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Nanocrystalline TiO_2–$HClO_4$ catalyzed three-component preparation of derivatives of 1-amidoalkyl-2-naphthol, 1-carbamato-alkyl-2-naphthol, 1-(α-aminoalkyl)-2-naphthol, and 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one

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Abstract 1-Amidoalkyl-2-naphthols, 1-carbamatoalkyl-2-naphthols, and 1-(α-aminoalkyl)-2-naphthols have been prepared by three-component reaction of 2-naphthol, aromatic aldehydes, and NH compounds, i.e. amides, carbamates, and secondary amines, respectively, in the presence of a catalytic amount of nanocrystalline TiO_2–$HClO_4$. In addition, 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives have been synthesized by reaction of 2-naphthol, aromatic aldehydes, and dimedone in the presence of the same nano catalyst. These reactions were studied under solvent-free conditions. This white acidic heterogeneous catalyst is very stable under the reaction conditions and was reused several times without significant loss of activity.

Keywords Nanocrystalline · TiO_2–$HClO_4$ · Reusable catalyst · Three-component reactions

Introduction

Nano particles of TiO_2 can catalyze reactions because of their low Lewis-acidic properties [1–3]. Recently, perchloric acid-coated TiO_2 nanoparticles have been prepared [4]. This catalyst (nanoTiO_2–$HClO_4$) has been used for trimethylsilylation of hydroxyl groups and cleavage of trimethylsilyl ethers [4]. The catalyst is easily prepared from a suspension of $HClO_4$ and nano TiO_2 (particle size 30–40 nm and BET specific area 34 $m^2\ g^{-1}$) [4]. Transmission electron microscopic analysis of

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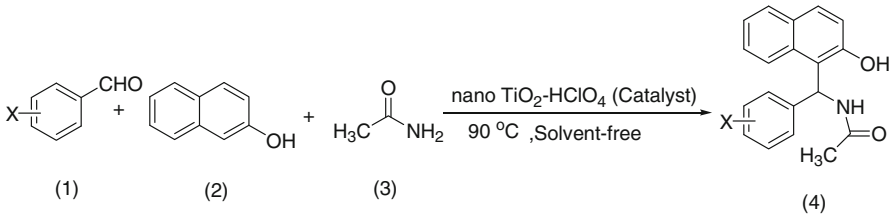


Scheme 1 Synthesis of 1-amidoalkyl-2-naphthols

TiO_2–$HClO_4$ showed that the nano catalyst aggregated after modification with $HClO_4$, with TiO_2 particle size increasing to 150 nm.

Multi-component reactions have proved a valuable asset in organic and medicinal chemistry; such procedures can be used for drug design and drug discovery, because of their simplicity, efficiency, and high selectivity [5, 6]. Synthesis of bioactive and complex molecules by this methodology is facile, rapid, and efficient, with minimum workup [5–7].

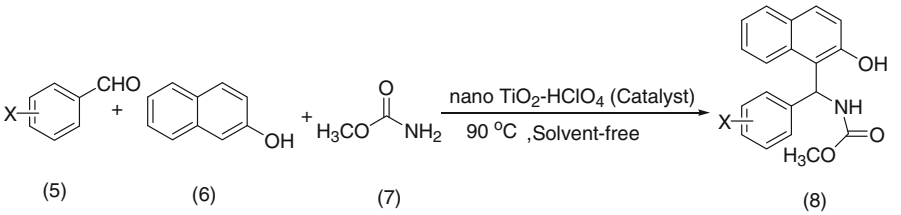
Compounds containing 1,3-amino oxygenated functional groups for example 1-amidoalkyl-2-naphthols, 1-carbamatoalkyl-2-naphthols, and 1-(α-aminoalkyl)-2-naphthols are frequently found in biologically active natural products and potent drugs, for example nucleoside antibiotics and HIV protease inhibitors [8–11]. 12-Aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives have attracted much interest because of their varied biological activity for example anti-inflammatory [12], antiviral [13], and antibacterial [14].

In continuation of our research on new synthetic methods in organic synthesis using heterogeneous catalysts [15, 16], we developed the synthesis of 1-amidoalkyl-2-naphthols (Scheme 1), 1-carbamato-alkyl-2-naphthols (Scheme 2), and 1-(α-aminoalkyl)-2-naphthols (Scheme 3) under solvent-free conditions in the presence of catalytic amounts of nanocrystalline titania coated with perchloric acid (NanoTiO_2–$HClO_4$). In addition, preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives under thermal, solvent-free conditions in the presence of the same catalyst is reported (Scheme 4).

