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Primary alkyl fluorides as regioselective alkylating reagents of lithium arene dianions. Easy prediction of regioselectivity by MO calculations on the dianion

Raquel P. Herrera, Albert Guijarro and Miguel Yus*

Departamento de Química Orgánica, Universidad de Alicante, Ap. 99, E-03080 Alicante, Spain

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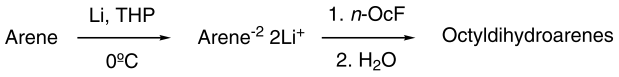
Abstract—Lithium arene dianions derived of polycyclic aromatic hydrocarbons, such as naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene and binaphtyl react cleanly with *n*-alkylfluorides to afford regiochemically controlled alkylated dihydroarenes after hydrolysis. These arene dianions can be easily prepared by simple treatment of the arene with lithium in THP. Unlike simple radical coupling, the alkylation of these species with alkyl fluorides apparently goes through a S_N2 transition state, despite the inertness of alkyl fluorides to undergo nucleophilic substitution. It is also atypical for reduced arenes, which tend to give ET reactions with other alkyl halides. Prediction of the regiochemistry was easily conducted by means of MO calculations (PM3) on the dianion, and in all cases were consistent with the experimental. © 2003 Elsevier Science Ltd. All rights reserved.

In the preceding paper we reported a mechanistic study that suggests that highly reduced arenes, like naphthalene dianion, react through a nucleophilic substitution reaction pathway with primary alkyl fluorides. This is an unexplored reaction that attracted our attention from both a theoretical standpoint as well as for its potential synthetic use. Conventional nucleophiles display in general low reactivity towards alkyl fluorides.[1] High laying LUMO energies of alkyl fluorides prevent easy access to these orbitals and certain transition states such as S_N2 are not easily reached. On the contrary, radical anions, dianions, and in general polyanions of arenes are not usually regarded as nucleophiles but rather as electron transfer (ET) reagents. In these species, the π-extended vacant orbitals of the arene (π-LUMOs) have been occupied by a number of extra electrons, often from an alkaline metal. The resulting polyanionic species have thus both very high laying and also highly delocalized electrons. This eventually dictates their reactivity, in many cases reminiscent of the alkaline metal they originated from. We describe in this paper the synthetic applications derived from the combination of arene dianions, which apparently react as nucleophiles and not necessarily as ET reagents with alkyl fluorides. The reaction products are regiochemically controled alkylated dihydroarenes. Among the arenes we included both benzenoid and non-benzenoid common polycondensated aromatic hydrocarbons such as naphthalene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene and 1,1′-binaphtyl. Naphthalene has the most negative redox potential among these arenes ($E_1^\circ=-2.53$ V in DMA/TBAB).[2] In the presence of an excess of Li powder it is doubly reduced in THP to its antiaromatic dianion, $Li_2C_{10}H_8$.[3] Based on reduction potential criteria, the remaining arenes are also expected to be reduced to the dianion under the same conditions. Thus, for instance, anthracene ($E_1^\circ=-2.04$ V, $E_2^\circ=-2.64$ V), phenanthrene ($E_1^\circ=-2.49$ V, $E_2^\circ=-3.13$ V), fluoranthene ($E_1^\circ=-1.78$ V, $E_2^\circ=-2.37$ V), pyrene ($E_1^\circ=-2.13$ V, $E_2^\circ=-2.86$ V) are capable of forming dianionic species by electrochemical means in DMA/TBABr, as measured by cyclic voltammetry.[2] In addition, the spectral properties of the alkaline salts of most of these dianions have been described (naphthalene,[4] anthracene,[5] phenanthrene,[5] chrysene,[5] pyrene).[6] They are actually formed by exposure of the arene to an alkaline metal in an appropriate solvent. Other higher polyanionic arenes are by no means excluded for certain arenes, e.g. for 1,1′-binaphthyl.



$$\text{Arene} \xrightarrow[0^{\circ}\text{C}]{\text{Li, THP}} \text{Arene}^{-2}\,2\text{Li}^{+} \xrightarrow[2.\ \text{H}_2\text{O}]{1.\ n\text{-OcF}} \text{Octyldihydroarenes}$$

Scheme 1. Preparation of regiochemically controlled octyldihydroarenes by alkylation of lithium arene dianions with *n*-octyl fluoride and hydrolysis with water.

