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Progress in the chemistry of 3-amino-9-ethylcarbazole

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Abstract: Generally, 3-amino-9-ethylcarbazole is considered a versatile compound not only for its unique electronic properties but also for its significance as a building block in synthetic, pharmaceutical, and material chemistry. The synthesis, chemical reactivity, and applications of 3-amino-9-ethylcarbazole are described in this review. The presence of the amino group at position 3 exhibits a unique reactivity with both C-2 and C-4. The reactions of 3-amino-9-ethylcarbazole are divided into three categories, reactions that involve the amino group and cyclization reactions that involve the amino group and C-2 and/or C-4. In this review, relevant and appropriate applications of the synthesized, isolated, and condensed carbazole derivatives are reported.

Key words: 3-Amino-9-ethylcarbazole, multicomponent reaction, arylation reactions, cyclization reactions, pyrrolo[2,3-*c*]carbazole, pyrido[3,2-*b*]carbazole

1. Introduction

Carbazole is considered a heterocyclic aromatic compound containing a tricyclic structure with two benzene rings fused on either side of the pyrrole ring. Carbazole is also considered a conjugated unit that possesses promising electronic and optical properties such as photoconductivity and photorefractivity.[1,2] Previous studies revealed that subsidiaries of carbazole have been additionally blended and applied in electronic devices such as organic light-emitting diodes (OLEDs).

Although carbazole derivatives exhibit various applications in the field of material science, many carbazoles also possess diverse pharmacological properties[3] such as antibacterial,[4] antifungal,[5] antituberculosis,[6,7] antiproliferative,[8] antiviral,[9] antitumor,[10] antiinflammatory,[11] antioxidant,[12] and antihistaminic[13] activities.

Among the substituted carbazoles, 3-aminocarbazole plays a significant role in the field of medicinal chemistry, where it is applied as a versatile precursor for the synthesis of several bioactive annulated carbazole derivatives.[14] 3-Aminocarbazoles are also considered useful substrates in the synthesis of various dyes and pigments, stabilizers for polymers, pesticides, photographic materials, and diagnostic reagents in cytochemical studies. For instance, 3-amino-9-ethylcarbazole has been widely used as a peroxidase and considered suitable for the colorimetric detection of antibodies in the diagnosis of certain diseases.[15]

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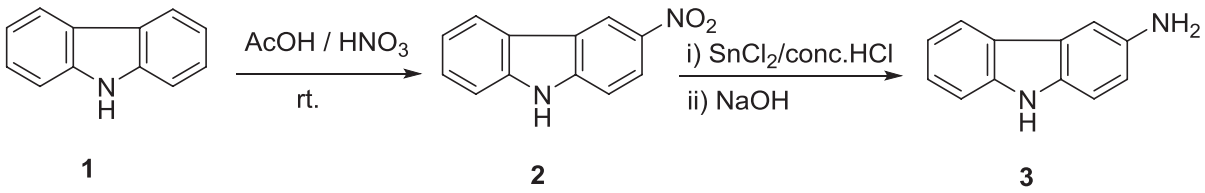
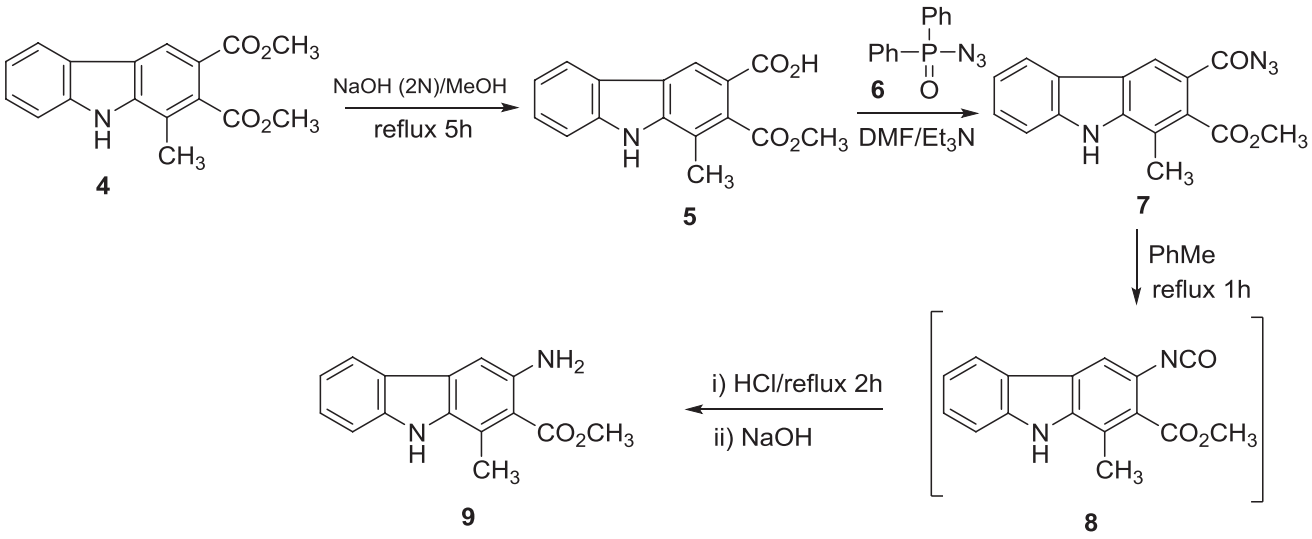
1.1. Methods of preparation of 3-aminocarbazoles

There are many synthetic approaches to obtain 3-aminocarbazole derivatives. Sadiq et al. reported the easiest method for the preparation of 3-aminocarbazole.[16] Thus, the nitration of carbazole **1** with a mixture of nitric acid and acetic acid at room temperature produced the regioselective 3-nitrocarbazole **2** with a yield of 93%. The reduction of the latter product with tin in the presence of concentrated hydrochloric acid followed by neutralization with sodium hydroxide produced 3-aminocarbazole **3** with a high chemical yield of 95% (Scheme 1).



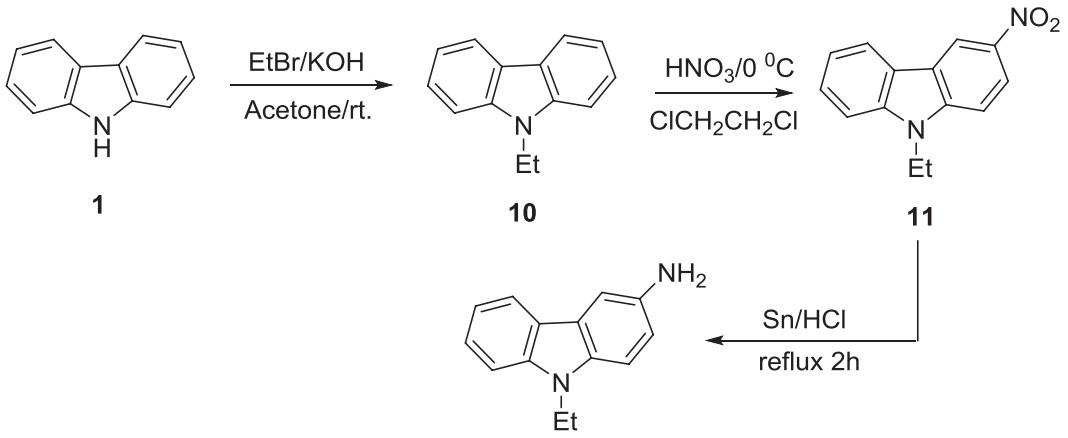
Scheme 1.

Fidesser et al.[17] reported a convenient method for synthesis of 3-aminocarbazole derivatives as a four-step process commencing with the regioselective base-catalyzed hydrolysis of dimethyl 1-methyl-9*H*-carbazole-2,3-dicarboxylate (**4**) to produce 2-(methoxycarbonyl)-1-methyl-9*H*-carbazole-3-carboxylic acid (**5**). Heating the latter carboxylic acid **5** with diphenylphosphorylazide (**6**) in dimethylformamide containing a catalytic amount of triethylamine afforded carbazolylazide **7**, which upon refluxing in toluene produced the nonisolable carbazolyl isocyanate **8**, which undergoes acid-catalyzed hydrolysis to afford methyl 3-amino-1-methylcarbazole-3-carboxylate (**9**) (Scheme 2).



Scheme 2.

A three-step reaction was used to synthesize 3-amino-9-ethylcarbazole. The first one is the alkylation of carbazole **1** with ethyl bromide in acetone at room temperature containing an equimolar amount of potassium hydroxide to produce 9-ethylcarbazole (**10**). Then the nitration of **10** with nitric acid in 1,2-dichloroethane at 0 °C gave 3-nitro-9-ethylcarbazole (**11**). Finally, the reduction of the latter product **11** with tin in the presence of hydrochloric acid yielded 3-amino-9-ethylcarbazole (**12**) (Scheme 3).[18–20]



Scheme 3.

2. Chemical reactivity

3-Amino-9-ethylcarbazole contains three nucleophilic sites and can be added to different types of electrophilic reagents. It has been shown that typical nucleophilic centers are the amino group at C-3 and the carbons of C-2 and C-4 (Chart). The nucleophilic behaviors of C-2 and C-4 were attributed to the mesomeric effect of the amino group that acted as enamine with a reactivity order of C-4 > C-2. These nucleophilic sites have been effectively employed to construct diverse types of fused heterocyclic systems with a carbazole nucleus such as pyrrole, thiazole, indolone, isoindole, pyridine, pyrimidine, chromene, quinazoline, phenanthroline, naphthyridine, and diindolophenazine.

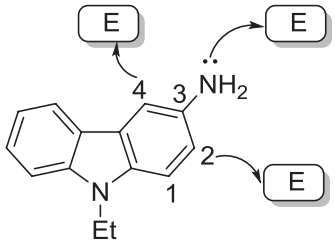


Chart. Chemical reactivity of compound **12**.

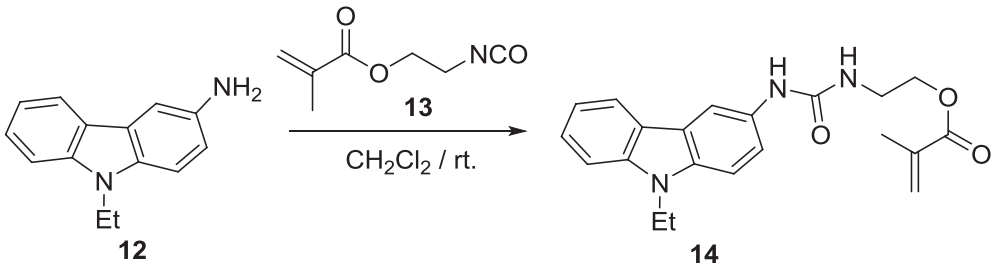
3. Reactions of 3-amino-9-ethylcarbazole

3.1. Reactions involving the amino group

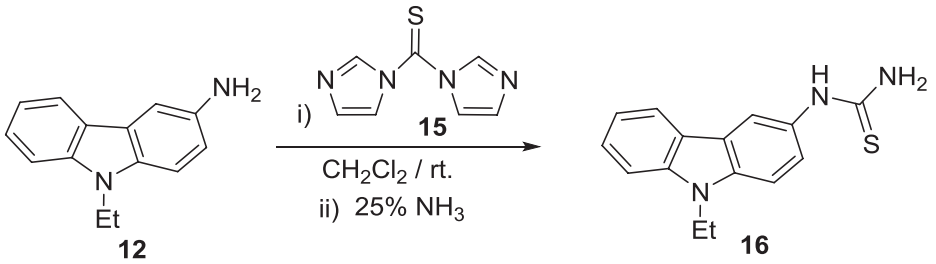
3.1.1. Addition reactions with isocyanate and thioamides

Wang et al.[21] recently reported the synthesis of 2-(3-(9-ethyl-9*H*-carbazol-3-yl))ureido)ethyl methacrylate (**14**), a purple fluorescent monomer, via the nucleophilic addition reaction of 3-amino-9-ethylcarbazole (**12**) with 2-isocyanatoethyl methacrylate (**13**) in methylene chloride at room temperature (Scheme 4). The obtained monomer **14** exhibits a broad range of material applications such as functional coatings, optical devices, chemosensors, organic LEDs, and laser active media.

