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First examples of lithium reagents addition in cyanine dyes series

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Abstract

The reactivity of the cyanine dyes towards nucleophilic reagents is currently being tested. As in the case of phosphine derivatives, carbanions attack the electrophilic C3 carbon of the pentamethine chain to give, with a good yield, new functionalized podands with cyano, keto, amino, amido, or enol-ether moieties.

Keywords: dyes; carbanions; iminium salts; Michael reaction.

Our continuous interest in the cyanine dyes synthesis has lead to versatile systems with new functionalities and/or physical properties.[1] Owing to the large application pattern of these dyes due mainly to their conjugated structure it seemed interesting to further explore their reactivity schemes towards nucleophilic reagents, a poorly documented area.[2] The goal of this research is connected with our attempts to lengthen the polymethine chain or to substitute it to obtain functionalized systems. In a previous paper,[3] the acidic activation of a pentamethine chain has lead to ramified tripodal phosphine ligands.

We will present here our preliminary results with soft nucleophiles, i.e. lithium derivatives of benzyl cyanide (α) and *N*,*N*-dimethylphenylacetamide (β). The reactions were carried out starting either from hemicarboxonium **I a**–**c** or symmetrical cyanine **II a**–**c**, both pentamethinium compounds (Scheme 1). The obtained products **III** and **IV** can be described as keto-enolether and diketo-addition compounds resulting from the hydrolysis of their transient intermediate and labelled with α or β indices following their starting metal reagents.

The low temperature addition of a lithium metallate on **I** or **II** first results in an intermediate (**1**–**4**; Scheme 1). The ^{1}H NMR data of two of the four intermediates in solution are given in the Experimental. They were identified by their chemical shifts, intensity, and coupling constants. When possible in **1** the most shielded signals were assigned to isomer **a**. Nevertheless, our attempts to isolate them by any method always afforded the corresponding oxo derivative **III** and **IV**. The results were the same whatever the nature of the amino group.

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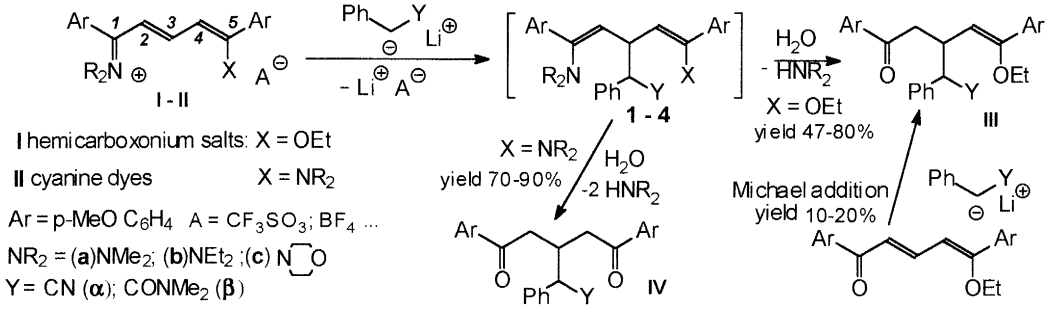
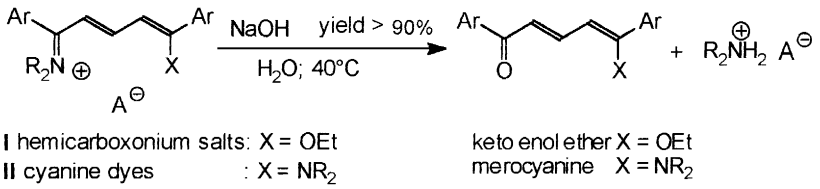


Scheme 1.