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* Corresponding author. Tel.: +34-965-903548; fax: +34-965-903549; e-mail: aguijarro@ua.es; yus@ua.es

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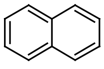
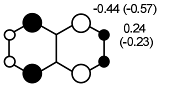
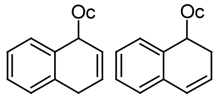
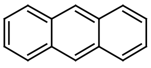
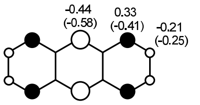
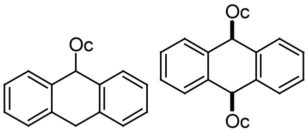
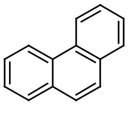
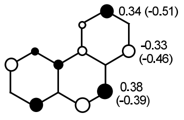
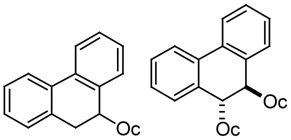
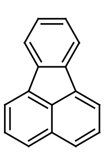
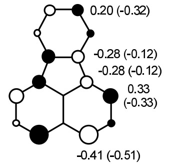
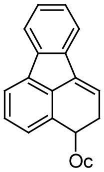
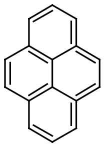
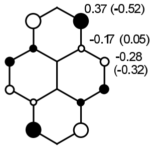
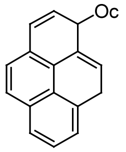
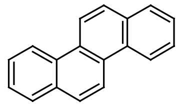
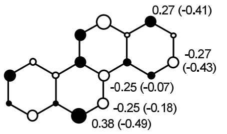
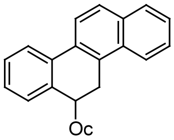
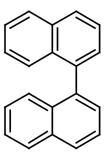
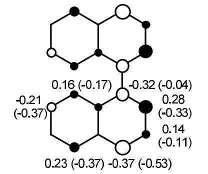
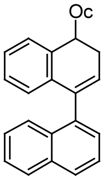
In a representative experiment, to a mixture of lithium powder (10 mmol) and chrysene (2.0 mmol), THP (10 mL, 0°C) was added and the reaction was stirred for 30 min at the same temperature under an inert Ar atmosphere. During that time part of the lithium powder dissolves. 1-Fluorooctane (2 mmol) is then added. After a few minutes, the reaction is hydrolyzed with water, the organic phase is extracted, treated with 0.1 mmol of hydroquinone and evaporated. The remaining mixture was purified by flash chromatography (hexanes, silica gel doped with 5% of hydroquinone) affording 6-octyl-5,6-dihydrochrysene in 73% yield (Scheme 1 and Table 1). In some cases, slightly better yields were obtained when all three reagents were mixed at once from the beginning. The reaction seems to proceed via dianion also in this case since: (a) 1-fluorooctane does not react with Li powder in the absence of an arene under the given conditions (which excludes a conceivable addition of octyllitium to the arene) and (b) the radical anion is not reactive enough to perform alkylations in many

Table 1. Preparation of octyldihydroarenes according to Scheme 1. PM3 HOMO coefficients and Mulliken charges (in parenthesis) for the arene dianion intermediates

No.	Arene	RHF-PM3 HOMO coeff. and Mulliken charges of arene^{-2}	Isolated regioisomer[a]	No.	Yield (%)[b]
1				**1a, 1b**	49, 35
2				**2a, 2b**	36, 57[c]
3				**3a, 3b**	22, 45[d] <1, 8[e]
4				**4a**	53[f] 0[e]
5				**5a**	72[f,g] 0[e]
6				**6a**	73[h] 0[e]
7				**7a**	58 0[e]

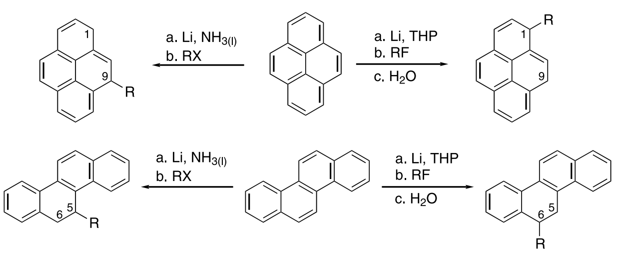
[a] All isolated compounds gave consistent NMR spectra and correlations (^{1}H-, ^{13}C-, DEPT, COSY, HSQC and HMBC) as well as HRMS and IR spectra. [b] For each drawn product, respectively in the same order as it appears in the table. [c] *cis* Geometry is obtained by alkylation of 9-alkyl-9,10-dihydroantracen-10-yl lithium, confirmed by comparison of the NMR chemical shifts with the *cis* and *trans*-9,10-diethyl-9,10-dihydronanthracene: Ahmad, N.-u.-d.; Cloke, C.; Hatton, I. K.; Lewis, N. J.; MacMillan, J. *J. Chem. Soc. Perkin Trans. 1*, **1985**, 1849. [d] *trans* Geometry is obtained by alkylation of 9-alkyl-9,10-dihydrophenantran-10-yl lithium, confirmed by comparison of the NMR chemical shifts with the *cis* and *trans*-9,10-diethyl-9,10-dihydrophenanthrene: Rabideau, P. W.; Harvey, R. G. *J. Org. Chem.* **1970**, *35*, 25. [e] Yield for arene radical anion (Ar$^{\cdot-}$ Li$^+$) instead of dianion under the same experimental conditions. [f] All reagents mixed at once. [g] Detected by ^{1}H-NMR in the reaction crude by comparison with the ^{1}H-NMR pattern of the 1,9-dihydropyrene: Harvey, R. G.; Rabideau, P. W. *Tetrahedron Lett.* **1970**, 3695, but isolated as 1-octylpyrene (**5b**): Zimerman, O. E.; Weiss, R. G. *J. Phys. Chem. A* **1999**, *103*, 9794. [h] 6-Octyl-5,6-dihydrochrysene, based on HMBC NMR experiments and by comparison with 5-alkyl-5,6-dihydrochrysene: Levy, L. A.; Sashikumar, V. P. *J. Org. Chem.* **1985**, *50*, 1760.

