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A New Approach to the Selective Alkylation of Difunctional Compounds

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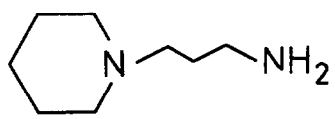
Abstract: Alkylation of some diamines containing both tertiary and primary amino groups is described; it proceeds exclusively with less nucleophilic tertiary amino group when an appropriate lanthanide chelate is added to the reaction mixture. Under similar conditions the alkylation of 3-(tetrahydro-2-thienyl)-pyridine affects both of its nucleophilic centers. Plausible explanations of this fact is discussed. The effect of the presence of different lanthanide complexes upon difunctional compound alkylation has been investigated.

The reactions with high regio- and stereoselectivity are of great importance in complicated organic syntheses. As a rule, such reactions are the result of the properly chosen reaction conditions, selective catalysts, reagents as well as functional group protection. We have reported[1] an alternative approach to the enhancement of organic reaction regioselectivity based upon the application of lanthanide chelates. It makes use of the ability of some lanthanide chelates, particularly *tris*-β-diketonates, to form labile complexes with certain organic compounds, that decrease markedly the reactivity of the functional groups, to which the chelates are bound. Depending on their nature, functional groups are very different in effectiveness of co-ordination to a lanthanide ion of the chelates. These chelates are hard Lewis acids, therefore they bond effectively only with hard Lewis bases. In addition, the co-ordination effectiveness depends to a great extent on steric environment of the co-ordination center. In the case of sterically hindered functional groups, similar to soft Lewis base centers, no or negligible complex formation takes place[2]. It seems probable to use these facts to protect hard Lewis base functional groups of a multifunctional compound by a simple addition of the appropriate lanthanide complex to the reaction mixture, carrying out a reaction with those groups which do not

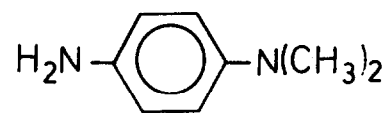
co-ordinate with the lanthanide chelate. This technique differs from the traditional protection of functional groups, including a protection by means of metal complexes[3], because it requires no tedious isolation of the compounds with protected groups. At the same time the lability of the complexes formed by lanthanide chelates allows to separate readily reaction end products and the protecting chelate. It has been found that lanthanide *tris*-β-diketonates could remain unchanged after the action of most reagents excluding strong acids, and can be used repeatedly, so they may be looked upon as selective inhibitors. Thus, the presence of *tris*-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl- 3,5-octanedionato)-lanthanum ($La(fod)_3$) allows a selective catalytic hydrogenation of carbon-carbon double bond without affecting a carbonyl group in the same compound[1]. The lanthanum complex co-ordinates with the carbonyl group, but not with the carbon-carbon double bond, and the latter is being hydrogenated.

In this paper we report the application of lanthanide *tris*-β-diketonates to the selective alkylation of compounds with two nucleophilic centers. Different complexes have been taken for the investigation in order to compare their effectiveness for that purpose: $Ln(fod)_3$ (Ln - lanthanide), $Ln(pta)_3$ (pta - 6,6,6-trifluoro-2,2-dimethyl-3,5-hexanedionato), $Ln(acac)_3$ (acac - 2,4-pentanedionato).

Firstly we examined the alkylation of diamines 1 and 2 with two hard Lewis base groups, one of which is sterically more hindered.



1

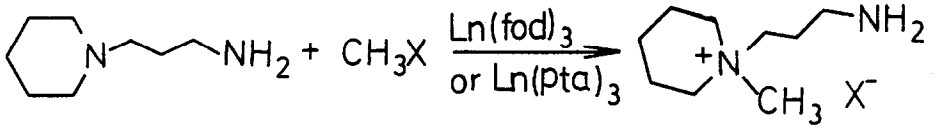


2

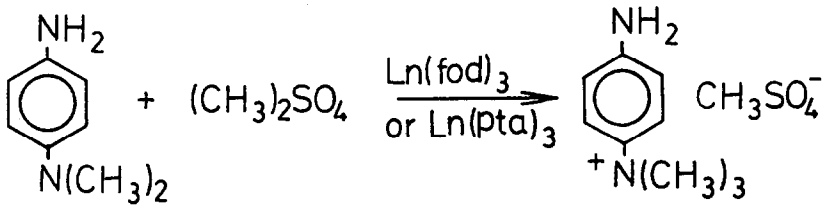
The alkylation of the tertiary amino group in the above compounds requires the primary amino group protection[4].