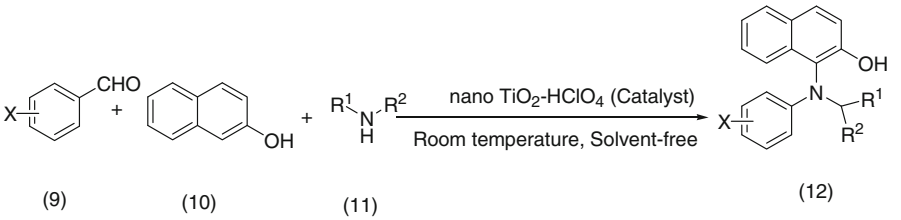
Experimental

Chemicals and materials

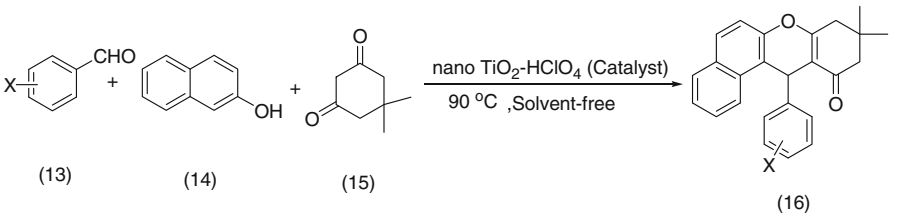
All reagents were purchased from Merck and Aldrich and were used without further purification. All yields refer to isolated products after purification. NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. Spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Jasco FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a Buchi 510 melting-point apparatus. TLC was performed on silica-gel Poly Gram SIL G/UV 254 plates.



Scheme 2 Synthesis of 1-carbamato-alkyl-2-naphthols



Scheme 3 Synthesis of 1-(α-aminoalkyl)-2-naphthols



Scheme 4 Synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-ones

Preparation of titania-supported perchloric acid (TiO_2–$HClO_4$) [4]

A suspension of nano TiO_2 (2 g) in Et_2O (30 mL) was prepared. $HClO_4$ (0.14 g, 1 mmol, as a 70 % aq. solution) was then added dropwise to the stirred suspension at room temperature. The mixture was stirred for 24 h. The mixture was concentrated and the residue was heated at 100 °C for 2 h under vacuum to furnish TiO_2–$HClO_4$ (0.013 mmol g^{-1}) as a white powder.

General procedure for preparation of 1-amidoalkyl-2-naphthols

Nano TiO_2–$HClO_4$ (5 mg) was added to a mixture of 2-naphthol (1 mmol), aldehyde (1 mmol), and acetamide (1.2 mmol). The mixture was stirred at 90 °C in an oil bath and the reaction was followed by TLC. After completion of the reaction, it was cooled to room temperature. The mixture was then diluted with dichloromethane and the catalyst was separated by centrifugation and washed with CH_2Cl_2 (2 × 5 mL) to check the reusability. The decanted solution containing the product

was evaporated to give the crude solid product which was recrystallized from aqueous EtOH (15 %).

Spectral details for two known products are given below.

N-[Phenyl-(2-hydroxynaphthalen-1-yl)methyl]acetamide (**4a**): mp 242–243 °C; IR (KBr, cm^{-1}): 3398, 3251, 3063, 1645, 1588, 1520, 1377, 1339, 1061, 818, 745, 699, 618; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 1.99$ (s, 3H), 7.20–1.11 (m, 4H), 7.26–7.23 (m, 4H), 7.34 (t, $J = 7.4$ Hz, 1H), 7.77 (d, $J = 9.1$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 7.85 (s, 1H), 8.47 (d, $J = 8.6$ Hz, 1H), 10.03 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.1, 40.6, 119.4, 119.5, 122.8, 123.7, 126.6, 126.6, 128.4, 128.7, 128.9, 129.4, 129.5, 132.2, 143.2, 153.7, 169.2 ppm.

N-[(3-Nitrophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide (**4i**): mp 237–239 °C; IR (KBr, cm^{-1}): 3377, 3090, 2595, 1644, 1530, 1351, 1233, 1152, 1063, 818, 707; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 2.02$ (s, 3H), 7.15 (t, $J = 8.1$ Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 1H), 7.24 (t, $J = 7.3$ Hz, 1H), 7.35 (t, $J = 7.3$ Hz, 1H), 7.52 (m, 2H), 7.74 (t, $J = 8.5$ Hz, 2H), 7.84 (br, 1H), 7.96–7.99 (m, 2H), 8.57 (d, $J = 8.1$ Hz, 1H), 10.15 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): 23.2, 48.3, 118.4, 118.8, 120.8, 121.7, 123.2, 127.2, 123.3, 128.8, 129.1, 130.2, 130.4, 132.6, 133.5, 145.8, 148.1, 153.8, 170.4 ppm.

General procedure for preparation of 1-carbamatoalkyl-2-naphthol derivatives

Nano TiO_2–$HClO_4$ (5 mg) was added to a mixture of 2-naphthol (1 mmol), aldehyde (1 mmol), and methyl carbamate (1.2 mmol). The mixture was stirred at 90 °C in an oil bath and the reaction was followed by TLC. After completion of the reaction, it was cooled to room temperature. The mixture was then diluted with dichloromethane and the catalyst was separated by centrifugation and washed with CH_2Cl_2 (2 × 5 mL) to check the reusability. The decanted solution containing the product was evaporated to give the crude solid product which was purified by recrystallization from aqueous EtOH (20 %).

