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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/18325

DOI URL: <http://dx.doi.org/10.21474/IJAR01/18325>



RESEARCH ARTICLE

STREAMLINED SYNTHESIS: ENHANCING THE LEIMGRUBER-BATCHO INDOLE ROUTE FOR ONE-POT TANDEM PRODUCTION OF 2,3-UNSUBSTITUTED INDOLES

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Manuscript Info

Manuscript History

Received: 26 December 2023

Final Accepted: 28 January 2024

Published: February 2024

Key words:-

2-Nitrotoluenes, Green Chemistry, Leimgruber-Batcho, Substituted Indoles, Economically Viable

Abstract

Aim: This study aims to create a new one-pot synthesis method for substituted indoles, focusing on efficiency, by-product reduction, and comparative advantages over conventional Leimgruber-Batcho reactions.

Methods: Researchers optimized a one-pot synthesis strategy for maximum yield, reduced by-products, and resource utilization, comparing it to traditional Leimgruber-Batcho reactions, ensuring a sustainable, environmentally friendly approach.

Results: The one-pot synthesis method efficiently produced substituted indoles with reduced environmental impact, yielding more than conventional reactions, shortened reaction times, and aligning with green chemistry principles.

Conclusions: The one-pot synthesis method for substituted indoles, using 2-nitrotoluenes and dimethylformamide dimethyl acetal, is a significant advancement in the field, offering improved efficiency, environmental sustainability, and higher yields compared to conventional methods, making it a more resource-effective and economically viable option.

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Introduction:-

The indole ring system serves as a crucial structural motif in numerous biologically active compounds, both natural and synthetic. Its prevalence extends to pharmaceutical agents, dyestuffs, and intermediates in pharmaceutical and agrochemical applications.¹⁻³ Despite considerable progress in indole ring construction methods over the past decades,⁴⁻¹⁰ organic chemists continue to seek more straightforward, economical, and environmentally friendly approaches for synthesizing various substituted indoles. Examples include transition-metal-catalysed synthesis,¹¹⁻¹³ and multistep one-pot synthesis.¹⁴⁻¹⁵

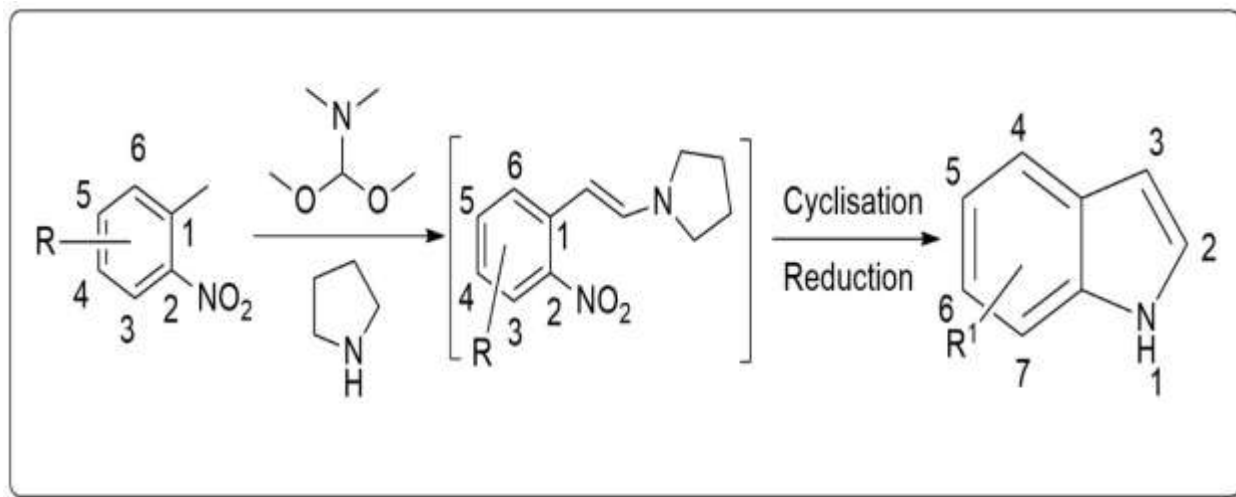
The Leimgruber-Batcho indole synthesis stands out as an important and efficient method, particularly for generating substituted indoles. Traditionally, this synthesis involves a two-step process, commencing with the condensation of a suitably substituted o-nitrotoluene with dimethylformamide dimethyl acetal (DMFDMA) to form an intermediate o-nitro phenylacetaldehyde enamine. Subsequently, a reductive cyclization yields the desired substituted indoles.¹⁶

