Applications of aminocarbazoles in heterocyclic synthesis

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DOI: http://dx.doi.org/10.3998/ark.5550190.p008.822

Abstract
Aminocarbazoles are versatile building blocks in organic synthesis. This review focuses on the application of aminocarbazoles to generate a large variety of fused carbazole heterocycles such as pyridocarbazoles, isomeric pyridocarbazoles, thiazolocarbazoles, pyrimidocarbazoles, pyrrolocarbazoles, indolocarbazoles, quino- and chromeno-carbazoles and many others. Many of these molecules exhibit promising biological activities.

Keywords: Aminocarbazoles, cyclization, one-pot syntheses, three component reactions, ellipticine

Table of Content

1. Introduction

Carbazole derivatives are widely utilized in medicinal,[1-5] organic,[6-7] and material chemistry.[8-9] In particular, aminocarbazoles and its derivatives have gained much attraction due to their prominent pharmacological activities.[10-30] The amino carbazole derivative has the potential of being active against Alzheimer's disease since the presence of an amino group at the indole nucleus has shown promising results as a rehabilitative medicine.[31] 1-Aminocarbazoles have been identified as Bcl-2 protein inhibitors,[32] NPY5 antagonists,[33] and anion receptors.[34] Aminocarbazoles are also useful intermediates for syntheses of various dyes and pigments, stabilizers for polymers, pesticides, photographic materials and diagnostic reagents in cytochemical studies. For example, 3-amino-9-ethylcarbazole has been widely used as a peroxidase suitable for the colorimetric detection of antibodies for the diagnosis of certain diseases.[35-38] Both polymeric and molecular amorphous derivatives of 3-aminocarbazoles have attracted interest of the researchers due to their semiconductive properties.[39-43] For these considerations, many synthetic approaches have been developed towards the syntheses of aminocarbazoles and their derivatives.[44-59]

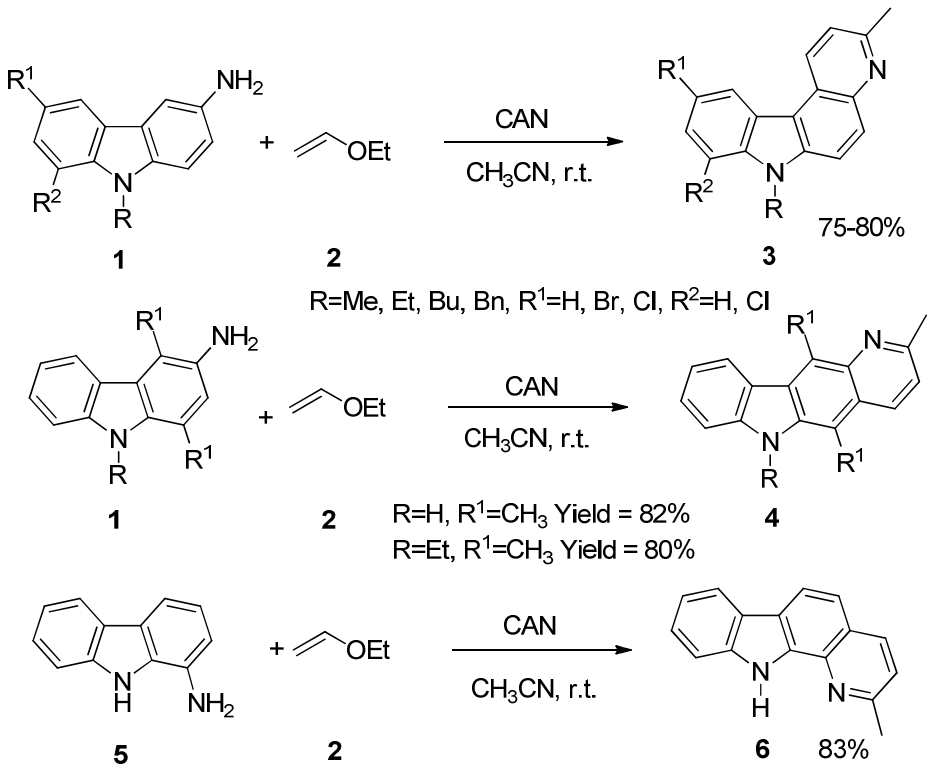
Aryl and heteroaryl-annulated carbazoles, such as pyridocarbazoles, indolocarbazoles, and pyrrolocarbazoles have attracted growing attention since they are distributed in numerous natural products with diverse useful bioactivities.[60-68] Aminocarbazoles have been an important synthon to construct pyridocarbazoles,[69] which are well known for their antitumor properties.[70,71] Also, aminocarbazoles have been used to prepare pyrimido[5,4-*b*]carbazole derivatives.[72] The main objective of the present survey is to provide the applications of aminocarbazoles in the synthesis of various heterocycles and provide useful and up-to-date data for organic and medicinal chemists.

2. Synthesis of Pyridocarbazoles

Pyridocarbazoles are important constituents of heteroannulated carbazoles and exhibit a wide spectrum of biological and medicinal activity such as treatment of breast cancer, intercalation into the DNA double helix, inhibition of topoisomerase II, and anti-HIV agent.[73-75]

2.1. Pyrido[2,3-*c*]carbazoles

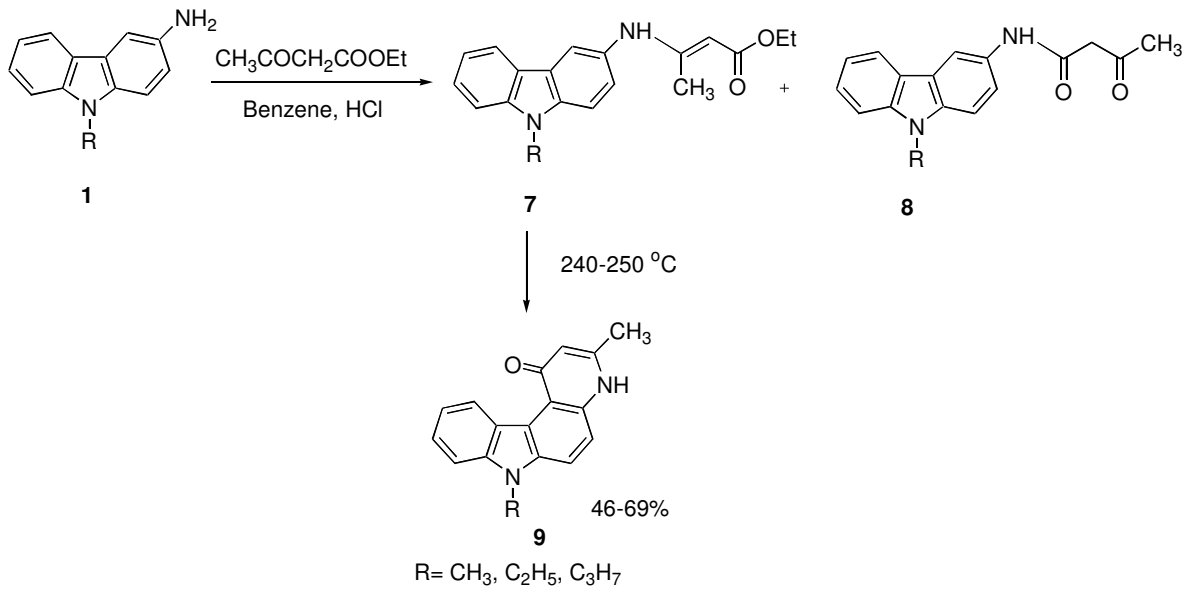
Pyrido[2,3-*c*]-, pyrido[2,3-*b*]-, and pyrido[2,3-*a*]carbazoles were synthesized from various 3-amino- and 1-aminocarbazoles *via* Povarov reaction with ethyl vinyl ether as the dienophile.[76] This transformation is catalyzed by cerium(IV) ammonium nitrate (CAN) under mild reaction conditions without a co-catalyst or ligand. The reaction of 3-aminocarbazoles **1**, ethyl vinyl ether **2** and CAN (10 mol%) in acetonitrile proceeded smoothly gave the corresponding pyrido[2,3-*c*]-carbazoles **3** in good yield. When the 3-aminocarbazole **1** was substituted by a methyl group at C4, a 3-amino-4-methylcarbazole, the products have the pyrido[2,3-*b*]carbazole skeleton **4**. On the other hand, when 1-aminocarbazole **5** was subjected to the Povarov reaction under same reaction conditions pyrido[2,3-*a*]carbazole **6** was obtained as the product (Scheme 1).



