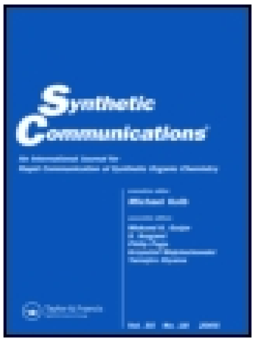

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N,N,N',N',N''-PENTAMETHYLDIPROPYLENETRIAMINE (PMDPTA): A VERSATILE AUXILIARY FOR SITE SELECTIVE LITHIATION REACTIONS

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Abstract: Efficient lithiation processes were developed with PMDPTA, a tridentate ligand of butyllithium reagent for site selective metallation of aromatic and heteroaromatic compounds.

Tertiary amines are known as accelerators of metallation reactions due to their destroyer effect on butyllithium (LIC) aggregates[1]. Series of tertiary diamines and triamines were tested in metallation reactions some decades ago[2]. Nowadays diamines, like N,N,N',N'-teramethylethylenediamine (TMEDA) or diazabicyclo-[2.2.2]octane (DABCO) are used in the most cases[3] even N,N,N',N',N''-pentamethyldiethylenetriamine (PMDTA) has been applied successfully in several

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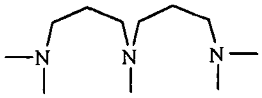
site selective metallation reactions[4, 5]. Recently we have reported the strong effect of the di- and tridentate ligands (TMEDA and PMDTA) on the regioselectivity of some lithiation reactions[6]. However PMDTA is more expensive than the diamines and this fact prevents the wide-ranging application of this complexing agent.

Now we describe the successfull application of another triamine, PMDPTA (**1**) in lithiation reactions. Activity and selectivity of an amine complexed butyllithium reagent strongly depend on the structure of the chelating agent. Therefore introduction of a new complexand (**1**) is always a challange. Until **1** has been known as an accelerator of uretane polymerization, only[7]. It is manufactured in industrial scale[7] and available in good quality and large quantity.



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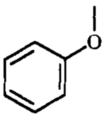
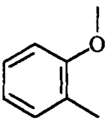
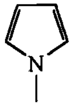
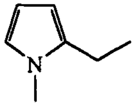
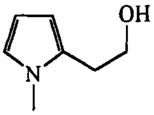
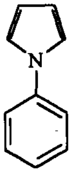
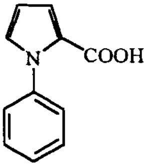
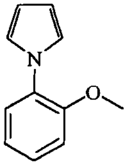
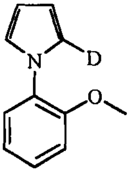
Behaviour of PMDPTA was tested in lithiation reactions of aromatic and heteroaromatic compounds (RH). One mole of LIC-PMDPTA reagent was used for one mole substrate in all experiments. The organometallic species formed were converted into stable molecules by electrophile reagents (ElX).

$$\text{R-H} \xrightarrow{\text{LIC-PMDPTA}} \text{R-Li} \xrightarrow{\text{ElX}} \text{R-El}$$

Table 1 contains our experimental data. The complexand (**1**) was stable during the reactions; neither decomposition nor lithiated side products were observed.

Versatility of PMDPTA can be recognized if we compared our experimental results with previous works published in the literature.

Table 1. Lithiation and functionalization of RH in the presence of **1**.

RH	Reaction conditions[a]	ElX	Product (yield)
 **2**	DEE, 25 °C, 2 h	CH_3I	 **6** (74 %)
 **3**	HEX, 25 °C, 1 h	C_2H_5I	 **7** (91 %)
	THF, 20 °C, 3 h		 **8** (70 %)
 **4**	DEE, -20 °C, 2 h	CO_2	 **9** (72 %)
 **5**	THF, -75 °C, 1 h	D_2O	 **10** (31 %)

[a] DEE: diethyl ether; HEX: hexane; THF: Tetrahydrofuran.

Solcum reported earlier that anisole (**2**) can not be lithiated completely if only two moles of butyllithium were used for one mole substrate[8] in the presence of stoichiometric (or less) amount of TMEDA. In contrast, we reacted only one equivalent of LIC-PMDPTA reagent with **2** and the product (2-methylanisole, **6**) was formed with high yield under mild conditions (Table 1).

