Preparation of methyl (2-hydroxynaphthalen-1-yl)(aryl)methyl/benzylcarbamate derivatives using magnesium (II) 2,2,2-trifluoroacetate as an efficient catalyst

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Multi-component condensation reactions of aldehydes, 2-naphthol and methyl/benzyl carbamate have been done by using magnesium 2,2,2-trifluoroacetate [$Mg(OOCCF_3)_2$] as an efficient catalyst. This methodology results in the synthesis of a variety of methyl (2-hydroxynaphthalen-1-yl)(aryl)methyl/benzylcarbamate derivatives in high yields. Despite their importance from pharmacological and synthetic points of view, comparatively few methods for the preparation of 1-carbamatoalkyl 2-naphthol derivatives have been reported *via* multi-component reactions of aldehydes, 2-naphthol and carbamate using acidic catalysts. Magnesium 2,2,2-trifluoroacetate [$Mg(OOCCF_3)_2$] has been prepared from the reaction of trifluoroacetic acid and magnesium chloride. The prepared catalyst has been characterised through a powder X-ray diffraction pattern.

Keywords: magnesium 2,2,2-trifluoroacetate, carbamate, X-ray diffraction, 1-carbamatoalkyl 2-naphthol, multi-component reaction

Carbamate skeletons are important components of natural products and versatile precursors for synthesis of pharmaceuticals such as mitomycin,[1,2] saxitoxin[3] and bleomycin.[4] In addition, carbamates are intermediates of the Curtius degradation route to amines.[5] They abound as nitrogen or oxygen protecting groups.[5] Therefore, the preparation of carbamate derivatives has attracted considerable attention.

Compounds containing both carbamate and a hydroxyl group such as 1-carbamatoalkyl 2-naphthols are of considerable interest because hydrolysis of carbamates can produce a variety of amino alcohols. These compounds are the main sub-structure of a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[6-11] 1-Carbamatoalkyl 2-naphthol derivatives are of significant importance because of their promising biological and pharmaceutical activities. Despite their importance from pharmacological and synthetic points of view, comparatively few methods for the preparation of 1-carbamatoalkyl 2-naphthol derivatives have been reported in the literature *via* multi-component reactions of aldehydes, 2-naphthol and carbamate using acidic catalysts.[12–21]

A general tendency in catalysis is to transform a successful homogeneous catalytic reaction into a heterogeneous process in which the catalyst can be easily separated from the reaction mixture, allowing its reuse and the design of continuous flow operations. The present work concentrates on the preparation and application of magnesium 2,2,2-trifluoroacetate [$Mg(OOCCF_3)_2$] as a new Lewis acid in the synthesis of a variety of 1-carbamatoalkyl 2-naphthol derivatives (Scheme 1).

Results and discussion

$Mg(OOCCF_3)_2$ has been prepared from the reaction of dry $MgCl_2$ with CF_3COOH. The crystallinity of pure $Mg(OOCCF_3)_2$ was examined by XRD studies. The XRD pattern of $Mg(OOCCF_3)_2$ is shown in Fig. 1 and reveals that the actual phase was $F_6MgC_4O_4$ (rhombohedral).

However, in a control reaction where no catalyst was used, no product was formed and conversion of 2-naphthol was found to be 0% after 2 h. This shows that the catalyst is essential for the product formation. Our investigation began with an evaluation employing different catalysts and the reaction of 4-chlorobenzaldehyde, 2-naphthol and methyl carbamate was chosen as a model of the reaction to form methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate (Scheme 2). Note that under the same reaction conditions, $Mg(OOCCF_3)_2$ exhibited much better activity than others and gave quite higher yields for this transformation. Therefore, $Mg(OOCCF_3)_2$ was selected as the active component for the preparation of 1-carbamatoalkyl 2-naphthols. The results are summarised in Table 1.

To choose the optimum conditions, initially, the reaction of 4-chlorobenzaldehyde, 2-naphthol and methyl carbamate was chosen as a model and the influence of $Mg(OOCCF_3)_2$ as

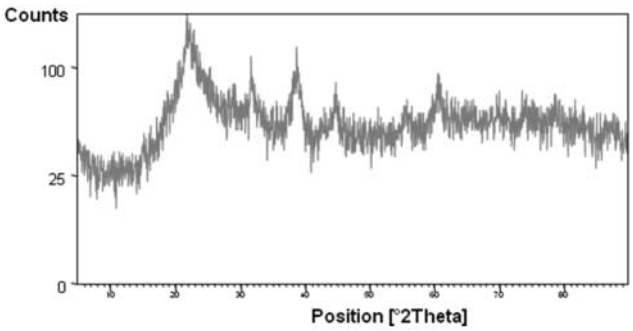
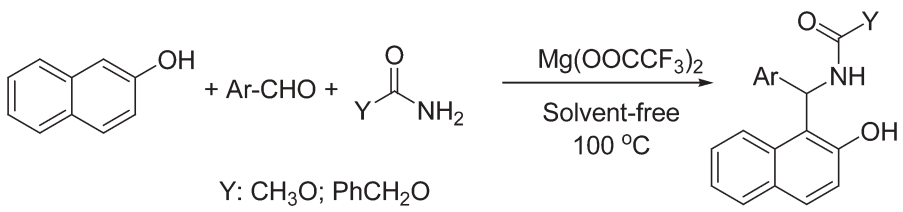


