DESIGN AND SYNTHESIS OF PYRANO[2,3-a] CARBAZOLES BY MULTICOMPONENT REACTION

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GRAPHICAL ABSTRACT

Abstract A facile, efficient, three-component reaction of 2,3,4,9-tetrahydro-1H-carbazol-1-one, malononitrile, and aromatic/heteroaromatic aldehydes in dimethylformamide (DMF) gave pyrano[2,3-a]carbazoles in good yields, at reflux condition, using a catalytic amount of piperidine.

Keywords Aldehydes; malononitrile; multicomponent reaction; piperidine; pyrano[2,3-a] carbazoles

INTRODUCTION

Multicomponent reactions (MCRs) are processes in which three or more reactants are combined in a single chemical step to produce products that incorporate substantial portions of all the reactants. MCRs have emerged as an attractive and powerful strategy for organic synthesis compared to multistep reactions because of the creation of several new bonds in a single-step reaction, low number of reaction and purification steps, selectivity, synthetic convergence, high atom economy, simplicity, and synthetic efficiency.\(^1\) Therefore, academic and industrial research groups have focused on the use of MCRs to synthesize a broad range of products.\(^2\) These reactions are also effective in building highly functionalized small organic molecules from readily available starting molecules in a single step with inherent flexibility for creating molecular complexity.\(^3\) Hence, MCRs are considered as a pivotal theme in the synthesis of many important heterocyclic compounds.

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Carbazoles and its derivatives are an important type of nitrogen-containing aromatic heterocyclic compounds. These carbazole alkaloids are isolated from taxonomically related higher plants of the genera *Murraya*, *Glycosmis*, and *Clausena*, which belong to the Rutaceae family. A large number of natural and synthetic carbazoles derivatives have been reported to exhibit diverse biological activities such as anti-HIV, antimicrobial, anti-inflammatory, antiencephalomycarditis, antiviral, antihistamine and antiseratonin, anticonvulsant and diuretic, fungicidal and anti-inflammatory, trypanocidal, vasodilator and beta-blocker, antidepressant, anticancer, trypanocidal, and mosquitocidal activities. Many of these carbazoles have oxygenated functionality at 1- or 2-positions and possess cytotoxic activity. Pyranocarbazole alkaloids are very attractive because of their fascinating structural features and potential biological activity, and they have prompted several research groups to develop synthetic strategies such as Fischer indolization, oxidative cyclization of diarylamines, and transition-metal-mediated and catalyzed processes for the total synthesis of naturally occurring pyranocarbazole compounds. These classes of compounds led to the discovery of many pyranocarbazole alkaloids. As specific examples, pyrano-carbazole alkaloids such as girinimbine, mupamine, mahanimbine, murrayanol, and mahanine have been isolated from plants of the Rutaceae family. Girinimbine was the first isolated pyrano[2,3-a] carbazole alkaloid. Carbazoles having α-pyrano as part of their structures with [2,3-a] fusion are biogenetically possible, as evident from the naturally available mupamine. Some of the naturally occurring pyrano carbazoles are represented in Fig. 1.

As part of our ongoing program directed toward the development of new methodologies for the synthesis and biological evaluation of diverse heterocyclic compounds, herein we disclose the synthesis of amino pyrano[2,3-a]carbazole in the presence of piperidine.

RESULTS AND DISCUSSION

To find the optimized conditions, a systematic study considering different variables affecting the reaction yield was carried out for the reaction of substituted 2,3,4,9-tetrahydro-1H-carbazol-1-ones with malononitrile and aromatic/
heteroaromatic aldehydes (3) as the model reaction (Scheme 1). The results have been summarized in Table 1. We found that the base and solvent have profound effects on the reaction yield.

The reaction condition was optimized using various base catalysts and DMF as solvent. The reaction conditions optimized using various bases are shown in Table 1. When K$_2$CO$_3$ and KOH were used as bases, the reaction time was longer and yield was less than 40%. Using triethylamine as base, the reaction time was 8 h and the product was obtained in poor yield. With morpholine and pyridine as bases, the reaction time was reduced to 6 h but moderate yield of 60% was obtained. The best yield for the reaction was obtained by switching to piperidine as the base in refluxing DMF as the solvent at 120 °C. Further increase in temperature beyond 120 °C does not influence the yield of the reaction.

