A Facile Solvent Free Synthesis of 3-arylidenechroman-4-ones Using Grinding Technique

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Abstract: An efficient method for the synthesis of 3-arylidenechroman-4-ones has been developed under solvent free conditions using grinding technique. Grinding of variously substituted chroman-4-ones with aromatic aldehydes in presence of anhydrous barium hydroxide at room temperature give 3-arylidenechroman-4-ones in high yield (75-92%). Products are obtained by just acidification of the reaction mixture in ice cold water. Reaction in solid state, with enhanced rate, high selectivity and manipulative simplicity are the attractive features of this environmentally benign protocol. The chroman-4-one derivatives required for the reaction have been obtained by polyphosphoric acid (PPA) catalysed cyclisation of phenoxypropanoic acids under microwave irradiations.

Keywords: 3-Arylidenechroman-4-ones, chroman-4-ones, phenoxypropanoic acids, anhydrous barium hydroxide, aromatic aldehydes, grinding.

Introduction

3-Arylidenechroman-4-ones belong to homoisoflavanoids, a class of naturally occurring oxygen heterocyclic compounds, with C-16 skeleton¹. Chroman-4-one derivatives are known to exhibit a broad range of pharmacological activities^{1,2} including anti-human-immune deficiency virus (HIV-I) properties² that causes acquired immune deficiency syndrome (AIDS). 3-Benzylidenechroman-4-ones have been reported to inhibit the growth of the sporogenesis and the enzymes involved in the infection mechanism of *Phytophthora parasitica*³ and also show antifungal activity⁴. These have also been found to display anti-inflammatory, analgesic, platelet anti aggregating⁵, hypocholesterolemic⁶ and antioxidant activities⁷. These are also used for the synthesis of some selective ligands required for

antiestrogen-binding sites⁸ and as precursors for the synthesis of various other homoisoflavonoids⁹.

The general synthesis of 3-arylidenechroman-4-ones involves the condensation of chroman-4-ones with aromatic aldehydes in the presence of acidic or basic reagents¹⁰. But the use of acidic reagents for the condensation is usually preferred^{11,12} as the chroman-4-one ring is more stable to acidic reagents¹³. Use of bases such as alcoholic KOH, NaOH, NaOCH₃, piperidine and acetic anhydride^{10,14} have also been reported for the synthesis of these compounds. In a recent approach Amberlyst-15 under MW irradiations have been reported for this reaction¹⁵. Ring closure of an acrylic acid derivative with trifluoroacetic anhydride in dichloromethane medium is also a route for the synthesis of 3-arylidenechroman-4-ones, but is not of much interest¹⁶.

Degradation of ecosystem due to toxic nature of chemicals used, poor yields, formation of isomeric products, complexity of the procedure and high temperature required for the reaction, are the major limitations with which the reported methods suffer. In these days, much emphasis is being laid by the chemists to develop synthetic procedures which could avoid the use of toxic and hazardous chemicals including solvents¹⁷. Grinding technique, due to its operational simplicity, now has got the attention of the chemists as an important tool for green synthesis¹⁸. In continuation of our work to develop eco-friendly organic transformations¹⁹, here in we are reporting, a facile solvent free green synthesis of 3-arylidenechroman-4-ones using grinding technique. (**Scheme 1**).

Scheme 1. Synthesis of 3-arylidenechroman-4-ones.

Experimental

Grinding in all the reaction was carried out in porcelain mortar with pestle. Melting points were determined in open capillary tubes and are uncorrected. The compounds were characterized from their spectral data (IR & ¹H-NMR) and by comparison with authentic sample. The ¹H NMR spectra were recorded on Bruker Avance II 400 spectrometer at 400 MHz in CDCl₃ using TMS as internal standard. Chemical shifts (δ) are reported in ppm and coupling constant in Hz. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates). Reaction involving the use of microwaves were carried out in a domestic microwave oven (Samsung output energy 900W, frequency 2450MHz, with temperature control arrangement No. CE 118KF) using 40% power for all the experiments.

*General procedure**Synthesis of chroman-4-ones (2 a-c)*

Phenoxypropanoic acid (15 g) was added to freshly prepared polyphosphoric acid (10 ml) in a round bottom flask fitted with guard tube and was thoroughly mixed by glass rod. The resulting mixture was then irradiated with microwaves for 30 seconds (6 x 5 sec.) using 40 % power of the oven, with shaking after each interval of 5 seconds. Pasty residue so obtained was decomposed with crushed ice (50 g). Cold suspension was then extracted with diethyl ether, washed with 10 % aq. sodium bicarbonate (2 x 25 ml) followed by water and dried over magnesium sulphate. The solvent was removed by distillation and residue thus obtained was recrystallised from petroleum ether-diethyl ether mixture to give product i.e. chroman-4-one derivatives (2 a-c).