Scheme 1

2.2. Pyrido[2,3-*c*]carbazol-1-ones

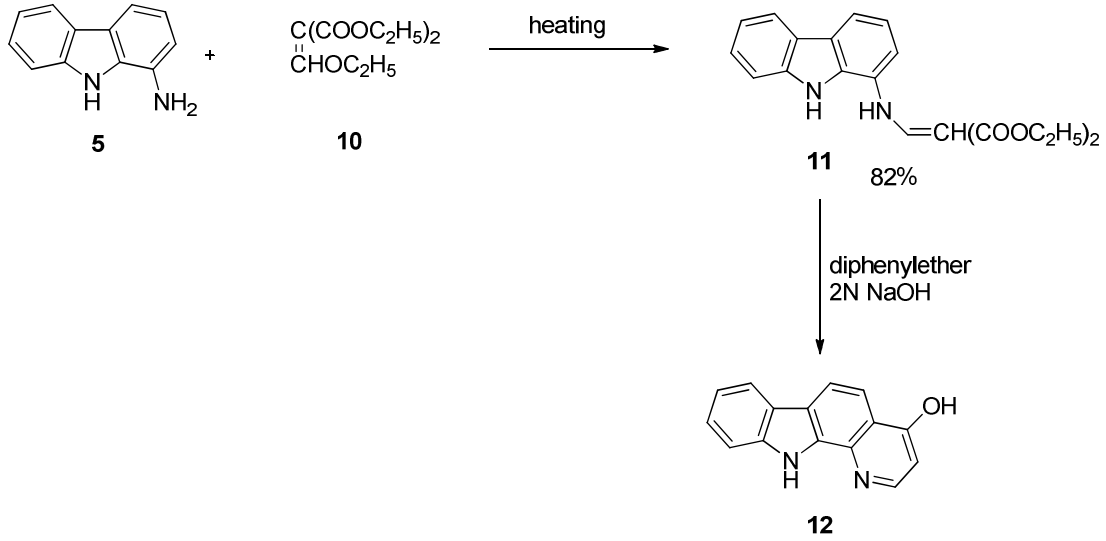
The reaction of 9-alkyl-3-aminocarbazoles **1** with ethyl-3-oxobutanoate in benzene in the presence of a catalytic amount of hydrochloric acid yielded mixture of two products the amide **8** and the condensation product ethyl 3-[(9-ethylcarbazol-3-yl)amino]-2-butenoate **7** in a 1:4 ratio. The condensation products **7** were cyclized to the corresponding 4,7-dihydropyrido[2,3-*c*]-carbazol-1-ones **9** upon heating in mineral oil at 240-250 °C (Scheme 2).[77] The synthesized compounds were studied by NMR spectra. Molecular modeling data supported the findings deduced from the ^{13}C-NMR and ^{1}H-NMR spectra.



Scheme 2

2.3. Hydroxypyridocarbazoles

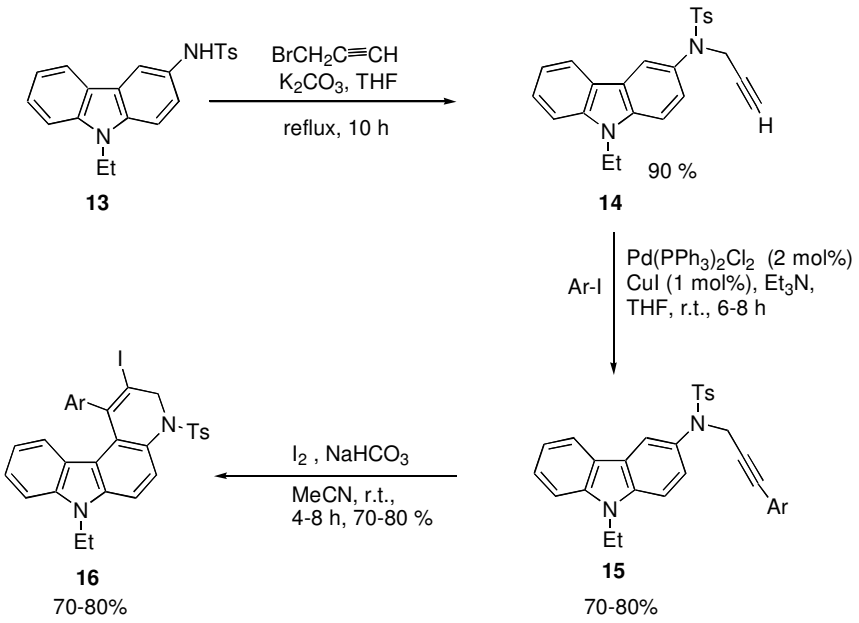
The reaction of 1-aminocarbazole **5** with ethoxymethylenemalonic ester **10** under mild heating conditions furnished *α*-carbethoxy-*β*-(1-carbazolylamino)acrylate **11** which was cyclized by heating under reflux in diphenyl ether. The resulting ester was hydrolyzed with aqueous alkali and the acid decarboxylated to the corresponding hydroxypyridocarbazole **12** (Scheme 3).[78]



Scheme 3

2.4. Dihydropyridocarbazoles

Recently, various iodo-substituted dihydropyridocarbazole derivatives were synthesized *via N*-propargylated 3-aminocarbazoles (Scheme 4).[79]



Scheme 4

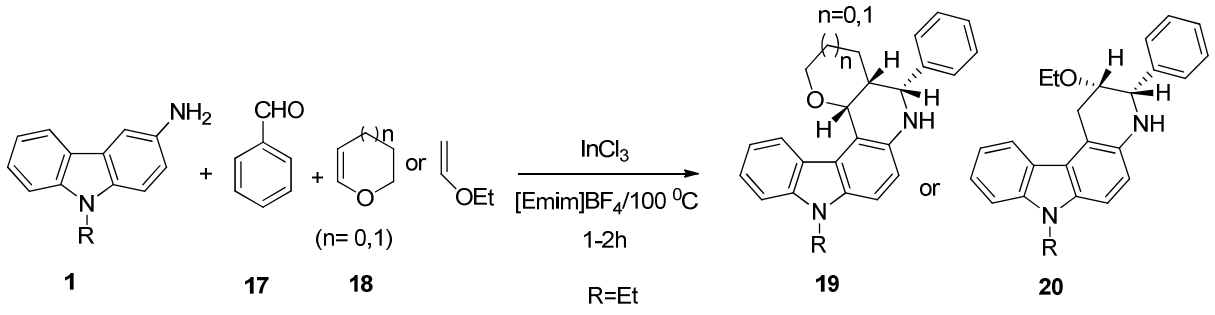
Propargylation of *N*-tosylated aminocarbazole **13** with propargyl bromide in the presence of K_2CO_3 in THF offered propargylated aminocarbazole **14** with good yield. The obtained product **14** was subjected to Sonogashira coupling with various aryl iodides in the presence of $Pd(PPh_3)_2Cl_2$ and CuI in THF yielded disubstituted alkynes **15**. Then iodocyclization reaction with iodine and $NaHCO_3$ in acetonitrile produced the corresponding iodo-substituted dihydropyridocarbazole derivatives **16** in good yields (Scheme 4).

