Short communication

Synthesis of Coumarins and 2,3-dihydroquinazolin-4(1*H*)-ones Using Trichloroacetic Acid as a Catalyst

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Abstract

Trichloroacetic acid was used as an efficient catalyst for the synthesis of coumarins from phenols and β-ketoesters and in an efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones through the condensation of 2-aminobenzamide with aldehydes or ketones under solvent-free conditions. The remarkable advantages offered by this method are short reaction times, simple procedure, and an easy work-up without using any chromatographic methods.

Keywords: Coumarins, 2,3-dihydroquinazolin-4(1*H*)-ones, trichloroacetic acid, solvent-free synthesis

1. Introduction

Coumarins have received considerable attention in the pharmaceutical industry owing to their broad range of biological activities.[1–3] Coumarin derivatives have been studied for different therapeutic applications such as antibacterial,[4] and anticancer[5] agents, anticoagulants,[6] inhibitors of steroid 5α-reductase[7] and HIV-1 protease inhibitors.[8] Furthermore, they have been used as efficient laser dyes, fluorescent brighteners, and as additives in food and cosmetics.[1,9-11]

The most widely applied method for the synthesis of coumarins is the Pechmann reaction as it involves the condensation of phenols with β-ketonic esters in the presence of a variety of acidic condensing agents. During recent years various solid acid catalysts have been employed for the synthesis of coumarins.[12–20]

Most of the reported protocols for the synthesis of coumarins suffered from the use of harmful organic solvents, high reaction temperatures, prolonged reaction times, low product yields, and complicated work-up procedures. Therefore, the development of simple, convenient, and environmentally acceptable approaches for the synthesis of coumarins is still demanding.

In addition, the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives have also attracted great interest for their biological and pharmacological activities.[21–22] The condensation of 2-aminobenzamide with aldehydes or ketones is one of the simplest and most direct methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones. Various acid catalysts have been used to accomplish this transformation.[23–25]

Trichloroacetic acid is a readily available and inexpensive solid reagent and it has been already used in our group for the synthesis of 1-amidoalkyl-2-naphthols,[26] dihydropyrano[2,3-*c*]pyrazoles,[27] tetrahydrobenzo[*a*]xanthen-11-ones and dibenzo[a,j]xanthenes.[28]

2. Experimental Section

2. 1. General Procedure for the Synthesis of Coumarins

A mixture of phenol (1 mmol), β-keto ester (1 mmol), and trichloroacetic acid (0.048 g, 30 mol%) was stirred at 100 °C for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane: 1/2). After completion of the reaction the solid catalyst was washed with water and product purified by recrystalization from ethyl acetate/n-hexane.

2. 2. General Procedure for the Synthesis of 2,3-dihydroquinazolin-4(1H)-ones

A mixture of 2-aminobenzamide (1 mmol), aldehyde/ketone (1 mmol), and trichloroacetic acid (0.016 g, 10 mol%) was stirred at 120 °C for the appropriate time as indicated in Table 1. The progress of the reaction was monitored by TLC (ethyl acetate/n-hexane: 1/2). After completion of the reaction the solid catalyst was washed with water and product purified by recrystalization from ethanol.

2. 3. Spectroscopic Data of Selected Products

7-Hydroxy-4-methyl coumarin (Table 1, entry 1). ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.32 (3H, s, CH_3), 6.08 (1H, s, CH), 6.66 (1H, s, ArH), 6.76 (1H, d, J = 8.5 Hz, ArH), 7.54 (1H, d, J = 8.75 Hz, ArH), 10.52 (1H, s, OH) ppm. IR (KBr): υ 3129, 1679, 1596, 1390 cm^{-1}.

5,7-Dihydroxy-4-methyl coumarin (Table 1, entry 2). ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.45 (3H, s, CH_3), 5.81 (1H, s, CH), 6.13 (1H, s, ArH), 6.22 (1H, s, ArH), 10.30 (1H, s, OH), 10.52 (1H, s, OH) ppm. IR (KBr): υ 3429, 3129, 1670, 1622, 1553 cm^{-1}.