Spectral details for two known products are given below.

Methyl (2-hydroxynaphthalen-1-yl)(phenyl)methyl carbamate (**8a**): mp 220–221 °C; IR (KBr, cm^{-1}): 3424, 3204, 1680, 1635, 1590, 1522, 1440, 1340, 1275, 1065, 1042, 938, 811, 743, 697; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.58$ (s, 3H), 6.88 (d, $J = 8.5$ Hz, 1H), 7.19–7.29 (m, 7H), 7.37 (d, $J = 7.3$ Hz, 1H), 7.67–7.85 (m, 3H), 7.90 (d, $J = 7.6$ Hz, 1H), 10.13 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): d 50.6, 52.2, 118.7, 119.5, 123.1, 123.6, 126.6, 126.9, 127.1, 128.7, 128.9, 129.1, 129.9, 132.5, 142.7, 153.4, 157.2 ppm.

Methyl (2-hydroxynaphthalen-1-yl)(4-nitrophenyl)methyl carbamate (**8e**): mp 209–211 °C; IR (KBr, cm^{-1}): 3425, 3267, 1687, 1627, 1605, 1514, 1433, 1342, 1271, 1249, 1069, 1047, 852, 824, 785, 741, 704; ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 3.62$ (s, 3H), 6.97 (d, $J = 8.2$ Hz, 1H), 7.20 (d, $J = 8.7$ Hz, 1H), 7.27 (t, $J = 7.1$ Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.48 (d, $J = 8.6$ Hz, 2H), 7.78–7.88 (m, 4H), 8.15 (d, $J = 8.5$ Hz, 2H), 10.21 (s, 1H, OH) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 50.7$, 52.4, 118.5, 118.9, 123.2, 123.3, 123.9, 127.4, 127.7, 128.7, 129.2, 130.5, 132.5, 146.6, 151.4, 153.5, 157.1 ppm.

General procedure for preparation of 1-(α-aminoalkyl)-2-naphthol derivatives

A mixture of 2-naphthol (1.0 mmol), amine (1.0 mmol), and aldehyde (1.2 mmol) was stirred at room temperature in the presence of nano TiO_2–$HClO_4$ (5 mg) as catalyst for an appropriate time. After completion of the reaction (indicated by TLC), the reaction mixture was dissolved in hot ethanol, the catalyst was recovered by filtration, and the product was recrystallized from ethanol.

Spectral details for two known products are given below.

1-((3-Bromophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol (**12b**): mp 185–186 °C; white solid; IR (KBr, cm^{-1}): 3128, 3052, 2964, 2851, 1660, 1455, 1236, 755; 1H NMR (300 MHz, DMSO-d_6) $\delta = 1.68$ (br, s, 6H, $-CH_2$), 2.78 (br, s, 4H, $-NCH_2$), 5.04(s, 1H, CH), 7.08–7.17 (m, 2H, ArH), 7.19-7.25 (m, 1H, ArH), 7.32–7.41(m, 2H, ArH), 7.48–7.51 (d, $J = 5.55$ Hz, 1H, ArH) 7.65 (t, $J = 9.94$ Hz, 3H, ArH), 7.77 (d, $J = 8.57$ Hz, 1H, ArH), 13.72 (s, 1H, OH). 13C NMR (75 MHz, DMSO-d_6) $\delta = 24.02$, 25.93, 71.45, 115.39, 120.01, 120.72, 122.41, 126.47, 127.64, 128.59, 128.90, 129.61, 130.37, 131.02, 132.15, 142.00, 155.

1-((4-Chlorophenyl)(dimethylamino)methyl)naphthalen-2-ol (**12g**): mp 130–132 °C; white solid; IR (KBr, cm^{-1}): 3129, 3061, 2976, 2848, 1629, 1462, 1240, 758; 1H NMR (300 MHz, DMSO-d_6) $\delta = 2.34$ (s, 6H, $-NCH_3$), 4.95 (s, 1H, CH), 7.08–7.45 (m, 4H, ArH), 7.50–7.53 (m, 3H, ArH), 7.65–7.83 (m, 3H, ArH), 9.98 (s, 1H, ArH). 13C NMR (75 MHz, DMSO-d_6) $\delta = 41.54$, 72.76, 116.32, 119.85, 121.14, 122.38, 126.42, 127.70, 128.48, 128.67, 128.83, 128.89, 129.75, 131.21, 142.37, 155.20.

General procedure for preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-ones

A mixture of 2-naphthol (1 mmol), dimedone (1 mmol), aldehyde (1 mmol), and nano TiO_2–$HClO_4$ (5 mg) was stirred in an oil-bath (90 °C). After completion of the reaction, the mixture was cooled to room temperature. The mixture was then diluted with dichloromethane, and the catalyst was separated by centrifugation and washed with CH_2Cl_2 (2×5 mL) to checking the reusability. The decanted solution containing the product was evaporated to give the crude solid product which was purified by recrystallization from aqueous ethanol (90 %).