The nucleophilic addition reaction of 3-amino-9-ethylcarbazole (**12**) with 1,10-thiocarbonyldiimidazole (TCDI) **15** in CH_2Cl_2 at room temperature in the presence of excess 25% ammonia solution yielded (9-ethyl-9*H*-carbazol-3-yl)-thiourea (**16**). Compound **16** showed anti-HCV activity and cytotoxicity (Scheme 5).[22]



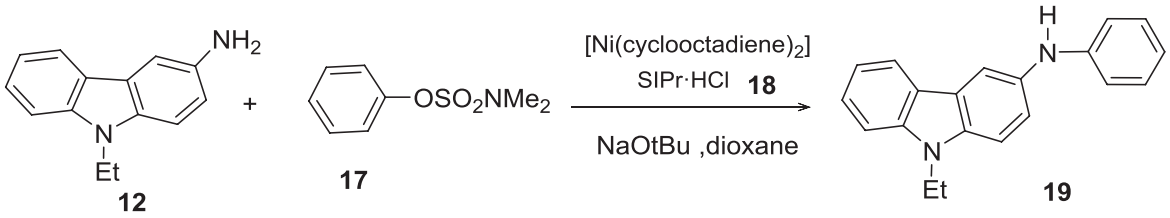
Scheme 4.



Scheme 5.

3.1.2. Substitution reaction with aryl sulfamate

The cross-coupling reaction of 9-ethyl-3-aminocarbazole (**12**) with phenyl dimethylsulfamate **17** in the presence of a catalytic amount of [Ni(cyclooctadiene)$_2$], SIPr • HCl **18**, and sodium *tert*-butoxide in dioxane at 80 °C yielded 9-ethyl-3-(phenylamino)carbazole (**19**) with a high yield of 95% (Scheme 6).[23]

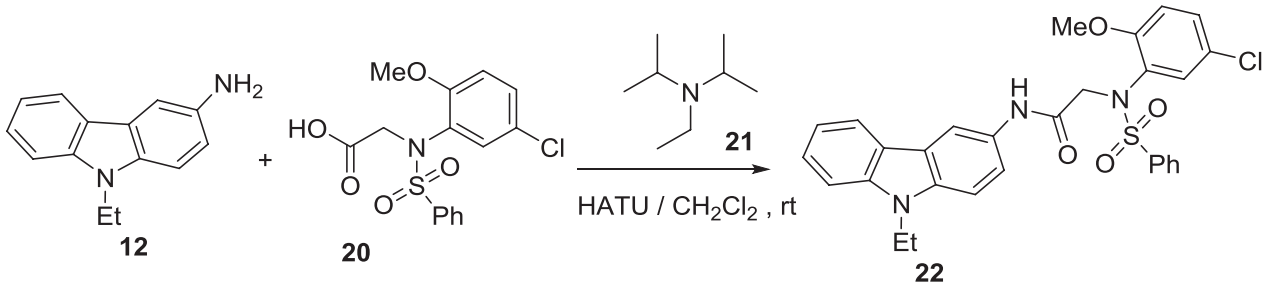


Scheme 6.

3.1.3. Acylation reactions

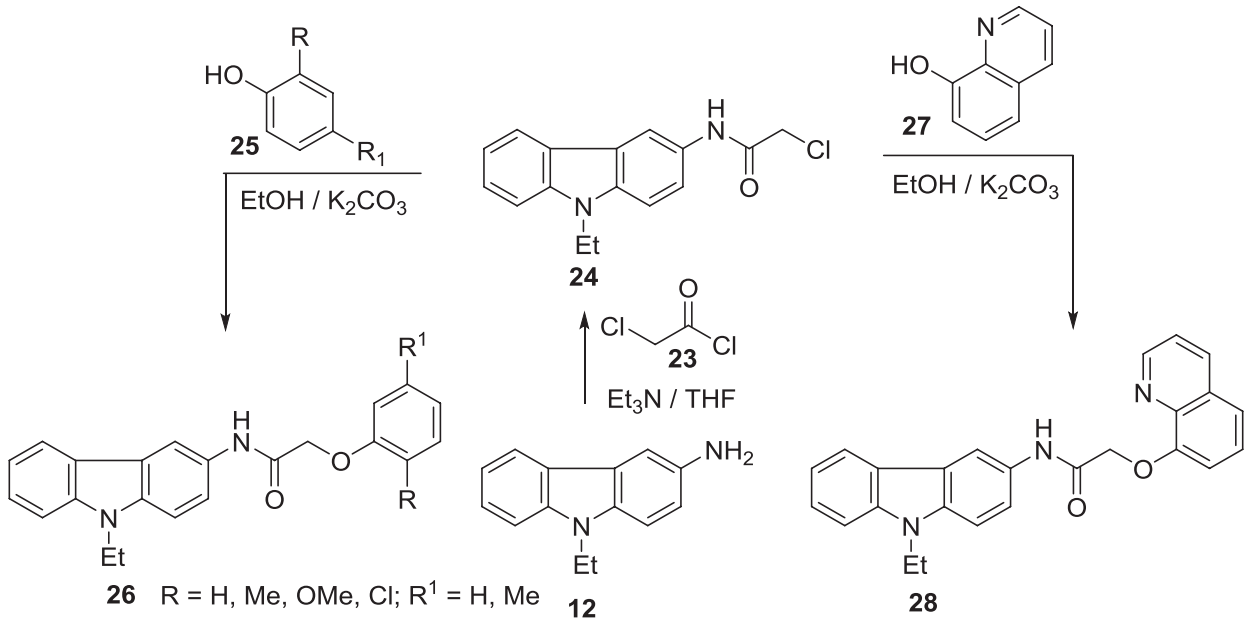
A four-component reaction of compound **12**, *N*-(5-chloro-2-methoxyphenyl)-*N*-(phenylsulfonyl)glycine (**20**), 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uroniumhexafluoro-phosphate (HATU), and *N*,*N*-diisopropylethylamine (DIPEA) **21** in CH_2Cl_2 at room temperature was used to synthesize 2-*N*-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide (**22**). Compound **22** has been used as a neuroprotective agent for Alzheimer disease (Scheme 7).[24]

A series of *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-(phenoxy)acetamide derivatives **26** using two-step reactions was synthesized by a research group from Turkey.[25] First, 9-ethyl-3-aminocarbazole (**12**) was treated with chloroacetylchloride **23** in THF containing a catalytic amount of triethylamine to produce 2-chloro-*N*-(9-ethyl-9*H*-carbazol-3-yl)acetamide (**24**) with good yield. The nucleophilic substitution reaction of **24** with a set of substituted phenols **25** in boiling ethanol containing anhydrous potassium carbonate afforded the target



Scheme 7.

compounds **26** with moderate yields (70%–78%). Similarly, the treatment of **24** with 8-hydroxyquinoline (**27**) under the same experimental conditions produced *N*-(9-ethyl-9*H*-carbazol-3-yl)-2-quinolin-8-yloxy)acetamide (**28**) (Scheme 8). The obtained compounds were evaluated for their in vitro antimicrobial and cytotoxic activities. Among the tested compounds, compound **28** showed notably antimicrobial activity and the lowest cytotoxic activity against mouse embryonic fibroblast (NIH/3T3) cells.

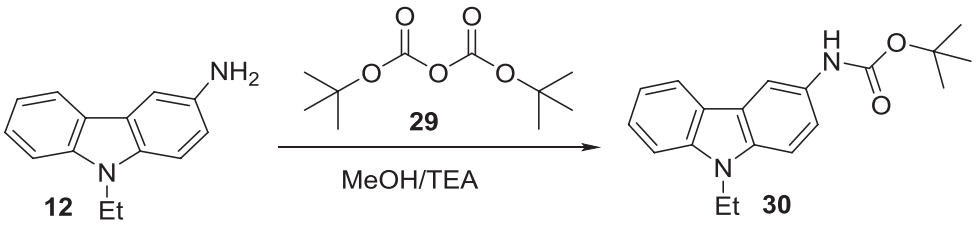


Scheme 8.

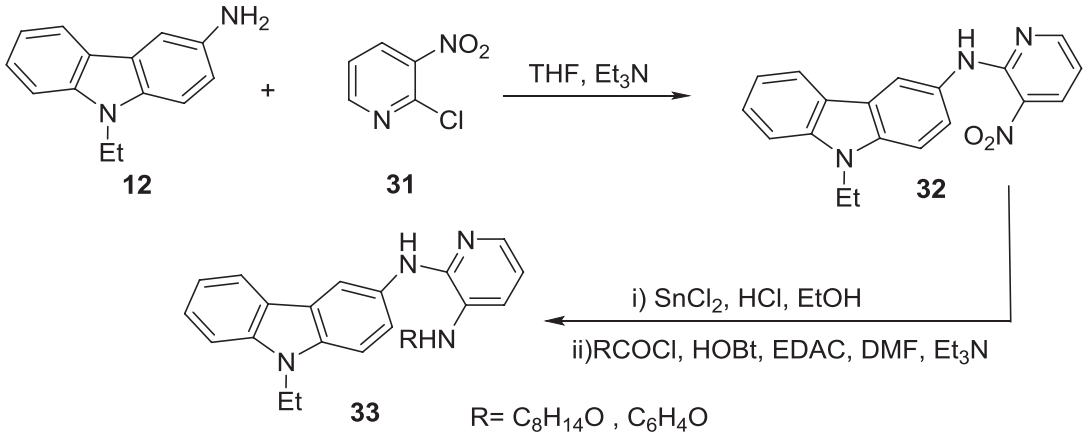
The synthesis of *tert*-butyl (9-ethyl-9*H*-carbazol-3-yl)carbamate (**30**) via the heating of compound **12** with di-*tert*-butyl dicarbonate **29** in methanol in the presence of a catalytic amount of triethylamine has been reported by Kant et al.[26] (Scheme 9).

3.1.4. Arylation reactions

o-Diamino-substituted pyridine derivatives **33** were synthesized in two sequential steps via the base-catalyzed nucleophilic aromatic substitution reaction of 2-chloro-3-nitropyridine (**31**) with 3-amino-9-ethylcarbazole (**12**) to produce **32** followed by reduction and in situ acylation with acid chlorides to yield 2,3-diamino-substituted pyridines **33** (Scheme 10).[27]

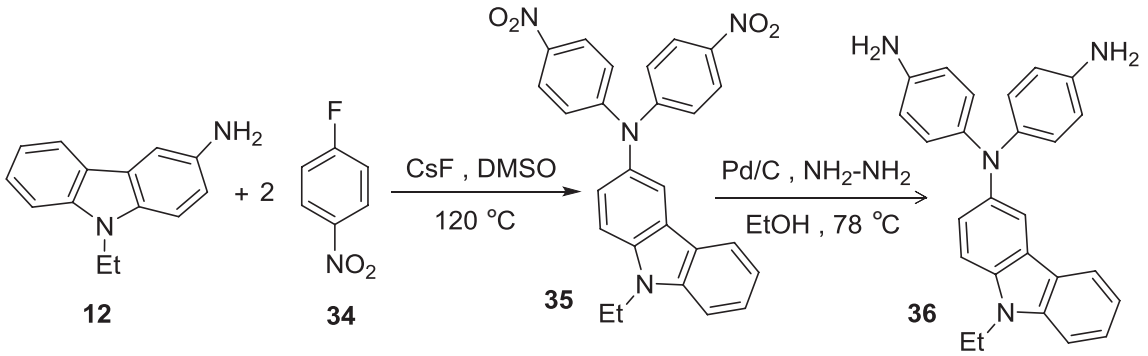


Scheme 9.



Scheme 10.

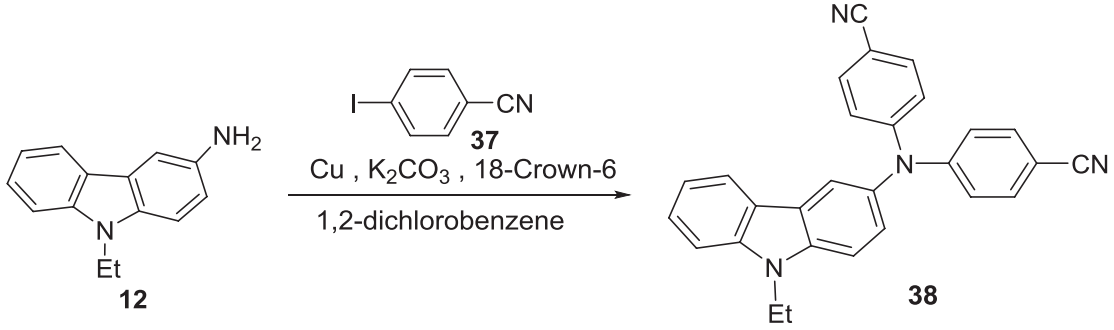
N^1-(4-Aminophenyl)-N^1-(9-ethyl-9H-carbazol-3-yl)benzene-1,4-diamine (**36**) was synthesized in two steps. 3-Amino-9-ethylcarbazole (**12**) was initially heated with two equimolar amounts of 4-fluoro-1-nitrobenzene (**34**) in DMSO containing a catalytic amount of cesium fluoride in an inert atmosphere of nitrogen to yield 3-amino-9-ethyl-N,N-bis(4-nitrophenyl)-9H-carbazole (**35**). Then the Pd/C-catalyzed reduction of compound **35** produced N^1-(4-aminophenyl)-N^1-(9-ethyl-9H-carbazol-3-yl)benzene-1,4-diamine (**35**) (Scheme 11). The newly synthesized carbazole derivative was tested using electronic devices such as LEDs, solar cells, and electrochromic devices.[28]



Scheme 11.

