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An efficient N-acylation of 1,2,3,4-tetrahydocarbazoles under solid grind methodology in dry media

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ABSTRACT

N-acylation of 1,2,3,4-tetrahydrocarbazole was carried out by grinding Substituted 1,2,3,4-Tetrahydrocarbazoles(1-3) in presence of anhydrous potassium carbonate with a mortar and pestle. The mixture was swirled with acylating agents and stirred with DMF at 0°C -5°C results faster reactivity and improved the yield of products **(4a-i)**.

KEYWORDS

Substituted 1, 2, 3, 4-tetrahydrocarbazoles;
N-acylation of 1, 2, 3, 4-tetrahydrocarbazoles;
Solid grind methodology;
Acylating agents;
Anhydrous potassium carbonate.

INTRODUCTION

In the recent years much interest has been seen in N-substitution of various type of Hetero-armoatic nucleus, mainly due to their promising pharmacological activities. A more number of N-substituted heterocycles such as microconazole, ketoconazole,genaconozole and bifonazole have gained unique importance due to broad spectrum of pharmacological activity[1]. N-acylation of heterocyclic compounds bearing an acid hydrogen atom to nitrogen like indole is generally accomplished by the treatment of these compounds with base and acylating agents. Since the indolyl anion exhibit ambident behavior as nucleophiles, substitution can occur either at carbon or nitrogen[2]. Generally, nitrogen substitution predominates when the cation is sodium or potassium ion, carbon substitution always predominate with cations like lithium or magnesium which are tightly bound to nitrogen[3]. There are numerous computational procedure like Microwave irradiations[4], and ultrasonic irradiations[5], methodology have also been developed in preparation of N-substituted heterocycles; reported with longer reaction time. The N-Substitution of indole moieties are challenging task, as the indole nitrogen is non-nucleophilic. Though PTC conditions have been reported as more advantages in terms of mildness of conditions, yield and convenience[6], there is an expectancy of shortening the reaction time and free from limitation related to PTC system. In many instance,the N-Substitution of heterocycles had been reported with poorer performance: longer reaction time and unsatisfactory yield[7].

The late 1980's there has been shown an interest in conducting the solid state reactions (ie in absence of solvent, on a solid support with or with out catalyst) which reveals several features like : reduced pollution,low costs, simplicity in process and handling of the reaction. These factors are highly substantial in the industrial practice. Toda and coworkers have reported numerous solid

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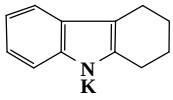
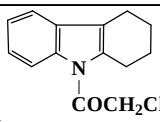
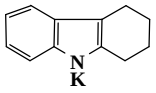
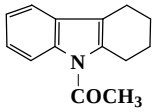
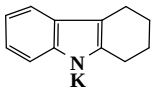
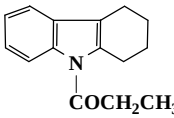
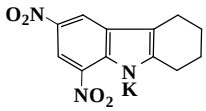
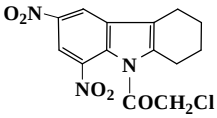
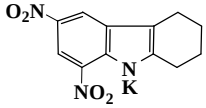
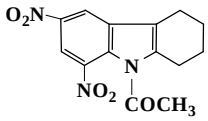
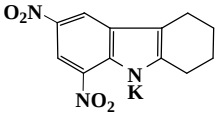
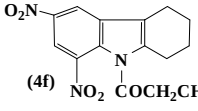
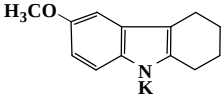
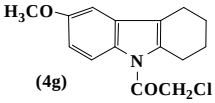
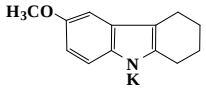
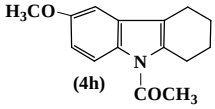
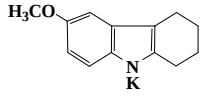
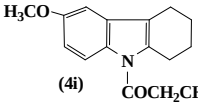
TABLE 1 : N-acylation of 1,2,3,4-tetrahydrocarbazoles under solid grind methodology

Entry	Potassium carbazolyl grind	Product (4a-i)	% yield	Reaction time (min)
1		 4a	98[a] 78[b]	10[c] 480[d]
2		 4b	92[a] 67[b]	18[c] 120[d]
3		 4c	90[a] 62[b]	15[c] 240[d]
4		 4d	90[a] 78[b]	12[c] 240[d]
5		 4e	86[a] 61[b]	10[c] 120[d]
6		 (4f)	85[a] 66[b]	18[c] 180[d]
7		 (4g)	94[a] 82[b]	16[c] 240[d]
8		 (4h)	92[a] 76[b]	10[c] 180[d]
9		 (4i)	86[a] 71[b]	12[c] 300[d]

