

Stereoselective Aminomethylation of m-Cresol with Chiral Amine Mediated by 4 Å Molecular Sieves Under Neat Conditions

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Abstract: Aminomethylation at ortho position was performed with respect to hydroxyl group of m-cresol in the presence of carefully dried 4 Å molecular sieves under neat conditions. One pot, two components, Mannich reaction of m-cresol with imine at 60 °C under Solvent-free conditions affords the corresponding aminomethylated products in good yields, with moderate stereoselectivity.

Keywords: Aminomethylation, mannich reaction, solvent-free conditions, m-Cresol, diastereoselectivity.

INTRODUCTION

New methods for the stereoselective aminoalkylation of electron – rich aromatic compounds are currently of great interest. Although a variety of methods for the aminoalkylation of electron-rich aromatic compounds are available [1, 2], new direct approaches that are stereoselective and mild enough to allow the preparation of single diastereoisomers are continuously attracting interest [3].

The Mannich reaction is one of the most important multi components reactions in organic synthesis and biosynthesis [4]. In the course of these three components aminoalkylation of aldehyds, C-N and C-C single bonds replace the C-O double bond.

Recently, it was reported the lithium perchlorate mediated one pot three components aminoalkylation of aromatic or aliphatic aldehydes with (trimethylsilyl) alkylamines and different nucleophiles [5].

Herein we describe an efficient straightforward and diastereoselective method for the aminoalkylation of m-cresol with chiral amine mediated by carefully dried 4 Å molecular sieves under solvent free conditions and diastereoselective method for the aminoalkylation of m – cresol with chiral amine mediated by carefully dried 4 Å molecular sieves under Solvent-free conditions and at 60 °C (Scheme 1).

RESULTS AND DISCUSSION

In the solvent free conditions aldehyde **1** and enantiopure (S)-1-phenylethyl amine **2** (Readily available commercially as the (S) enantiomer) produce the imine **3** as an intermediate at room temperature after 30 minutes. Up on the addition of meta cresol to the reaction mixture, aminomethylated new products **5** and **6** were formed in 85% isolated yield, and also with moderate diastereoselectivity dr (75:25) (Scheme 1).

The diastereomeric purity was determined by ¹HNMR analysis of products.

The structure of products was confirmed by their spectral data and was characterized by comparison of IR, NMR (¹H and ¹³C) spectra and also X-ray crystallographic data with those reported in the literature (Scheme 2).

CONCLUSION

In summary, a one-pot, three-component diastereoselective aminomethylation of m-cresol have been achieved in good yields and with moderate selectivity.

EXPERIMENTAL

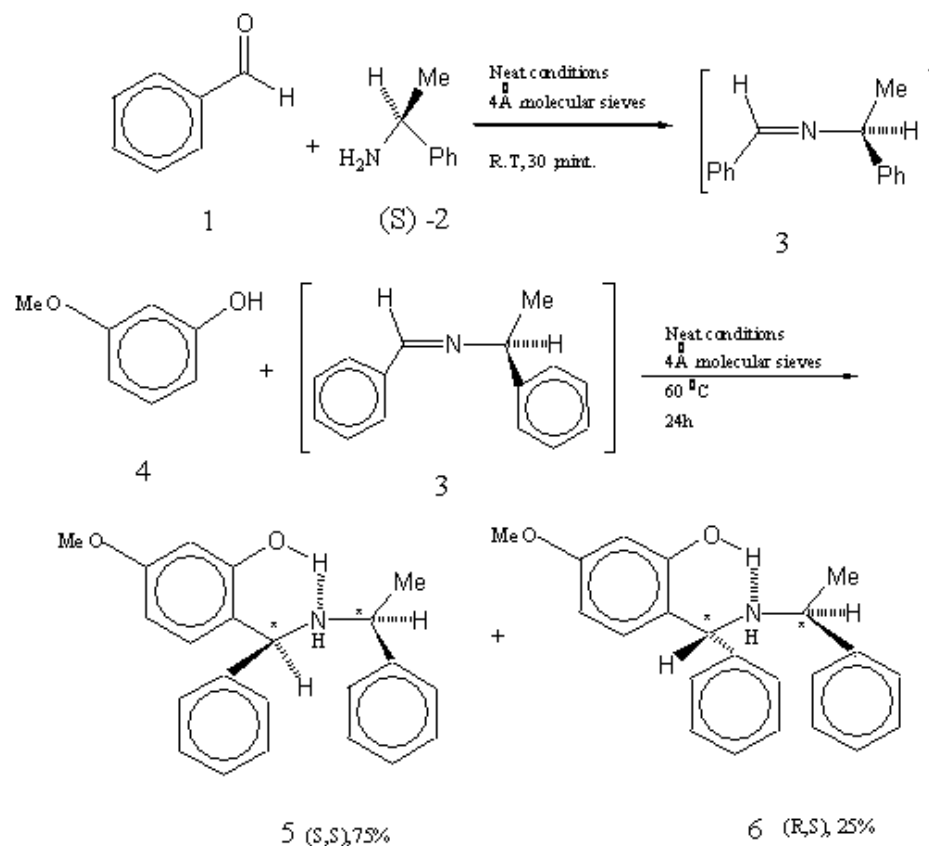
General Procedure for Diastereoselective Aminomethylation of m-Cresol