7-Hydroxy-4-phenyl coumarin (Table 1, entry 9). ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.45 (3H, s, CH_3), 5.81 (1H, s, CH), 6.13(1H, s, ArH), 6.22 (1H, s, ArH), 10.30 (1H, s, OH), 10.52 (1H, s, OH) ppm. IR (KBr): υ 3429, 3129, 1670, 1622, 1553 cm^{-1}**.**

2,3-Dihydro-2-phenylquinazolin-4(1*H*)-one (Table 2, entry 1). ^{1}H NMR (250 MHz, DMSO-d_6): δ 5.73 (1H, s, CH), 6.65–6.74 (2H, m, ArH), 7.08 (1H, s, NH), 7.22–7.60 (7H, m, ArH), 8.25 (1H, s, NH–CO) ppm. IR (KBr): υ 3303, 3184, 3059, 2933, 1656, 1611, 1511, 1439 cm$^{-1.}$

2,3-Dihydro-2-(4-nitrophenyl)quinazolin-4(1*H*)-one (Table 2, entry 4). ^{1}H NMR (250 MHz, DMSO-d_6): δ 5.88 (1H, s, CH), 6–63–6.75 (2H, m, ArH), 7.21–7.27 (1H, m, ArH), 7.33 (1H, s, NH), 7.58(1H, d, J = 7.75 Hz , ArH), 7.71 (2H, d, J = 7.5, ArH), 8.23 (2H, d, J = 7.5 Hz, ArH), 8.53 (1H, s, NH-CO) ppm. IR (KBr): υ 3445, 3280, 2922, 2854,1647,1610,1519, 1519 cm^{-1}.

2,3-Dihydro-2-(2-chlorophenyl)quinazolin-4(1*H*)-one (Table 2 entry 5). ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.11 (1H, s, CH), 6.69–6.75 (2H, m, ArH), 7.0 (1H, s, NH), 7.20–7.23 (1H, m, ArH) ,7.36–7.40 (3H, m, ArH), 7.63 (2H, d, J = 6.25 Hz , ArH), 8.21 (1H, s, NH-CO) ppm. IR (KBr): 3361, 3194, 3064, 2922, 1646, 1615, 1503 cm^{-1}.

2,3-Dihydro-2-(4-methoxyphenyl)quinazolin-4(1*H*)-one (Table 2 entry 7): ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.72 (3H, s, CH_3), 5.68 (1H, s, CH), 6.62–6.73 (2H, m, ArH), 6.90–6.98 (3H, m, NH and ArH), 7.18–7.25 (1H, m, ArH), 7.39 (2H, d, J = 8.25, ArH), 7.59 (1H, d, J = 7.75, ArH), 8.15 (1H, s, NH–CO) ppm. IR (KBr): υ 3297, 3181, 3053, 2932, 1670, 1609, 1572, 1514, 1463 cm^{-1}.

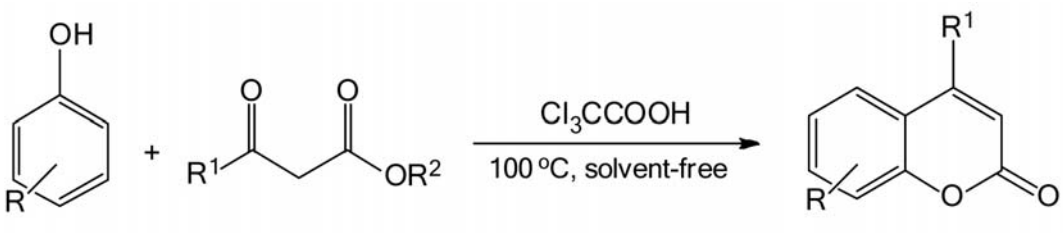
2,3-Dihydro-2-(4-methylphenyl)quinazolin-4(1*H*)-one (Table 2 entry 9). ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.26 (3H, s, CH_3), 5.67 (1H, s, CH), 6.60–6.72 (2H, m, ArH), 7.04 (1H, s, NH), 7.14–7.23 (3H, m, ArH), 7.34 (2H, d, J = 7.75 Hz, ArH), 7.57 (1H, d, J = 7.5 Hz, ArH), 8.23 (1H, s, NH-CO) ppm. IR (KBr): υ 3312, 3194, 3062, 2934, 1658,1 610 cm^{-1}.