Fig. 1 X-ray diffraction patterns of $Mg(OOCCF_3)_2$.



Scheme 1 Preparation of 1-carbamatoalkyl-2-naphthol derivatives.

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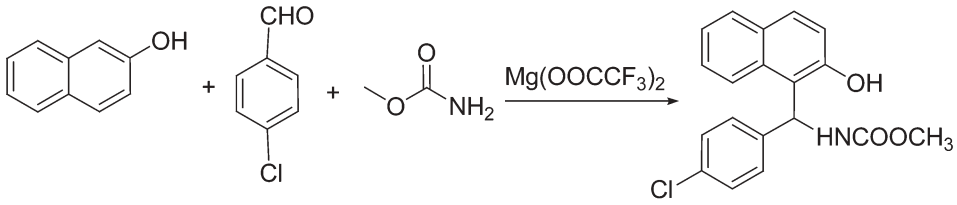


Scheme 2 Preparation of methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate using $Mg(OOCCF_3)_2$ as catalyst.

catalyst was examined to find the optimal conditions for the reaction. As shown in Table 1, in the absence of catalyst no product was obtained (entry 1). Our investigations show that the use of catalyst is unavoidable for this transformation. Among the tested solvents such as methanol, ethanol, water, dichloromethane, *n*-hexane, ethyl acetate and a solvent-free system, condensation of 4-chlorobenzaldehyde, 2-naphthol and methyl carbamate is more facile and proceeded to give highest yield, under solvent-free conditions (Table 2, entries 1–7). Next, the effect of temperature and amount of catalyst on the rate of the reaction was investigated (Table 2, entries 8–14). It was found that the reaction using $Mg(OOCCF_3)_2$ (0.1 mmol) at 100 °C provided the best yield (Table 2, entry 12). The results are summarised in Table 2.

We then explored the scope and efficiency of these procedures for the synthesis of a wide variety of substituted 1-carbamatoalkyl 2-naphthols (Scheme 1, Table 3). As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aromatic aldehydes were investigated (Table 3, entries 1–10). However, when aromatic aldehydes with electron-withdrawing groups (such as nitro) were reactants, the reaction time was shorter than that with electron-donating groups (such as methyl). Though *meta*- and *para*- substituted aromatic aldehydes gave good results, *ortho*-substituted aromatic aldehydes (such as 2-chloro and 2-nitro) gave lower yields and a longer reaction time because of the steric effects. As a result, the reaction of butyraldehyde with 2-naphthol and methyl carbamate failed to give any product (Table 3; Entry 16). Encouraged by the results obtained with methyl carbamate, we turned our attention to benzyl carbamate (Table 3). As shown in Table 3, the reactions of 2-naphthol and aryl aldehydes with benzyl carbamate under the mentioned reaction conditions progressed smoothly and the desired products were obtained in good yields. (Table 3, entries 11–15).

The work-up procedure is very straightforward; that is, the products were isolated and purified by simple filtration and crystallization from ethanol. Our protocol avoids the use of dry media during the reaction process, making it superior to the previous methods.

To exhibit the merit of the present work in comparison with previously reported results, we compared results of PPA-SiO_2,[12] *p*-TSA/[bmim]Br,[13] Brønsted acidic ionic liquid,[14] SiO_2–$NaHSO_4$,[15] 4-(1-imidazolium) butane sulfonate[16] and $HClO_4$–SiO_2,[17] in the synthesis of methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate. As shown in Table 4, $Mg(OOCCF_3)_2$ can act as an effective catalyst with respect to the reaction yield of the product.

Table 1 Catalyst screening

Entry	Catalyst	Time/min	Yield/%[a]
1	–	120	–
2	Trifluoroacetic acid (0.2 mmol)	50	50
3	$MgCl_2$ (0.2 mmol)	100	55
4	MgO (0.2 mmol)	210	35
5	ZnO (0.2 mmol)	150	40
6	$CaCl_2$ (0.2 mmol)	140	45
7	$BaCl_2$ (0.2 mmol)	100	60
8	$ZnCl_2$ (0.2 mmol)	120	67
9	$Mg(OOCCF_3)_2$ (0.2 mmol)	15	89

[a]Isolated yield; reaction condition: 4-chlorobenzaldehyde (1 mmol), 2-naphthol (1 mmol) and methyl carbamate (1.3 mmol); solvent-free, 100 °C.

