

## PREPARATION OF DEUTERATED TOLUIDINES AND XYLIDINES

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### SUMMARY

Deuteration in definite positions of the aromatic ring system or in the side chain of different methyl anilines is achieved in  $D_2O$  under different conditions: at  $150^\circ C$  and pH 3 deuteration occurs in ortho/para positions; whereas at  $250^\circ C$  and pH 3 a total deuteration of the aromatic system takes place (overall deuteration 82-99%). Perdeuteration (81-99% in the aromatic ring, 60-99% in the side chain) is obtained in high acidic medium ( $pH \leq 1$ ) and at  $250^\circ C$ . The yield of the deuterated methyl anilines is generally high (40-100%) so that this reaction is a more attractive route for preparing methyl anilines and their derivatives than the conventional ways of synthesis. By using  $T_2O$  instead of  $D_2O$  it should be possible to prepare the appropriate tritium-labelled compounds.

### INTRODUCTION

Toluidines and xylidines are of particular interest as versatile reagents for the preparation of perdeuterated or partially and totally ring deuterated aromatic compounds. For neutron spectroscopy of solid organics we needed derivatives of toluidine in gram quantities with an extremely high degree of deuteration<sup>5)</sup>. On account of missing experimental details in the literature we report a simple method for their preparation in large quantities and high yields.

## EXPERIMENTAL

The degree of deuteration was determined by NMR-spectroscopy: Varian T-60 coupled with a Nicolet Time Averaging System 1020 A. Spectroscopy was performed either directly with the resulting reaction-mixture  $D_2O/DCl$ /methyl aniline-deuterochloride or in  $CCl_4$  after releasing the aniline with NaOD and re-exchange of the amine protons. Reference for integration was the signal of the methyl group or of the amine protons.

The values in Tables 1 and 2 are the mean values of five measurements.

The used chemicals were Merck p.a., the purity of the  $D_2O$  used was 99.89 %.

H/D Exchange

## a) Ring-proton exchange:

40.0 gms of methyl aniline-hydrochloride dissolved in 50 ml  $D_2O$  are refluxed for 2 h and evaporated to dryness. The residue is dissolved in  $D_2O$  (ca 40 ml), the solution acidified to pH 3 with  $DCl$  and heated for 10 h at  $150^\circ C$  for o/p deuteration, and 24 h at  $250^\circ C$  for total ring deuteration in a V2A container provided with a glass-vessel. The mixture is evaporated to dryness and the residue recrystallised from  $D_2O$  or  $D_2O$ -steam distilled after neutralisation.

## b) Total exchange (perdeuteration) of ring- and methyl protons

20.0 gms of methyl aniline-hydrochloride, treated as above, are heated for 48 h at  $250 - 270^\circ C$  and at pH -0.5. The mixture is evaporated to dryness and further heated for another 24 h under the same conditions for complete deuteration. Clean up and purification is performed as described for ring proton exchange.

D/H Re-exchange of the ring-deuterium:

20 gms of the deuterated methyl aniline-hydrochloride (table 2) are heated in distilled water for 10 h at  $150^\circ C$  and pH 3 for re-exchange in the o/p position of the aromatic ring, or for 18 h at  $250^\circ C$  for total re-exchange, respectively. The mixture is evaporated to dryness and purification is performed as described in the other examples.

## RESULTS AND DISCUSSION

The deuteration of the aromatic ring of methyl anilines in acidic medium and in heavy water as deuterium source proceeds according to the experimental conditions and in agreement with mechanistic considerations either to an H/D exchange in the ortho/para positions (relative to the amino-group) or to a total ring deuteration.

The observation of simultaneous methyl proton exchange during attempted ring deuteration on the other hand is rather surprising: heating of the reaction mixture methyl aniline/D<sub>2</sub>O/DCI for 24-64 h at 250°C and pH-values  $\leq 1$  in a stainless steel vessel leads, besides a ring deuteration up to 99 %, to a 60 % exchange of the methyl protons which can be brought up to 96 % after renewal of the heavy water and further heating for another 24 hours. The observed exchange can be explained by proton mobility of the methyl-group<sup>(1-3)</sup>. Although the experiments for clarifying the mechanism of this reaction have not yet been completed, it is established that the reaction rate increases considerably with decreasing pH. For this, two reasons may be decisive: the equilibrium of the reaction may be totally shifted to the side of the "methyl activating" anilinium with increasing acidity so that more exchangeable material is present:  $(R - ND_2 + D_3O^{(+)}) \rightleftharpoons R - ND_3^{(+)} + D_2O$ . On the other hand it is also possible that the mobility is generated or intensified by an "Aromat-D<sub>3</sub>O<sup>(+)</sup>" complex which in the case of the present anilinium is only formed under very strong acidic conditions.

A further possibility that the H/D exchange in the methyl group is catalysed by metal traces<sup>4)</sup> originating from the wall of the V2A-container (as impurities) can be excluded. Addition of the main metal components or their chlorides to the reaction mixture has no observable effect on the exchange.

In congruence with the mechanistic concept of electrophilic aromatic substitution the methyl anilines tested by us undergo a nearly 100 % exchange in the o/p position at moderate temperatures (150°C, 10-24 h). m-Toluidine shows in contrast to its o-isomer an unexpected high preference for deuteration in the ortho position: after a 4 hours exchange at 100°C the percentage of ortho<sub>2</sub>-to para-substitution is nearly 80:20 in m-toluidine and 50:50 (free ortho to para position) in the o-isomer respectively (Table 1). All

methyl anilines do not undergo any exchange in the m-position to the amino group under the conditions used for complete o/p deuteration. Additional respectively simultaneous H/D exchange to 70-98% takes place in m-position only at significant higher temperature and extended reaction time (see Tables 1 and 2)

The experimental conditions of the aimed and selective deuteration of methyl anilines are summarized in the tables 1 and 2 and also represented for p-toluidine in the following scheme.

