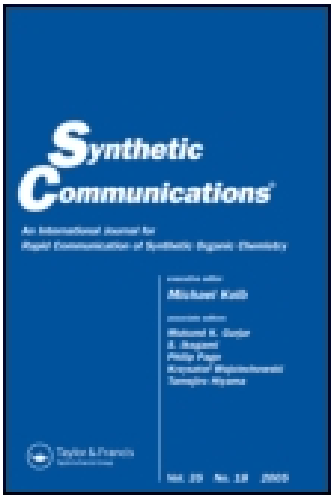

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Ezhumalai Yamuna [a] & Karnam Jayarampillai Rajendra Prasad [b]

[a] Department of Chemistry , Tamkang University , Tamsui , Taiwan

[b] Department of Chemistry , Bharathiar University , Coimbatore , India

Accepted author version posted online: 16 May 2014.Published online: 16 Jul 2014.

To cite this article: Ezhumalai Yamuna & Karnam Jayarampillai Rajendra Prasad (2014) $InCl_3$-Assisted Synthesis of Pyrano[2,3-a]carbazoles via Multicomponent Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:18, 2656-2661, DOI: 10.1080/00397911.2014.910526

To link to this article: http://dx.doi.org/10.1080/00397911.2014.910526

Synthetic Communications®, 44: 2656–2661, 2014

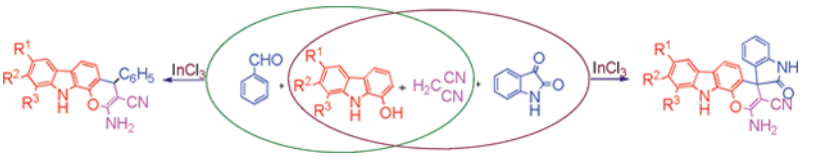
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2014.910526

$InCl_3$-ASSISTED SYNTHESIS OF PYRANO[2,3-*a*] CARBAZOLES VIA MULTICOMPONENT REACTION

Ezhumalai Yamuna[1] and Karnam Jayarampillai Rajendra Prasad[2]

[1]*Department of Chemistry, Tamkang University, Tamsui, Taiwan*
[2]*Department of Chemistry, Bharathiar University, Coimbatore, India*

GRAPHICAL ABSTRACT



Abstract *A facile, efficient, and environmentally friendly protocol for the synthesis of pyrano[2,3-a]carbazoles has been developed by one-pot multicomponent reaction of benzaldehyde/isatin with malononitrile and 1-hydroxycarbazoles in the presence of $InCl_3$ as catalyst.*

Keywords Heterocycles; 1-hydroxy carbazoles; $InCl_3$; multicomponent reaction; pyrano[2,3-*a*]carbazoles

INTRODUCTION

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon bonds in synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade there have been tremendous developments in three- and four-component reactions and great efforts continue to be made to develop new MCRs.[2]

The carbazole nucleus is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[3] As specific examples, pyranocarbazole alkaloids such as grinimbine, mupamine, and mahanimbine possess mosquitocidal, antimicrobial, anti-inflammatory, and

Received January 1, 2014.

Address correspondence to K. J. R. Prasad, Department of Chemistry, Bharathiar University, Coimbatore-641046, India. E-mail: prasad_125@yahoo.com

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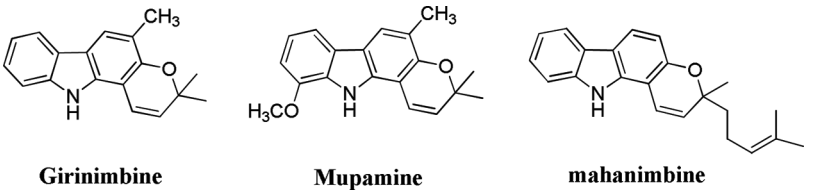


Figure 1. Oxygenated carbazole alkaloids.

antioxidant activities (Fig. 1).[4] Furthermore, it has been reported that sharing of the indole 3-carbon in the formation of spiroindoline derivatives highly enhances biological activity.[5] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[6]

In recent years, indium trihalides have emerged as mild and water-tolerant Lewis acids, imparting high regio- and chemoselectivity in various organic transformations. They can be conveniently used in both aqueous and nonaqueous media and in addition, they can be recovered from aqueous layer on workup and recycled for use in subsequent reactions. Further, $InCl_3$ has been found to be highly effective in hetero-Diels–Alder reaction,[7] Pall–Knorr condensation,[8] Friedel–Crafts reaction,[9] and domino reaction.[10] The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods.

For our synthetic strategy the easily accessible 1-hydroxycarbazoles were employed as suitable synthons for deriving 1-oxygenated pyranocarbazole compounds. Recently we reported the synthesis of 3- and 4-substituted pyrano [2,3-*a*]carbazol-2-ones[11–14] but most of the procedures suffer from limitations such as difficult workup and poor yields.

In continuation of our research interest, herein we report a novel and multicomponent one-pot synthesis of pyrano[2,3-*a*]carbazoles from 1-hydroxy carbazoles and malononitrile with benzaldehyde/isatin in the presence of $InCl_3$.