A mixture of benzaldehyde (2 mmol, 0.21 g), (S) (-)-1-phenyl ethylamine (3 mmol, 0.36g) and carefully dried 4 Å molecular sieves (0.5g) under Solvent-free conditions were placed in a 25 ml flask under argon and stirred for 30 min. m-Cresol (2 mmol) was added *via* a syringe. Following the progress of the reaction by TLC and ¹H NMR. The reaction mixture was stirred at 60 °C for 24h. After completing of the reaction 1,2- dichloroethane (20 ml) and water (20 ml) were added. The organic phase was separated, dried over MgSO₄ and the solvent was removed using a rotary evaporator.

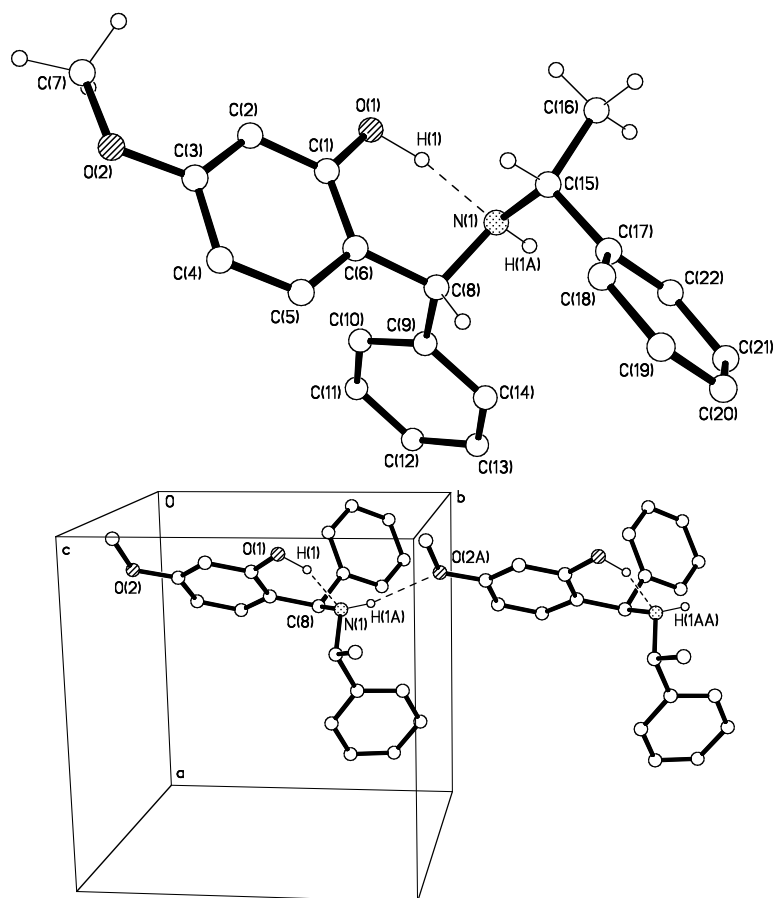
The crude product was further purified by column chromatography on silicagel eluting with petroleum ether/ ethyl acetate (5:3). Two diastereoisomers (**5** and **6**) as white and colorless crystals were obtained, respectively. The melting point of diastereoisomer **5** was 173-175 °C as colorless crystals and also m.p for diastereoisomer **6** was 175-178 °C as needle crystals afforded.

All compounds were characterized on the basis of spectroscopic data's as followed (IR, NMR, MS, X-ray crystallography).

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Scheme 1.



Scheme 2. Selected X-Ray crystallographic data for the major diastereomer 5.

