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Stereoselective aminomethylation of m-cresol with chiral amine mediated by 4Å molecular sieves under neat conditions

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ABSTRACT

Aminomethylation at ortho position with respect to hydroxyl group of m-cresol in presence carefully dried 4Å molecular sieves under neat conditions. One pot, two component, Mannich reaction of m-cresol with imine at 60^0C temperature 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.

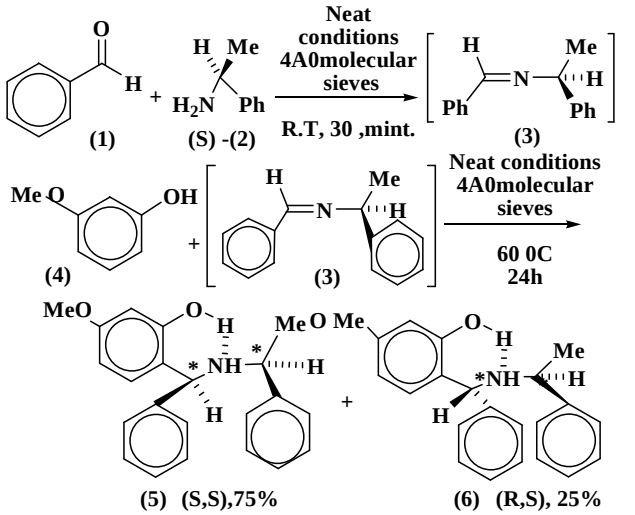
INTRODUCTION

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-component reactions in organic synthesis and biosynthesis[4]. In the course of this three component aminoalkylation of aldehyds, C-N and C-C single bonds replace the C-O double bond.

Recently, it was reported the litium perchlorate-mediated one-pot three-component aminoalkylation of aromatic or aliphatic aldehydes with (trimethylsilyl) alkylamines and different nucleophiles, including electron-rich aromatic cpmpounds[5].

Herein we describe an efficient straightforward and disteroselective method for the aminoalkylation of m-cresol with chiral amine mediated by carefully dried 4Åmolecular sieves under solvent free conditions and diastereoselective method for the aminoalkylation of m-cresol with chiral amine mediated by carefully dried 4Å molecular sieves under solvent free conditions and at 60^0C temperature (SCHEME 1).



SCHEME 1

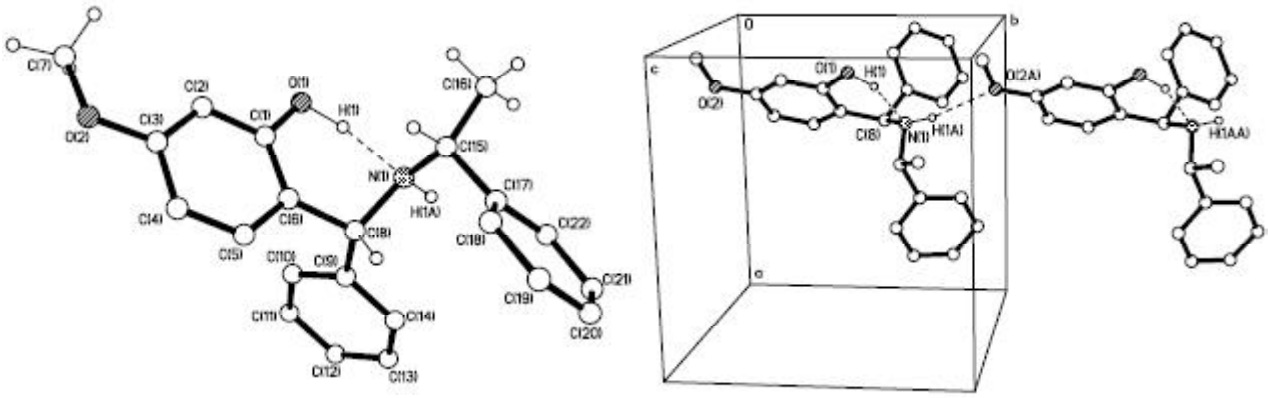
RESULTS AND DISCUSSION

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 and 30 minutes. Up on addition of meata cresol to the reaction mixture, aminomethylated products 5,6 were formed in 85% isolated yield, and also with moderate diastereoselectivity dr (75:25) (SCHEME 1).

The diasteromeric purity was determined by ^{1}HNMR analysis of products. Completing the reaction over longer times and under different conditions did not effect any improvement in the yields of products.

The structure of products were confirmed by their spectral data and were characterized by comparison of IR, NMR (^{1}H and ^{13}C) and MS spectra and also X-ray crystallographic data's[6].

Selected X-Ray crystallographic data for the major diastreoisomer (5)



SCHEME 2

TABLE 1: Crystal data and structure refinement for diastreoisomer (5)

Identification code	pcbp60	
Chemical formula	$C_{22}H_{23}NO_2$	
Formula weight	333.41	
Temperature	120(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 9.7077(4) Å	α = 90°
	b = 9.2828(2) Å	β = 90.122(2)°
	c = 10.1588(5) Å	γ = 90°
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 goniostat	Bruker-Nonius 95mm CCD camera on κ-ϕ and 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 θ=25.00°	98.8 %	
Intensity decay	0%	Intensity decay
Reflections collected	7164	Reflections collected
Reflections collected	7164	
Independent reflections	3032 (R_{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 (Å²) 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 diastreoisomer (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)-(11)	1.385(3)	C(11)-C(12)	1.379(3)
C(12)-(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)-(16)	1.528(3)	C(17)-C(18)	1.389(3)
C(17)-(22)	1.393(3)	C(18)-C(19)	1.395(3)
C(19)-(20)	1.369(3)	C(20)-C(21)	1.383(3)
C(21)-(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 diastreoisomer (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

EXPERIMENTAL

General procedure for diastereoselective amino methyl ation of m- cresol

A mixture of benzaldehyde (2 mmol, 0.21 g), S(-)-1- phenyl ethylamine (3 mmol, 0.36g) and carefully dired 4Å molecular sieves (0.5g) under solvent free conditions were placed in a 25 ml flask under argon and stirred for 30 min, at room temperature. m-Cresol (2 mmol) was added via a syringe. Following the progress of the reaction by TLC and ^{1}H NMR, the reaction mixture was stirred at 60^{0}C temperature for 24h. After completing of reaction 1,2-dichloroethane (20 ml) and water (20 ml) were added. The organic phase was separated, dried over $MgSO_4$ and the solvent was removed using a rotary evaporator.

The crude products was further purified by column chromatography on silicagel eluting with petrolium ether/ ethyl acetate (5:3). Two diastereoisomers (5,6) as white and colorless crystals were obtained, Respectively. The melting point of diastereoisomers 5 was 75-78^{0}C and also m.p for diastereoisomer 6 was 78-8^{0}C.

TABLE 5: Torsion angles [°] for diastreoisomer (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(2)
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 diastreoisomer (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)

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

Selected spectroscopic data for the magor distre oisomer (5)

^{1}H NMR (400 MHZ, $CDCl_3$): δ1.55 (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, 2H), 6.7 (S, 1H), 7.30-7.9(m, 10H) ^{13}C NMR (400 MHZ, CD Cl_3), δ, 23.4 (CH_3) , 56.9(CH), 60.6 (CH), 70.5 (CH_3), 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.

CONCLUSION

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

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