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This method enjoys widespread application due to the ease of preparation of starting materials, mild reaction conditions for both steps, and high functional group compatibility.¹⁷⁻¹⁹

However, drawbacks, such as extended reaction times and intricate isolation procedures for enamine intermediates,²⁰⁻²¹ prompted modifications to the Leimgruber-Batcho reaction. Variations have been explored, including changes to the applied base, the reducing reagents, and the available acetals of dimethylformamide.²²⁻²³

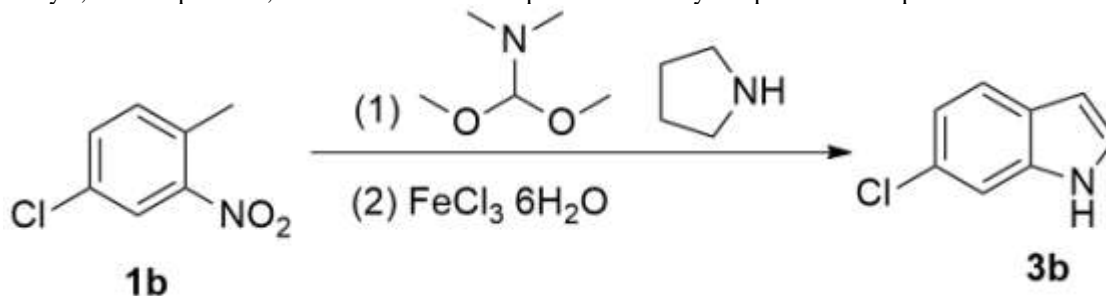


Scheme 1:- Synthesis of substituted indoles.

In this study, we present a concise, fast, and efficient method for synthesizing indoles through the Leimgruber-Batcho reaction, conducted as a one-pot process directly from o-nitrotoluene derivatives to the corresponding indole products (see Scheme 1). Notably, our method simplifies the procedure, yielding higher product yields in significantly shorter reaction times compared to conventional Leimgruber-Batcho indolization routes.²⁴⁻²⁵ This advancement not only enhances the efficiency of indole synthesis but also addresses some of the limitations associated with the traditional approach.

Results and Discussion:-

Our investigation commenced with an exploration of the one-pot reaction involving 4-chloro-2-nitrotoluene (1b) and DMF-DMA, denoted as the standard reaction in Scheme 1 with R = Cl (Table 1). Encouragingly, the anticipated product 3b was successfully obtained when the reaction was conducted in DMF, a solvent conventionally used in the initial step of the classic Leimgruber-Batcho indole synthesis (Table 1, entry 1), indicating the feasibility of one-pot indole synthesis via the Leimgruber-Batcho reaction. However, the total yield of 3b was modest at 36% within 10 hours. Recognizing the factors influencing this one-pot reaction, including solvent, additive, reducing agent, catalyst, and temperature, we embarked on a comprehensive study to optimize these parameters.



Solvent selection emerged as a pivotal factor influencing both the yield and reaction rate (Table 1). Dioxane exhibited the highest efficacy (Table 1, entries 1-5), followed by toluene, THF, DMF, and methanol. DMF proved unsuitable due to its inhibitory effect on $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, Raney Ni and Pd/C in catalytic hydrogenation reactions. Pyrrolidine, employed as an additive, particularly in excess, significantly enhanced the reaction (Table 1, entries 4, 6, and 10), facilitating both the generation of compound A with higher reactivity and o-nitrotoluene deprotonation.