Table 1. Crystal Data and Structure Refinement for Diastereoisomer 5

Identification code	pcbp60	
Chemical formula	C ₂₂ H ₂₃ NO ₂	
Formula weight	333.41	
Temperature	120(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, P2 ₁	
Unit cell parameters	a = 9.7077(4) Å	$\alpha = 90^\circ$
	b = 9.2828(2) Å	$\beta = 90.122(2)^\circ$
	c = 10.1588(5) Å	$\gamma = 90^\circ$
Cell volume	915.45(6) Å ³	
Z	2	
Calculated density	1.210 g/cm ³	
Absorption coefficient μ	0.077 mm ⁻¹	
F(000)	356	
Crystal colour and size	colourless, 0.64 × 0.44 × 0.16 mm ³	
Reflections for cell refinement	2595 (θ range 1.02 to 27.48°)	
Data collection method	Bruker-Nonius 95mm CCD camera on κ -goniostat	
	ϕ & ω scans	
θ range for data collection	3.04 to 25.00°	
Index ranges	h -10 to 11, k -11 to 10, l -12 to 11	
Completeness to $\theta = 25.00^\circ$	98.8 %	
Intensity decay	0%	
Reflections collected	7164	
Independent reflections	3032 ($R_{\text{int}} = 0.0427$)	
Reflections with $F^2 > 2\sigma$	2572	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.952 and 0.988	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0408, 0.0978	
Data / restraints / parameters	3032 / 1 / 235	
Final R indices [$F^2 > 2\sigma$]	R1 = 0.0390, wR2 = 0.0789	
R indices (all data)	R1 = 0.0557, wR2 = 0.0848	
Goodness-of-fit on F^2	1.058	
Absolute structure parameter	-0.4(12)	
Extinction coefficient	0.085(7)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.217 and -0.240 e Å ⁻³	

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters (\AA^2) for *pcbp60*. U_{eq} is Defined as One Third of the Trace of the Orthogonalized U^{ij} Tensor

	x	y	z	U_{eq}
O(1)	0.13879(13)	0.49559(16)	0.40370(15)	0.0351(4)
C(1)	0.20539(17)	0.3916(2)	0.33244(19)	0.0247(4)
C(2)	0.17373(18)	0.2491(2)	0.36063(19)	0.0253(4)
C(3)	0.23353(17)	0.1394(2)	0.28841(19)	0.0247(4)
C(4)	0.32669(18)	0.1720(2)	0.1883(2)	0.0272(5)
C(5)	0.35856(19)	0.3137(2)	0.1641(2)	0.0252(5)
C(6)	0.29997(17)	0.4280(2)	0.23411(19)	0.0231(4)
O(2)	0.20687(13)	-0.00422(15)	0.30819(14)	0.0321(4)
C(7)	0.0960(2)	-0.0381(2)	0.3966(2)	0.0354(6)
C(8)	0.33611(18)	0.5821(2)	0.19967(19)	0.0227(4)
C(9)	0.25069(17)	0.6465(2)	0.08808(18)	0.0243(4)
C(10)	0.12404(18)	0.5926(2)	0.0493(2)	0.0290(5)
C(11)	0.05142(19)	0.6563(3)	-0.0527(2)	0.0360(5)
C(12)	0.1050(2)	0.7734(3)	-0.1187(2)	0.0401(6)
C(13)	0.2318(2)	0.8291(3)	-0.0798(2)	0.0429(6)
C(14)	0.3031(2)	0.7664(2)	0.0229(2)	0.0347(5)
N(1)	0.32331(14)	0.67679(19)	0.31643(15)	0.0241(4)
C(15)	0.44488(17)	0.6726(2)	0.40558(18)	0.0254(4)
C(16)	0.4092(2)	0.7561(3)	0.53060(19)	0.0338(5)
C(17)	0.57413(18)	0.7283(2)	0.33910(19)	0.0249(5)
C(18)	0.68594(18)	0.6379(2)	0.31775(19)	0.0285(5)
C(19)	0.8032(2)	0.6875(2)	0.2527(2)	0.0346(5)
C(20)	0.8087(2)	0.8263(2)	0.2075(2)	0.0349(5)
C(21)	0.6989(2)	0.9184(2)	0.2284(2)	0.0363(5)
C(22)	0.5830(2)	0.8698(2)	0.2941(2)	0.0314(5)

