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To explore Grignard's reaction in the synthesis of structurally related compounds of Carbinoxamine and evaluate Anti histaminic activity

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Abstract: Carbinoxamine, 2-[p-chloro-α-[(2-dimethylamino) ethoxy] benzyl]pyridine, is a aminoalkyl ether, a potent antihistaminic drug[1]. In an attempt to synthesize Carbinoxamine derivatives by Grignard reaction which gave better yield and the method is looked economic from existing procedures[2,3]. Substituted 2-benzylpyridinecarbinols are used as intermediates and have been synthesized by Grignard exchange reaction between 2-bromopyridine and 2-chlorobutane. This is a novel method, which can be used for synthesis of Carbinoxamine derivatives.

Antihistaminic activity was evaluated by histamine – induced skin reactions in guinea pigs. Hartley guinea pigs were used. Chlorpheniramine maleate was selected as standard drug. Some of the synthesized compounds have shown significant activity.

Key words: Carbinoxamine, Chlorpheniramine, Grignard's reaction, Antihistaminic drugs.

Introduction:

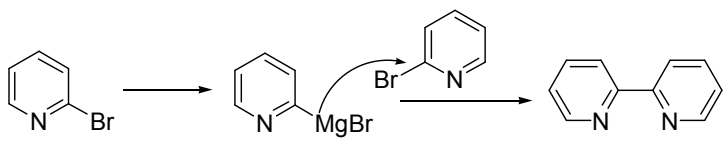
Substituted 2-benzylpyridinecarbinol is an intermediate for synthesis of Carbinoxamine, a potent antihistaminic agent[1]. previously carbinol was synthesized by a) The reaction of aryl aldehyde with 2-pyridiylmagnesium bromide b) condensation of picolinic acid with aryl aldehyde c) The reaction of pyridillithium and aryl aldehyde at -40 ^{o}C The yield by first two methods is very low 19.4-49%, and the yield by third method is high 90%, but requires very low temperature and the reagents required were very expensive [2, 3, 4]. In an attempt to make procedure more economic we have synthesized carbinol by Grignard exchange reaction between 2-bromopyridine and 2-chlorobutane at 0 ^{o}C.

Recently Gregory B. Dudley et al [5] have synthesized several pyridine carbinol by anionic rearrangement but requires handling of LDA, crown ether and n-BuLi like reagents.

E.C. Ashby et al [6] reported the preparation of 2-pyridylmagnesium bromide with 2-bromopyridine and magnesium results in the formation of bipyridyls (scheme I). Our experience also matches with others.

So, in an attempt to find efficient procedure for the synthesis we thought of altering the reaction conditions and to modify existing procedure, to solve the purpose, Grignard exchange reaction at low temperature come to rescue.

Scheme I: Formation of bipyridyls



We were pleased to see the progress of reaction between 2-butylmagesiumchloride and 2-bromopyridine at 0 - 5 ^{o}C followed by the addition of corresponding aryl aldehyde gave 80 - 90 % yields of carbinol at the end of reaction.

In an attempt to synthesize potent derivatives of carbinoxamine (H_1-bolcker), we have modified substitutions on aryl group; changes were made on alkyl side chain and terminal nitrogen atom. Compounds **5a, 6a, 7a, 10a** have shown very significant antihistaminic activity while compounds **8a** and **9a** shown significant activity. This would lead to conclusion that electron withdrawing substituents on benzene ring plays an important role in assigning antihistaminic activity to compound.

Material and Methods

Genereal:

Anhydrous tetrahydrofuran (THF), 2-chloro pyridine, Sodium tertiary butoxide (STB) were purchased from Alkali metals ltd, Bangalore. Magnesium metal, N, N-dimethyl ethyl chloride, N,N-dimethylamino-2-propyl chloride, (2-chloroethyl) piperidin, 2-chloro butane were taken from R.L. Fine chemicals pvt. ltd. Bangalore, *p*-chloro benzaldehyde purchased from NR chemicals, Bangalore. Reactions were performed under an atmosphere of nitrogen. Apparatus was assembled hot and flushed with nitrogen, and then allowed to cool under nitrogen. Reactions were carried out in four necked round-bottom flasks equipped with a condenser, stirrer, addition flask and thermometer. Addition flask was attached with standard taper joints to allow nitrogen flow while reagents being added. IR recorded with liquid state Nicolet IR 200. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ solution on instrument Bruker Spectrospin 400 and 200 MHz. Mass spectra recorded by electron impact ionization and HR-ESIMS.

