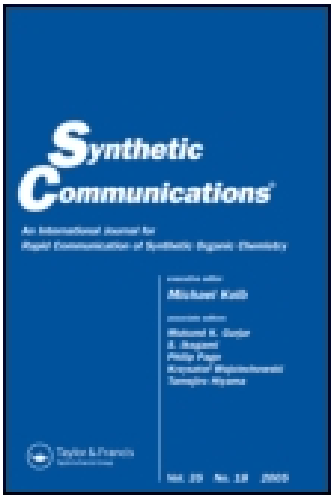

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

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Accepted author version posted online: 08 Nov 2013.Published online: 19 Mar 2014.

To cite this article: Prasanta Gogoi , Sandhya Rani Gogoi , Namita Devi & Pranjit Barman (2014) Aluminium Chloride-Catalyzed Synthesis of 4-Benzyl Cinnolines from Aryl Hydrazones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:8, 1142-1148, DOI: 10.1080/00397911.2013.853799

To link to this article: http://dx.doi.org/10.1080/00397911.2013.853799

Synthetic Communications®, 44: 1142–1148, 2014

ISSN: 0039-7911 print/1532-2432 online
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ALUMINIUM CHLORIDE–CATALYZED SYNTHESIS OF 4-BENZYL CINNOLINES FROM ARYL HYDRAZONES

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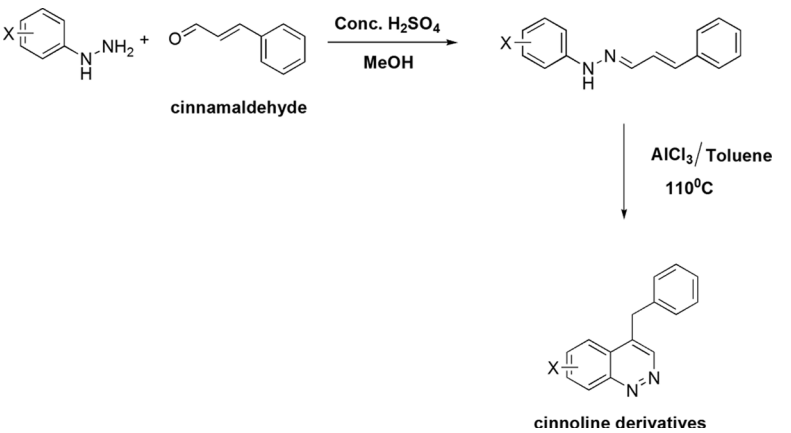
GRAPHICAL ABSTRACT



Abstract *An efficient synthesis of 4-benzyl cinnolines from aryl phenylallylidene hydrazone is described. In this report aluminium chloride as a Lewis acid catalyst and toluene as a solvent are used for the synthesis. This method is expected to more advantageous than the other reported methods of synthesis of the cinnoline rings because of its low cost, better yield, and benign reaction conditions.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Aluminium chloride; aryl hydrazones; 4-benzyl cinnolines

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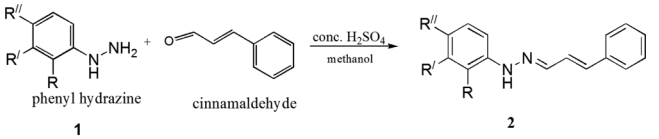
INTRODUCTION

Cinnolines have received considerable interest because of their wide range of pharmacological profiles.[1] Many of these compounds have attracted considerable attention in recent years for their roles in biological processes. These compounds possess antibacterial,[2] antitumor,[3] anti-inflammatory,[4] antifungal,[5] anticancer,[6] and phosphodiesterase inhibitorys[7] properties. Some cinnolines have antileukemic[8] and antipsychotic[9] properties. Some of these compounds show electrochemical properties,[10–12] in addition to their use as agrochemicals.[13] The chemistry of cinnolines has received much attention and many methods of synthesis of these compounds have been developed. Most syntheses of cinnolines involve arenediazonium salts,[14,15] intramolecular arylation,[16] arylhydrazones,[17–19] arylhydrazines,[20] and nitriles[21] as the starting materials. Recently, a Cu-catalyzed dehydrogenative cyclization of phenyl hydrazones to cinnoline has been reported.[22] However, the requirement of strong basic media is a limitation of the reported cyclization of phenylhydrazones into cinnolines.

