A SIMPLE AND RAPID SYNTHESIS OF 4*H*-4-OXO-1-BENZOPYRAN-3-YL AND 1,3-DIARYLPYRAZOL-4-YL PROPANOIC ACIDS

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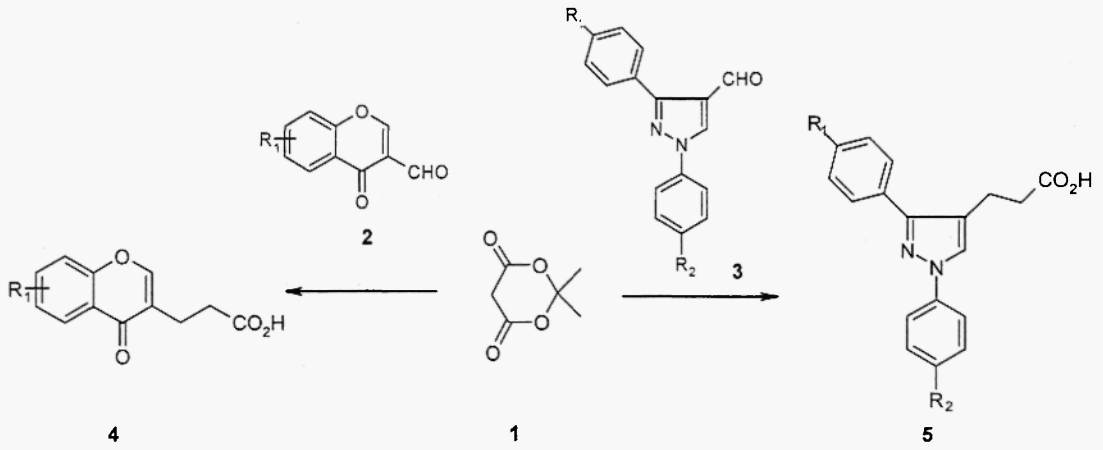
Abstract : A simple and rapid synthesis of 4*H*-4-oxo-1-benzopyran-3-yl (4a-h) and 1,3-diarylpyrazol-4-yl propanoic acids (5a-h) using Meldrum's acid (1) from the corresponding carboxaldehydes (2 & 3) is reported herein.

Introduction

A variety of pharmacological activities such as antifungal, antibacterial and anticoagulant activities have been reported for benzopyrans[1]. 4-Oxo-1-benzopyran-3-carboxaldehydes are versatile intermediates and found their application in the synthesis of a variety of heterocycles bearing benzopyranone[2] system and also functionalized benzopyranones[3]. These compounds undergo condensation reaction with active methylene compounds such as dimedone[4], malonic acid[4] and phenylacetic acids[5] forming the corresponding methylene derivatives. Pyrazole ring constitutes an important pharmacophore in a number of biologically active molecules[6]. In view of their medicinal importance the synthesis of functionalized benzopyrans and pyrazoles is a subject of interest to many organic chemists. Recently some propanoic acids have been reported useful in the treatment of diabetes mellitus, hyperlipidemia impaired glucose tolerance, inflammatory diseases and arteriosclerosis[7].

Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane) is a versatile synthon with remarkable activity and is of tremendous use in organic synthesis[8]. Araldehydes react with this in the presence of triethylamine-formic acid adduct to give arylpropanoic acids[9]. However, this method has received little attention in the synthesis of heteroaryl propanoic acids. A lone example for the synthesis of benzopyran-3-yl propanoic acid was reported by Nohara et. al[10] by refluxing benzopyran-3-carboxaldehyde with malonic acid in pyridine at 110°C followed by hydrogenation of the corresponding benzopyranyl acrylic acid at 90°C using palladium black as catalyst. Where as pyrazol-4-yl propanoic acid was prepared by Na-Hg reduction of the corresponding unsaturated acid[11]. However, the reported methods for the synthesis of benzopyranyl and pyrazolyl propanoic acids involve multi steps and use of expensive reagents in the reduction step. In continuation of our work on library synthesis of various substituted benzopyrans[12] and pyrazoles[13,14] we report herein a simple one step synthesis of title compounds using Meldrum's acid. (Scheme-1)



Scheme-1

Results & Discussions

Various 4H-4-oxo-1-benzopyran-3-carboxaldehydes **1** on reaction with Meldrum's acid **2** in presence of triethylamine-formic acid[19] under reflux conditions for 2-3 hr gave the corresponding 4H-4-oxo-1-benzopyran-3-yl propanoic acids **4** in good yields (Scheme-1). A variety of benzopyran-3-carboxaldehydes such as 6-halo, 6-methyl and 6- nitro derivatives were reacted with Meldrum's acid to check versatility of the reactions and the corresponding propanoic acids **4** were obtained in good yields. The same reaction was applied to pyrazole-4-carboxaldehydes **3** also, to get the corresponding propanoic acids **5**. All the synthesized compounds **4** and **5** have been characterized by infrared ^{1}H NMR and elemental analyses. In the ^{1}H NMR spectra, the propanoic acid **4** and **5** are characterized by two sets of triplets around δ 2.6-2.8 apart from benzopyran and pyrazole protons.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer system 2000 FT IR spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Varian 200 MHz instrument with TMS as internal standard and in $CDCl_3$. Chemical shifts were expressed in δ ppm.

General procedure for the synthesis of 4H-4-oxo-1-benzopyran-3-yl propanoic acids 4.

