Monatshefte für Chemie 138, 997–999 (2007)
DOI 10.1007/s00706-007-0666-6
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Alum ($KAl(SO_4)_2 \cdot 12H_2O$) Catalyzed One-Pot Synthesis of Coumarins under Solvent-Free Conditions

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Received February 11, 2007; accepted (revised) February 14, 2007; published online July 20, 2007

Summary. Alum ($KAl(SO_4)_2 \cdot 12H_2O$) is used as an efficient catalyst in the *Pechmann* condensation of phenol derivatives with β-keto esters leading to the formation of coumarins in excellent yields under solvent-free conditions. This methodology offers significant improvements for the synthesis of coumarins with regard to the yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents.

Keywords. Heterocycle; *Pechmann* condensation; Coumarins; Solvent-free, Alum.

Introduction

Coumarin and its derivatives form an important class of benzopyrones found in Nature. They are a structural subunit in many complex natural products and have shown various biological activities, such as antitumor [1], anti-HIV [2], antioxidation [3], tumor necrosis factor-a (TNF-a) inhibition [4], antimicrobial activity [5], serine protease inhibition [6], and anticancer activity [7]. The widespread biological activities of coumarin derivatives have aroused great interest in the area of synthesis chemistry and pharmacology.

The *Pechmann* reaction is a most commonly used method for the preparation of coumarins [8]. The reaction involves condensation of very simple starting materials *i.e.* phenols and β-keto esters in the presence of a variety of acidic condensing agents. Various reagents like H_2SO_4, P_2O_5, $FeCl_3$, $ZnCl_2$, $POCl_3$, $AlCl_3$, *PPA*, HCl, phosphoric acid, and trifluoroacetic acid are used to effect this condensation [9]. However, in the current context of environmental impact, these methods are not attractive as they require catalysts in excess, for example, sulfuric acid in 10–12 equivalents [10], trifluoroacetic acid in 3–4 equivalents [11], and P_2O_5 in 5-fold excess [12]. Further, such reactions require long reaction times and in some cases gave low yields. The present drive therefore is towards the development of more effective, non-stoichiometric, preferably heterogeneous catalysts. To overcome these problems some environmentally benign procedures have been reported, such as using solid supports [13], ionic liquids [14], and solid *Lewis* acids [15]. $KAl(SO_4)_2 \cdot 12H_2O$ (alum) with mild acidity, involatility, and incorrositivity, is insoluble in common organic solvents and was used recently as an easily available acidic catalyst in different reactions [16].

Results and Discussion

In continuation of our interest in using solid acidic catalysts in organic reactions [17], here we wish to report an efficient and environmentally benign procedure for the synthesis of coumarins *via Pechmann* condensation in the presence of catalytic amounts of alum. For optimizing the reaction conditions, the reaction of resorcinol with ethyl acetoacetate in the presence of alum at different temperatures was investigated. The best results were obtained with

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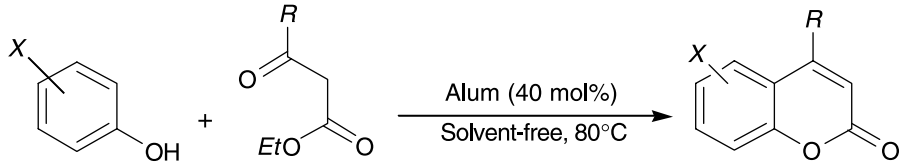
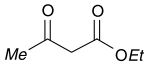
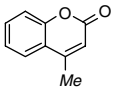
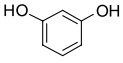
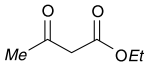
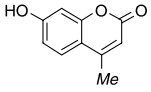
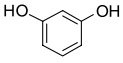
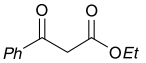
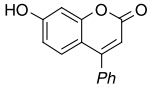
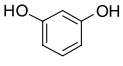
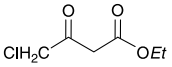
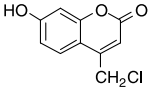
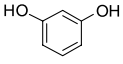
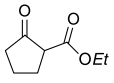
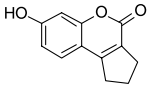
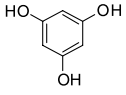
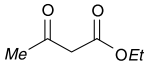
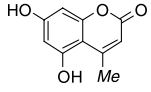
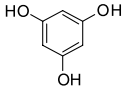
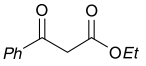
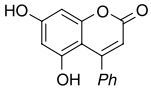
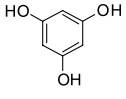
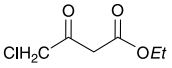
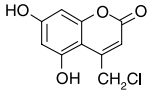
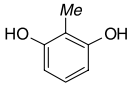
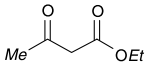
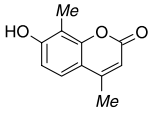
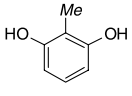
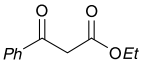
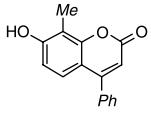
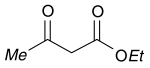
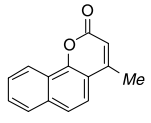
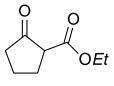
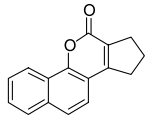


