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(REVIEW ARTICLE)

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# A review on synthesis methods of tricyclic 1,2,3,4-tetrahydrocarbazoles

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## Abstract

In this review article, we discussed old to new synthetic methods used for the preparation of 1,2,3,4-Tetrahydrocarbazole (THCz) based on reported literature. Around the worldwide, various researchers energetically reported new synthetic methods for tetrahydrocarbazoles preparation using conventional method or microwave method or use of catalyst. This review will be helpful to synthetic and medicinal chemist to find selective method for the preparation of 1,2,3,4-Tetrahydrocarbazoles with good percentage yield and less time. This review will also useful to medicinal chemist to design new biologically active tetrahydrocarbazoles based on reported synthetic methods.

**Keywords:** Tetrahydrocarbazole (THcz); Synthesis; Fischer Indole; Microwave (MW)

## 1. Introduction

1,2,3,4-Tetrahydrocarbazole [THCz] is a tricyclic aromatic structure consisting of a five membered pyrrole ring fused with one side benzene ring and other side cyclohexane ring respectively [1-3]. Tetrahydrocarbazole (THCz) structure is majorly present in natural products and biologically active compounds [4-7] (Fig. 1). THCz have received lot of attention in medicinal chemistry and possess a wide variety of potential pharmacological activities such as anti-Alzheimer [8], antimicrobial [9], hypoglycemic [10], antifungal [11], anticancer [12], antipsychotic activity [13], and antiemetic [14], anti-inflammatory [15] etc. (Fig. 1).

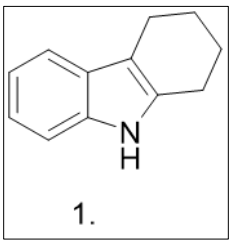


**Figure 1** Structure of 1,2,3,4-Tetrahydrocarbazole (1)

A lot of strategy available for the preparation of 1,2,3,4-tetrahydrocarabzole scaffold in literature. However, Fischer indole synthesis approach is most common synthetic method used for the preparation of tetrahydrocarbazole scaffold and also play important role in preparation of various natural products [5, 16-18]. Various research groups synthesized tetrahydrocarbazoles based on Fischer indole method using starting material phenyl hydrazine and cyclohexanone

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using conventional, microwave and catalyst approach. In this review article, we covered synthetic methods of 1,2,3,4-tetrahydrocarbazoles based on conventional or microwave or catalyst based on reported review literature. In 2020, Ajit Nangare et al. and co-workers published the review article on topic synthetic derivatives of aromatic carbazole [19]. TY Chaudhari et al. published in detail on topic various synthetic methods to the preparation of tetrahydrocarbazoles [5]. This review will give researchers to idea in short way to find out the preparation of 1,2,3,4-tetrahydrocarbazoles from conventional approach or microwave method or use of catalyst.

## 2. Synthetic methods to prepare substituted or unsubstituted tricyclic 1,2,3,4-tetrahydrocarbazoles

### 2.1. Borsche-Drechsel cyclization reaction for the synthesis of 1,2,3,4-tetrahydrocarbazole.

The acid-catalyzed rearrangement of cyclohexanone phenylhydrazone (2) gives 1,2,3,4-tetrahydrocarbazole (1) (Scheme 1) [20-21].

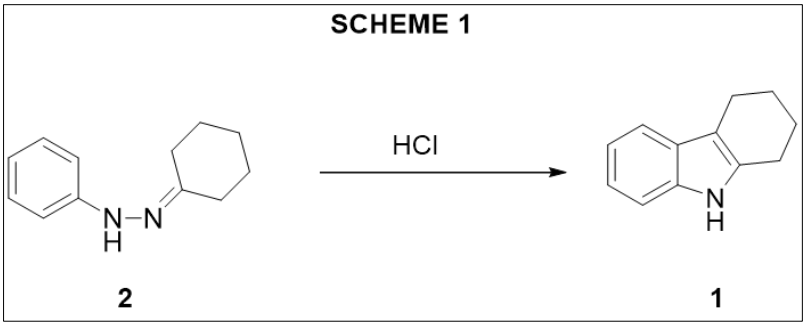


**Figure 2** Synthesis of 1,2,3,4-tetrahydrocarbazole (1)

### 2.2. Fischer-Borsche reaction for the synthesis of substituted 1,2,3,4-tetrahydrocarbazole.

The method involves the condensation reaction of 4-methoxy phenyl hydrazine (3) with substituted cyclohexanone (4) with to form arylhydrazone (5) based on Fischer indole synthesis method which further undergoes sigmatropic rearrangement in the presence of acetic acid/HCl gave substituted 1,2,3,4-tetrahydrocarbazole (6) [22, 23] (Scheme 2).

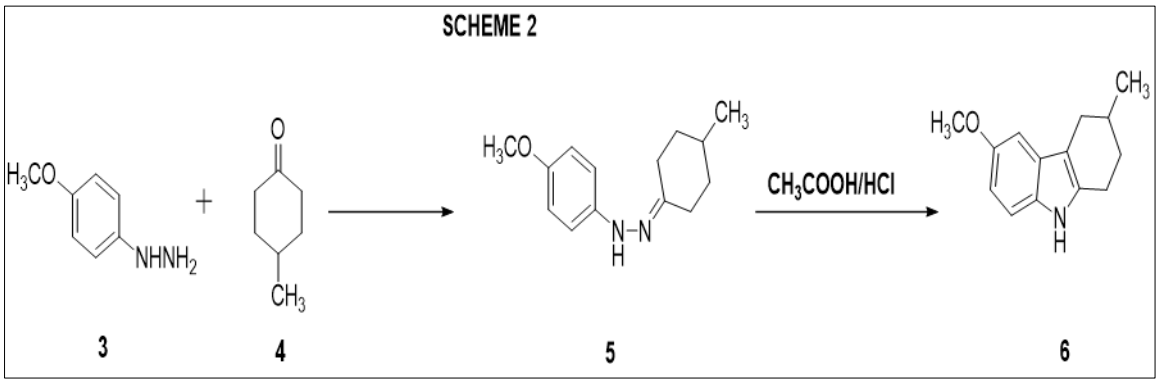


**Figure 3** Synthesis of substituted 1,2,3,4-tetrahydrocarbazole (6)

### 2.3. CU Rogers et al. reported aqueous alcohol- mineral acid method for the preparation of 1,2,3,4-tetrahydrocarbazole

