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Improved Synthesis of 1,2,3,4-tetrahydrocarbazoles under ultrasonic irradiation

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ABSTRACT

Synthesis of 1,2,3,4-tetrahydrocarbazoles from cyclohexanone with a series of phenylhydrazines is carried out in excellent yields with 1:3 glacial acetic acid :trifluoroacetic acid as catalyst via Fischer –indolization reactions under ultrasonic irradiation method. © 2008 Trade Science Inc. - INDIA

KEYWORDS

Fischer –indolization;
1,2,3,4-Tetrahydrocarbazoles;
Glacial acetic acid;
Trifluoroacetic acid (1;3);
Ultrasonic irradiations.

1. INTRODUCTION

Fischer indole synthesis by thermal cyclization using glacial acetic acid is remains the most commonly employed method for the preparation of indoles^[1]. Some other reagents such as p- toluene sulphonic acid and phosphorous trichloride have also been used to catalyze fisher indolization reactions, sometimes even at or below room temperature^[2]. In acidic conditions, the intermediate aryl hydrazones underwent rearrangement to produce an ene-hydrazine^[3]. The intramolecular nucleophilic attack on β -nitrogen of this ene-hydrazine eliminates the ammonia which affords the Indole product^[4]. The reaction does however occur more rapidly in the presence of strong acid and this is interpreted as protonation of β -nitrogen, facilitating the electro cyclic step^[5]. Fischer cyclizations are required higher temperature :

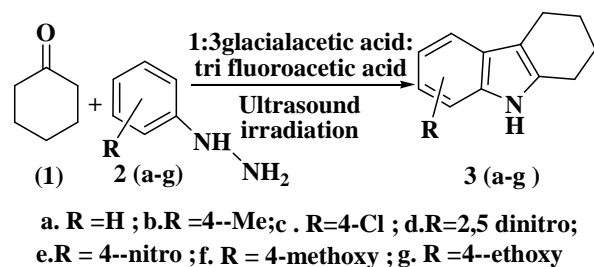
However trifluoroacetic acid allows thermal cycliza-

tion of ene-hydrazine at temperatures as low as possible^[6].

Recently, Chloroaluminate ionic liquid mediated microwave irradiation has been shown to be an efficient method for the fisher indolization^[7]. Ultrasound irradiation has been used more frequently in organic synthesis in recent years^[8]. Compared with traditional method, this method is more convenient and easily controlled. A great number of organic reactions can be carried in higher yields with shorter reaction time under ultrasound irradiation. In view of the advantages of ultrasonic irradiation for synthetic utility, we have applied the ultrasonic irradiations for the synthesis of 1,2,3,4-tetrahydro carbazoles.

2. RESULTS AND DISCUSSION

Most of the products described herein were prepared by using ultrasonic irradiation method. As shown



in TABLE 1 several phenyl hydrazines underwent clean and remarkably fast indolization with cyclohexanone under ultrasonic irradiation at 45-50°C. Variety of easily accessible enolizable ketones is commercially available for Fischer indolization. In contrast, only a limited number of aryl hydrazines are in market. Generally, aryl hydrazines are prepared by the reduction of aryl diazonium salts, which are in turn, obtained from aniline starting materials^[9].

The dramatic improvement observed is with regard to reaction time and also in the yield of the products. Many of the reactions are completed, over a period of 15-120 minutes. Steven et al have been reported that 1 : 1 glacial acetic acid-trifluoroacetic acid, as an effective catalysis for cyclization of hydrazones at 50°C on a solid support resin^[10]. However hydrazones were not isolated during the cyclization, they implied that more acidic conditions are required for better indolization.

We reasoned that a similar tactic might provide a convergent synthetic strategy for the Fischer indolization-preparation of 1,2,3,4- tetrahydrocarbazoles. And also, we attempted the indolization, catalysis with 1: 1 glacial acetic acid and trifluoroacetic acid under thermal conditions at 50°C, but did not produce any remarkable yield of carbazole compounds. But, there was a significant improvement in the production of yield of 1,2,3,4-tetrahydrocarbazoles under ultrasonic irradiations at 45-50°C. The effect of reaction conditions on the indolizations of cyclohexanone with several phenyl hydrazines under ultrasound irradiation was summarized in TABLE 1. When the molar ratio of the glacial acetic acid and trifluoroacetic acid was 1:2 and 1:3, the yields of **3a** increased to 88%-98% respectively. It was then determined that 1:3 glacial acetic acid-trifluoroacetic acid is the optimal indolization conditions for ultrasonic irradiation method.