The process was compatible with aromatic/heteroaromatic aldehyde, substituted benzaldehydes, and heterocyclic carbaldehyde as component 3 in the reaction (Table 2).

**Scheme 1.** Synthesis of pyrano[2,3-a]carbazoles.

**Table 1.** Effects of base and solvent

| Entry | Base      | Solvent | Time (h) | T (°C) | Yield (%) |
|-------|-----------|---------|----------|--------|-----------|
| 1     | —         | DMF     | 10       | 80     | 22        |
| 2     | K$_2$CO$_3$ | DMF     | 10       | 80     | 35        |
| 3     | KOH       | DMF     | 8        | 80     | 39        |
| 4     | Et$_3$N   | DMF     | 8        | 80     | 42        |
| 5     | Morpholine| DMF     | 6        | 80     | 58        |
| 6     | Pyridine  | DMF     | 6        | 80     | 60        |
| 7     | Piperidine| DMF     | 6        | 80     | 73        |
| 8     | Piperidine| DMF     | 6        | 90     | 76        |
| 9     | Piperidine| DMF     | 6        | 100    | 80        |
| 10    | Piperidine| DMF     | 3        | 120    | 95        |
Table 2. Synthesis of pyrano[2,3-\(a\)]carbazoles using aromatic/heteroaromatic aldehydes

| Compound | Precursor | Aldehyde | Product | Yield (%) |
|----------|-----------|----------|---------|-----------|
| 4a       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | 80        |
| 5a       | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) | 85        |
| 6a       | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | 95        |
| 7a       | ![Image](image10.png) | ![Image](image11.png) | ![Image](image12.png) | 70        |

(Continued)
| Compound | Precursor | Aldehyde | Product | Yield (%) |
|----------|-----------|----------|---------|-----------|
| 8a       | ![Image](image1.png) | ![Image](image2.png) | ![Image](image3.png) | 65        |
| 4b       | ![Image](image4.png) | ![Image](image5.png) | ![Image](image6.png) | 82        |
| 5b       | ![Image](image7.png) | ![Image](image8.png) | ![Image](image9.png) | 87        |
Table 2. Continued

| Compound | Precursor | Aldehyde | Product | Yield (%) |
|----------|-----------|----------|---------|-----------|
| 5c       | ![Compound 5c Structure](image) | ![Aldehyde 5c Structure](image) | ![Product 5c Structure](image) | 87 |
| 6c       | ![Compound 6c Structure](image) | ![Aldehyde 6c Structure](image) | ![Product 6c Structure](image) | 90 |
| 7c       | ![Compound 7c Structure](image) | ![Aldehyde 7c Structure](image) | ![Product 7c Structure](image) | 72 |
6-Methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (1a) was reacted with malononitrile (2), benzaldehyde (3), and piperidine in DMF for 3 h (Scheme 1), which afforded compound 4a.

The infrared (IR) spectrum of 4a shows an absorption band at 3272 cm\(^{-1}\) due to the presence of the NH group and asymmetric and symmetric stretchings at 3414 and 3365 cm\(^{-1}\) corresponding to the amino group. A sharp band at 2207 cm\(^{-1}\) confirmed the presence of the cyano group (CN). Its \(^1\)H NMR spectrum shows a broad singlet at \(\delta\) 9.24 due the indole NH proton. The eight aromatic protons appeared as a multiplet between \(\delta\) 7.13–7.54. A singlet at \(\delta\) 5.13 implied the presence of amino protons (NH\(_2\)). The four aliphatic protons of C\(_5\) and C\(_6\) appeared as a multiplet between \(\delta\) 2.64 and 2.84. Methyl protons appeared as a singlet at \(\delta\) 2.44. The total number of protons matched perfectly with its structure. Its \(^{13}\)C NMR spectrum shows the presence of 23 carbons. The molecular ion peak appears at \(m/z\) 353. The elemental

Scheme 2. Mechanism for the formation of compounds 4-8.
analysis agreed well with the proposed molecular formula C_{23}H_{19}N_{3}O. All the spectral and analytical data revealed the product as 2-amino-8-methyl-4-phenyl-5,6-dihydro-11H-pyrano[2,3-a]carbazol-3-carbonitrile (4a). The generality of the reaction was tested with various aromatic/heteroaromatic aldehydes to form the corresponding products, which are represented in Table 2.