A mixture of 108 g. phenylhydrazine (7) and 1.5 moles of hydrochloric acid was stirred and refluxed while 98 g. of cyclohexanone (8) was added during one hour gave 1,2,3,4-tetrahydrocarbazole (1). The yield of the reaction was found 95 %. [24] (Scheme 3).

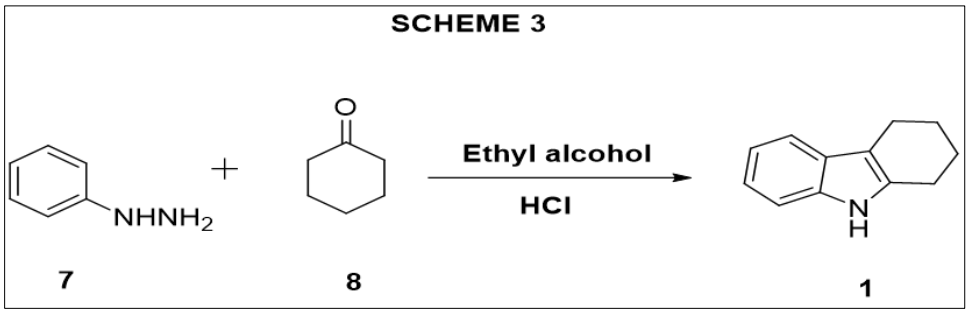


**Figure 4** Synthesis of 1,2,3,4-tetrahydrocarbazole (1)

### 2.4. A Loffler and D. Ginsburg prepared 1,2,3,4-tetrahydrocarbazole from thermal cyclization of the oxime of 2-phenylcyclohexanone.

Heating the starting material oxime of 2-phenylcyclohexanone (9) in aqueous ethanol give 1,2,3,4-tetrahydrocarbazole (1) [25, 26].

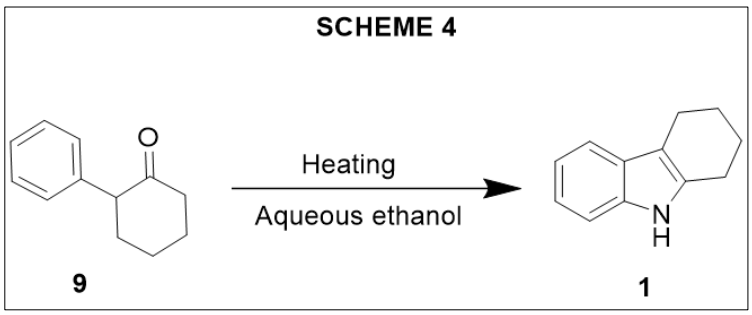


**Figure 5** Synthesis of 1,2,3,4-tetrahydrocarbazole (1)

### 2.5. N. A. Jones and M. L. Tomlins prepared some 1,2,3,4-tetrahydrocarbazoles from various aromatic amines with 2-hydroxycyclohexanone

Condensation reaction of unsubstituted or substituted aromatic amines (10 a-e) with 2-hydroxycyclohexanone (11) with a trace of hydrochloric acid and heated in an oil-bath give some 1,2,3,4-tetrahydrocarbazoles (1, 12-15) (Scheme 5). The yield of the product (1, 12-15) was found 37-81% depends on position and also electron withdrawing or donating group substitution on aromatic amine (10 a-e) [27]

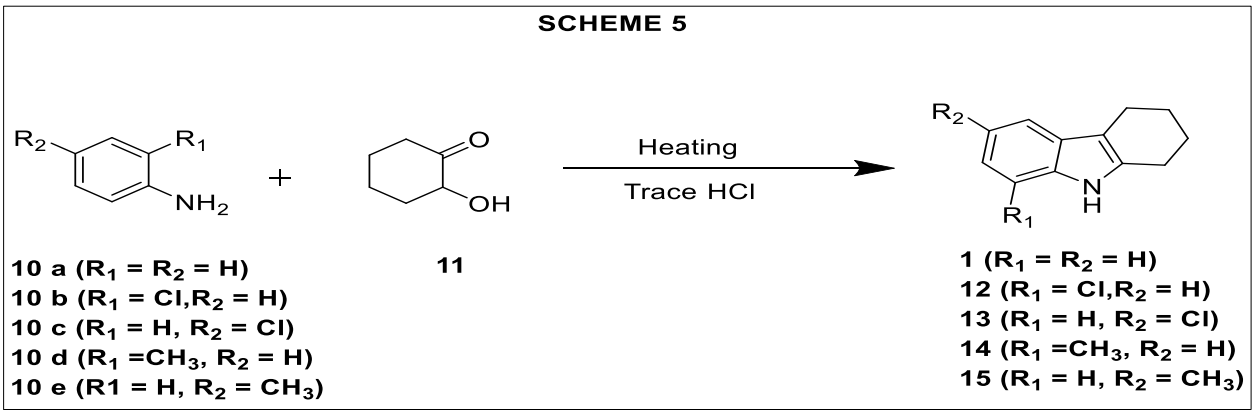


**Figure 6** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (1, 12-15)

### 2.6. K. D. Berlin and co-workers synthesized some 1,2,3,4-Tetrahydrocarbazoles

Reaction of unsubstituted or substituted phenyl hydrazine (7 or 16) with substituted cyclohexane (17-19) gave substituted `1,2,3,4-tetrahydrocarbazoles (20-23) [27] (Scheme 6). The yield of the product (20-23) was found 28-89%.