[a]Percent of the product when the reactions were carried out by employing solid grind of 1,2,3,4 –tetrahydrocarbazoles with anhydrous potassium carbonate, [b]Percent of the product when the reactions were carried out by refluxing the reactant in DMF, [c]Reaction time when the reactions were carried out by employing solid grind of 1,2,3,4 –tetrahydrocarbazoles with anhydrous potassium carbonate, [d]Reaction time when the reactions were carried out by refluxing the reactant in DMF

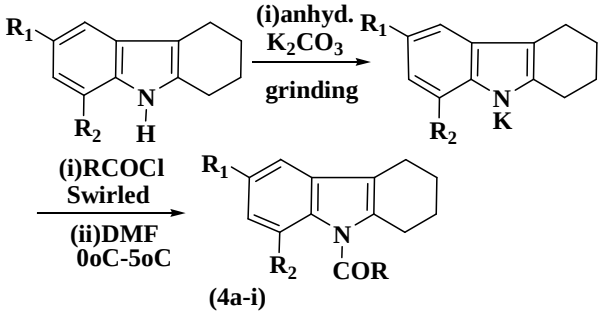
state reactions in order to improve the yield[8]. It was found that the solid grind methodology usually leads to faster and cleaner process. Therefore we decided to explore the use of solid gird methodology for N-acylation of tetrahydocarbazoles to increase the yield . In this present communication, we described that the solid grind methodology for N-acylation of 1,2,3,4-tetrahy drocrabazoles shorten the reaction time and improved the yield of products.Solid state N-acylations occurs more efficiently than does its solution counterpart.

RESULTS AND DISCUSSION

The results in TABLE 1 show that the reactions proceeded with fast reactivity and high yield. Our investigation showed that the reactions proceeded rapidly in solid grid methodology than refluxing the reagents in solvent. Verity of 1,2,3,4-tetrahydrocarbazoles were ground with anhydrous potassium carbonate in mortar and pestle for about 15 minutes and swirled with acylating agents(chloroacetyl chloride, acetyl chloride, Propinoyl Chloride) in round bottom flask since the acylating agents are more toxic and corrosive. Finally, DMF was added in the reaction mixture and stirred at 0-5^{0}C.Upon stirring the liquid reaction mixtures, became pasty and slummy at the different reaction time(shown in TABLE 1).This semisolid residue was washed with excess of water and filtered and dried under anhydrous magnesium sulphate. These compounds were evaluated by spectral analysis.

We also prepared these compounds by applying conventional reflux methodology with 1,2,3,4-tetrahydrocarbazoles and potassium carbonate and acylating agents. The results were tabulated in table -1. In fact, a similar substitution reactions underwent fast and gave more yield by applying solid-grind methodology .

According to common knowledge, the aprotic solvent dissolve the base potassium carbonate chiefly through their bonding to the potassium cation and releases carbonate anion to generate carbazolyl anion which in turn attacks acyl chlorides of acylating agents.However, 1,2,3,4-tetrahydrocarbazoles grind with potassium carbonate in mortar and pestle would produce potassium carbazolyl complex since host-guest complexation are rapid in solid state reactions. In fact,the DMF solvates loosely held potassium ion from potassium carbazolyl complex and increases the nucleophilicity of carbazolyl anion which could makes the attack of acyl chloride of acylating agent easier. It was discovered that generation of potassium carbazolyl an-



1.R_1=R_2=H 2. R_1=R_2=NO_2 3. R_1=OCH_3:R_2=H

4a. R_1=H ; R_2=H ; R=CH_2Cl
4b. R_1=H ; R_2=H ; R=CH_3
4c. R_1=H ; R_2=H ; R=CH_2CH_3
4d. R_1=NO_2 ; R_2=NO_2 ; R=CH_2Cl
4e. R_1=NO_2 ; R_2=NO_2 ; R=CH_3
4f. R_1=NO_2; R_2=NO_2 ; R=CH_2CH_3
4g. R_1=OCH_3 ; R_2=H ; R=CH_2Cl
4h. R_1=OCH_3 ; R_2=H ; R=CH_3
4i. R_1=OCH_3 ; R_2=H ; R=CH_2CH_3

SCHEME 1 : N-acylation of 1,2,3,4-tetrahydrocarbazoles under Solid grind methodology

ion in solid state grind shows remarkable acceleration effect on the acylation of carbazoles. While this process could completed within 20 minutes in DMF. The same reaction was rather tedious when applying conventional methodology. The disappearance of N-H bands at 3410$cm^{-1}$for 1,2,3,4-tetrahydrocarbazoles and appearance of a strong band at 1705cm^{-1} for carbonyl stretching conformed the N-acylation of 1,2,3,4-tetrahydrocarbazoles. The disappearance of N-H peak at 10.8 also confirmed the N-acylation of carbazoles.