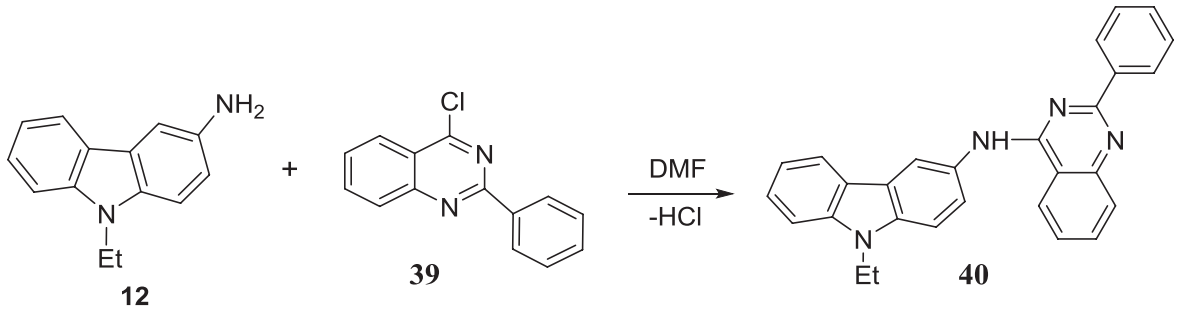
The synthesis of 3-di(4-cyanophenyl)amino-9-ethylcarbazole (**38**) using an improved Ullmann coupling reaction of compound **12** with 4-iodobenzonitrile **37**, copper, and 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) in the presence of a catalytic amount of anhydrous potassium carbonate in 1,2-dichlorobenzene has

been reported by Skuodis et al.[29] (Scheme 12). Compound **38** was used in glass formation with glass transition temperatures ranging from 77 to 111 °C.



Scheme 12.

The nucleophilic displacement reaction of 4-chloro-2-phenylquinazoline (**39**) with compound **12** in boiling dimethylformamide was used to obtain 9-ethyl-*N*-(2-phenylquinazolin-4-yl)-9*H*-carbazol-3-amine (**40**) (Scheme 13).[30]



Scheme 13.

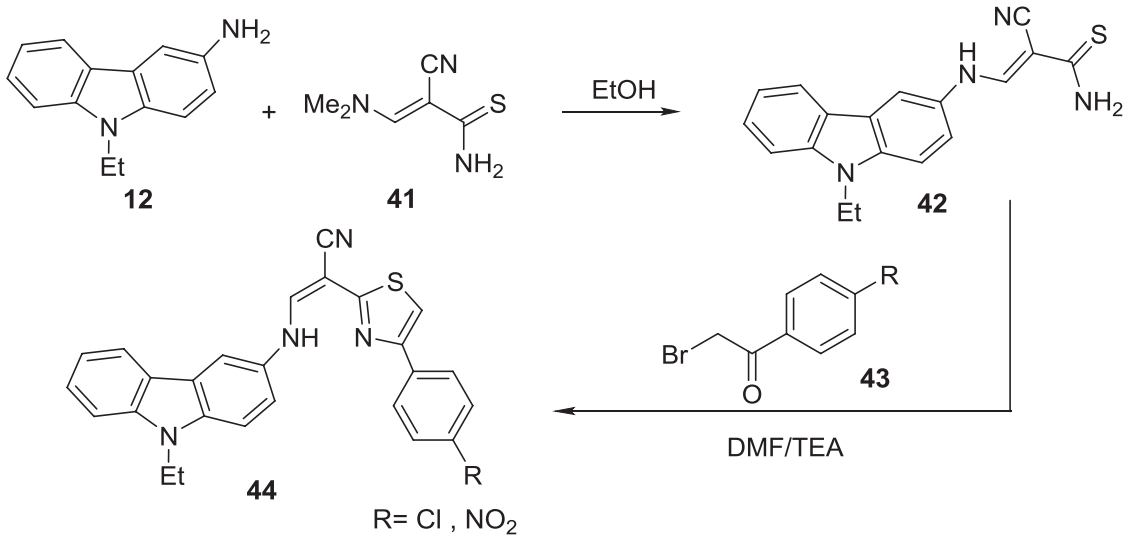
3.1.5. Substitution reactions with enamine

2-Cyano-3-(9-ethyl-9*H*-carbazol-3-yl)propenethioamide (**42**) was produced by the transamination of 3-amino-9-ethylcarbazole (**12**) with 2-cyano-*3-(N,N*-dimethylamino)propenethioamide (**41**) in boiling ethanol. The thiazole derivatives **44** were achieved by the Hantzsch reaction of thioamide **42** with *p*-substituted phenacyl bromides **43** in DMF containing a catalytic amount of triethylamine at 80 °C. The latter compounds have been used in medicinal chemistry and drug discovery research because of their low toxicity (Scheme 14).[31]

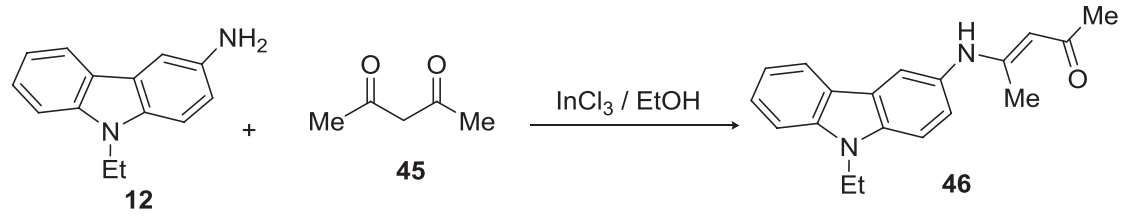
3.1.6. Condensation reactions with aldehydes and ketones

The condensation reaction of acetylacetone **45** with 3-amino-9-ethylcarbazole (**12**) in boiling ethanol containing catalytic amounts of indium chloride was used to synthesize (*Z*)-4-((9-ethyl-9*H*-carbazol-3-yl)amino)pent-3-en-2-one (**46**) with good yield (Scheme 15). Compound **46** was applied as an antagonist for lung cancer.[32]

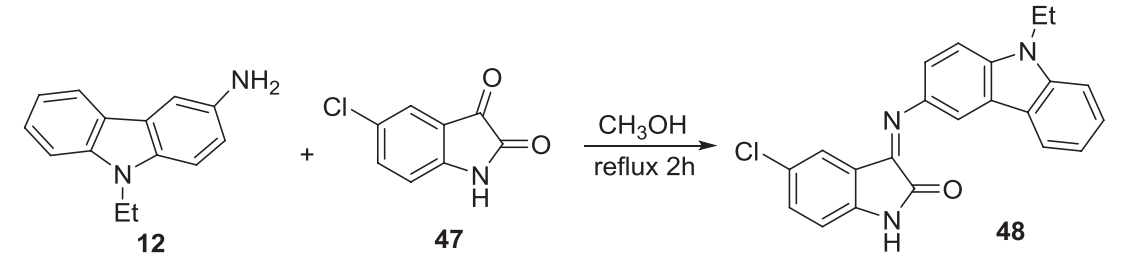
5-Chloro-3-((9-ethyl-9*H*-carbazol-3-yl)imino)indolin-2-one (**48**), an anticancer agent, was yielded by the condensation reaction of 3-amino-9-ethylcarbazole (**12**) with 5-chloroisatin **47** in refluxing methanol (Scheme 16).[33]



Scheme 14.



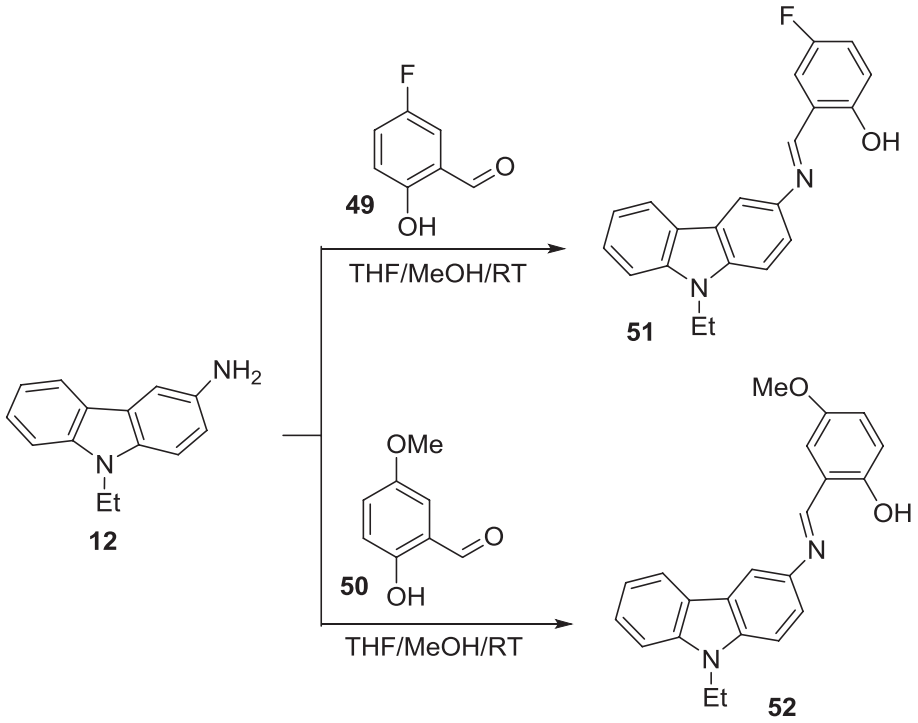
Scheme 15.



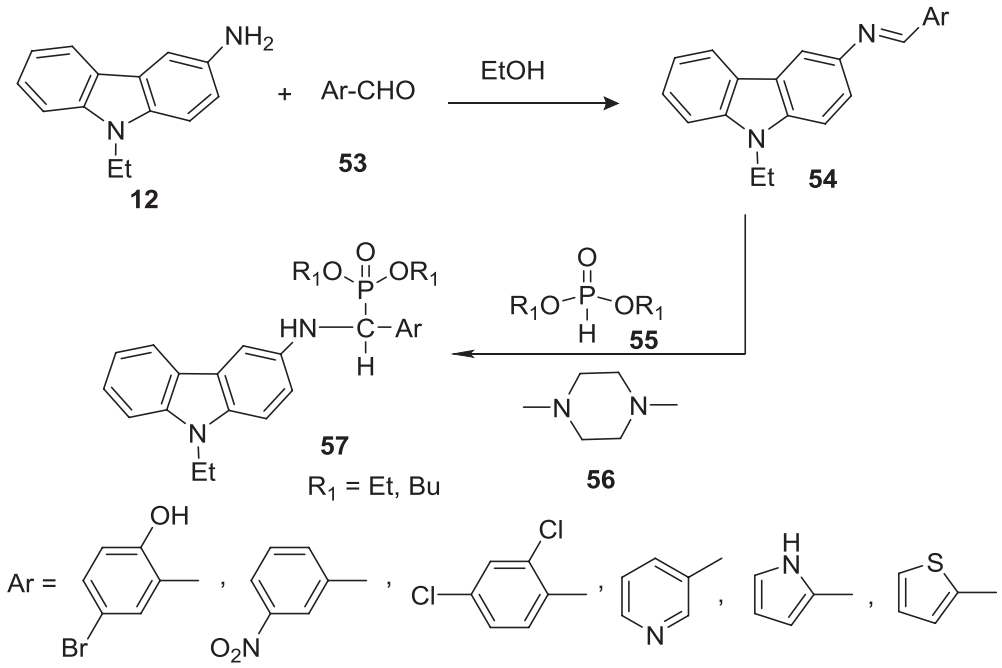
Scheme 16.

The respective Schiff bases 2-((9-ethyl-9*H*-carbazole-6-ylimino)methyl)-4-fluorophenol (**51**) and 2-((*E*)-((9-ethyl-9H-carbazole-6-ylimino)-methyl)-4-methoxyphenol (**52**) were produced by the condensation of compound **12** with each of 5-flurosalicyaldehyde (**49**) and 5-methoxysalicyaldehyde (**50**) in a mixture of tetrahydrofuran and methanol (2:1) at room temperature (Scheme 17). The synthesized Schiff bases **51** and **52** exhibited aggregation-induced emission enhancement (AIEE) behavior in H_2O:THF (60:40, v/v).[34]

Rasheed et al.[35] have described the synthesis of new α-aminophosphonates **57** by the condensation reaction of compound **12** with substituted aromatic aldehydes **53** in refluxing ethanol to yield Schiff base **54**, which underwent the nucleophilic addition reaction with dialkyl phosphates **55** in the presence of 1,4-dimethylpiperazine (**56**) as a basic catalyst (Scheme 18). It has been reported that the obtained compounds were evaluated as antimicrobial and antioxidant agents. In addition, the results showed that some of the tested compounds possessed good dual antimicrobial and antioxidant activities.