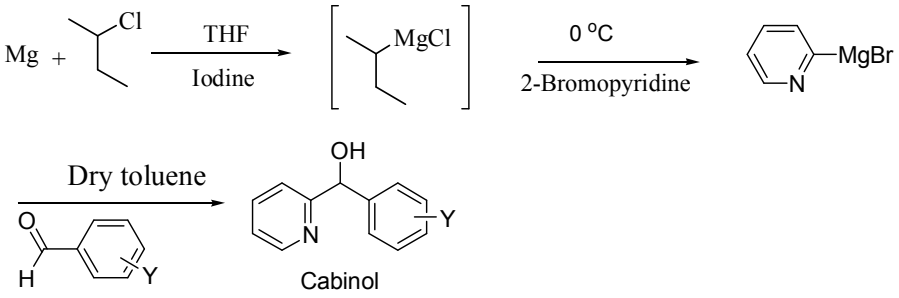
Synthesis of substituted carbinol (1a-3a)

2-butylmagnesiumchloride was synthesized by Grignard's reaction between magnesium metal (12g, 0.4967 mole) and 2-chlorobutane (45.5g, 0.497mole). Then it was cooled to 0 ^{o}C under nitrogen atmosphere. After this, 2-bromopyridine (0.3821 moles) dissolved in 100ml of dry toluene was added dropwise at a temperature 0 ^{o}C. After stirring solution 30 min at 0 ^{o}C, substituted benzaldehyde (0.3821 moles) dissolved in 100ml dry toluene was added dropwise at 0 ^{o}C then, solution stirred at 0 ^{o}C for 2 hrs.

To the above reaction mixture 60 g of NH_4Cl in 100ml water was added slowly and stirred for 30 min to get intermediate carbinol. The toluene layer and water layer was separated; product was extracted into additional 3×50ml toluene. Combined toluene layers were washed with 2×50 ml water, separated from water, then dried over sodium sulphate and concentrated under vacuum to get the carbinol. Yield **1a** = 80%, **2a** = 90%, **3a** = 85%.

Substituted carbinols were synthesized shown in **scheme(II).**

Scheme II: Synthesis of carbinol and derivatives



1a, Y=H, 80%
2a, Y=Cl, 90%
3a, Y=Br, 85%

Synthesis of Carbinoxamine (4a):

To carbinol **2a** (15g, 0.068 moles) dissolved in 25 ml dry toluene was added sodium tertiary butoxide (6.5g, 0.06 moles) under nitrogen atmosphere, with stirring. Then, N, N-dimethyl ethyl chloride (13.8g, 0.096 moles) dissolved in 25 ml of dry toluene was added dropwise. The green color solution formed which was refluxed at 110 ^{o}C for 6 hrs.

Then, reaction mixture cooled, 100ml water was added. Toluene and water layers were separated. Product was extracted into 2×50 ml toluene and then water washings 2×50 ml were given to combined toluene layer. After this, toluene layer was dried over sodium sulfate and concentrated to give carbinoxamine. The yield was found to be 85 %.

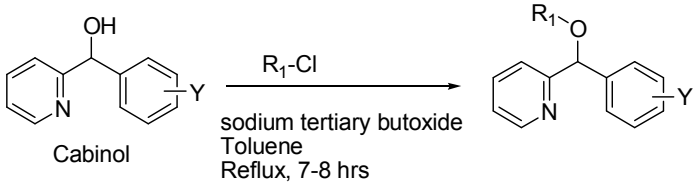
Similarly, compounds (**5a-10a**) were synthesized using substituted tertiary amine and substituted carbinol as shown in *Table I*.