The yield of 1,2,3,4-tetrahydrocarbazoles (20-23) depends on substitution group on phenyl hydrazine and cyclohexanone ring respectively [28].

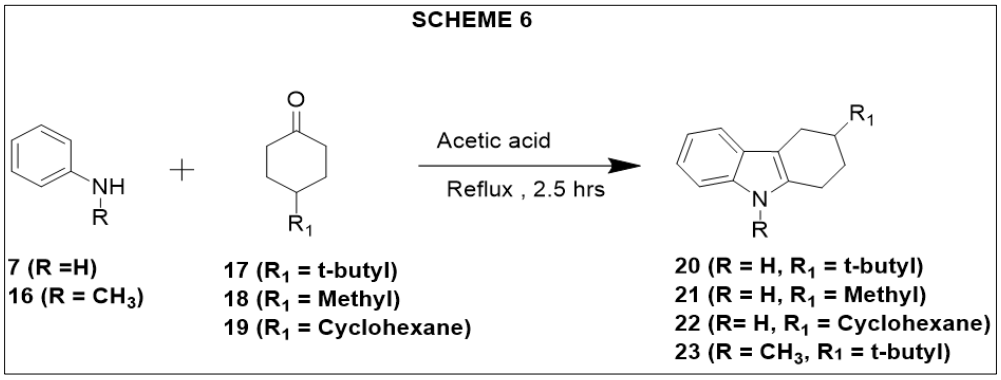


**Figure 7** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (20-23)

### 2.7. Palladium-catalyzed synthesis of 1,2,3,4-tetrahydrocarbazoles

Heating the reaction mixture of 2-bromo-4,6·dimethylaniline 24a-c and cyclohexane-l,3-dione 25a or dimedone 25 b gave compounds bromoenaminone 26 a-f. Further reaction of compound 26 a-f with tetrakis[tripbenyIphosphine] palladium [Pd($PPh_3$)$_4$] (2 mol%) in hexamethylphosphoramide (HMPA) in the presence of sodium bicarbonate gave the corresponding substituted tetrahydrocarbazoles 27 a-f (Scheme 7). [29]. The yield of the reaction was found 72-77 %.

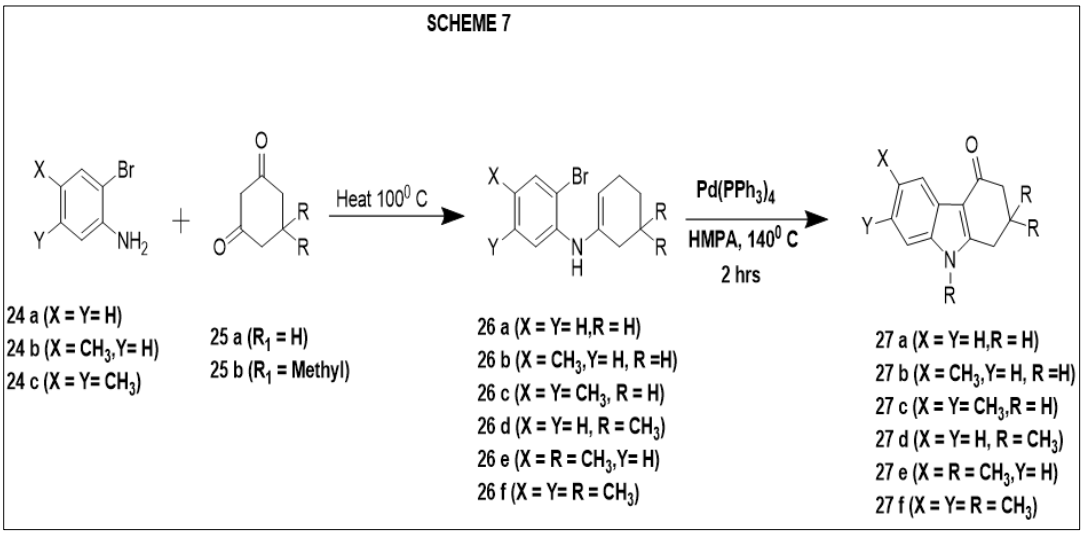


**Figure 8** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (27 a-f)

### 2.8. Regiocontrolled Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles

The two-step procedure involved the preparation of substituted 1,2,3,4-tetrahydrocarbazoles (31 a-e). First step involves first the regiospecific arylation of silyl enol ethers (28 a-e) with o-nitrophenylphenyliodonium fluoride (29) gave (30 a-e). Reduction of the nitro group on the aromatic ring in compound 30 a-e in the presence of $TiCl_3$ and further spontaneous condensation of the aniline with the keto group gave substituted 1,2,3,4-tetrahydrocarbazoles (31 a-e) (Scheme 8) [30]. The yield of the product (31 a-e) was found 60-88 %. The yield was low found (60%) in product 31 e due to methoxy substitution in silyl enol ethers 31 e.