The structures of the products were deduced from their elemental analysis data and from their IR, mass, ^1H NMR, and ^13C NMR spectra.

The possible mechanism for the formation of the products 4–8 is shown in Scheme 2. The initial step is the formation of arylidene malononitrile intermediate I from Knoevenagel condensation of aldehyde with malononitrile. Then the intermediate I on Michael addition with C2 carbanion of 2,3,4,9-tetrahydro-1H-carbazol-1-one gives ketimine intermediate II, and this intermediate undergoes tautomerism to give another intermediate III, which on intramolecular cyclization gives the final compound.

**CONCLUSION**

In conclusion, we have established a fast and efficient route for the synthesis of pyrano[2,3-a]carbazoles by multicomponent reaction of 2,3,4,9-tetrahydro-1H-carbazol-1-one with malononitrile and aromatic/heteroaromatic aldehydes in DMF, and the reaction condition was optimized using various bases. The best yield of product was obtained using piperidine as base under refluxing condition. All the synthesized compounds were characterized by IR, ^1H NMR, ^13C NMR, and mass spectroscopic techniques.

**EXPERIMENTAL**

Melting points (mp) were determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degrees centigrade (°C). A Nicolet Avatar model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm\(^{-1}\)). ^1H NMR and ^13C NMR spectra were recorded on Bruker AV 400 (400 MHz, ^1H, and 100 MHz, ^13C) spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Mass spectra (MS) were recorded on an Auto Spec EI+ Shimadzu QP 2010 Plus gas chromatography–mass spectrometry (GC-MS) instrument. Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. X-ray diffraction measurements were performed on a Bruker Kappa Apex-II diffractometer equipped with an Oxford Cryostream chiller and graphite monochromatized CuK alpha radiation. The purity of the products was tested by thin-layer chromatography (TLC) with plates coated with silica gel G; petroleum ether and ethyl acetate were used as developing solvents.

**General Procedure for the Synthesis of 2-Amino-4-aryl/heteroaryl-5, 6-dihydro-11H-pyrano[2,3-a]carbazol-3-carbonitriles 4–8**

A mixture of an appropriate 2,3,4,9-tetrahydro-1H-carbazol-1-one (1, 1 mmol), malononitrile (2, 1 mmol), and aromatic/heteroaromatic aldehyde (3, 1 mmol) in
DMF (10 mL) was refluxed at 120°C for 3 h in the presence of piperidine (4 drops). After the completion of the reaction, the excess solvent was evaporated and the solid poured into ice-cold water. The obtained solid was filtered, dried, and purified by column chromatography over silica gel using petroleum ether–ethyl acetate (98:2) to yield the respective product.

2-Amino-8-methyl-4-phenyl-5,6-dihydro-11H-pyrano[2,3-a]carbazol-3-carbonitrile (4a)

Yellow solid; mp 255–257°C; yield: 80%; IR (KBr, cm⁻¹) νmax: 3414 (asym), 3365 (sym), 3272 (NH), 2207 (CN); ¹H NMR (400 MHz, CDCl₃) (ppm) δH: 2.44(s, 3H, C₆-H₃), 2.64–2.68 (m, 2H, C₅-2H), 2.80–2.84 (m, 2H, C₆-2H), 4.11 (s, 1H, C₄-H), 5.13 (s, 2H, NH₂), 7.13–7.54 (m, 8H, C₂, C₉, C₁₀, C₂', C₃', C₄', C₅' & C₆'-H), 9.24 (b s, 1H, N₁₁-H); ¹³C NMR (100 MHz, CDCl₃) (ppm) δc: 19.56, 21.42, 26.21, 60.03, 111.69, 116.00, 118.25, 119.19, 120.20, 124.70, 125.70, 127.26, 128.44 (2C), 128.81, 128.93, 129.40, 130.05, 136.22, 136.33, 137.37, 148.64, 150.96; MS: m/z (%) (M⁺, 100) 353. Anal. calcd. for C₂₃H₁₉N₃O: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.11; H, 5.38; N, 11.82%.