EXPERIMENTAL

General Acetyl chloride,Chloroacetyl chloride and Propinoyl Chloride (S.D.Fine Chemical, India)were purchased from commercial sources and used as such. The 1,2,3.4 -tetrahydrocarbazoles 1-3 were prepared by using fischer-indolization methodology[9]. IR (KBr) spectra were recorded on a Perkin Elmer 883IR spectrophotometer. ^{1}H NMR spectra on jeol GSX 400 (400MHz) NMR spectrometer. Mass spectra were recorded using Joel GC mate and MAL-DI-TOF LD. Elemental analysis were performed with Heraeus CHN rapid analyzer.Column chromatography was performed using silicagel(100-200mesh).

General procedure for the preparation of N-(acetyl)1, 2, 3, 4-tetrahydrocarbazoles (4a-i)

A mixture of 1,2,3,4-tetrahydrocarbazole **(1g)** and anhydrous potassium carbonate was ground in mortar. The solid grind was added to the acylating agents (1mmol)in 250ml round bottom flask and swirled for few minutes. Then the mixture was stirred with DMF at 0-5^{0}C for 30-45 minutes. The residue was filtered off, washed with excess of water and crystallized from ethylacetate to give **(4a-i)** (SCHEME 1).

(4a) : N-(chloroacetyl)-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3069,2925,2855,1705,1228 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 4.45(2H,s),8.37-8.42(m, ArH) Anal. Calcd.: C,67.88: H,5.70: N,5.65. Found: C,67.80: H,5.78: N,5.16; MS(EI):m/z: 248.08$[M+H]^+$

(4b) : N-(acetyl)-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3070,2860,2866,1702,1225 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.20 (3H,s) 2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal. Calcd.: C,78.84: H,7.09: N,6.57.:Found: C,78.64: H,7.12: N,6.45; MS(EI):m/z: 214.42 $[M+H]^+$

(4c) : N-(propionyl)-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr):3054, 2942, 2854, 2842, 1708, 1233 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,) 1.07(3H,t), 2.34-2.47(2H,t)2.44(2H,q) 2.59- 2.73(2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal. Calcd.: C,79.26: H,7.54: N,6.16.:Found: C,79.58: H,7.65:N,6.23; MS(EI):m/z: 228.03 $[M+H]^+$

(4d) : N-(chloroacetyl)-6,8-dintro-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3111, 2938, 2845, 1708, 1635, 1519, 1228 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.34-2.47(2H,t) 2.59- 2.73 (2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal.calcd.: C, 49.79: H,3.58: N,12.44.:Found: C,49.76: H,3.32: N,12.20 ; MS(EI):m/z: 338.15 $[M+H]^+$

(4e) : N-(acetyl)-6,8-dinitro-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3102, 2880, 2858, 1710, 1688, 1520, 1225^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal.calcd.: C,55.45: H,4.32: N,13.86.:Found: C,55.34: H,4.12: N,13.56; MS(EI):m/z:304.32 $[M+H]^+$

(4f) : N-(propionyl), 6,8-dinitro-1, 2, 3, 4-tetrahydro

carbazole: IR (KBr):3108, 2935, 2825, 1706, 1618, 1540,1244 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal.calcd.: C,56.78: H,4.76: N,13.24.:Found: C,56.57: H,4.63: N,13.55; MS(EI):m/z: 318.20$[M+H]^+$

(4g) : N-(chloroacetyl)-6,methoxy-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3034,2928,2845, 1712,1216 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62 (4H, m,)2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 8.37-8.42 (m, ArH), 8.58 (NH,1H). Anal. Calcd.: C,64.87: H, 5.81: N,5.04.:Found: C,64.52: H,5.46: N,5.23: MS (EI):m/z: 278.15$[M+H]^+$

(4h) : N-(acetyl)-6,methoxy-1, 2, 3, 4-tetrahydro carbazole: IR (KBr): 3024,2858,2846,1701,1220 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62(4H, m,)2.34-2.47(2H,t) 2.59- 2.73(2H,t,), 8.37-8.42(m, ArH), 8.58 (NH,1H). Anal. Calcd.: C,74.05: H,7.04: N,5.76.: Found: C,74.34: H,7.62: N,5.53.; MS(EI):m/z: 244.52$[M+H]^+$

(3i) : N-(propionyl)-6,methoxy-1, 2, 3, 4-tetrahydrocarbazole: IR (KBr): 3180, 2830,2872, 1704,1253 ^{1}HNMR (400MHz,$CDCl_3$) δ: 1.58-1.62 (4H, m,)2.34-2.47(2H,t) 2.59-2.73(2H,t,), 8.37-8.42 (m, ArH), 8.58 (NH,1H). Anal. Calcd.: C,74.68: H,7.44: N,5.44.:Found: C,74.43: H,7.52: N,5.20. MS (EI):m/z: 258.30$[M+H]^+$

CONCLUSION

In conclusion, N-acylation of 1,2,3,4 tetrahydro carbazoles was carried out in good yields using solid grind methodology. The present procedure is carried out in a shorter reaction time and cleaner process.

ACKNOWLEDGMENTS

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