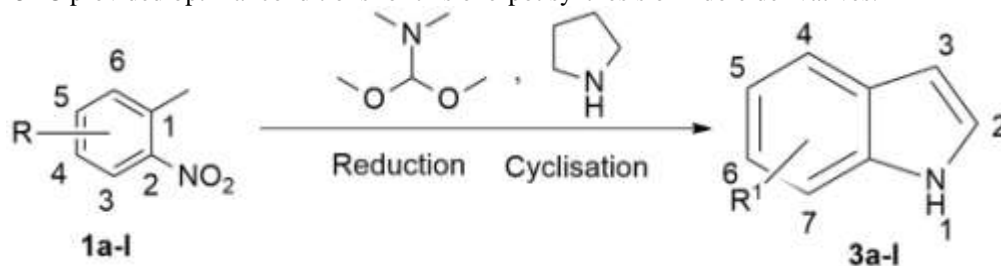
Other nitrogenous nucleophilic reagents, such as diethyl amine, piperazine, and morpholine, yielded inferior results compared to pyrrolidine (Table 1, entries 7-9).

Table 1:- Optimization of the one-pot synthesis.^a

Entry	Solvents	Additives	Reducing Agents	Time / Hrs	Temp / C	Yield
1	DMF	Pyrrolidine	85% N ₂ H ₄	10	45	37
2	THF	Pyrrolidine	85% N ₂ H ₄	10	45	64
3	Toluene	Pyrrolidine	85% N ₂ H ₄	10	45	75
4	MeOH	Pyrrolidine	85% N ₂ H ₄	10	45	12
5	Dioxane	Pyrrolidine	85% N ₂ H ₄	18	45	57
6	Dioxane	Pyrrolidine	Hydrogen	6	45	90
7	Dioxane	Diethyl amine	85% N ₂ H ₄	24	45	22
8	Dioxane	Piperazine	85% N ₂ H ₄	15	45	5
9	Dioxane	Morpholine	85% N ₂ H ₄	15	45	5
10	Dioxane	Morpholine	85% N ₂ H ₄	32	45	5
11	Dioxane	Pyrrolidine	85% N ₂ H ₄ (6 equiv)	9	45	63
12	Dioxane	Pyrrolidine	85% N ₂ H ₄ (2equiv)	15	45	28
13	Dioxane	Pyrrolidine	60% N₂H₄	7	45	82
14	Dioxane	Pyrrolidine	Hydrogen	6	45	85
15	Dioxane	Pyrrolidine	30% N ₂ H ₄	8	45	77
16	Dioxane	Pyrrolidine	85% N H	14	45	35
17	Dioxane	Pyrrolidine	85% N H	14	45	45
18	Dioxane	Pyrrolidine	85% N ₂ H ₄	6	20	70
19	Dioxane	Pyrrolidine	85% N ₂ H ₄	5	60	76
20	Dioxane	Pyrrolidine	85% N ₂ H ₄	10	45	46

^a Reaction conditions: **1b** (4 mmol), DMF DMA (4.8 mmol), additive (5 equiv), hydrazine (10 equiv), catalyst: 200 mg Ferric chloride hexahydrate, in solvent (50 ml), under nitrogen atmosphere, Reduction temperatures, Isolated yields, Catalyst: 200 mg Ferric chloride hexahydrate.

Utilizing hydrogen gas as the reducing agent remarkably improved the yield of product **3b** to 85% within 6 hours. Considering safety and scalability, hydrogen (H₂) was deemed a favourable reducing agent compared to hydrazine hydrate (Table 1, entries 6 and 14). Hydrazine hydrate concentration variations influenced yields and reaction rates, with decreasing concentrations resulting in lower yields and reaction rates, possibly due to the production of 1-hydroxyindoles as by-products (Table 1, entries 4, 13, and 14). Optimization indicated that the reaction conducted in dioxane with pyrrolidine (5 equiv), 85% hydrazine hydrate (10 equiv), and Ferric chloride hexahydrate (200 mg) at 45 °C provided optimal conditions for this one-pot synthesis of indole derivatives.



