



KAl(SO₄)₂·12H₂O: An efficient catalyst for the synthesis of 3,5-bis-(arylmethylidene)- tetrahydropyran-4-ones

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ABSTRACT

An efficient, convenient and cost-effective method to synthesize 3,5-bis-(arylmethylidene)-tetrahydropyran-4-one derivatives using alum (KAl(SO₄)₂·12H₂O) as catalyst was performed in aqueous media. This method has several advantages such as environmental friendliness, high yields and simple workup procedure.

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Keywords

Alum,
Aqueous media,
3,5-bis-(arylmethylidene)tetrahydropyran-4-ones;
Condensation reaction.

Introduction

3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones are very important group of heterocycles that have many applications in both pharmaceutical and industrial research. They are also used widely in bioorganic applications,¹ and as useful and key precursors in the synthesis of a number of heterocyclic compounds.² On the other hand, only a few methods are available in the literature for the synthesis of these bioactive molecules. The important methods include the reaction of tetrahydropyran-4-one or tetrahydrothiopyran-4-one with substituted benzaldehydes in the presence of catalysts such as Ba(OH)₂ in MeOH,³ a mixture of MgBr₂·OEt₂ and Et₃N in MeOH,⁴ LiClO₄-TMSNEt₂,⁵ HCl in AcOH,⁶ molecular iodine⁷ and a mixture of LiBr-Et₃N in CH₂Cl₂.⁸ However, many of these methods suffer drawbacks such as low yield of the products, require additional reagent and take long duration for completion of the reaction. Therefore, to avoid these limitations, the discovery of a new and efficient process for the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-one derivatives in aqueous media is of prime interest.

Organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheap and environmentally friendly solvents, but also because it exhibits unique reactivity and selectivity, which is different from those of conventional organic solvents.⁹ In this respect, the development of water tolerant catalysts has rapidly become an area of intense research.

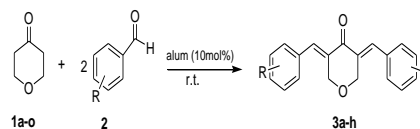
These findings prompted us to investigate the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones derivatives in aqueous media catalyzed by alum.

Alum, KAl(SO₄)₂·12H₂O, was found to be effective in the synthesis of *cis*-isoquinolic acids,^{10a} mono- and di-substituted 2,3-dihydroquinazolin-4(1H)-ones,^{10b} dihydropyrimidines *via*

the Biginelli reaction,^{10c} coumarins,^{10d} 1,3,4-oxadiazoles,^{10e} dibenzoxanthenes,^{10f} 1,5-benzodiazepines,^{10g} trisubstituted imidazoles,^{10h} etc. However, there are no examples of the use of alum as a catalyst for the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-one derivatives.

Result and discussion

In continuation of our previous work on the applications of cheap and ecofriendly materials as catalysts for the development of new synthetic methodologies,¹¹ in the present paper we report a simple and facile synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-one derivatives by treatment of aryl aldehydes with tetrahydropyran-4-one catalyzed by alum in aqueous media at room temperature (Scheme 1, Table 1). We first examined the condensation process by employing benzaldehyde (1a) and tetrahydropyran-4-one (2) as model substrates. When 1a (1 mmol) was treated with 2 (2 mmol) in the presence of a catalytic amount of alum (10 mol%), the desired product 3a was obtained in 96 % yield. Varying the percentage of the catalyst showed that 10 mol% of alum was optimal (Table 2, entry 4); the use of larger amounts of catalyst did not improve yields (Table 2, entries 5, 6), whereas decreasing the amount of catalyst decreased yields (Table 2, entries 1–3). In the absence of alum, the reaction did not proceed.



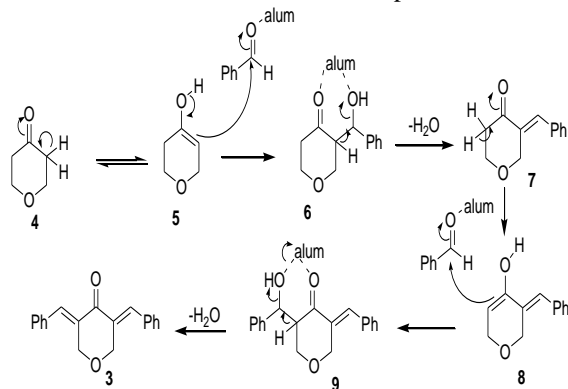
Scheme 1.

With this result, we extended this method to a variety of aldehydes to investigate its scope and generality. The results are summarized in Table 1. Benzaldehyde and other aromatic

aldehydes containing electron-withdrawing groups (such as halide and nitro) or electron-donating groups (such as methyl, methoxy and hydroxyl) were treated with tetrahydropyran-4-one (2) to give the corresponding 3,5-bis-(arylmethylidene)-tetrahydropyran-4-one derivatives in good to excellent yields.

A role of alum has been proposed to activate the aldehyde by binding of alum with the oxygen atom^{10a} which ultimately enhances the electrophilicity of the aldehyde and leads to a decrease in reaction time. The proposed mechanism is shown in Scheme 2.

In all cases, the reactions proceed rapidly and go to completion within 30–60 min at room temperature.



Scheme 2: Proposed mechanism for the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones.