3. Synthesis of Isomeric Ellipticine Derivatives

Ellipticine, an alkaloid and several of its derivatives exhibit promising results in the treatment of osteolytic breast cancer metastases, brain tumors, kidney sarcoma, and myeloblastic leukemia.[80] More recent studies have also indicated activity against HIV.[81] The main reason for the interest in ellipticine and its derivatives for clinical purposes is their high efficiency against several types of cancer, limited toxic side effects, and a complete lack of hematological toxicity.[82]

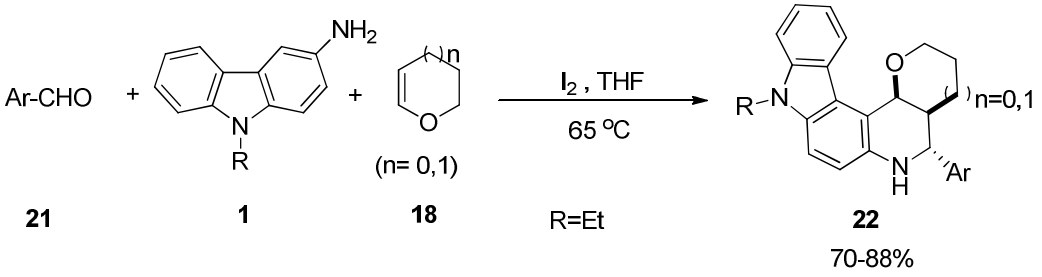
An efficient, three component, one-pot synthesis of new isomeric ellipticine derivatives **19, 20** were prepared through an intermolecular imino Diels–Alder reaction of 3-aminocarbazoles **1** and benzaldehyde **17** with electron-rich alkenes **18** such as 3,4-dihydro-2*H*-pyran, 2,3-

dihydrofuran and ethyl vinyl ether catalyzed by $InCl_3$ (10 mol%) in ionic liquid (Scheme 5).[83] In the case of substituted benzaldehydes, reductive amination was observed.



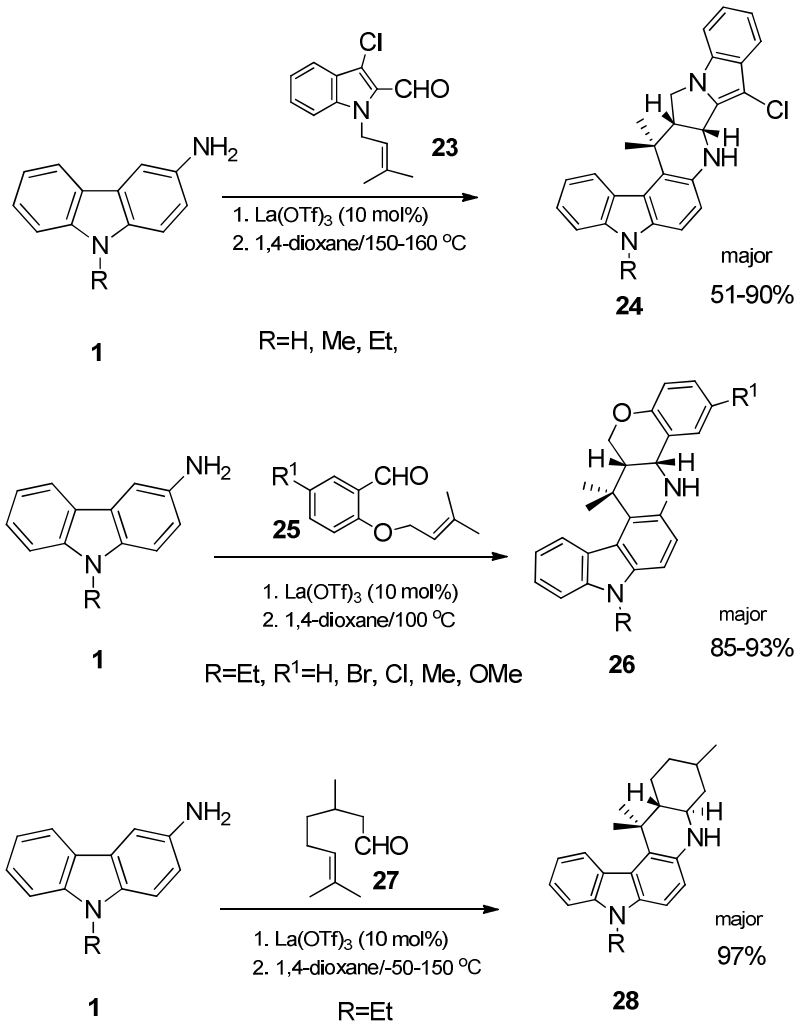
Scheme 5

Similarly, a mild, efficient and highly selective approach to the synthesis of cryptolcarbazole derivatives **22** via three-component reactions of 3-amino-9-ethylcarbazole **1** and aromatic aldehydes **21** with electron-rich alkenes **18** was reported (Scheme 6).[84] It was found that the tetrahydropyran ring and six-membered piperidine rings were *cis* fused and *trans* to Ar substituent. Products were obtained in good to high yields, with high selectivity being confirmed by X-ray diffraction analysis.



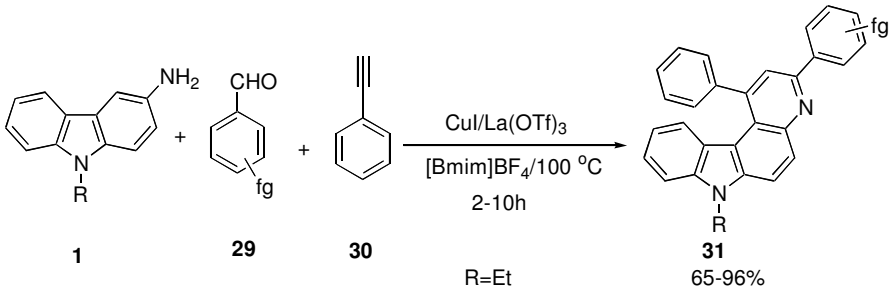
Scheme 6

Various isomeric ellipticine derivatives were synthesized from aminocarbazoles utilizing a novel [4+2] cycloaddition reaction (Scheme 7).[85] The imino Diels-Alder reaction of *N*-prenylated-2-formyl-3-chloroindole **23** with various substituted aminocarbazoles **1** in the presence of $La(OTf)_3$ (10 mol %) under the optimized conditions yielded the corresponding imino Diels-Alder products **24** in excellent yields. Cycloaddition of **1** with **25** at 100 °C proceeded efficiently in 1,4-dioxane to afford **26** in excellent yield with higher diastereoselectivity ratio; the cis isomer is the major product. Similarly, the reaction of aminocarbazoles **1** with aliphatic aldehyde **27** as a dienophile proceeded smoothly to afford **28** with good yield. Interestingly, in this case the *trans* isomer was the major product.



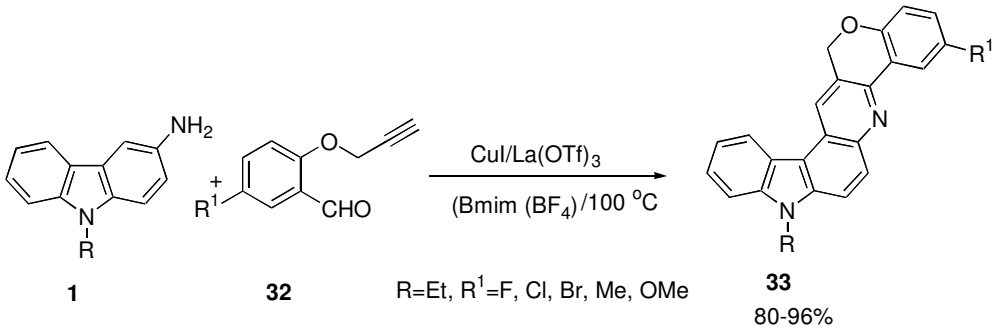
Scheme 7

In another work, a one-pot synthesis of isomeric ellipticine derivatives through CuI/La(OTf)$_3$ catalyzed sequential inter/intramolecular cyclization of substituted alkynes with imines followed by aromatization was reported (Scheme 8).[86] The reaction of imine derived from aminocarbazole **1** and aldehyde **29** with phenylacetylene **30** in the presence of CuI/La(OTf)$_3$ in [Bmim]BF$_4$ afforded **31** along with the side product. One equivalent of imine underwent the cyclization with phenylacetylene to dihydropyridocarbazole, which further aromatized to the product **31**. CuI was found to be efficient and necessary catalyst to activate the triple bond. It was observed that substituents having an electron poor or electron rich or heteroaromatic group gave the desired products in good to excellent yields.