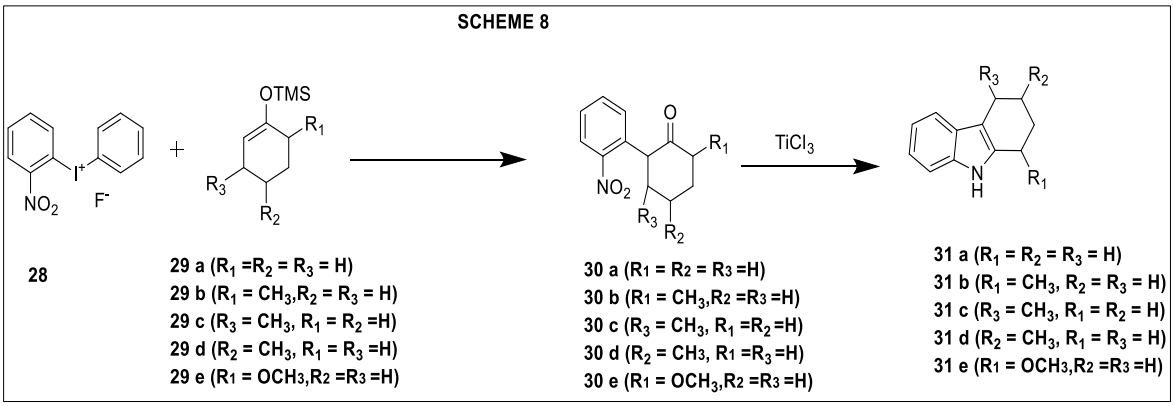


**Figure 9** Synthesis of substituted 1,2,3,4-tetrahydrocarbazole (31 a-e)

### 2.9. Synthesis of 1,2,3,4-tetrahydrocarbazole using various zeolite catalysts

D. Bhattacharya et al. and co-workers prepared 1,2,3,4-tetrahydrocarbazoles (33 a-d) using various zeolites catalyst like H-ZSM-12, H-beta, H-mordenite, H-Y, H-ZSM-22, H-EU-1, H-ZSM-5 with various arylhydrazines such as phenylhydrazine (32 a,), o-tolylhydrazine (32 b), p-tolylhydrazine (32 c) and 1,1-diphenylhydrazine (32 d) with cyclohexanone (8) in acetic acid based on Fisher's indole method (Scheme 9) [31]. The yield of the reaction was found 35-69 %.

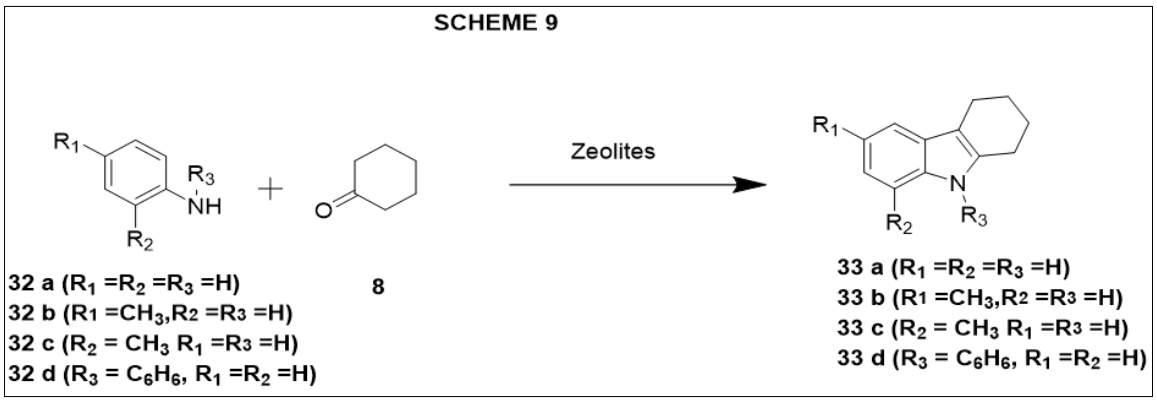


**Figure 10** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (33 a-d)

## 3. MW assisted synthesis of 1,2,3,4-tetrahydrocarbazoles using catalyst K-10 montmorillonite clay

A. Dhakshinamoorthy et al. reported 1,2,3,4-tetrahydrocarbazole (1) preparation from reaction of phenylhydrazine (7) and cyclohexanone (8) in the presence of solid acid catalyst (namely K-10 montmorillonite clay) was microwave irradiated at 600 W for 3 minutes in methanol medium [32] (Scheme 10). The yield of the 1,2,3,4-tetrahydrocarbazole (1) was found in conventional method 94 % and microwave method (96%) respectively.

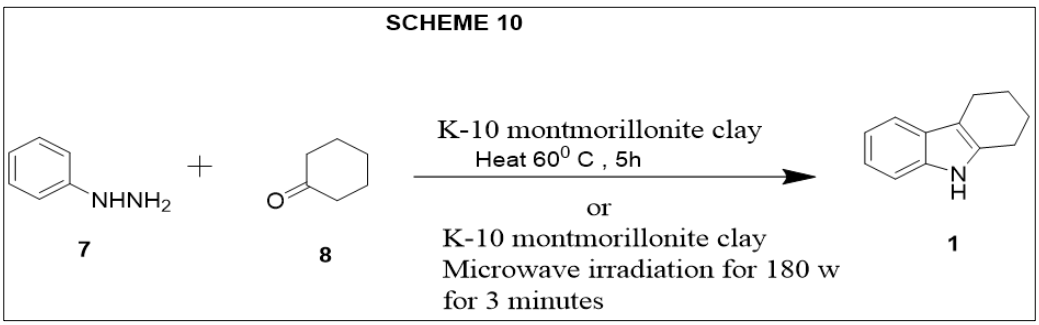


**Figure 11** Synthesis of 1,2,3,4-tetrahydrocarbazole (1)

### 3.1. Vera Barbieri and Maria Grazia Ferlin reported MW assisted synthesis of substituted 1,2,3,4-tetrahydrocarbazoles

Reaction of 2-methoxy-4-nitro-phenylhydrazine with cyclohexanone in the presence of acetic acid was MW irradiation at 100 W at the temperature $140^0$ C give 6-nitro, 8-methoxy 1,2,3,4-tetrahydrocarbazole **35** (**Scheme 11**) [33]. The yield of the product (**35**) was found 80 %.

