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Impact of Reaction Dynamics on Synthesis of Novel Nitrogen containing Aldehydes

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ABSTRACT

Impact of solvent dynamics, base employed and temperature conditions on the synthesis of novel Nitrogen containing aldehydes was studied.Piperazine, pyrrolidine and piperidine aldehydes were obtained in maximum yield and purity with the K_2CO_3 base in presence of DMF solvent and at 80^0 C temperatures.The synthesized compounds were characterized by IR, ^{1}HNMR and MS Spectroscopy.

Key words: Nitrogen-containing-aldehyde, Reaction dynamics, N-arylation.

INTRODUCTION

Nitrogen containing compounds are used as structural components of pharmaceuticals and agrochemicals due to their high biological activities[1]. There are many nitrogen containing chemicals, ranging from simple structural compounds as pyridine to complicated compounds as pharmaceutical ingredients and their number is growing rapidly year by year[2].Pyrrolidine based compounds have wide application in pharmaceutics ranging from use in the treatment of cancer[3],obesity[4], fungal and viral infections[5], HIV infection[6] and diabetes[7-8].Piperazine nucleus is one of the most important heterocycle, exhibiting remarkable pharmacological activities as anthelminitis[9], anti- HIV agent, antanginals[10], urological[11] and anticonvulsant compounds[12]. Piperidine and its derivatives are ubiquitous building blocks in the synthesis of pharmaceuticals compounds like anti depressant drug[13-14] and vasolidators[15]. Piperidine is also commonly used in sequencing of DNA[16] and in solid phase peptide synthesis[17].

As per the review about recent trends in chemistry of pyrrolidine, piperazine and piperidine derivatives, their demand in pharmaceuticals is increasing and still lies scope for the exploration of pharmaco-kinetics of these compounds.

All these facts were driving force to study the synthesis of 4(-4methyl piperazine-l-yl) benzaldehyde, (4- pyrrolidin-l-yl) benzaldehyde and (4-piperidine-l-yl) benzaldehyde.The present work is concerned solely with the chemistry i.e. the yield of the above mentioned products, for which the dynamics of the environment (solvent, base and temperature) can be responsible.

Study of different parameters on the synthesis of aldehyde

In continuation to explore the pharmaceutical significance of N-arylated moiety, thepiperazine, piperidine and pyrrolidinemoieties, it was planned to conduct a thorough study of the different parameters on the yield of 4-(4-methyl-piperazine-l-yl) benzaldehyde, (4-pyrrolidine-l-yl) benzaldelyde and (4-piperidine-l-yl) benzaldehyde. The systematic study was carried out keeping in view their significance on the yield by virtue of effect of bases, solvents and temperature conditions as depicted in Table 1-3.

Table 1: Effect of different bases

S. No	Name of Base Used	% Yield obtained 1a	1b	1c
1.	K_2CO_3	92%	94%	89%
2.	$CsCO_3$	88%	90%	80%
3.	Na_2CO_3	87%	84%	73%
4.	$KHCO_3$	85%	80%	60%
5.	$NaHCO_3$	80%	76%	50%

Table 2: Effect of different solvents

S. No	Name of Base Used	% Yield obtained 1a	1b	1c
1.	DMF	95%	96%	90%
2.	DMSO	90%	89%	84%
3.	Toluene	70%	65%	62%
4.	Xylene	75%	75%	50%
5.	Methanol	No reaction	No reaction	No reaction
6.	Acetone	No reaction	No reaction	No reaction

EXPERIMENTAL

All the melting points were carried out in open capillary tubes and are uncorrected. The Thin Layer Chromatography was performed on precoated silica plates and Iodine vapor is used for visualization. IR spectra were recorded in KBr disc on Shimadzu FT-IR 8300 spectrophotometer. ^{1}HNMR spectra were recorded in DMSO-d6 on a Brucker Advance II- 400 MHz Spectrometer using TMS as an internal standard. Mass spectra were recorded on VG7070H mass spectrometer.

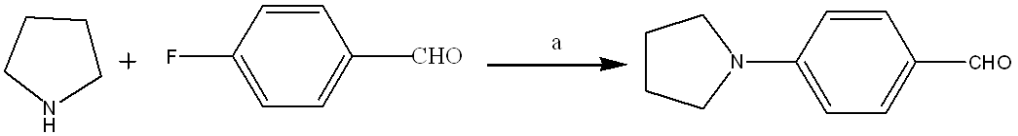
Synthesis of 4-(4-methyl piperazine-l-yl) benzaldehyde[1a]