Spectral details for two known products are given below.

9,9-Dimethyl-12-(2-bromophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**16f**): mp 171–172 °C; IR (KBr, cm^{-1}): 2955, 1652, 1596, 1373, 1228, 1185. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 0.97$ (s, 3H), 1.11 (s, 3H), 2.25 (d, $J = 16.3$ Hz, 1H), 2.33 (d, $J = 16.2$ Hz, 1H), 2.58 (s, 2H), 5.68 (s, 1H), 7.21–7.24 (m, 2H), 7.27–7.35 (m,3H), 7.39–7.46 (m, 2H), 7.76–7.81 (m, 2H), 7.88 (d, $J = 8.2$ Hz, 1H), ^{13}C NMR (75 MHz, DMSO-d_6): $d = 27.1$, 29.2, 32.2, 34.1, 41.2, 50.7, 113.8, 116.9, 117.0, 120.1, 123.4, 125.1, 127.1, 128.6, 129.2, 130.2, 131.3, 131.2, 131.6, 143.8, 147.5, 164.1, 196.9.

9,9-Dimethyl-12-*m*-tolyl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one (**16j**): mp 179–181 °C; IR (KBr, cm^{-1}): 2955, 1648, 1598, 1373, 1229, 1186. ^{1}H NMR (300 MHz, DMSO-d_6) $\delta = 0.98$ (s, 3H), 1.11 (s, 3H), 2.18 (s, 3H), 2.24 (d,

Table 1 Optimization of conditions for preparation of *N*-[(4-chlorophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide from 4-chlorobenzaldehyde, 2-naphthol, and acetamide in the presence of different amounts of nano TiO_2–$HClO_4$ as catalyst and at different temperatures under solvent-free conditions

Entry	Catalyst (mg)	Temperature (°C)	Time (min)	Yield (%)[a]
1	15	25	60	Trace
2	10	60	50	35
3	7	60	45	50
4	2	90	13	83
5	5	90	10	94
6	8	90	10	95

[a] Yields are for isolated pure product

$J = 16.2$ Hz, 1H), 2.31 (d, $J = 16.2$ Hz, 1H), 2.55 (s, 2H), 5.67 (s, 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 7.22–7.30 (m, 2H), 7.32–7.38 (m, 2H), 7.42–7.46 (m, 1H), 7.34–7.78 (m, 2H), 8.1 (d, $J = 8.5$ Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): $d = 20.9$, 27.2, 29.2, 32.2, 34.2, 41.4, 50.9, 114.5, 117.0, 117.9, 123.6, 124.8, 126.7, 128.2, 128.3, 128.6, 128.9, 131.4, 131.5, 135.6, 141.8, 147.8, 163.8, 196.8,

Results and discussion

To study the effect of catalyst loading and temperature, the three component condensation reaction used for synthesis of *N*-[(4-chlorophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide from 4-chlorobenzaldehyde, 2-naphthol, and acetamide, in the presence of nano TiO_2–$HClO_4$ as catalyst, was selected as model reaction under solvent-free conditions (Table 1). The reaction was performed with different amounts of nano TiO_2–$HClO_4$ as catalyst (2, 5, 7, 8, 10, 15 mg) and at different temperatures (25, 60, 90 °C). As is apparent from Table 1, 5 mg nano TiO_2–$HClO_4$ as a catalyst at 90 °C afforded the product in 10 min with 94 % yield.

Next, the three-component condensation reaction of aromatic aldehydes, 2-naphthol, and acetamide under the optimized conditions was investigated for preparation of 1-amidoalkyl-2-naphthol derivatives. A wide range of substituted and structurally diverse aldehydes, with nano TiO_2–$HClO_4$ as catalyst, enabled synthesis of the corresponding products in high to excellent yields (Table 2).

Recycling of the nano TiO_2–$HClO_4$ was studied using reaction of 4-chlorobenzaldehyde, 2-naphthol, and acetamide as model reaction (Experimental section). The recovered catalyst was reused six times without significant loss of its activity (Fig. 1).

To show the merit of this work in comparison with results reported in the literature, we compared the result obtained by use of nano TiO_2–$HClO_4$ with those obtained by use of reported catalysts used for synthesis of *N*-[(4-chlorophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide. As shown in Table 3, nano TiO_2–$HClO_4$ acts as a suitable catalyst with regard to reaction times and product yield (Table 3).

