HETEROCYCLES, Vol 22, No. 9, 1984

A NOVEL SYNTHESIS OF 6-METHOXY AND 7-METHOXY FLAVONOLS

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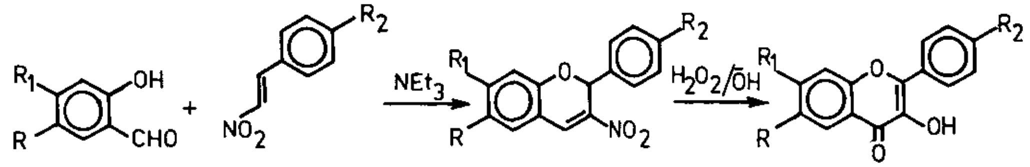
Abstract —— Condensation of 4-methoxy- (1) or 5-methoxy- (2) salicylaldehyde with ω-nitrostyrene (3-6) in the presence of triethylamine yields 7-methoxy or 6-methoxy-3-nitro-2H-flavene (7-13), which on treatment with alkaline hydrogen peroxide yields the corresponding flavonol (7a-13a).

In view of the reported antiviral, antitumor and antibiotic activities of the flavonols[1], 6-methoxy- and 7-methoxyflavonols can be expected to have interesting biological properties. However, the synthesis of 6-methoxyflavonols is hitherto unknown. Herein we wish to report a facile preparation of 6-methoxyflavonols starting with o-hydroxybenzaldehyde (1) and ω-nitrostyrene (3-6). The method is also extended for the synthesis of 7-methoxyflavonols[2-5].



1. $R=H, R_1=OMe$
2. $R=OMe, R_1=H$

3. $R_2=H$
4. $R_2=Me$
5. $R_2=OMe$
6. $R_2=Cl$

7. $R=R_2=H, R_1=OMe$
8. $R=H, R_1=OMe, R_2=Me$
9. $R=H, R_1=R_2=OMe$
10. $R=OMe, R_1=R_2=H$
11. $R=OMe, R_1=H, R_2=Me$
12. $R=R_2=OMe, R_1=H$
13. $R=OMe, R_1=H$ $R_2=Cl$

7a.– 13a.

In a typical synthesis of 3-nitro-2H-flavenes[6,7], equimolar amounts of o-hydroxybenzaldehyde (1 or 2) and ω-nitrostyrene (3-6) were taken in a round bottom flask and warmed on a water bath to melt, to which a catalytic amount of triethylamine was added and the reaction mixture was left at room temperature for 18 h. The glassy substance so obtained was dissolved in dichloromethane and filtered. The residual solid was washed several times till the washings became colourless. Evaporation of the solvent and crystallization from methanol gave the pure product (*Table 1*).

Table 1 Physical and spectral properties of nitroflavenes

Compound[a] No.	Yield %	Mp[b] °C	ms m/e M^+	nmr ($CDCl_3$/TMS) δ (ppm)
7	26.5	140-141	283	3.7 (3H,s), 6.6(1H,s), 6.4-6.64(2H,m), 7.2-7.36(6H,m), 8.08(1H,s).
8	33	108-110	297	2.32(3H,s), 3.80(3H,s), 6.56(1H,s), 6.4-6.64(2H,m), 7.1-7.25(5H,m), 8.07(1H,s).
9	29	114-116	313	3.78(3H,s), 3.79(3H,s), 6.52(1H,s), 6.29-6.95(5H,m), 7.21-7.28(2H,m), 8.06(1H,s).
10	76	125-126	283	3.79(3H,s), 6.56(1H,s), 6.75-6.98 (3H,m), 7.36(5H,s), 8.04(1H,s).
11	82	137-138	297	2.3(3H,s), 3.78(3H,s), 6.52(1H,s), 6.72-6.77(3H,m), 7.06-7.32(4H,m), 8.02(1H,s).
12	84	139-140	313	3.78(3H,s), 3.8(3H,s), 6.5(1H,s), 6.72-6.97(5H,m), 7.22-7.28(2H,m), 8.02(1H,s).
13	78	132-133	317	3.8(3H,s), 6.54(1H,s), 6.7-7(3H,m), 7.31(4H,s), 8.05(1H,s).

a - *Satisfactory elemental analyses were obtained.*

b - The melting points given are uncorrected.
7-methoxynitroflavenes (7-9) showed two typical ir bands at 1325 and 1560 Cm^{-1} (NO_2) whereas 6-methoxynitroflavenes (10-13) showed bands at 1300 and 1510 Cm^{-1} (NO_2).

3-Nitroflavene was converted to the corresponding flavonol by adding sodium hydroxide (1 ml, 2N) and hydrogen peroxide (2 ml, 15%) to a well stirred suspension of nitroflavene (1.5 mmole) in methanol (10 ml). Stirring was continued for further 30 min. The flavonol formed was filtered and recrystallized from methanol (Table 2).

Table 2

Compound[a,b] No.	Yield %	Mp[c] °C	Molecular formula or lit Mp[5]	ms m/e M^+	uv (CHCl$_3$) λ max$_{nm}$(log ϵ)
7a	88	178-179	179-180	268	255(4.34), 323(4.29), 340(4.28)
8a	91	208-209	$C_{17}H_{14}O_4$	282	256(4.25), 322(4.26), 345(4.32)
9a	89	196-197	196-197	298	259(4.49), 320(4.40) 352(4.55)
10a	86	187-188	$C_{16}H_{12}O_4$	268	257(4.17), 330(4.23), 350sh(4.13)
11a	94	144-145	$C_{17}H_{14}O_4$	282	256(4.24), 335(4.32), 351sh(4.28)
12a	92	165-167	$C_{17}H_{14}O_5$	298	255(4.26), 340sh(4.35), 352(4.38)
13a	83	195-196	$C_{16}H_{11}ClO_4$	302	257(4.47), 333(4.56), 351sh(4.47)

a - Satisfactory microanalyses were obtained.

b - All products displayed appropriate ^{1}H nmr in aggrement with their structures.

c - The melting points given are uncorrected.

The ir spectra (Nujol) showed typical absorption of 3-hydroxyflavones at ν = 1620-1640 Cm^{-1} (C=O) and ν = 3260-3300 Cm^{-1} (OH).

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Received, 16th April, 1984