Histamine – Induced skin reactions in guinea pigs: Male std: Hartley guinea pigs were used. Under light ether anesthesia, 0.3 mg of histamine was injected intradermally (i.d.) in a volume of 0.1 ml at two points on the shaved back immediately after intravenous injection (i.v.) of 1 ml of 2.5% Pontamine sky blue. The animals were sacrificed by bleeding 30 min after the histamine injection and the skin was removed for determination of the area of bluing spots. The area of bluing spots was used as a measure of the increase in microvascular permeability in the skin caused by histamine. Compounds were suspended in a 5% gum arabic solution and administered *p.o.* in a volume of 0.2 ml per 100 g body weight 1 h before the histamine injection. Here chlorpheniramine maleate is used as standard.

Anti-Histaminic activity:

Experiment [7]:

Table I: Synthesis of carbinoxamine and its derivatives from various carbinol



code	-Y	-R_1	% yield
4a	*para* -Cl	$-CH_2CH_2N(CH_3)_2$	85
5a	*para* -Cl	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	82
6a	*para* -Cl	$-CH_2CH_2CH_2N(CH_3)_2$	89
7a	*para* -Cl	$-CH_2CH_2NC_5H_{12}$	85
8a	-H	$-CH_2CH_2N(CH_3)_2$	80
9a	-H	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	80
10a	*meta* -Br	$-CH_2CH_2N(CH_3)_2$	81

Table II: Anti histaminic activity observed for synthesized compounds.

Compound	H_1 *invivo,* % inhibition (3mg/kg, p.o)
5a	76**
6a	72**
7a	63**
8a	32*
9a	36*
10a	58**
Chlorpheniramine Maleate	98**

n=5, Data were analysed by one way ANOVA followed by Dunnet's-t-test.
Values are *P<0.05, **P<0.01 versus control

TableIII: Spectroscopic analysis of synthesized compounds:

