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Dramatic Effect of Substituents and TMEDA Additive on the Regioselectivity of Directed Orthometalation of Tetrasubstituted Aromatics

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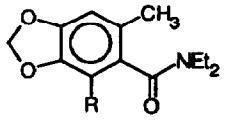
***Abstract** : The regioselectivity of the directed orthometalation of tetrasubstituted aromatic N,N-diethylamides was found to depend of the ring substituents and of the base used. A dramatic effect of the additive TMEDA to s-butyllithium has been observed which could be explained in terms of steric bulk.*

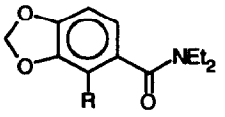
Directed orthometalation has become a useful tool for the regiocontrolled synthesis of highly substituted aromatic rings. It consists generally in the preparation of aromatic anions *ortho* to a directing group such as carboxamide, ether, carbamate, etc., using a strong base followed by alkylation[1, 2] or introduction of a protecting group.[3] Formation of the anion occurs generally with a high degree of regioselectivity. Thus, by a careful choice of the position and the nature of the directing groups, it is possible to select one position among two and to achieve the synthesis of polysubstituted aromatics in a highly predictable way. In the course of our programme for the total synthesis of Amaryllidaceaes alkaloids and congeners,[4, 5] we were faced with the problem of synthesis of pentasubstituted aromatic moieties suitable for the formation of benzylic anions. The regioselective introduction of a methyl group was planned using directed orthometalation of suitable tertiary amides. In this paper we report some of our results which show a dramatic influence of the substituents and of the base used in the metalation of aromatic rings having two ortho directing group in *para* position.

Highly substituted N,N-diethylbenzamides **1** and **2** were required for our programme. The preparation of **2** was planned via compound **5** which was prepared from piperonylic acid by standard reactions and submitted to directed ortho metalation and subsequent alkylation with iodomethane. The use of s-butyllithium as a base gave 90% yield of the expected compound **2** having a methyl group *ortho* to the amide directing group. Identical results in terms of yield and regioselectivity were obtained when TMEDA was added to s-butyllithium prior to addition of the benzamide.

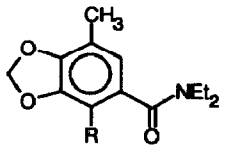
The preparation of **1** needed first protection at position 2 and was planned via compounds **6** and **3**. Directed orthometalation of piperonylamide **4** with s-butyllithium gave the expected corresponding anion, *ortho* to both directing groups, which reacted with trimethylsilylchloride to give the known compound **6**.[6]



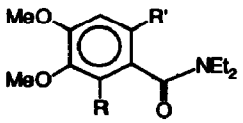
1 R = H
2 R = OMe
3 R = $SiMe_3$



4 R = H
5 R = OMe
6 R = $SiMe_3$



7 R = $SiMe_3$



8 R = $SiMe_3$, R' = H
9 R = $SiMe_3$, R' = Me
10 R = OMe, R' = H
11 R = OMe, R' = Me

Introduction of the methyl group in **6** was attempted using the same procedure, but surprisingly, metalation using s-butyllithium followed by alkylation with iodomethane gave a 3/2 mixture of the regioisomers **7** and **3** as seen from the ^1H nmr spectra. In contrast using a TMEDA/s-butyllithium mixture as a base, the major product was **3** together with less than 15 % of isomer **7**. Identical results were obtained in a less coordinating solvent such as a hexane-ether mixture. The results are summarized in the Table.

Table: Orthometalation and methylation of tetrasubstituted aromatics **5**, **6**, **8** and **10**[7]

Entry	Starting Compound	RLi-Additive	Solvent	Yield %	Products ratio	
1	**5**	sBuLi or sBuLi-TMEDA	THF	90	**2** (100)	-
2	**6**	sBuli	THF	88	**3** (40)	**7** (60)
3	**6**	sBuLi	Hexane-Et_2O 1/1	78	**3** (30)	**7** (70)
4	**6**	sBuli then TMEDA[a]	THF	87	**3** (40)	**7** (60)
5	**6**	sBuli-TMEDA[b]	THF	81	**3** (83)	**7** (17)
6	**6**	sBuLi-TMEDA[c]	THF	90	**3** (85)	**7** (15)
7	**8**	sBuLi-TMEDA	THF	90	**9** (100)	-
8	**8**	sBuLi	THF	90	**9** (100)	-
9	**10**	sBuLi or sBuLi-TMEDA	THF	70	**11** (100)	-

a) s-BuLi was added to a solution of compound **6**, then TMEDA was added.
b) s-BuLi was added to a solution of the amide and TMEDA.
c) The amide was added to a solution of s-BuLi and TMEDA.

The methylation of compound **8** using s-butyllithium-TMEDA has been reported recently by Snieckus *et al.*[3] Our above mentioned results, prompted us to examine compound **8** in the ortho metalation using s-butyllithium alone. However, the same result was obtained as in the presence of TMEDA: **9** was isolated in 90 % yield. In this case, despite the presence of the trimethylsilyl group at C-2, metalation occurs only at C-6 whatever base is used. Finally, the trimethoxy derivative **10** was also metalated using s-

butyllithium and then methylated to provide the expected amide **11**. The observed regioselectivities in the reactions of substrates **5**, **6**, **8** and **10** with the differents bases are summarised in the graphical abstract.