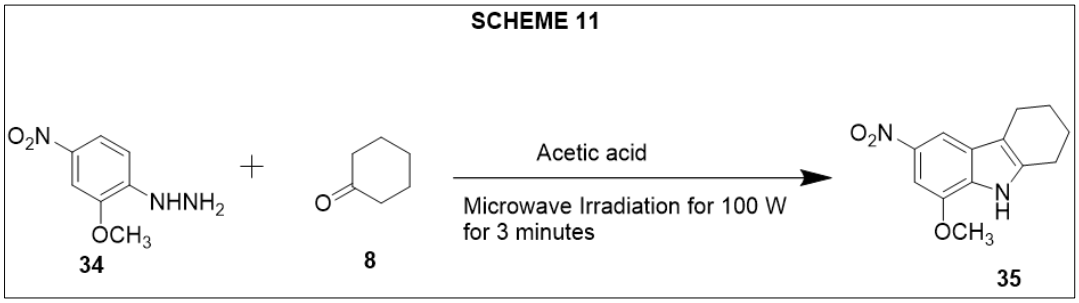


**Figure 12** Synthesis of substituted 1,2,3,4-tetrahydrocarbazole (35)

### 3.2. MW assisted one pot synthesis of 1,2,3,4-Tetrahydrocarbazoles

Jing Chen et al. and co-workers reported synthesized 1,2,3,4-tetrahydrocarbazoles (38 a-i) from reaction of starting material 2-bromocyclohexanones (37) and substituted anilines (36 a-i) in molar ratio 1: 3 using different solvents, such as toluene, 1,4-dioxane, ethanol, tert-butanol, and 2-ethoxyethanol under microwave-irradiation conditions also different time [34]. The yield (84%) was found best for 10 min time using a MW of 325 W in 2-ethoxyethanol solvent (Scheme 12).

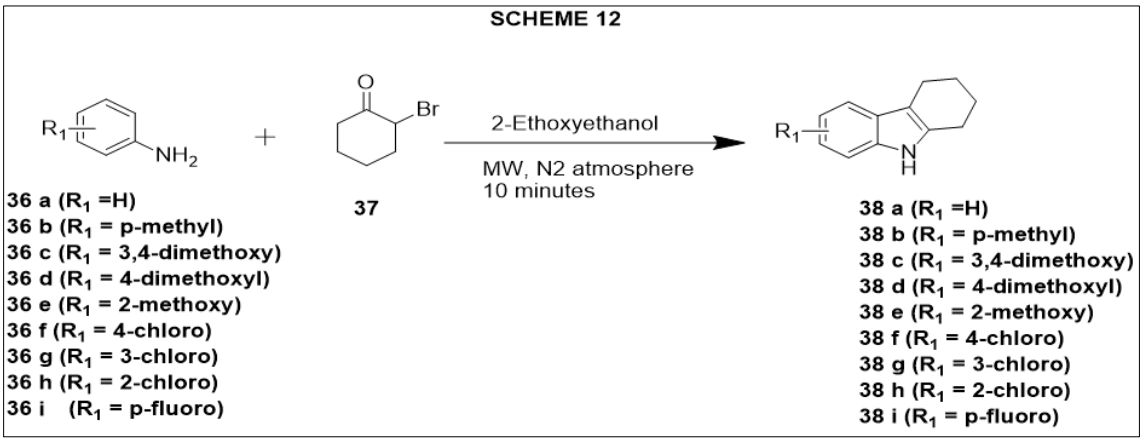


**Figure 13** Synthesis of substituted 1,2,3,4-tetrahydrocarbazole (38 a-i)

### 3.3. Synthesis of 1,2,3,4-tetrahydrocarbazoles from 2-(2-nitrophenyl)-2-cyclohexene-1-ones

Tricia L. Scott et al. and coworkers reported synthesis of 1,2,3,4-tetrahydrocarbazoles (1, 1a-1e) from reduction of 2-(2-nitrophenyl)-2-cyclohexene-1-ones (39 a-f) using palladium on carbon under 1 atm of hydrogen gas at ambient temperature [35] (Scheme 13). The yield of the reaction was found 62-94 %.

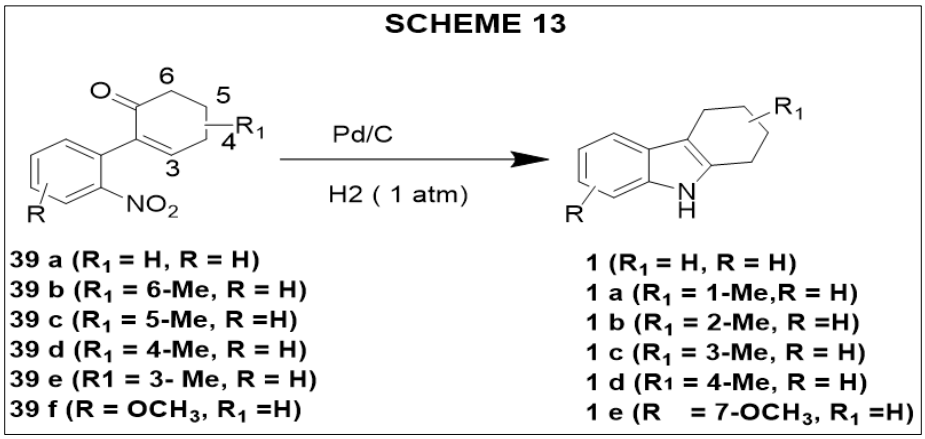


**Figure 14** Synthesis of substituted 1,2,3,4-tetrahydrocarbazole (1-1e)

### 3.4. Synthesis of substituted 1,2,3,4-tetrahydrocarabzoes using Fischer idolization method

T. Surendiran and co-workers reported the synthesized 1,2,3,4-tetrahydrocarabzoes (41) from the reaction of substituted phenylhydrazine (40) with cyclohexanone (8), with catalytic amount of glacial acetic acid and trifluoroacetic acid (1: 3) was under ultrasound irradiations using Fischer idolization method [36] (Scheme 14). The yield of the reaction was found 77-92 %

