A Platinum Open Access Journal
for Organic Chemistry

Review

Free to Authors and Readers

DOAJ Seal

Arkivoc **2025** (3) 202512448

Synthetic approaches of the unsung members of the pyridocarbazole family

Sarah J. Wright and Songeziwe Ntsimango*

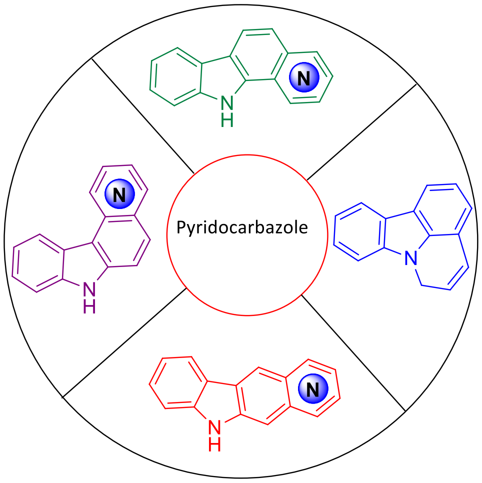
Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits 2050,
Johannesburg, South Africa
Email: Songeziwe.ntsimango@wits.ac.za

Dedication to Professor Hans-Günther Schmalz on the occasion of his retirement and his contribution to the advancement of organic chemistry in South Africa

Received 08-04-2025 **Accepted** 10-27-2025 **Published on line** 11-11-2025

Abstract

Pyridocarbazoles have enjoyed a sustained interest in the synthetic organic chemistry community. However, a review of such efforts has mostly been reserved for the pyrido[*b*]carbazole subfamily, and to a limited extent, the pyrido[*jk*]carbazole core. The pyrido[*a*]- and pyrido[*c*]carbazole subclasses have been neglected in review literature and only appear in scattered publications. This review summarized the synthetic contributions of the lesser known pyridocarbazole family members. The reviewed literature spans from 1949 to 2024. This works aims to highlight synthetic developments across all the pyridocarbazole subfamilies, encouraging future reviews to adopt a more comprehensive scope.



Keywords: Pyrido[*a*]carbazole, pyrido[*b*]carbazole, pyrido[*c*]carbazole, pyrido[*jk*]carbazole, DNA intercalates

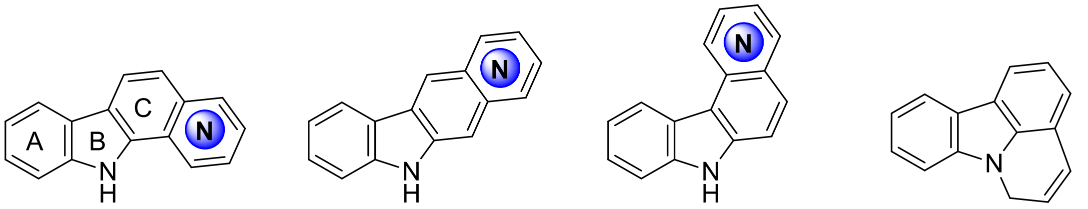
Cite as *Arkivoc* **2025** (3) 202512448
DOI: https://doi.org/10.24820/ark.5550190.p012.448

Table of Contents

1. Introduction

The chemical literature is replete with review articles on pyridocarbazoles.[1-3] However, upon closer inspection, it becomes evident that these reviews focus almost exclusively on a single member of a four-member family. The other pyridocarbazole isomers are typically mentioned only in passing, often as unintended side products in the synthesis of pyrido[*b*]carbazoles, the more celebrated member of this family of compounds. One could easily be misled into thinking that pyrido[*b*]carbazole is the only representative of the pyridocarbazole family, as even publications describing the synthesis of other isomers often reference previous studies centred solely on this one subfamily.

The pyridocarbazole framework could be described as arising from the fusion of the indole nucleus, in the 2,3-position, with an isoquinoline or quinoline fragment. Pyridocarbazoles are structurally related to indoloquinolines, where the nitrogen atom resides on the C ring, instead of ring D. Indoloquinolines have been regularly reviewed[4-5] and fall outside the scope of this review; thus, they will be omitted. Thirteen constitutional isomers result from combining the two moieties in that fashion. These can be divided structurally into four subfamilies, namely, pyrido[*a*]-, pyrido[*b*]-, pyrido[*c*]- and pyrido[*jk*]carbazoles (Figure 1). The pyrido[*jk*]carbazole differs substantially from the other three subfamilies, and due to space limitations, its synthesis and bio-activities are omitted in this review. The reader is directed to a recent review for this subfamily.[6]

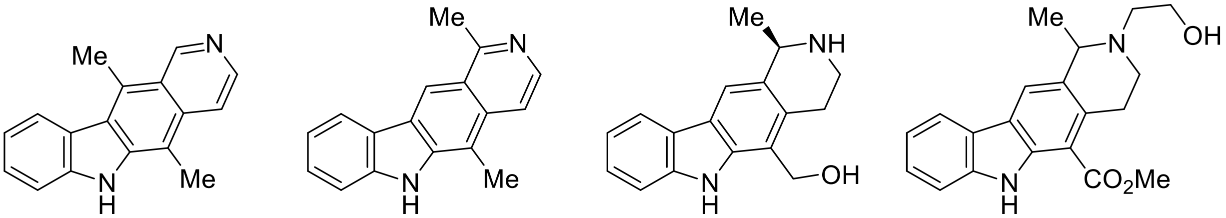


Pyrido[*a*]carbazoles Pyrido[*b*]carbazoles Pyrido[*c*]carbazoles pyrido[*jk*]carbazole

Figure 1. Pyridocarbazole subfamilies.

1.1 Bioactivity of pyridocarbazoles

The synthesis and biological evaluation of this class was inspired by the naturally occurring alkaloids bearing a pyrido[*b*]carbazole core, such as Ellipticine (**1**), Olivacine (**2**), (-)-Janetinine (**3**), and (±)-Stritida B (**4**) (Figure 2); hence, it has received more attention than other sub-members.



Ellipticine (**1**) Olivacine (**2**) (–)-Janetinine (**3**) (±)-Stritida B (**4**)

Figure 2. Naturally occurring pyridocarbazole.

Ellipticine (**1**) and Olivacine (**2**) show significant anticancer properties.[7-10] This is largely resultant of their ability to intercalate into DNA's double helix due to their structural similarity to the DNA base pairs as well as their polycyclic nature, which allows them to penetrate the hydrophobic region of the cell.[7,9,11] In addition, their ability to inhibit topoisomerase II results in the accumulation of unrepaired DNA damage in the cell, leading to apoptosis, adding another level to their cytotoxicity.[7,9,12] Despite the promise shown in these compounds, side effects stopped their clinical trials and derivatives of these compounds had to be prepared to increase their potency and selectivity.[13] This has led to the synthesis of derivatives of **1** and **2**, with various side groups, dimers such as ditercalinium, which can bisintercalate DNA as well as coupling derivatives to steroids such as estradiol to increase the specificity of the target such as breast tumours.[14-15] (-)-Janetinine (**3**) is much less researched, however, it has been shown to induce quinone reductase induction making it a cancer chemopreventive agent.[16-17] No information on the properties of (±)-Stritida have been published to our knowledge.

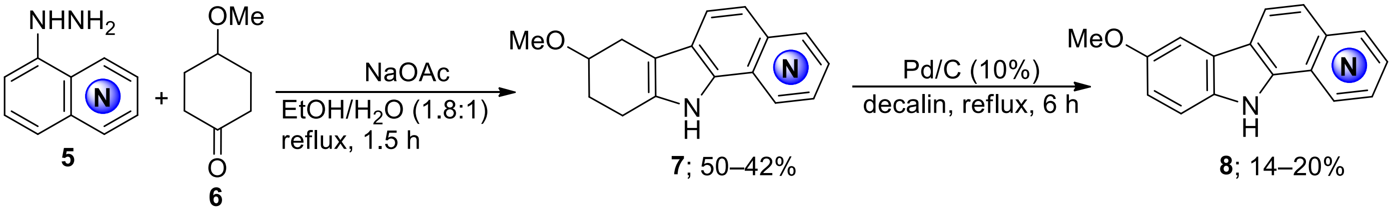
1.2 Organisation of the review

Due to the lack of reviews focusing on the synthesis of the pyrido[*a*]- and pyrido[*c*]carbazole families, the current review will focus on them, with the hope that in the future, all four subfamilies will be reviewed together. We chose to treat the two subclasses separately. The sub-sections are further divided based on the ring that is constructed last to form the pyridocarbazole nucleus.

2. Discussion

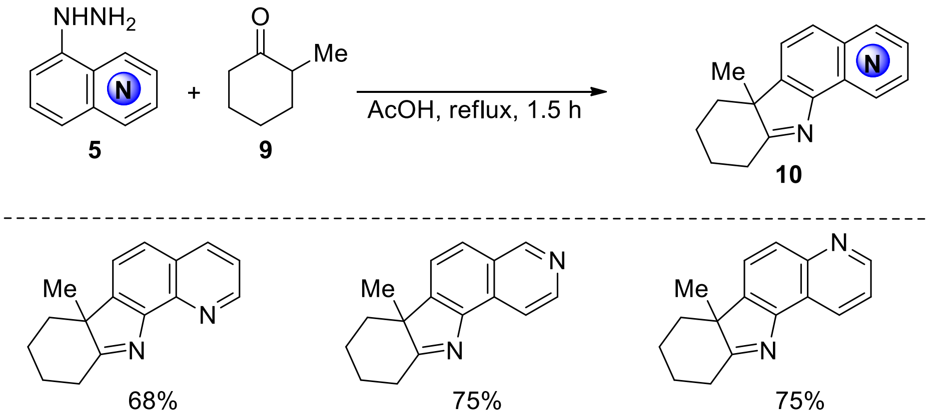
2.1 Synthesis of pyrido[*a*]carbazole

2.1.1 Through the construction of Ring B. The Borsche–Drechsel carbazole synthesis,[18] a special case of the well-known Fischer-indole synthesis, is the most commonly used method for accessing the pyridocarbazole framework. The first reported syntheses of pyrido[*a*]carbazole, pyrido[*b*]carbazole, and pyrido[*c*]carbazole subclasses were achieved by Manske and Kulka using this method.[19-20] Their syntheses involved cyclisation of the suitably substituted hydrazone intermediates, which were easily obtainable from the condensation of ketones and hydrazines.[17-20] Since the Borsche–Drechsel carbazole synthesis leads to the formation of dihydro- or tetra-hydro-pyridocarbazoles, a dehydrogenation step is necessary to form the fully aromatic scaffolds. However, it was found that the hydrazine derived from 6-aminoisoquinoline proved unstable, and therefore, the synthesis of 7*H*-pyrido[3,4-*c*]carbazole, which would have required the condensation between 6-hydrazinylisoquinoline and cyclohexanone could not be achieved.[21] The Borsche–Drechsel carbazole synthesis is reflected in the work by Lescot and co-workers, where hydrazinylquinoline or hydrazinylisoquinoline analogues **5** were reacted with 4-methoxycyclohexanone (**6**) to give the corresponding tetrahydropyrido[*a*]carbazole derivatives **7** (Scheme 1).[22] Subsequent oxidation of compounds **7** with Pd/C in boiling decalin gave the fully aromatic pyrido[*a*]carbazole analogues **8**. This strategy mirrors the synthesis of pyrido[*a*]carbazoles reported by other groups.[23-25]



Scheme 1. Borsche–Drechsel carbazole synthesis of 8-methoxy-pyrido[*a*]carbazoles.

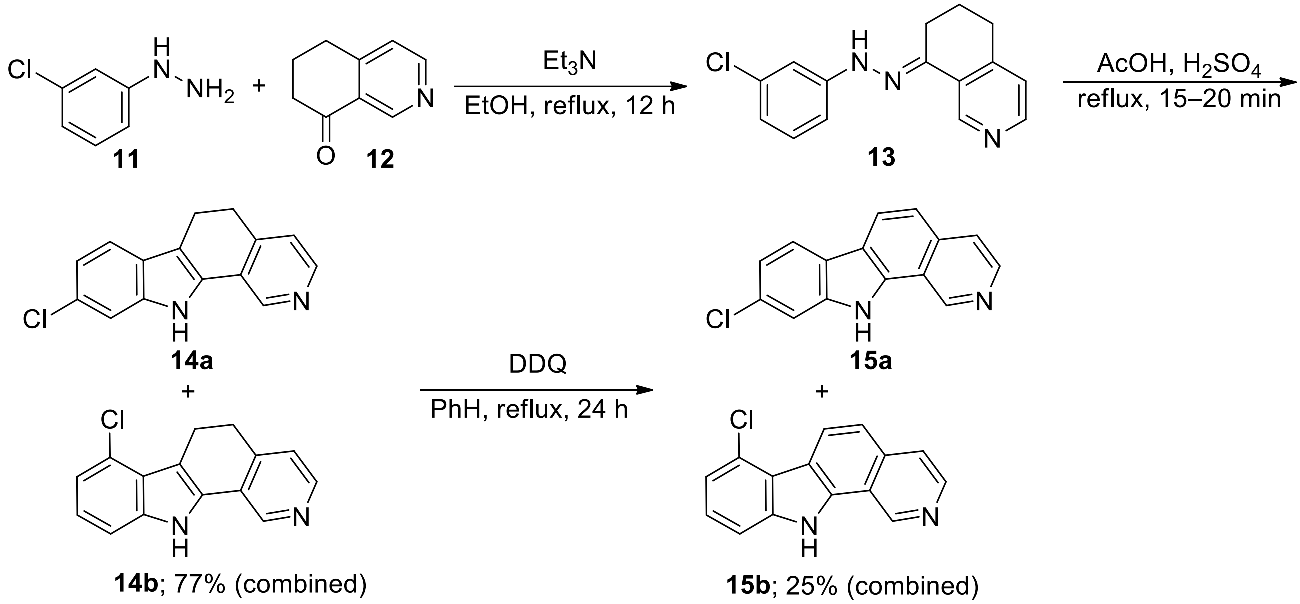
Three tetrahydropyrido[*a*] carbazoles **10** containing an angular methyl group on the 6-position were synthesised from hydrazinylquinolines or hydrazinylisoquinoline **5** and 2-methylcyclohexanone (**9**), as shown in Scheme 2.[26] The report does not offer any reason for the omission of the cyclisation between 8-hydrazinylisoquinoline and 2-methylcyclohexanone (**9**).



