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ORIGINAL PAPER

Magnesium bis(trifluoromethane)sulfonimide: an efficient catalyst for the synthesis of coumarins under solvent-free conditions

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Abstract Magnesium bis(trifluoromethane)sulfonimide [$Mg(NTf_2)_2$] is an efficient catalyst for the synthesis of coumarins via the Pechmann condensation reaction of phenols and β-ketoesters under solvent-free conditions.

Keywords Coumarins · $Mg(NTf_2)_2$ · Pechmann condensation · Solvent-free

Introduction

Coumarin and its derivatives are important owing to their wide use in synthetic chemistry and their biological activities. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [1], and in the preparation of insecticides, optical brighteners [2], and dispersed fluorescent and laser dyes [3]. A large number of natural products containing the coumarin moiety are also known [4]. Coumarins can be synthesized by various methods such as Pechmann [5], Perkin [6], Knoevenagel [7], Reformatsky [8], and Wittig [9] reactions. Among these, the Pechmann reaction is one of the most common procedures for the preparation of coumarin and its derivatives. This method involves the condensation of phenols with β-ketoesters in the presence of condensing agents. Different reagents such as H_2SO_4 [5], $AlCl_3$ [10], P_2O_5 [11], CF_3COOH [12], *p*-TsOH [13], $BiCl_3$ [14], silica sulfuric acid [15], $H_3PW_{12}O_{40}$ [16], $Sm(NO_3)_3{\cdot}6H_2O$ [17], $TiCl_4$ [18], $InCl_3$ [19], I_2 [20], $ZrCl_4$ [21], $HClO_4{\cdot}SiO_2$ [22], $NaHSO_4{\cdot}SiO_2$ [23], CAN [24], $LiClO_4$ [25], $KAl(SO_4)_2{\cdot}12H_2O$ [26], nanocrystalline sulfated zirconia [27], zeolite [28], and $SO_4^{2-}/Ce_xZr_{1-x}O_2$ solid acid [29] are known to affect the Pechmann condensation. This reaction was also reported using ionic liquids [30, 31], ultrasound [32], and microwave irradiation [33]. Although each of the above methods has its own merits, some of the methods employed earlier for this conversion are associated with certain drawbacks such as long reaction times and the use of a large amount of catalyst.

In recent years, metal bis(trifluoromethane)sulfonimides have been successfully used for the acetylation of phenols and alcohols [34], [2 + 2] cycloadditions of siloxyalkynes with carbonyl compounds [35], Friedel–Crafts acylation reactions [36], cycloisomerization of 1,6-dienes [37], and aminolysis of lactones with amines [38]. However, many metal bis(trifluoromethane)sulfonimides are not available commercially and involve high cost for their preparation and therefore are not a good contender for general use. $Mg(NTf_2)_2$ is commercially available and cheaper, and therefore better suited for catalytic use. Previously, we reported the use of $Eu(NTf_2)_3$ [39] and $Mg(NTf_2)_2$ [40] as efficient catalysts for organic synthesis. In continuation to our work, I herein report an efficient procedure for the synthesis of coumarins from phenols and β-ketoesters in the presence of 1 mol% of $Mg(NTf_2)_2$ under solvent-free conditions (Scheme 1).

Results and discussion

The reaction of phenol and ethyl acetoacetate in the presence of $Mg(NTf_2)_2$ was chosen as a model to optimize the reaction conditions and the results are listed in Table 1. No product was detected in the absence of the catalyst. It was

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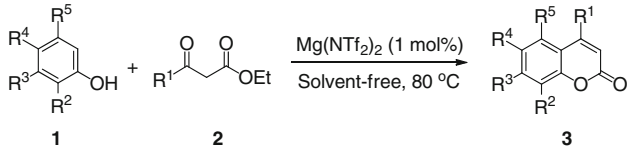

Scheme 1

Table 1 Effect of the amount of catalyst on the reaction of phenol and ethyl acetoacetate under solvent-free conditions using $Mg(NTf_2)_2$ as a catalyst