Table 3. Bond Lengths [Å] and Angles [°] for Diastereoisomer 5

O(1)–C(1)	1.369(2)	C(1)–C(2)	1.388(3)
C(1)–C(6)	1.400(3)	C(2)–C(3)	1.384(3)
C(3)–O(2)	1.373(2)	C(3)–C(4)	1.396(3)
C(4)–C(5)	1.374(3)	C(5)–C(6)	1.399(3)
C(6)–C(8)	1.514(3)	O(2)–C(7)	1.439(2)
C(8)–N(1)	1.482(2)	C(8)–C(9)	1.525(3)
C(9)–C(10)	1.384(3)	C(9)–C(14)	1.392(3)
C(10)–C(11)	1.385(3)	C(11)–C(12)	1.379(3)
C(12)–C(13)	1.392(3)	C(13)–C(14)	1.380(3)
N(1)–C(15)	1.487(2)	C(15)–C(17)	1.517(3)
C(15)–C(16)	1.528(3)	C(17)–C(18)	1.389(3)
C(17)–C(22)	1.393(3)	C(18)–C(19)	1.395(3)
C(19)–C(20)	1.369(3)	C(20)–C(21)	1.383(3)
C(21)–C(22)	1.385(3)		
O(1)–C(1)–C(2)	117.23(16)	O(1)–C(1)–C(6)	121.22(18)
C(2)–C(1)–C(6)	121.55(17)	C(3)–C(2)–C(1)	119.93(17)
O(2)–C(3)–C(2)	123.91(16)	O(2)–C(3)–C(4)	116.10(17)
C(2)–C(3)–C(4)	119.99(18)	C(5)–C(4)–C(3)	118.99(18)
C(4)–C(5)–C(6)	122.90(17)	C(5)–C(6)–C(1)	116.61(17)
C(5)–C(6)–C(8)	120.28(16)	C(1)–C(6)–C(8)	123.08(17)
C(3)–O(2)–C(7)	116.46(15)	N(1)–C(8)–C(6)	110.83(15)
N(1)–C(8)–C(9)	108.43(15)	C(6)–C(8)–C(9)	114.60(16)
C(10)–C(9)–C(14)	118.63(18)	C(10)–C(9)–C(8)	123.44(18)
C(14)–C(9)–C(8)	117.92(16)	C(9)–C(10)–C(11)	120.61(19)
C(12)–C(11)–C(10)	120.53(19)	C(11)–C(12)–C(13)	119.3(2)
C(14)–C(13)–C(12)	120.0(2)	C(13)–C(14)–C(9)	120.93(19)
C(8)–N(1)–C(15)	113.85(14)	N(1)–C(15)–C(17)	112.09(14)
N(1)–C(15)–C(16)	108.18(14)	C(17)–C(15)–C(16)	112.70(16)
C(18)–C(17)–C(22)	117.97(18)	C(18)–C(17)–C(15)	120.74(18)
C(22)–C(17)–C(15)	121.27(17)	C(17)–C(18)–C(19)	120.9(2)
C(20)–C(19)–C(18)	120.1(2)	C(19)–C(20)–C(21)	119.99(19)
C(20)–C(21)–C(22)	120.0(2)	C(21)–C(22)–C(17)	121.08(19)

Table 4. Hydrogen Coordinates and Isotropic Displacement Parameters (Å²) for Diastereoisomer 5

	x	y	z	U
H(1)	0.190(2)	0.582(3)	0.378(2)	0.053
H(2)	0.1111	0.2270	0.4294	0.030
H(4)	0.3675	0.0973	0.1377	0.033
H(5)	0.4232	0.3351	0.0968	0.030
H(7A)	0.1199	-0.0059	0.4857	0.053
H(7B)	0.0806	-0.1425	0.3971	0.053
H(7C)	0.0119	0.0108	0.3674	0.053
H(8)	0.4348	0.5836	0.1716	0.027
H(10)	0.0865	0.5112	0.0932	0.035
H(11)	-0.0360	0.6191	-0.0775	0.043
H(12)	0.0559	0.8155	-0.1899	0.048
H(13)	0.2693	0.9103	-0.1240	0.051
H(14)	0.3891	0.8056	0.0496	0.042
H(1A)	0.3090(19)	0.769(3)	0.287(2)	0.029
H(15)	0.4613	0.5699	0.4308	0.030
H(16A)	0.3855	0.8556	0.5076	0.051
H(16B)	0.4887	0.7560	0.5902	0.051
H(16C)	0.3306	0.7104	0.5742	0.051
H(18)	0.6825	0.5411	0.3478	0.034
H(19)	0.8793	0.6248	0.2398	0.041
H(20)	0.8879	0.8594	0.1618	0.042
H(21)	0.7029	1.0150	0.1977	0.044
H(22)	0.5083	0.9339	0.3088	0.038