2,3-Dihydro-2-(4-fluorophenyl)quinazolin-4(1*H*)-one (Table 2 entry 10). ^{1}H NMR (250 MHz, DMSO-d_6): δ 5.74 (1H, s, CH), 6.65–6.73 (2H, m, ArH), 7.08 (2H, s, NH), 7.16–7.24 (3H, m, ArH), 7.48–7.60 (3H, m, ArH), 8.27 (1H, s, N-CO) ppm. IR (KBr): υ 3424, 3300, 3184, 2924, 655, 1611, 1515 cm^{-1}.

2-Spirocyclopentyl-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, entry 13). ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.63–1.65 (4H, m, $2CH_2$), 1.74–1.76 (4H, m, $2CH_2$), 6.57–6.71 (3H, m, NH and ArH), 7.15–7.21 (1H, m, ArH), 7.59 (1H, d, J = 7.5, ArH), 8.06 (1H, s, NH–CO) ppm. ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 22.4, 38.92, 77.5, 114.7, 115, 117, 127.6, 133.4, 147.9, 163.9 ppm. IR (KBr): υ 3163, 2939, 1639, 1614, 1516, 1483, 1429, 1383, 1322 cm^{-1}**.**

3. Results and Discussion

As part of our continuing effort toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[26–31] we became interested in research of an efficient method to construct the coumarin scaffold under solvent-free conditions. Initial study was directed toward treatment of resorcinol with ethyl acetoacetate under solvent-free condi-



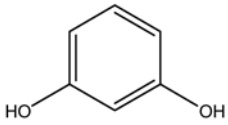
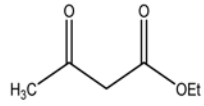
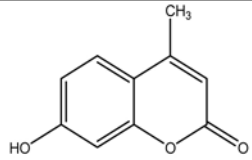
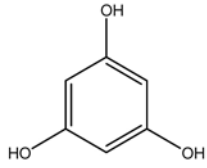
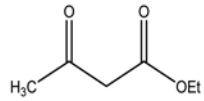
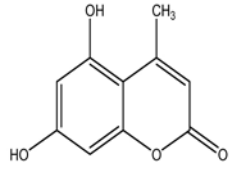
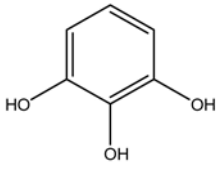
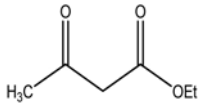
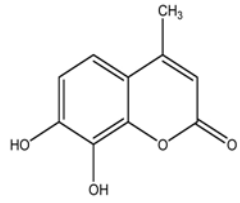
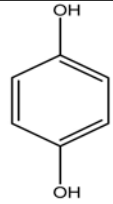
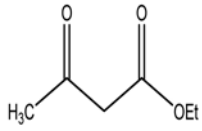
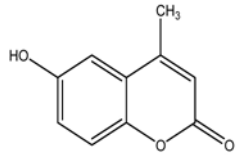
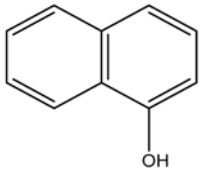
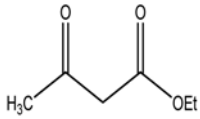
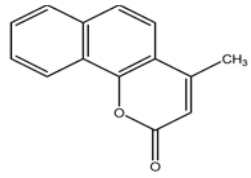
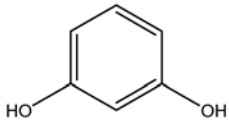
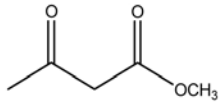
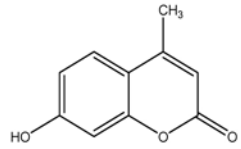
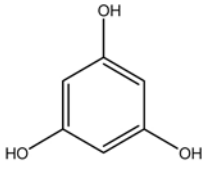
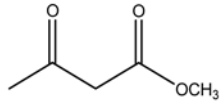
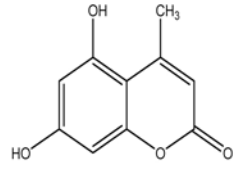
Scheme 1. Synthesis of coumarins.