To assess the generality of our one-pot methodology, we applied the optimized conditions to synthesize various substituted indoles (Table 2).

Table 2:- Optimization of the one-pot synthesis.

Entry	R	1	Time/hrs	R ¹	3	Yield /% ^a
1	H	1a	10	H	3a	71
2	4-Cl	1b	5.5, 24 ^b	6-Cl	3b	92, 32 ^b
3	4-Br	1c	3.5, 31 ^b	6-Br	3c	82, 37 ^b
4	4-NO	1d	5	6-NH	3d	52, 35 ^b
5	5-CH ₃	1e	14	5-CH ₃	3e	65
6	5-CN	1f	2.5	5-CN	3f	66
7	5-Cl	1g	6	5-Cl	3g	68
8	4,5-Cl	1h	5	5,6-Cl	3h	92
9	6-Cl	1i	9	4-Cl	3i	55
10	6-NH ₂	1j	6.5	4-NH ₂	3j	34
11	3-Cl	1k	9	7-Cl	3k	70
12	3-CH ₃	1l	21	7-CH ₃	3l	53

^a Isolated yields. ^b Data reported for the classic Leimgruber-Batcho routes.^{7a}

The results demonstrated the smooth performance of all o-nitrotoluene derivatives with diverse substituents, achieving higher reaction rates compared to literature-reported values. Importantly, our one-pot protocol consistently delivered higher yields than conventional Leimgruber-Batcho routes. Notably, the yield of 3b reached 92%, surpassing the 32% obtained via conventional routes. Nonetheless, the synthesis of 7-methylindole (3l) exhibited a relatively low yield, possibly due to steric effects, a phenomenon observed in literature reports as well. Substituent type and position significantly influenced both yields and reaction rates, with electron-withdrawing groups enhancing reactivity. In summary, our study presents a streamlined and efficient one-pot synthesis of indoles via the Leimgruber-Batcho reaction, demonstrating improved yields and reaction rates compared to conventional methods.

Experimental

General Procedure for One-Pot Reaction from O-nitrotoluenes

A 100 mL three-necked flask, fitted with a magnetic stir bar and a condenser, was loaded with o-nitrotoluenes (4 mmol), DMF-DMA (4.8 mmol), pyrrolidine (20 mmol), and dioxane (50 mL) under a nitrogen atmosphere at 102 °C for 2.5-22 hours. The reaction progress was monitored using TLC. Upon cooling the reaction mixture to 45 °C, 0.2 g of Ferric chloride hexahydrate was introduced, followed by the addition of 0.8 g of 85% hydrazine hydrate, resulting in vigorous gas evolution. Subsequent additions of 0.8 g of 85% hydrazine hydrate occurred at 30-minute intervals, with the temperature maintained at 45 °C. Upon completion of the reaction, the mixture was cooled to room temperature, and the catalyst was filtered off and meticulously washed with 5 × 10 ml dichloromethane or acetone. The filtrate underwent evaporation under reduced pressure, and the resulting residue was purified via column chromatography on silica gel, using a dichloromethane and petroleum ether mixture as the eluent, yielding the desired product 3.

Conclusions:-

In Conclusion, this work presents a streamlined and effective one-pot tandem methodology for synthesizing substituted indoles from o-nitrotoluenes, derived from the Leimgruber-Batcho reaction. This approach not only eliminates the need for isolating potentially unstable enamine intermediates but also significantly reduces the generation of by-products and chemical wastes. Importantly, findings demonstrate that the overall yields achieved through the one-pot procedure are approximately twice as high, achieved in a shorter reaction time, compared to traditional step-by-step processes. Furthermore, study reveals that o-nitrotoluenes substituted with electron-withdrawing groups exhibit higher reactivities and yields compared to those with electron-donating groups.

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