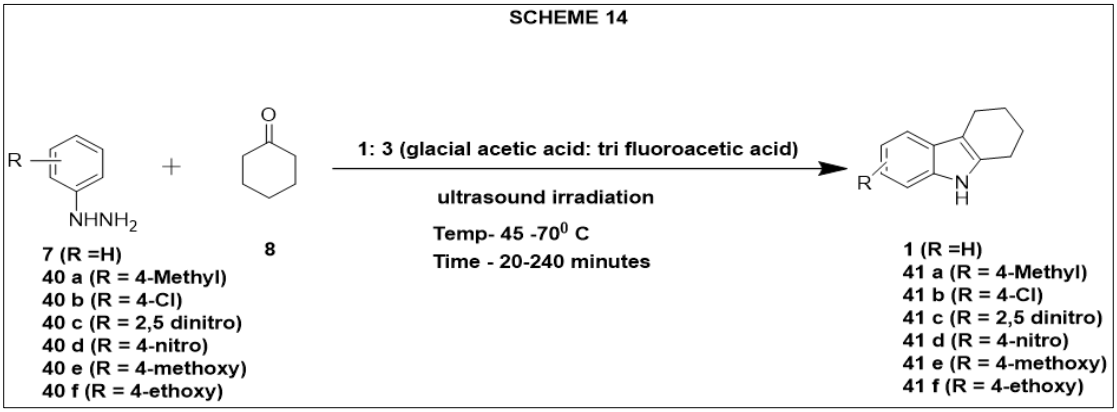


**Figure 15** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (1, 41 a-f)

### 3.5. Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles using ceric ammonium nitrate (CAN)

Reaction of substituted phenylhydrazine hydrochlorides (7, 42 a-e) with cyclohexanone (8) using ceric ammonium nitrate (CAN) via known Fischer indole synthesis method [37]. The yield of the reaction was found 85-95 %. (1, 43 a-e) (Scheme 15).

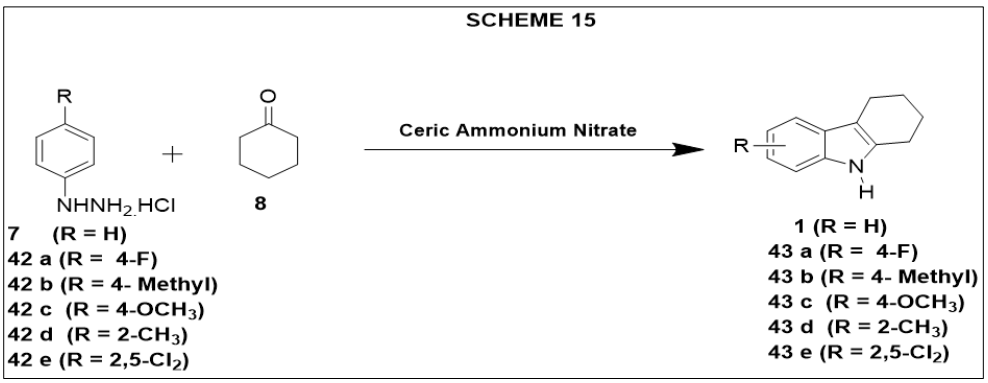


**Figure 16** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (1, 43 a-c)

### 3.6. MW assisted Fischer Indole Synthesis of 1,2,3,4-tetrahydrocarbazoles

Reaction of substituted phenylhydrazine (7, 44 a, 44 b) cyclohexanone (8) and zinc chloride were MW at 600 W for 3 min, give 1,2,3,4-tetrahydrocarbazole with 76 % yield. However, when zinc chloride was replaced with p-toluene sulfonic acid (p-TSA), the reaction yield found excellent 91-93% of 1, 2, 3, 4-tetrahydrocarbazoles (1, 45 a and 45 b) [38]

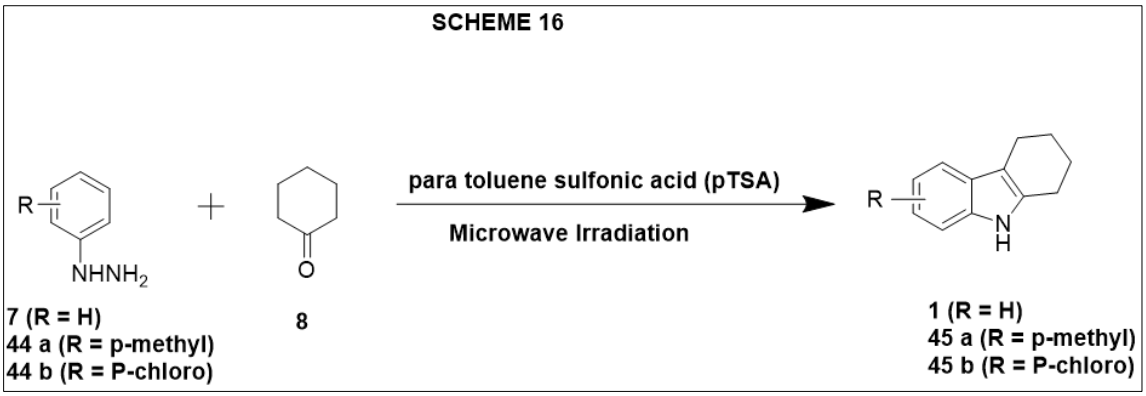


**Figure 17** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (1, 45 a-b)

### 3.7. N. Campbell and E. B. McCall prepared some 1,2,3,4-Tetrahydrocarbazoles from 2-Chlorocyclohexenone

Condensation reaction of 2-chlorocycohexanone (46) with aromatic primary or secondary amines (47 a-g) gives substituted 1,2,3,4-tetrahydrocarbazoles (48 a-g) [39] (48 a-g) (Scheme 17). However, aromatic primary or secondary amines contains at least one unsubstituted ortho-position. The yields of products were found of 30-60 %. Reaction was found less effective when 2-Chlorocycloohexenone was replaced with 2-bromocycloohexenone