Table 2 Three-component synthesis of 1-amidoalkyl-2-naphthol derivatives by reaction of aldehydes, 2-naphthol, and acetamide in the presence of nano TiO_2–$HClO_4$ (5 mg) as catalyst

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting point m.p (°C)/L m.p (°C) [Ref.]
1	PhCHO	**4a**	9	91	242–243/(241–243) [17]
2	4-ClC_6H_4CHO	**4b**	10	94	223–225/(224–227) [17]
3	4-FC_6H_4CHO	**4c**	11	93	204–207/(203–205) [18]
4	2-ClC_6H_4CHO	**4d**	10	89	196–198/(194–196) [18]
5	3-$MeOC_6H_4CHO$	**4e**	12	92	204–206/(203–205) [19]
6	2-MeC_6H_4CHO	**4f**	11	90	201–202/(200–202) [20]
7	4-$NO_2C_6H_4CHO$	**4g**	10	89	249–251/(248–250) [21]
8	3,4-di$MeOC_6H_3CHO$	**4h**	12	91	234–236/(235–236) [19]
9	3-$NO_2C_6H_4CHO$	**4i**	11	89	237–239/(236–237) [18]
10	4-MeC_6H_4CHO	**4j**	10	90	228–229/(220–230) [21]
11	4-BrC_6H_4CHO	**4k**	11	91	227–228/(228–230) [19]

[a] Yields are for isolated pure products

Known pure products were characterized by comparison of their physical data (melting points, IR, ^1H and ^{13}C NMR) with those of the known compounds

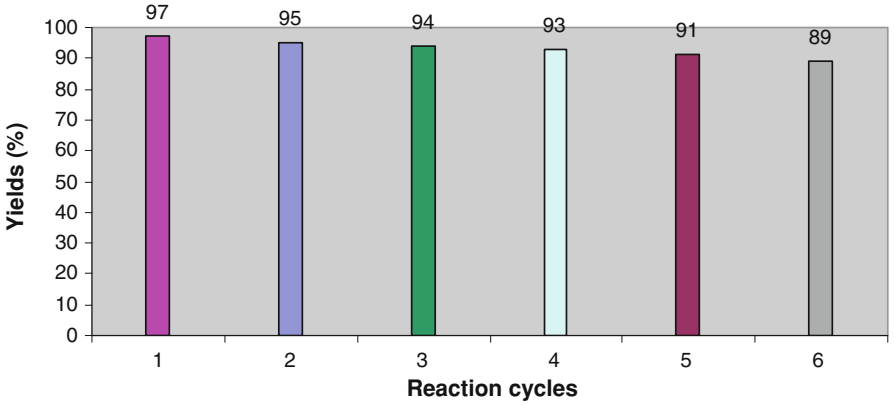


Fig. 1 Recycling of nano TiO_2–$HClO_4$ as catalyst in the preparation of *N*-[(4-chlorophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide

We also used nano TiO_2–$HClO_4$ in the condensation reaction of 2-naphthol, aldehyde, and methyl carbamate under solvent-free conditions for preparation of 1-carbamato-alkyl-2-naphthol derivatives (Scheme 2). Reaction of 4-chlorobenzaldehyde, 2-naphthol, and methyl carbamate was selected as model. The reaction was performed in the presence of different amounts of catalyst, nano TiO_2–$HClO_4$ (2, 5, 7, 8, 10, 15 mg), and at different temperatures (25, 60, 90 °C) under solvent-free conditions. The best results were obtained with 5 mg nano TiO_2–$HClO_4$ at 90 °C. The three-component condensation reaction of aromatic aldehydes, 2-naphthol, and methyl carbamate under optimized conditions for preparation of 1-carbamato-alkyl-

Table 3 Comparison the results of nano TiO_2–$HClO_4$ with catalysts reported for synthesis of *N*-[(4-chlorophenyl)-(2-hydroxynaphthalen-1-yl)methyl]acetamide under solvent-free conditions

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a] [Ref.]
1	Ferric hydrogen sulfate (5 mol %)	Solvent-free, 85 °C	25	88 [19]
2	*N*-(4-Sulfonic acid) butyl triethyl ammonium hydrogen sulfate (5 mol %)	Solvent-free, 120 °C	10	85 [22]
3	$Bi(NO_3)_3.5H_2O$ (20 mol %)	Solvent-free, 80 °C	90	92 [23]
4	Nano-sulfated zirconia (0.2 g)	Solvent-free, 120 °C	35	92 [24]
5	[Bmim]Br (1 g)	Solvent-free, 130 °C	30	90 [25]
6	Nano TiO_2–$HClO_4$(5 mg)	Solvent-free, 90 °C	10	94 (this work)

[a] Yields are for isolated pure products and are based on reaction of 4-chlorobenzaldehyde, 2-naphthol, and acetamide

Table 4 Three-component synthesis of 1-carbamato-alkyl-2-naphthol derivatives by reaction of aldehydes, 2-naphthol, and methyl carbamate in the presence of nano TiO_2–$HClO_4$ (5 mg) as catalyst under solvent-free conditions at 90 °C

