Rapid Communication


S Selvi & P T Perumal

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India.

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A new convenient synthesis of 4-ethoxy-4H-1-benzopyrano-[4,3-c] pyrazoles from o-hydroxyacetophenone 2,4-dinitrophenyl-hydrazones is described.

Vilsmeier Haack reaction is primarily an ad hoc procedure for the facile synthesis of aldehydes.\(^1\),\(^2\) A number of heterocycles have also been synthesised using this reaction.\(^3\),\(^5\) We have been focussing attention on exploiting the intramolecular cyclisation potential of halomethyleniminium salts formed under Vilsmeier condition for exploring new and simple synthetic strategies in organic synthesis. Recently, synthesis of many heterocyclic compounds and biological activities of some of them have been reported by our group.\(^6\)\(^-\)\(^10\)

The skeleton of benzopyran widely occurs in plants\(^11\)\(^-\)\(^13\) and is associated with diverse physiological applications.\(^14\),\(^15\) Benzopyrano[4,3-c]pyrazoles are found to exhibit many pharmacological activities such as arthropodicidal, immunostimulant, immunomodulator activity etc.\(^16\)\(^-\)\(^18\)

To further illustrate the scope and utility of Vilsmeier cyclisation, it was of interest to synthesise new [1]benzopyrano[4,3-c]pyrazole derivatives. Literature review showed that the Vilsmeier reaction of acetophenone phenylhydrazones resulted in pyrazole aldehyde by NH group cyclisation\(^19\),\(^20\) and similarly o-hydroxyacetophenone yielded coumarin aldehyde by OH group cyclisation.\(^21\),\(^22\) Based on this, we envisaged that the Vilsmeier reaction of o-hydroxyacetophenone phenylhydrazones which contains NH as well as OH functions to furnish benzopyrano[4,3-c]pyrazoles by double cyclisation. Herein, we present our observation on the action of chloromethyleniminium salt derived from POCl\(_3\)-DMF \textit{in situ} against o-hydroxyacetophenone phenylhydrazones in an attempt to synthesise the target molecule (Scheme I).

The reaction proceeded smoothly in the case of 2,4-
dinitrophenylhydrazone derivatives. However the unsubstituted phenylhydrazones yielded complicated products; in fact we obtained a mixture of about six compounds which were not separable by chromatographic methods. Structurally, the product appears to be a pyranoid derivative with an anomic centre.

A possible mechanism for the product formation is illustrated in Scheme II. The chloromethylenium salt 2 reacts with the methyl group of 1 to yield 3 which undergoes intramolecular cyclisation by the nucleophilic attack of NH group resulting in 4. A second formylation occurs at the pyrazole moiety leading to an iminium species 5. Here, we expected a straightforward cyclisation of 5 involving OH nucleophile to give 6. But we could not observe any spectral characteristics for this product and in fact pyrazole aldehyde derivative 7 was obtained and the structure was confirmed by X-ray analysis.23 There may be an equilibrium between 5 and 6, and aqueous work-up might have led to the exclusive formation of 7. The product 7 was easily cyclised to 8 by refluxing in ethanol containing catalytic amount of hydrochloric acid. The yields and melting points of pyrazole aldehydes and [1]benzopyrano[4,3-c]pyrazoles are given in Table I.

In conclusion, we have demonstrated an efficient synthesis of [1]benzopyrano[4,3-c]pyrazoles. The enantio selective studies and the screening of these compounds for their biological activities will be of future interest.

**Experimental Section**

**Typical procedure for pyrazole aldehyde 7.** Compound 1 (0.005 mole) was dissolved in 6mL DMF and kept in ice cold condition. To this 1.5 mL...
POCl₃ was added drop by drop with stirring. After stirring at room temperature for about 4 hr, the reaction mixture was poured into crushed ice. The yellowish orange solid obtained was filtered, washed with water and dried. The crude product obtained was purified by column chromatography on silica gel 60-120 mesh using ethyl acetate-pet. ether as eluent (3:7).

Spectral data for compound 7b: ¹H NMR (300 MHz, DMSO-d₆): δ 9.98(s, 1H, CHO), 9.49(s, 1H, OH), 8.74(s, 1H, Ar H), 8.61(s, 1H, pyrazole H), 8.54(d, J=10.3 Hz, 1H, Ar H), 8.03(d, J=8.7 Hz, 1H, Ar H), 7.57(d, J=8.7 Hz, 1H, Ar H), 6.53(d, J=10.3 Hz, 1H, Ar H), 6.51(s, 1H, Ar H), 3.82(s, 3H, OCH₃); ¹³C NMR (75 MHz, DMSO-d₆): δ 158.15, 161.75, 156.18, 153.42, 145.73, 142.75, 134.24, 131.04, 127.44, 125.93, 120.63, 108.86, 105.74, 103.13, 102.45, 101.40, 54.80; MS(m/z): 355(M⁺), 337(M-75), 291(M-121), 275(M-137), 69, 43; Anal. Calcd for C₁₉H₁₈N₂O₄: C, 55.34; H, 3.91; N, 13.58. Found: C, 55.27; H, 3.87; N, 13.49%.

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References