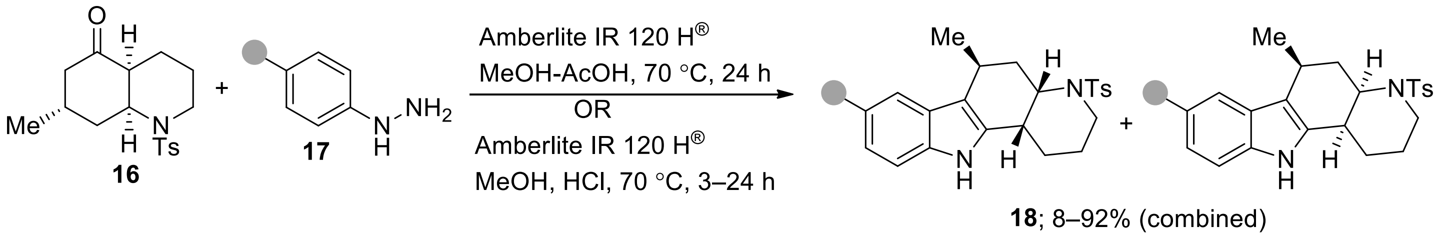
Scheme 2. Borsche–Drechsel carbazole synthesis of pyrido[*a*]carbazoles containing an angular methyl group.

The reports discussed above employ the fully aromatic hydrazinylquinolines or hydrazinylisoquinolines to yield the corresponding pyridocarbazoles with unsaturation on ring A. It is also possible to synthesise pyridocarbazoles with aromatic ring A, with unsaturation on ring C, or on both rings C and D. The former approach was demonstrated by the group of Ferlin, which reported on the reaction between 3-chlorophenylhydrazine **11** and dihydroisoquinolinone derivative **12** to form hydrazone **13**. Subsequent cyclisation of hydrazone **13** in refluxing acetic and sulphuric acid mixture produced isomeric dihydropyrido[*a*]carbazole analogues **14a** and **14b** (Scheme 3).[27] Subsequent DDQ oxidation of the inseparable mixture of **14a** and **14b** gave the corresponding fully aromatic pyrido[*a*]carbozole derivatives **15a** and **15b**, which could not be separated. The same report also discloses a synthesis of other pyrido[*a*]carbazole derivatives, which were further elaborated into dimethylamino-substituted derivatives that were investigated as potential antiproliferative agents, DNA intercalators, and topoisomerase II inhibitors.[27]

The group of Rutjes disclosed the synthesis of octahydro-1*H*-pyrido[3,2-*a*]carbazole analogues **18** through the reaction of *cis*-decahydroquinoline derivative **26** and a range of phenylhydrazines **17** (Scheme 4).[28] The report also showed that the formation of the epimers **18** occurs as a result of the acid-induced retro-aza-Michael ring-opening of the β-amino ketone fragment. The concomitant recyclization to the more stable epi-*cis*-decahydroquinoline and the subsequent reaction with phenylhydrazines **17** led to the corresponding diastereomers **18**.[28]



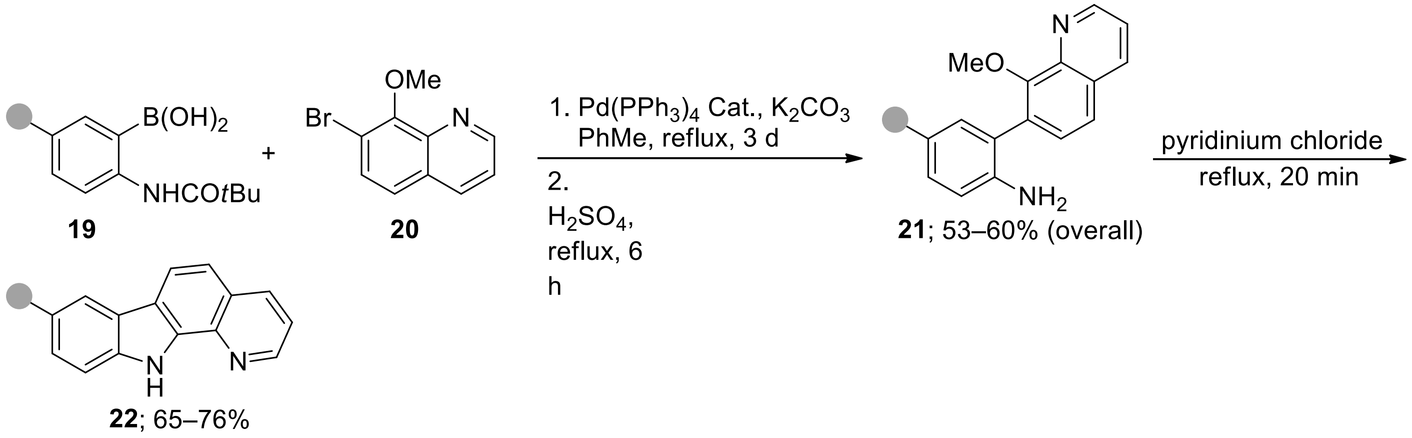
Scheme 3. The synthesis of chlorinated pyrido[*a*]carbazoles through the Borsche–Drechsel reaction.



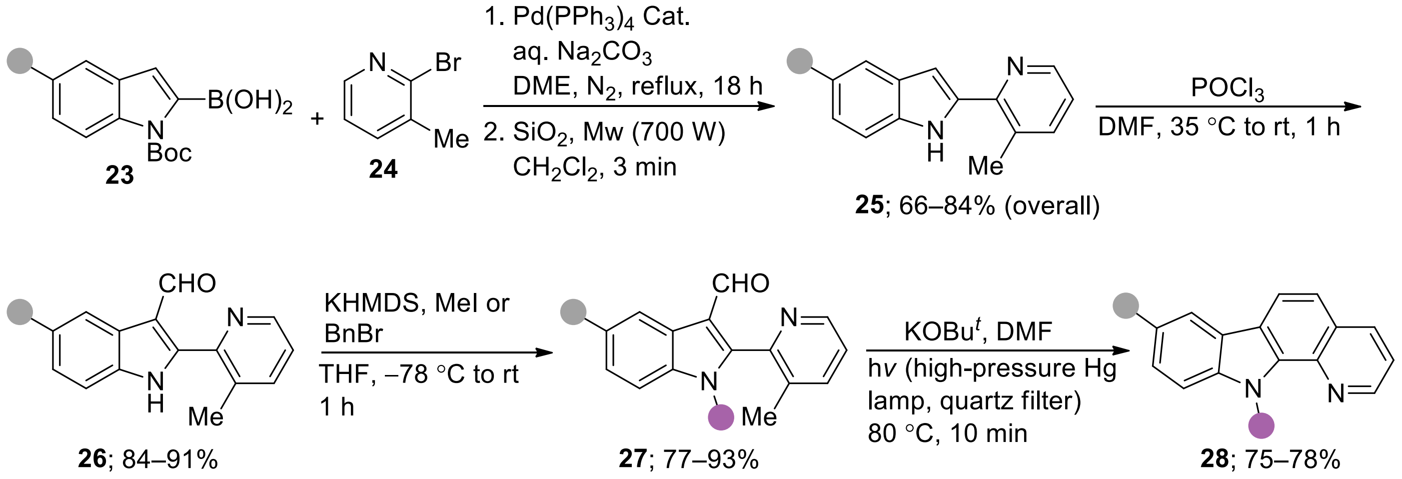
Scheme 4. The synthesis of chiral octahydro-1*H*-pyrido[3,2-*a*]carbazole using Borsche–Drechsel reaction.

Quéguiner and co-workers achieved the synthesis of pyrido[2,3-*a*]carbazole analogues **22** via C–N bond forming reaction of biaryl aniline-quinoline intermediates **21** on reflux in pyridinium chloride (Scheme 5).[29] The requisite biaryl intermediates **21** were obtained in two steps through the Suzuki-Miyaura coupling between *ortho*-phenyl-carbamate boronic esters **19** and 7-bromo-8-methoxyquinoline (**20**), giving biaryl carbamates, which were hydrolysed to biaryl aniline-quinoline intermediates **21**. This strategy is also reflected in the work of Håheim et al., where it was used to synthesise 11*H*-pyrido[2,3-*a*]carbazole, 11*H*-pyrido[3,2-*a*]carbazole, 7*H*-pyrido[2,3-*c*]carbazole, and 7*H*-pyrido[3,2-*c*]carbazole.[30]

De Koning and colleagues achieved the synthesis of 11*H*-pyrido[2,3-*a*]carbazole derivatives via the synthetic sequence displayed in Scheme 6.[31] Their synthesis relied on the Suzuki-Miyaura coupling reaction between *Boc*-protected 2-indolyl boronic acid derivatives **23** and 2-bromo-3-methylpyridine (**24**), subsequent deprotection gave 2-pyridyl-indole **25**. Vilsmeier-Haack formylation of **25** gave aldehyde **26**, followed by *N*-alkylation to yield **27** that was transformed to 11*H*-pyrido[2,3-*a*]carbazole derivatives **28** upon UV irradiation.[31] The mechanism of the photo-induced cyclization is unclear. However, on an earlier report, the authors speculated that the aldehyde intermediates undergo photoenolization, followed by 6π-electrocyclic process forming an alcohol intermediate that undergoes dehydration to afford fully aromatised benzene ring.[32]



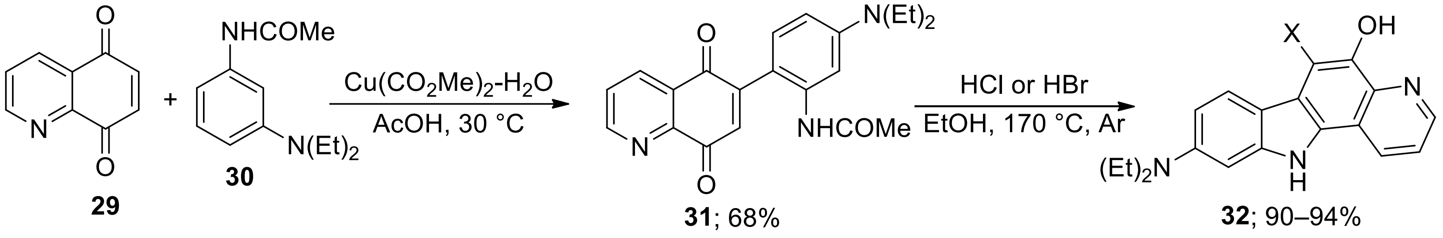
Scheme 5. Pyridinium chloride mediated C–N bond formation in the synthesis of pyrido[2,3-*a*]carbazole core.



Scheme 6. Photochemical cyclisation leading to the formation of pyrido[2,3-*a*]carbazole core.