Entry	Catalyst loading/mol%	Time/min	Yield/%[a]
1	0	120	0
2	0.25	90	41
3	0.5	60	76
4	1	60	87
5	3	60	87
9	5	60	87
7	10	60	87

Reaction conditions: phenol (1 mmol) and ethyl acetoacetate (1 mmol) at 80 °C in the presence of the indicated amount of catalyst under solvent-free conditions

[a] Isolated yields

Table 2 Effect of temperature on the reaction of phenol and ethyl acetoacetate under solvent-free conditions using $Mg(NTf_2)_2$ as a catalyst

Entry	Temperature/°C	Time/min	Yield/%[a]
1	40	180	32
2	60	90	67
3	70	75	81
4	80	60	87
5	85	55	87
6	90	50	83

Reaction conditions: phenol (1 mmol) and ethyl acetoacetate (1 mmol) at the indicated temperature under solvent-free conditions

[a] Isolated yields

surprising to discover that 0.25 mol% of $Mg(NTf_2)_2$ could accelerate the reaction, but the reaction afforded the corresponding product in a low yield. Further study showed that the use of 1 mol% of $Mg(NTf_2)_2$ was sufficient to provide a satisfactory yield in 60 min. An increase in the amount of catalyst did not produce a better result.

Then, the effect of temperature on the reaction was studied and the results are listed in Table 2. No reaction was observed after stirring the reaction mixture at room temperature for 240 min under solvent-free conditions. The reaction proceeded smoothly with increasing temperature; the yield increased to 87 % at 80 °C. However, no significant increase in the yield was observed when the reaction temperature was raised from 80 to 90 °C. Therefore, 80 °C was chosen as the reaction temperature for all further reactions.

Table 3 Effect of solvent on the reaction of phenol and ethyl acetoacetate using $Mg(NTf_2)_2$ as a catalyst

Entry	Solvent	Time/min	Yield/%[a]
1	Dioxane	120	50
2	Acetonitrile	75	74
3	1,2-Dichloroethane	90	70
4	Toluene	120	52
5	None	60	87

Reaction conditions: phenol (1 mmol) and ethyl acetoacetate (1 mmol) in the indicated solvent (5 cm^3) or under solvent-free conditions at 80 °C

[a] Isolated yields

The reaction was carried out in different solvents such as dioxane, MeCN, 1,2-dichloroethane, and toluene, and also without solvent. As shown in Table 3, the best result was obtained when the reaction was carried out under solvent-free conditions and the catalyst worked in heterogeneous conditions. The lower isolated yields in solvents may be due to the decreased concentrations of substrates. The use of solvent-free conditions is advantageous because it avoids the use of potentially toxic and non-environmentally friendly organic solvents.

To show the general applicability of the method, the reaction of various phenols and β-ketoesters in the presence of 1 mol% of $Mg(NTf_2)_2$ at 80 °C under solvent-free conditions was investigated and the results are summarized in Table 4. In all cases, various substituted phenols reacted smoothly with β-ketoesters to give a range of coumarin derivatives. Short reaction times were observed (25–60 min) regardless of structural variations in the phenols or β-ketoesters. Phenols carrying either electron-donating or electron-withdrawing substituents all reacted smoothly to give the corresponding 4-substituted coumarins in high yields. Ethyl acetoacetate, ethyl benzoylacetate, and ethyl trifluoroacetoacetate reacted similarly to produce coumarins. For phenol (Table 4, entry 1), the reaction time is reduced drastically in contrast to the reported procedure [14]. According to the literature, 4-nitrophenol failed to give a coumarin derivative in the presence of $TiCl_4$ as the catalyst [18]. In contrast, $Mg(NTf_2)_2$ afforded the coumarin **3f** in high yield (Table 4, entry 6).