Lithiation of 1-methylpyrrole (**3**) was accomplished by *Chadwick* with a large excess of LIC-TMEDA reagent for achieving fast and complete metallation in hexane or terahydrofuran[2]. On the other hand *Brittain et al.* prepared 2-ethyl-1-methyl-pyrrole (**7**) with 69 % yield when **3** was treated with butyllithium alone in terahydrofuran for 12 hours followed by ethyliodide addition[9]. These informations together with the previously mentioned observation of *Solcum*[8] (less than one equivalent TMEDA is enough for anisole metallation) inspired us to check the effect of the substrate/complexand molar ratio on the yield of metallation. 1-Methylpyrrole (**3**) was subjected to lithiation both in hexane and tetrahydrofuran in the presence of one equivalent of butyllithium and 0.1 equivalent of complexing agent (TMEDA). Iodoethane was used as electrophile and the product composition was determined by gas chromathography. The results are presented in Table 2. It shows, that only partial metallation occured within two hours in hexane and the yields are even worse in tetrahydrofuran.

In contrast, equivalent amount of LIC-PMDPTA reagent leaded to complete lithiation of **3** (Table 1).

The reaction has great practical importance especially when ethyleneoxide is used as electrophile because the product (2-hydroxyethyl-1-methylpyrrole, **8**) is the precursor of 2-hydroxyethyl-1-methyl-pyrrolidine, a valuable intermediate of remedies[10]. Compound **8** was prepared by a conventional five steps synthesis[10]. Now, with our method, **8** can be produced from **3** in a "one pot" reaction with good yield and quality.

Efficient site selective monolithiation of 1-phenylpyrrole (**4**) and 1-(2-methoxy-phenyl)pyrrole (**5**) with LIC-PMDPTA (Table 1.) have also shown that PMDPTA

Table 2. Lithiation of **3** in the presence of 0.1 equivalent of TMEDA

Time	Yield of **7**	
(minutes)	in HEX	in THF
30	35 %	8 %
60	37 %	14 %
120	54 %	29 %

acts as well as PMDTA did in that kind of reactions. Consequently, **1** is really a versatile auxiliary and can be used in regioselective lithiation reactions with good results.

Experimental

All commercial starting materials were purchased from FLUKA AG and Merck-Schuchardt and were used without further purification. PMDPTA was delivered by NITROIL Rt. Hungary, a daughter company of NITROIL Europe Handels GmbH, Hamburg. Butyllithium was supplied by CHEMETALL GmbH Lithium Division, Frankfurt.

Compounds **4** and **5** were synthetized from commercially available starting materials according to the literature method[11]. Diethyl ether and terahydrofuran were obtained anhydrous by distillation over sodium wire after the characteristic blue colour of in situ generated sodium diphenylketyl was found to persist. TMEDA, PMDTA and **1** were also distilled over sodium wire before use. Distilled, dry hexane was kept over molecular sieves. Concentration of the buthyllithium solution was determined by a double titration method[12].

All experiments were carried out in Schlenk-flasks under dry nitrogen atmosphere. All the starting materials and the products (**6**[13], **7**[2], **8**[10], **9**[14] and **10**[6]) are known compounds. Their purity and structure were determined by gas chromatography (column: SE-30, 2m, 80 → 200 °C) and ^{1}H-NMR spectroscopy. ^{1}H-NMR spectra were recorded in deuteriochloroform solution at 250 MHz; chemical shifts refer to the signal of tetramethylsilane ($\delta = 0$ ppm).

Typical example: preparation of 2-hydroxyethyl-1-methylpyrrole (8)

1-Methylpyrrole (9.7 g, 120 mmol) and **1** (24.1 g, 120 mmol) were solved in dry tetrahydrofuran (120 ml) under nitrogen atmosphere. The stirred solution was cooled to -10 °C then 1.5 M butyllithium solution (85 ml, 130 mmol) in hexane was added. The cooling bath was removed and the mixture was stirred at 20 °C for 3 hours. It was re-cooled to - 10 °C before addition of a cold, 5 M solution of oxirane (29 ml, 145 mmol) in dry tetrahydrofuran. After 3 hours stirring at 20 °C water (40 ml) was added, the phases were separated and the organic solution was dried over sodiumsulfate before concentration in vacuo. Fractionated distillation of the residue resulted in 2-hydroxyethyl-1-methylpyrrole (**8**): 10.5 g, (70 %), bp.: 80-82 °C/0.4 mmHg.

^{1}H-NMR δ: 6.57 (1H, t, J 2.5), 6.06 (1H, t, J 3.1), 5.9 (1H, m), 3.80 (2H, t, J 6.6), 3.58 (3H, s), 2.83 (2H, t, J 6.6), 1.9 (1H, broad s).

Anal.: $C_7H_{11}NO$ (125.16): calcd. C: 67.18, H: 8.86; found C: 67.23, H: 8.92 %.

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