Effectiveness and site of the lanthanide complex co-ordination with the diamine can be appreciated analyzing the proton NMR shifts induced by paramagnetic complexes[2]. In Table 1 the specific lanthanide-induced shift (LIS) values for ^{1}H-NMR signals of 1 and 2 caused by $Eu(fod)_3$ are set out. It can be seen that the signals of protons closest to the primary amino group are shifted most. It indicates that the compounds in question bond to europium ion through their primary amino group, probably because of steric hindrances in the close vicinity of the tertiary amino group. In light of this fact we suggested that only the tertiary amino group

alkylation of 1 and 2 in the presence of equimolar amount of $Eu(fod)_3$ or similar complex will occur. It proved to be the case in our experiments. The reaction between 1 or 2 and methyl iodide or dimethyl sulfate in the presence of $Ln(fod)_3$ (Ln – La, Eu, Pr, Yb) in equimolar ratio leads to corresponding quaternary ammonium salts with high yield (scheme 1) in benzene solution.



3, X=I
4, X=CH_3SO_4



5

Scheme 1

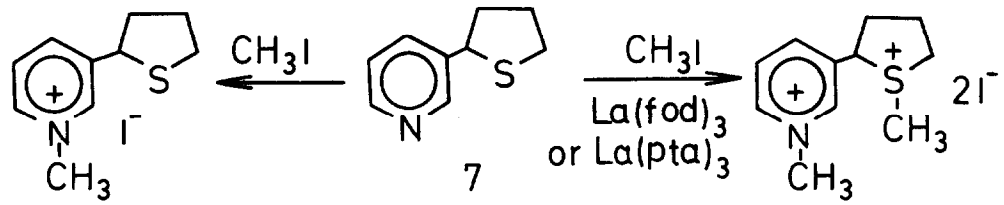
It is noteworthy that the salts formed precipitate from the reaction mixture while the complex remains in the solution, where it can be used again. To use the complex once more a simple addition of new portions of the diamine and alkylating agent to the mixture is enough.

The use of $La(pta)_3$ in lieu of $La(fod)_3$ leads to the similar results, whereas addition of much more available $La(acac)_3$ to the reaction mixture, as it follows from ^{1}H-NMR spectral data, has no influence on the alkylation reaction course. Obviously, $La(acac)_3$ does not co-ordinate with amines so easily as $La(fod)_3$ or $La(pta)_3$, and this seems to be caused by $La(acac)_3$ molecules ability to form stable hydrates and associates with each other.

It was of interest to examine an influence of lanthanide complex co-ordination on the alkylation of compounds containing both soft and hard Lewis base groups. We have investigated the possibility to alkylate such weak bases as organic sulfides in the presence of compounds with pyridine-type nucleophilic center. It is well-known that in contrast to pyridine bases, sulfides form weak complexes or do not react with

lanthanide *tris*-β-diketonates at all[2]. An equimolar mixture of pyridine and tetrahydrothiophene was chosen as a model system. The alkylation of this mixture by methyl iodide in benzene solution leads preferably to the pyridinium salt, less than 30% of S-methyltetrahydrothiophenium iodide 6 were detected by ^{1}H-NMR among the resulting products. The same reaction but in the presence of equimolar amount of La(fod)$_3$ (calculating on pyridine) gives about 78% of the sulfonium salt. Similar results were obtained with some other Ln(fod)$_3$ complexes as well as with Y(fod)$_3$: 73%, 74%, 67%, 63%, 74%, 77% of 6, when Ln is Y, Pr, Eu, Tb, Yb, Lu respectively. Obviously, unlike nature of diketonate ligands, the nature of the lanthanide ion in the complexes used for protection of hard Lewis base groups is not very important.

The result of 3-(tetrahydro-2-thienyl-)pyridine 7 alkylation is at first glance in contrast to that described above for the model mixture of pyridine and tetrahydrothiophene. ^{1}H-NMR analysis of the end products showed that the reaction between 7 and methyl iodide leads to the pyridinium salt 8, but in the presence of La(fod)$_3$ or La(pta)$_3$ no formation of the appropriate sulfonium salt 9 was observed, the *bis*-salt 10, alongside the compound 8 was obtained (scheme 2). Alkylation of 4-(methylmercapto)aniline 11, which has less nucleophilic sulphur center than 7, gives in the presence of La(fod)$_3$ only the product of N-alkylation – (4-methylthiophenyl)methylammonium methylsulfate 12.