Scheme 8

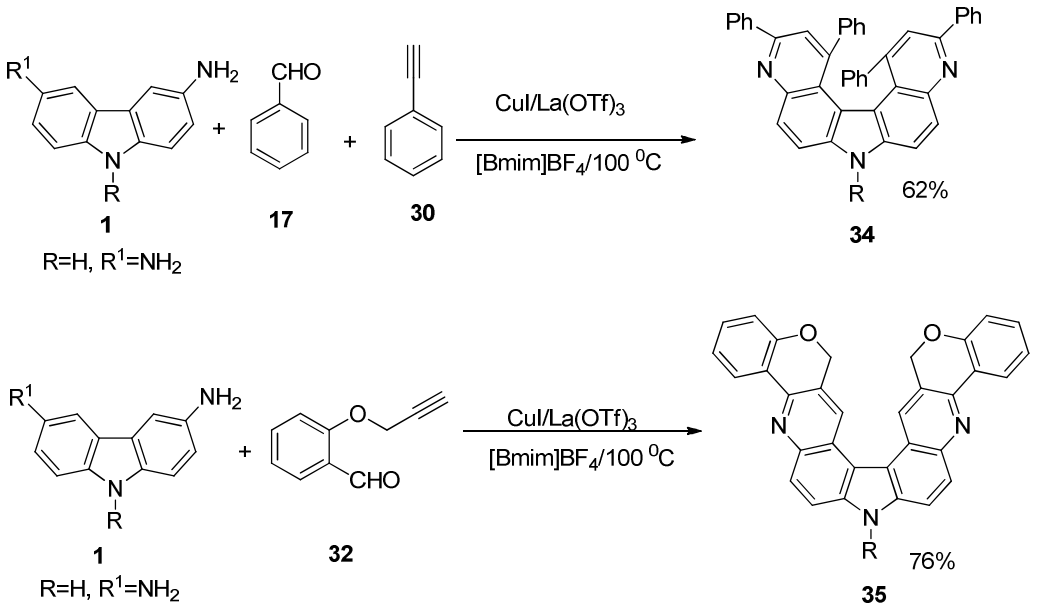
The reaction of *O*-propargylated salicylaldehydes **32** with 3-aminocarbazole **1** in the presence of CuI/La(OTf)$_3$ in ionic liquid yielded the corresponding intramolecular cyclization products **33** in excellent yields and the cyclization occurs through the fourth position of the carbazole ring (Scheme 9).



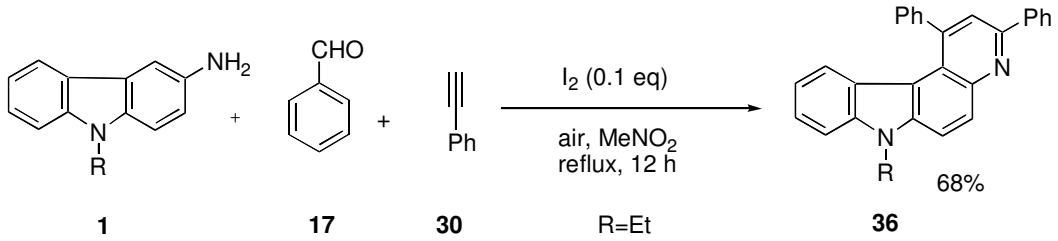
Scheme 9

Similarly, the intermolecular reaction of diaminocarbazole **1** with benzaldehyde **17**, phenylacetylene **30** under the same reaction conditions proceeded well and furnished the corresponding product **34** in 62% yield (Scheme 10). The structure of the product **34** was confirmed by single crystal analysis. Also, the intramolecular pathway of diaminocarbazole **1** with *O*-propargylated salicylaldehyde **32** gave the product **35** in 76% and there was no monocyclized product observed.

A one-pot synthesis of quinolines *via* molecular iodine-catalyzed and air-mediated tandem condensation/imino-Diels-Alder/isomerization/oxidation of simple readily available amines, aldehydes, and alkynes was reported.[87] This methodology was extended to the polycyclic aromatic 9-ethylcarbazol-3-amine. The reaction of 9-ethylcarbazol-3-amine **1**, benzaldehyde **17** and phenylacetylene **30** in nitromethane in the presence of molecular iodine and air produced the ellipticine isomer **36** in 68% yield (Scheme 11). This has been done by assembling the quinoline core *via* a one-pot three component reaction from [3+2+1] atom fragments by formation of three new bonds.



Scheme 10

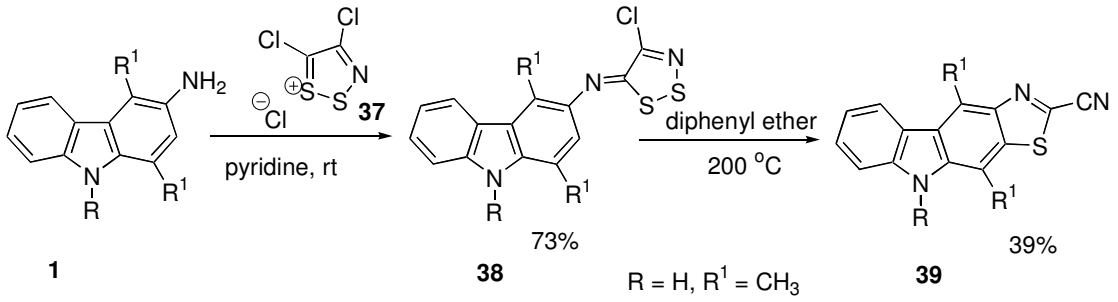


Scheme 11

4. Synthesis of Thiazolocarbazoles

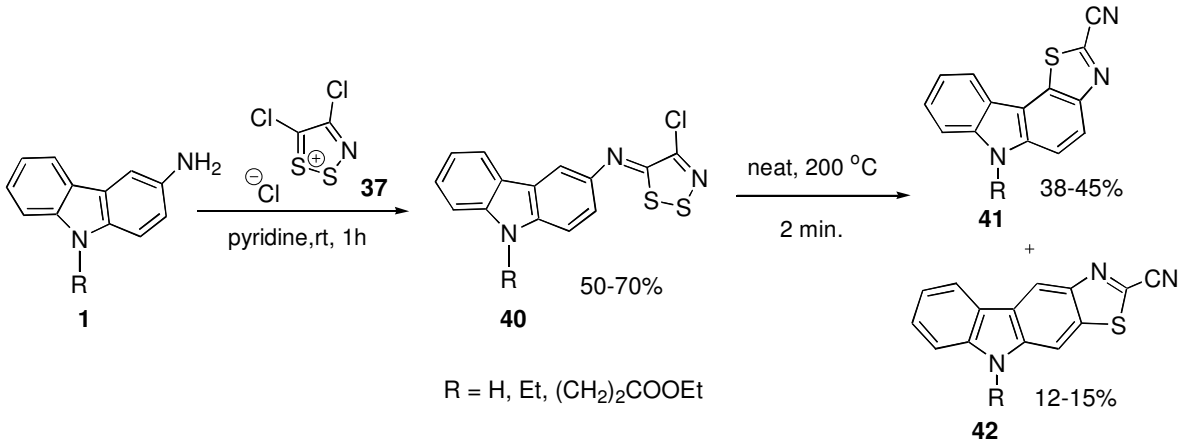
4.1. Thiazolocarbazolecarbonitriles

2-Cyanobenzothiazole is an important pharmacophore with proven and potential bioactivities.[88] Reaction of aminocarbazole **1** with 4,5-dichloro-1,2,3-dithiazolium chloride **37** was carried out in dichloromethane at room temperature, followed by addition of pyridine, to give the desired (1,2,3-dithiazol-5-ylideneamino)carbazole **38** in 73% yield. Compound **38** was heated at 200 °C in the presence of diphenyl ether for 30 minutes to afford the thiazolocarbazolecarbonitrile **39** (Scheme 12).[89]