Table 2 Optimisation of the reaction conditions in the preparation of methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate

Entry	Catalyst (mmol)	T/°C	Solvent	Time/min	Yield/%[a]
1	0.2	Reflux	H_2O	500	–
2	0.2	Reflux	CH_2Cl_2	500	35
3	0.2	Reflux	Methanol	500	60
4	0.2	Reflux	Ethanol	500	67
5	0.2	Reflux	n–hexane	500	40
6	0.2	Reflux	Ethyl acetate	500	55
7	0.2	100	–	18	85
8	0.2	–	–	300	–
9	0.2	80	–	100	70
10	0.2	120	–	15	81
11	0.04	100	–	40	73
12	0.1	100	–	20	87
13	0.32	100	–	19	75
14	0.4	100	–	20	70

[a]Isolated yield.

Conclusion

In conclusion, we have presented an efficient and powerful method for the preparation of 1-carbamatoalkyl 2-naphthols catalysed by $Mg(OOCCF_3)_2$. The reactions were carried out under solvent-free conditions with short reaction times and produce the corresponding products in good yields. The present methodology offers several advantages such as good yields, simple procedure, shorter reaction times and milder conditions and the products were purified without resorting to chromatography.

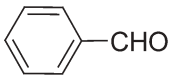
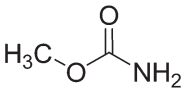
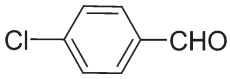
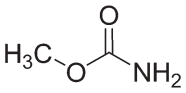
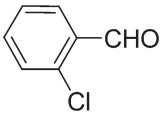
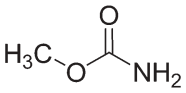
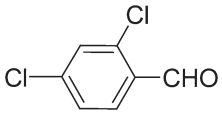
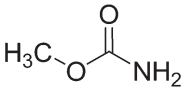
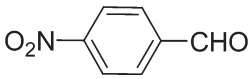
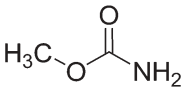
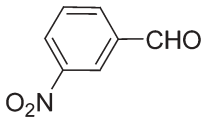
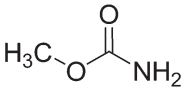
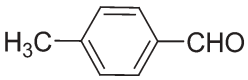
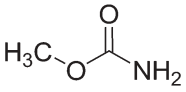
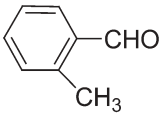
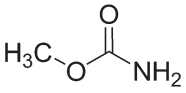
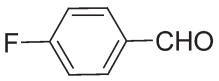
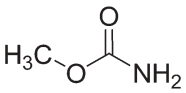
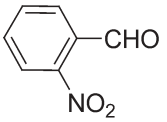
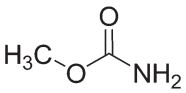
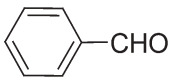
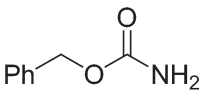
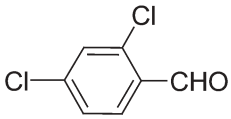
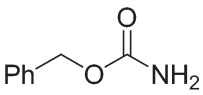
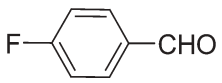
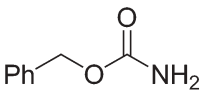
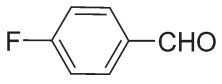
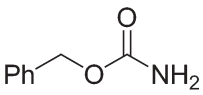
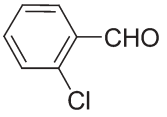
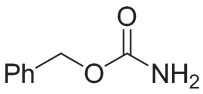
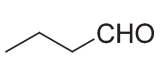
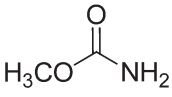
Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Perkin Elmer 781 spectrophotometer. Elemental analysis was performed on a Heraeus CHN-O-Rapid analyser. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates. The powder X-ray diffraction patterns were measured with D_8, Avance, Bruker, axis, diffractometer using CuKα irradiation.