Scheme 1

Table 1. Synthesis of coumarins by the reaction of phenols with β-ketoesters in the presence of 40 mol% of alum

Entry	Phenol	β-Ketoester	Product	Time/h	Yield/%	Ref.[a]
1				3	80	[15e]
2				2	92	[15a]
3				2	91	[15d]
4				3	86	[15a]
5				3	88	[14a]
6				2	90	[15a]
7				2.5	90	[15d]
8				3	90	[15a]
9				2	91	[15d]
10				2	95	[15d]
11				3	87	[15d]
12				3	81	[14a]

[a] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by reported procedures

40 mol% of alum at 80°C (92% yield). Encouraged by the above results, other coumarin derivatives were synthesised under the same conditions (Scheme 1).

Several types of phenolic substrates and β-keto esters with different functionalities were used in the reaction. As can be seen in Table 1, the reaction was found to be adaptable to a variety of substrates and the yields, in general, were very high (80–95%). The experimental procedure is very simple and work-up includes the addition of H_2O followed by filtration. Hence there will not be any unnecessary acidic waste stream to create environmentally hazardous pollution.

In conclusion, we developed an efficient and simple alternative for the preparation of substituted coumarins *via* the alum-catalyzed *Pechmann* reaction under solvent-free conditions. Prominent among the advantages of this new method are operational simplicity, good yields, short reaction times, and an easy work-up procedure.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on a FT-IR 102MB BOMEM apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. All the products are known compounds, which were characterized by melting point, IR, ^{1}H and ^{13}C NMR spectral data, and mass spectroscopy.

General Procedure for the Synthesis of Coumarins

Phenolic substrate (1 mmol), 1 mmol β-keto ester, and 0.4 mmol alum were mixed together in a round bottom flask. The mixture was stirred at 80°C for the appropriate time (see Table 1). After completion of the reaction as indicated by TLC (eluent: *n*-hexane/ethyl acetate = 2/1), H_2O was added to the mixture and it was filtered. The crude product was recrystallized from ethanol.

Acknowledgement

Financial support by the Research Council of Shahid Beheshti University is gratefully acknowledged.

References

[1] Weber US, Steffen B, Siegers CP (1998) Res Commun Mol Pathol Pharmacol **99**: 193

[2] a) Ptail AD, Freyer AJ, Drake SE, Haltiwanger RC, Bean MF, Taylor PB, Caranfa MJ, Breen AL, Bartus HR, Johnson RK, Hertzberg RP, Westley JW (1993) J Med Chem **36**: 4131; b) Zhao H, Neamati N, Hong HX, Mazumder A, Wang SM, Sunder S, Milne GWA, Pommier Y, Burke TB (1997) J Med Chem **40**: 242