Table 1. Synthesis of hydrazone derivatives (**2**)



a: R=H, R′ = H,R″=H
b: R=C_2H_5, R′ = H,R″=H
c: R=H,R′ = H,R″=$PhCH_3$
d: R=H,R′ = H, R″ =CH_3
e: R=H,R′ = H, R″ =Cl
f: R = H, R′ = H,R″= OCH_3
g:R = H,R′ = H, R″=CH_2CH_3
h:R= CH_3, R′ = H, R″= H
i: R = H, R′= CH_3, R″= H
j:R = H, R′= CH_2CH_3, R″ = H
k:R= H, R′= OCH_3,R″ = OCH_3
l: R=F, R′=H,R″ = H
m: R=NO_2, R′=NO_2,R″ = H
n: R=H, R′=NO_2,R″ = H

Entry	Substrate	Product (**2**)	Time (min)	Yield (%)[a]
1	**1a**	**2a**	20	65
2	**1b**	**2b**	15	60
3	**1c**	**2c**	12	85
4	**1d**	**2d**	10	65
5	**1e**	**2e**	12	75
6	**1f**	**2f**	15	65
7	**1g**	**2g**	14	60
8	**1h**	**2h**	15	67
9	**1i**	**2i**	13	55
10	**1j**	**2j**	14	59
11	**1k**	**2k**	16	54
12	**1l**	**2l**	12	85
13	**1m**	**2m**	10	95
14	**1n**	**2n**	10	90

[a]Isolated yield of **2**.

In this article we present a general method for the formation of 4-benzyl cinnolines, adhering to our objective of developing a protocol that can fulfil the necessity for a benign, less expensive, and safe synthetic method, by using a catalytic amount of aluminium chloride in toluene as the solvent.

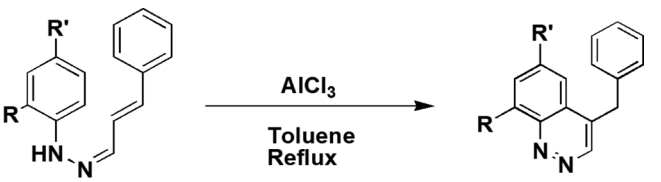
RESULTS AND DISCUSSION

Initially a series of hydrazones of cinnamaldehyde prepared as per the reported[23] method are presented in Table 1 **(2a–n).** In the next step, the hydrazones are subjected to an $AlCl_3$-aided cyclization to the respective 4-benzylcinnolines **(3a–n)** and their characterizations are presented in Table 2. A probable mechanism of the cyclization reaction is presented in if Scheme 1. It is an intramolecular electrophilic aromatic substitution leading to dihydrocinnoline and its dehydrogenation gives the final product.

The cyclization is initiated by $AlCl_3$-aided tautomerization of the imino azomethine group of the hydrazone **(A)** into the azo group of the azo tautomers **(B).** The cinnoline hetero ring closure then takes place with the $AlCl_3$-activated benzene ring. The stabilized final products **(3a–n)** are then formed by rearomatization of the *para*-benzoquinoid form due to reorganization of the π electrons. In our screening of a few Lewis acid catalysts in this cyclization reaction we have found the best result with $AlCl_3$ Table 3.

Our solvent of choice is toluene because it has been found that this reaction gives the best result in toluene as the solvent in comparison with other solvents Table 4.

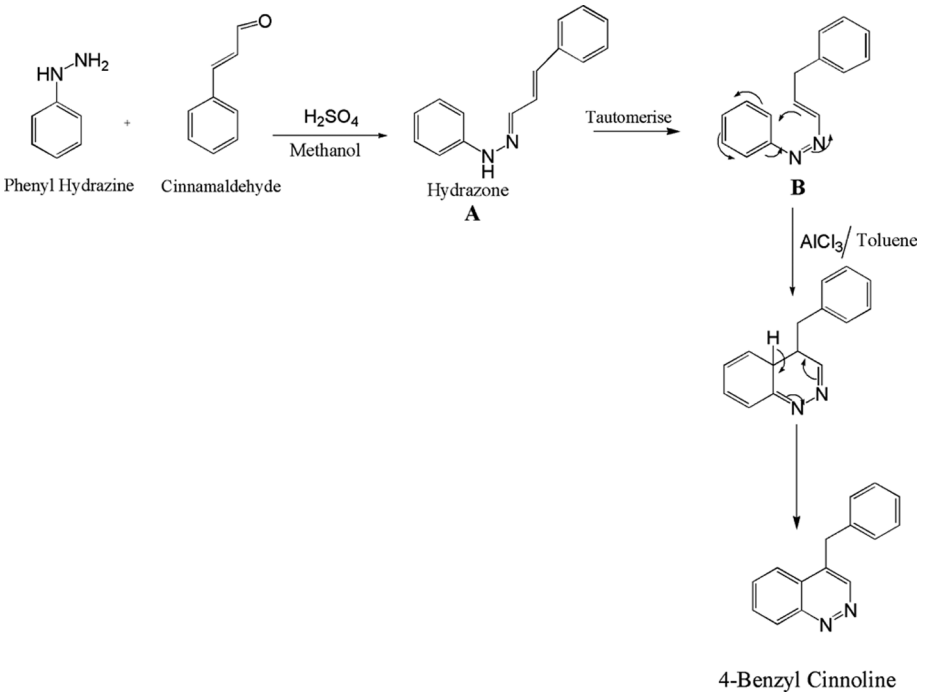
Table 2. Formation of 4-benzyl cinnolines from cinnamaldehyde-derived phenyl hydrazones



2 **3**

Entry	Substrate (**2**)	Product (**3**)	Time (h)	Yield (%)[a]
1	**2a**	**3a**	7	74
2	**2b**	**3b**	9	90
3	**2c**	**3c**	5	65
4	**2d**	**3d**	10	80
5	**2e**	**3e**	8	48
6	**2f**	**3f**	5	70
7	**2g**	**3g**	6	65
8	**2h**	**3h**	8	67
9	**2i**	**3i**	6	71
10	**2j**	**3j**	7	65
11	**2k**	**3k**	4	82
12	**2l**	**3l**	11	Trace
13	**2m**	**3m**	15	Trace
14	**2n**	**3n**	12	Trace

[a]Isolated yield of **3**.