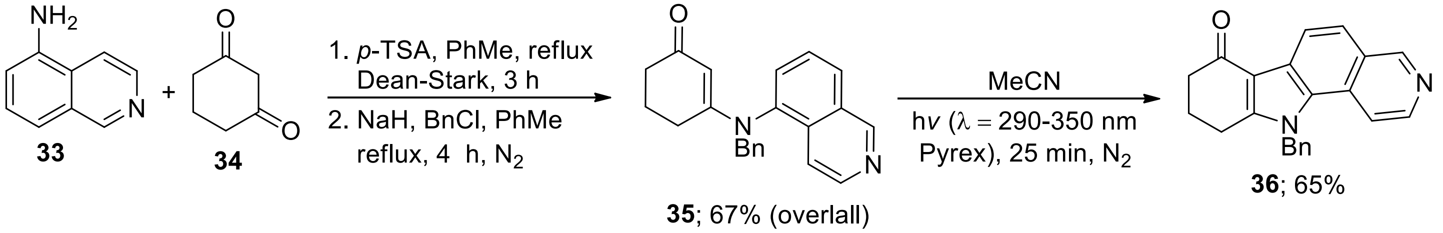
Yoshida and colleagues reported on a concise synthesis of pyrido[3,2-*a*]carbazole derivative via a two-step sequence that involved oxidative coupling of quinoline-5,8-dione (**29**) and *m*-acetylamino-*N*,*N*-diethylaniline (**30**) in the presence of copper(II) acetate and acetic acid, forming 6-aryl-quinolinedione **31** (Scheme 7).[33] Treatment of biaryl **31** with hydrochloric or hydrobromic acid facilitated cyclisation, giving chlorinated or brominated pyrido[3,2-*a*]carbazole analogues **32**, respectively. These were then oxidised and metallated to give complexes that absorb light in the near-IR region for applications in information recording systems.[33]

Likewise, Blache and colleagues disclosed the synthesis of reduced pyrido[4,3-*a*]carbazol-7-one framework employing the B ring formation approach.[34] Their synthetic route involved the condensation of 5-aminoisoquinoline (**33**) and 1,3-cyclohexanedione **34**, yielding secondary vinylogous amide, which was converted into the tertiary vinylogous amide **35** on *N*-alkylation with benzyl chloride (Scheme 8). Enaminone **35** was photocyclized on irradiation at 290-350 nm in acetonitrile, furnishing 11-benzyl-8,9,10,11-tetrahydro-7*H*-pyrido[4,3-*a*]carbazol-7-one (**36**). The same group described a similar synthesis of pyrido[2,3-*c*]carbazole core and the isomeric indolo[2,3-*c*]quinoline framework.[35]



29 **30** **31**; 68% **32**; 90–94%

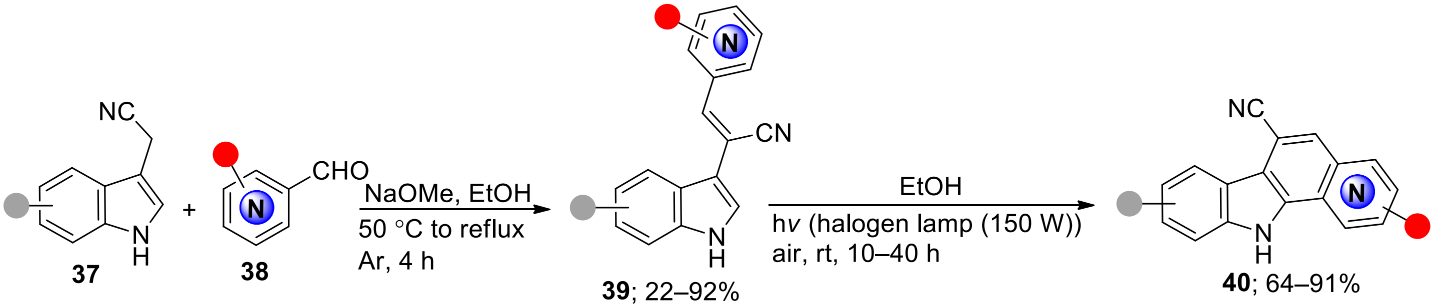
Scheme 7. Hydrochloric or hydrobromic acid facilitated cyclisation to yield the pyrido[3,2-*a*]carbazole framework.



33 **34** **35**; 67% (overlall) **36**; 65%

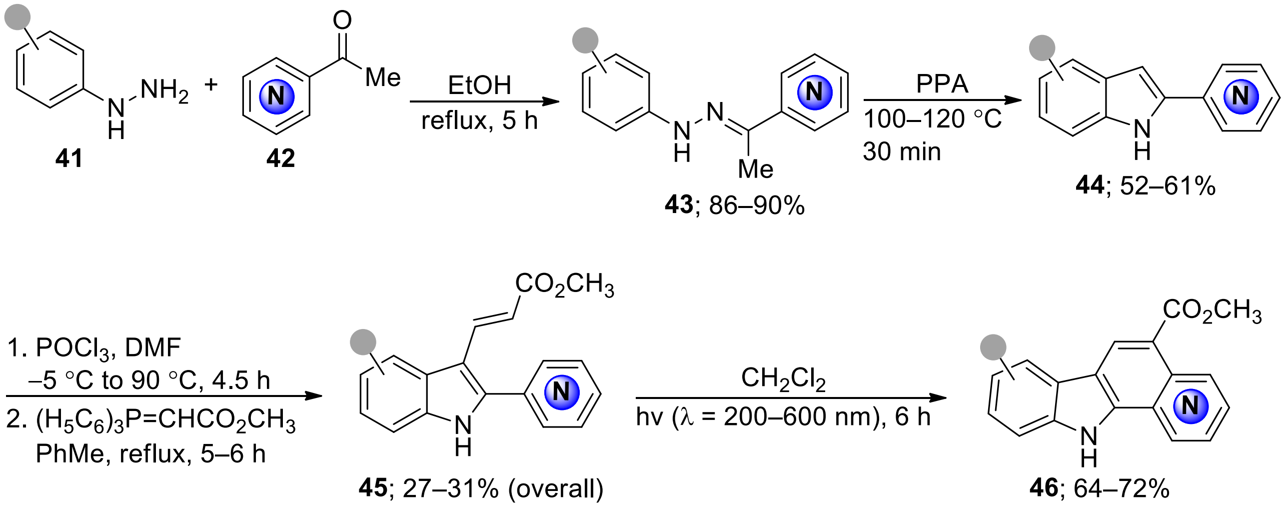
Scheme 8. Formation of pyrido[4,3-*a*]carbazole derivative through enaminone photocyclisation.

2.1.2 Through the construction of Ring C. The synthesis of the pyrido[*a*]carbazole via the formation of ring C relies on the elaboration of the indole unit tethered with the pyridine fragment. A case in point is the two-step synthesis of pyrido[*a*]carbazole nucleus as reported by Labriere and co-workers (Scheme 9).[36] Their synthesis relied on the Knœvenagel condensation between indol-3-ylacetonitrile derivatives **37** and formylpyridine analogues **38** to form indolyl-pyridinyl-acrylonitrile **39** in poor to excellent yields. The Knœvenagel adducts **39** were subsequently transformed to their corresponding pyrido[*a*]carbazole analogues **40** on irradiation with halogen lamp (150 W). However, the photocyclization step lacks regioselectivity, as the target pyrido[*a*]carbazole **40** is produced alongside other regioisomers.[36] Despite this lack of regioselectivity, this method is versatile, as it was used to prepare other polycyclic heteroarene compounds such as benzo-carbazole and pyrido-pyrroloisoquinolines.[36]



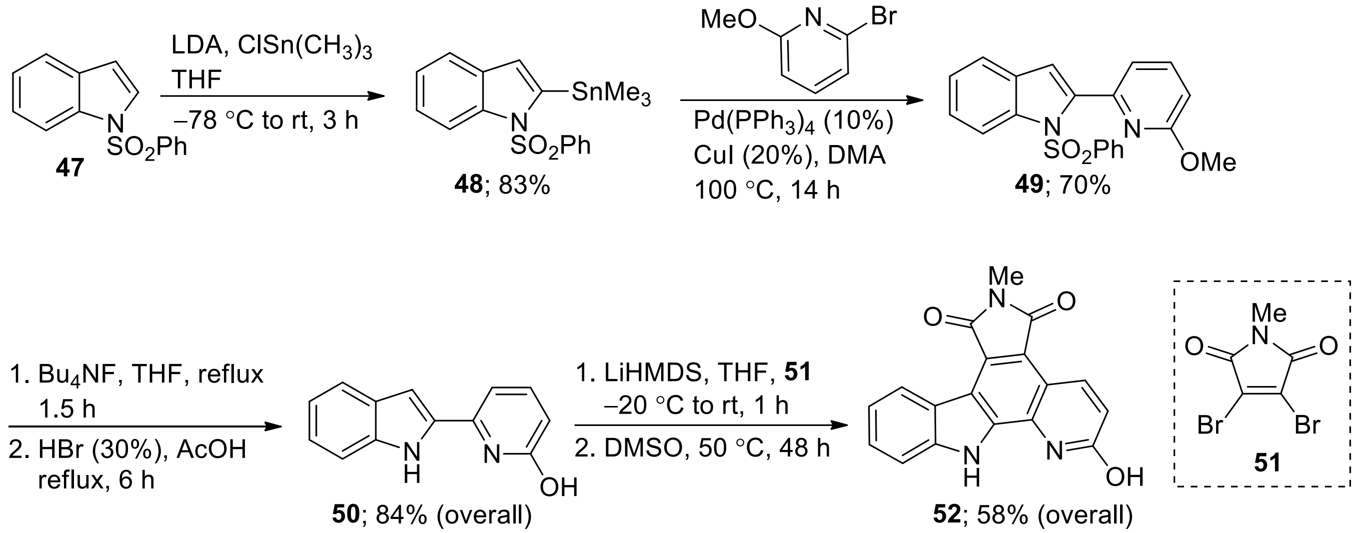
Scheme 9. Synthesis of the pyrido[*a*]carbazole derivatives through Knoevenagel condensation and photocyclization.

Lemster and colleagues reported the synthesis of methyl 11*H*-pyrido[3,2-*a*]carbazole-5-carboxylate derivatives **46** (Scheme 10).[37] The first step in their reaction sequence involved the condensation of phenylhydrazine derivatives **41** and commercially available acylated pyridines **42** to give hydrazone intermediates **43**, followed by heating in PPA to give 2-pyridyl-indole analogues **44**. Formylation and subsequent Wittig reaction of the resulting aldehydes with methyl 2-(triphenylphosphoranylidene)acetate produced methyl vinyl esters **45**. Photochemical 6π-electrocyclisation of 2-pyridyl-3-vinylindoles **45**, followed by aromatization, resulted in pyrido[*a*]carbazole analogues **46**. The ester moiety was further transformed into an amide functionality. The resulting compounds were investigated for their antitumor activity alongside thieno[2,3-*a*]-carbazole, which was accessed via the same reaction sequence as the related pyrido-carbazole derivatives.[37]



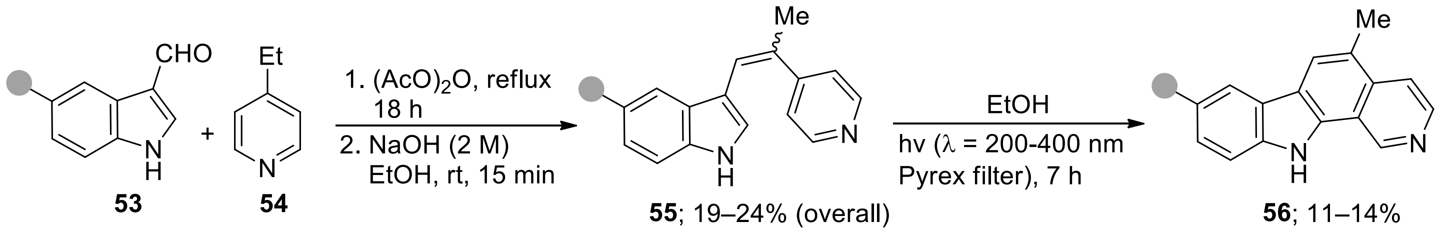
Scheme 10. Photochemical 6π-electrocyclisation of 2-pyridyl-3-vinylindoles.

Routier and his team reported the synthesis of maleimide annulated pyrido[*a*]carbazole analogues.[38] Their synthetic route is delineated in Scheme 11. Their synthesis commenced with the phenylsulfonyl-directed lithiation of 1-(phenylsulfonyl)-1*H*-indole (**47**), followed by lithium-metal exchange with chlorotrimethylstannane, yielding 2-trimethylstannyl-indole **48**, which then participated in a Stille coupling on reacting with 2-bromo-6-methoxypyridine, furnishing 2-pyridyl-indole intermediate **49**. Removal of the benzenesulfonyl group, followed by hydrobromic acid/acetic acid facilitated demethylation, yielding hydroxypyridine **50**. Ring C was constructed through a two-step direct (het)arylannulation sequence that involved the reaction between 2-hydroxypyridyl-indole **50** and 3,4-dibromo-maleimide **51** to form pyrido[*a*]carbazole derivative **52**. A related strategy was reported by the group of Meggers to access maleimide annulated pyrido[*a*]carbazole, which were further elaborated to metallo-pyridocarbazole complexes and were investigated as protein kinase inhibitors.[39-40]



Scheme 11. Ring C construction via a two-step direct (het)arylannulation sequence.

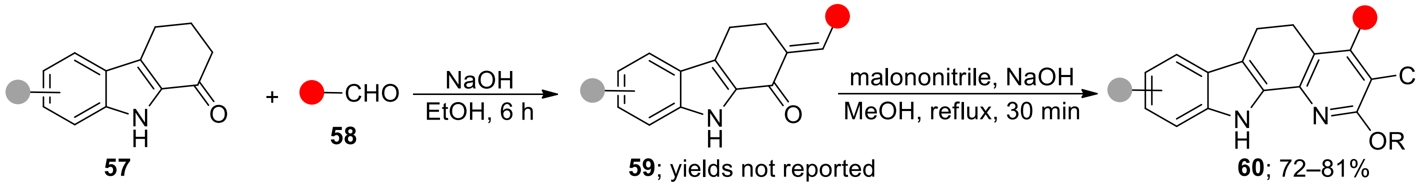
Lescot and colleagues disclosed a synthesis of pyrido[3,4-*a*]carbazole as shown in Scheme 12.[22] Their strategy relied on *N*-acylation/condensation reaction between 3-formylindole derivatives **53** and 4-ethylpyridine (**54**) to form *N*-acylated vinyl-pyrido indoles, which were treated with ethanolic sodium hydroxide giving deprotected vinyl-pyrido indoles **55**. Photochemical induced 6π-electrocyclization, and subsequent aromatisation produced pyrido[3,4-*a*]carbazole analogues **56**.[22]



Scheme 12. Photocyclisation of vinyl-pyrido indoles, forming pyrido[3,4-*a*]carbazole derivatives.