In addition, we compared the efficacy of $Mg(NTf_2)_2$ against other catalysts such as $Mg(ClO_4)_2$, $LiNTf_2$, $Mg(OTf)_2$, and $Cu(OTf)_2$ at 80 °C under solvent-free conditions. No 4-methylcoumarin (**3a**) was obtained after 8 h by the treatment of phenol with ethyl acetoacetate in the presence of $Cu(OTf)_2$ (1 mol%). $LiNTf_2$ (5 mol%)

Table 4 Synthesis of coumarins via Pechmann condensation of phenols with β-ketoesters (R^1–CO–CH_2–COOEt) catalyzed by $Mg(NTf_2)_2$

Entry	Phenol	R^1	Product	Time/min	Yield/%[a]	M.p./°C	
						Found	Reported
1	C_6H_5–OH	CH_3	**3a**	60	87	82–83	80–81 [15]
2	3-HO–C_6H_4–OH	CH_3	**3b**	25	96	183–184	182–184 [28]
3	3-CH_3–C_6H_4–OH	CH_3	**3c**	25	95	131–133	131–132 [18]
4	3-CH_3O–C_6H_4–OH	CH_3	**3d**	25	98	156–157	156–158 [18]
5	3,5-$(HO)_2$–C_6H_4–OH	CH_3	**3e**	25	97	286–288	285–287 [15]
6	4-NO_2–C_6H_4–OH	CH_3	**3f**	60	92	150–152	151–154 [17]
7	C_6H_5–OH	Ph	**3g**	60	85	102–104	100–102 [41]
8	3-HO–C_6H_4–OH	Ph	**3h**	35	95	253–255	255–257 [15]
9	3,5-$(HO)_2$–C_6H_4–OH	Ph	**3i**	35	96	243–245	241–242 [15]
10	3-HO–C_6H_4–OH	CF_3	**3j**	25	97	178–179	–
11	3-NH_2–C_6H_4–OH	CF_3	**3k**	25	98	221–223	–
12	1-Naphthol	CH_3	**3l**	45	94	154–155	152–153 [15]

Reaction conditions: phenols (1 mmol) and β-ketoesters (1 mmol) in the presence of 1 mol% of $Mg(NTf_2)_2$ at 80 °C under solvent-free conditions

[a] Isolated yields

Table 5 Reuse of the catalyst for the synthesis of **3a**

Entry	Yield/%[a]
0	87
1	86
2	84
3	83
4	78

[a] Isolated yields

afforded **3a** in 61 % yield after 2 h. $Mg(ClO_4)_2$ (10 mol%) and $Mg(OTf)_2$ (10 mol%) afforded **3a** in yields of 48 and 30 % after 2 and 3 h, respectively. The above representative examples demonstrated the superiority of $Mg(NTf_2)_2$.

We also investigated the reusability and recycling of $Mg(NTf_2)_2$. After the reaction of phenol with ethyl acetoacetate at 80 °C under solvent-free conditions, more than 90 % of $Mg(NTf_2)_2$ could be easily recovered by a simple extraction with water. The recovered $Mg(NTf_2)_2$ catalyzed the same reaction without significant decrease in catalytic activity even after the fourth run (Table 5).

In order to evaluate the efficiency of this work in comparison with previously reported procedures, synthesis of 4-methylcoumarin (**3a**) was considered as a representative example. As shown in Table 6, the yield of the present method is better or comparable with those of others. Furthermore, $Mg(NTf_2)_2$ is stable in water, easily recovered, and reusable.

In conclusion, $Mg(NTf_2)_2$ is an efficient catalyst for the synthesis of coumarins from phenols and β-ketoesters under solvent-free conditions. The advantages of this protocol include short reaction times, a simple work-up procedure, high yields, and the use of a catalytic amount of a commercially available catalyst.