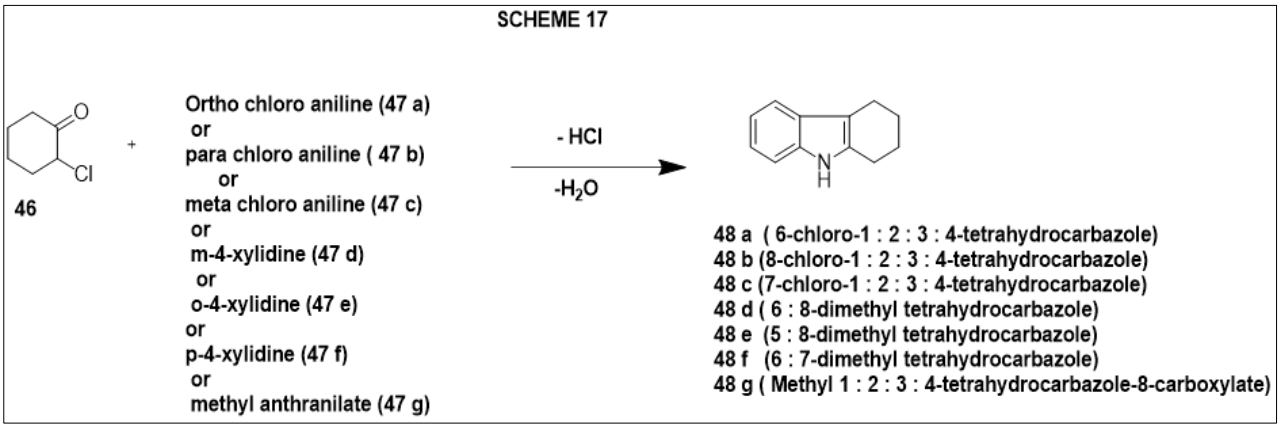


**Figure 18** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (48 a-g)

### 3.8. Synthesis of substituted 1,2,3,4-Tetrahydrocarbazoles by Petasis reaction

Reaction of substituted phenyl hydrazine (49) with substituted aryl boronic acid (50) and glyoxylic acid (51) in dichloromethane solvent was stirred at room temperature gave substituted N-Boc phenyl hydrazine derivatives (52) which further reacted cyclohexanone (8) afforded substituted 1,2,3,4-Tetrahydrocarbazoles compounds (53). [40] (Scheme 19)

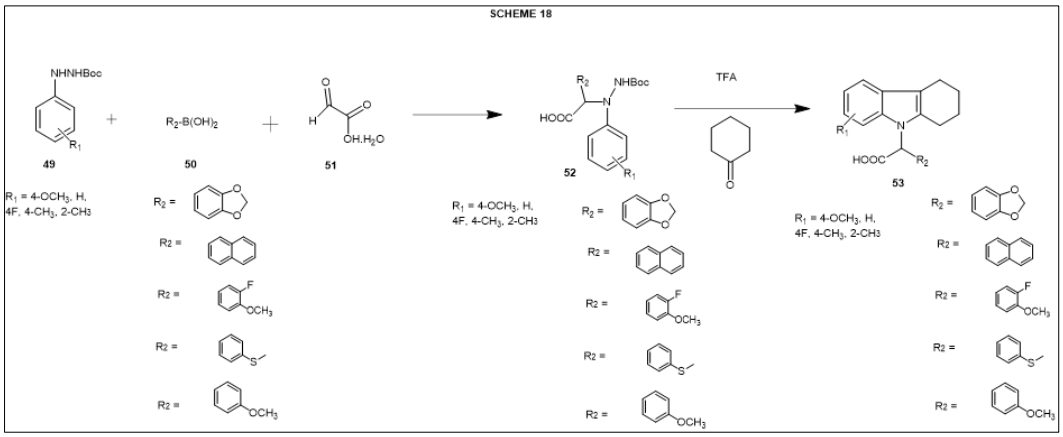


**Figure 19** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (53)

### 3.9. Synthesis of substituted 1,2,3,4,9-tetrahydro-1H-carbazoles and 2,3,4,9-tetrahydro-1H-carbazoles using bmim (BF4) ionic liquid

Reaction of substituted phenylhydrazine (54) and substituted cyclohexanone (55), using a 1-butyl-3-methylimidazolium tetrafluoroborate [bmim (BF4)] ionic liquid afforded 1,2,3,4,9-tetrahydro-1H-carbazole (56 a) and substituted 2,3,4,9-tetrahydro-1H-carbazoles 56 b-j (Scheme 19) [41]. The yield of the reaction was found 29-49 %.

