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Recent trends in the synthesis of carbazoles: an update

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ABSTRACT

The carbazole nucleus is a predominant feature of a vast array of heterocyclic compounds. It occurs in naturally occurring alkaloids, optoelectronic materials, and anion-binding ligands. Due to their various applications, there have appeared a plethora of synthetic methods for the construction of carbazoles. In this update, we focus on the recent developments and studies related to the synthesis of carbazoles spanning the period 2008–2011. Particular emphasis is placed on the methods involving cycloadditions and transition metal-assisted intramolecular aminations.

Contents

Abbreviations: MOM, methoxymethyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBA, tetra-*n*-butylammonium; CPBA, chloroperbenzoic acid; PIDA, phenyliodonium diacetate; PIFA, phenyliodonium bis(trifluoroacetate); BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; SEM, [2-(trimethylsilyl)ethoxy]methyl; PivOH, pivalic acid; NBS, *N*-Bromosuccinimide; Boc, *tert*-butoxycarbonyl; CBz, carboxybenzyl; PEG, polyethylene glycol.

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1. Introduction

Carbazoles are a distinguished class of aromatic heterocyclic nuclei (Fig. 1). They are prevalent as structural motifs in various synthetic materials and naturally occurring alkaloids. Carbazoles exhibit material properties as optoelectronic materials,[1] conducting polymers,[2] and synthetic dyes.[3] For example, polyvinylcarbazoles (PVK)[4] have been extensively studied for their applications in photorefractive materials and xerography. Recently, some poly(2,7-carbazole) derivatives have been used in polymer solar cells.[5] They are also widely used in organic light-emitting diodes as green, red, and white emitters. The molecular and optical properties of carbazoles can be engineered by structural modifications on the C-2, -3, -6, -7, and -9 positions.[6] Some benzo[*a*]-, benzo[*c*]-, and indolo [3,2-*b*]-carbazoles have been utilized as molecular platforms for luminescent, hole-transporting, and host materials in organic light-emitting devices.[7] In recent years, carbazole-containing ligands have been found to be effective as anion receptors.[8] For example, 3,6-dichlorocarbazole-1,8-diamide derivatives exhibit anion-binding ability through hydrogen bonding.

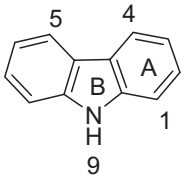

Fig. 1. Structure of carbazole.

Carbazoles prominently embody a wide range of plant natural products. A large number of them are endowed with profound biological activities, which include antitumor, psychotropic, anti-inflammatory, antihistaminic, antibiotic, and anti-oxidative activities. The structural attributes of such carbazole-based natural products are multifarious. One of their major structural features is the presence of nuclear hydroxyl groups. The quinone functionality is also frequently encountered. In addition, prenyl groups are often found in some natural carbazoles. A large array of bioactive carbazole natural products and synthetic derivatives are found to contain annulated rings such as those in ellipticine derivatives (**1**)[9] (Fig. 2), staurosporine (**2**),[10] carbazomycin B (**3**),[11] carbazomadurin A (**4**),[12] clausenamine A (**5**),[13] etc. Moreover, the carbazole moiety is considered as one of the pharmacophores in the cardiovascular pharmaceuticals carvedilol (**6**),[14] and carazolol (**7**),[15] which are used in the treatment of hypertension, ischemic heart disease, and congestive heart failure.

In view of the growing importance of carbazoles, a large body of synthetic strategies has been reported in the literature. In recent years, the synthesis of these bioactive carbazole alkaloids has been extensively reviewed by Knolker et al.[16] Traditionally, the synthesis of carbazoles relies upon nitrene insertion, Fischer indolization, Pummerer cyclization, Diels–Alder reaction, dehydrogenative cyclization of diarylamines, etc. In more recent years, transition metal-mediated C–C and C–N bond formation, cyclotrimerization, benzannulation, Suzuki–Miyaura coupling, ring-closing metathesis, etc. have been investigated. These reactions follow two modes: (i) the formation of an A or C ring from substituted indole derivatives and (ii) the formation of a B ring from benzene derivatives. Many of these strategies are continuously innovated to address issues related to regiochemical selectivity and efficiency. In this article, we have summarized the recent synthetic methods, the classification of which is based on the formation of the ring-forming strategic bond.

2. Formation of A (benzene) rings

2.1. Via electrocyclic reactions

2.1.1. Electrocyclic reactions of allenyl indole derivatives. For the synthesis[17] of the 1-oxygenated 1,3-disubstituted carbazole alkaloids, mukonine (**8**) and clausine E (**9**), Hibino et al. have employed an allene-mediated electrocyclic reaction involving the indole 2,3-bond (Scheme 1). Nucleophilic addition of lithium methoxyacetylide or ethoxyacetylide (prepared in situ from chloroacetaldehyde dimethyl acetal or chloroacetaldehyde diethyl acetal with lithium diethylamide) with 2-formylindolylacrylates (**10**) and (**11**), followed by MOM protection, afforded propargyl ethers **12** and **13**. These precursors, upon reaction with TBAF, gave 1,2,3-trisubstituted carbazole esters **14** and **15**, respectively, in moderate-to-good yields. Apparently, the reactions proceeded through allenyl intermediates **16** and **17**. Oxidation of **14** and **15** with DDQ, followed by deprotection of the MOM group, provided the 2-formyl-1-hydroxycarbazole **18**. From **18**, clausine E (**9**) and mukonine (**8**) were synthesized in four steps.

Similarly, carbazomadurin A (**19**) was synthesized from 3,8-bis-*O*-SEM-carbazole **20**[12a] (Scheme 2). The Suzuki–Miyaura cross-coupling reaction of **20** with boronate **21** in the presence of Na_2CO_3 and $Pd(PPh_3)_4$ was the key step for formation of the product. The resulting cross-coupling product was treated with TBAF, followed by $NaBH_4$, to provide carbazomadurin A (**19**).

2.1.2. Electrocyclization of enamino indole precursors. The synthesis of functionalized carbazoles developed by Mohanakrishnan et al.[18] centers around electrocyclization of an in situ-generated enamine **22** through the interaction of 1-phenylsulfonyl-2-methyl-3-vinylindole **23a** with DMF·DMA (dimethyl formamide·dimethyl acetal) or DMA·DMA (dimethyl acetamide·dimethyl acetal) at a moderate temperature (Scheme 3). The enamine **22** underwent electrocyclization, followed by aromatization of dihydrocarbazole **24** via elimination of dimethylamine.

The enamine-based electrocyclization methodology was applied to a variety of vinylindoles to afford the respective carbazoles. Some examples are shown in Table 1. The electrocyclization