Nucleophilic addition of organolithium reagents to cyanine dyes. A new access to functionalized hexatrienes

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Abstract—The possibility for extending a pentamethine carbon chain by the use of an appropriate pair of electrophilic substrates, a cyanine dye- and nucleophilic-organolithium reagent is explored. A new synthetic approach to differently functionalized hexatrienes was achieved as a result of spontaneous or accelerated on silica gel surface Hofmann type elimination of the initially formed adducts. A series of trifunctional ligands were obtained by means of a two-step reduction with Pd/C and LAH. © 2001 Elsevier Science Ltd. All rights reserved.

While the reactivity of polymethine dyes towards nucleophiles has been a subject of numerous studies,[1] the data concerning organometallic reagents as specific nucleophiles are isolated. The synthesis[2] and the reactivity of the cyanine dyes is of our current interest due to the versatility of their design for specific purposes in non linear optics[3] or biological applications.[4] In general, the reactivity is determined by a relative thermodynamic stability of the polymethine system and hence, tendency towards regeneration after the reaction.[1] The second important factor is the charge alternation, thus even-numbered carbon atoms of the cyanine chain being negatively charged and odd-numbered ones positively charged. Recently we investigated the reaction of pentamethinecyanine dyes and hemicarboxonium salts substituted by terminal aromatic groups with 'soft' metal reagents, i.e. lithiated phenylacetic acid derivatives.[5] The nucleophilic attack was found to occur regioselectively on the central

C3 carbon atom due either to steric control imposed by the aromatic substituents or better acid–base fit according to the Pearson's theory. A deeper understanding of the factors controlling the regioselectivity of the addition of organometallic reagents to cyanine dyes is of major importance since it implies the possibility of deliberately ramify or lengthen the cyanine chain by an appropriate choice of the electrophile/nucleophile partners.

To rationalize this regioselectivity, herein we present a study of the behavior of model pentamethinecyanines in which the steric hindrance for C1/C5 attack is avoided, towards 'hard' (acetic acid derivatives) and 'soft' (benzyl cyanide) metal reagents.[6]

The model pentamethine cyanines **II** were obtained from the corresponding all-*trans*-5-amino-2,4-pentadienals **I**[7] following the Scheme 1.
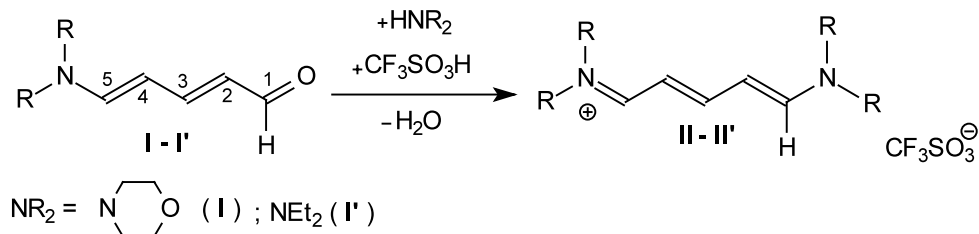
Scheme 1.