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting point m.p (°C)/L m.p (°C) [Ref.]
1	PhCHO	**8a**	3	90	220–221/(217–218) [26]
2	4-ClC_6H_4CHO	**8b**	3	94	202–203/(198–200) [26]
3	3-ClC_6H_4CHO	**8c**	4	89	199–201/(196–198) [26]
4	2,4-diClC_6H_4CHO	**8d**	3	91	195 dec/(192 dec) [26]
5	4-$NO_2C_6H_4CHO$	**8e**	5	90	209–211/(205–207) [26]
6	2,5-di$MeOC_6H_3CHO$	**8f**	3	92	223 dec/(215 dec) [26]
7	3-$NO_2C_6H_4CHO$	**8g**	4	90	251 dec/(252 dec) [26]
8	Propanal	**8h**	50	–	–
9	*n*-Heptanal	**8i**	50	–	–

[a] Yields are for isolated pure products

Known pure products were characterized by comparison of their physical data (melting points, IR, ^1H and ^{13}C NMR) with those of the known compounds

2-naphthol derivatives was then investigated (Table 4). A wide range of substituted and structurally diverse aldehydes were used and the corresponding products were synthesized in high to excellent yields, which demonstrated that this method tolerates both electron-withdrawing and electron-donating constituents (Table 4). We then examined aliphatic aldehydes, for example propanal and *n*-heptanal, instead of benzaldehyde in the reaction. Then, all the starting materials in the reaction remained intact without formation of any side products (for example the aldol condensation product) after 50 min (Table 4, Entries 8, 9).

Recycling of the nano TiO_2–$HClO_4$ was studied for this reaction also. The recovered catalyst was reused in six runs without significant loss of its activity (Fig. 2).

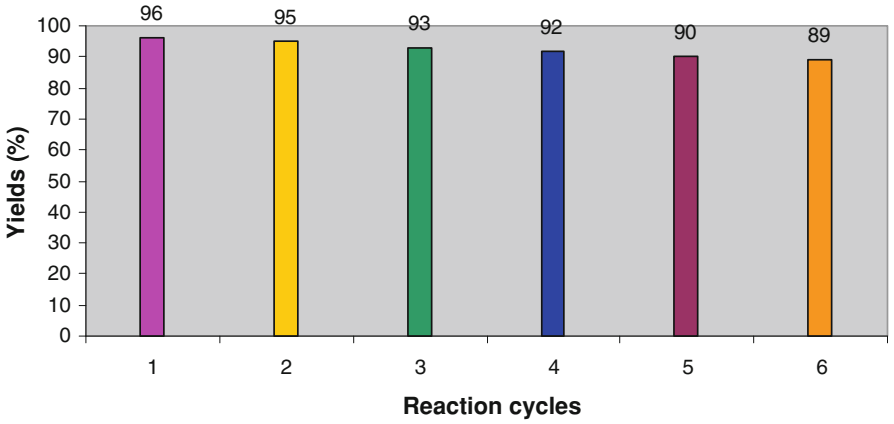


Fig. 2 Recycling of nano TiO_2–$HClO_4$ as catalyst in the preparation of methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl carbamate

To show the applicability of this work in comparison with results reported in the literature, for example for use of silica-supported sodium hydrogen sulfate (0.05 g) at 100 °C [26] and 4-(1-imidazolium)butane sulfonate (10 mol %) at 80 °C [27], we summarized some of the results for preparation of methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl carbamate in Table 5. The results show that nano TiO_2–$HClO_4$ (5 mg under ambient and solvent-free conditions) is the most efficient catalyst with regard to reaction time; the yields obtained are also indicative of its wide applicability.

In continuation of our research on new applications of the catalyst, preparation of 1-(α-aminoalkyl)-2-naphthol derivatives was studied (Scheme 3). To study the effect of catalyst loading and temperature on three-component condensation reactions for synthesis of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol the solvent-free reaction of 4-chlorobenzaldehyde, 2-naphthol, and piperidine in the presence of nano TiO_2–$HClO_4$ as catalyst was selected as model reaction (Table 6). The reaction was performed with different amounts of nano TiO_2–$HClO_4$ as catalyst (2, 5, 7 mg) under ambient conditions (Table 6). We found that 5 mg nano TiO_2–$HClO_4$ was the most effective in catalyzing preparation of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol.

Next, three-component condensation of aromatic aldehydes, 2-naphthol, and amines, under the optimized conditions, for preparation of 1-(α-aminoalkyl)-2-naphthol derivatives was investigated. A wide range of substituted and structurally diverse aldehydes and amines, with nano TiO_2–$HClO_4$ as catalyst, were used to synthesize the corresponding products in high to excellent yields (Table 7).

Recycling of the nano TiO_2–$HClO_4$ was studied by using reaction of 4-chlorobenzaldehyde, 2-naphthol, and piperidin as model reaction (Experimental section). The recovered catalyst was reused in six runs without any significant of its activity (Fig. 3).