Scheme 12

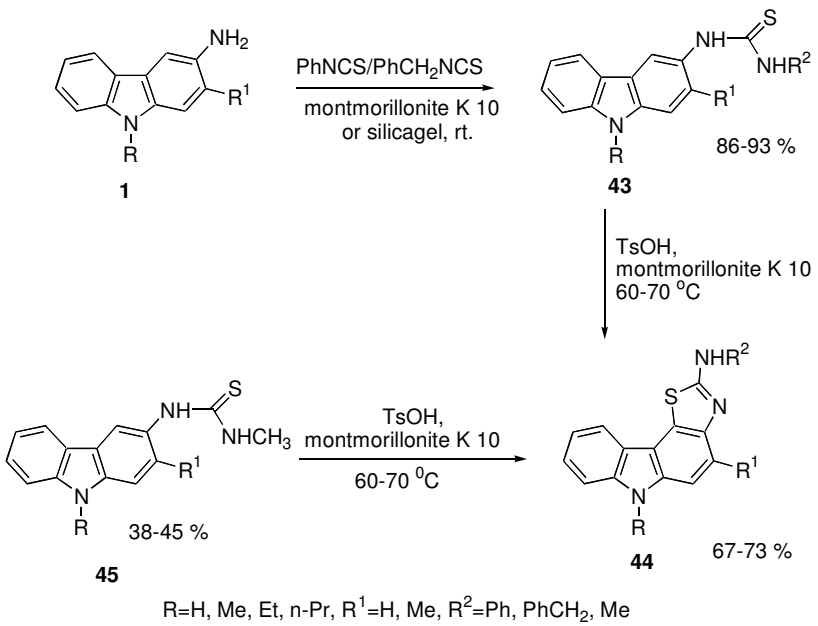
Following a similar strategy, demethylated analogues of ellipticine were prepared from various 3-aminocarbazoles **1** *via* the corresponding imino-1,2,3-dithiazoles **40**. Whatever thermolysis conditions were used, the wanted linear thiazolocarbazolecarbonitriles **42** were the minor products, whilst their angular counterparts **41** were the major ones (Scheme 13).



Scheme 13

4.2. 2-Aminothiazolocarbazoles

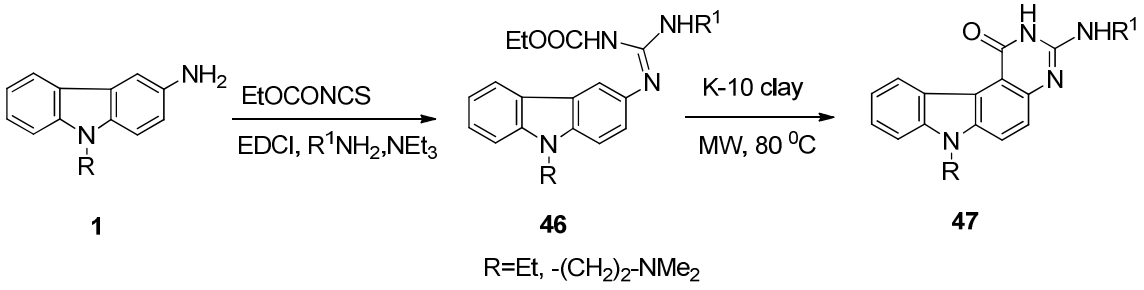
The 3-aminocarbazoles **1** were condensed with phenyl and benzyl isothiocyanates on montmorillonite K10 clay or TLC-grade silica gel at room temperature to furnish the *N*-phenyl and *N*-benzylthioureidocarbazoles **43**. The later compounds **43** were adsorbed on montmorillonite K10 clay impregnated with *p*-toluenesulfonic acid (1:1, w/w) and heated at 60-70 ºC to afford the 2-anilino and 2-benzylaminothiazolo[4,5-*c*]carbazoles **44** regioselectively in high yields. The cyclisation was also effective for the *N*-methylthioureidocarbazoles **45** (Scheme 14).[90]



Scheme 14

5. Synthesis of Pyrimidocarbazoles

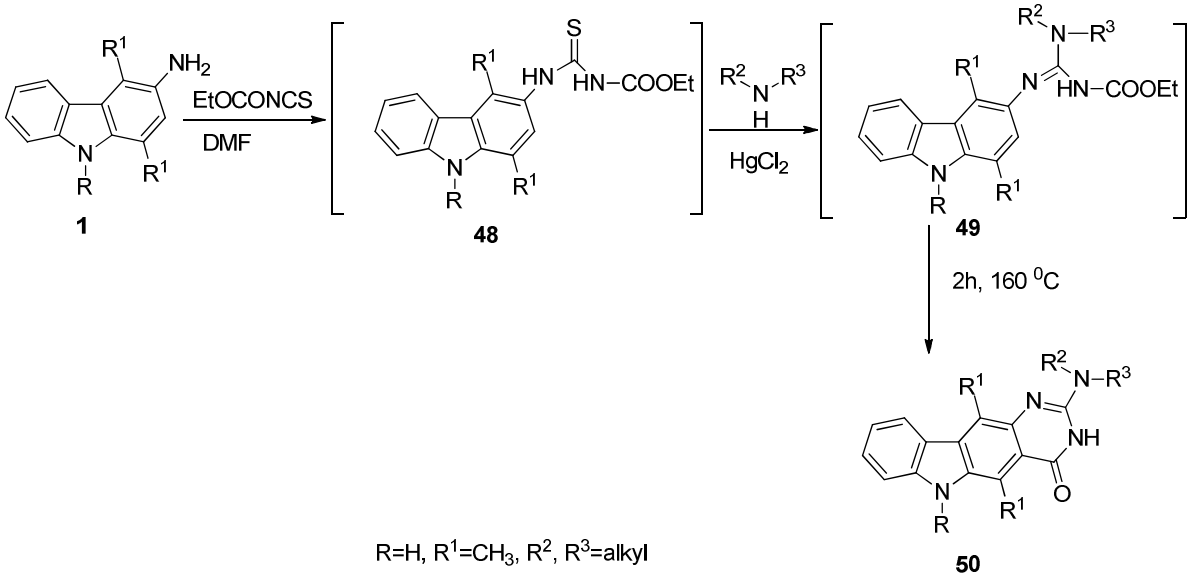
The ethoxycarbonyl protected guanidine intermediate **46** was prepared in two steps realized in one-pot and in nearly quantitative yield from 3-aminocarbazole **1**. The intermediate **46** was subjected to Friedel–Crafts intramolecular cyclization under microwave irradiation using montmorillonite K-10 clay as a catalyst to gave tetracyclic pyrimido[4,5-*c*]carbazole **47** in 77% yield (Scheme 15).[91] The pyrimido[4,5-*c*]carbazole derivative showed significant micromolar IC_{50} against cancer cell lines.