2.1.3 Through the construction of Ring D. Generally, the synthesis of pyridocarbazoles via the construction of ring D is very rare. Indeed, to date, most of the reports that delineate the construction of pyrido[*a*]carbazoles emanate from the group of Prasad. The only exception is the improbable report by Saravanabhavan et al.[41] The reaction sequence cannot result in the claimed products. In addition, the NMR spectra presented do not match the claimed compounds.[41]

Generally, the strategy of the Prasad group relied on annulation reactions of tetrahydrocarbazolones with aldehydes or alkynes and nitriles or vinyl amines as nitrogen atom sources.[42-49] For example, the reaction between tetrahydrocarbazolones **57**, aldehyde **58,** and gave compound **59**, which formed pyrido[*a*]carbazoles **60** upon cyclisation with malononitrile in the presence of NaOH in refluxing methanol (Scheme 13).[50]

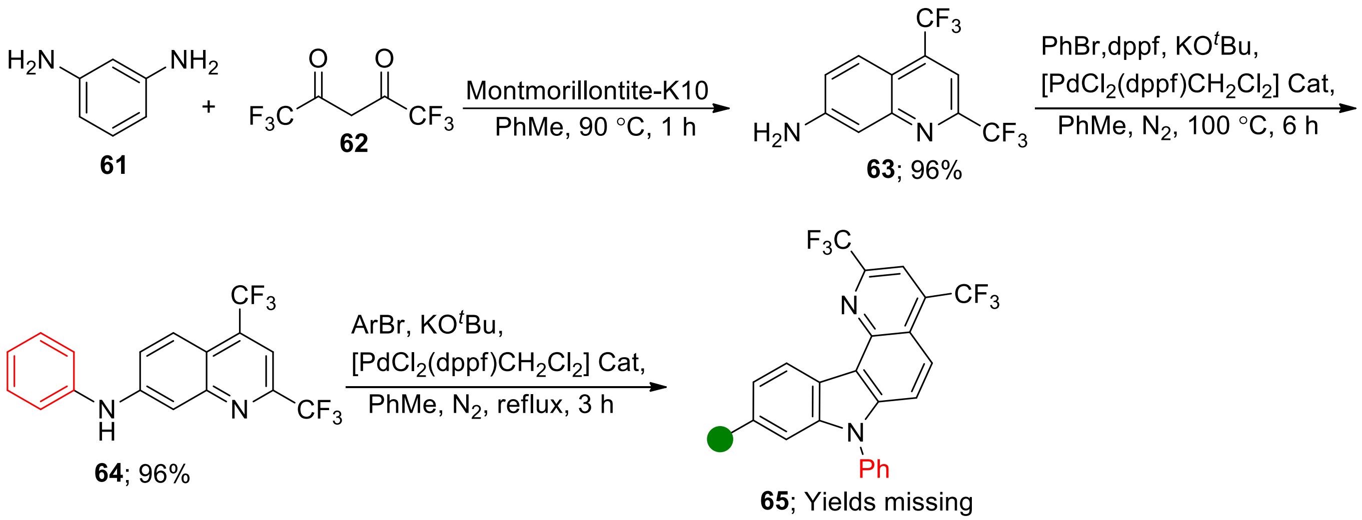


Scheme 13. Step-wise condensation and cyclisation leading to dihydropyrido[2,3-*a*]carbazole nucleus.

The same group also reported on the one-pot synthesis of similar 6,11-dihydro-5*H*-pyrido[2,3-*a*]carbazole analogues from the reaction of 1-oxo-tetrahydrocarbazole, aldehydes, and malononitrile.[43-45]

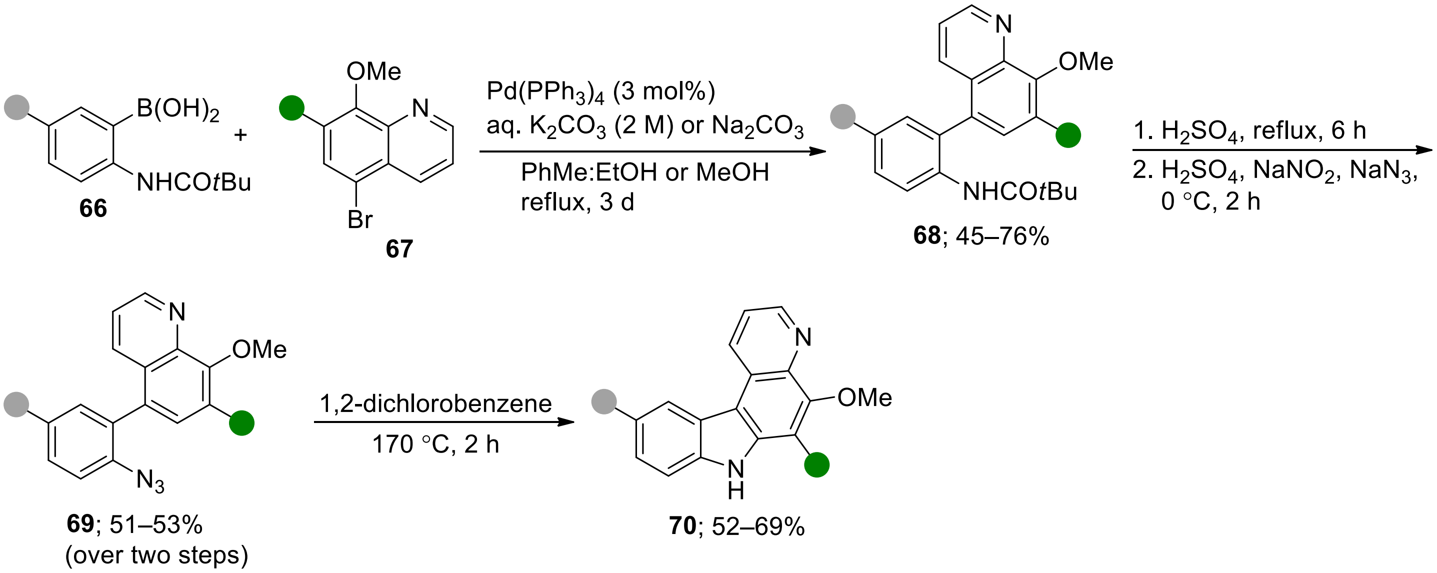
2.2 The synthesis of pyrido[*c*]carbazole

2.2.1 Through the construction of Ring B. The synthesis of this subfamily through ring B formation as the final step in constructing the pyrido[*c*]carbazole skeleton relies on the cyclisation of *N*,*N*-phenylquinoline amine or biaryl phenylquinoline. The former strategy was demonstrated by Sakuma et al.[51] Their expedient synthesis is depicted in Scheme 14 below. The Combes quinoline synthesis between *m*-phenylenediamine **61** and hexafluoroacetylacetone **62** led to 7-aminoquinoline derivative **63**, which was subjected to Buchwald-Hartwig coupling by reacting with phenylbromide using Pd(dppf)Cl_2·CH_2Cl_2 complex as a catalyst, yielding *N*,*N*-phenylquinoline amine **64**. Diarylamine **64** was again subjected to similar reaction conditions to form pydiro[*c*]carbazole analogues **65**, in what is presumably a second Buchwald-Hartwig amination, followed by intramolecular oxidative coupling of the resulting triarylamines to form the pyrido[*c*]carbazole skeleton.[51]



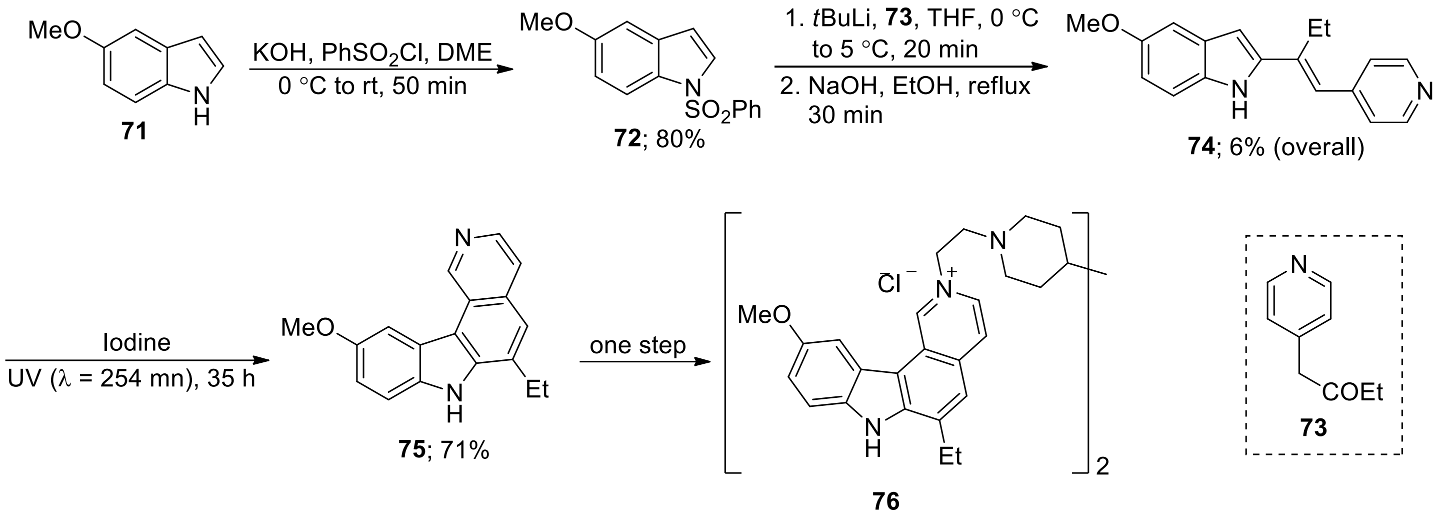
Scheme 14. Buchwald-Hartwig amination/intramolecular oxidative coupling cascade in the synthesis of pyrido[3,2-*c*]carbazole nucleus.

Queguiner and colleagues demonstrated the biaryl phenylquinoline cyclisation strategy to access the pyrido[*c*]carbazole framework, as shown in Scheme 15 below.[52] This approach relied on the Suzuki-Miyaura coupling reaction between *O*-phenylenecarbamate boronic acid **66** and 5-bromoquinoline derivatives **67**, to form biaryl carbamates **68**. *Boc* group removal yields aniline analogues, which were converted to azide **69**. The ring B-forming reaction involved heating the azides **69** in 1,2-dichlorobenzene, yielding pyrido[2,3-*c*]carbazole derivatives **70**.



Scheme 15. Buchwald-Hartwig amination/intramolecular oxidative coupling cascade to access the pyrido[3,2-*c*]carbazole nucleus.

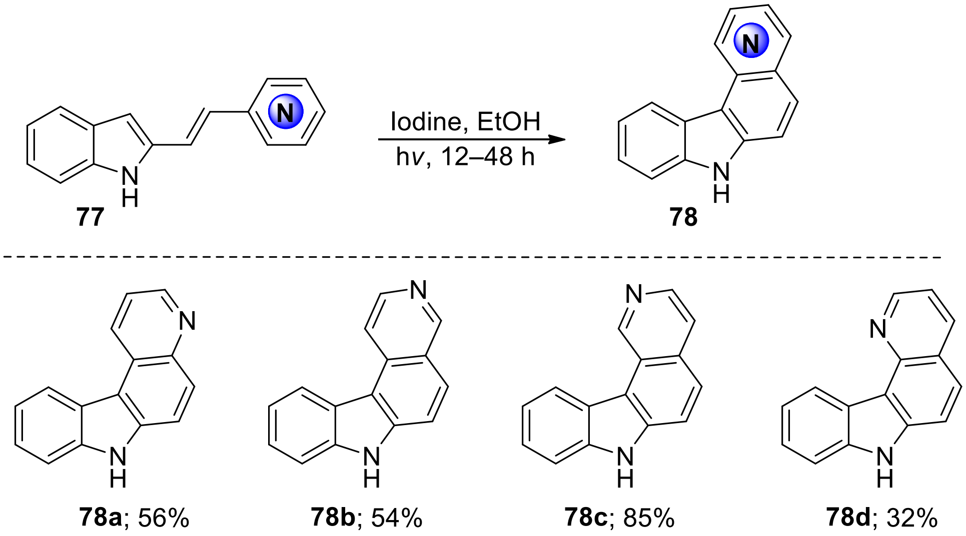
2.2.2 Through the construction of Ring C. The photocyclisation of 2-(pyridinylvinyl)-indole intermediates has been exploited in furnishing the central benzene ring (ring C) of the pyrido[*c*]carbazole skeleton. The earliest example of this approach was reported by Husson et al.[53] This approach has found utility in the synthesis of ditercalinium chloride (NSC335153) **76**. This anticancer agent contains the pyrido[4,3-*c*]carbazole structural fragment (Scheme 16).[54] The requisite 2-(pyridinylvinyl)-indole intermediate **74** was obtained in three steps from 5-methoxy-indole **71**. The first step involved the sulfonation of 5-methoxy-indole **71** to give sulfonamide **72,** followed by treatment with nBuLi and quenching with ketone **73**, resulting in a tertiary alcohol. Refluxing the resulting alcohol in ethanolic sodium hydroxide achieved both the dehydration and desulfination to form 2-(pyridinylvinyl)-indole **74**. Subsequent iodine mediated photocyclisation/oxidation, yielded pyrido[*c*]carbazole **75**, which was subjected to further *N*-alkylation on the nitrogen atom of the pyridine moiety, furnishing the target ditercalinium chloride **76**. The same group employed the photoannulation/oxidation of 2-pyridinyl vinyl-indole derivatives approach in other reports.[55-57]