The electron rich hydrazine, 4-methyl phenylhydrazine (TABLE 1, 3b), underwent fast reactivity in the

TABLE 1 : Synthesis of 1,2,3,4 tetrahydrocarbazoles under ultrasound irradiation

Entry	Hydrazine HCl	Temp. (°C)	Time (minutes)	%1,2,3,4-tetrahydro carbazoles	Melting point (°C)
(3a)	Phenyl	50	120 ^a	77	118
		50	60 ^b	78	
		50	46 ^c	88	
		50	40 ^d	88	
		50	14 ^e	98	
(3b)	4-methyl phenyl	60	40 ^d	88	122
		50	18 ^e	98	
(3c)	4-chloro phenyl	70	120 ^d	79	142
		45	16 ^e	98	
(3d)	2,5-dinitro phenyl	70	240 ^d	80	150
		70	120 ^e	88	
(3e)	4-nitro phenyl	75	-	No product	-
		75	-	No product	-
(3f)	4-methoxy phenyl	60	60 ^d	82	98
		50	35 ^e	96	
(3g)	4-ethoxy phenyl	70	60 ^d	80	87
		50	20 ^e	92	

^aIndolization under thermal conditions using glacial acetic acid as catalyst; ^bIndolization under thermal condition using 1:1 glacial acetic acid: trifluoroacetic acid; ^cIndolization under thermal condition using 1:2 glacial acetic acid: trifluoroacetic acid; ^dIndolization under thermal condition using 1: 3 glacial acetic acid: trifluoroacetic acid; ^eIndolization under ultrasonic irradiation in 1: 3 glacial acetic acid: trifluoroacetic acid

optimal conditions of the catalysis under ultrasonic irradiations.. However the electron deficient hydrazine, 4-nitro phenylhydrazine did not proceed to completion of the reaction under this procedure (3e, TABLE 1). But other electron deficient hydrazines, 4-methoxy phenylhydrazine and 4-ethoxy phenylhydrazine (TABLE 1, 3f, 3g and 3h) were shown compatible rate of reaction with electron rich hydrazine. It may be that the electron deficient hydrazines are prone to N-N bond cleavage of hydrazone, which could accelerate by ultrasound irradiation.

In order to verify the effect of ultrasound irradiation, in absence of ultrasound, we have performed the reaction of cyclohexanone with phenylhydrazines by refluxing at various temperatures around 55°C-70°C and the yield of the products were obtained in 72%-88%. It was clear that the ultrasound could accelerate the reaction of fisher indolization.

We also monitored the effect of different irradiation frequencies on the reaction. When the frequency was

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raising from 25 KHz to 59KHz, the yield of the 1,2,3,4 tetrahydrocarbazole (**3a**) was get reduced from 98%-94%. It seems that the lower frequency of ultrasound irradiation can improve the yield of carbazoles. It is possible that as the ultrasonic frequency is increased, the production of cavitations in liquids decreases^[11].

3. EXPERIMENTAL SECTION

General

Melting points were measured in open capillaries are uncorrected. ¹H NMR spectra were recorded on GSX Jeol spectrometer using TMS as internal standard. Microanalyses were done on a Perkin -Elumer Model 240 CHN analyzer. Sonication was performed in a shanghai Branson -CQX ultrasonic cleaner with a frequency of 25 KHz and a nominal power 500W. The reaction flask was located in the maximum energy area in the cleaner and the addition or removal of water was used to control the temperature of the water bath.