In 4.0 ml of DMF, 1-methyl piperazine (0.1 gm. 0.001mol) was dissolved. To this solution K_2CO_3 (0.20gm, 0.00015 mol) was added and heated at 80^{0}C with stirring. After 30 min 4-flurobenzaldehyde (0.124 gm, 0.001mol) was added and heating was continued for 6 hours. On completion of reaction, the reaction mixture was cooled and added drop wise to ice-water. The separated product was filtered and dried. The product obtained was pure and used further without any purification.(M.P. 60-62^{0}C)

Table 3: Effect of different Temperature

S. No	Name of Base Used	% Yield obtained 1a	1b	1c
1)	80-90^{0}C	92%	86%	90%
2)	110-120^{0}C	55%	60%	50%
3)	150-160^{0}C	Decomposed*	Decomposed*	Decomposed*

*- no of spots formed on TLC



Spectral Analysis

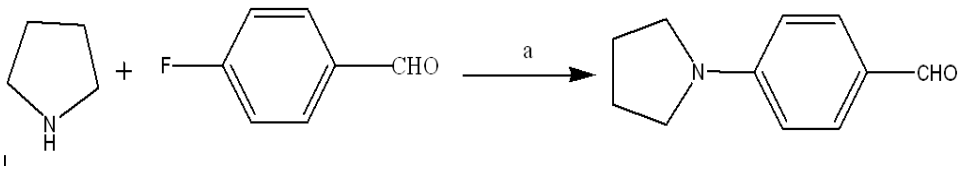
IR:(cm^{-1}): 1686 (C=O); 1561 (C=C).

^{1}HNMR :.(DMSO) δppm : 2.0 (s,3H,CH_3); 2.3 (t,4h,CH_2); 3.3 (t,4H CH_2); 7.2 (dd, 2H, aromatic) 8.1 (dd, 2H, aromatic) ; 9.9 (s, 1H, CHO)

Mass: Mass (m/z): 204

Synthesis of (4-Pyrrolidine-l-yl) benzaldehyde [1b]

In 4.0 ml of DMF of pyrrolidine (0.1 gm, 0.001mol) was dissolved. To this solution K_2CO_3 (0.27 gm, 0.002mol) was added and heated at 80^{0}C with stirring. After 30 min 4- fluorobenzaldehyde (0.174 gm, 0.001 mol) was added and heating was continued for six hours. On completion of reaction, the reaction mixture was cooled and added dropwise to ice water. The separated product was filtered and dried. The product obtained was pure and used further without any purification (M.P- 88^0 C)



Spectral Analysis

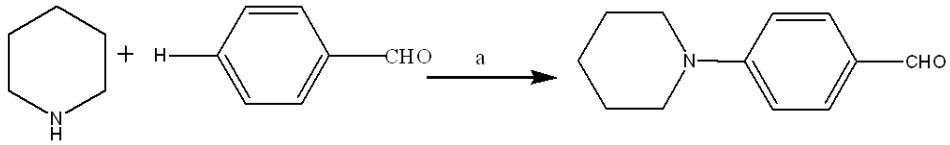
IR:(Cm^{-1}) : 1653 (C=O); 1524 (C=C).

^{1}HNMR :(DMSO) δppm: 2.2 (t,4H, CH_2), 3.2 (t, 4H, CH_2), 6.4 (d, 2H,aromatic) 7.7.(d, 2H,aromatic), 9.8 (s, 1H CHO).

Mass: Mass (m/z) -175(M^+ion)

Synthesis of (4-piperidine-l-yl-) benzaldehyde [1c]

In 4.0ml of DMF of piperidine (0.0gm, 0.001mol) was dissolved. To this solution K_2CO_3 (0.27gm, 0.002mol) was added and heated at 80^{0}C with stirring. After 30 min 4-fluorobenzaldehyde



(0.175 gm, 0.001mol) was added and heating was continued for six hours. On completion of reaction, the reaction mixture was cooled and added drop wise to ice water. The separated product was filtered and dried. The product obtained was pure and used further without any purification. (M.P.-289^{0}C)

Spectral Analysis

IR:(cm^{-1}): 1651 (C=O), 1597 (C=C)

^{1}HNMR (DMSO) δppm: 3.3 (t, 6H,CH_2), 3.5 (t,4H,CH_2),6.9 (d, 2H,aromatic), 7.6 (t,2H, aromatic) ,9.7 (s,1H,CHO).

Mass: Mass (m/z): 189.

CONCLUSION

Our studies showed that K_2CO_3 was the most effective base, while the use of other bases such as $CsCO_3$and Na_2CO_3 was less successful. DMF was found to be the optimal solvent, although the use of DMSO was also effective.

In conclusion, the synthesis of wide variety of Nitrogen containing aldehydes is described with proper choice of base, solvent and temperature conditions. This work is underway to ameliorate difficulties which remain, especially in finding suitable reaction dynamics that efficiently increases the yield.

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