Experimental

All the reagents and aromatic aldehydes were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded on KBr matrices with a Perkin-Elmer 1430 spectrophotometer (Manasquan, NJ, USA). ¹H NMR spectra were recorded on a Varian Model Mercury Plus 200 MHz NMR spectrometer (Lake Forest, CA, USA). Mass spectra [ES-MS] were recorded on a Water-Micro Mass Quattro-II spectrometer (Welltech Enterprises, Inc., Capitol Heights, MD, USA).

Typical Procedure for the Preparation of 3,5-Bis-(arylmethylidene)-tetrahydropyran-4-ones

In a 50 mL round bottom flask tetrahydropyran-4-one (10 mol), aldehyde (20 mol) were stirred in the presence of alum (0.1mmol) in water (10 mL) at room temperature for an appropriate time (Table 1). The course of the reaction was monitored by TLC (20% ethyl acetate in light petrol). At the end of the reaction, a syrupy liquid was obtained which when allowed to stand at room temperature for 30 min gave a solid. The solid so obtained was washed with saturated Na₂S₂O₃ solution and dried over anhydrous MgSO₄ to get the crude product. The crude was subjected to purification by recrystallization from ethyl acetate.

Spectral Data of Representative Compounds

(3Z,5Z)-3,5-Dibenzylidene-tetrahydropyran-4-one (3a). IR (KBr, cm⁻¹) 1667, 1610, 1582; ¹H NMR (CDCl₃) δ 4.88 (d, 4H, J ¼ 2 Hz), 7.20–7.46 (m, 10H), 7.78 (t, 2H, J ¼ 2 Hz); LC-MS: m/z (%) 276 (Mp), 144, 131, 115.

(3Z,5Z)-3,5-bis(4-Methylbenzylidene)-tetrahydropyran-4-one (3b). IR (KBr, cm⁻¹) 1667, 1605, 1508, 1266; ¹H NMR (CDCl₃) δ 2.32 (s, 6H), 4.87 (d, 4H, J ¼ 2 Hz), 7.16 (s, 8 H), 7.75 (t, 2H, J ¼ 2 Hz); LC-MS: m/z (%) 304 (Mp), 289, 130, 115.

(3Z,5Z)-3,5-bis(4-Chlorobenzylidene)-tetrahydropyran-4-one (3c). IR (KBr, cm⁻¹) 1672, 1612, 1560, 1264, 1090; ¹H NMR

(CDCl₃): δ 4.80 (d, 4H, J ¼ 2 Hz), 7.25 (d, 4H, J ¼ 7 Hz), 7.40 (d, 4H, J ¼ 7 Hz), 7.70 (t, 2H, J ¼ 2 Hz); LC-MS: m/z (%) 344 (Mp), 253, 141, 115.

(3Z,5Z)-3,5-bis(4-Methoxybenzylidene)-tetrahydropyran-4-one (3d). IR (KBr, cm⁻¹) 1594, 1560, 1508; ¹H NMR (CDCl₃) δ 3.79 (s, 6H), 4.88 (d, 4H, J ¼ 2 Hz), 6.86 (d, 4H, J ¼ 9 Hz), 7.24 (d, 4H, J ¼ 9 Hz), 7.72 (t, 2H, J ¼ 2 Hz); LC-MS: m/z (%) 336 (Mp), 305, 146, 131.

(3Z,5Z)-Tetrahydro-3,5-bis[(thiophen-2-yl)methylene]pyran-4-one (3h). IR (KBr, cm⁻¹) 1662, 1592, 1186; ¹H NMR (CDCl₃): 4.90 (d, 4H, J ¼ 2 Hz), 7.00–7.50 (m, 6H), 7.87 (br s, 2H); LC-MS: m/z (%) 288 (Mp), 260, 122.

Conclusion

In conclusion a rapid, efficient and cost-effective procedure has been developed for the synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones. The procedure is simpler and faster than the protocols published to date. It is also consistent with a green chemistry approach since no heating or additional equipment is required. The catalyst used is inexpensive, non-toxic, non-corrosive and readily available chemical that is commonly found in most organic chemistry laboratories. The simplicity, together with the use of inexpensive, non-toxic and environmentally benign catalyst-alum at 25 C is a remarkable feature of the procedure.

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Table 1. Alum catalyzed synthesis of 3,5-bis-(arylmethylidene)-tetrahydropyran-4-ones derivatives (4a-h)^a

Compound ^b R	Time(min)	Yield(%) ^c	M. P. (°C)		
			Found	Reported ⁷	
3a	C ₆ H ₅	30	96	184-186	186
3b	4-MeC ₆ H ₄	40	96	110-112	109-110
3c	4-Cl C ₆ H ₄	40	96	168-170	169
3d	4-OMe C ₆ H ₄	40	95	180-182	180
3e	-CH=CH- C ₆ H ₅	40	94	204-206	205
3f	2-pyridyl	30	94	188-190	190
3g	2-furyl	30	94	172-174	173
3h	2-thiophyl	30	94	195-197	196

^aReaction conditions: tetrahydropyran-4-one (1mmol) and aldehyde (2mmol), were stirred in the presence of alum (10 mol%) in H₂O (10 mL) at room temperature.

^bCompounds were characterized by IR, ¹H NMR, mass spectroscopy and compared with reported data.

^cIsolated yield.

Table 2 Optimization of molar ratio of catalyst for the model reaction

Entry	Mole %	Yield/% ^a
1	0	Trace
2	2	35
3	5	65
4	10	96
5	15	95
6	20	93

^aYields refer to pure isolated products