Table 6 Comparison of efficiency of various catalysts in the synthesis of **3a** under solvent-free conditions

Catalyst (mol%)	Temp./°C	Time/min	Yield/%[a]	Ref.
$BiCl_3$ (5)	125	240	73	[14]
Silica sulfuric acid (15)	80	120	70	[15]
$H_3PW_{12}O_{40}$ (2)	90	45	95	[16]
$Sm(NO_3)_3{\cdot}6H_2O$ (10)	80	90	50	[17]
$TiCl_4$ (50)	r.t.	70 s	60	[18]
$InCl_3$ (10)	130	240	65	[19]
I_2 (1)	80	180	76	[20]
$KAl(SO_4)_2{\cdot}12H_2O$ (40)	80	180	80	[26]
[bmim]Cl·$2AlCl_3$ (100)	120	120	40	[31]
$Mg(NTf_2)_2$ (1)	80	60	87	This work

[a] Isolated yields

Experimental

All reagents were commercially available and were used without further purification. Melting points were determined on an XT4A electrothermal apparatus equipped with a microscope. NMR spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra were recorded on a Waters Micromass GCT. IR spectra were recorded on a Nicolet

FTIR-750 spectrometer. Elemental analyses were performed on a Perkin Elmer 240-C instrument. All solvents were dried by standard procedures.

General procedure for the synthesis of coumarins

A mixture of phenolic substrate **1** (1 mmol), *β*-ketoester **2** (1 mmol), and $Mg(NTf_2)_2$ (0.01 mmol, 1 mol%) was stirred at 80 °C until the reaction was completed (monitored by TLC). The reaction mixture was cooled to room temperature and then poured into crushed ice. The crystalline product was collected by filtration and washed with cold H_2O. The pure product **3** was obtained by recrystallization from hot EtOH. Except for compounds **3j** and **3k**, all products are known compounds. The spectroscopic and physical data for all known compounds were found to be identical to those described in the literature.

7-Hydroxy-4-(trifluoromethyl)coumarin (**3j,** $C_{10}H_5O_3F_3$) M.p.: 178–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62 (d, 1H, J = 8.8 Hz, ArH-5), 6.93 (dd, 1H, J = 8.5, 2.4 Hz, ArH-6), 6.88 (d, 1H, J = 2.4 Hz, ArH-8), 6.61 (s, 1H, COCH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 104.6 (ArC-8), 107.5 (ArC-10), 113.4 (q, J_{C-F} = 5.7 Hz, C-3), 115.0 (ArC-6), 123.3 (q, J_{C-F} = 273.1 Hz, CF_3), 127.7 (ArC-5), 142.5 (q, J_{C-F} = 32.4 Hz, C-4), 157.8 (ArC-9), 159.9 (ArC-7), 163.3 (C = O) ppm; IR (KBr): $\bar{\nu}$ = 3,392 (OH), 1,711 (C=O) cm^{-1}; MS (EI): *m/z* (%) = 230 (M^+, 100), 202 (99), 174 (21), 105 (12), 69 (37).

7-Amino-4-(trifluoromethyl)coumarin (**3k,** $C_{10}H_6O_2NF_3$) M.p.: 221–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45 (d, 1H, J = 8.8 Hz, ArH-5), 6.78 (dd, 1H, J = 8.8, 2.2 Hz, ArH-6), 6.65 (d, 1H, J = 2.2 Hz, ArH-8), 6.48 (s, 1H, COCH), 5.92 (br s, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 101.1 (ArC-8), 104.1 (ArC-10), 109.5 (q, J_{C-F} = 5.7 Hz, C-3), 113.4 (ArC-6), 123.5 (q, J_{C-F} = 273.1 Hz, CF_3), 127.3 (ArC-5), 142.2 (q, J_{C-F} = 31.8 Hz, C-4), 155.1 (ArC-9), 158.4 (ArC-7), 160.5 (C=O) ppm; IR (KBr): $\bar{\nu}$ = 3,451, 3,359 (NH_2), 1707 (C=O) cm^{-1}; MS (EI): *m/z* (%) = 229 (M^+, 100), 201 (88), 173 (20), 104 (19), 69 (15).

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