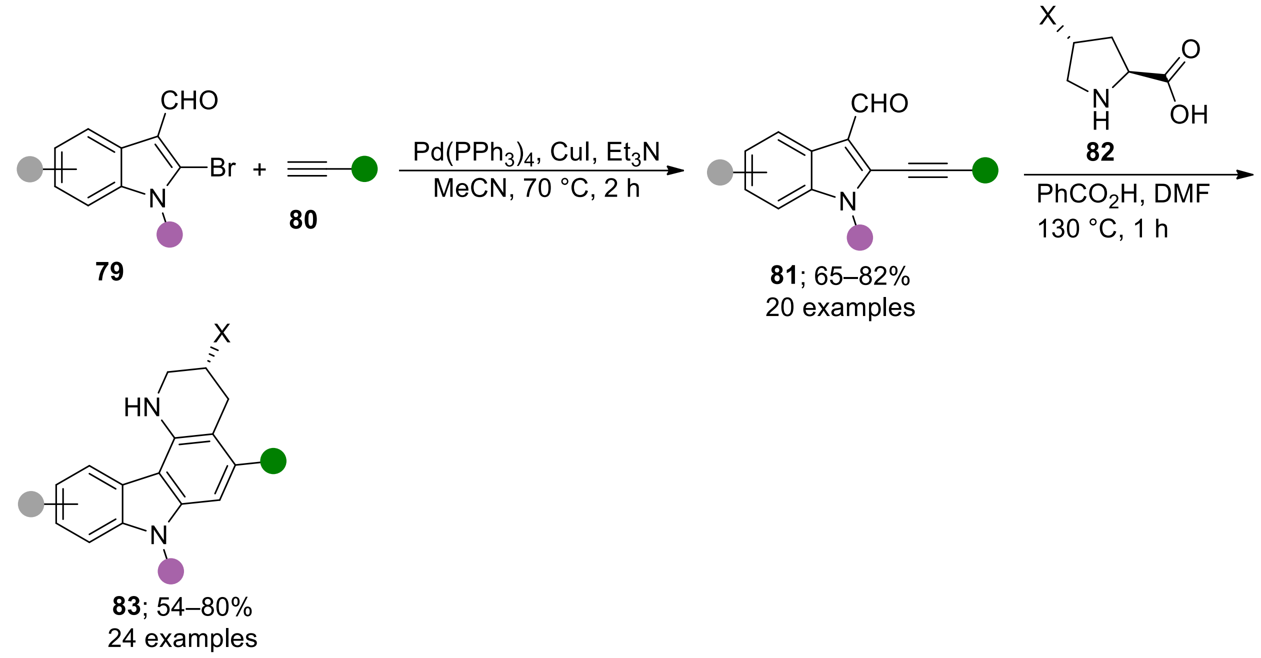
Scheme 16. The synthesis of ditercalinium chloride via photoannulation/oxidation sequence.

The earlier work by Silva and Snieckus had established the versatility of this strategy when they demonstrated the synthesis of all four pyrido[*c*]carbazole isomers **78a**-**d**, through photocyclisation of suitably substituted 2-pyridinyl vinyl-indoles **77** (Scheme 17).[58]

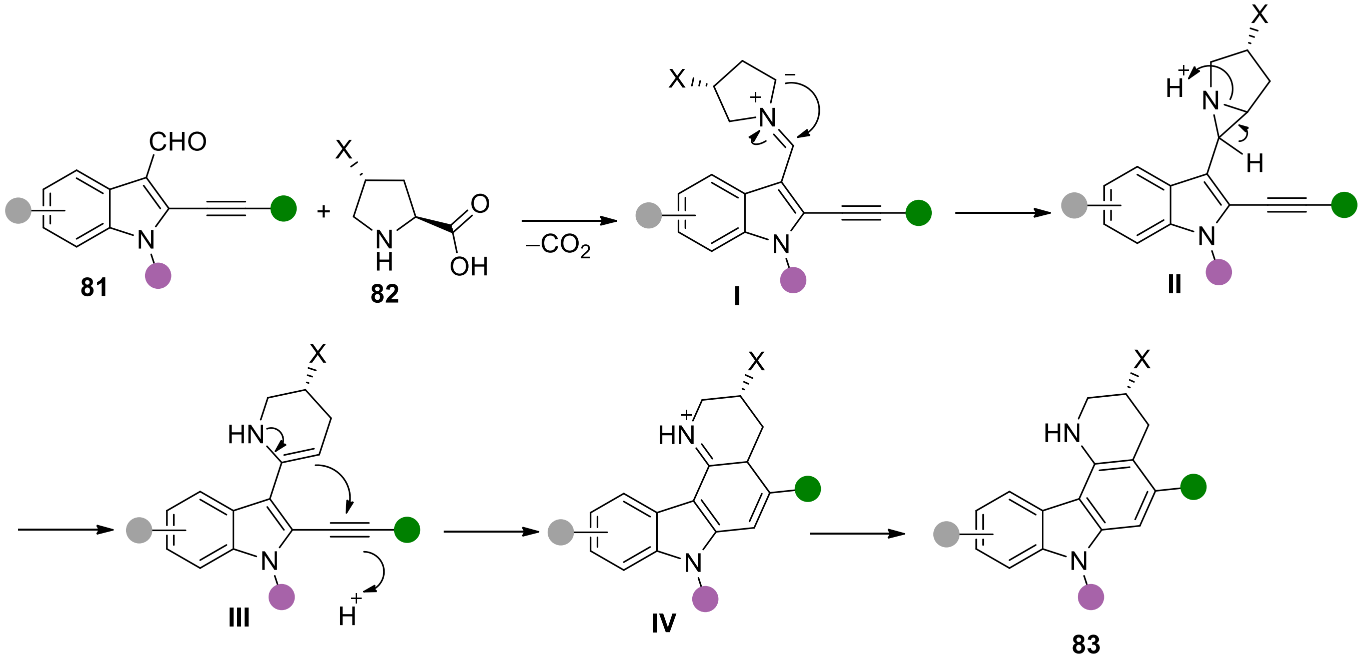
Verma *et al.* disclosed an expedient method to access the tetrahydropyridocarbazole nucleus that depends on a C–C and C–N bond-forming decarboxylation/cyclisation cascade (Scheme 18).[59] Their reaction sequence involved the Sonogashira functionalisation of the commercially available 2-bromoinodole-3-carbaldehyde derivatives **79** and terminal alkynes **80** to give *ortho*-alkynylaldehydes **81**, which then participated in an annulation reaction on heating in the presence of L-proline or *trans*-4-hydroxy-L-proline **82** and benzoic acid using DMF as solvent, resulting in the formation of tetrahydropyridocarbazole derivatives **83**. This reaction is of wider scope concerning the alkyne moiety.



Scheme 17. The Snieckus synthesis of pyrido[*c*]carbazoles through iodine-mediated photocyclisation.



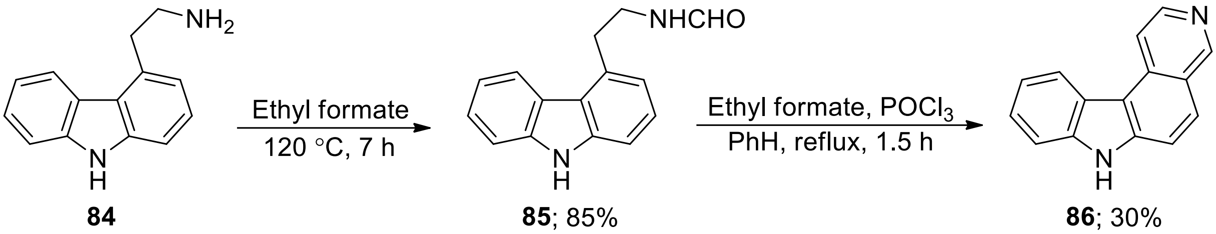
Scheme 18. The decarboxylation/cyclisation cascade to access the tetrahydropyrido[3,2-*c*]carbazole core.



Scheme 19. The proposed mechanism for annulation reaction between indole derivative **81** and proline **82** to tetrahydropyrido[3,2-*c*]carbazole core.

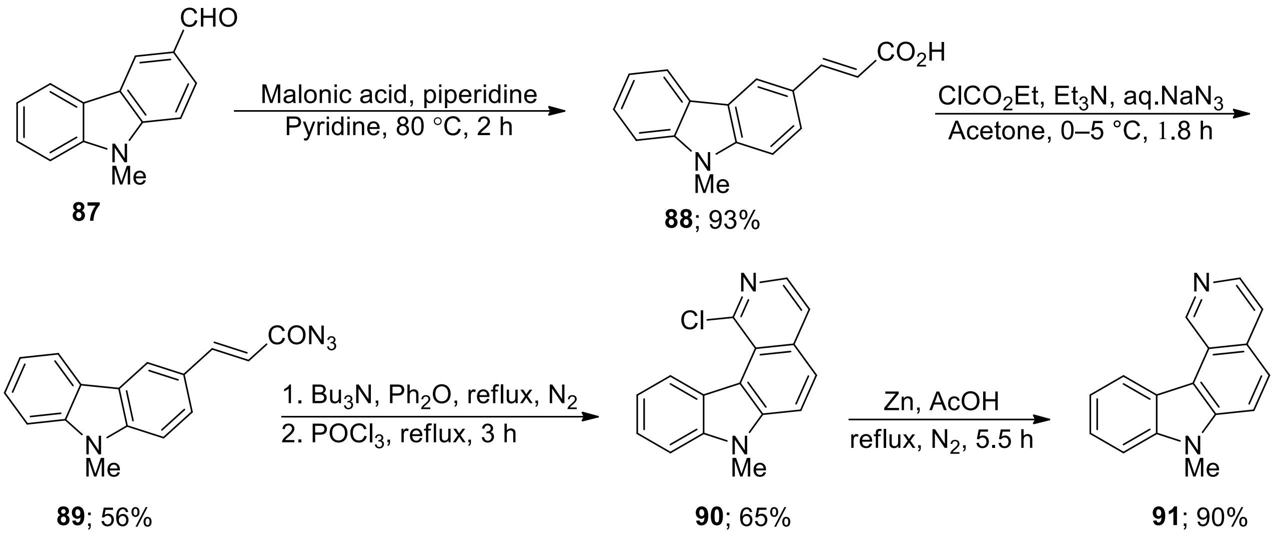
The authors suggested two possible pathways for the union of **81** and **82** to give tetrahydropyrido[3,2-*c*]carbazole nucleus in **83**. One of the pathways is shown in Scheme 19. The union between the aldehyde functionality of **81** and **82** followed by decarboxylation of the putative imine leads to azomethine ylide **I**. Intramolecular annulation of the azomethine ylide leads to the formation of azabicyclo[3.1.0]hexane, which undergoes an acid induced fragmentation forming enamine **III**. An acid-assisted intramolecular annulation between the enamine functionality and the alkyne group leads to the formation of ring C, completing the tetrahydropyrido[3,2-*c*]carbazole framework in intermediate **IV**. Aromatisation of ring C forms **83**. An alternate suggested pathway involves the formation of 1,4-dihydrocyclopenta[*b*]indole intermediate, which undergoes ring expansion to form hexahydropyrrolo[1',2':1,7]azepino[4,3-*b*]indole, followed by ring contraction to form the tetrahydropyrido[3,2-c]carbazole backbone. Isomerizations lead to **83**.[59]

2.2.3 Through the construction of Ring D. The pyrido[*c*]carbazole skeleton can be viewed as an indole fused with a quinoline nucleus. Therefore, synthesizing the pyrido[*c*]carbazole nucleus via the construction of ring D as the final step mostly relies on classical quinoline or isoquinoline synthesis methods. Named reactions like Bischler-Napieralski, Skraup, Conrad–Limpach, Povarov, and Combes quinoline synthesis have been employed in the pyrido[*c*]carbazole skeletal synthesis context, with suitably functionalised carbazole motifs serving as advanced intermediates. The two-step synthesis of 7*H*-pyrido[3,4-*c*]carbazole (**86**) from 2-carbazol-4-yl-ethylamine (**84**), reported by Manske and Kulka, is exemplary (Scheme 20).[17] The formylation of **84** gave the β-carbazolylethylformamide **85**, which was followed by a Bischler-Napieralski cyclisation on treatment with $POCl_3$ in boiling benzene, presumably via dihydropyrido[3,4-*c*]carbazole intermediate, which is oxidised at some point during the operation to the fully aromatic product **86**. The harsh reaction conditions reflect the technology of that time.