It is well documented that the physicochemical properties of a polymethine cyanine chain are related to its conjugated structure. A charge alternation is observed, rendering the odd numbered chain carbons positive and the even ones negatively charged. The same is observed in the case of carboxonium precursors or hemicarboxonium salts **I**. This will influence the addition site of a nucleophilic reagent, the C1–5 or C3 being accessible. The ^{13}C NMR spectra of our compounds are in accordance with these assumptions, showing in $CDCl_3$ largely deshielded C1–5 carbons around 170 (**II**) and 175–176 ppm (**I**), whereas the C3 are near 162 ppm for both.[4] To rationalize these results, we have undertaken a semi-empirical charge calculation with AM1 method after geometry optimization of **I** and **II** model compounds (program Hyperchem 5.01; 1996). As expected, we observed the alternate charge repartition in both cases. Moreover, for the positive carbon atoms, the partial charge on the end carbon atoms is two times higher than the central C3 one (0.250/0.125). Thus, following this study, the end carbons seemed more favourable for a nucleophilic attack. Nevertheless, we observed only reactions involving the central C3 carbon. The reaction must be either under steric control due to the aromatic substituents, or that regioselectivity corresponds to a better fit between a soft base, the metallate and the delocalized chain, a soft acid. This fact is somewhat different from the basic hydrolytic attack of hemicarboxonium or cyanine dyes in which the nucleophilic hydroxyl ions eliminate one amino group to give a neutral keto-enolether or a merocyanine after C1 or C5 addition.[5] In this case, a hard base like OH^- may introduce the change in the orientation of the reaction (Scheme 2).



Scheme 2.

Moreover, in the case of **I**, the addition on the prochiral C3 induces the formation of diastereoisomers. Thus, after hydrolysis, we obtain two isomers of **III** in a ratio reflecting the size of the incoming metal reagent [i.e. 50/50 for the benzyl cyanide and 75/25 for the *N*,*N*-dimethylphenylacetamide] in respect of the enol-ether or ene-amine moiety in the intermediate.

We checked that products **III** are also accessible by conjugate addition of the same metallates to keto-enolethers (see Scheme 1) in our general experimental conditions, but the yields are rather poor. Hence, the investigated nucleophilic attack of lithium reagents on cyanine dyes is a synthetically valuable alternative of the classical Michael reaction.[6]

In conclusion, our synthetic pathway gives access to a wide range of new podands with extended functionalities and/or chirality. To our knowledge, they present unprecedented arrangements of complexing moieties with cyano, keto, amino, amido or enol-ether functions.

1. General experimental procedure

All reactions were carried out under a dry argon atmosphere. The solvents were dried and freshly distilled prior to use. Column chromatography was performed on silica gel 60 Merck (0.040–0.063 mm)

Metallation: The lithium reagents were prepared either by the use of LDA at −40°C or by direct reaction with butyl lithium in the case of *N*,*N*-dimethylphenylacetamide (for benzyl cyanide, butyl lithium adds to CN group). Thus, 1 mmol *N*,*N*-dimethylphenylacetamide, dissolved in 2 ml dry ether was added to 1.1 mmol of LDA prepared in 2 ml of the same solvent at −40°C and the reaction mixture was kept stirring for 30 min at this temperature.

Synthesis: 1 mmol of the corresponding hemicarboxonium or cyanine salt dissolved in 4 ml of dry acetonitrile was added at −40°C to a solution of 1 mmol of the lithium derivative in ether. After 30 min, the reaction mixture was allowed to warm to room temperature and the stirring was continued for 1 h. At the end of the reaction time the solvent was evaporated in vacuum and the products were isolated by column chromatography.

*Spectral data for the intermediates **1** and **2***: As **1** is closely related to **3** and **2** to **4**, we give only data for the formers.

1. NR_2=NEt_2; X=OEt; Y=CN (as diastereoisomeric mixture **a**/**b**=50/50).

^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.93 **a** (t, 3H, J=7.2, NCH_2CH_3), 0.98 **b** (t, 3H, J=7.2, NCH_2CH_3), 1.28 **a** (t, 3H, J=7.0, OCH_2CH_3), 1.32 **b** (t, 3H, J=7.0, OCH_2CH_3), 2.83 **a** (q, 2H, J=7.2, NCH_2CH_3), 2.88 **b** (q, 2H, J=7.2, NCH_2CH_3), **a**+**b**: 3.10–3.26 (m, 2H, H-3), 3.66–3.86 (m, 18H, 4*OCH_3+2*OCH_2CH_3+2*CHCN), 4.37 (d, 1H, J=10.3, H-4), 4.44 (d, 1H, J=9.7, H-4), 4.70 (d, 1H, J=10.5, H-2), 4.76 (d, 1H, J=9.7, H-2), 6.35–7.23 (m, 26H, H arom.).