cases. Table 1 contains the yields for the reductive alkylation of the above mentioned arenes.

One of the most important facts concerning this reaction is that products showed little contamination due to different regioisomers. More complex mixtures of regioisomers would be expected if they were formed by coupling between radicals, which is likely to be a less selective reaction. In most cases, only the major regioisomer of alkylation was isolated and analyzed. After the alkylation step has taken place, the resulting monoanion is protonated. This might give rise to additional regioisomers (e.g. 1,4- and 1,2-dihydronaphthalenes, 49 and 35% yield respectively). In some cases the product of dialkylation occurs along with the monoalkylation (e.g. anthracene and phenanthrene). In these cases, the experimental conditions needed to minimize undesired polyalkylation products have not been optimized.

We have been able to reproduce the regioselectivity displayed experimentally by means of simple semiempirical calculations on the dianion.[7] We have collected in Table 1 the calculated HOMO coefficients for every dianion (isolated Ar^{-2}, no counterion) and the Mulliken charges for each carbon atom. In all cases, the highest HOMO coefficient dictates the regioselectivity observed, rather than the charge on a given carbon atom (see for instance phenantherene). The transition state for the alkylation seems to be driven by the overlap of orbitals rather than Coulombic forces, regardless of the charged nature of the dianion and the highly polarized C–F bond. In the remaining cases, the carbon bearing the highest coefficient also concentrates the charge. A priory, a fairly symmetrical S_N2 reaction pathway would fit reasonably well in all these arguments. It is also significant that, in several cases, the arene radical anion was unable to afford substantial amounts of alkylated products (e.g. fluoranthene, pyrene, chrysene and 1,1′-binaphtyl). In some of these cases there is an ET reaction, however, octane being chiefly the main reaction product.

This methodology complements the current methodologies of reductive alkylation of polycyclic arenes, allowing access to a new set of regioisomers, their regiochemistry being dictated by the HOMO coefficients of the dianion. It is important to remark that other reductive alkylation techniques, such as the alkaline metal reduction in $NH_{3(l)}$, afford different alkylated regioisomers even though arene dianions are active participants in the course of the reaction. For instance, pyrene,[8] and chrysene,[9] react with $Li/NH_{3(l)}$ followed by alkylation affording 9-alkyldihydropyrene and 5-alkyldihydrocrysene, whereas alkylation of the dianion with alkyl fluorides afford the complementary 1-alkyl and 6-alkyl dihydroarenes, respectively (Scheme 2). Fluorantene also behaves in a similar manner.[10] Different sequences of reaction involving (a) protonation of the dianion (in NH_3) followed by alkylation versus (b) alkylation of the dianion (in THP) followed by protonation, explains this apparent misconduct. In THF, the crude mixtures are contaminated with the 4-hydroxybutyl framework originated from the solvent cleavage, proton abstraction being also a recurrent problem in this solvent.[3,8]



Scheme 2. Comparison of the regiochemical outcome with other reductive alkylation methodologies.

In conclusion, the observed reaction can be explained invoking the participation of arene dianions. This fact is supported by the isolation of alkylated dihydroarenes as the main reaction products, and the regioselectivity displayed, which in all cases matched the calculated. Dianions presumably react with alkyl fluorides through a S_N2 mechanism, as suggested in the preceding paper. It would be interesting to discern why there is an apparent switch from ET (electron transfer) to a S_N mechanism as the carbon–halogen bond strengths from C–I to C–F, and also why reactivity switches from ET to S_N2 when arene dianions are used instead of arene radical anions with alkyl fluorides. This is currently the subject of further experimental and theoretical investigations.

Acknowledgements

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98W) afforded singlet ground states of comparable coefficients/charges on atoms. Further studies will include UHF calculations.

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