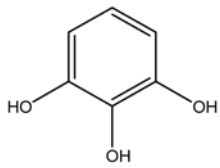
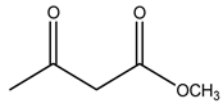
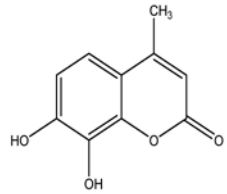
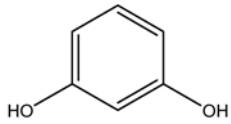
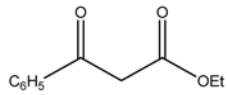
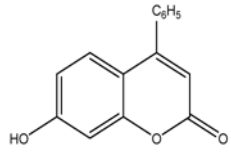
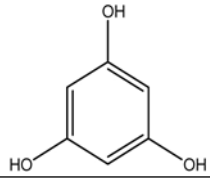
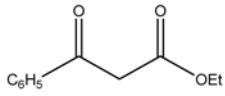
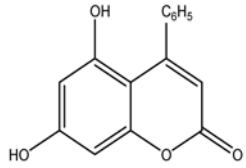
tions in the presence of a catalytic amount of trichloroacetic acid (30 mol%) at 100 C.

To our delight the complete conversion of reactants and 80% isolated yield was obtained after 90 min. Among the reaction conditions studied (EtOH, THF, H_2O, MeCN, toluene, and solvent-free), solvent-free reactions were demonstrated as the best one.

The scope of this methodology was further tested by the reaction of various phenols. Different coumarins were prepared in the presence of trichloroacetic acid as catalyst (30 mol%) in short reaction times at room temperature with good yields (Table 1). After completion of the reaction trichloroacetic acid can be separated from the reaction mixture by washing of the solid product with water.

Table 1. Synthesis of coumarins.

Entry	Phenol	β-keto esters	Product	Time (min)	Yield (%)	m. p. (°C) found	m. p. (°C) lit.[ref.]
1				90	82	188–190	186–188[17]
2				5	84	280–282	280–281[13]
3				90	73	240–242	240–247[15]
4				120	70	184–186	184–186[18]
5				120	70	152–154	156[14]
6				50	86	188–190	186–188[17]
7				5	83	280–282	280–281[13]

Entry	Phenol	β-keto esters	Product	Time (min)	Yield (%)	m. p. (°C) found	m. p. (°C) lit.[ref.]
8				75	87	240–242	243–244[18]
9				90	79	–247–250	255[14]
10				90	79	239–242	246[14]

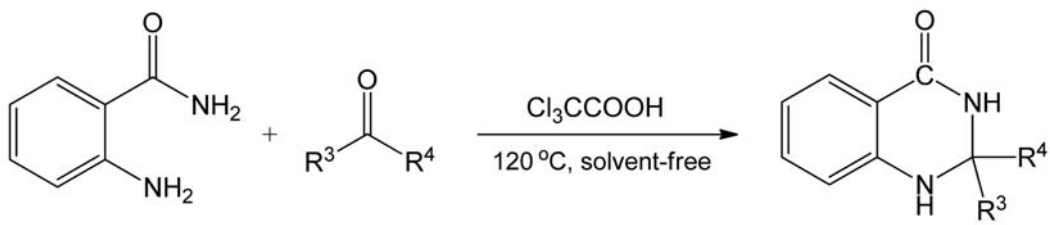
As shown in Table 1, phenols with electron-donating groups are easily converted to the corresponding coumarins under the same reaction conditions. When the reaction was triggered with phenols bearing electron-withdrawing groups, starting materials remained intact even after prolonged reaction time.