To show the merit of this work in comparison with results reported in the literature, we compared results obtained by use of nano TiO_2–$HClO_4$ with results

Table 5 Comparison of results obtained by use of nano TiO_2–$HClO_4$ with results reported for other catalysts used for synthesis of methyl (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl carbamate under solvent-free conditions

Entry	Catalyst (mg)	Conditions	Time (min)	Yield (%)[a] [Ref.]
1	Silica-supported sodium hydrogen sulfate (50 mg)	Solvent-free, 100 °C	6	92 [26]
2	4-(1-Imidazolium)butane sulfonate (10 mol %)	Solvent-free, 80 °C	120	82 [27]
3	Nano TiO_2–$HClO_4$ (5 mg)	Solvent-free, 90 °C	3	94 (this work)

[a] Yields are for isolated pure products and are based on the reaction of 4-chlorobenzaldehyde, 2-naphthol, methyl carbamate

Table 6 Optimization of conditions for preparation of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol from 4-chlorobenzaldehyde, 2-naphthol, and piperidine in the presence of different amounts of nano TiO_2–$HClO_4$ as a catalyst under ambient conditions

Entry	Catalyst (mg)	Time (min)	Yield (%)[a]
1	2	42	81
2	5	25	93
3	7	25	94

[a] Yields are for isolated pure products

reported for other catalysts in the synthesis of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol. As shown in Table 8, nano TiO_2–$HClO_4$ is a suitable catalyst with regard to reaction times and yields of the products.

In addition, we used nano TiO_2–$HClO_4$ in condensation reaction of 2-naphthol, aldehyde, and dimedone under solvent-free conditions for preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives (Scheme 4). For optimization, reaction of 4-chlorobenzaldehyde, 2-naphthol, and dimedone was selected as model. The reaction was conducted in the presence of different amounts of catalyst, nano TiO_2–$HClO_4$ (2, 5, 7, 8, 10, 15 mg) and at different temperatures (25, 60, 90 °C) under solvent-free conditions. The best results were obtained with 5 mg catalyst nano TiO_2–$HClO_4$ at 90 °C. The three-component condensation reaction of aromatic aldehydes, 2-naphthol, and dimedone under the optimized conditions was then investigated for preparation of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives. A wide range of substituted and structurally diverse aldehydes were used and the corresponding products were synthesized in high to excellent yields, which demonstrated this method tolerates both electron-withdrawing and electron-donating constituents (Table 9).

Recycling of the nano TiO_2–$HClO_4$ was studied using reaction of 4-chlorobenzaldehyde, 2-naphthol, and dimedone as model reaction (Experimental section). The recovered catalyst was reused in several runs without significant loss of its activity (Fig. 4).

Table 7 Three-component synthesis of 1-(α-aminoalkyl)-2-naphthol derivatives by reaction of aldehydes, 2-naphthol, and amines in the presence of nano TiO_2–$HClO_4$ (5 mg) as catalyst

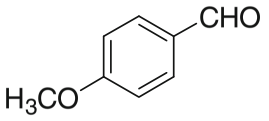
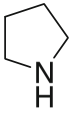
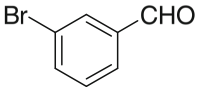
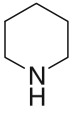
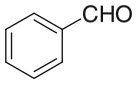
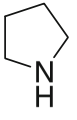
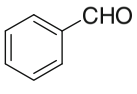
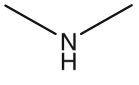
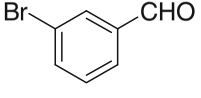
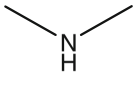
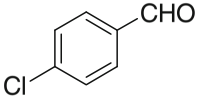
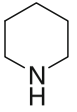
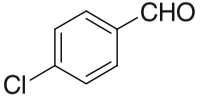
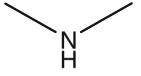
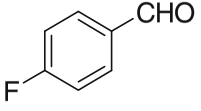
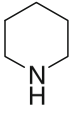
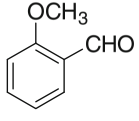
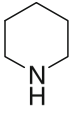
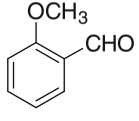
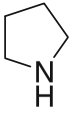
Entry	Aldehyde	Amine	Product	Time (min)	Yield (%)[a]	Melting point m.p (°C)/L. m.p (°C) [Ref.]
1			**12a**	22	92	98–100/(99) [28]
2			**12b**	24	91	185–186/(183) [28]
3			**12c**	25	91	180–181/(178–179) [28]
4			**12d**	30	90	171–172/(170) [28]
5			**12e**	27	92	88–89/(87) [28]

Table 7 continued

Entry	Aldehyde	Amine	Product	Time (min)	Yield (%)[a]	Melting point m.p (°C)/L. m.p (°C) [Ref.]
6			**12f**	26	93	140–141/(138–140) [28]
7			**12g**	27	92	130–132/(128–130) [28]
8			**12h**	24	90	152–153/(150) [28]
9			**12i**	26	91	182–184/(181) [28]
10			**12j**	25	90	161–163/(162) [28]

[a] Yields are for isolated pure products

Known pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H and ^{13}C NMR) with those of the known compounds