RESULTS AND DISCUSSION

We initially examined the reaction of 1-hydroxycarbazole **1**, benzaldehyde, and malononitrile in the presence of various catalysts using the same solvent system at varying temperatures to yield pyrano[2,3-*a*]carbazoles. Using *p*-TsOH, tin(II) chloride, zinc chloride (entries 5 and 6 of Table 1) gave only poor to moderate yields. Morpholine, ceric ammonium nitrate (CAN), and ytterbium triflate gave reasonable yields (entries 8, 9, and 10 of Table 1). Indium(III) chloride (entries 1–4), on the other hand, showed promising results. Ytterbium triflate as the catalyst facilitated the formation of pyrano[2,3-*a*]carbazoles in good yields (around 80%). With $InCl_3$ as the catalyst the reactions proceeded smoothly in an even shorter reaction time with similarly good yields, thus indicating $InCl_3$ as the most efficient catalyst of those tested (Table 1). To optimize the reaction conditions we evaluated the most suitable catalyst loading. With 10, 15, 20, and 25 mol% of $InCl_3$ the yields progressively

Table 1. Comparison of the efficiency of $InCl_3$ with other catalysts for the synthesis pyrano[2,3-*a*]carbazoles

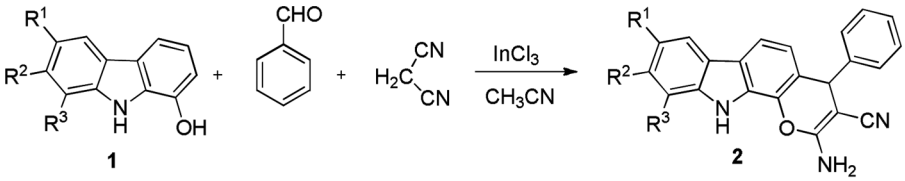
Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%) 2a	Yield (%) 3a
1	$InCl_3$ (10 mol%)	CH_3CN	90	8	80	82
2	$InCl_3$ (15 mol%)	CH_3CN	85	5	80	85
3	$InCl_3$ (20 mol%)	CH_3CN	90	6	85	85
4	$InCl_3$ (25 mol%)	CH_3CN	70	1.5	95	93
5	*p*-TsOH (25 mol%)	CH_3CN	70	24	45	46
6	$SnCl_2.H_2O$ (25 mol%)	CH_3CN	70	12	56	35
7	$ZnCl_2$ (25 mol%)	CH_3CN	70	15	54	38
8	Morpholine (25 mol%)	CH_3CN	70	18	65	59
9	CAN (25 mol%)	CH_3CN	70	14	60	52
10	$Yb(OTf)_3$ (25 mol%)	CH_3CN	70	10	80	76

improved with loading until reaching a maximum of $>90\%$ at 25 mol%. No additional increase was observed upon further increasing the load of $InCl_3$.

The reaction was found to be general and use of this method with various 1-hydroxycarbazoles[15] with benzaldehyde afforded highly substituted 2-amino-4-phenyl-4,11-dihydropyrano [2,3-*a*]carbazole-3-carbonitrile in good yield as shown in Scheme 1 (Table 2, entries 1–4).

Subsequently, we also investigated the reaction of compounds **1** with isatin instead of benzaldehyde. Reactions proceeded smoothly and gave another series of 2′-amino-2-oxo-11′*H*-spiro[indoline-3,4′-pyrano[2,3-*a*]carbazole]-3′-carbonitrile in excellent yields (Scheme 2, Table 2, entries 5–8).

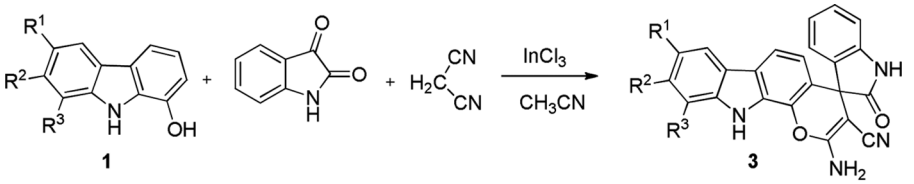
The structures of the products were deduced from their elemental analysis data and from their infrared (IR), mass, ^{1}H NMR, and ^{13}C NMR spectra. The IR spectrum of **2a**, for example, shows absorption peaks at 3472, 3413, 3313, and 2194 cm^{-1}, which attest to the presence of amino, indole NH, and cyano groups, respectively. Similarly, for compound **3a** the IR spectrum showed 3432, 3329, and 3290 cm^{-1} for the NH_2 and carbazole NH groups, and at 2217 cm^{-1} for the cyano group, as expected. The ^{1}H NMR spectrum of compounds **2b–d** is as expected. Compound **2a**, for example, exhibits a series of signals in the aromatic region of the spectrum



Scheme 1. Synthesis of 2-amino-4-phenyl-4,11-dihydropyrano[2,3-*a*]carbazole-3-carbonitrile.