Synthesis of 3-arylidenechroman-4-ones (3 a-k)

A mixture of chroman-4-one (4 mmol), aromatic aldehyde (4.1 mmol) and anhydrous barium hydroxide (2.5 g) was taken in a mortar and ground well with pestle for 5 minutes. Progress of the reaction was checked on TLC. For completion of the reaction, reaction mixture was left at room temperature for 5 minutes. It was then worked up by acidifying the reaction mixture in ice cold conditions, when solid residue was separated out which was suction filtered, washed with water and recrystallised from petroleum ether-diethyl ether mixture to give 3-arylidenechroman-4-one (3 a-k). Spectral data of the compounds synthesized are given below.

6-methyl-3-(4'-methylbenzylidene)chroman-4-one (3e):

IR (KBr): 1667 cm^{-1} (C=O).

$^1\text{H-NMR}$ (CDCl_3): δ 3.04 & 3.30 (each s, 6H, 2 x CH_3), 5.33 (d, 2H, $-\text{OCH}_2-$, $J = 1.84$ Hz), 6.86 (d, $J = 8.4$ Hz, 1H, H-8), 7.20-7.31 (m, 5H, H-7, H-2', H-3', H-5', H-6'), 7.81 (d, $J = 1.80$ Hz, 1H, H-5), 7.55 (s, 1H, =CH - Ph).

6-methyl-3-(4'-methoxybenzylidene)chroman-4-one (3f):

IR (KBr): 1667 cm^{-1} (C=O).

$^1\text{H-NMR}$ (CDCl_3): δ 2.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.35 (d, $J = 1.8$ Hz, 2H, $-\text{OCH}_2-$), 6.87 (d, $J = 8.4$ Hz, 1H, H-8), 6.8 – 7.59 (m, 5H, H-7, H-2', H-3', H-5', H-6'), 7.74 (d, 1H, H-5, $J = 1.8$ Hz), 7.85 (s, 1H = CH-).

6-bromo-3-benzylidenechroman-4-one (3g):

IR (KBr): 1670 cm^{-1} (C=O).

$^1\text{H-NMR}$ (CDCl_3): δ 5.35 (d, $J = 1.84$ Hz, 2H, $-\text{OCH}_2-$), 6.88 (d, $J = 8.8$ Hz, 1H, H-8), 7.26-7.32 (m, 3H, H-3', H-4', H-5'), 7.44-7.46 (m, 2H, H-2', H-6'), 7.55-7.58 (dd, $J = 2.52$ Hz, & 8.76 Hz, 1H, H-7), 7.89 (s, 1H, =CH-), 8.13 (s, 1H, H-5).

6-bromo-3-(4'-methoxybenzylidene)chroman-4-one (3h):

IR (KBr): 1670 cm^{-1} (C=O).

$^1\text{H-NMR}$ (CDCl_3): δ 3.86 (s, 3H, OCH_3), 5.37 (d, $J = 1.8$ Hz, 2H, $-\text{OCH}_2-$), 6.87 (d, $J = 8.8$ Hz, 1H, H-8), 6.96-6.98 (m, 2H, H-3', H-5'), 7.26-7.29 (m, 2H, H-2', H-6'), 7.53 (dd, $J = 2.56$ & 8.8 Hz, 1H, H-7), 7.84 (s, 1H, =CH-), 8.11 (d, $J = 2.52$ Hz, 1H, H-5).