A mixture of 4-oxo-benzopyran-3-carboxaldehyde (**2**, 0.1 mol), Meldrum's acid (**1**, 0.1 mol) and triethylamine formic acid (75 ml), was refluxed at 95-100°C 2-3 hr. Until the disappearance of **1** as monitored by TLC (ethylacetate : hexane, 1:1). It was cooled to room temperature and poured onto ice water. The mixture was acidified to pH 2 with 6 NHCl. The pale yellow precipitate was filtered washed with water and recrystallized from ethylacetate to give pure **4** as crystalline solids (Table-1).

General procedure for the synthesis of 1,3-diarylpyrazol-4-yl propanoic acids 5.

A mixture of 1,3-diarylpyrazole-4-carboxaldehyde (**3**, 0.1 mol), Meldrum's acid (**1**, 0.1 mol) and triethylamine formic acid (75 ml) was refluxed at 95-100°C for 2-3 hr. Until the disappearance of **3** as monitored by TLC (ethylacetate : hexane, 1:1). It was cooled to room temperature and poured onto ice water. The mixture was acidified pH 2 with 6 NHCl. The pale yellow precipitate was filtered washed with water and subjected column chromatography by eluting with hexane as silica gel to get pure **5** as white crystalline solids (Table-1).

Table–1 : Physical and spectral data of 4 & 5

Compd*	R_1	R_2	Yield %	m.p °C	Mol. formula	^{1}H NMR, δ ppm ($CDCl_3$ + DMSO-d_6)
4a	H	-	68	165	$C_{12}H_{10}O_4$	2.76(m, 4H), 7.42(m, 2H), 7.67(m, 1H), 7.90(s, 1H), 8.22(dd, 1H)
4b	F	-	84	176	$C_{12}H_9FO_4$	2.66(m, 2H), 2.83(m, 2H), 7.41(s, 1H), 7.53(m, 2H), 7.93(dd, 1H)
4c	Cl	-	86	180	$C_{12}H_9ClO_4$	2.64(m, 2H), 2.85(m, 2H), 7.42(d, *J* = 8.1 Hz, 1H), 7.61(dd, *J* = 8.1 & 2 Hz, 1H), 7.94(s, 1H), 8.16(d, *J* = 2.0 Hz, 1H),
4d	Br	-	85	179	$C_{12}H_9BrO_4$	2.64(m, 2H), 2.83(m, 2H), 7.51(d, 1H), 7.71(m, 1H), 7.95(s, 1H), 8.18(d, *J* = 2.0 Hz, 1H)
4e	CH_3	-	66	175	$C_{13}H_{12}O_4$	2.38(s, 3H), 2.48(m, 2H), 2.56(m, 2H),7.48(d, *J* = 8.1 Hz, 1H), 7.57(dd, *J* = 8.1 & 2.41 Hz, 1H), 7.82(s, 1H), 8.19(s, 1H), 12.20(bs, 1H)
4f	6-Cl, 7-CH_3	-	71	217	$C_{13}H_{11}ClO_4$	2.53(s, 3H), 2.62(m, 2H), 2.83(m, 2H), 7.43(s, 1H), 7.16(s, 1H), 8.19(m, 1H)
4g	5,7-diMe	-	67	145	$C_{14}H_{14}O_4$	2.38(s, 3H), 2.63(m, 2H), 2.80(s, 3H), 2.93(m, 2H), 6.92(s, 1H), 7.04(s, 1H), 7.78(m, 1H)
4h	NO_2	-	65	198	$C_{12}H_9NO_6$	2.64(m, 2H), 2.78(m, 2H), 7.68(d, *J* = 8.1 Hz, 1H), 8.05(s, 1H), 8.51(dd, *J* = 8.1 & 2.4 Hz, 1H), 9.04(d, *J* = 2.1 Hz, 1H)
5a	H	H	76	138	$C_{18}H_{16}N_2O_2$	2.67(t, *J* = 2.4 Hz, 2H), 3.05(t, *J* = 2.4 Hz, 2H), 7.26-7.73(m, 10H), 7.83(s, 1H)
5b	OCH_3	H	72	142	$C_{19}H_{18}N_2O_3$	2.63(t, *J* = 2.3 Hz, 2H), 3.02(t, *J* = 2.3 Hz, 2H), 3.79(s, 3H), 7.32-7.71(m, 9H), 7.81(s, 1H)
5c	Cl	H	71	150	$C_{18}H_{15}ClN_2O_2$	2.64(t, *J* = 2.3 Hz, 2H), 3.01(t, *J* = 2.3 Hz, 2H), 7.29-7.72(m, 9H), 7.82(s, 1H)
5d	Br	H	73	157	$C_{18}H_{15}BrN_2O_2$	2.63(t, *J* = 2.3 Hz, 2H), 3.02(t, *J* = 2.3 Hz, 2H), 7.26-7.73(m, 9H), 7.81(s, 1H)
5e	H	Cl	76	131	$C_{18}H_{15}ClN_2O_2$	2.64(t, *J* = 2.3 Hz, 2H), 3.01(t, *J* = 2.3 Hz, 2H), 7.29-7.71(m, 9H), 7.81(s, 1H)
5f	H	Br	70	141	$C_{18}H_{15}BrN_2O_2$	2.62(t, *J* = 2.3 Hz, 2H), 3.02(t, *J* = 2.3 Hz, 2H), 7.30-7.72(m, 9H), 7.82(s, 1H)
5g	Cl	Br	75	143	$C_{18}H_{14}ClBrN_2O_2$	2.64(t, *J* = 2.3 Hz, 2H), 3.01(t, *J* = 2.3 Hz, 2H), 7.29-7.71(m, 8H), 7.83(s, 1H)
5h	Br	Cl	74	152	$C_{18}H_{14}ClBrN_2O_2$	2.63(t, *J* = 2.3 Hz, 2H), 3.02(t, *J* = 2.3 Hz, 2H), 7.30-7.72(m, 8H), 7.82(s, 1H)

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