[3] Yun BS, Lee IK, Ryoo IJ, Yoo ID (2001) J Nat Prod **64**: 1238

[4] a) Cheng JF, Ishikawa A, Ono Y, Arrhenius T, Nadzan A (2003) Bioorg Med Chem **13**: 3647; b) Cheng JF, Chen M, Wallace D, Tith S, Arrhenius T, Kashiwagi H, Ono Y, Ishikawa A, Sato H, Kozono T, Ato H, Nadzan AM (2004) Bioorg Med Chem Lett **14**: 2411

[5] Zaha AA, Hazem A (2002) Microbiologica **25**: 213

[6] Whittaker M, Floyd CD, Brown P, Gearing AJH (1999) Chem Rev **99**: 2735

[7] Maly DJ, Leonetti F, Backes BJ, Dauber DS, Harris JL, Craik CS, Ellman JA (2002) J Org Chem **67**: 910

[8] Sethna SM, Phadke R (1953) Org React **7**: 1

[9] a) Appel H (1935) J Chem Soc 1031; b) Woods LL, Sapp J (1962) J Org Chem **27**: 3703; c) Ahmad ZS, Desai RD (1937) Proc Indian Acad Sci Chem Sci **5A**: 277; d) Robinson R, Weygand F (1941) J Chem Soc 386; e) Nadkarni AJ, Kudav NA (1981) Ind J Chem Sect B **20**: 719

[10] Russell A, Frye JR (1941) Org Synth **21**: 22

[11] Woods LL, Sapp J (1962) J Org Chem **27**: 3703

[12] a) Simmonis H, Remmert P (1914) Chem Ber **47**: 2229; b) Robertson A, Sandrock WF, Henry CB (1931) J Chem Soc 2426

[13] a) Reddy BM, Patil MK, Lakahmanan P (2006) J Mol Catal A Chem **256**: 290; b) Rodriguez-Dominguez JC, Kirsch G (2006) Tetrahedron Lett **47**: 3279; c) Maheswara M, Siddaiah V, Damu GLV, Rao YK, Rao CV (2006) J Mol Catal A Chem **255**: 49

[14] a) Khandekar AC, Khadilkar BM (2002) Synlett 152; b) Potdar MK, Rasalkar MS, Mohile SS, Salunkhe MM (2005) J Mol Catal A Chem **233**: 249

[15] a) Rodriguez-Dominguez JC, Kirsch G (2006) Synthesis 1895; b) Valizadeh H, Shockravi A (2005) Tetrahedron Lett **46**: 3501; c) De SK, Gibbs RA (2005) Synthesis 1231; d) Sharma GVM, Reddy JJ, Lakshmi PS, Krishna PR (2005) Tetrahedron Lett **46**: 6119; e) Bahekar SS, Shinde DB (2004) Tetraheron Lett **45**: 7999

[16] Dabiri M, Salehi P, Otokesh S, Baghbanzadeh M, Kozehgary Gh, Mohammadi AA (2005) Tetrahedron Lett **46**: 6123

[17] a) Dabiri M, Salehi P, Mohammadi AA, Baghbanzadeh M (2005) Synth Commun **35**: 279; b) Salehi P, Dabiri M, Baghbanzadeh M, Bahramnejad M (2006) Synth Commun **36**: 2287; c) Dabiri M, Salehi P, Mohammadi AA, Baghbanzadeh M, Kozehgiry G (2004) J Chem Res (S) 570; d) Salehi P, Dabiri M, Zolfigol MA, Bodaghi Fard MA (2003) Tetrahdron Lett **44**: 2889; e) Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M (2005) Synlett 1155; f) Salehi P, Dabiri M, Khosropour AR, Roozbehniya P (2006) J Iran Chem Soc **3**: 98; g) Salehi P, Dabiri M, Zolfigol MA, Bodaghi Fard MA (2003) Heterocycles **60**: 2435; h) Salehi P, Dabiri M, Zolfigol MA, Baghbanzadeh M (2005) Tetrahedron Lett **46**: 7051; i) Salehi P, Dabiri M, Zolfigol MA, Otokesh S, Baghbanzadeh M (2006) Tetrahedron Lett **47**: 2557; j) Baghbanzadeh M, Salehi P, Dabiri M, Kozehgary Gh (2006) Synthesis 344