2. NR_2=X=$N(CH_2CH_2)_2O$; Y=$CONMe_2$.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.52–2.70 (m, 8H, 2×$N(CH_2CH_2)_2O$), 2.85 and 2.89 (2s, 6H, $N(CH_3)_2$), 3.34 (m, 1H, H-3), 3.53–3.67 (m, 8H, 2*$N(CH_2CH_2)_2O$), 3.69 (d, 1H, J=7.6, $CHCONMe_2$), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.52 (d, 1H, J=10.1, H-2), 4.90 (d, 1H, J=10.2, H-4), 6.52–7.28 (13H, H arom).

Compound **III**$\boldsymbol{\alpha}$: Yield 80% as diastereoisomeric mixture **a**/**b**=50/50 (column chromatography, Et_2O: petroleum ether 35–60°C(PE)=1:2).

Isomer **a** (R_f=0.26, ether:hexane=1:1): oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, 3H, J=7.1, OCH_2CH_3), 3.03 (dd, 1H, ^{2}J=16.9, ^{3}J=3.7, H-2), 3.13–3.24 (m, 1H, H-3), 3.30 (dd, 1H, ^{2}J=16.9, ^{3}J=7.2, H-2), 3.70 (s, 3H, OCH_3), 3.78 (q, 2H, J=7.1, CH_3CH_2), 3.83 (s, 3H, OCH_3), 4.23 (d, 1H, J=4.1, C*H*-CN), 4.69 (d, 1H, J=10.9, H-4), 6.52–7.88 (m, 13 H, H arom.). IR (film, ν, cm^{-1}) 1671 (CO), 2239 (CN). FABMS (MNBA) *m/z*=456 (M^+). Anal. calcd for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.29; H, 6.23; N, 3.21.

Isomer **b** (R_f=0.25, ether:hexane=1:1): oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, 3H, J=6.7, OCH_2CH_3), 2.85 (dd, 1H, ^{2}J=4.6, ^{3}J=2.8, H-2), 3.30–3.38 (m, 1H, H-3), 3.41 (q, 2H, J=6.7, CH_3CH_2), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.56 (d, 1H, J=10.1, H-4), 4.99 (d, 1H, J=5.6, C*H*-CN), 6.79–7.75 (m, 13 H, H arom.). IR (film, ν, cm^{-1}) 1671 (CO), 2239 (CN). FABMS (MNBA) *m/z*=456 (M^+). Anal. calcd for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.63; H, 6.59; N, 3.40.

Compound **III**$\boldsymbol{\beta}$: Yield 47% as diastereoisomeric mixture **a**/**b**=28/72 (column chromatography, Et_2O:PE=3:2). Isomer **a** (R_f=0.35, ether): oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.24 (t, 3H, J=6.9, CH_3CH_2), 2.55 (dd, 1H, ^{2}J=15.0, ^{3}J=7.3, H-2), 2.89 and 2.91 (2s, 6H, N $(CH_3)_2$), 3.17 (dd, 1H, ^{2}J=15, ^{3}J=5.7, H-2), 3.41–3.47 (m, 1H, H-3), 3.77 (q, 2H, J=6.9, CH_3CH_2), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.16 (d, 1H, J=7.0, C*H*-$CON(CH_3)_2$), 4.99 (d, 1H, J=10.5, H-4), 6.67–7.96 (m, 13 H, H arom.). IR (film, ν, cm^{-1}) 1641 (CO amide), 1669 (CO ketone). MS (CI) *m/z*=502 (M^+).