It seems that the differences observed between the different compounds could be related to the presence of a trimethylsilyl group at the aromatic ring, but also to the presence of the additive TMEDA in the anion generation. It is likely that H-5 and H-6 have approximately the same acidity in compounds **5** and **6**, thus steric hindrance could be taken into account. In compound **6**, the presence of the sterically demanding trimethylsilyl group at C-2 probably induces a change in steric surrounding of H-6 by modifying the conformation around the amide bond. Evidences for such conformational effects were obtained from nOe measurements on compounds **5** and **6**. A nOe effect (2%) is detected between one of the aromatic protons, probably H-6, and the CH_2 group of the NEt_2 moiety in compound **6**. It thus may be concluded that the H-6 proton is relatively close to the NEt_2 group and consequently hindered by this bulky substituent. Thus, kinetic deprotonation occurs mainly at C-5. One of the possible consequences is also that the carbonyl group cannot assume the most favourable orientation required for complexation with the base thus lowering the ortho directing effect. This is not the case when a smaller methoxy group is present at C-2, as in compound **5**, where metalation occurs *ortho* to the most powerful directing group ($CONEt_2$). No significant nOe can be detected between H-6 and NEt_2 in compound **5**. Concerning the amide **8**, the results could also be rationalized in terms of steric hindrance. In this case, the methoxy group at C-4 adopts a conformation which overcrowds the H-5 proton, as confirmed again by nmr techniques which show an important nOe (6.7%) between H-5 and the MeO group. As a consequence, deprotonation at C-6 becomes easier than at C-5 and the ortho directing effect could take place. The same explanation holds for compound **10**.

Despite of a number of reported examples of metalation in the presence of TMEDA, its role is not yet clearly defined as recently summarized by Collum.[8] In our work, the modification observed in the abstraction of a sterically hindered proton *ortho* to a strong directing group could be interpretated as follows: when s-butyllithium is used as the base, abstraction of the less hindered proton assisted by the ether *ortho* directing group is preferred, because of the bulky polymeric structure (tetra -or hexameric) of s-butyllithium.[9, 10] Upon addition of TMEDA the polymeric structure of s-butyllithium likely changes to a dimeric structure including TMEDA.[11, 12] This base is then less sterically demanding and preferential abstraction of the more hindered proton occurs assisted by the tertiary amide *ortho* directing group.[13] One may conclude from this study that in most cases TMEDA might be unnecessary to perform ortholithiation except when a sterically hindered proton is concerned. One role of TMEDA should be the deaggregation of the alkyllithium species even in strongly coordinating solvents such as THF thereby increasing the efficiency of the base toward hindered protons.[14]

References and Notes

1. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306-312.
2. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
3. Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372-4385.
4. Chapleur, Y.; Chrétien, F.; Khaldi, M. Recent Developments in the Enantiospecific Synthesis of Amaryllidacae Alkaloids In *Antibiotics and Antiviral Compounds, Chemical Synthesis and Modification;* Krohn, K.; Kirst, E.; Maas, H. Eds.; Verlag Chemie: Weinheim,1993; pp 380-388.
5. Chrétien, F.; Ibn Ahmed, S.; Masion, A.; Chapleur, Y. *Tetrahedron* **1993**, *49*, 7463-7478.
6. Thompson, R. C.; Kallmerten, J. *J. Org. Chem.* **1990**, *55*, 6076-6078.
7. A typical experiment was as follows: to a solution of benzamide **6** (1 mmol) in THF (7 ml) under nitrogen at -78°C was added s-BuLi (1.1M in hexane, 1.2 ml, 1.3 mmol). The resulting solution was stirred for 15 minutes then methyl iodide (0.15 ml, 2.1 mmol) in THF (2 ml) was added. The reaction mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature and treated with a saturated solution of NH_4Cl (2.0 ml). The solution was diluted with water (10 ml) and extracted with diethylether (3x40 ml). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Preparative HPLC gave pure **7** and **3**[6]. Analytical data of compound **7**: Rf = 0.30 (ACOEt/Hexane 2:3); *ir* ν_{max} 1629; ^{1}H **nmr** δ 0.25 (s, 9H, Si(CH_3)$_3$), 1.06 (t, 3H, CH_3 amide), 1.21 (t, 3H, CH_3 amide), 2.16 (s, 3H, CH_3 benzylic), 3.21 (q, 2H, CH_2 amide), 3.60 (q, 2H, CH_2 amide), 5.90 (s, 2H, CH_2 methylenedioxy), 6.49 (s, 1H, *H-6*); ^{13}C **nmr** δ -0.64, -0.41, -0.21 (Si(CH_3)$_3$), 12.42, 12.64 (CH_3 amide), 14.35 (CH_3 benzylic), 38.99, 43.44 (CH_2 amide), 99.97 (CH_2 methylenedioxy), 113.93 (*C-5* aromatic), 119.02 (*C-2* aromatic), 121.60 (*C-6* aromatic), 135.68 (*C-1* aromatic), 144.39, 152.48 (*C-3* and *C-4* aromatic), 171.74 (*CO* amide).
8. Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448-454.
9. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664-4670.
10. Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308-337.
11. Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191-7198.
12. The higher reactivity of dimeric n-butyllithium versus the tetrameric form has been demonstrated see: McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. -R. *J. Am. Chem. Soc.* **1984**, *107*, 1810-1815.
13. A similar explanation has been proposed by Harmon and Shirley to explain the metalation of 2-methylanisole with n-butyllithium-TMEDA, see: Harmon, T. E.; Shirley, D. A. *J. Org. Chem.* **1974**, *39*, 3164-3165.
14. Increase of the reactivity of n-butyllithium by TMEDA has been evoked to explain the increase of yield in the TMEDA-n Buli mediated metalation of ortho-t-butyl anisole, see: Slocum, D. W.; Koonsvitsky, B. P. *J. Org. Chem.* **1973**, *38*, 1675-1677.

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