Scheme 15

Several 2-dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-ones **50** were prepared in a simple one-pot reaction starting from 3-aminocarbazoles.[92] The aminocarbazoles **1** were treated with ethoxycarbonylisothiocyanate to give thiourea intermediates **48**, followed by

the addition of an alkylamine and $HgCl_2$ to give ethoxycarbonylguanidine intermediates **49**. The reaction mixture was then heated at 160 ºC to give the 2-dialkylamino-5,11-dimethyl-6*H*-pyrimido[5,4-*b*]carbazol-4(3*H*)-ones **50** (Scheme 16).

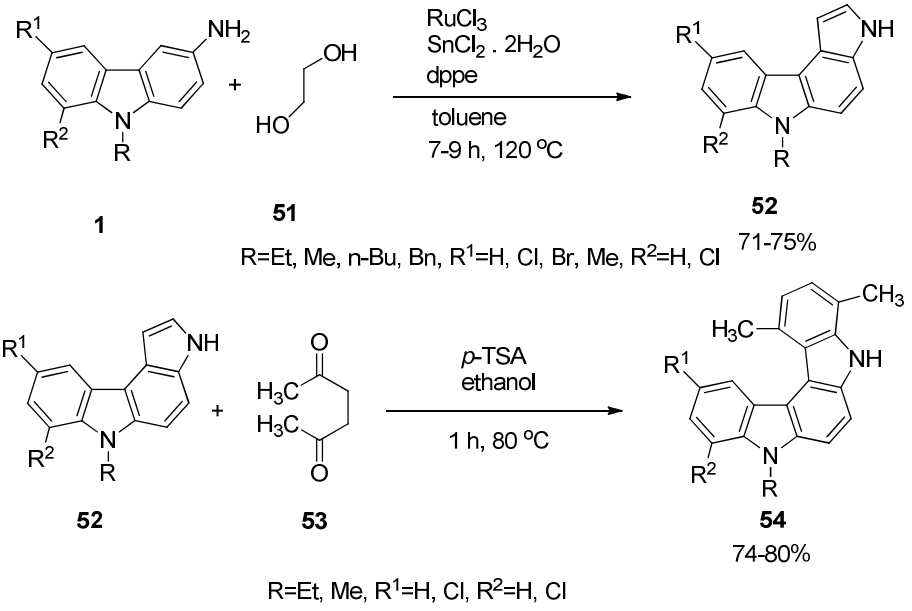


Scheme 16

6. Synthesis of Pyrrolo- and Indolo-carbazoles

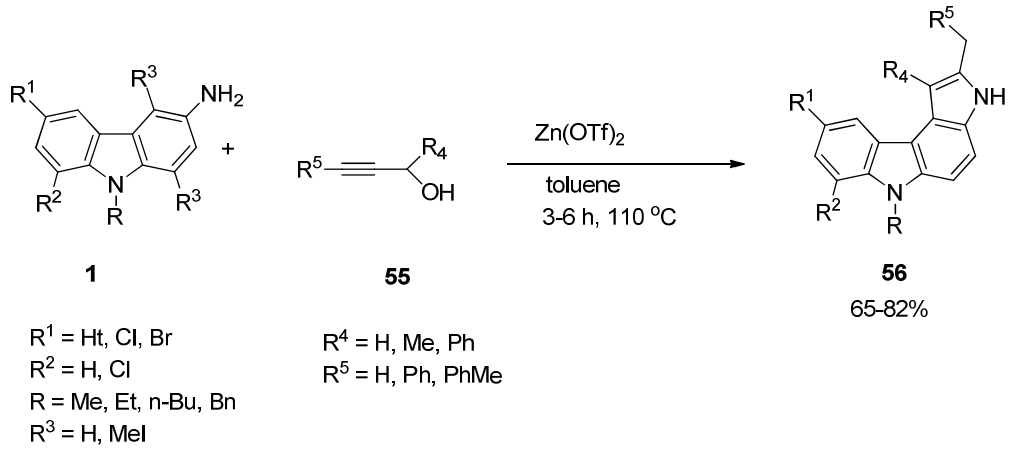
Pyrrolo[2,3-*a*] and [3,4-*c*]carbazoles have great importance due to their inhibiting properties toward pim kinase inhibitors[93] and Chk1 inhibitors,[94] respectively. Indolocarbazole, the benzene analog of pyrrolocarbazole have received great attention because of their existence in many natural products with potent biological activities.[95]

Pyrrolo[2,3-*c*]carbazoles **52** were synthesized from *N*-alkylated-3-aminocarbazoles **1** and ethylene glycol **51** via heteroannulation reaction using $RuCl_3/SnCl_2$ (Scheme 17).[96] The best yields were obtained when the reactions were carried out in toluene. It was observed that without the addition of $SnCl_2$ heteroannulation reaction did not proceed. $RuCl_3$ was found to be an efficient catalyst in this reaction compared with other catalysts. The authors found that dppe was the most effective ligand for this reaction. The desired indolo[2,3-*c*]carbazoles **54** were successfully synthesized in good yields by reacting acetonylacetone **53** with various pyrrolo-[2,3-*c*]carbazoles **52** using *p*-toluenesulfonic acid as a catalyst.



Scheme 17

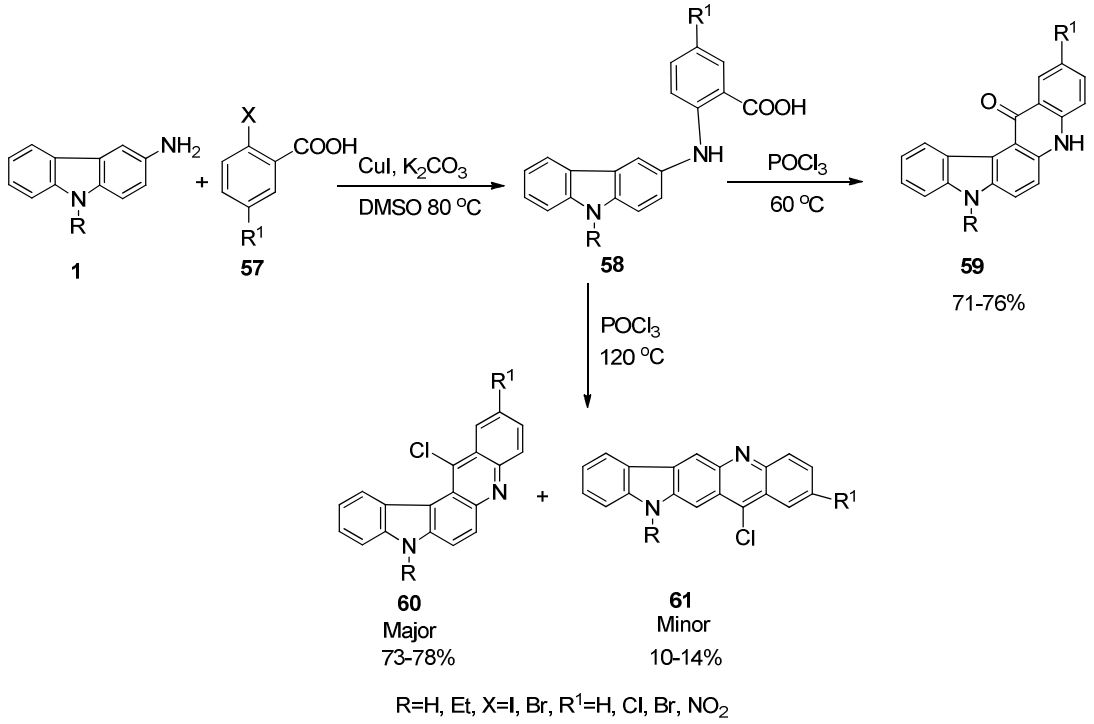
Pyrrolo[2,3-*c*]carbazoles **56** were also synthesized by zinc triflate catalyzed heteroannulation reaction of 3-aminocarbazoles with substituted propargyl alcohols **55** moderate to good yields (Scheme 18).[97] This transformation proceeded with good regioselectivity and without the addition of additives or ligands.