The reaction was investigated in the temperature range −40° to +25°C (Scheme 2). The introduction of the pentamethinium salt to the clear solution of the corresponding lithium reagent resulted in the immediate disappearance of the deep red-brownish color of the pentamethinium dye. Simultaneous TLC analysis of the reaction mixture on silica gel (CH_2Cl_2/MeOH = 9/1) showed a quantitative consumption of the cyanine dye and the appearance of a new yellow spot. After warming to room temperature, the reaction mixture turned back to deeply colored. The rapidity of this process depended on the particular nucleophile used. For example with the lithium reagent of benzyl cyanide, the process of coloration started immediately after removal of the refrigerating bath, while in the other cases the solution remained clear for several hours at room temperature.
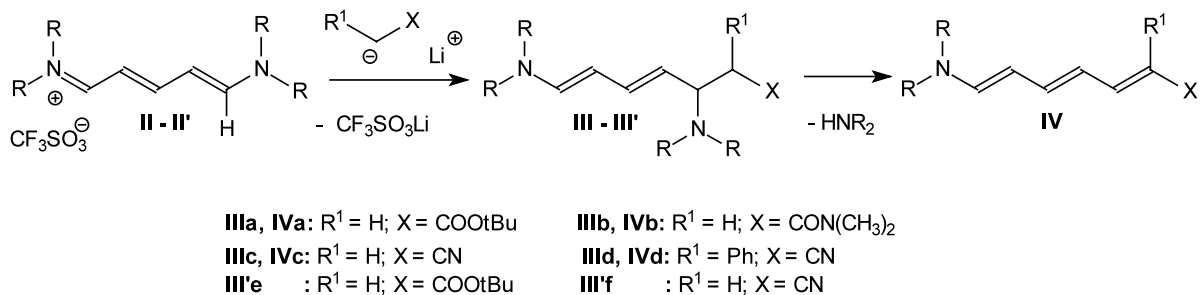
A detailed analysis of the crude reaction mixtures by a series of ^1H, ^{13}C, DEPT, $^1H/^{13}C$ correlation, and COSY experiments proved unambiguously that the 'hard' lithium reagents (acetic acid derivatives) added quantitatively and with a complete regioselectivity to the terminal C1/C5 carbon atoms, thus furnishing adducts III with lengthened and functionalized carbon chain. Additional evidence was provided by the conversion of III to V in high yields by means of catalytic reduction with Pd/C (Scheme 3).

In the case of the lithium reagent of benzyl cyanide the spectra of the crude III were too complicated. It was identified only by the result of the reduction step. The product thus obtained was found to have structure VII, obviou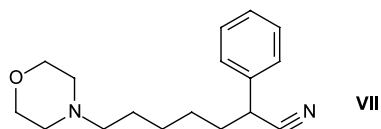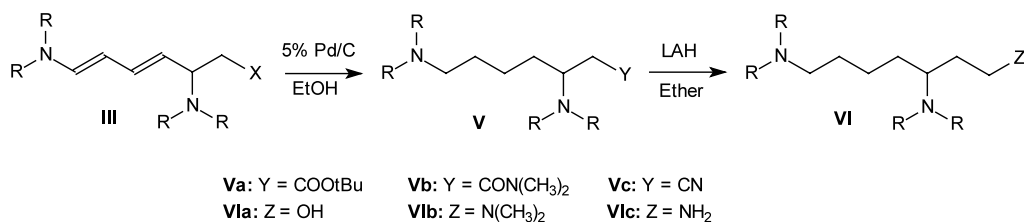sly resulting from addition of the 'soft' metallate to the terminal C1/C5 carbon atoms, followed by a spontaneous Hofmann type elimination of the morpholine moiety.

This finding drew our attention to the yellow spots always observed in the course of TLC monitoring of the reaction. It seemed now, that these yellow products resulted from analogous Hofmann's elimination reaction. Since IIIa–c are stable enough in solution (as proved by conversion to V or repeated recording of ^1H NMR spectra during several days) obviously in these cases the process is accelerated on the silica gel surface. The retarded elimination in comparison with IIId is probably due to the less acidic character of the C2 hydrogen. Having in mind the above considerations, we turned our efforts to the isolation of the yellow products by means of a short-way column chromatography. Actually, flash chromatography of the crude reaction mixtures III afforded new differently functionalized hexatrienes IVa, IVc and IVd in fair yields. Only in the case of IVb, although the elimination occurs (following the MS-data), no pure product was isolated.

The stereochemistry of the newly formed double bond seems to depend on the steric bulk of the nucleophile used. Thus, in the case of more sterically demanding benzyl cyanide and *tert*-butyl acetate the elimination occurs stereospecifically, while in the case of acetonitrile *cis/trans* isomers in 1:1 ratios were formed. The observed C1/C5 regioselectivity of the addition of the 'hard' lithium reagents (acetic acid derivatives) could be explained with the combined effect of both electronic (acid-base fit) and steric factors. In the case of the 'soft' lithium reagent (benzyl cyanide) the steric effect seems

IIIa, IVa: R^1 = H; X = COOtBu   **IIIb, IVb**: R^1 = H; X = CON(CH$_3$)$_2$
IIIc, IVc: R^1 = H; X = CN   **IIId, IVd**: R^1 = Ph; X = CN
III'e : R^1 = H; X = COOtBu   **III'f** : R^1 = H; X = CN

Scheme 2.