Anal. calcd for $C_{31}H_{35}NO_5$: C, 74.23; H, 7.03; N, 2.79. Found: C, 74.60; H, 7.15; N, 2.48.

Isomer **b** (R_f=0.33, ether): crystals from benzene/hexane, m.p. 126°C.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.15 (t, 3H, J=6.9, C*H*$_3$CH$_2$), 2.72 (dd, 1H, ^{2}J=13.4, ^{3}J=4.5, H-2), 2.90 and 2.91 (2s, 6H, N (CH_3)$_2$), 3.37–3.68 (m, 4H, CH_3C*H*$_2$+H-2+H-3), 3.73 (s, 3H, OCH_3), 3.85 (d, 1H, J=7.1, C*H*-CON(CH_3)$_2$), 3.86 (s, 3H, OCH_3), 5.0 (d, 1H, J=10.7, H-4), 6.41–8.02 (m, 13 H, H arom.). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 18.4 (CH_3), 35.8 (CH_3N), 36 (C-3), 37.3 (*C*Ph), 38.6 (OCH_2), 39 (C-2), 49.6 and 55.2 (2×OCH_3), 113.5 (C*o*Ph), 125.5–130.5 (Ph, *Ph*OMe and C-4), 138.3 (C*i*Ph), 163.3 (C*i*PhOMe), 159.5 (C-5), 172.6 (CON), 199.1 (CO).

IR (film, ν, cm^{-1}) 1641 (CO amide), 1669 (CO ketone). MS (CI) *m/z*=502 (M^+).

Anal. calcd for $C_{31}H_{35}NO_5$: C, 74.23; H, 7.03; N, 2.79. Found: C, 74.13; H, 7.29, N, 2.34.

Compound **IV**$\boldsymbol{\alpha}$: Yield 90% (column chromatography, Et_2O:PE=1:2), oil.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.02–3.25 (m, 5H, 2×CH_2+H-3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.62 (d, 1H, PhC*H*CN, J=3.6), 6.85–7.96 (m, 13 H, H arom.). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 35.8 (C-3), 35.8 and 37.6 (2×CH_2), 40.3 (*C*Ph), 55.4 and 56.2 (2×CH_3O), 113.7 (C*o*Ph), 119.36 (CN), 127.8–133.9 (Ph and *Ph*OMe), 133.94 (C*i*Ph), 169.7 (C*i*PhOMe), 196.3 and 196.7 (2×CO). IR (film, ν, cm^{-1}) 1670 (CO), 2240 (CN). MS (CI) *m/z*=428 (M^+). Anal. calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C; 75.66; H, 5.68; N, 3.43.

Compound **IV**$\boldsymbol{\beta}$: Yield 72% (column chromatography, Et_2O:PE=3:1), oil.

^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.89 (dd, 1H, ^{2}J=17.0, ^{3}J=6.9, H-2), 2.91 (s, 6H, N (CH_3)$_2$), 2.97–3.18 (m, 2H, CH_2), 3.24–3.40 (m, 1H, H-3), 3.45 (dd, 1H, ^{2}J=16.3, ^{3}J=7.1, H-2), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.47 (d, 1H, J=7.9, COC*H*N(CH_3)$_2$), 6.82–6.96 (m, 13H, H arom.). ^{13}C NMR ($CDCl_3$, 250 MHz) δ 35.8 (CH_3N), 36 (C-3), 37.3 (*C*Ph), 38.6 and 39 (2×CH_2), 49.7 and 55.3 (2×CH_3O), 113.5 (C*o*Ph), 127.2–137.6 (Ph and *Ph*OMe), 133.9 (C*i*Ph), 163.3 (C*i*PhOMe), 172.6 (CON), 198.8 and 199.1 (2×CO). MS (CI) *m/z*=428 (M^+). IR (film, ν, cm^{-1}) 1640 (CO amide), 1673 (CO ketone). Anal. calcd for $C_{25}H_{33}NO_5$: C, 70.23; H, 7.78; N, 3.28. Found: C, 70.57; H, 7.90; N, 3.47.

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