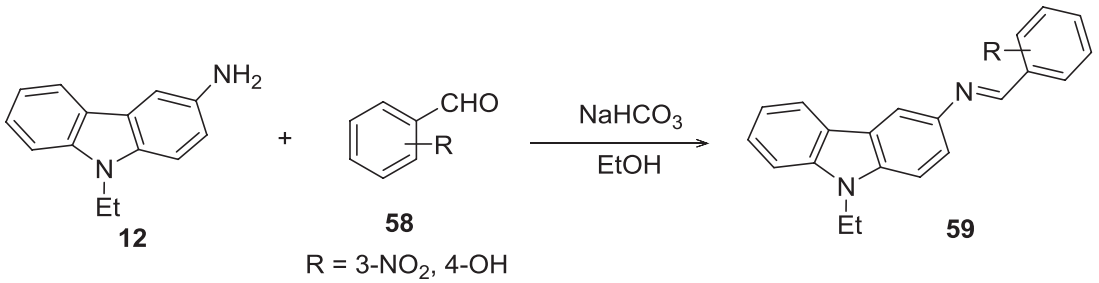


Scheme 17.



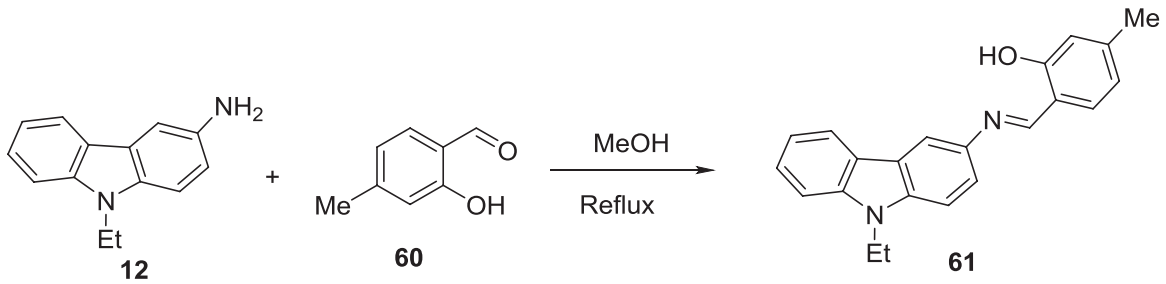
Scheme 18.

The condensation of compound **12** with substituted benzaldehyde **58** in ethanol containing a catalytic amount of sodium bicarbonate at room temperature was employed to obtain 9-ethyl-*N*-(substituted-benzylidene)-9*H*-carbazol-3-amines **59** (Scheme 19).[36,37]



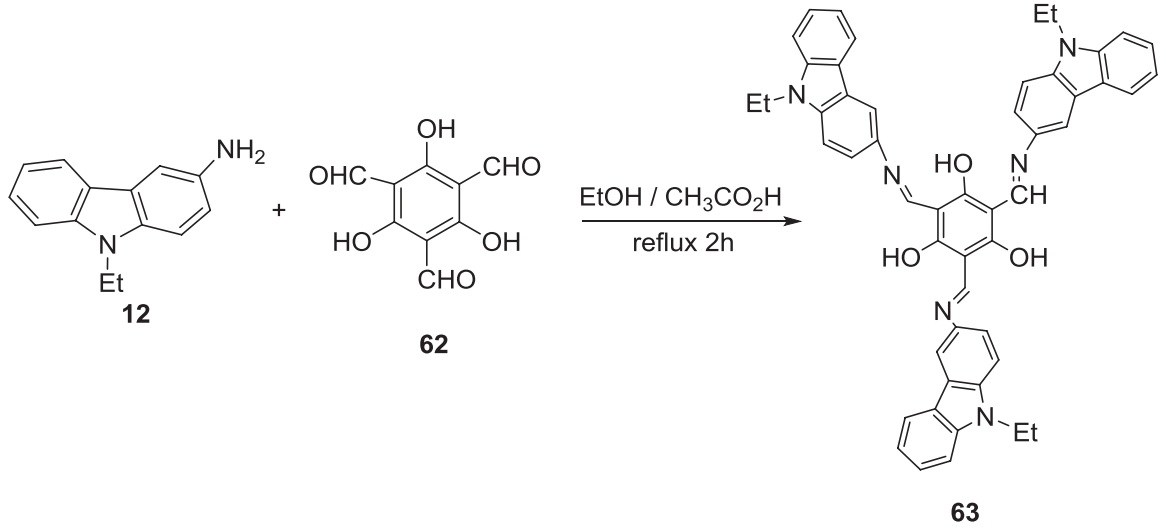
Scheme 19.

2-(9-Ethylcarbazol-3-yliminomethyl)-5-methylphenol (**61**) was produced by the treatment of compound **12** with 2-hydroxy-4-methyl benzaldehyde **60** in methanol under Schlenk reaction conditions (Scheme 20).[38]



Scheme 20.

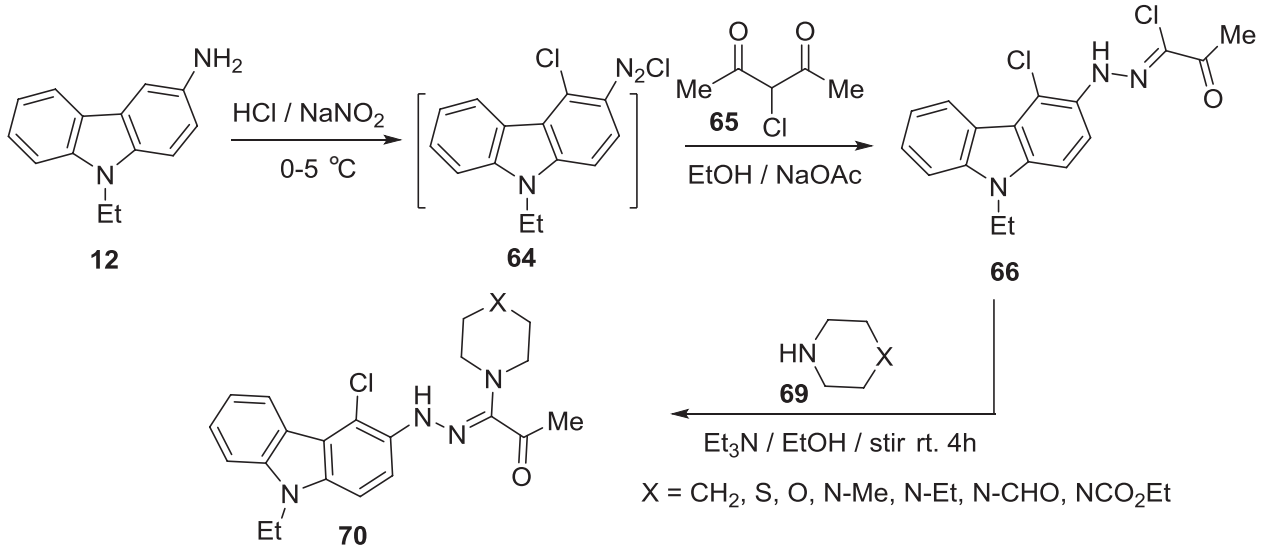
The preparation of a new three-binding site "ON–OFF–ON" fluorescent probe, triformylphloroglucinol 3-amino-9-ethylcarbazole hydrazone **63**, has been reported by Xu et al.[39] In order to detect copper ion and its application for cell imaging, this probe can serve as a fluorescent chemosensor. The condensation of compound **12** with triformylphloroglucinol **62** in refluxing ethanol containing a catalytic amount of acetic acid was used to synthesize this probe (Scheme 21).



Scheme 21.

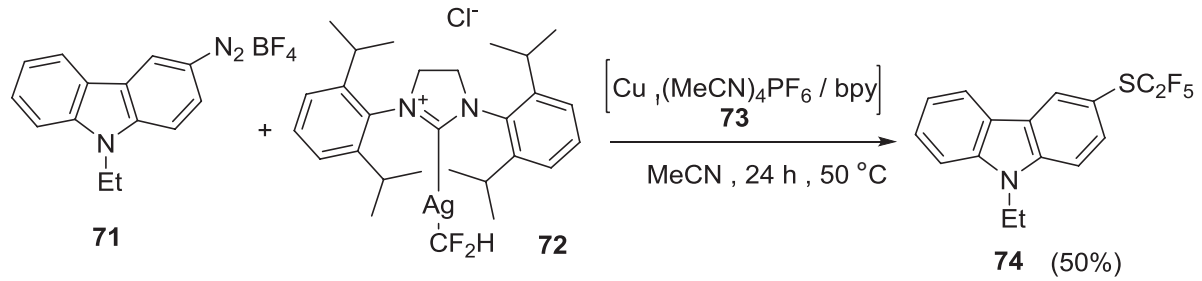
3.1.7. Diazocoupling reaction

Abdullah et al.[40] reported that the diazotization of **12** with nitrous acid afforded the nonisolable diazonium chloride **64**, which underwent in situ coupling with 3-chloro-2,4-pentanedione (**65**) in buffered ethanolic sodium acetate solution, affected acetyl cleavage, and yielded the corresponding hydrazonoyl chloride **66**. N^1-(4-Chloro-9-ethylcarbazol-3-yl)amidrazones **70** were produced by the nucleophilic displacement reactions of **66** with an appropriate secondary cyclic amine **67** in ethanol containing a catalytic amount of triethylamine at room temperature (Scheme 22). Single crystal X-ray crystallographic analysis was used to unambiguously determine the chemical structure of one isolated amidrazone. The fact that some of the tested compounds possess high potency against methicillin-resistant *Staphylococcus aureus* and *Bacillus cereus* was revealed by antibacterial evaluation of the synthesized amidrazone.



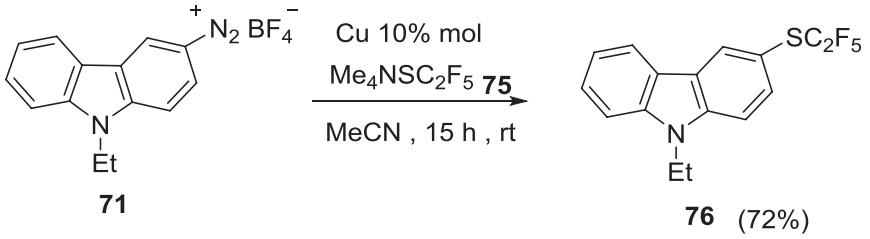
Scheme 22.

9-Ethyl-3-((perfluroethyl)thio)-9*H*-carbazole (**74**) with a moderate yield of 50% was prepared by Sandmeyer-type difluoromethylthiolation reaction of 9-ethyl-3-((tetrafluro-λ^5-boranyl)diazenyl)-9*H*-carbazole (**71**) with [(SIPr)Ag(CF_2H)] **72** and $[Cu(CH_3CN)_4]PF_6$ **73** in acetonitrile in the presence of bipyridine as a catalyst. The prepared compound **74** was applied as a crop-protecting agent (Scheme 23).[41]



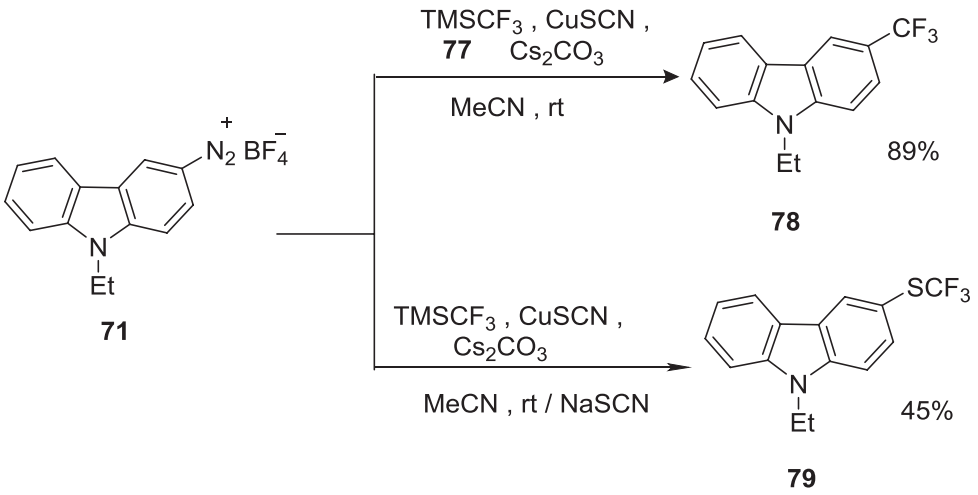
Scheme 23.