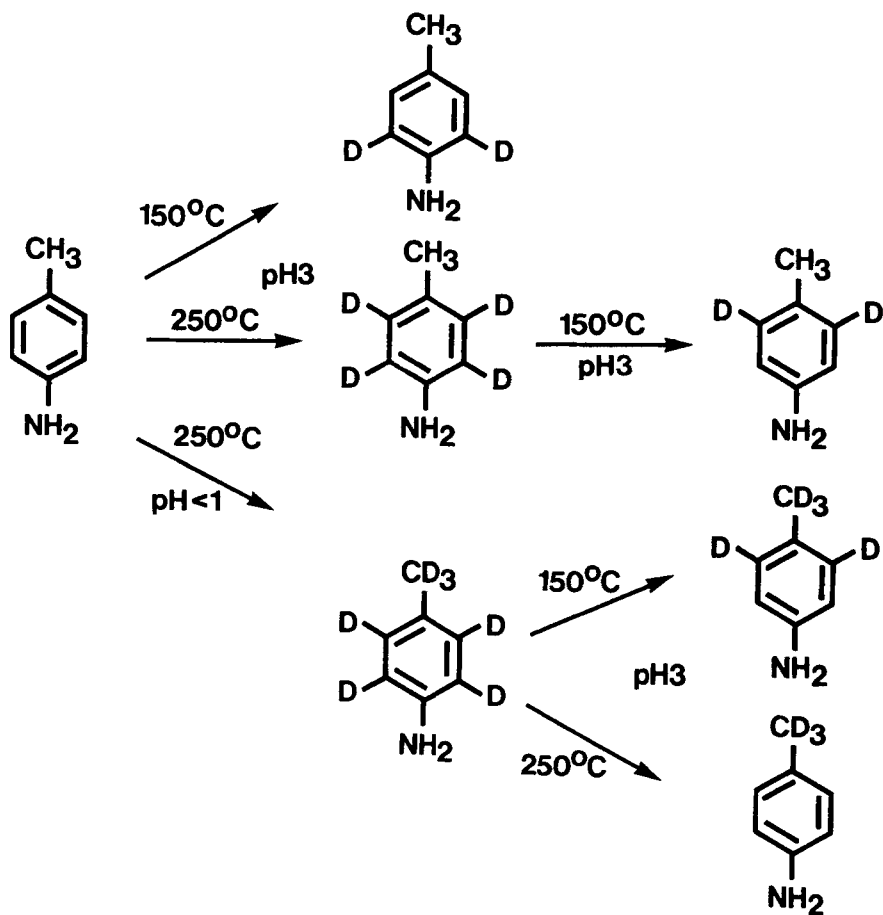


Table 1 Deuteration of methyl anilines<sup>†)</sup>

Starting amine	Temp. (C)	Time (h)	pH	Percentage deuteration in different positions relative to the amino group									overall deuteration in exchangeable positions (%)	yield (%)
				2	6	3	5	4	CH <sub>3</sub>					
p-toluidine	150	10	3	99	99	0	0	-	0	0	0	99	96	
	220	18	3	99	99	98	98	-	0	0	0	98.5	95	
	250	2x24	0	99	99	96	96	-	96	0	0	97.2	76	
o-toluidine	100	4	3	-	70	0	0	70	0	0	0	70	94	
	100	24	3	-	98	0	0	98	0	0	0	98	95	
	250	46	3	-	98	98	98	98	0	0	0	98	90	
250	64	-0.5	-	97	97	97	97	97	93	0	96.2	82		
m-toluidine	100	4	3	78	78	-	0	19	0	0	0	58.3	100	
	100	20	3	82	82	-	0	50	0	0	0	71.3	100	
	220	24	3	99	99	-	0	96	0	0	0	98	93	
250	48	3	99	99	-	92	96	0	0	0	96.5	60		
250	64	-0.5	98	98	-	92	98	60	0	0	89.2	41		
2,3-dimethyl-aniline	180	10	3	-	93	-	0	93	0	0	0	93	100	
	250	18	3	-	97	-	97	97	0	0	0	97	95	
	250	64	0	-	96	-	96	96	86	0	0	93.5	61	
2,5-dimethyl-aniline	180	10	3	-	96	0	-	96	0	0	0	96	100	
	250	18	0	-	96	93	-	96	86	0	0	92.8	96	
3,4-dimethyl-aniline	100	4.5	3	82	0	-	82	-	-	-	-	82	95	
	250	46	-0.5	91	91	-	70	-	79	-	-	82.8	80	

<sup>†)</sup> 0% deuteration: no deuteration was found with NMR-Spectroscopy, used for the determination of the degree of deuteration.

Table 2 Re-exchange of the deuterated methyl anilines<sup>†)</sup>

Starting amine	Temp. (C°)	Time (h)	pH	Percentage rest-deuteration in different positions relative to the amino group						overall deuteration in not ex-changed positions (%)	yield (%)
				2	6	3	5	4	CH <sub>3</sub>		
Tetradeutero-p-toluidine	150	10	3	0	0	99	99	-	0	99	92
Perdeutero-p-toluidine	150	10	3	0	0	99	99	-	96	98	93
p-toluidine	150	18	3	0	0	0	0	-	96	96	87

<sup>†)</sup> 0 % rest-deuteration: no rest-deuteration was found with NMR-Spectroscopy, used for the determination of the degree of deuteration.

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