Research Article

Facile Transformation of Cinnolines into Indoles

S. Mumtazuddin*, AK. Azad, Wasi Ahmad and Prabhat Bharti

University Department of Chemistry, B. R. A. Bihar University, Muzaffarpur- 842001, Bihar, India.

ABSTRACT

This paper reports single step conversion of some cinnolines into indoles by ring transformation reaction; nitrogen extrusion from the former has been carried out by the application of Zn/CH_3COOH.

Keywords: Ring transformation, Cinnolines, Indoles.

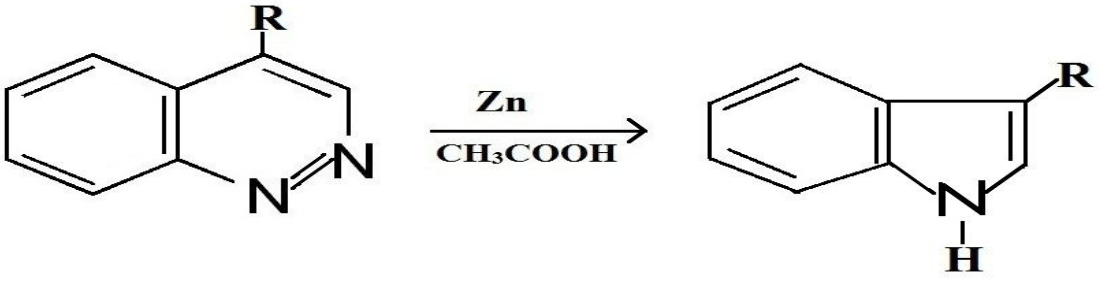
INTRODUCTION

The Indole scaffold represents one of the most important structural subunits for the discovery of new drug candidates. The fact that many alkaloids contain the indole nucleus, the recognition of the importance of essential amino acid tryptophan in human nutrition and the discovery of plant hormones have prompted a massive search on indole chemistry, giving rise to a vast number of biologically active natural and synthetic products, with a wide range of therapeutic targets, such as anti inflammatories, phosphodiesterase inhibitors, 5-hydroxy tryptamine receptor agonists and antagonists, cannibinoid receptor agonists and HMG-CoA reductase inhibitors[1].

Besides, indole nucleus is present in medicines/agents having antifungal, analgesic, anticancer, antihypertensive, antihistamines, anti HIV, antioxidant, antidiabetic, photochemotherapeutic, antidepressant, tranquilising, anticonvulsant, thrombin catalytic, antitubercular, insecticidal, antiviral and antimicrobial activities[2].

For these reasons synthesis of indoles have been performed by us by ring transformation method. Ring transformation has in recent times been taken up quite successfully as an alternative to the classical methods[3-6].

We have been successful in synthesising Indole (2a) and methyl Indole-3-carboxylate (2b) by the action of Zn/CH_3COOH on cinnoline (1a) and methyl cinnoline-4-carboxylate (1b) respectively according to scheme 1.



(1)
(a) R = H
(b) R = $COOCH_3$

(2)
(a) R = H
(b) R = $COOCH_3$

(Scheme-1)

EXPERIMENTAL

Indoles (2 a-b): A 250-ml, round-bottomed flask equipped with a magnetic stirrer was charged with cinnolines (1 a-b, 0.005 mol) and glacial acetic acid (55 ml). Zinc dust (3.25g, 0.05mol) was added and the reaction mixture was stirred at room temperature for 4 hr. A second portion of zinc dust (3.25 g, 0.05 mol) was added and the reaction mixture was stirred for an additional 16 hr. The zinc dust was removed by filtration and the residue was washed with ether (100 ml). The filtrate and washed were combined, made basic (pH 10) with the addition of saturated sodium bicarbonate, and extracted with ether (2×100 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the product was effected by chromatography on a 4.5× 9 cm column of silica gel (CH_2Cl_2 eluent), collecting 20-ml fractions. The fractions were analyzed by thin-layer chromatography (Kieselgel 60, CH_2Cl_2 eluent) and those containing product were combined and concentrated in vacuo to give cinnolines (2a-b) as solids, recrystallised from ethyl acetate-hexane.

2a	
Yield	48%
M.P.	52-54%
Elemental analysis Calc. for C_8H_7N Found	 C, 82.05%; H, 5.98%; N, 11.96% C, 82.02%; H, 5.93%; N, 11.91%
I. R. (Nujol Mull): υ_{max}/cm^{-1}	3886, 3493, 3060, 1616, 1577, 1505, 1488, 1418,1366, 1338, 1278, 1248, 1206, 1120, 870, 612, 606.
I^1H NMR: δ_H ($CDCl_3$)	7.81 (s, 1H, N-H), 7.64-7.11 (m, 4H, Ph), 7.05 (s, 1H, C_2-H), 6.52 (s, 1H, C_3-H)
Mass: m/z	118, 117 (M^+, 100%), 90, 89, 63

2b	
Yield	57%
M.P	149-152^{0}C
Elemental Analysis Calc. for $C_{10}H_9NO_2$ Found	 C, 68.57; H, 5.14; N, 8 C, 68.53; H, 5.11; N, 8.14
I.R (Nujol Mull): υ_{max}/cm^{-1}	3239, 2927, 2866, 1666, 1449, 1373, 1197
^1H NMR: δ_H (DMSO-d_6)	12 (s, 1H, N-H), 8.13 (s, 1H, C_2-H), 8.05 (d, 1H, C_4-H), 7.52 (d, 1H, C_7-H), 7.22 (t, 2H, C_5-H & C_6-H), 3.83 (s, 3H,$COOCH_3$)
Mass: m/z	175 (M^+), 144(100%), 116, 89

RESULTS AND DISCUSSION

Indoles have been synthesised by ring transformation reaction from cinnolines in a single step in reasonable yields. Yield has considerable improved (from 48% to 57%) upon the introduction of an electron withdrawing carbomethoxy group in the heterocyclic nucleus.

REFERENCES

1. De Sa Alves, Fernando R, Barreiro EJ, Fraga M and Alberto C. From nature to drug discovery: The indole scaffold as a ‘privileged structure’. Mini Reviews in Medicinal Chemistry. 2009;9(7): 782-793.
2. Sharma V, Kumar P and Pathak D. Biological importance of the indole nucleus in recent years: A comprehensive review. Journal of Heterocyclic Chemistry. 2010; 47(3):491-502.
3. Chunduru VSR and Rao VR. Synthesis of coumarin substituted triazola thiadiazine derivatives via ring transformation reaction. Journal of Heterocyclic Chemistry. 2013;50(1):159-163.
4. Joshi U. Novel pyrrole C-nucleosides by nitrogen extrusion from pyridazine C-nucleosides. Tetrahedron Letters. 2004;45: 1031-1033.
5. Boger DL, Coleman RS, Panek JS and Yohannes D. Thermal cycloaddition of dimethyl 1,2,4,5-triazine-3,6-dicarboxylate with electron rich olefins: 1,2-diazine and pyrrole introduction. Preparation of octamethylporphin(OMP). J. Org.Chem. 1984;49:4405-4409.
6. Mumtazuddin S, Sinha SK, Prabhat Bharti and Surendra Kumar. Facile transformation of 1,2-diazines into pyrroles. J Chemtracks. 2008;10(1&2):155-156.