



New and practical synthesis of 1,4-dihydrobenzopyrano-pyrazoles[†]

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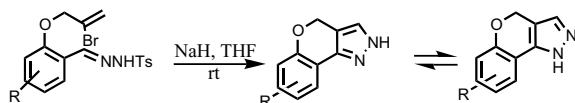
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Abstract—A new method for the synthesis of 1,4-dihydrobenzopyranopyrazoles using bromovinyl hydrazones has been described involving a [3+2] intramolecular cycloaddition. © 2001 Elsevier Science Ltd. All rights reserved.

Hydrazones and derivatives of aldehydes have been proven to be versatile starting materials viz., as a source of deoxygenation exemplified by the Wolf–Kishner reduction,¹ vinyl anion equivalents in the Shapiro reaction² and also as precursors for diazo compounds. This diversified behaviour of hydrazones and in particular, tosylhydrazones, prompted our group to look into this functionality. Our efforts in this direction resulted in a serendipitous discovery of alkylative fragmentation of tosylhydrazones when there is a heteroatom α to the tosylhydrazone functionality.³ To further exploit the usefulness of this class of compounds, it was proposed to examine, whether, under the influence of non nucleophilic bases such as NaH, a dipole is generated which could be further trapped with dipolarophiles (intramolecular) to result in the formation of dihydrobenzopyranopyrazoles and quinolinopyrazoles (Scheme 1).

This class of compounds have excellent pharmacological properties especially as antiallergic compounds.⁴ The findings in this direction are reported herein (Table 1).



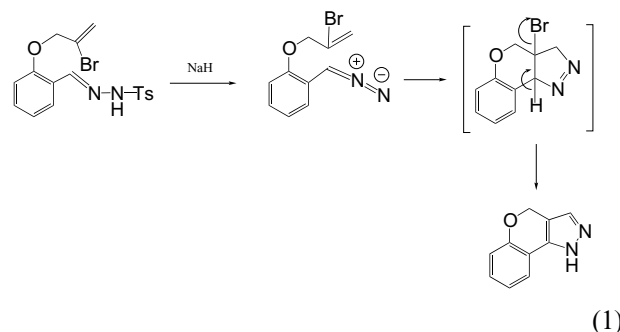
Scheme 1.

Keywords: benzopyrano pyrazoles; tosyl hydrazones; 2,3-dibromo-1-propene.

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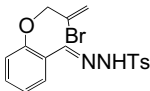
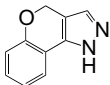
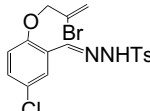
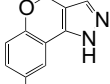
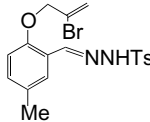
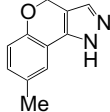
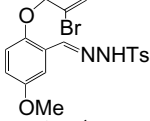
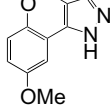
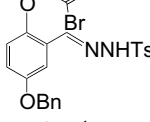
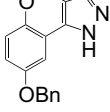
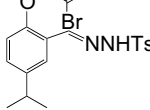
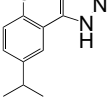
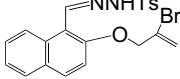
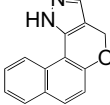
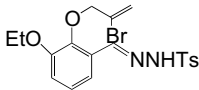
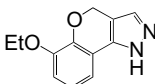
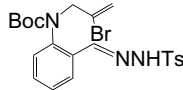
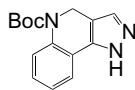
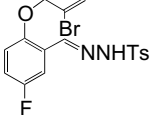
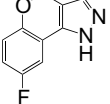
Surprisingly, for the synthesis of this class of compounds there are very limited procedures available⁵ which include photochemical cycloaddition.⁶



In the initial study, *o*-hydroxy benzaldehyde was *O*-alkylated with 2,3-dibromo-1-propene and then derivatized as a tosylhydrazone. The substrate thus obtained (entry 1, Table 1) was stirred in THF in the presence of 3 equiv. of NaH for 8 h to observe clean formation of pyrazole derivative **1b** in 90% isolated yield.

In a second experiment, 4-methyl-2-formyl phenol was prepared through alkylation with 2,3-dibromo-1-propene and tosylhydrazone and subjected to a cycloaddition reaction and clean formation of the cycloadduct was obtained in 86% yield. Mechanistically, it is anticipated that the initially formed diazo compound⁷ (Eq. 1) undergoes a [3+2] cycloaddition reaction followed by HBr elimination to yield the more stable desired product. To further prove the generality of the present protocol, various substituted aryl substrates were prepared which include a chloroderivative (entry 2), a *p*-methoxyphenol derivative (entry 4), the benzyloxy derivative (entry 5), an isopropyl phenol derivative (entry 6) and a naphthyl derivative (entry 7),

Table 1. Conversion of vinyl bromide hydrazones to 1,4-dihydrobenzopyranopyrazoles

Entry	Substrate a	Product ^a b	Yields(%) ^b
1			90
2			85
3			86
4			84
5			83
6			82
7			81
8			85
9			80
10			80

^a Products characterized by ¹H NMR, mass spectroscopy and IR spectroscopy^b Yields calculated after column chromatography

which all responded well to the reaction protocol. Entry 9 demonstrated the formation of a quinolinopyrazole derivative in 80% isolated yield.

In conclusion, a practical synthesis of 1,4-dihydrobenzopyranopyrazoles and quinolinopyrazoles is demonstrated, under practical conditions, which provide access to a hitherto not easily accessible class of heterocycles in excellent yields. Further work to prove the mechanistic pathway and biological activity is currently being investigated.

General procedure for cyclization of vinyl bromide hydrazone

To sodium hydride (35.2 mg, 1.46 mmol) in dry THF (8 mL) was added hydrazone **1a** (200 mg, 0.48 mmol) at 0°C, and the reaction mixture was stirred for 12 h at room temperature. After quenching the reaction mixture with saturated ammonium chloride solution, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulphate and concentrated under vacuum. The crude

material was chromatographed (silica gel 60–120 mesh, ethyl acetate:hexane 4:6) to give the pure product **1b** 75.5 mg (90% yield).

Spectroscopic data for compound **4b**: ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.7 (s, 1H), 7.3 (s, 1H), 7.2 (d, 1H, $J=4.8$ Hz), 6.6–6.8 (m, 2H), 5.2 (s, 2H), 3.8 (s, 3H). ^{13}C NMR (400 MHz, $\text{DMSO}-d_6$) 152.0, 146.0, 141.0, 121.6, 118.0, 115.7, 112.5, 109.2, 104.2, 61.3, 53.4. Mass: 217 (M^+), 202, 176, 133. Anal. calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$: C, 65.34, H, 4.98, N, 13.85 found C, 65.32, H, 4.96, N, 13.81; IR (KBr): 3427, 2935, 3120, 1124 cm^{-1} .

Acknowledgements

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