Va: Y = COOtBu   **Vb**: Y = CON(CH$_3$)$_2$ **Vc**: Y = CN
VIa: Z = OH   **VIb**: Z = N(CH$_3$)$_2$ **VIc**: Z = NH$_2$

Scheme 3.

to be of crucial importance, as far as in this case the partial charge difference between C3 and C1/C5 carbon atoms is weaker (0.120 versus 0.135 in the case of morpholine-dye and 0.118 versus 0.144 in the case of diethylamino-dye) than in the case of substituted chains (0.125/0.250). (Hyperchem 5.01 (1997) charge distribution calculated after semi-empirical geometry optimization of either diethylamino or di-morpholino derivatives by AM1 Hamiltonian.)

As mentioned before, catalytic reduction of **III** with 5% Pd/C in dry ethanol resulted with high yields in stable trifunctional ligand **V** with lengthened carbon chain. Additional derivatization was achieved by means of a second reduction step of **V** with LAH (Scheme 3).

In conclusion the present study contributes to the understanding of the regioselectivity of addition of organometallic reagents to cyanine dyes. It seems to be a function of a subtle balance between the electronic and steric factors with the predominance of the latter in the case of bulky reagents. Our results outline, in general, the possibility for extending or for ramifying of the carbon chain by the use of an appropriate pair of electrophilic substrate, a cyanine dye- and nucleophilic-organolithium reagent. This new synthetic approach to differently functionalized hexatrienes, key compounds to numerous natural products,[8] was achieved as a result of spontaneous or accelerated on silica gel surface Hofmann type elimination of the initially formed adducts. A series of trifunctional ligands were obtained by means of two-step reduction with Pd/C and LAH.

1. General experimental procedures

The reactions were performed under a dry argon atmosphere. Acetonitrile was dried, distilled and kept over molecular sieves. Diethyl ether was kept over sodium and treated with LiAlH$_4$ before use. Merck–Schuchardt 15% BuLi (in hexane) was used in the lithiation of diisopropylamine (preparation of LDA). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 MHz spectrometer with TMS as the internal standard and CDCl$_3$ or CD$_3$CN as the solvent. The latter was specially dried over molecular sieves. Column chromatography was performed on silica gel 60 Merck (0.040–0.063 mm).

1.1. Synthesis of symmetrical cyanine dyes II and II′

To a mixture of 10 mmol of the starting aldehyde and 15 mmol of the corresponding amine (1.5 equiv.), dissolved in 5 ml of dry ethanol, 15 mmol (1.5 equiv.) of trifluoromethanesulfonic acid was added drop wise at room temperature under vigorous stirring. The addition resulted in highly exothermic reaction, and the appearance of a deep red-brownish color of the solution was observed. After the addition was completed, the reaction mixture was boiled under

reflux for 2 h. The evaporation of the solvent in vacuum gave a dark red-brownish oil. TLC and ^{1}H NMR analysis of the crude products showed some impurities, the main of which was the quaternary salt between the starting amine and the trifluoromethanesulfonic acid. Analytically pure cyanine dyes were obtained after two-fold washing with small portions of water of the methylene chloride solution of **II** or by column chromatography on silica, CH$_2$Cl$_2$/MeOH (80/20), in the case of **II′**.

1.2. Metallation

The lithium reagents were prepared by the use of LDA at −40°C. In the case of *N,N*-dimethylacetamide the metallation was performed at 0°C. Thus, to 1.1 mmol of LDA, prepared in 2 ml of dry ether (without elimination of hexane), 1 mmol of the corresponding CH-acid dissolved in 2 ml of the same solvent was added dropwise at the desired temperature and the reaction mixture was kept stirring for 30 min.