Pentafluoroethyl thioether derivatives **76** were produced by the Sandmeyer reaction of carbazole 3-diazonium salts **71** with $Me_4N_SC_2F_5$ **75** containing a catalytic amount of elemental copper at room temperature (Scheme 24).[42]



Scheme 24.

Similarly, 3-(trifluromethyl)-9-ethyl-9*H*-carbazole (**78**) was produced by the Sandmeyer-type coupling reaction of the diazonium salt **71** with trifluromethyltrimethylsilane ($TMSCF_3$) **77** in acetonitrile containing 1.5 equivalent amount of cesium carbonate in the presence of 0.5 equivalent amount of copper thiocyanate at room temperature. The formation of 3-((trifluro)thio))-9-ethyl-9*H*-carbazole (**79**) resulted from the addition of sodium thiocyanate as a sulfur source to the previous reaction mixture (Scheme 25).[43]



Scheme 25.

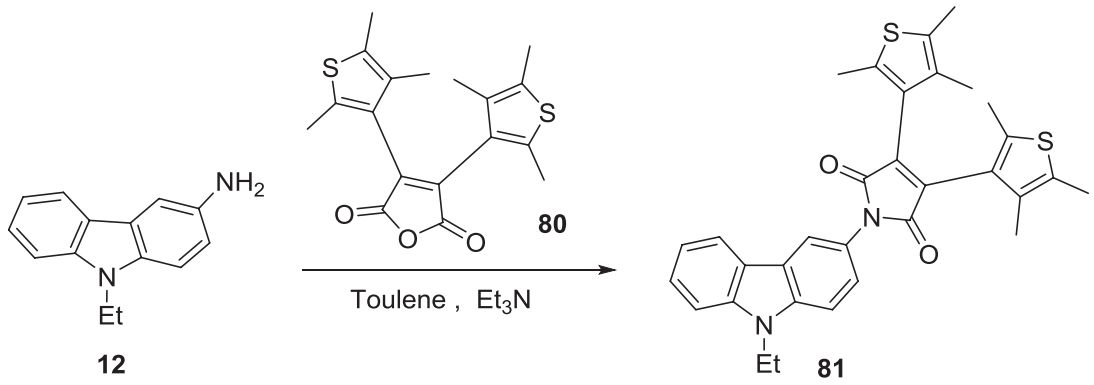
3.2. Cyclization reactions involving the amino group

3.2.1. Formation of pyrrole

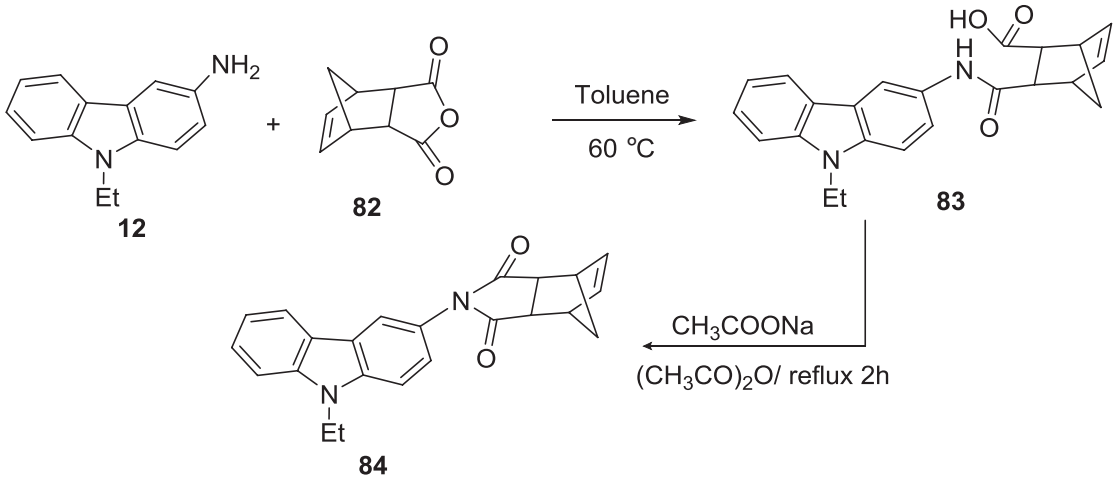
The treatment of compound **12** with 3,4-bis(2,4,5-trimethylthiophen-3-yl)furan-2,5-dione (**80**) in toluene under reflux containing a catalytic amount of triethylamine to afford 1-(9-ethyl-9*H*-carbazol-3-yl)-3,4-bis(2,4,5-trimethyl-thiophen-3-yl)-1*H*-pyrrole-2,5-dione **(81)** is reported (Scheme 26).[44]

3.2.2. Formation of isoindole

The reaction of compound **12** with *exo*-norbornene-5,6-dicarboxylic anhydride (**82**) in toluene produced norborneneamic acid **83**, which led to the formation of 2-(9-ethyl-9*H*-carbazol-3-yl)-3*a*,4,7,7*a*-tetrahydro-1*H*-4,7-methanoisoindole-1,3-(2*H*)-dione (**84**) with good yield (82%) upon heating with acetic anhydride containing anhydrous sodium acetate (Scheme 27).[45]



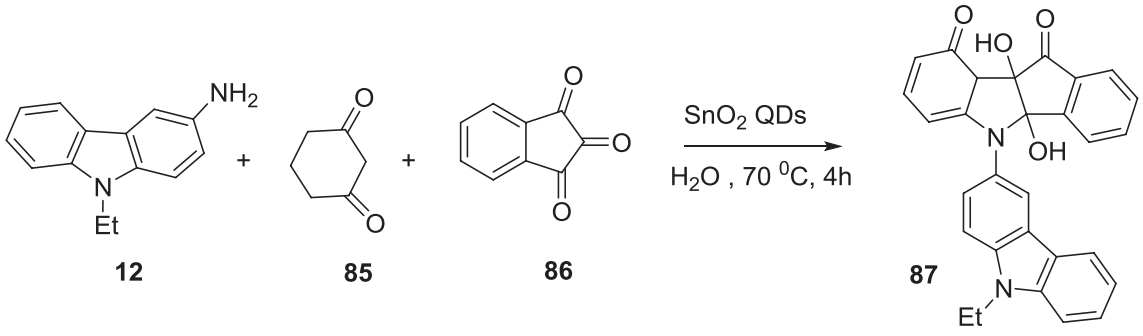
Scheme 26.



Scheme 27.

3.2.3. Formation of indeno[1,2-*b*]indolone

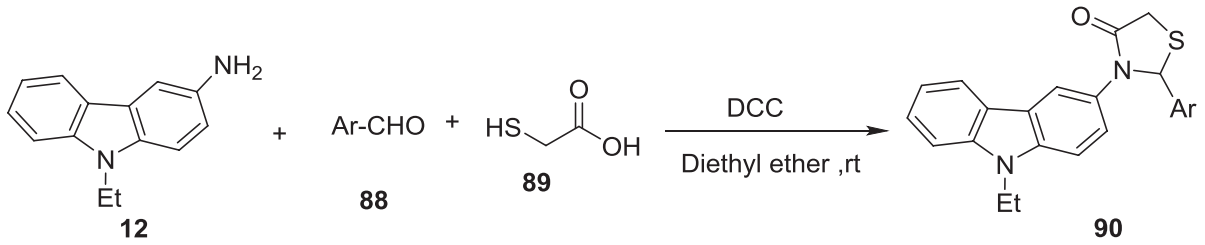
To produce 5-(9-ethyl-9*H*-carbazol-3-yl)-4b,9b-dihydroxy-4b,5,9a,9b-tetrahydro-indeno[1,2-*b*]indole-9,10-dione (**87**) derivative with good yield (82%), SnO_2 quantum dots (QDs), nanomaterials with a grain size less than 5 nm, catalyzed the one-pot three-component reaction of compound **12**, cyclohexane-1,3-dione (**85**), and 1*H*-indene-1,2,3-trione (**86**) in water at 70 °C as reported by Pradhan et al.[46] (Scheme 28).



Scheme 28.

3.2.4. Formation of thiazolidin-4-ones

The one-pot three-component reaction of compound **12**, aromatic aldehydes **88**, and 2-mercaptoacetic acid **89** in dry ether containing dicyclohexylcarbodimide (DCC) at room temperature was used to synthesize easily a series of novel 2-aryl-3-*N*-(9-ethylcarbazol-3-yl)thiazolidin-4-ones **90**. To produce Schiff bases, the reaction mechanism was proposed via the initial condensation of 3-aminocarbazole with aromatic aldehydes, which adds in situ to 2-mercaptoacetic acid to yield the target compounds (Scheme 29).[47]

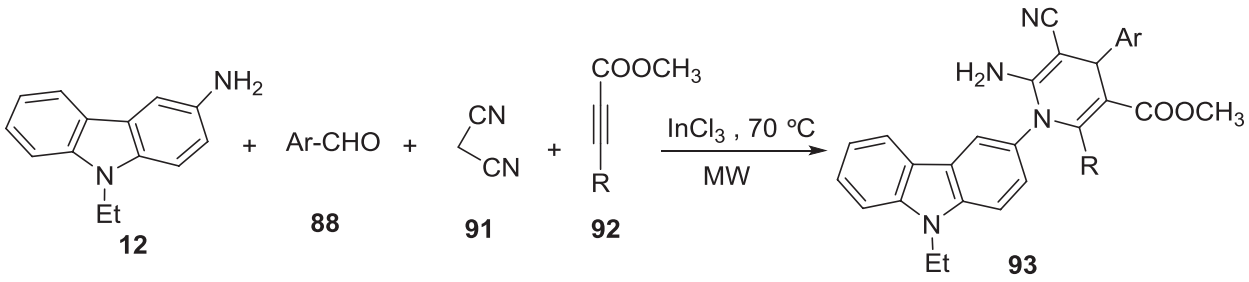


Ar = 4-CH_3O-C_6H_4, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-NO_2-C_6H_4, C_6H_5, C_4H_4O

Scheme 29.

3.2.5. Formation of pyridines

Yamuna et al. reported a simple, efficient, and environmentally benign microwave-assisted $InCl_3$ catalyzed synthesis of *N*-carbazolyl dihydropyridine derivatives **93** by a four-component reaction of compound **12**, malononitrile **91**, aromatic aldehydes **88**, and acetylenic esters **92** (Scheme 30).[48]

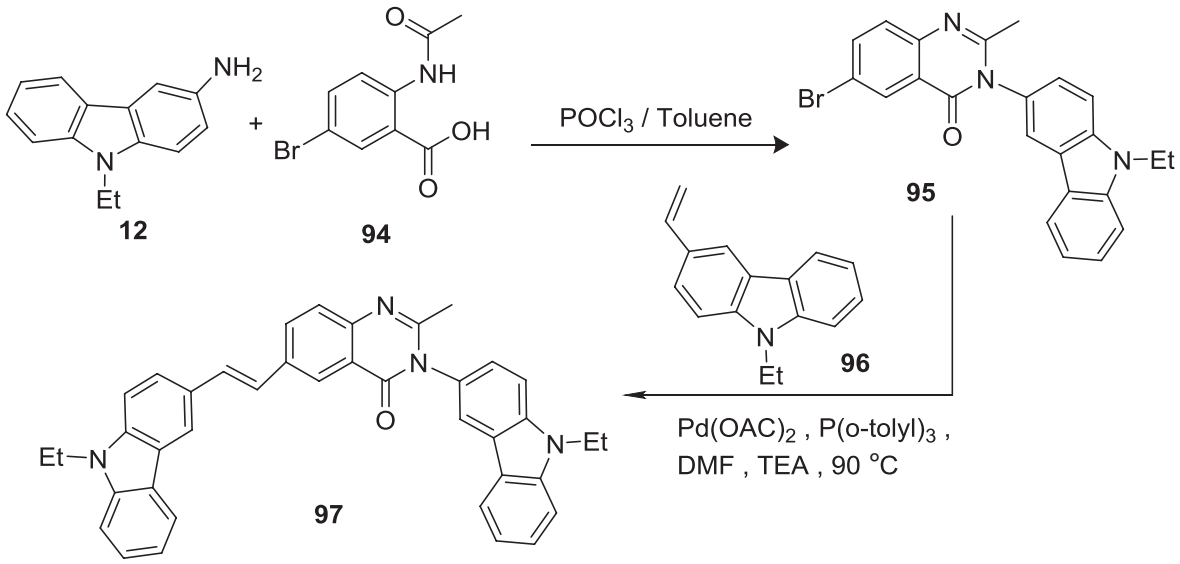


Ar = 4-CH_3O-C_6H_4, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-NO_2-C_6H_4, C_6H_5, C_4H_4O; R = H, $COOCH_3$

Scheme 30.