General procedure for the syntheses of 1,2,3,4 tetrahydrocarbazoles

A mixture of 1:3 glacial acetic acid: trifluoroacetic acid (1.2 ml) and Cyclohexanone (**1**) (1.25mmole) in 50 ml ethanol was added with Phenyl hydrazines **2a-g** (2.5mmole) in drop wise into the 50ml Pyrex flax. Then, the mixture was irradiated in the water bath of an ultrasonic cleaner at the temperature for the period as indicated in TABLE 1. The reaction mixture was poured into crushed ice. The precipitate was separated by filtration, washed with water and recrystallized from ethanol to obtain the 1,2,3,4 tetrahydrocarbazoles. The structure of the compounds was elucidated by comparing their melting points with literature and the spectra data of ¹H NMR and ¹³C NMR

3a: 1, 2, 3, 4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) 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). ¹³C NMR (75MHZ, CDCl₃) δ: 25.50, 26.34, 29.50, 108.30, 115.61, 118.82, 120.1, 122.60, 127.60, 137.00, Anal.calcd.: C, 84.17: H, 7.65: N, 8.18.: Found: C, 84.20: H, 7.56 : N, 8.16:

3b: 6- methyl-1, 2, 3, 4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) δ: 1.60-1.64(4H,

m), 2.01(bS) 2.57- 2.72(4H, t), 8.38-8.44(m, ArH), 8.56 (NH, 1H). ¹³C NMR (75MHZ, CDCl₃) δ: 24.49, 24.70, 25.91, 26.43, 29.58, 108.35, 115.68, 118.86, 135.62, 137.10, 142.05, 147.22. Anal.calcd.: C, 84.12: H, 8.16 : N, 7.56.: Found: C, 84.20: H, 8.06 : N, 7.52: O

3c: 6-Chloro-1, 2, 3, 4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) δ: 1.42-1.50(4H, m), 2.51- 2.63(4H, t), 7.02, (m, ArH), 8.24-8.32(m, ArH), 8.43 (NH, 1H). ¹³C NMR (75MHZ, CDCl₃) δ: 23.51, 25.65, 25.30, 29.55, 107.20, 114.51, 118.70, 132.52, 138.03, 145.05, 146.53. Anal.calcd.: C, 70.07: H, 5.88 : N, 16.81.: Found: C, 70.57: H, 5.68 : N, 16.72

3d: 5, 8- dinitro-1, 2, 3, 4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) δ: 1.58-1.62(4H, m), 2.59- 2.73(4H, t), 8.37-8.42(m, ArH), 8.58 (NH, 1H). ¹³C NMR (75MHZ, CDCl₃) δ: 24.50, 25.93, 26.34, 29.50, 108.30, 115.61, 118.82, 135.60, 137.00, 142.00, 147.20. Anal.calcd.: C, 55.17: H, 4.24 : N, 16.09.: O, 24.50. Found: C, 55.20: H, 4.26 : N, 16.12: O, 24.52

3f: 6-Methoxy -1,2,3,4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) δ: 1.56-1.60 (4H, m), 2.70-2.74(4H, t), 3.73(s, -OCH₃ 3H), 7.56-7.65(m, ArH), 8.32 (NH, 1H). ¹³C NMR (75MHZ, CDCl₃) δ: 25.20, 26.73, 35.34, 35.71, 56.00, 96.61, 107.22, 113.24, 113.24, 121.58, 123.89, 137.20, 153.18. Anal.calcd.: C, 77.61: H, 7.46 : N, 6.96. Found: C, 77.59: H, 7.42 : N, 6.89.

3g. 6-ethoxy-1, 2, 3, 4-tetrahydrocarbazole

¹H NMR (400MHz, CDCl₃) δ: 1.33(3H, t), 1.58-1.62(4H, m), 2.59- 2.73(4H, t), 3.88(2H, q), 8.37-8.42(m, ArH), 8.58 (NH, 1H). ¹³C NMR (75MHZ, CDCl₃) δ: 14.50, 24.50, 25.93, 26.34, 29.50, 64.34, 108.30, 115.61, 118.82, 135.60, 137.00, 142.00, 147.20. 152.08 Anal.calcd.: C, 78.10: H, 7.96: N, 6.51.: O, 7.43. Found: C, 78.16: H, 7.82: N, 6.41.: O, 7.53.

CONCLUSION

In conclusion, synthesis of 1,2,3,4 tetrahydro carbazoles was carried out in good yields, using Fischer indolization catalysis of glacial acetic acid and

trifluoroacetic acid under ultrasound irradiations. The present procedure is carried out in a shorter reaction time and obtained a higher yield.

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