodium proved to be the most convenient to handle the reactions (Table 1, Entries 6–8). Thus the interaction of DA $\mathbf{1}^{2-}$ sodium salt with butyl chloride provides 4-butyl-4-phenylcyclohexa-2,5-dienone (**2a**) as the main product, along with a small amount 4-butylbiphenyl (**3a**),[13] other components of the reaction mixture were starting nitrile **1** and butyl halide (Table 1, Entry 1). The formation of dienone **2** as the main reaction product allows us to propose the following pathway. At first, DA $\mathbf{1}^{2-}$ is alkylated predominantly at position 1 of biphenylic moiety with the formation of 1-butyl-4-cyano-1-phenylcyclohexa-2,5-dien-4-yl anion ($\mathbf{1\text{-}Alk_1^-}$), which is less reactive than DA $\mathbf{1}^{2-}$ in relation to the primary alkyl chloride under low experimental temperature (−40 ÷ −33 °C). Being sufficiently stable under inert reaction conditions, anion $\mathbf{1\text{-}Alk_1^-}$ is oxidized into dienone **2a** by oxygen while processing of the reaction mixture. As regards the minor alkylaromatic product **3a**, its formation is obviously due to DA $\mathbf{1}^{2-}$ alkylation at position 4, followed by rapid decyanation of thus formed unstable anion $\mathbf{1\text{-}Alk_4^-}$, thus restoring aromaticity and providing 4-butylbiphenyl.

The sequential treating of DA $\mathbf{1}^{2-}$ sodium salt with 1 equiv. of butyl chloride and, after about an hour, 1 equiv. of more reactive reagent – methyl iodide – led mainly to isomeric (*trans*- and *cis*-) 4-butyl-1-methyl-4-phenylcyclohexa-2,5-dienecarbonitrile (**4ab**), together with minor amount of dienone **2a** and butylbiphenyl **3a** (Table 1, Entry 2). The utilization of $Br(CH_2)_5CN$, $Br(CH_2)_5CO_2Et$ or $Br(CH_2)_5Br$ (Entries 3–5) instead of methyl iodide provided corresponding 4-butyl-1-(ω-X-alkyl)-1,4-dihydroderivatives **4ac**–**4ae** as the main reaction products. In accordance with the obtained results, the addition of two equiv. of butyl bromide to DA $\mathbf{1}^{2-}$ sodium salt (Table 1, Entry 6) led to the isomeric 1,4-dibutyl-4-phenylcyclohexa-2,5-dienecarbonitriles (**4aa)** as the major product. In significantly fewer amounts the reaction mixture contained butylbiphenyl **3a** and a new type of dihydroderivative – 4-(1-butylcyclohexa-2,5-dienyl)benzonitrile (**5a**). Lithium and potassium salts of DA $\mathbf{1}^{2-}$, when reacting with butyl bromide, gave the same products in similar amounts (Table 1, Entries 7 and 8). The reaction selectivity markedly lowered when butyl iodide was used instead of alkyl bromides: some di- and tributyldihydrobiphenyls in amounts comparable to products **3a**, **4aa** and **5a** were obtained (Table 1, Entry 9). Typically, such decrease in selectivity of cyanoarene AF alkylation was observed due to electron transfer (*ET*) mechanism in the cases when alkyl iodide as well as tertiary alkyl halide were used.[7]

The interaction of DA $\mathbf{1}^{2-}$ sodium salt with 1 equiv. of secondary alkylating reagent – cyclohexyl bromide – provided 4-cyclohexyl-4-phenylcyclohexa-2,5-dienone (**2g**); 4-cyclohexylbiphenyl (**3g**)[14] and 1,4-dicyclohexyl-4-phenylcyclohexa-2,5-dienecarbonitrile (**4gg**) also formed in a much smaller amount (Table 1, Entry 10). The sequential treating of a suspension of DA $\mathbf{1}^{2-}$ sodium salt first with cyclohexyl bromide, and after an hour – butyl bromide, led to formation of the isomeric 4-butyl-1-cyclohexyl-4-phenylcyclohexa-2,5-dienecarbonitriles (**4ga**) as the major products (Table 1, Entry 11). If 3 equiv. of cyclohexyl bromide were used and the reaction time was increased from 1 to 4 h, the major product became 1,4-dicyclohexyldihydroderivative (**4gg**) (Table 1, Entry 12).

The structures of all new products were defined by NMR and IR spectroscopic analysis and supported by mass-spectroscopy. In addition, we carried out X-ray single-crystal analysis for *trans*-**4ac**, *cis*-**4ae**, **2g**, and *trans*-**4gg** as representatives for typical products structure (Fig. 1).

The X-ray diffraction studies revealed that in all studied compounds hexadienyl cycles are planar (the highest atom deviation from the cycle plane is 0.043 A in **4ac**). In compound **2g**, bond lengths of the cyclohexadienone fragment are close to the same lengths in the 4,4-diphenyl-2,5-cyclohexadienone.[15] For derivatives