Scheme 1. A plausible mechanism for the formation of 4-benzyl cinnolines.

Table 3. Screening of Lewis acid catalysts for cyclization reaction

Entry	Lewis acid	Time (h)	Yield (%)[a]
1	$TiCl_4$	9	34
2	$AlCl_3$	7	74
3	$FeCl_3$	8	23
4	$InCl_3$	12	Trace
5	$SnCl_2.2H_2O$	9.5	44

[a]Isolated yield of **3a**.

Table 4. Optimization of reaction conditions for the preparation of 4-benzylcinoline

Entry	Solvent	Time (h)	Yield (%)[a]
1	CH_3CN	6	20
2	THF	5	48
3	**Toluene**	**7**	**74**
4	DCM	4	44
5	DMF	7	50
6	DMSO	8	40
7	CCl_4	7	35

[a]Isolated yield of **3a**.

It is more likely that $AlCl_3$ activates the azo group as an electrophile, and therefore arene is the nucleophile. This may be the reason why the presence of inductively activating alkyl group(s) in the aryl ring favor the cyclization step, whereas the presence of strong resonatingly deactivating nitro group(s) in the ring disfavor the cyclization reaction.

CONCLUSION

In conclusion, we have been able to develop a benign, safe, and quite efficient method for the synthesis of 4-benzyl cinnolines from easily preparable aryl hydrazones of cinnamaldehyde in the presence of Lewis acid catalyst aluminium chloride. Good yields of cinnolines, a very simple workup procedure, and easy and safe method of preparation are the advantages.

EXPERIMENTAL

All solvents and chemicals were purchased commercially and used without further purification. Melting points were determined by open glass capillary method and are uncorrected. NMR spectra were recorded on a FT-NMR Bruker Avance II 400-MHz instrument (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) using $CDCl_3$ as solvent and tetramethylsilene (TMS) as an internal reference. Infrared (TR) spectra were recorded on a Nicolet Impact 410 FT-IR spectrometer. Solid samples were examined as a thin film between KBr salt plates. Mass spectra were recorded on a LC-MS Waters ZQ-4000 instrument. Elemental analyses were carried out in a Perkin-Elmer model 240 analyzer.

Typical Procedure for the Synthesis of 4-Benzyl Cinnoline (3a)

Anhydrous $AlCl_3$ (10 mol%) and toluene (4.0 mL) were added to a round-bottomed flask equipped with a reflux condenser with 1-(phenyl)-2-(3-phenyl-allylidene) hydrazine (1.1 g, 0.5 mmol). The flask was placed in a hot oil bath and stirred at 110 °C for 7 h. Upon completion of the reaction the mixture was filtered and diluted with water. The precipitated product was collected and purified by column chromatography on silica gel using ethyl acetate / hexane (10–25%) to give 4-benzylcinnoline **(3a).**

Selected Data

Yellowish solid; mp: 103 °C (lit.[24] 104.5°C); IR υ/(KBr) cm^{-1}: 3089 cm^{-1} (Ar-H), 2846 cm^{-1} (C-H), 1592 cm^{-1} (N=N), 1280 cm^{-1} (-C-N=N), 1195 cm^{-1} (-N=N-C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.81 (d, J=7.5 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H), 7.44–7.38 (m, 5H), 7.26 (s, 1H) 4.62 (s, 1H); [13]C NMR (100 MHz, $CDCl_3$) δ 152.2, 148.1, 138.6, 137.3, 135.5, 132.8, 131.2, 129.1, 128.7, 126.3, 125.2, 120.2, 54.4; Mass: *m/z* 221.1 $[M+H]^+$. Anal. calcd. for $C_{15}H_{12}N_2$ (220): C, 81.79; H, 5.49; N, 12.72. Found: C, 81.43; H, 5.55; N, 12.75.

SUPPORTING INFORMATION

Full experimental and spectral details can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

The authors are grateful to K. Mohan Rao, head of the Sophisticated Analytical Instrument Facility (SAIF), Northeastern Hill University (NEHU), Shillong, for NMR and mass spectroscopy support of this research and CIF of Tezpur University. We thank S. K. Bhattacharjee, Department of Chemistry, Gauhati University, Guwahati, Assam, India, for valuable suggestions.

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