These results promoted us to utilize trichloroacetic acid for the synthesis of other recently developed heterocylic compounds, i.e, 2,3-dihydroquinazolin-4(1*H*)-ones by using acetic acid[29] tris(hydrogensulfato)boron,[30] boric acid[31] and sodium dihydrogen phosphate.[31] Herein we report our results in the construction of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones through the condensation of 2-aminobenzamide with aldehydes or ketones using trichloroacetic acid. To optimize the reaction conditions, investigations were initiated with condensation of benzaldehyde as a model compound with 2-aminobenzamide in presence of trichloroacetic acid at various experimental conditions. The best yield (75%) was obtained at 120 °C after 4 minutes of reaction, using 0.032 g of trichloroacetic acid.

To show the generality of this method the optimized reaction was used for the synthesis of various derivatives. For example, aromatic aldehydes carrying different functional groups reacted satisfactorily under the optimized reaction conditions as can be seen in Table 2. Moreover, cyclic ketones were equally amenable to these conditions providing the corresponding 2-spirocycloalkyl-2,3-dihydroquinazolin-4(1*H*)-ones in good yields. Advantages of newly developed method are short reaction times, operational simplicity, good yields, and an easy work-up procedure without using any chromatographic methods. It is worthy to note that in previous reports condensation of 2-aminobenzamide and aldehydes were carried out under harsh reaction conditions and longer reaction times.

4. Conclusions

The procedure has been described for the synthesis of coumarin derivatives through the Pechmann reaction and an efficient one-pot synthesis of 2,3-dihydroquinazolin-4(1H)-ones using trichloroacetic acid as a solid catalyst under solvent-free conditions. The advantages of this procedure are short reaction times, operational simplicity, and high yields. In many cases the product crystallized directly from the reaction mixture in high purity without using column chromatography. We believe that this method



Scheme 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Table 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.[a]

Entry	Aldehyde/Ketone	Time (min)	Yield (%)	m. p. (°C)	
				found	lit.[ref.]
1	Benzaldehyde	4	75	210–212	216–218[23]
2	4-Cyanobenzaldehyde	4	79	250–253	250–253[31]
3	2-Nitrobenzaldehyde	2	78	198–200	190–192[25]
4	4-Nitrobenzaldehyde	4	84	199–201	198–200[25]
5	2-Chlorobenzaldehyde	3	80	208–211	208–210[31]
6	4-Chlorobenzaldehyde	4	74	206–207	205–206[21]
7	4-Methoxybenzaldehyde	2	82	189–191	193–195[24]
8	2-Methoxybenzaldehyde	3	79	206–208	209–212[31]
9	4-Methylbenzaldehyde	2	79	220–223	223–225[25]
10	4-Fluorobenzaldehyde	2	86	196–198	202–201[31]
11	4-Bromobenzaldehyde	1	90	198–200	200–202[21]
12	Cyclohexanone	4	78	220–223	217–219[24]
13	Cyclopentanone	4	82	255–257	257–260[24]

[a] All products are known compounds and their structures were confirmed by comparison with known physical and spectroscopic (NMR and IR) data.

exhibits a practical alternative to existing procedures for the synthesis of these heterocyles.

5. References

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Abstract

Avtorji v prispevku poročajo o uporabi triklorocetne kisline kot učinkovitega katalizatorja pri sintezi kumarinov iz fenolov in β–ketoestrov ter pri učinkoviti sintezi 2,3–dihidrokinazolin–4(1*H*)–onov s kondenzacijo 2–aminobenzamida z aldehidi in ketoni v reakcijah brez topila. Bistvene prednosti opisane metode so kratki reakcijski časi, enostavnost postopka in preprosta izolacija produkta, brez uporabe kromatografskih metod.