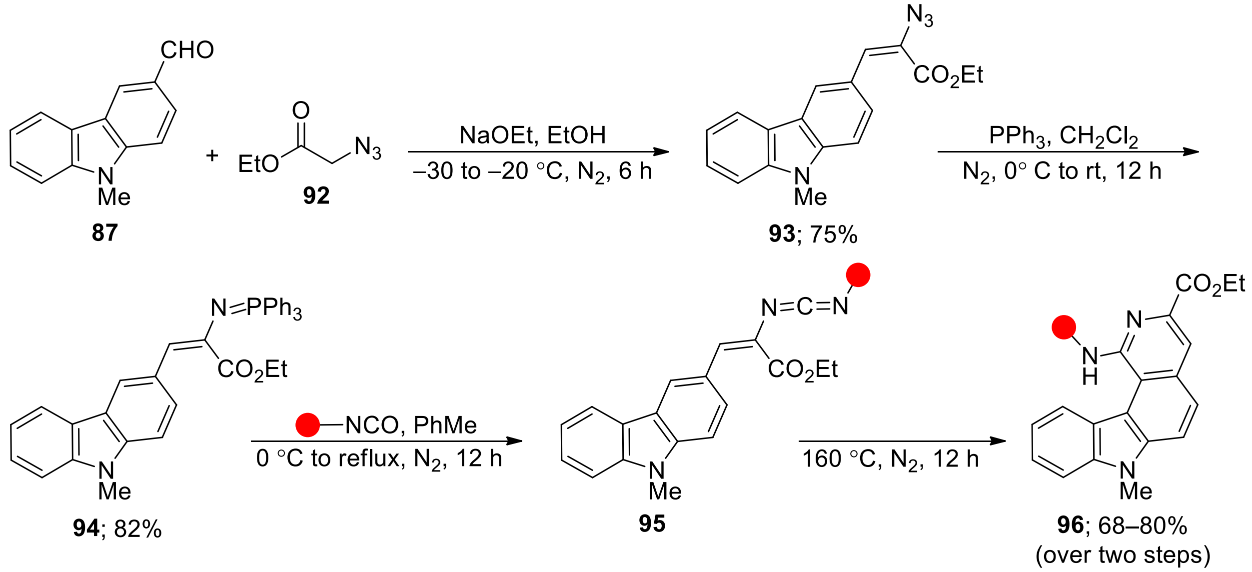
Scheme 20. The Bischler-Napieralski cyclisation in the synthesis of 7H-pyrido[3,4-*c*]carbazole.

The two-carbon tether linking the preformed carbazole fragment and the incipient pyridine ring does not have to be saturated. A vinyl tether is, in fact, desirable as it negates the requisite oxidation step to form the fully aromatic ring. Ray and colleagues reported on this approach starting from aldehyde **87**, as delineated in Scheme 21.[60] The Doebner modification of the Knoevenagel condensation/decarboxylation between aldehyde **87** and malonic acid led to the formation of 3-carboxyethenylcarbazole **88**. The reaction of **88** with sodium azide gave acryloyl azide **89**, which, on boiling in diphenyl ether, in the presence of tributylamine, underwent the Curtius rearrangement, presumably forming the corresponding formamide. Concomitant cyclisation of the putative formamide fashioned a pyridone intermediate, dehydration with $POCl_3$ gave chloride **90**, which was reduced with metallic zinc in refluxing acetic acid to give pyrido[3,4-*c*]carbazole derivative **91**. A similar synthetic route starting with a 4-methyl derivative of **87** led to the pyrido[*b*]carbazole skeleton.[60]



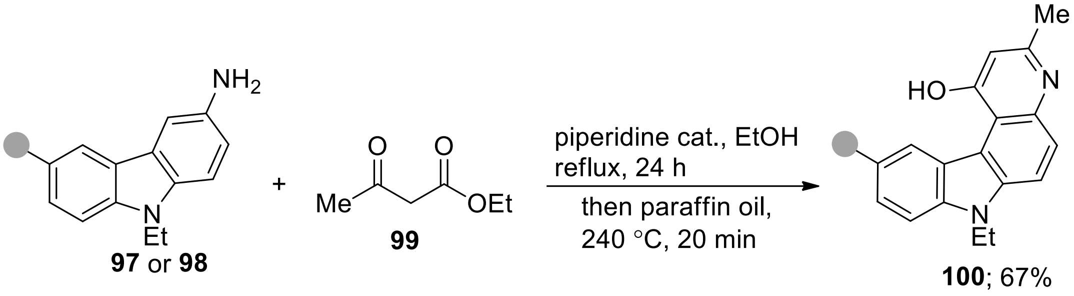
Scheme 21. The Curtius rearrangement/cyclisation sequence in the synthesis of pyrido[4,3-*c*]carbazole framework.

In a similar vein, Molina and co-workers achieved the synthesis of pyrido[3,4-*c*]carbazole analogues **96** as shown in Scheme 22.[61] Knoevenagel condensation between aldehyde **87** and ethyl azidoacetate **92** gave ethyl α-azido acrylate **93**. Staudinger decomposition of the azide functionality of **93** on treatment with triphenylphosphine, furnished iminophosphorane **94**, which were subjected into an aza-Wttig type reaction with various aliphatic or aromatic isocyanates to their corresponding carbodiimides **95**. The carbodiimides could be isolated pure after column chromatographic operation, or could be telescoped directly to the subsequent thermal cyclisation on heating, neat at 160 °C to fashion pyrido[3,4-*c*]carbazole analogue **96**. Unsurprisingly, the corresponding pyrido[*b*]carbazole isomers that could have resulted from cyclisation on C-2 were not detectable by thin layer chromatography or ^{13}C-NMR analysis.[61] Similarly to the example by Ray and colleagues,[60] it was necessary to block C-4 of the carbazole nucleus with a methyl group to obtain the pyrido[*b*]carbazole framework using this route.[61]



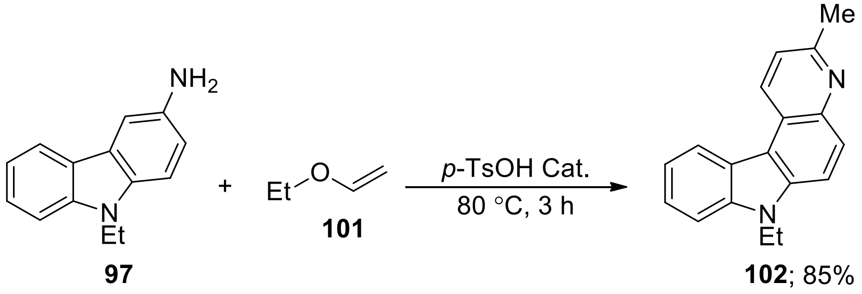
Scheme 22. Thermal cyclisation of carbodiimide derivatives forming the pyrido[4,3-*c*]carbazole skeleton.

A strategy that has attracted considerable attention and utility in the context of pyridocarbazole core syntheses involves cyclisation reactions between 3-amino-9*H*-carbazole and its derivatives, with three carbon surrogates; these include β,γ-unsaturated α-ketocarboxylic acid,[62] crotonaldehyde,[63] glycerol,[64] and diethyl malonate.[65] The report by Perche and Saint-Ruf, as depicted in Scheme 23, serves as an example.[66] Their work involved the condensation of ethyl acetoacetate with 9-ethyl-9*H*-carbazol-3-amine (**97**) or 9-ethyl-6-methyl-9*H*-carbazol-3-amine (**98**) to form pyridocarbazoles **100**. This strategy has been extended to annulated 7*H*-pyrido[2,3-*c*]carbazole motifs as reflected in recent reports.[67-69]



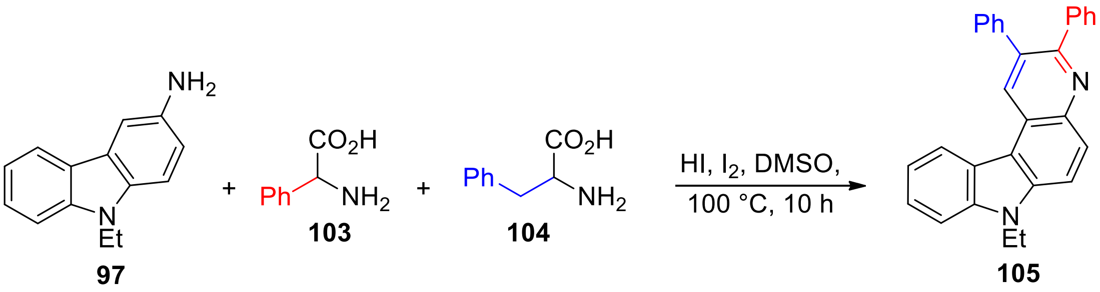
Scheme 23. Condensation of 3-amino-carbazole derivative and ethyl acetoacetate.

The utility of 3-amino-9*H*-carbazole derivatives is by no means confined to preformed 3-C reactants, but could participate in other types of reactions. For example, the use of the Povarov reaction to access 7-ethyl-3-methyl-7*H*-pyrido[2,3-*c*]carbazole (**102**) from the reaction of 9-ethyl-9*H*-carbazol-3-amine (**97**) and two mole equivalents of ethyl vinyl ether **101**, using *p*-toluenesulfonic acid as a catalyst has been reported (Scheme 24).[70] This work is based on an earlier report by Viji and Nagarajan, which demonstrated the utility of this method in the synthesis of pyrido[*a*]carbazole and pyrido[*b*]carbazole subfamilies.[71]



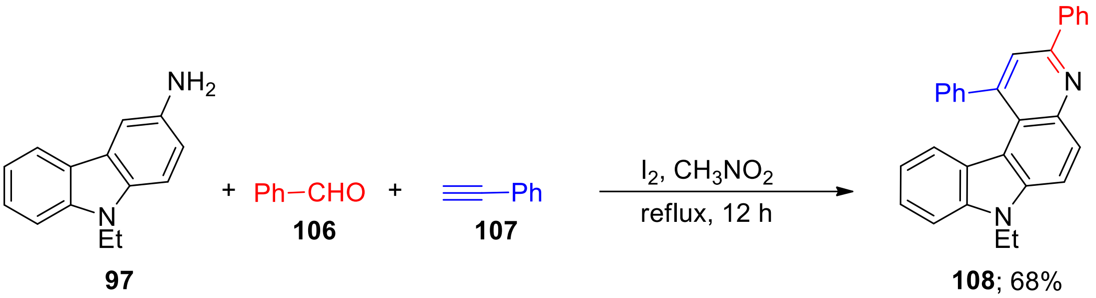
Scheme 24. Reaction of 3-amino-carbazole derivative with ethyl vinyl ether.

Xiang *et al.* reported on iodine-mediated decarboxylation and oxidative deamination of phenylglycine **103** and phenylalanine **104** to the corresponding aldehydes, which were then trapped with 9-ethyl-9*H*-carbazol-3-amine (**97**), to construct new C−N and C−C bonds selectively, giving 7-ethyl-2,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (**105**) as the sole product (Scheme 25).[72]



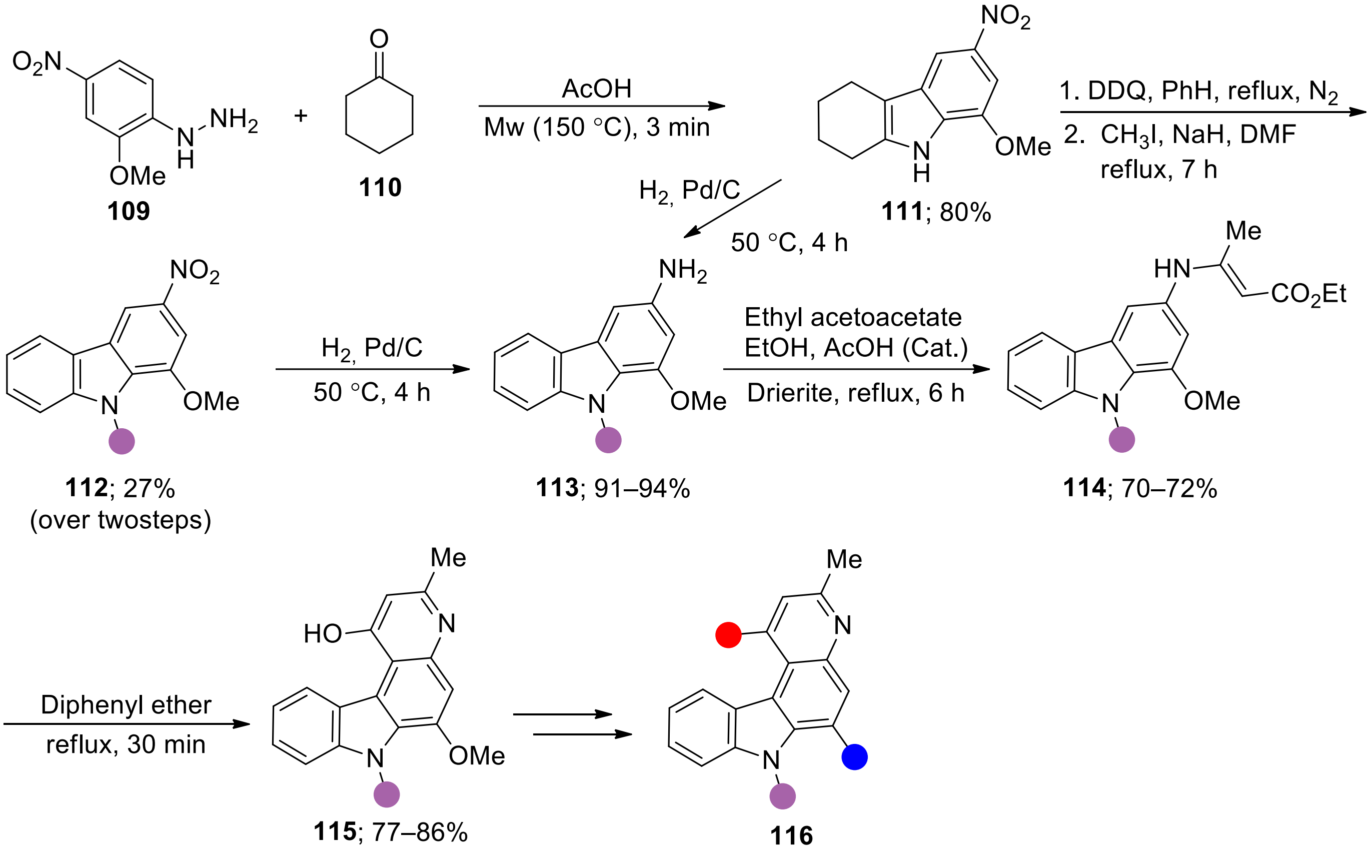
Scheme 25. Multicomponent synthesis of the pyrido[2,3-*c*]carbazole nucleus between *N*-ethyl-3-amino-carbazole and amino acids.