8 7 10

Scheme 2

The most convincing explanation of these results is the following. There is no doubt that La(fod)$_3$ or La(pta)$_3$ co-ordinate to the pyridine nitrogen atom of 7, while the sulfide group does not react with the complex. It is proved by the LIS values for proton NMR signals of 7 caused by Eu(fod)$_3$ (Table 1), which are the largest for 2-H and 6-H of the pyridine ring. Therefore, the alkylation of 7 in the presence of a lanthanide chelate is most likely to proceed with non-complexed sulfide group. But after such an alkylation the salt may lose the ability to react with the chelate. The salts of that kind are known to co-ordinate quite weakly with lanthanide *tris*-β-diketonates, bonding to a complex through

their anion[5]. As a result, the pyridine ring becomes accessible for the second alkylation, and it occurs actually with formation of *bis*-salt **10**. An alternative process is the methyl group migration[6], so that sulfonium salt **9** could convert into the pyridinium salt **8**, but this is unlikely to take place under mild reaction conditions. As distinct from **7** both heterocycles of the model mixture are independent. The chelate added to this mixture forms the complex exclusively with pyridine before alkylation of tetrahydrothiophene and after it, thereby preventing its alkylation. *Bis*-alkylation are scarcely probable in the case of **1** or **2** due to approximately same basicity of their amino groups. Moreover, for compound **2** above process is unlikely because of the primary amino group nucleophilicity decrease after the alkylation of the tertiary one.

4-(Methylmercapto)aniline co-ordinates with $La(fod)_3$ through its amino group (Table 1). However, too low nucleophilicity of sulphur in this compound causes the alkylation to proceed only with free, non-coordinated molecules, with only **12** being formed.

EXPERIMENTAL

General Procedures.

^{1}H-NMR spectra were measured with Bruker WP-100 SY (100 MHz for protons) spectrometer. TMS was used as an internal standard. The LIS values were determined as described previously[2]. 3-(Tetrahydro-2-thienyl)pyridine was prepared by the pyrolysis of the appropriate sulfone[7].

Methylation of (I) with methyl iodide or dimethyl sulfate.

$La(fod)_3$ (850 mg, 0.83 mmol) or $La(pta)_3$ (601 mg, 0.83 mmol) was added to a stirred solution of **1** (118 mg, 0.83 mmol) in 5 ml of dry benzene. After the whole complex had been dissolved, methyl iodide (118 mg, 0.83 mmol) or dimethyl sulfate (105 mg, 0.83 mmol) was added. The reaction mixture was allowed to react overnight. The solid (III or IV) was filtered off and washed with benzene, precipitated from methanol with benzene. The compound **3** was obtained in 96% yield, **4** - in 88% yield.

^{1}H-NMR for **3** ($(CD_3)_2SO$) δ): 1.40-2.10 (8H, m), 2.9 (2H, t), 3.02 (3H, s), 3.15-3.55 (6H, m), 7.71 (2H, s).

The combined filtrate and washings which contain $La(fod)_3$ or $La(pta)_3$ were usable for the repeated alkylation. They were evaporated to about 5 ml and new portions of the diamine and methyl iodide or dimethyl sulfate were added. The mixture was kept for 24 h again to afford new portion of **3** or **4**. In this manner, we repeated the alkylation three times with one and the same complex, and neither yield decreasing nor end product contamination were observed.

The alkylation of **2** by dimethyl sulfate was carried out analogously, but an inert atmosphere is desirable for this procedure to avoid the oxidation of the starting compound[8]. The salt **5** was obtained in 80% yield, ^{1}H-NMR ($(CD_3)_2SO$) δ): 3.37 (3H, s), 3.47 (9H, s), 5.5 (2H, s(broad)), 6.63 (2H, d, J=8.9Hz), 7.53 (2H, d).

Table 1. Specific Lanthanide Induced Shifts (LIS) of ^{1}H-NMR Signals for the Compounds **1**, **2**, **7**, **11**, Caused by $Eu(fod)_3$ (Solvent - $CDCl_3$)

Compound	LIS values, p.p.m. (type of the protons)
1-(3-aminopropyl) piperidine **1**	86.7 (NH_2), 23.0 (3'-CH_2), 12.6 (2'-CH_2), 8.0 (1'-CH_2), 4.0 (2-CH_2,6-CH_2), 3.4(3-CH_2, 5-CH_2)
N,N-dimethyl-1,4-phenylenediamine **2**	109.0 (NH_2), 17.0 (3-H,5-H), 4.0 (2-H,6-H), 1.3 (CH_3)
3-(tetrahydro-2-thienyl)pyridine **7**	39.2 (2-H,6-H), 12.5 (4-H,5-H), 9.5 (2'-H), 3.3 (5'-CH_2)
4-(methylmercapto) aniline **11**	107 (NH_2), 17.0 (2-H,6-H), 3.7 (3-H, 5-H), 1.6 (CH_3)

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8. Addition of $La(fod)_3$ or $La(pta)_3$ to the solution of **2** in $CDCl_3$ or C_6D_6 is associated with the escaping of the compound signals in ^{1}H-NMR spectra when working without inert atmosphere, and the mixture turns dark blue. In all likelihood, this is caused by formation of free radical particles from **2** and air oxygen, what is proved by appearance of EPR signals from the solution.