code	IR (cm^{-1})	NMR (ppm)	Mass
1a	3300	**^{1}HNMR: :**δ 4.2(s, 1H, -OH), δ5.79 (s, 1H, -CH), δ 7.19-8.61 (m, 9H aromatic) **^{13}CNMR:**76.5, 120, 124, 127, 129, 136.5, 138.2, 148.7, 158.5	**HRESI-MS: :** calculated for $C_{12}H_{11}NO$(185.22184), found 185.2124 **EI:** m/z 185, 186, 77
2a	3148	**^{1}HNMR:**δ 5.35(s, 1H, -OH), δ5.72 (s, 1H, -CH), δ 7.10-8.56 (m, 8H aromatic) **^{13}CNMR:** 77, 120, 128, 129, 136, 133, 136, 148, 158.	**HRESI-MS:** calculated for $C_{12}H_{10}ClNO$ (219.6669) found 219.6543.
4a	3050,1577, 1358	**^{1}HNMR:**δ 2.25 (s, 6H, 2-CH_3), δ 2.58-2.61(t, 2H, -CH_2), δ3.58-3.62 (t, 2H, -CH_2), δ5.47(s, 1H, –CH), δ7.09-8.50 (m, 8H, aromatic) **^{13}CNMR:** 45.9, 60, 65.2, 81.5, 120, 124.2, 128.9, 132.6, 133.4, 136, 148.7, 158.6	**HRESI-MS:** calculated for $C_{16}H_{19}ClN_2O$ (290.78786) found 290.74568 **EI:** m/z 290, 220, 203, 57
5a	3052, 1332	**^{1}HNMR:** δ 0.89-1.04(m, 3H, -CH_3), δ 2.00-2.09 (d, 2H, -CH_2) δ 2.16(s, 6H, 2-CH_3), δ 3.3-3.5(m, 1H, –CH), δ 5.42(s, 1H, –CH), δ 7.09-8.51 (m, 8H, aromatic).**^{13}CNMR:**15, 32.1, 46.1, 61.9, 75.4, 82.2, 120.9, 124.1, 128.8, 128.9, 132.6, 133.7, 136.2, 148.8, 158.6.	**HRESI-MS:** calculated for $C_{18}H_{23}ClN_2O$ (318.84102) found 318.94388
6a	3054,1589	**^{1}HNMR:** δ 1.7-2.0 (p, 2H, -CH_2), δ 2.20-2.61(t, 6H, 2-CH_3), δ 2.27-2.5(t, 2H, -CH_2), δ3.50-3.57 (t, 2H, -CH_2), δ5.44(s, 1H, –CH), δ7.09-8.512 (m, 8H, aromatic) **^{13}CNMR:** 27.9, 46.1, 55.8, 67.4, 82, 121, 124.2, 128.8, 130, 132.7, 133.7, 136.2, 148.7, 158.7.	**HRESI-MS:** calculated for $C_{17}H_{21}ClN_2O$ (304.81444) found 304.87333 **EI:** m/z 304, 218, 203, 167, 139, 102.
7a	1590, 1196	**^{1}HNMR:** δ 1.19-2.55 (m, 10H, 5-CH_2), δ 2.62-2.68 (t, 2H, -CH_2), δ 3.4-3.66(t, 2H, -CH_2), δ5.47(s, 1H, –CH), δ7.09-8.51 (m, 8H, aromatic). **^{13}CNMR:** 25.9, 54.6, 55.4, 65.8, 81.8, 121, 124.2,128.5, 128.9, 132.5, 133.5, 136.2, 148.7, 158.6	**HRESI-MS:** calculated for $C_{19}H_{23}ClN_2O$ (330.85172) found 330.87232 **EI:** m/z 329, 203, 167, 140, 128, 112.
8a	3061, 1599, 1267	δ 2.9 (s, 6H, 2CH_3), δ 3.6(t, 2H, -CH_2), δ 3.8(t, 2H, -CH_2), δ5.4(s, 1H, –CH), δ7.2-9.02 (m, 9H, aromatic) **^{13}CNMR:** 45.9, 60.2, 65.5, 120.9, 124.5, 127.5, 128.1, 128.8, 134.5, 136.5, 148.8, 158.5.	**HRESI-MS:** calculated for $C_{16}H_{20}N_2O$ (256.3428) found 256.2343 **EI:** m/z 256, 257, 258, 77, 112.
9a	3059, 1265, 1589	**^{1}HNMR:**δ 1.0-1.04 (d, 3H, CH_3), δ 2.083-2.145(d, 2H, -CH_2), δ 2.18(s, 6H, -2CH_3), δ5.45(s, 1H, –CH), δ7.1-8.5 (m, 9H, aromatic). **^{13}CNMR:** 15, 32.2, 46.2, 62, 75.4, 82.2, 121, 124.5, 128.1, 128.8, 134.5, 136.2, 158.5	**HRESI-MS:** calculated for $C_{18}H_{24}N_2O$ (284.39596) found 284.23535**.**
10a	3059, 1593	**^{1}HNMR:** δ 2.27(s, 6H, -2CH_3), δ 2.54-2.58 (t, 3H, -CH_2), δ 3.52-3.58 (t, 2H, -CH_2), δ4.50 (s, 1H, –CH), δ7.16-8.51 (m, 8H, aromatic) **^{13}CNMR:** 45.7, 60, 65.2, 81, 121, 123, 124.2, 126.5, 130.8, 131. 133, 136.8, 137, 149, 159.	**HRESI-MS:** calculated for $C_{16}H_{19}BrN_2O$ (335.23886) found 335.23512.

Results and Discussion

Compounds **5a, 6a, 7a, 10a** have shown very significant antihistaminic activity while compounds **8a** and **9a** shown significant activity. This suggests that electron withdrawing substituent on benzene ring important for activity. An economical procedure established in the experiments than any other procedure in literature known. Further we are trying to synthesize some compounds containing electron withdrawing groups such as nitro, fluoro and bromo on benzene ring with various other side chains.

Structures of the compounds were determined by IR, NMR and mass spectroscopy as shown in **Table III**

Conclusion

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