The isomeric 7-ethyl-1,3-diphenyl-7*H*-pyrido[2,3-*c*]carbazole (**108**) was similarly produced in a single multicomponent reaction between 9-ethyl-9*H*-carbazol-3-amine (**97**), benzaldehyde (**106**) and phenylacetylene (**107**) under iodine catalytic conditions (Scheme 26).[73]



Scheme 26. Three-component reaction between *N*-ethyl-3-amino-carbazole, benzaldehyde, and phenylacetylene.

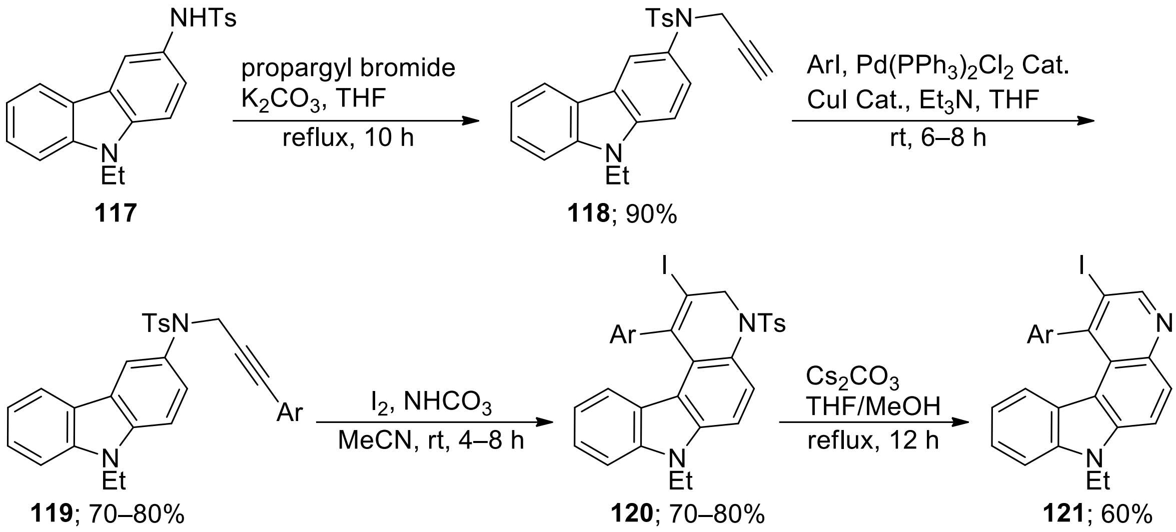
This approach is not limited to one-pot reactions, but is also reflected in multistep syntheses. A case in point is the synthesis of the pyrido[2,3-*c*]carbazole skeleton by Ferlin and co-workers.[74] Their synthetic route involved the Borsche–Drechsel carbazole synthesis between phenyl hydrazine analogue **109** and cyclohexanone **110**, resulting in tetrahydrocarbazole derivative **111** (Scheme 27). This compound was also obtained in two steps, via the initial isolation of the intermediate hydrazone, followed by cyclisation in a separate synthetic step.[74] Tetrahydrocarbazole derivative **111** was oxidised with DDQ in boiling benzene to form the fully aromatised carbazole core, part of which was *N*-methylated to **112.** The nitro groups of the carbazole derivatives **111** and **112** were reduced with palladium on carbon under a hydrogen atmosphere to give aniline derivatives **113** in excellent yield. Subsequent *N*-alkylation of the aniline nitrogen gave β-aminoacrylates **114** in good yields. The β-aminoacrylates **114** were subjected to the Conrad–Limpach quinoline synthesis on boiling in diphenyl ether to fashion 7*H*-pyrido[2,3-*c*]carbazol-1-ol derivatives **115**, which were further elaborated to the more decorated pyrido[2,3-*c*]carbazole analogues **116** that were shown to intercalate DNA. In addition, some of the compounds that were tested contained sub-micromolar activities against topoisomerases I and II.



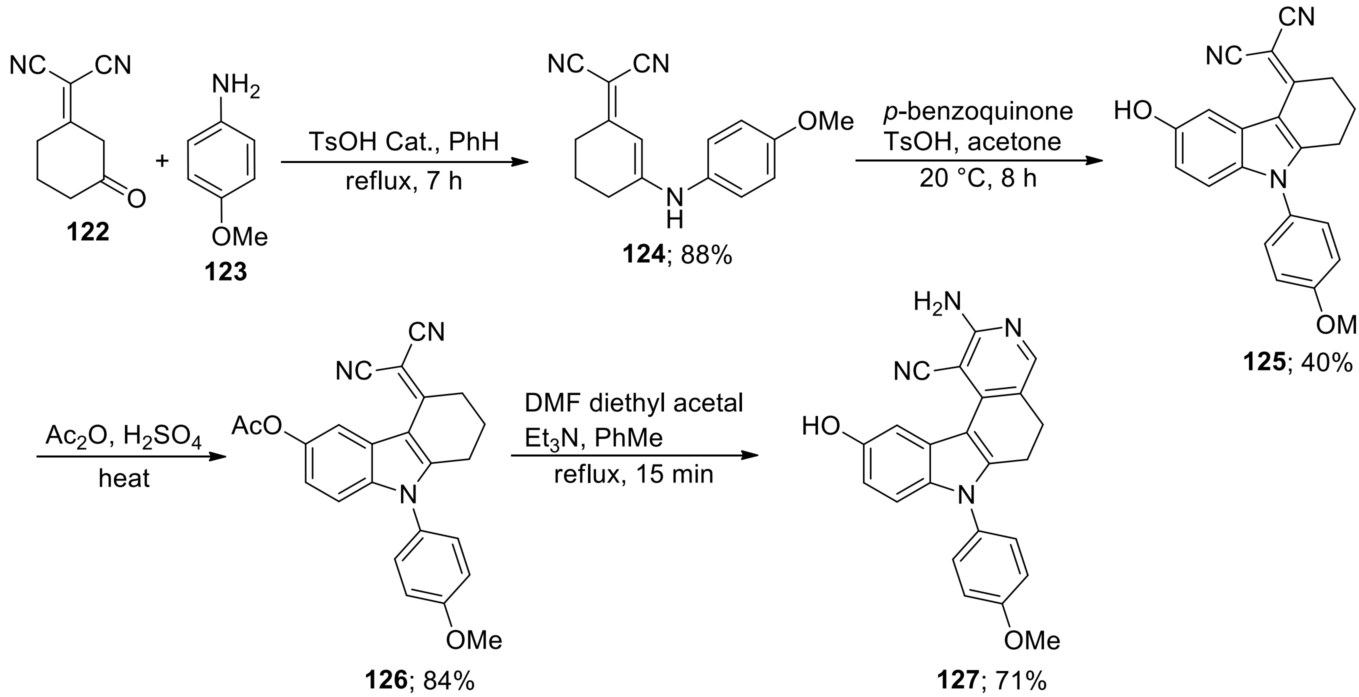
Scheme 27. Utilisation of the Conrad–Limpach quinoline synthesis to obtain 7*H*-pyrido[2,3-*c*]carbazole derivatives.

The choice of the three-carbon alkylating agent for Jella and Nagarajan[75] was the propargyl group, which was appended to the sulfonamide **117** to give compound **118**, followed by the conversion to an internal alkynes **119** through the Sonogashira coupling on reacting with various aryl iodides (Scheme 28). Compounds **119** underwent iodocyclisation to give iodo-dihydropyrido[2,3-*c*]carbazoles **120**. The phenyl-substituted substrate was further oxidised to the fully aromatic iodopyrido[2,3-*c*]carbazole **121**.

The group of Granik demonstrated the synthesis of the 6,7-dihydro-5*H*-pyrido[3,4-*c*]carbazole core through the reaction sequence shown in Scheme 29.[76] Their synthesis commenced with the reaction of β,γ-enone **122** with 4-methoxyaniline (**123**), to give extended enamine **124**. Enamine **124** then underwent Nenitzescu reaction when treated with equimolar amounts of p-benzoquinone and TsOH in acetone, yielding tetrahydrocarbazole derivative **125**, followed by the acylation of the hydroxyl functionality, giving ester **126**. Compound **126** was then condensed with DMF diethyl acetal, producing the corresponding 3-dimethylaminomethylidene intermediate, followed by pyridine cyclisation of the adjacent nitrile and the enamine functionalities, and concomitant O-deacetylation, furnishing pyrido[3,4-*c*]carbazole derivative **127**. The resulting amino and nitrile functional groups of compounds **127** were used as handles for further elaboration to the annulated pyrido[*c*]carbazole analogues.[76]



Scheme 28. Iodocyclisation of propargyl sulphonamides to access the pyrido[2,3-*c*]carbazole core.



Scheme 29. Condensation of methylenemalononitrile derivative and DMF diethyl acetal to produce the 7*H*-pyrido[3,4-*c*]carbazole framework.

Conclusions

This review highlights that pyridocarbazole synthesis remains an active research area, employing a wide range of synthetic strategies. We anticipate that continued innovation will yield new synthetic approaches to access these biologically significant scaffolds.

Acknowledgements

We are grateful to the National Research Foundation (NRF) Thuthuka (grant number TTK200304507920), Pretoria, South Africa, and the New Generation of Academics Programme (nGAP) for financially supporting this work.

References

1. Álvarez, M.; Joule, J. A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, p 235.
2. Gribble, G.W. *Synlett* **1991**, 289.
   https://doi.org/10.1055/s-1991-20733
3. Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1985**, *23*, 1277.
4. Håheim, K. S.; Sydnes, M. O. *Chem. Rec.* **2024**, *24*, No. e202300362.
   https://doi.org/10.1002/tcr.202300362
5. Wang, N.; Switalska, M.; Wang, L.; Shaban, E.; Hossain, M. I.; El Sayed, I. E. T.; Wietrzyk, J.; Inokuchi, T. *Molecules* **2019**, *24*, 2121.
   https://doi.org/10.3390/molecules24112121
6. Thongsornkleeb, C.; Tummatorn, J.; Ruchirawat, S. *Chem Asian J.* **2022**, *17*, No. e202200040.
   https://doi.org/10.1002/asia.202200040
7. Chabowska, G.; Moreira, H.; Tylińska, B.; Barg, E. *Anticancer Agents Med. Chem.* **2022**, *22*, 2419.
   https://doi.org/10.2174/1871520621666211214104926
8. Courseille, C.; Pelaprat, D.; Tsai, C. C. *Acta Cryst.* **1988**, *44*, 2154.
   https://doi.org/10.1107/S0108270188008558
9. Tylińska, B.; Dobosz, A.; Spychała, J.; Cwynar-Zając, Ł.; Czyznikowska, Ż.; Kuźniarski, A.; Gębarowski, T. *Int. J. Mol. Sci.* **2021**, *22*, 8492.
   https://doi.org/10.3390/ijms22168492
10. Paul, S.; Mallick, A.; Majumdar, T. *Chem. Phys. Lett.* **2015**, *634*, 29.
    https://doi.org/10.1016/j.cplett.2015.05.051
11. Bendirdjian, J. P.; Delaporte, C.; Roques, B. P.; Jacquemin-Sablon, A. *Biochem. Pharmacol.* **1984**, *33*, 3681.
    https://doi.org/10.1016/0006-2952(84)90157-6
12. Gao, Q.; Williams, L. D.; Egli, M.; Rabinovich, D.; Chen, S. L.; Quigley, G.; Rich, A. *Proc. Natl. Acad. Sci.* **1991**, *88*, 2422.
    https://doi.org/10.1073/pnas.88.6.2422
13. Garbay-Jaureguiberry, C.; Barsi, M. C.; Jacquemin-Sablon, A.; Le Pecq, J. B.; Roques, B. P. *J. Med. Chem.* **1992**, *35*, 72.
    https://doi.org/10.1021/jm00079a009
14. Peek, M. E.; Lipscomb, L. A.; Bertrand, J. A.; Gao, Q.; Roques, B. P.; Garbay-Jaureguiberry, C.; Williams, L. D. *Biochemistry.* **1994**, *33*, 3794.
    https://doi.org/10.1021/bi00179a002
15. Maroun, R. C.; Roques, B. P. *Biophysical Chem.* **1991**, *39*, 45.
    https://doi.org/10.1016/0301-4622(91)85005-B
16. Ndongo, J. T.; Mbing, J. N.; Monteillier, A.; Tala, M. F.; Rütten, M.; Mombers, D.; Cuendet, M.; Pegnyemb, D. E.; Dittrich, B.; Laatsch, H.; *J. Nat. Prod.* **2018**, *81*, 5.