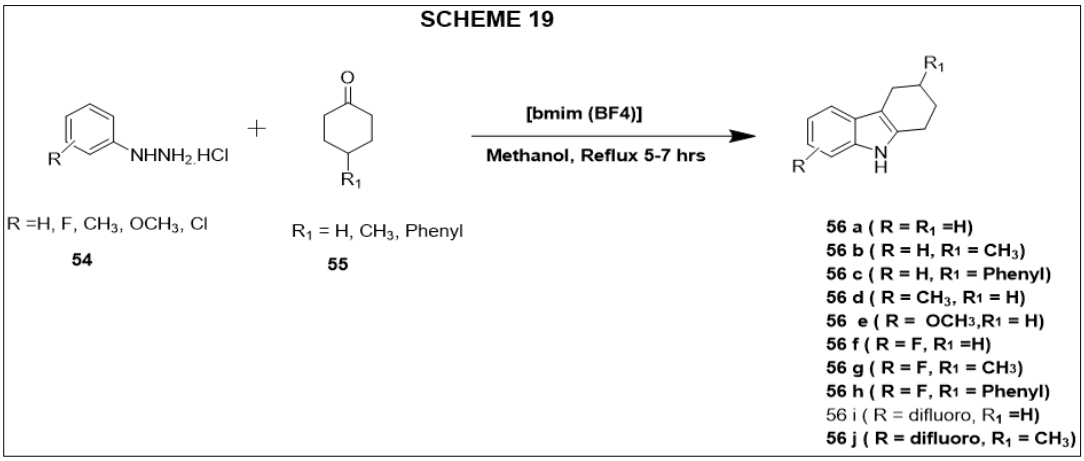


**Figure 20** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles and 2,3,4,9-tetrahydro-1H-carbazoles (56 a-j)

## 4. Synthesis of 1-Oxo-1,2,3,4-tetrahydrocarbazoles

An acid catalyzed ring closure of 3-indolebutyric acid (**57**) in the presence of polyphosphoric acid (PPA) gave 1-Oxo-1, 2, 3, 4-tetrahydrocarbazoles (**58**) [42, 43]. The yield of the reaction was found 84 %.

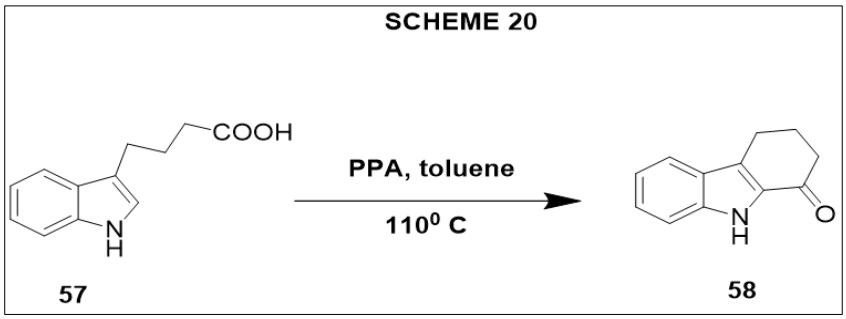


**Figure 21** Synthesis of 1-Oxo-1,2,3,4-tetrahydrocarbazoles

### 4.1. Synthesis of substituted 1-Oxo-1,2,3,4-tetrahydrocarbazoles

Reaction of substituted phenyl hydrazine hydrochlorides (**59**) with substituted 2-aminocyclohexanone hydrochlorides (**60**) based on Fischer indole synthesis method in mild condition 2N NaOH and 80 % acetic acid give substituted 1-Oxo-1,2,3,4-tetrahydrocarbazoles (**61**) (**Scheme 21**).[44] The yield of the reaction was found 45-94 %.

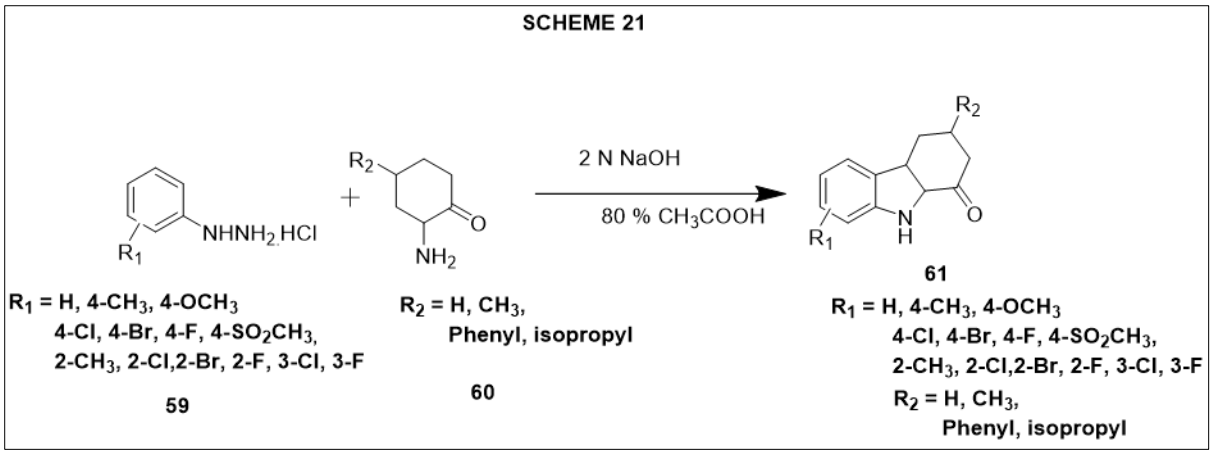


**Figure 22** Synthesis of substituted 1,2,3,4-tetrahydrocarbazoles (61)

## 5. Conclusion

In this review article, we covered various synthetic method for the preparation of 1,2,3,4-tetrahydrocarabzoles based on conventional, microwave and catalyst approach. Now day's use of catalyst is become popular and it is very useful in the synthesis of complex natural products. Catalyst gives a short way to prepare complex or multistep molecule. However, availability and cost of catalyst is very important to synthetic and medicinal chemist. Generally, most of the preparation of 1,2,3,4-tetrahydrocarabzoles based on Fischer indole synthesis method in review literature. Substitution like hydrogen and electron donating or electron withdrawing group due to inductive or mesomeric effect plays a major role for the preparation of 1,2,3,4-tetrahydrocarabzoles in good yield and less time in review literature [1,5,34,45,46]. This review gives a detail idea of availability and selection of various synthetic method available for preparation of 1,2,3,4-tetrahydrocarabzoles based on conventional, microwave and catalyst approach with percentage yield.

## Compliance with ethical standards

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*Disclosure of conflict of interest*

Authors have declared none conflict of interest in this review article.

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