1.3. Synthesis of III and IV

To 1.2 mmol of the stirred ethereal solution of the lithium metallate 1 mmol of the corresponding cyanine salt, dissolved in 4 ml of dry acetonitrile, was added at −40°C. After 30 min, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 h. After evaporation of the solvent in vacuum with precaution against moisture, the samples for NMR investigations were prepared by the use of CD$_3$CN, dried over molecular sieves 3 Å.

1.4. Catalytic reduction of III and IV to V and VI

After the obtaining of **III** (**IV**) the solvents were removed under vacuum. The residue was dissolved in dry ethanol (10 ml for 1 mmol of the starting adduct) and then transferred under argon in a two-necked round-bottomed flask supplied with stirring bar. The catalyst (5% Pd/C, 400 mg for 1 mmol of **III** or **IV**) was introduced and the flask was connected with the system for hydrogenation. The reduction was carried out under atmospheric pressure at room temperature and the process was monitored by TLC. The reaction was completed in 5 h. The catalyst was removed by filtration and carefully washed with ethanol. After ethanol removal under vacuum the pure **V**(**VI**) were obtained by means of column chromatography (methylene chloride/ methanol = 95/5).

1.5. Reduction of V to VII

To an ethereal suspension of 2 mmol LAH in 6 ml of dry ether, cooled to −78°C, a solution of 1 mmol of **V** in 4 ml ether was added drop wise under argon atmosphere. The reaction mixture was then allowed to reach room temperature and worked up by a standard procedure. The adducts **VII** thus obtained are TLC and spectroscopically pure (^{1}H, ^{13}C NMR).

2. Physical data of selected compounds

2.1. II: 1,5-Bis-(morpholino)-pentadienylium triflate

Yield: 68%, red-brownish solid after drying in high vacuum, strongly hygroscopic. MS (EI) m/z (rel. int.) = 237 (M$^+$, 12). Anal. calcd for $C_{14}H_{21}F_3N_2O_5S$ (386.39): C, 43.52; H, 5.48; N, 7.25. Found: C, 43.28; H, 5.30, N, 7.47. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 3.59 (t, 4H, N(CH_2CH$_2$)$_2$O); 3.66 (t, 4H, N(CH_2CH$_2$)$_2$O); 3.77–3.83 (m, 8H, 2×N(CH$_2$CH_2)$_2$O); 5.93 (t, 2H, J=12.2, H-2+H-4); 7.66 (d, 2H, J=11.9, H-1+H-5); 7.73 (t, 1H, J=12.5, H-3). ^{13}C NMR (CDCl$_3$, 250 MHz, DEPT): δ 46.8 and 54.4 (2×N(CH$_2$CH$_2$)$_2$O); 65.7 and 66.8 (2× N(CH$_2$CH$_2$)$_2$O); 103.4 (C-2+C-4); 160.4 (C-1+C-5); 165.2 (C-3).

2.2. IIIc: 3,7-Bis-morpholino-4,6-heptadiene nitrile

^{1}H NMR (CD$_3$CN, 250 MHz): δ 2.30–2.47 (m, 4H, N(CH_2CH$_2$)$_2$O); 2.6 (dd, 2H, J=5.0 and 2, H-2); 2.89 (t, 4H, N (CH_2CH$_2$)$_2$O,); 3.18–3.30 (m, 1H, H-3); 5.16 (dd, 1H, J=14.3 and 8.1, H-4); 5.19 (dd, 1H, H-6, J=13.6 and 9.9, H-6); 6.12 (dd, 1H, J=15.5 and 10.3, H-5); 6.2 (d, 1H, J=13.6, H-7). ^{13}C NMR (CD$_3$CN, 250 MHz, DEPT): δ 21.7 (C-2); 49 and 50. (2×N(CH_2CH$_2$)$_2$O); 64.6 (C-3); 66.5 and 67.3 N(CH$_2$CH_2)$_2$O); 118.1 (CN); 100.7 (C-6); 119.7 (C-4); 135.2 (C-5); 144.6 (C-7).