3.2.6. Formation of quinazolines

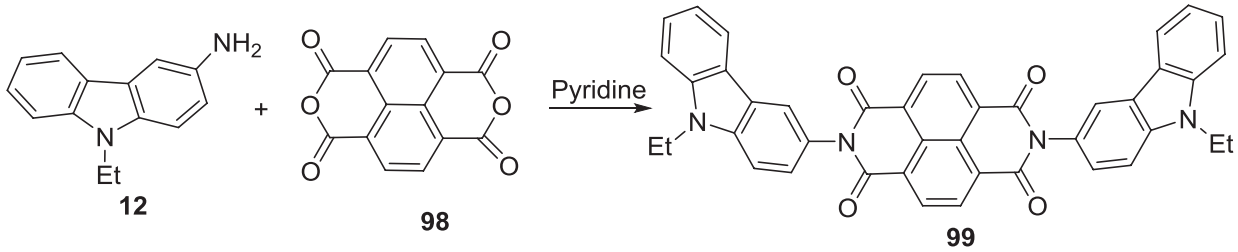
6-Bromo-3-(9-ethyl-9*H*-carbazol-3-yl)-2-methylquinazolin-4(3H)-one (**95**) was produced by heterocyclization of 3-aminocarbazole **12** with 2-acetamido-5-bromobenzoic acid (**94**) in boiling toluene containing $POCl_3$. 3-(9-Ethyl-9*H*-carbazol-3-yl)-5-((*E*)-2-(9-ethyl-9*H*-carbazol-3-yl)ethenyl)-2-methylquinazolin-4(3H)-one (**97**), which is a high-triplet energy material for phosphorescent OLEDs, was produced by the coupling of compound **95** with 9-ethyl-3-vinyl-9*H*-carbazole (**96**), palladium acetate, and tri(*o*-tolyl)phosphine in DMF containing triethylamine as a basic catalyst (Scheme 31).[49]



Scheme 31.

3.2.7. Formation of benzo[*lmn*][3,8]phenanthroline

The condensation reaction of two equivalents of 3-aminocarbazole **12** with isochromeno[6,5,4-*def*]isochromene-1,3,6,8-tetraone (**98**) in dry boiling pyridine was used to obtain 2,7-bis(9-ethyl-9*H*-carbazol-3-yl)benzo[*lmn*][3,8] phenanthroline-1,3,6,8-(2*H*,7*H*)-tetrone (**99**) (Scheme 32). Compound **99** exhibits multielectrochromic behavior, reasonable redox stability, coloration efficiency, and reasonable response time.[50]



Scheme 32.

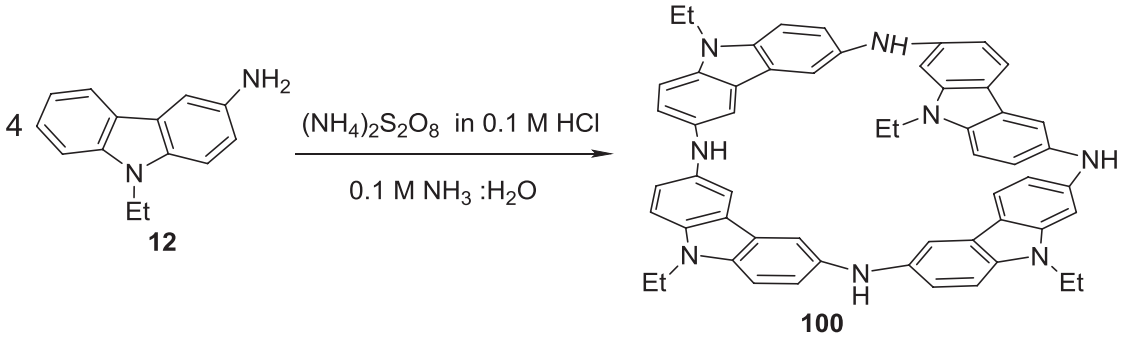
3.2.8. Formation of 2,4,6,8-tetraaza-1,3,5,7-tetracarbazola-cyclooctaphane

The synthesis of novel macrocyclic amine-linked oligocarbazole (OCB) hollow microsphere **100** by one-step chemical oxidative oligomerization of compound **12** with ammonium persulfate (APS) in aqueous methanol has been reported by Liao et al.[51] (Scheme 33). For the removal of lead from contaminated water, compound **100** exhibited high efficacy.

3.3. Cyclization reactions involving the amino group and C-2

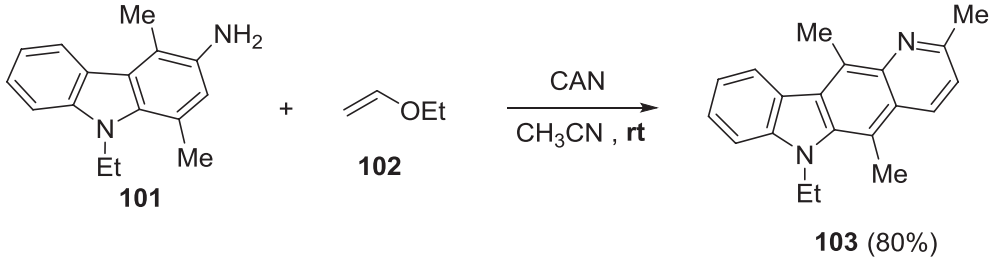
3.3.1. Formation of pyrido[3,2-*b*]carbazoles

6-Ethyl-2,5,11-trimethyl-6*H*-pyrido[3,2-*b*]carbazole (**103**) with good yield and high regioselectivity was prepared by the Povarov (imino Diels–Alder) reaction of 3-amino-9-ethyl-1,4-dimethyl-9*H*-carbazole (**101**) with



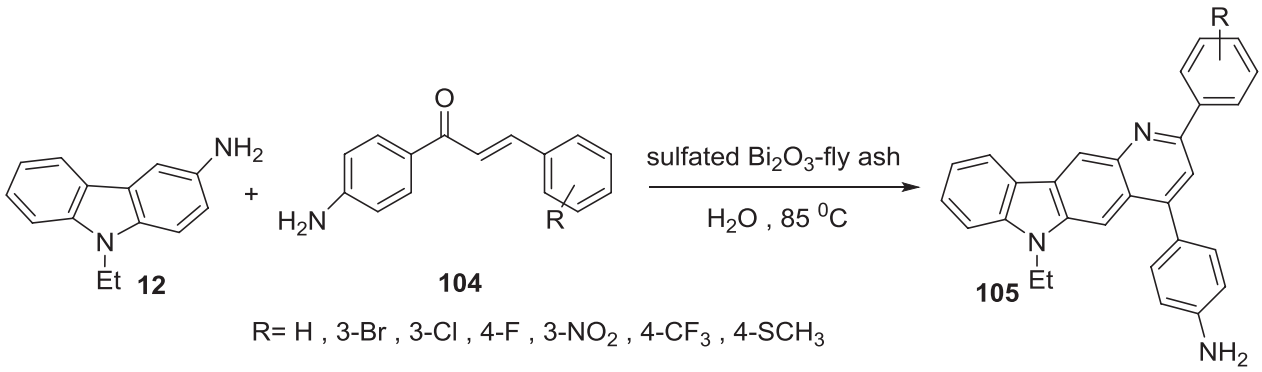
Scheme 33.

ethyl vinyl ether **102** as dienophile in acetonitrile containing catalytic amounts of cerium(IV) ammonium nitrate (CAN, 10 mol%) (Scheme 34).[52]



Scheme 34.

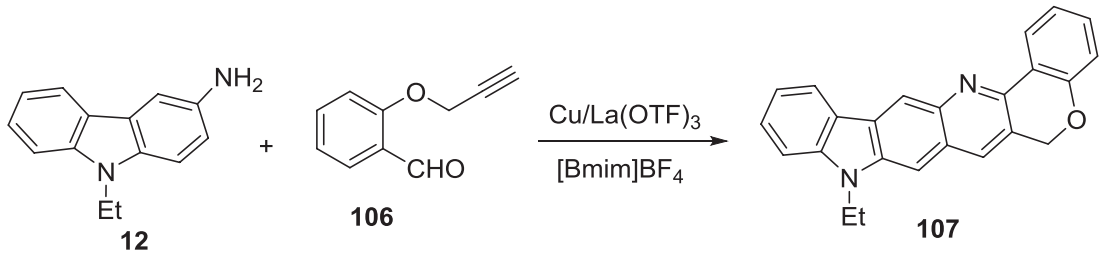
To obtain 2,3-diaryl-6-ethyl-6*H*-pyrido[3,2-*b*]carbazole derivatives **105**, sulfated Bi_2O_3-fly ash (12 wt%) was used as a green catalyst in the Michael addition reaction of compound **12** with chalcones **104** as described by Murthy and Thirunarayanan[53] (Scheme 35).



Scheme 35.

3.3.2. Formation of chromeno[3',4':5,6]pyrido[3,2-*b*]carbazole

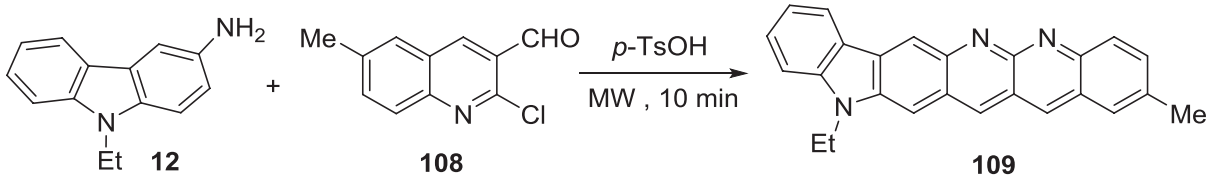
The nucleophilic addition reaction of compound **12** with 2-(pro-2-yn-1yloxy)benzaldehyde (**106**) in 1-butyl-3-methylimidazolium tetrafluroborate ([Bmim]BF_4) ionic liquid containing a catalytic amount of CuI/La(OTf)$_3$ was used to obtain the polyheterocyclic ring system 9-ethyl-6,9-dihydrochromeno[3',4':5,6]-pyrido[3,2-*b*]carbazole (**107**) (Scheme 36).[54]



Scheme 36.

3.3.3. Formation of benzo[6,7][1,8]naphthyridino[3,2-*b*]carbazole

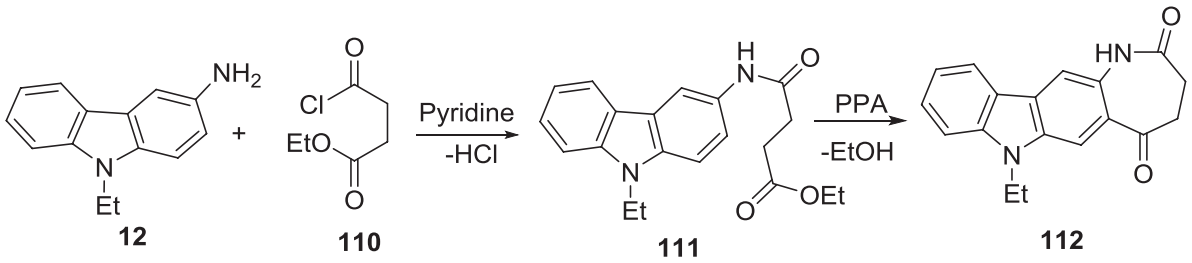
12-Ethyl-2-methyl-12*H*-benzo[6,7][1,8]-naphthyridino[3,2-*b*][1,8]carbazol**e** (**109**) was prepared in good yield (92%) by the microwave-assisted cyclocondensation of compound **12** with 2-chloro-6-methyl-3-formylquinonline (**108**) in the presence of a catalytic amount of *p*-toluene sulfonic acid (Scheme 37).[55]



Scheme 37.

3.3.4. Formation of azepino[3,2-*b*]carbazoles

In order to obtain 7-ethyl-3,4-dihydroazepino[3,2-*b*]carbazole-2,5-(1*H*, 7*H*)-dione (**112**), ethyl 4-((9-ethyl-9*H*-carbazol-3-yl)amino-4-oxobutanoate (**111**) is synthesized via the acylation of compound **12** with ethyl succinoyl chloride **110** in pyridine, which is followed by cyclization in warming polyphosphoric acid (PPA) under the Friedel–Crafts acylation reaction, as reported by Agrawal et al.[56] (Scheme 38). Compound **112** showed promising in vitro antimicrobial activities against several types of bacterial and fungal species and also showed potential CNS-depressant activity in mice by photoactometer.