https://doi.org/10.1021/acs.jnatprod.7b00958

17. Cuendet, M.; Oteham, C. P.; Moon, R. C.; Pezzuto, J. M. *J. Nat. Prod.* **2006**, *69*, 3. https://doi.org/10.1021/np050362q
18. Ali, R. *Tetrahedron* **2023**, *148*, 133692. https://doi.org/10.1016/j.tet.2023.133692
19. Manske, R. H. F.; Kulka, M. *Can. J. Res.* **1949**, *27*, 291. https://doi.org/10.1139/cjr49b-019
20. Kulka, M.; Manske, R. H. F. *Can. J. Res.* **1952**, *30*, 711. https://doi.org/10.1139/v52-084
21. Manske, R. H. F.; Kulka, M. *J. Am. Chem. Soc.* **1950**, *72*, 4997. https://doi.org/10.1021/ja01167a046
22. Lescot, E.; Muzard, G.; Markovits, J.; Belleney, J.; Roques, B. P.; Le Pecq, J.-B. *J. Med. Chem.* **1986**, *29*, 1732. https://doi.org/10.1021/jm00159a028
23. Romeiro, G. A.; Ferreira, V. F.; dos Costa, M. S.; Joaquim, A. M.; Carneiro, J. W. M.; Kammerer, B. *Spectroscopy* **2001**, *15*, 19. https://doi.org/10.1155/2001/957870
24. Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 671. https://doi.org/10.1039/JR9520001668
25. Barbieri, V.; Ferlin, M. G. *Tetrahedron Lett.* **2006**, *47*, 8289. https://doi.org/10.1016/j.tetlet.2006.09.099
26. Fathalipour, S.; Shahrokhian, N.; Afghan, A.; Baradaran, M. M. *Asian J. Chem.* **2010**, *22*, 5808.
27. Ferlin, M. G.; Gia, O.; Via, L. D. *ChemMedChem* **2011**, *6*, 1872. http://doi.org/10.1002/cmdc.201100233.
28. Bosch, C.; López-Lledó, P.; Bonjoch, J.; Bradshaw, B.; Nieuwland, P. J.; Blanco-Ania, D.; Rutjes, F. P. J. T. *J. Flow Chem.* **2016**, *6*, 240. https://doi.org/10.1556/1846.2016.00016
29. Trecourt, F.; Mallet, M.; Mongin, F.; Queguiner, G. *Tetrahedron* **1995**, *51*, 11743. https://doi.org/10.1016/0040-4020(95)00726-O
30. Håheim, K. S.; Lindbäck, E.; Tan, K. N.; Albrigtsen, M.; Helgeland, I. T. U.; Lauga, C.; Matringe, T.; Kennedy, E. K.; Andersen, J. H.; Avery, V. M.; Sydnes, M. O. *Molecules* **2021**, *26*, 3268. https://doi.org/10.3390/molecules26113268
31. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1705. https://doi.org/10.1039/B001685n
32. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787. https://doi.org/10.1039/a908361h
33. Yoshida, K.; Oga, N.; Kadota, M.; Ogasahara, Y.; Kubo, Y. *J. Chem. Soc. Chem. Commun.* **1992**, 1114. https://doi.org/10.1039/C39920001114
34. Blache, Y.; Benezech, V.; Chezal, J.-M.; Boule, P.; Viols, H.; Chavignon, O.; Teulade, J.-C.; Chapat, J.-P. *Heterocycles* **2000**, *53*, 905. http://doi.org/10.3987/com-99-8837
35. Aragon, P.-J.; Yapi, A.-D.; Pinguet, F.; Chezal, J.-M.; Teulade, J.-C.; Blache, Y. *Chem. Pharm. Bull.* **2007**, *55*, 1349. http://doi.org/10.1248/cpb.55.1349
36. Labriere, C.; Lozach, O.; Blairvacq, M.; Meijer, L.; Guillou, C. *Eur. J. Med. Chem.* **2016**, *124*, 920.

http://doi.org/10.1016/j.ejmech.2016.08.069

37. Lemster, T.; Pindur, U.; Lenglet, G.; Depauw, S.; Dassi, C.; David-Cordonnier, M.-H. *Eur. J. Med. Chem.* **2009**, *44*, 3235.
https://doi.org/10.1016/j.ejmech.2009.03.026
38. Bourderioux, A.; Kassis, P.; Merour, J.-Y.; Routier, S. *Tetrahedron* **2008**, *64*, 11012.
https://doi.org/10.1016/j.tet.2008.09.101
39. Pagano, N.; Wong, E. Y.; Breiding, T.; Liu, H.; Wilbuer, A.; Bregman, H.; Shen, Q.; Diamond, S. L.; Meggers, E. *J. Org. Chem.* **2009**, *74*, 8997.
https://doi.org/10.1021/jo901641k
40. McQuade, D. T.; O'Brien, A. G.; Dorr, M.; Rajaratnam, R.; Eisold, U.; Monnanda, B.; Nobuta, T.; Lohmannsroben, H.-G.; Meggers, E.; Seeberger, P. H. *Chem. Sci.* **2013**, *4*, 4067.
https://doi.org/10.1039/C3SC51846A
41. Saravanabhavan, M.; Murugesan, V.; Sekar, M. *J. Photochem. Photobiol.* **2014**, *133*, 145.
http://doi.org/10.1016/j.jphotobiol.2014.02.020
42. Ratheesh, A. K.; Prasad, K. J. R. *ChemistrySelect* **2020**, *5*, 4898.
https://doi.org/10.1002/slct.202000281
43. Arya, K. R.; Rajendra Prasad, K. J. R. *Synth. Commun.* **2018**, *48*, 1465.
https://doi.org/10.1080/00397911.2018.1455211
44. Murali, K. Sparkes, H. A.; Pandiyan, B. V.; Prasad, K. J. R. *New J. Chem.* **2017**, *41*, 8242.
https://doi.org/10.1039/c7nj00643h
45. Indumathi, T.; Fronczek, F. R.; Prasad, K. J. R. *J. Mol. Str.* **2012**, *1016*, 134.
https://doi.org/10.1016/j.molstruc.2012.01.032
46. Sridharan, M.; Beagle, L. K.; Zeller, M.; Prasad, K. J. R. *J. Chem. Res.* **2008**, 572.
https://doi.org/10.3184/030823408X361110
47. Danish, I. A.; Prasad, K. J. R. *Collect. Czech. Chem. Commun.* **2005**, *70*, 223.
https://doi.org/10.1135/cccc20050223
48. Danish, I. A.; Prasad, K. J. R. *Org. Prep. Proced. Int.* **2004**, *36*, 371.
https://doi.org/10.1080/00304940409458682
49. Shanmugasundaram, K.; Prasad, K. J. R. *Heterocycles* **1999**, 51, 2163.
50. Arya, K. R.; Sparkes, H. A.; Prasad, K. J. P. R. *J. Chem. Sci.* **2018**, *130*, 1.
https://doi.org/10.1007/s12039-018-1428-1
51. Sakuma, M.; Fuchi, Y.; Usui, K.; Karasawa, S. *Chem. Asian J.* **2019**, *14*, 3938.
https://doi.org/10.1002/asia.201901200
52. Trecourt, F.; Mongin, F.; Mallet, M.; Queguiner, G. *J. Heterocyclic Chem.* **1995**, *32*, 1261.
https://doi.org/10.1002/jhet.5570320428
53. Husson, H.P.; Thal, C.; Potier, P.; Wenkert, E. *J. Org. Chem.* **1970**, *35*, 442.
https://doi.org/10.1021/jo00827a032
54. Léon, P.; Garbay-Jaureguiberry, C.; Le Pecq, J.-B.; Roques, B. P. *Tetrahedron Lett.* **1985**, *26*, 4929.
https://doi.org/10.1016/S0040-4039(00)94988-8
55. Léon, P.; Garbay-Jaureguiberry, C.; Barsi, M. C.; Le Pecq, J.-B.; Roques, B. P. *J. Med. Chem.* **1987**, *30*, 2074.
https://doi.org/10.1021/jm00394a024
56. Pelaprat, D.; Oberlin, R.; Le Guen, I.; Roques, B. P. *J. Med. Chem.* **1980**, *23*, 1330.
https://doi.org/10.1021/jm00186a009
57. Pelaprat, D.; Delbarre, A.; Le Guen, I.; Roques, B. P. *J. Med. Chem.* **1980**, *23*, 1336.

https://doi.org/10.1021/jm00186a010

58. De Silva, O.; Snieckus, V. *Synthesis* **1971**, 254.
https://doi.org/10.1055/s-1971-21708
59. Verma, S.; Mishra, P. K.; Kumar, M.; Sur, S.; Verma, A. K. *J. Org. Chem.* **2018**, *83*, 6650.
https://doi.org/10.1021/acs.joc.8b00980
60. Karmakar, A. C.; Kar, G. K.; Ray, J. K. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1997.
https://doi.org/10.1039/P19910001997
61. Molina, P.; Fresneda, P. M.; Almendros, P. *Tetrahedron* **1991**, *47*, 4175.
https://doi.org/10.1016/S0040-4020(01)86454-1
62. Dalton, L. K.; Demerac, S.; Teitei, T. *Aust. J. Chem.* **1969**, *22*, 185.
https://doi.org/10.1071/CH9690185
63. Karale, U. B.; Shinde, A.; Gaikwad, V. R.; Kalari, S.; Gourishetti, K.; Radhakrishnan, M.; Poornachandra, Y.; Amanchy, R.; Chakravarty, S.; Andugulapati, S. B.; Rode, H. B. *Bioorg. Chem.* **2023**, *139*, No. 106698.
https://doi.org/10.1016/j.bioorg.2023.106698
64. Perche, J.-C.; Saint-Ruf, G.; Buu-Hoi, N. P. *J. Chem. Soc. Perkin 1* **1972**, 260.
https://doi.org/10.1039/P19720000260
65. Kumaresan, P.; Sekar, R.; Ezhumalai, Y.; Matthias, Z.; Prasad, K. J. R. *J. Heterocyclic Chem.* **2022**, *59*, 1752.
https://doi.org/10.1002/jhet.4503
66. Perche, J.-C.; Saint-Ruf, G. *J. Heterocyclic Chem.* **1974**, *11*, 93.
https://doi.org/10.1002/jhet.5570110123
67. Zhang, M.-M.; Wang, J.; Wang, X.-S. *J. Heterocyclic Chem.* **2017**, *54*, 1378.
https://doi.org/10.1002/jhet.2717
68. Reddy, P. N.; Padmaja, P. *ARKIVOC* **2015**, *46*, 244.
http://doi.org/10.3998/ark.5550190.p008.822
69. Bondock, S.; Alqahtani, S.; Fouda, A. M. *Turk. J. Chem.* **2019**, *43*, 369.
https://doi.org/10.3906/kim-1811-6
70. Pal, P.; Bag, S.; Burman, M. D.; Nandi, R. K.; Bhowmik, S. *ChemistrySelect* **2024**, *9*, No. e202402561.
https://doi.org/10.1002/slct.202402561
71. Viji, M.; Nagarajan, R. *Synthesis* **2012**, *44*, 253.
https://doi.org/10.1055/s-0031-1289967
72. Xiang, J.-C.; Wang, Z.-X.; Cheng, Y.; Xia, S.-Q.; Wang, M.; Tang, B.-C.; Wu, Y.-D.; Wu, A.-X. *J. Org. Chem.* **2017,** *82*, 9210.
https://doi.org/10.1021/acs.joc.7b01501
73. Li, X.; Mao, Z.; Wang, Y.; Chen, W.; Lin, X. *Tetrahedron* **2011**, *67*, 3858.
https://doi.org/10.1016/j.tet.2011.03.087
74. Ferlin, M. G.; Marzano, C.; Gandin, V.; Dall'Acqua, S.; Via, L. D. *ChemMedChem* **2009**, *4*, 363.
https://doi.org/10.1002/cmdc.200800368
75. Jella, R. R.; Nagarajan, R. *Synlett* **2011**, *4*, 529.
https://doi.org/10.1055/s-0030-1259530
76. Lyubchanskaya, V. M.; Alekseeva, L. M.; Granik, V. G. *Russ. Chem. Bull.* **2006**, *55*, 1659.
https://doi.org/10.1007/s11172-006-0470-1

Authors’ Biographies

Sarah J. Wright obtained her honours at the University of the Witwatersrand, where she is currently a PhD candidate in organic chemistry under the supervision of Dr Songeziwe Ntsimango and Prof Charles de Koning. Her research is focused on cyclobutenones and their annulation reactions.

Songeziwe Ntsimango obtained his PhD at the University of the Witwatersrand under the supervision of Prof. Charles de Koning. During this time, he was an exchange student at Johannes Gutenberg-Universität Mainz, hosted by Prof. Dr. Till Opatz. He undertook a short research visit at Ludwig-Maximilians-Universität München (LMU), with Dr Dino Berthold. He holds a lecturer position at the University of the Witwatersrand, Johannesburg, South Africa. His research interests lie within method development, focusing on the synthesis of *N*-heterocyclic compounds and small rings.