6-bromo-3-(3'-methoxybenzylidene)chroman-4-one (3i):IR (KBr): 1669 cm^{-1} (C=O). $^1\text{H-NMR}$ (CDCl_3): δ 3.84 (s, 3H, OCH_3), 5.35 (d, $J = 1.84$ Hz, 2H, $-\text{OCH}_2-$), 6.82-6.98 (m, 4H, H-8, H-2', H-4', H-5'), 7.37 (t, 1H, H-6'), 7.57 (dd, $J = 2.52$ & 8.76 Hz, 1H, H-7), 7.85 (s, 1H, =CH-), 8.13 (d, $J = 2.51$ Hz, 1H, H-5).**6-bromo-3-(4'-methylbenzylidene)chroman-4-one (3j):**IR (KBr): 1670 cm^{-1} (C=O). $^1\text{H-NMR}$ (CDCl_3): δ 2.41 (s, 3H, CH_3), 5.36 (d, $J = 1.88$ Hz, 2H, $-\text{OCH}_2-$), 6.87 (d, $J = 8.76$ Hz, 1H, H-8), 7.21 (d, $J = 8.16$ Hz, 2H, H-3', H-5'), 7.25-7.27 (m, 2H, H-2', H-6'), 7.55 (dd, $J = 2.52$ & 8.8 Hz, 1H, H-7), 7.86 (s, 1H, =CH-), 8.12 (d, $J = 2.56$ Hz, 1H, H-5).**6-bromo-(2',4'-dimethoxy benzylidene)chroman-4-one (3k):**IR (KBr): 1668 cm^{-1} (C=O). $^1\text{H-NMR}$ (CDCl_3): δ 3.85 (s, 6H, $2 \times \text{OCH}_3$), 5.25 (d, $J = 1.72$ Hz, 2H, $-\text{OCH}_2-$), 6.49-6.54 (m, 2H, H-3', H-5'), 6.85 (d, $J = 8.8$ Hz, 1H, H-8), 6.98 (d, $J = 8.4$ Hz, 1H, H-6'), 7.53 (dd, $J = 2.56$ & 8.76 Hz, 1H, H-7), 8.01 (s, 1H, =CH-), 8.12 (d, $J = 2.52$ Hz, 1H, H-5).**Results and Discussions**

In an attempt to develop solvent free, green synthesis of 3-arylidenechroman-4-ones, a mixture of chroman-4-one, benzaldehyde and anhydrous barium hydroxide in a mortar was ground well with pestle for 5 minutes. Colour of the reaction mixture turned to yellow, indicating about the progress of reaction and was confirmed by TLC (**Figure 1**), when a new product was found to have formed. For the completion of the reaction, reaction mixture was left at room temperature and chroman-4-one was found to have reacted completely after 5 minutes. Reaction mixture on acidification in ice cold water gave a single solid product which was identified as *E*-3-benzylidenechroman-4-one from its spectral data and melting point comparison with literature value. Following this procedure differently substituted 3-arylidenechroman-4-ones were obtained by reacting variously substituted chroman-4-ones with aromatic aldehydes (**Table 1**).

Figure 1. Photographs of the reaction mixture in mortar showing color transition taking place during reaction indicating the progress of reaction.

The methods, reported so far make use of organic solvents either during condensation reactions or during extraction processes. Some methods though are simple but due to the prolonged refluxing are not widely accepted¹⁴. In case of piperidine, 3-arylidenechroman-4-ones formed initially undergo exo-endo double bond migration to give a mixture of isomeric products¹⁰. Here in this case, the reactions take place at room temperature with enhanced rate and good selectivity. Use of toxic organic solvent was totally eliminated as no extraction was required to obtain the product.

Chroman-4-ones required for the reaction has been obtained by a modified route involving the polyphosphoric acid (PPA) catalysed cyclisation of phenoxypropanoic acid using microwave irradiations.

Table 1. Physical data of the compounds synthesized.

Compounds	R	R ₁	R ₂	R ₃	Time [min] (x+ y) ^a	m.p., °C [Lit.]	% yield
2a	H	-	-	-	-	38-40 (38.5) ²⁰	78
2b	CH ₃	-	-	-	-	35-36(35-36) ²¹	75
2c	Br	-	-	-	-	78-79 (77-79) ²²	77
3a	H	H	H	H	5 + 5	111-112 (112) ²⁰	89
3b	H	H	H	OCH ₃	5 + 5	130-132 (133-134) ²³	87
3c	H	H	OCH ₃	H	5 + 10	103-104 (103-104) ²⁴	85
3d	CH ₃	H	H	H	5 + 10	146-147 (147-148) ²⁵	87
3e	CH ₃	H	H	CH ₃	5 + 10	126-28	83
3f	CH ₃	H	H	OCH ₃	5 + 10	108-10	88
3g	Br	H	H	H	5 + 10	158-60	92
3h	Br	H	H	OCH ₃	5 + 10	166-67	91
3i	Br	H	OCH ₃	H	5 + 10	112-13	88
3j	Br	H	H	CH ₃	5 + 10	156-58	86
3k	Br	OCH ₃	H	OCH ₃	5 + 15	168-69	89

^a x- Grinding time, y- time for which reaction mixture was kept at room temperature.

Conclusion

This appears to be a simple and highly efficient procedure for the synthesis of 3-arylidenechroman-4-ones as it requires much shorter time for the completion of the reaction and yields of the products are high. More over it is simple and eco-friendly protocol as it avoids the use of solvent at any stage of reaction or isolation process.

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