Table 5. Torsion Angles [°] for Diastereoisomer 5

O(1)-C(1)-C(2)-C(3)	177.44(17)	C(6)-C(1)-C(2)-C(3)	-1.7(3)
C(1)-C(2)-C(3)-O(2)	-179.08(17)	C(1)-C(2)-C(3)-C(4)	0.7(3)
O(2)-C(3)-C(4)-C(5)	-179.56(18)	C(2)-C(3)-C(4)-C(5)	0.7(3)
C(3)-C(4)-C(5)-C(6)	-1.1(3)	C(4)-C(5)-C(6)-C(1)	0.1(3)
C(4)-C(5)-C(6)-C(8)	-178.07(19)	O(1)-C(1)-C(6)-C(5)	-177.80(17)
C(2)-C(1)-C(6)-C(5)	1.3(3)	O(1)-C(1)-C(6)-C(8)	0.3(3)
C(2)-C(1)-C(6)-C(8)	179.40(18)	C(2)-C(3)-O(2)-C(7)	9.0(3)
C(4)-C(3)-O(2)-C(7)	-170.77(17)	C(5)-C(6)-C(8)-N(1)	-152.00(16)
C(1)-C(6)-C(8)-N(1)	30.0(2)	C(5)-C(6)-C(8)-C(9)	84.9(2)
C(1)-C(6)-C(8)-C(9)	-93.1(2)	N(1)-C(8)-C(9)-C(10)	-104.0(2)
C(6)-C(8)-C(9)-C(10)	20.4(3)	N(1)-C(8)-C(9)-C(14)	75.47(19)
C(6)-C(8)-C(9)-C(14)	-160.15(16)	C(14)-C(9)-C(10)-C(11)	0.4(3)
C(8)-C(9)-C(10)-C(11)	179.89(17)	C(9)-C(10)-C(11)-C(12)	0.9(3)
C(10)-C(11)-C(12)-C(13)	-1.4(3)	C(11)-C(12)-C(13)-C(14)	0.6(3)
C(12)-C(13)-C(14)-C(9)	0.7(3)	C(10)-C(9)-C(14)-C(13)	-1.2(3)
C(8)-C(9)-C(14)-C(13)	179.3(2)	C(6)-C(8)-N(1)-C(15)	81.57(18)
C(9)-C(8)-N(1)-C(15)	-151.84(15)	C(8)-N(1)-C(15)-C(17)	63.6(2)
C(8)-N(1)-C(15)-C(16)	-171.55(16)	N(1)-C(15)-C(17)-C(18)	-115.9(2)
C(16)-C(15)-C(17)-C(18)	121.8(2)	N(1)-C(15)-C(17)-C(22)	62.1(3)
C(16)-C(15)-C(17)-C(22)	-60.2(2)	C(22)-C(17)-C(18)-C(19)	-0.3(3)
C(15)-C(17)-C(18)-C(19)	177.85(18)	C(17)-C(18)-C(19)-C(20)	-0.8(3)
C(18)-C(19)-C(20)-C(21)	1.2(3)	C(19)-C(20)-C(21)-C(22)	-0.5(3)
C(20)-C(21)-C(22)-C(17)	-0.6(3)	C(18)-C(17)-C(22)-C(21)	0.9(3)
C(15)-C(17)-C(22)-C(21)	-177.17(18)		

Table 6. Hydrogen Bonds for Diastereoisomer 5 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...N(1)	0.98(3)	1.69(2)	2.614(2)	156(2)
N(1)-H(1A)...O(2')	0.92(2)	2.34(2)	3.171(2)	150.7(16)

Symmetry operations for equivalent atoms
'x,y+1,z

Selected Spectroscopic Data for the Major Diastereoisomer 5

¹H NMR (400 MHz, CDCl₃): δ ppm, 1.55 (d, J= 6.8 Hz, 3H), 2.42 (br s, 1H), 3.84 (s, 3H), 3.95 (m, 1H), 4.9 (s, 1H), 6.44 – 6.76 (dd, J=7Hz, 2H), 6.7 (s, 1H), 7.30 – 7.9 (m, 10H)
¹³C NMR (400 MHz, CDCl₃): δ ppm, 23.4 (CH₃), 56.9 (CH), 60.6 (CH), 70.5 (CH₃), 113.2, 120.4, 121.3, 122.7, 126.7, 127.7, 127.9, 128.1, 128.9, 129.0, 129.1, 129.3, 130, 130.1, 133, 141.9, 143.5, 157.7 IR (KBr), 3220, 1080 cm⁻¹ also crystallographic data was attached (Tables 1-6).

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