2-Amino-10-methyl-4-phenyl-5,6-dihydro-11H-pyrano[2,3-a]carbazol-3-carbonitrile (4b)

Yellow solid; mp 243°C; yield: 82%; IR (KBr, cm⁻¹) νmax: 3464 (asym), 3370 (sym), 3235 (NH), 2208 (CN); ¹H NMR (400 MHz, CDCl₃) (ppm) δH: 2.58 (s, 3H, C₁₀-CH₃), 2.87–2.86 (m, 2H, C₅-2H), 2.71–2.69 (m, 2H, C₆-2H), 4.01 (s, 1H, C₄-H), 5.17 (s, 2H, NH₂), 7.56–7.10 (m, 8H, C₇, C₈, C₉, C₂', C₃', C₄', C₅', & C₆'-H), 9.33 (b s, 1H, N₁₁-H); ¹³C NMR (100 MHz, CDCl₃) (ppm) δc: 21.03, 21.42 (2C), 26.21, 60.03, 111.69, 116.00 (2C), 118.25, 119.19, 120.21, 124.70, 125.82, 127.26, 128.41, 128.81, 128.93, 129.40, 130.05, 136.33, 137.37, 148.64, 150.96; MS: m/z (%) (M⁺, 100) 353. Anal. calcd. for C₂₃H₁₉N₃O: C, 78.16; H, 5.42; N, 11.89. Found: C, 78.11; H, 5.38; N, 11.82%.

2-Amino-8-chloro-4-phenyl-5,6-dihydro-11H-pyrano[2,3-a]carbazol-3-carbonitrile (4c)

Yellow solid; mp 255°C; yield: 83%; IR (KBr, cm⁻¹) νmax: 3412 (asym), 3353 (sym), 3235 (NH), 2210 (CN); ¹H NMR (400 MHz, CDCl₃) (ppm) δH: 2.66–2.70 (m, 2H, C₅-2H), 2.79–2.83 (m, 2H, C₆-2H), 4.11 (s, 1H, C₄-H), 5.16 (s, 2H, NH₂), 7.24–7.53 (m, 8H, C₇, C₈, C₉, C₂', C₃', C₄', C₅', & C₆'-H), 9.36 (b s, 1H, N₁₁-H); ¹³C NMR (100 MHz, CDCl₃) (ppm) δc: 22.07 (2C), 30.09, 58.41, 111.29, 113.72 (2C), 118.10, 119.60, 120.09, 122.11, 124.25, 125.62, 126.49, 128.15, 129.36, 129.50, 132.00, 134.05, 135.19, 144.75, 151.50; MS: m/z (%) (M⁺, 100) 373, (M⁺ + 2) 375. Anal. calcd. for C₂₂H₁₆ClN₃O: C, 70.68; H, 4.31; N, 11.24. Found: C, 70.72; H, 4.28; N, 11.19%.
Yellow solid; mp 256 °C; yield 82%; IR (KBr, cm⁻¹) νmax: 3477 (asym, NH₂), 3342 (sym, NH₂), 3205 (NH), 2201 (CN); ¹H NMR (400 MHz, CDCl₃) (ppm) δH: 2.88–2.84 (m, 2H, C₅-2H), 2.71–2.69 (m, 2H, C₆-2H), 4.10 (s, 1H, C₄-H), 5.18 (s, 2H, NH₂), 7.69–7.17 (m, 9H, C₇-C₈-C₉-C₁₀-C₂₀-C₃₀-C₄₀-C₅₀-C₆₀-H), 9.35 (b s, 1H, N₁₁-H); ¹³C NMR (100 MHz, CDCl₃) (ppm) δC: 20.39 (2C), 27.51, 59.30, 111.05, 114.14 (2C), 119.20, 121.10, 122.01, 123.02, 126.41, 127.15, 127.47, 128.09, 128.50, 128.81, 132.01, 135.38, 138.03, 145.56, 153.65; MS: m/z (%) (M⁺, 100) 353.

Anal. calcd. for C₂₂H₁₇N₃O: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.83; H, 5.10; N, 12.41%.

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SUPPLEMENTAL MATERIAL
Supplemental data for this article can be accessed on the publisher’s website.

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