Table 2. Reaction of 1-hydroxycarbazoles with benzaldehyde/isatin and malononitrile in the presence of $InCl_3$

Entry	R^1	R^2	R^3	Reactant	Product	Yield (%)
1	H	H	H	Benzaldehyde	**2a**	95
2	H	CH_3	H	Benzaldehyde	**2b**	92
3	H	H	CH_3	Benzaldehyde	**2c**	90
4	CH_3	H	H	Benzaldehyde	**2d**	90
5	H	H	H	Isatin	**3a**	93
6	H	CH_3	H	Isatin	**3b**	90
7	H	H	CH_3	Isatin	**3c**	90
8	CH_3	H	H	Isatin	**3d**	94



1,3 a) R^1, R^2, R^3= H
b) R^1, R^3= H, R^2= CH_3;
c) R^1, R^2= H, R^3= CH_3
d) R^1= CH_3, R^2, R^3= H;

Scheme 2. Synthesis of 2′-amino-2-oxo-11′*H*-spiro[indoline-3,4′-pyrano[2,3-*a*]carbazole-3′-carbonitrile.

at δ 11.23–6.74, one singlet arising from the benzylic proton (δ 4.88), and a broad singlet for the two amine protons (δ 6.69). The identities of the other compounds **2b–d** and **3a–d** were established in similar ways with all spectroscopic data readily assignable.

CONCLUSION

In summary, this method offers easy access to pyrano[2,3-*a*]carbazoles with varied substitution patterns in very good yields. Furthermore, good yields, simple reaction conditions, easy purification, and economical availability of the catalyst make this facile and superior method for the synthesis of pyrano[2,3-*a*]carbazoles. Biological evaluation of these derivatives is under way.

EXPERIMENTAL

Melting points (mp) were determined on Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and are uncorrected. They are expressed in degree centigrade (°C). IR spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer (Shimadzu, Japan) using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Bruker AMX 400 and AMX 500 (400 MHz and 500 MHz (^1H), 100 MHz and 125 MHz (^{13}C) NMR) spectrometers at Indian Institute of Science,

Bangalore, and Indian Institute of Technology, Chennai, using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Microanalyses were performed on a Vario EL III model CHNS analyzer (Vario, Germany) at the Department of Chemistry, Bharathiar University. The purity of the products was tested by thin-layer chromatography (TLC) with plates coated with silica gel-G with petroleum ether and ethyl acetate as developing solvents.

Procedure for the Preparation of Pyrano[2,3-*a*]carbazoles (2a)

$InCl_3$ (25 mol%) dissolved in CH_3CN was added to a mixture of 1-hydroxycarbazole (1 mmol), malononitrile (1 mmol), and benzaldehyde (1 mmol) and subjected to microwave irradiation (Biotage microwave oven, 70 °C, 2 bar pressure) for 10 min. The progress of the reaction was monitored by TLC. Upon cooling, the product precipitated from the reaction mixture, which was filtered, dried, and recrystallized from ethanol.

2-Amino-4-phenyl-4,11-dihydropyrano[2,3-*a*]carbazole-3-carbonitrile (2a)

Light yellow solid (0.320 g, 95%); mp: 244 °C; IR (KBr) 3472, 3413, 3313, 2194, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.88 (s, 1H, benzylic hydrogen), 6.69 (s, 2H, 2-NH2), 6.74 (d.,1H, 5-H, $J = 8.0$ Hz), 7.14 (t, 1H, 9-H, $J = 8.0$ Hz), 7.22–7.16 (m, 3H, 2′-H, 4′-H & 6′-H), 7.28 (t, 2H, 3-H & 5-H, $J = 8.0$ Hz), 7.36 (dt, 1H, 8-H, $Jo = 8.0$ Hz, $Jm = 1.5$ Hz), 7.54 (d, 1H, 10-H, $J = 8.0$ Hz), 7.73 (d,1H, 6-H, $J = 8.0$ Hz), 8.00 (d, 1H, 7-H, $J = 8.0$ Hz), 11.23 (bs, 1H, 11-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 41.40, 58.00, 112.26, 116.76, 119.45, 119.60, 119.68, 120.59, 120.97, 122.81, 123.76, 126.22, 127.23, 127.98, 129.10, 134.98, 140.70, 146.73, 160.46. MS: m/z (%) 337 (M^+, 100), 260 (26), 222, (21), 165 (18), 145 (14), 141(12), 119 (9), 115 (12). Anal. calcd. for $C_{22}H_{15}N_3O$: C, 78.32; H, 4.48; N, 12.46%. Found: C, 78.36; H, 4.43; N, 12.50%.

ACKNOWLEDGMENTS

Our sincere thanks go to the chairman, NMR Research Centre, IISc, Bangalore; SAIF, IIT Madras, Chennai; and the director, ISO Quality Assurance Cell, Indian Institute of Chemical Technology, Hyderabad, for providing access to their NMR and mass spectral facilities and use of a Biotage microwave oven, Madurai Kamaraj University, Madurai.

FUNDING

We acknowledge URF, Bharathiar University, for the award of a research fellowship.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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