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Rapid Communication

A facile synthesis of [1]benzopyrano[4,3-*c*]pyrazole using Vilsmeier reagent

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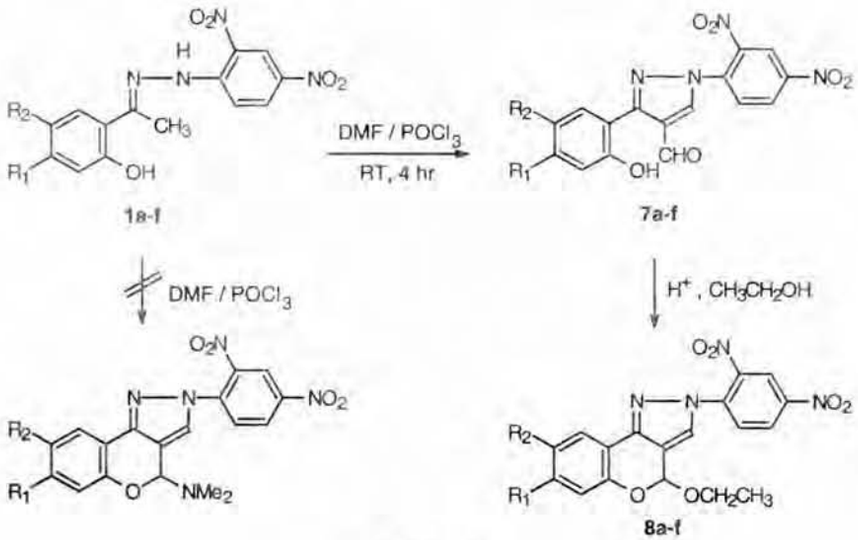
A new convenient synthesis of 4-ethoxy-4H-1-benzopyrano-[4,3-*c*] pyrazoles from *o*-hydroxyacetophenone 2,4-dinitrophenylhydrazones is described.

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 *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-



Scheme I

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 anomeric centre.

A possible mechanism for the product formation is illustrated in **Scheme II**. The chloromethyleniminium 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**.

Table I — Synthesis of pyrazole aldehydes**7** and benzopyrano[4,3-*c*]pyrazoles **8**.

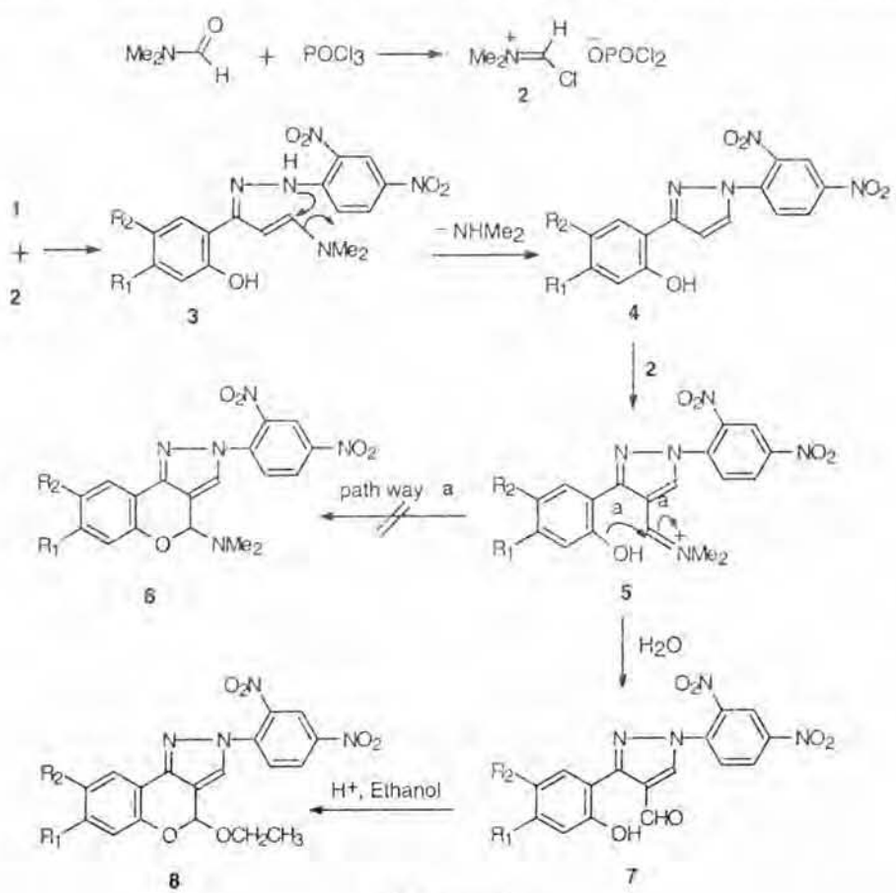
	Substituent		Product 7[a]		Product 8[a]	
Reactant	R_1	R_2	Yield(%)	mp(^{0}C)[b]	Yield(%)	mp(^{0}C)[b]
1a	H	H	68	162	61	187
1b	H	OCH_3	58	173	64	182
1c	H	CH_3	61	160	64	163
1d	H	Cl	73	190	76	208
1e	H	OH	32	193(dec)	36	208(dec)
1f	OCH_3	H	57	148	52	150

[a]Products were characterised by ^{1}H NMR, ^{13}C NMR, IR and mass spectra
[b]Melting points recorded were uncorrected.

