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REGIOSELECTIVE AROMATIC RING FUNCTIONALIZATION OF DOPAMINE ANALOGUES

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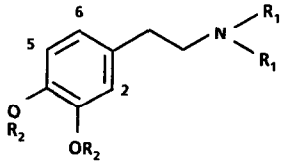
Summary: The selective aromatic ring functonalization of tetramethyl dopamine **2** at C_2 and C_5 was achieved via alkyllithium-induced carbanion formation at r.t. and -78°, respectively. The C-6 substitution was affected via palladium acetate mediated cyclometallation.

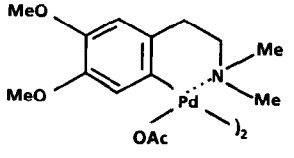
Dopamine (**1**, R_1=R_2=H), one of the most important neurotransmitters in the nervous system, has a relatively simple structure, yet is involved in remarkably complicated biological processes.[1] Our interest in the biological properties and the synthesis of dopamine analogues led us to



1 R_1=R_2=H
2 R_1=R_2=Me

the investigation of selective functionalization of the aromatic ring. Previous work by Heck[2] on the ortho palladation of benzylamine with palladium acetate was applied by Holton[3] to a regioselective orthopalladation of a 3,4 disubstituted benzyl amine. A sterically accessible orthocarbon was included in the arylpalladium complex which enabled the functionalization of this carbon. Our approach centered on the application of this palladium chemistry to the homologous phenethylamines.

Thus, tetramethyl dopamine **2**, was dissolved in benzene and was stirred with 1.1 eq. of $Pd(OAc)_2$ at r.t. for 72 hrs. The palladated complex[2] **3** obtained was then treated with



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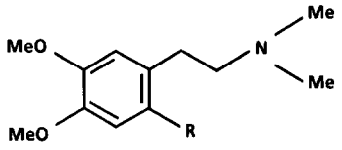
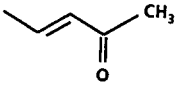
carbon monoxide in methanol[2] at 40 psi at r.t. Upon basicification with Et_3N, compound **4a** was isolated in a yield of 50%.

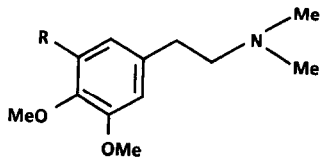


4a R = $-CO_2Me$

4b R = 

The NMR spectra[4] of **4a** confirmed the position of the ester group with two singlets at 6.70 and 7.43 ppm for the two aromatic protons. Treatment of complex **3** with 1 eq. of NaCl in aqueous acetone followed by methyl vinyl ketone in refluxing toluene containing excess triethylamine[5] for 1 hr. gave adduct **4b** in 65% yield. Only trans adduct has been isolated.

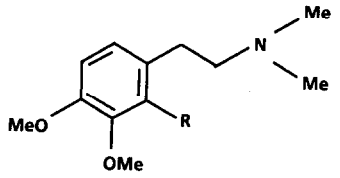
For the introduction of substituents at C-2 and C-5, lithiation by alkyl lithium was investigated. Earlier, the directing effect of various functional groups attached to the aromatic ring was studied by Slocum[6] who used tetramethylethylenediamine (TMEDA) as co-solvent in reversing the site of metalation in p-methoxy-N,N-diamethylbenzylamine. This subject was recently reviewed by Narasimhan.[7] Thus tetramethyl dopamine **2** was metallated directly with sec. BuLi at -78° in ether with 3% TMEDA as co-solvent and the product was quenched with ethylisocyanate at -78°. Compound **5a** was the only product isolated (52%).



5a R = CONHEt

5b R = CH_2OH

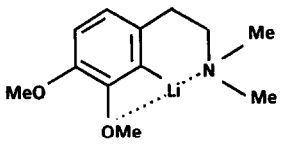
Similarly, the lithiation product of **2** (-78° ether-3% TMEDA) was reacted with paraformaldehyde. The reaction took place at 0°C and it gave a mixture of products **5b** and **6b** in a ratio



6a R = CONHEt

6b R = CH_2OH

of 2.6:1[4] (52% combined isolated yield). This composition probably reflected the equilibraton of C-5 anion initially formed at -78° to the more stable anion **7** at 0°C. Thus n-BuLi was added to **2** in ether at 0°C, followed by stirring at r.t.



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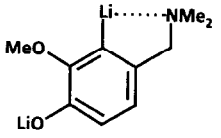
overnight. The addition of ethylisocyanate or paraformaldehyde at 0°C gave **6a**[4] in 70% yield or **6b**[4] in 40% yield, respectively; no regioisomers were isolated. (A similar observation was made by Hlasta and Bell[8] on a dianion metallation reaction of N,N-dimethylvanillylamine (2 n-BuLi, THF, r.t.). A exclusive C-6 lithiated anion **8** was responsible for the single product isolated.)



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References:

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2. J.M. Thompson and R.F. Heck, J. Org. Chem., **40**, 2667 (1975).

3. R.A. Holton and R.G. Davis, J. Am. Chem. Soc., **99**, 4175 (1977).

4. Structures were consistent with IR, NMR and MS data. All new compounds gave correct analytical data. Yields given were not optimized.

4a, ^{1}HNMR ($CDCl_3$) 2.31(s,6), 2.50(m,2), 3.10(m,2), 3.86(s,3), 3.88(s,3), 3.90(s,3), 6.70(s,1), 7.43(s,1).

4b, 2.32(s,6), 2.38(s,3), 2.45(m,2), 2.85(m,2), 3.88(s,3), 3.90(s,3), 6.52(d,J=16Hz,1), 6.70(s,1), 7.05(s,1), 7.77(d,J=16Hz,1).

5a, 1.23(t,J=7Hz,3), 2.26(s,6), 2.35-2.90(m,4), 3.47(dt,J=7,6Hz,2), 3.84(s,3), 3.86(s,3), 6.83(d,J=2Hz,1), 7.49(d,J=2Hz,1) 7.80(t,J=6Hz,1).

5b, 2.25(s,6), 2.30-2.85(m,4), 3.83(s,3), 3.85(s,3), 4.65(s,1), 4.65(s,1), 6.68(d,J=2Hz,1), 6.73(d,J=2Hz,1).

6a, 1.24(t,J=7Hz,3), 2.23(s,6), 2.30-2.90(m,4), 3.45(qd,J=7,6Hz,2), 3.77(s,6), 6.23(t,J=6Hz,1), 6.79(d,J=8Hz,1), 6.91(d,J=8Hz,1).

6b, 2.23(s,6), 2.35-2.85(m,4), 3.85(s,3), 3.90(s,3), 4.61(s,2), 6.79(d,J=8Hz,1), 6.90(d,J=8Hz,1).

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