Scheme 18

7. Synthesis of Quino- and Chromeno-carbazoles

Quino and chromenocarbazoles were synthesized from aminocarbazoles in two steps based on C–N and C–O bond formation through Ullmann–Goldberg condensation followed by intramolecular Friedel–Crafts cyclization.[98] As shown in Scheme 19, the condensation of 3-amino-9-ethylcarbazole **1** with various *o*-iodobenzoic acids **57** in presence of CuI and K_2CO_3 without any ligand in DMSO at 80 ºC to give products **58**. The later compounds **58** were subjected to cyclization with $POCl_3$ at 60 ºC to afford the corresponding products **59** in good yields. The reaction works well for other substituted *o*-halobenzoic acids. When the reaction was performed at 120 ºC, two regioisomeric quinocarbazoles were formed. Compounds **60** were formed as a major products along with minor products **61** (Scheme 19).

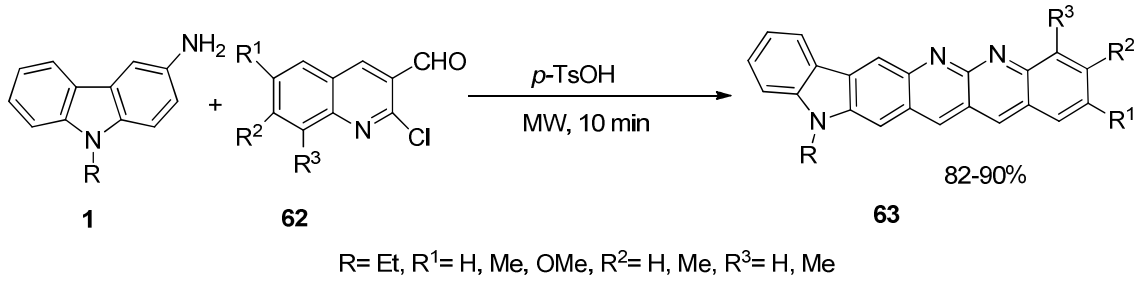


Scheme 19

8. Synthesis of Fused Naphthyridines

Benzonaphthyridines have recently been patented as new generation growth regulators, fungicides, bactericides, herbicides, and insecticides. Moreover, some benzo[*h*]naphthyridines exhibit remarkable biological and pharmacological activities such as antimalarial and as antagonists of the 5-HT4 receptor.[99]

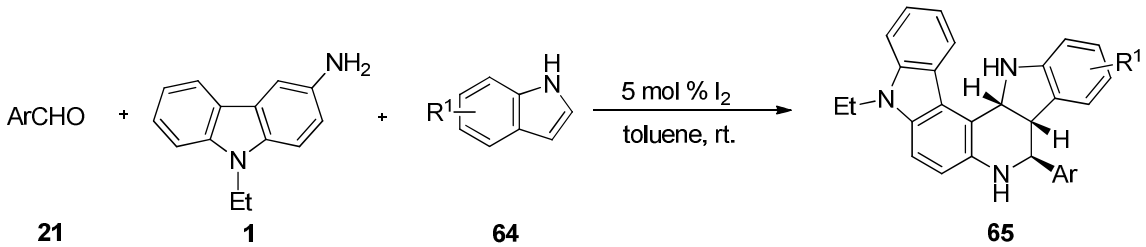
Microwave assisted *p*-TsOH-catalyzed synthesis of benzo[6,7][1,8]naphthyridino[3,2-*b*]-carbazoles **63** *via* a one pot reaction of 3-amino-9-ethylcarbazole **1** and 2-chloro-3-formylquinolines **62** was reported (Scheme 20).[100] The remarkable catalytic activity of *p*-TsOH was superior to other reported catalysts with respect to yields and reduced reaction times.



Scheme 20

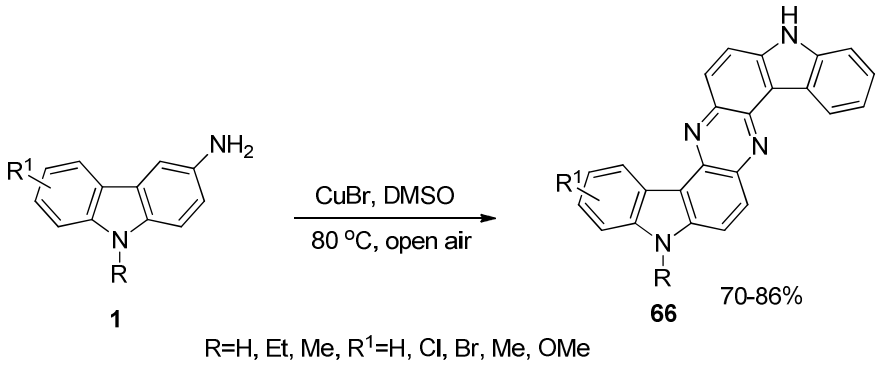
9. Synthesis of other Heterocycles

A three-component synthesis of *exo*-tetrahydroindolo[3,2-*c*]quinoline derivatives **65** from the reaction of an aromatic aldehydes **21**, 9-ethyl-9*H*-carbazol-3-amine **1** and indoles **64** with iodine as catalyst in toluene was reported (Scheme 21).[101] The advantages of this method include mild reaction conditions, moderate yields, high stereoselectivity, metal-free catalyst, and operational simplicity.



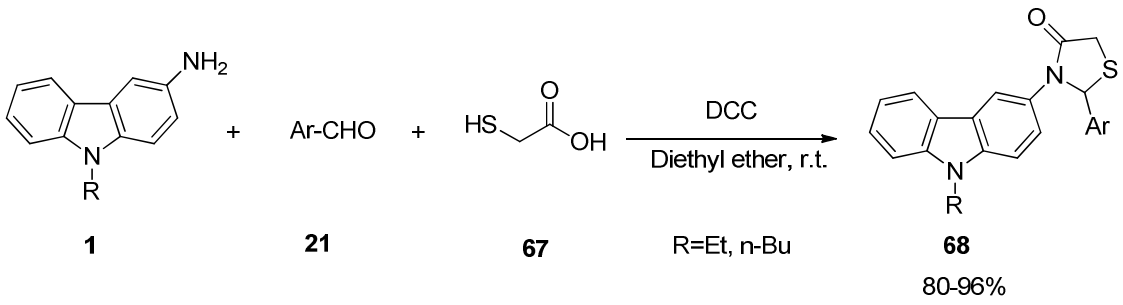
Scheme 21

Diindolophenazine derivatives **66** were synthesized by the aerobic oxidative coupling of 3-aminocarbazoles **1** in the presence of catalytic CuBr in DMSO at 80 ºC while open to air (Scheme 22).[102] After screening a variety of solvents and catalysts, the best result was obtained in DMSO at 80 ºC for six hours using copper(I) bromide as the catalyst. DMSO may play the role of ligand by coordinating the copper salts. A variety of substituents such as Me, OMe, Cl, Br are tolerated well on the aminocarbazole.



Scheme 22

A convenient one-pot three-component synthesis of 2-aryl-3-(9-alkylcarbazol-3-yl)thiazolidin-4-ones **68** from reaction of 3-amino-9-alkylcarbazoles **1**, aromatic aldehydes **21** and 2-mercaptoacetic acid **67** by using dicyclohexylcarbodimide as cyclizing agent in dry ether at room temperature was reported (Scheme 23).[103] This protocol has advantages of mild condition, short reaction time, high yield and simple workup procedure.