2.3. IVc: 1-Cyano-6-morpholino-hexatriene

Yield: 73% (as 1:1 mixture of *cis/trans* isomers around the new double bond, flash chromatography on silica gel, ether); deep-dark oil, R_f=0.63 (ether). MS (EI) m/z (rel. int.) = 190 (M$^+$, 65). ^{1}H NMR (CDCl$_3$, 250 MHz, for 1:1 mixture of *cis* and *trans* isomers): δ 3.13 (t, 8H, N(CH_2CH$_2$)$_2$O); 3.72 (t, 8H, N(CH_2CH$_2$)$_2$O,); 4.77 (d, 1H, J=10.4, H-6-*cis*); 4.97 (d, 1H, J=15.3, H-6-*trans*); 5.22–5.35 (m, 2H), 5.39 (dd, 1H, J=14.3 and 11.2); 6.35–6.60 (m, 5H); 6.75 (t, 1H, J=11.1); 6.94 (dd, 1H, J=15.9 and 10.2). ^{13}C NMR (CDCl$_3$, 250 MHz, DEPT for 1:1 mixture of *cis* and *trans* isomers): δ 48.4. (N(CH_2CH$_2$)$_2$O); 66.1 (N(CH$_2$CH_2)$_2$O); 88.2 (C-6-*cis*); 89.9 (C-6-*trans*); 99.5 and 99.7; 118.3 and 118.4 (CN); 118.8 and 119.4; 143.3 and 143.4; 147.5 and 147.6; 150.5 and 151.7.

2.4. Vc: 3,7-Bis-morpholino-heptane nitrile

Yield: 85% (after column chromatography on silica gel, methylene chloride:methanol = 95:5); oil R_f=0.41 (CH$_2$Cl$_2$:MeOH = 9:1). MS (EI) m/z (rel. int.) = 281 (M$^+$, 63). Anal. calcd for $C_{15}H_{27}N_3O_2$: C, 64.02; H, 9.67; N, 14.94. Found: C, 64.30; H, 9.43; N, 14.68. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 1.20–1.64 (m, 6H, H-4+H-5+H-6), 2.33 (d, 2H, H-7), 2.37–2.66 (m, 10H, H-2+2× N(CH_2CH$_2$)$_2$O); 2.80–2.85 (m, 1H, H-3); 3.62–3.75 (m, 8H, N(CH$_2$CH_2)$_2$O); ^{13}C NMR (CDCl$_3$, 250 MHz): δ 17.5 (C-2); 24.0, 26.2, 30.3 (C-4, C-5 and C-6); 48.5 and 53.7 (2×N(CH$_2$CH$_2$)$_2$O); 58.6 (C-7); 60.8 (C-3); 66.9 and 67.0 (2×N(CH$_2$CH_2)$_2$O); 118.8 (CN).

2.5. VII: 2-Phenyl,7-morpholino-heptane nitrile

Yield: 83%; oil R_f=0.28 (CH$_2$Cl$_2$:MeOH = 95:5). MS (EI) m/z (rel. int.) = 272 (M$^+$, 58). Anal. calcd for $C_{17}H_{24}N_2O$: C, 74.96; H, 8.88; N, 10.28. Found: C, 74.63; H, 8.67; N, 10.40. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 1.20–1.54 (m, 6H, H-4+H-5+H-6), 1.84–1.99 (m, 2H, H-3); 2.32–2.48 (m, 6H, N(CH_2CH$_2$)$_2$O+H-7), 3.65–4.36 (m, 5H, N(CH$_2$CH_2)$_2$O+H-2); 7.29–7.69 (m, 5H, C$_6$H$_5$); ^{13}C NMR (CDCl$_3$, 250 MHz): δ 26.0, 26.6, 26.7, 35.6 (C-3, C-4, C-5 and C-6); 35.6 (C-2); 53.4 (N(CH_2CH$_2$)$_2$O); 58.6 (C-7), 66.7 (N(CH$_2$CH_2)$_2$O), 120.7 (CN), 126.8–128.9 (Ph), 135.8 (Ci-Ph).

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