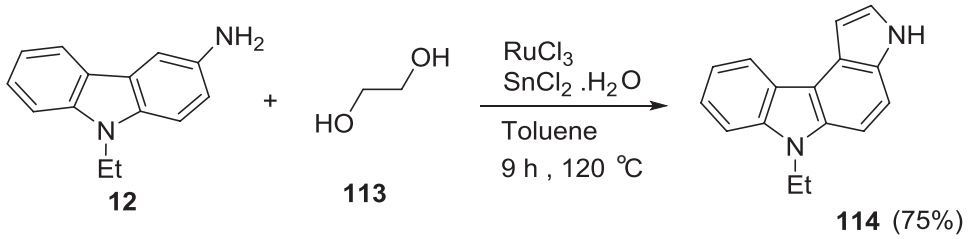


Scheme 38.

3.4. Cyclization reactions involving the amino group and C-4

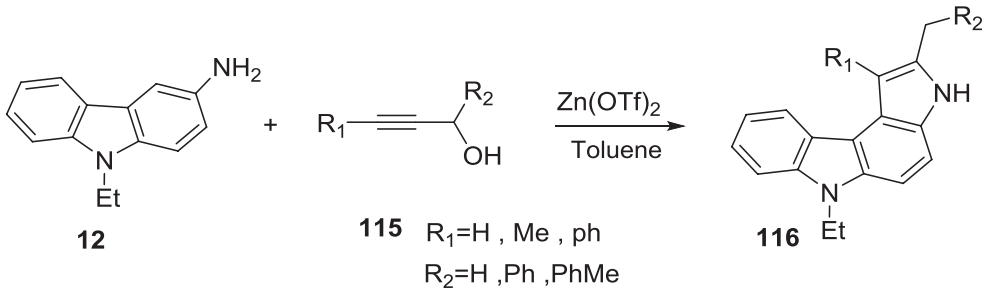
3.4.1. Formation of pyrrolo[2,3-*c*]carbazoles

6-Ethyl-3,6-dihydropyrrolo[2,3-*c*]carbazole (**114**) was obtained in good yield (75%) by the catalytic heteroannulation reaction of compound **12** with ethylene glycol (**113**) using a mixture of Lewis acid $RuCl_3/SnCl_2$ in refluxing toluene (Scheme 39).[57]



Scheme 39.

Similarly, pyrrolo[2,3-*c*]carbazole derivatives **116** were obtained by the treatment of compound **12** with substituted propargyl alcohols **115** in boiling toluene containing a catalytic amount of zinc triflate (Scheme 40).[58]



Scheme 40.

3.4.2. Formation of quinolino[3',4':4,5]pyrrolo[2,3-*c*]carbazoles

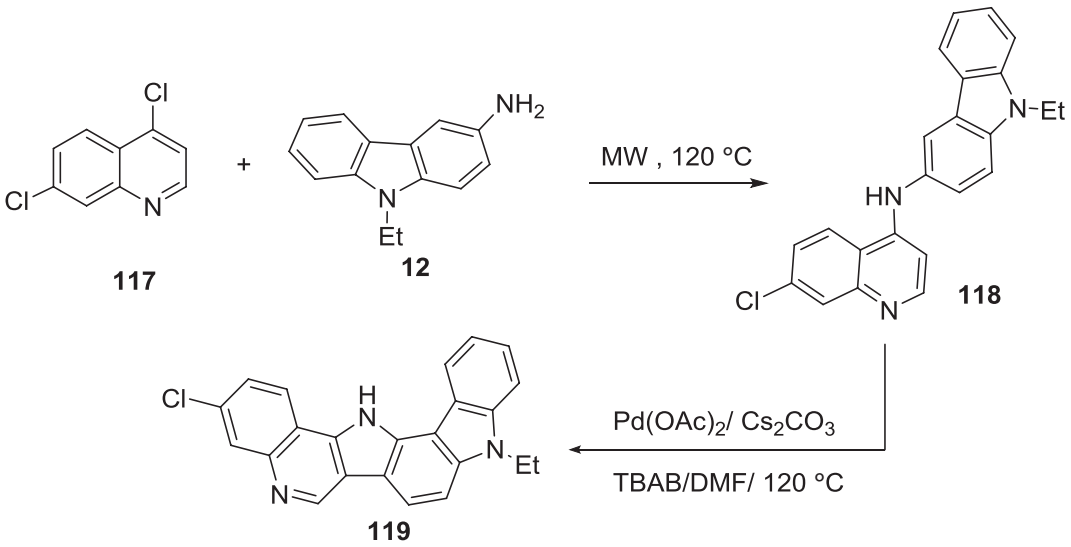
N-(7-Chloro-4-quinolinyl)-3-amino-9-ethyl-9*H*-carbazole (**118**) was prepared by the microwave-assisted nucleophilic displacement reaction of 4,7-dichloroquinoline (**117**) with compound **12**. Treatment of compound **118** with a mixture of tetrabutylammonium bromide (TBAB), Cs_2CO_3, and 5 mol% of palladium(II) acetate in boiling dry DMF produced 3-chloro-9-ethyl-9,14-dihydroquinolino[3',4':4,5]-pyrrolo[3,2-*c*]-carbazole (**119**) (Scheme 41).[59]

3.4.3. Formation of pyrido[2,3-*c*]carbazoles

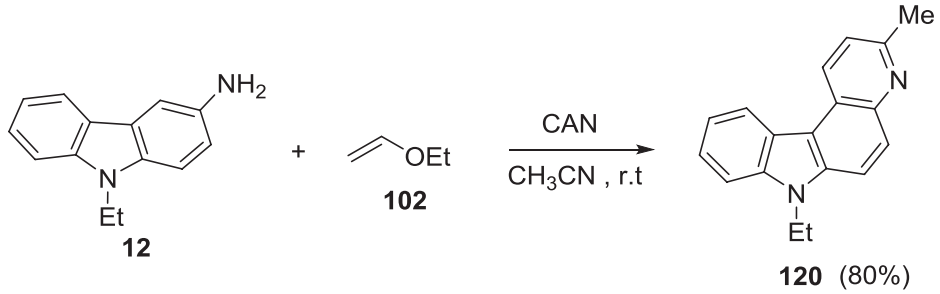
7-Ethyl-3-methyl-7*H*-pyrido[2,3-c]carbazole (**120**) with high regioselectivity was synthesized by the Povarov reaction of compound **12** with ethyl vinyl ether **102** in acetonitrile containing a catalytic amount of cerium(IV) ammonium nitrate (10 mol%) at room temperature (Scheme 42).[60]

In order to obtain 2-ethoxy-7-ethyl-3-phenyl-2,3,4,7-tetrahydro-1*H*-pyrido[2,3-*c*]carbazole (**122**) as an analogue of ellipticine, indium trichloride (10 mol%) catalyzed the regioselective intermolecular imino Diels–Alder reaction of 9-ethyl-3-(*N*-benzylidene)-aminocarbazole, generated in situ by the condensation of compound **12** with benzaldehyde **121**, and ethyl vinyl ether **102**, as electron-rich alkene, in [Bmin]BF_4 ionic liquid (Scheme 43).[61]

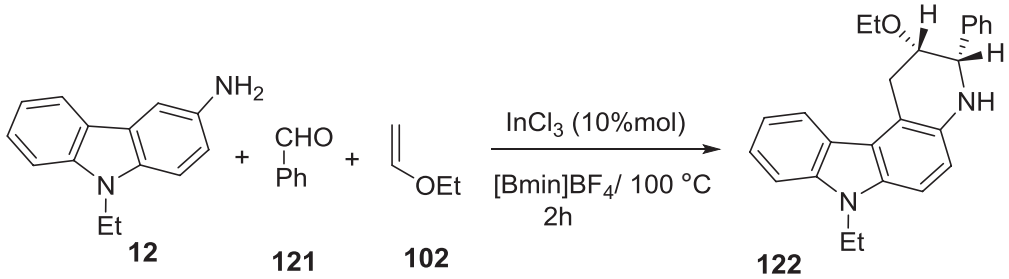
A mixture of ethyl-3-((9-ethyl-9*H*-carbazol-3-yl)amino)but-2-enoate (**124**) and *N*-(9-ethyl-9*H*-carbazol-3-yl)-3-oxobutanamide (**125**), which could be separated by fraction crystallization, was obtained upon heating compound **12** with ethyl 3-oxobutanate **123** in dry benzene containing a catalytic amount of HCl. Upon heating



Scheme 41.



Scheme 42.

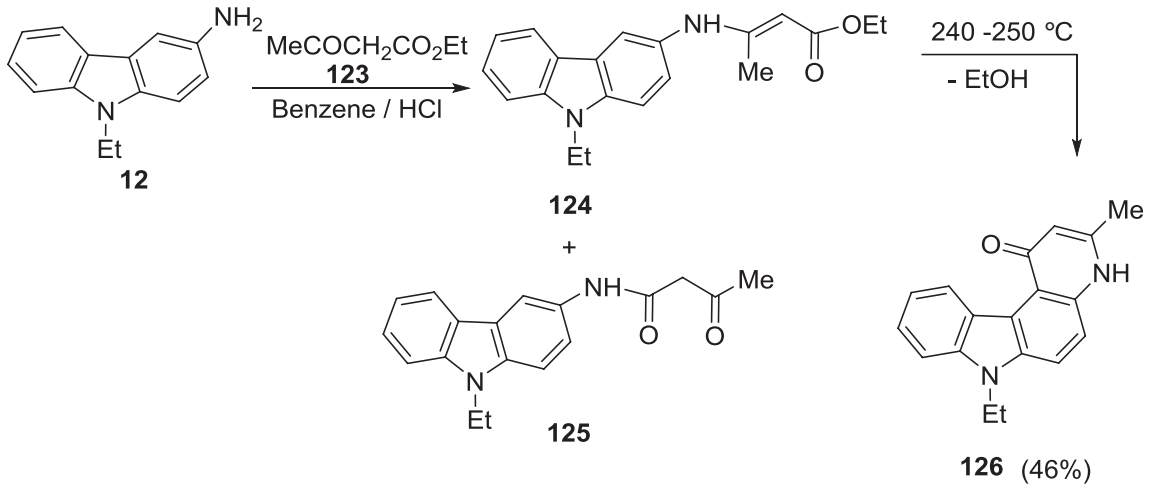


Scheme 43.

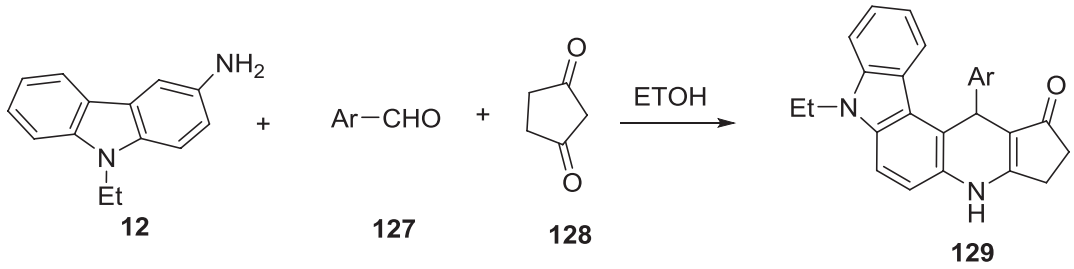
in mineral oil at 240–250 °C, compound **124** could easily be cyclized to 7-ethyl-3-methyl-4,7-dihydro-pyrido[2,3-*c*]-carbazol-1-one (**126**) (Scheme 44).[62]

3.4.4. Formation of cyclopenta[5,6]pyrido[2,3-*c*]carbazoles

The catalyst-free one-pot three-component synthesis of 12-aryl-7-ethyl-3,4,7,12-tetrahydrocyclopenta-[5,6]-pyrido [2,3-*c*]carbazol-1(2*H*)-one derivatives **129** by refluxing compound **12** with aromatic aldehydes **127** and cyclopentane-1,3-dione **128** in ethanol has been reported by Zhang et al. Pyrido[2,3-*c*]carbazole derivatives **129** have been medically applied as anticancer agents (Scheme 45).[63]



Scheme 44.

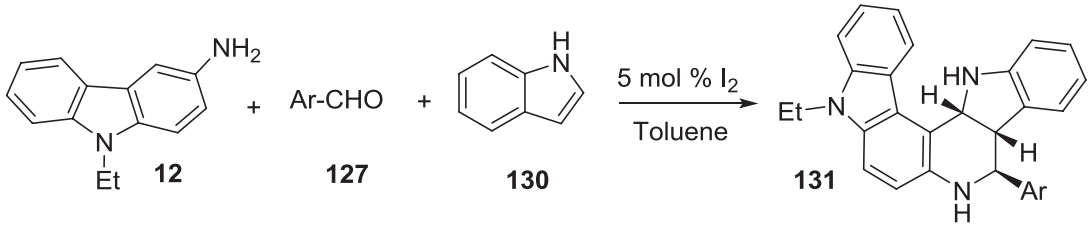


Ar = 4-CN-C_6H_4 , 4-Cl-C_6H_4 , 3-Br-C_6H_4 , 4-$NO_2C_6H_4$, 4-Me-C_6H_4 , 3,4$Cl_2C_6H_3$

Scheme 45.