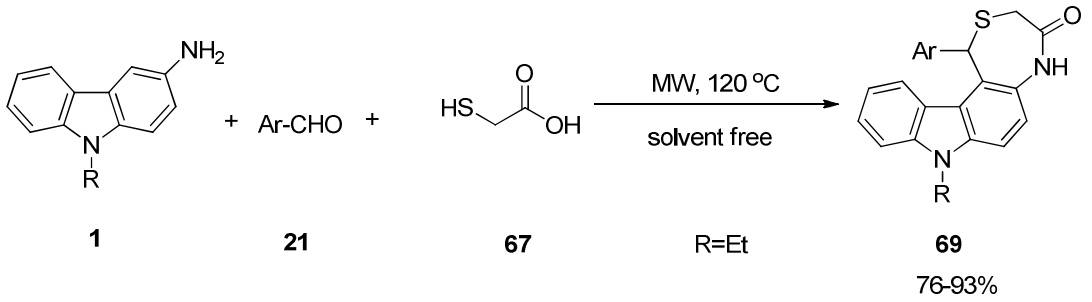


Scheme 23

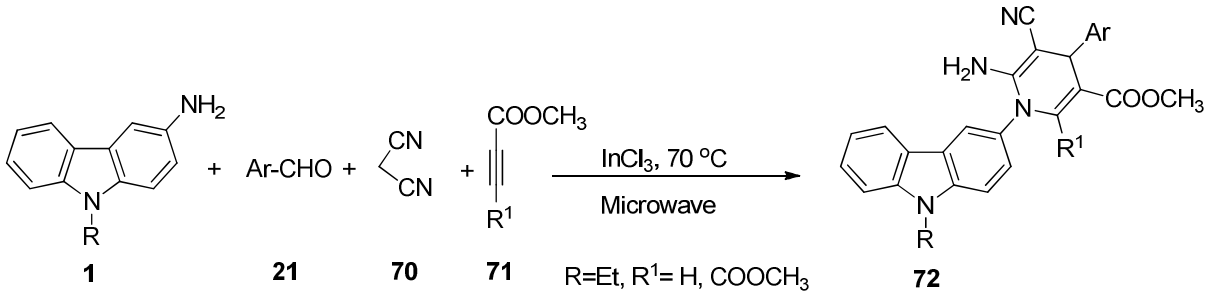
The reaction of aromatic aldehydes **21**, 3-amino-9-ethylcarbazole **1** and mercaptoacetic acid **67** under microwave irradiation (MW) under solvent free conditions offered the corresponding 1,4-thiazepine derivatives **69** (Scheme 24).[104] The screen of solvent revealed that solvent-free condition was the best suitable condition for this reaction. These compounds have been subjected to testing for *in vitro* antioxidant and cytotoxic activities, resulting in the finding that these 1,4-thiazepine derivatives not only have significant antioxidant activity, but also exhibit remarkably selective cytotoxicity to carcinoma cell line HCT 116.

Microwave-assisted eco-friendly four component reaction of 3-amino-9-ethylcarbazole **1**, aromatic aldehydes **21**, malononitrile **70** and acetylenic esters **71** using indium trichloride as catalyst offered *N*-carbazolyldihydropyridines **72** in good yields (Scheme 25).[105] The transformation was believed to proceed *via* Knoevenagel condensation, Michael addition, followed by tautomerization leading to the formation of products. The remarkable catalytic activity of $InCl_3$

was superior to the other reported catalysts. Dimethyl acetylenedicarboxylate also showed very high reactivity. The use of microwave heating reduced reaction times and resulted in higher yields.

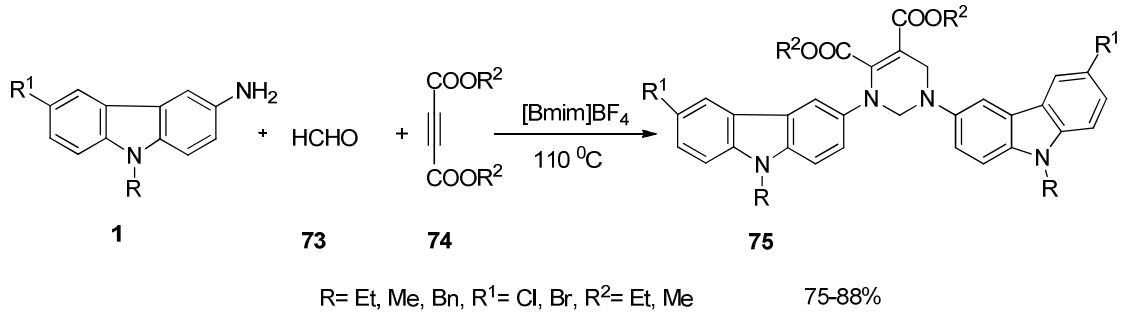


Scheme 24



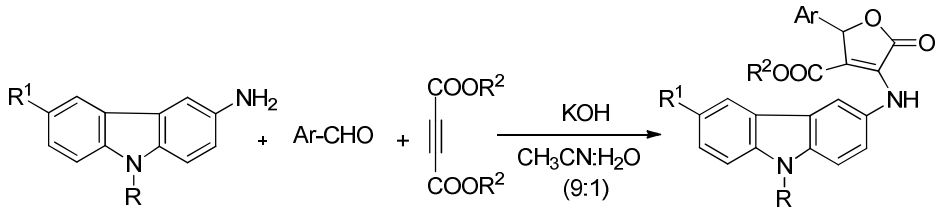
Scheme 25

An ionic liquid mediated, one-pot three-component strategy to synthesize carbazolyltetrahydropyrimidine derivatives **75** from 3-aminocarbazoles **1**, formaldehyde **73** and dialkyl acetylenedicarboxylates **74** was reported (Scheme 26).[106] It was observed that the maximum yield was obtained in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]) without any catalyst.



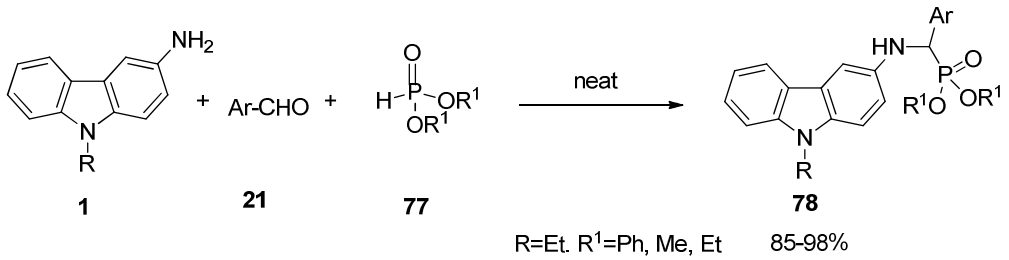
Scheme 26

Similarly, a three-component reaction of 3-aminocarbazoles **1**, dialkyl acetylene-dicarboxylates **74** and aromatic/heterocyclic aldehydes **21** for the synthesis of (carbazolylamino) furan-2(5*H*)-one derivatives **76** was reported (Scheme 27).[106] It was found that potassium hydroxide was superior to the other bases.



Scheme 27

Carbazole-based α-aminophosphonates[107] are known to possess considerable microbial and antioxidant behavior. The Kabachnik-Fields reaction of aminocarbazole **1** with aromatic aldehydes **21** and diphenyl/dialkyl phosphites **77** in the absent of catalyst under neat conditions at 25 ^{o}C gave the corresponding α-aminophosphonates **78** (Scheme 28).[108] This protocol has advantages of absence of catalyst under mild conditions and short period of times. The structure for one of these compounds has been confirmed by X-ray crystallography.



Scheme 28

10. Conclusions

This review highlights the advances in the use of aminocarbazoles as starting materials in the synthesis of wide variety of heterocycles of carbazole framework. Aminocarbazoles can become promising tools for diversity oriented synthesis.

11. Acknowledgements

Padmaja thankful to DST, Govt. of India for providing financial support in the form of Inspire Faculty Fellowship. Narayana Reddy thanks to DST-SERB for a Start-Up Research Grant.

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