Magnesium 2,2,2-trifluoroacetate [$Mg(OOCCF_3)_2$]; typical procedure

A 50 mL suction flask was equipped with a dropping funnel. The gas outlet was connected to a vacuum system through an alkaline solution trap. Anhydrous $MgCl_2$ (10 mmol) was charged into the flask and trifluoroacetic acid (20 mmol) was added dropwise over a period of 30 min at room temperature. HCl evolved immediately. After completion of the addition, the mixture was shaken for 30 min at

Table 3 Preparation of 1-carbamatoalkyl-2-naphthol derivatives using $Mg(OOCCF_3)_2$ as catalyst (0.1 mmol, 100 °C)

Entry	Aldehyde	Carbamate	Time/min	Yield/%[a]	M.p. [lit. m.p./°C][ref]
1			21	85	210–212 [213][7]
2			20	87	201–203 [206][7]
3			25	83	[181–183 [182–184][7]
4			30	90	189–191 [192][9]
5			10	92	206–208 [205–207][9]
6			15	89	249–251 [252][9]
7			35	88	188
8			40	83	228–230 [230–232][8]
9			20	90	203–205 [202–204][7]
10			20	82	237–239 [241–242][9]
11			20	81	180–182 [179–180][9]
12			10	87	202
13			5	88	200–202 [205–207][8]
14			20	84	188–190 [185–186][9]
15			30	79	165–167 [163–165][9]
16			250	–	–

[a] Isolated yield.

Table 4 Comparison results of $Mg(OOCCF_3)_2$ with other catalysts reported in the literature

Entry	Catalyst	Condition	Time/min	Yield/%[a]
1	PPA-SiO_2	Solvent-free; 100 °C	6	90
2	SiO_2–$NaHSO_4$	Solvent-free; 100 °C	3.5	81
3	$HClO_4$-SiO_2	Solvent-free; 85 °C	5	90
4	4-(1-imidazolium) butane sulfonate	Solvent-free; 80 °C	120	78
5	*p*-TSA/[bmim]Br	Solvent-free; 60 °C	55	76
6	Brønsted acidic ionic liquid	Solvent-free; 90 °C	2	87
7	$Mg(OOCCF_3)_2$	Solvent-free; 100 °C	21	85

[a] Isolated yield; based on the preparation of methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate.

100 °C, while the residual HCl was eliminated by suction. Finally, a white solid $Mg(OOCCF_3)_2$ was obtained in 95% yield.

To a mixture of benzaldehyde (1 mmol), 2-naphthol (1 mmol) and methyl carbamate (1.3 mmol) was added $Mg(OOCCF_3)_2$ (0.025 g; 0.1 mmol) and the mixture was heated at 100 °C in an oil bath for the appropriate time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the mass was cooled to 25 °C and the mixture was dissolved in pure acetone. The catalyst was removed by simple filtration. The solvent was evaporated and the solid product was purified by recrystallisation from ethanol.

Methyl (2-hydroxynaphthalen-1-yl)(p-tolyl)methylcarbamate (Table 2, entry 7): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 6.83 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 2H), 7.11–7.27 (m, 4H), 7.37 (t, *J* = 6.8 Hz, 1H), 7.63 (brs, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 6.0 Hz, 1H, NH), 10.12 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 22.2, 51.8, 53.2, 120.1, 120.6, 124.1, 127.6, 127.8, 128.0, 130.0, 130.1, 130.2, 130.8, 133.6, 137.0, 140.9, 154.5, 158.1, ppm; IR (KBr, cm^{-1}): 3422, 3306, 3025, 2950, 1687, 1628, 1579, 1555, 1518, 1436, 1377, 1272, 1243, 1182, 1141, 1067, 1040, 940, 852, 816, 781, 748, 708. $C_{20}H_{19}NO_3$: Found: C, 74.81; H, 5.99; N, 4.39. requires: C, 74.75; H, 5.96; N, 4.36%.

Benzyl (2,4-dichlorophenyl)(2-hydroxynaphthalen-1-yl)methylcarbamate (Table 2, entry 12): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.02 (d, *J* = 12.8 Hz, 1H), 5.08 (d, *J* = 12.7 Hz, 1H), 6.87 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.28–7.60 (m, 10H), 7.74–7.80 (m, 2H), 8.02–8.11 (m, 2H), 9.98 (s, 1H, OH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): 51.1, 67.1, 117.8, 120.2, 124.0, 124.3, 128.1, 128.2, 129.1, 129.3, 129.9 (2C), 130.2, 130.3, 131.3, 132.9, 133.6, 134.2, 134.8, 138.7, 140.4, 155.2, 157.2 ppm; IR (KBr, cm^{-1}): 3415, 3342, 3065, 2935, 1686, 1628, 1586, 1513, 1432, 1372, 1340, 1305, 1270, 1243, 1212, 1139, 1069, 1054, 936, 879, 844, 819, 744; $C_{25}H_{19}Cl_2NO_3$: Found: C, 66.41; H, 4.25; N, 3.14; requires: C, 66.38; H, 4.23; N, 3.10%.

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