3.4.5. Formation of indolo[2',3':4,5]pyrido[2,3-*c*]carbazoles

A stereoselective Povarov reaction leading to *exo*-9-aryl-5-ethyl-5,8,9,9a,14,14a-hexahydroindolo-[2',3':4,5]-pyrido [2,3-*c*]carbazoles **131** via a three-component reaction of compound **12**, aromatic aldehydes **127**, and indole **130** in boiling toluene containing a catalytic amount of iodine (5 mol%) has been reported by Wang et al. (Scheme 46).[64]



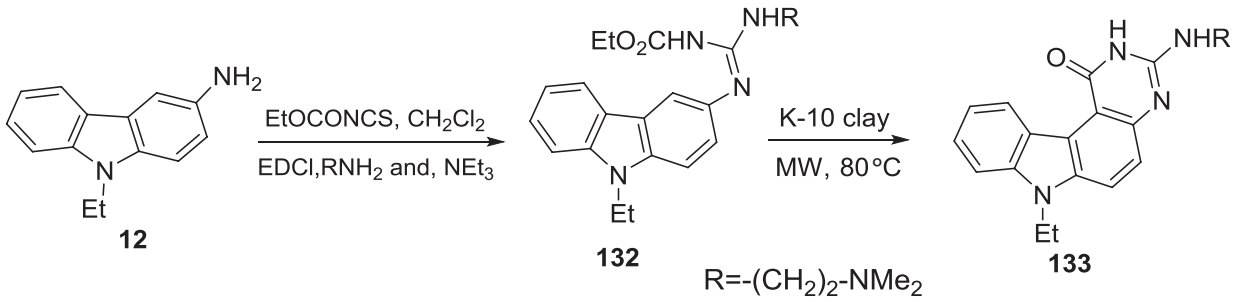
Ar = 4-CN-C_6H_4 , 4-Cl-C_6H_4 , 3-Br-C_6H_4 , 4-$NO_2C_6H_4$, 4-Me-C_6H_4 , 3,4$Cl_2C_6H_3$

Scheme 46.

3.4.6. Formation of pyrimido[4,5-*c*]carbazoles

N-Ethoxycarbonyl-N'-(carbazol-3-yl)guanidine derivative **132** was obtained by the base-catalyzed nucleophilic addition of compound **12** to ethoxycarbonyl-isothiocyanate followed by in situ treatment of the adduct with

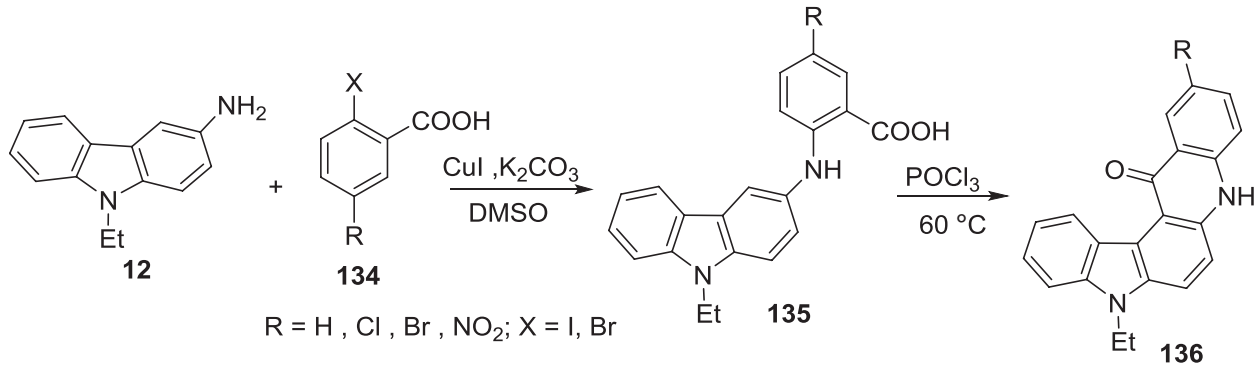
N^1, N^1-dimethylpropane-1,3-diamine. The microwave-assisted Friedel–Craft intramolecular cyclization of compound **132** in the presence of a catalytic amount of montmorillonite K-10 clay produced pyrimido[4,5-*c*]carbazole derivative **133** (Scheme 47).[65] The latter compound **133** showed significant micromolar IC_{50} against cancer cell lines.



Scheme 47.

3.4.7. Formation of indolo[3,2-*a*]acridines

2-(9-Ethyl-9*H*-carbazolylamino)benzoic acids **135** were obtained by the Ullmann–Goldberg condensation reaction of compound **12** with *o*-halobenzoic acids **134** in DMSO containing anhydrous potassium carbonate. The corresponding 8-ethyl-5,8-dihydro-13*H*-indolo[3,2-*a*]-acridin-13-ones (**136**) were obtained by cyclization of the latter products **135** in $POCl_3$ at 60 °C (Scheme 48).[66]

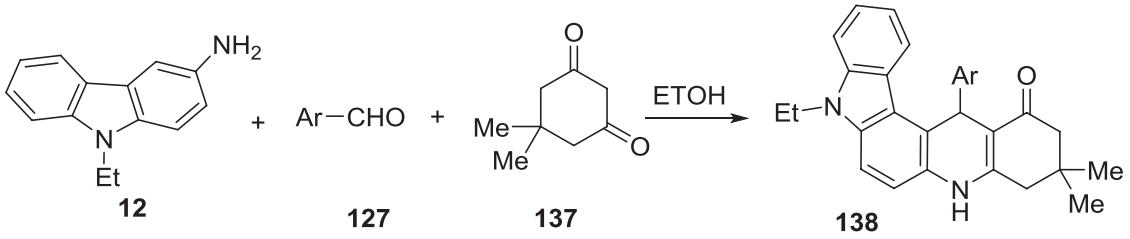


Scheme 48.

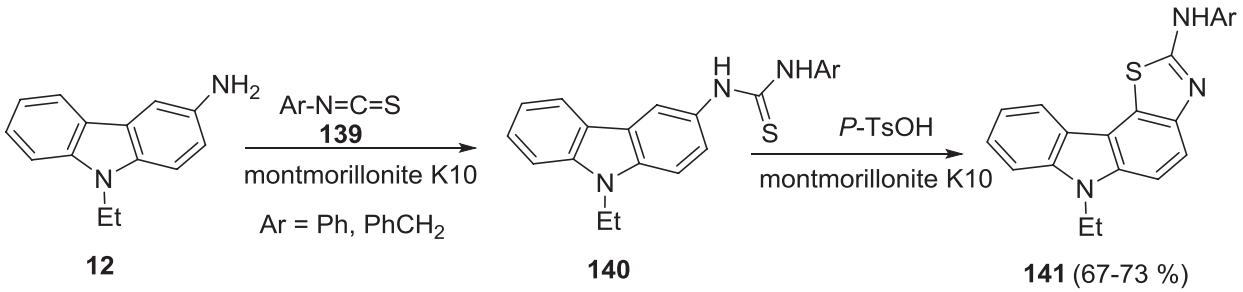
The one-pot three-component reaction of compound **12** with aromatic aldehydes **127** and 5,5-dimethyl cyclohexane-1,3-dionen **137** in refluxing ethanol under catalyst-free conditions was used to synthesize 13-aryl-8-ethyl-3,3-dimethyl-2,3,4,5,8,13-hexahydro-1*H*-indolo-[3,2-*a*]acridin-1-ones **138** with high regioselectivity (Scheme 49).[67]

3.4.8. Formation of thiazolo[4,5-*c*]carbazoles

N-Aryl-thioureido carbazoles **140** were produced by the nucleophilic addition of compound **12** to aryl isothiocyanates **139** on montmorillonite K-10 clay at room temperature. The 2-arylaminothiazolo[4,5-*c*]carbazoles **141** were formed regio-selectively with good yields (67%–73%) when compounds **140** were adsorbed on montmorillonite K-10 clay saturated with *p*-toluene sulfonic acid (1:1, w/w) and heated at 70 °C (Scheme 50).[68]



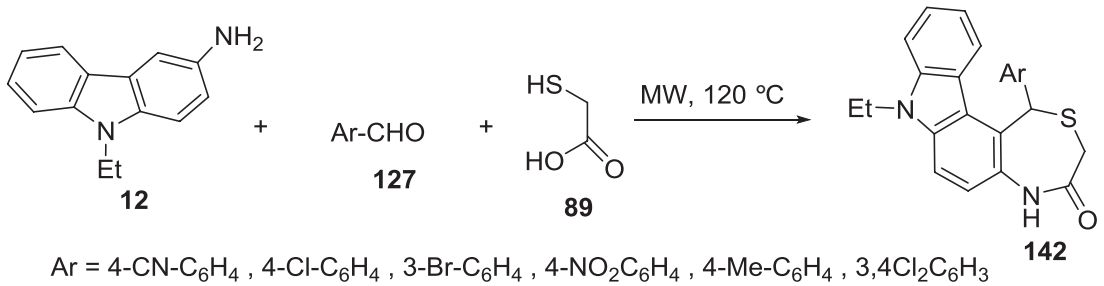
Scheme 49.



Scheme 50.

3.4.9. Formation of [1,4]thiazepino[5,6-*c*]carbazoles

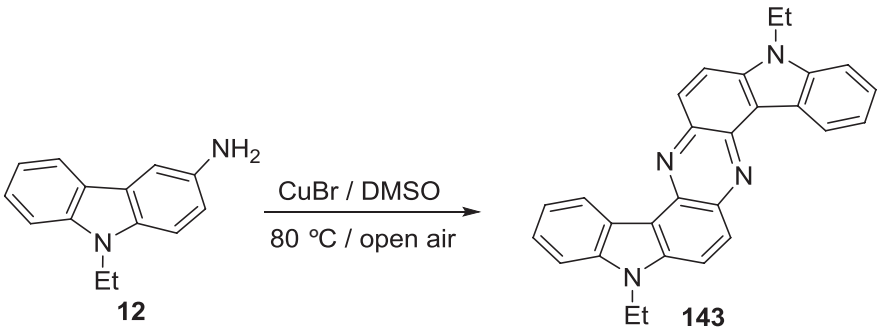
Shi et al. have reported the synthesis of novel functionalized 1-aryl-8-ethyl-5,8-dihydro-1H-[1,4]thiazepino[5,6-*c*]-carbazol-4(3*H*)-ones (**142**) by the microwave- assisted reaction of compound **12** with aromatic aldehydes **127** and 2-mercaptoacetic acid **89** under solvent-free conditions (Scheme 51).[69] The fact that the synthesized compounds show noteworthy antioxidant activity and exhibit remarkably selective cytotoxicity to carcinoma cell line HCT 116 is revealed by evaluation of their antioxidant and anticancer activities.



Scheme 51.

3.4.10. Formation of diindolo[3,2-*a*:3',2'-*h*]phenazine

Meesala and Nagarajan[70] have reported a simple and efficient method for the synthesis of 1,9-diethyl-1,9-dihydrodiindolo[3,2-*a*:3',2'-*h*]phenazine (**143**) through the aerobic oxidative coupling of compound **12** in the presence of a catalytic amount of CuBr (10 mol%) in DMSO at 80 °C while open to air (Scheme 52).



Scheme 52.

4. Conclusion

In this study, the advances in the chemistry, chemical reactivity, and applications of 3-amino-9-ethylcarbazole are reviewed. 3-Aminocarbazole can interact as mono- and bifunctional reagents capable of being applied in a wide range of addition, substitution, condensation, and cyclization reactions. Three active sites are used to determine the reactivity of 3-aminocarbazole. One of the sites is related to the amino group and the others two sites are associated with C-2 and C-4. The reactivity of two adjacent carbon atoms is enhanced and the nucleophilic addition at these sites is promoted by the strong electron-donating potential of the amino group. It is also reported that 3-amino-9-ethylcarbazole undergoes cyclization reactions involving either an amino group or an amino group with C-2 and/or C-4, thus forming pyrrole, thiazole, indolone, pyridine, pyrimidine, quinazoline, phenanthroline, naphthyridine, indeno[1,2-*b*]indolone, indolo[3,2-*a*]acridines, indolo[2',3':4,5]pyrido[2,3-*c*]carbazoles, thiazolo[4,5-*c*]carbazoles, and [1,4]thiazepino[5,6-*c*]carbazoles. In addition, we also discussed the medicinal and material applications of the obtained carbazoles. In conclusion, additional interesting applications of 3-amino-9-ethylcarbazole are also anticipated in future.

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