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



Scheme II

$POCl_3$ 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: ^{1}H NMR(300 MHz, DMSO-d_6): 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, OCH_3); ^{13}C NMR(75 MHz, DMSO-d_6): δ 185.15, 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; IR(KBr): 3428, 1674, 1607, 1517, 1342, 1216 cm^{-1}; MS(m/z): 367(M-17), 355(M-29), 336(M-48), 264(M-120), 236(M-148); Anal. Calcd for $C_{17}H_{12}N_4O_7$: C, 53.13; H, 3.15; N, 14.58. Found: C, 52.93; H, 3.13; N, 14.43%.

Procedure for 2-(2,4-dinitropheny!)-4-ethoxy-1-4*H*-benzopyrano[4,3-*c*]pyrazole 8. The crude pyrazole obtained above was refluxed in 80 mL ethanol containing one or two drops of hydrochloric acid for about 1 hr. The reaction mixture was cooled to room temperature and kept in refrigerator for one day. The yellow colour product obtained was filtered and dried. The crude product obtained was subjected to column chromotography(silica gel 60-120 mesh) using ethyl acetate - pet. ether as eluent(2:8).

Spectral data for compound 8b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.72(s, 1H, Ar H), 8.43(d, *J*=8.4 Hz, 1H, Ar H), 7.83(d, *J*=8.7 Hz, 1H, Ar H), 7.73(d, *J*=8.4 Hz, 1H, Ar H), 7.43(s, 1H, Pyrazole H), 6.65(d, *J*=8.7, 1H, Ar H), 6.61(s, 1H, Ar H), 6.32(s, 1H), 4.02(q, 1H, OCH_A), 3.82(q, 1H, OCH_B), 3.78(s, 3H, OCH_3), 1.25(t, *J*=6.9Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.11, 153.54, 147.4, 145.15, 137.09, 128.02, 127.37, 126.49, 125.44, 124.26, 121.14, 116.61, 109.11, 108.42, 102.99, 94.80, 63.98, 55.45, 15.15; IR (KBr): 1603, 1541, 1485, 1342, 1219cm^{-1}; MS(m/z): 412(M^+), 383(M-29), 367(M-45), 341(M-71), 337(M-75), 291(M-121), 275(M-137), 69, 43; Anal.Calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.58. Found: C, 55.27; H, 3.87; N, 13.49%.

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References

1 Marson C M, *Tetrahedron*, 48, **1992**, 3659.
2 Meth Cohn O, *Heterocycles*, 35, **1993**, 539.
3 Lloyd D & Tuker K S, *J Chem Soc Perkin Trans 1*, **1981**, 726.
4 Jutz C, Kirchlechner R, & Seidel H J, *Chem Ber*, 102, **1969**, 2301.
5 Meth Cohn O & Tarnowski B, *Adv Heterocycl Chem*, 31, **1982**, 207.
6 Majo V J & Perumal P T, *J Org Chem*, 61, **1996**, 6523.
7 Amaresh R R & Perumal P T, *Synth Commun*, 27, **1997**, 337.
8 Majo V J & Perumal P T, *Tetrahedran Lett*, 38, **1997**, 6889.
9 Selvi S & Perumal P T, *Tetrahedron Lett*, 38, **1997**, 6263.
10 Selvi S & Perumal P T, *Synth Commun*, 29, **1999**, 73.
11 Katritzky A R, Comprehensive heterocyclic chemistry, Vol (Pergamon Press Oxford), **1984**.
12 Narasimhan N S, Paradkar M V & Chitguppi V P, *Tetrahedron Lett*, **1968**, 5501.
13 Dutta N L & Quasim C, *Indian J Chem*, 7, **1968**, 307.
14 Loubinnouz B, Colin J L & Colin D A, *Tetrahedran Lett*, 43, **1987**, 93.
15 Carney R W J, Benzene W L, Jtkunski W, Renzi A A, Dorfman Z & Stevens J, *J Mednl Chem*, 9, **1996**, 516.
16 Harrison Charles, Lahm, George Philip, Shapiro, Rafel *Eur Pat*, 386, **1990**,392; *ChemAbstr*, 114, **1991**, pp164216y.
17 Doria, Gian Federio, Isetta, Anna Maria, Ferrari, Mario, Trizio, Domenico *Eur Pat*, 274, **1988**, 443; *Chem Abstr*, 111, **1989**, 443.
18 Bowen, John Rosindale, Hunney ball, Ian Michael, Titman, Roger Demard, *Eur Pat*, 354, **1990**, 693; *Chem Abstr*, 113, **1990**, pp177601.
19 Kira M, Abdoul Enein M N & Korkor M I, *J Heterocyclic Chem*, 7, **1970**, 25.
20 Kira M, Nofal Z & Gadalla K Z, *Tetrahedron Lett*, **1970**, 4215.
21 Kagal S A, Madhavan Nair P & Venkataraman K, *Tetrahedron Lett*, **1962**, 593.
22 Akira Nohara, Tomonobu Umetani & Yasushi Sanno, *Tetrahedron Lett*, **1973**, 1995.
23 Shanmuga Sundara Raj S, Jeyakanthan J, Selvi S, Velmurugan D, Fun H K & Perumal P T, *Acta Cryst*, C55, **1999**, 1667.