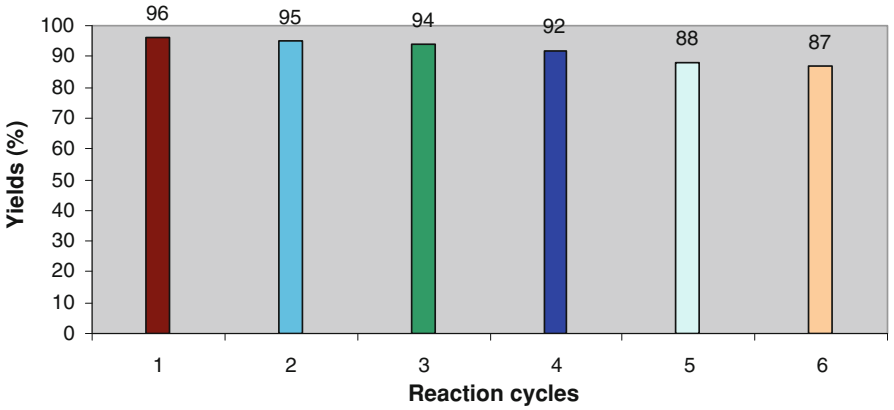


Fig. 3 Recycling of nano TiO_2–$HClO_4$ as catalyst in the preparation of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol

Table 8 Comparison of results obtained by use of nano TiO_2–$HClO_4$ with results reported for other catalysts used for synthesis of 1-((4-chlorophenyl)(piperidin-1-yl)methyl)naphthalen-2-ol under solvent-free conditions

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a] [Ref.]
1	Non-ionic surfactant	Water (2 mL)	120	86 [28]
	Triton X-100 (5 mol %)	Room temperature		
2	$LiClO_4$ (5 M)	Ether, room temperature	60	65 [29]
3	$Cu(OTf)_2{\cdot}SiO_2$ (10 mol %)	Solvent-free, 40 °C	60	95 [30]
4	Fe–Fe–PEG (0.5 mmol)	15 mL water	240	70 [31]
		Room temperature		
5	Nano TiO_2–$HClO_4$ (5 mg)	Solvent-free, room temperature	3	94 (this work)

[a] Yields are for isolated pure products and are based on reaction of 4-chlorobenzaldehyde, 2-naphthol, and piperidine

To show the merit of this work in comparison with results reported in the literature, we compared results for nano TiO_2–$HClO_4$ with results reported for other catalysts used in the synthesis of 9,9-dimethyl-12-(4-chlorophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one. As shown in Table 10, nano TiO_2–$HClO_4$ can act as a suitable catalyst with regard to reaction times and yields of the products.

Conclusion

New applications of nanocrystalline TiO_2–$HClO_4$ as an efficient catalyst for three component preparation of 1-amidoalkyl-2-naphthols, 1-carbamato-alkyl-2-naphthols, 1-(α-aminoalkyl)-2-naphthols, and 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-

Table 9 Three-component synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives by reaction of aldehydes, 2-naphthol, and dimedone in the presence of nano TiO_2–$HClO_4$ (5 mg) as a catalyst at 90 °C

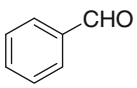
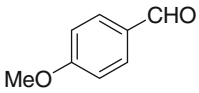
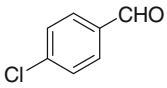
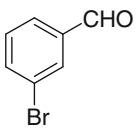
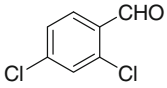
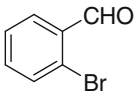
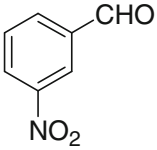
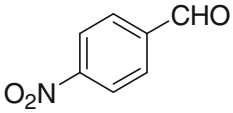
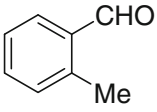
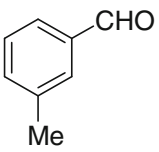
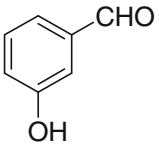
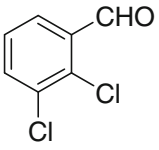
Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting Point m.p (°C)/Lit. m.p (°C) [Ref.]
1		**16a**	22	92	151–152/(151–153) [32]
2		**16b**	20	92	203–204/(204–205) [32]
3		**16c**	18	93	180–181/(180–182) [32]
4		**16d**	25	90	162–163/(161–164) [33]
5		**16e**	23	93	181–182/(181–182) [34]
6		**16f**	27	89	171–172/(170–172) [33]
7		**16g**	23	88	170–171/(168–170) [32]
8		**16h**	25	90	177–178/(178–180) [32]
9		**16i**	28	91	161–163/(160–163) [33]

Table 9 continued

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Melting Point m.p (°C)/Lit. m.p (°C) [Ref.]
10		**16j**	29	87	179–181/(178–180) [33]
11		**16k**	29	92	239–240/(240–241) [32]
12		**16l**	31	90	225–227/(223–225) [33]

[a] Yields are for isolated pure products

Known pure products were characterized by comparison of their physical data (melting points, IR, ^1H and ^{13}C NMR) with those of the known compounds

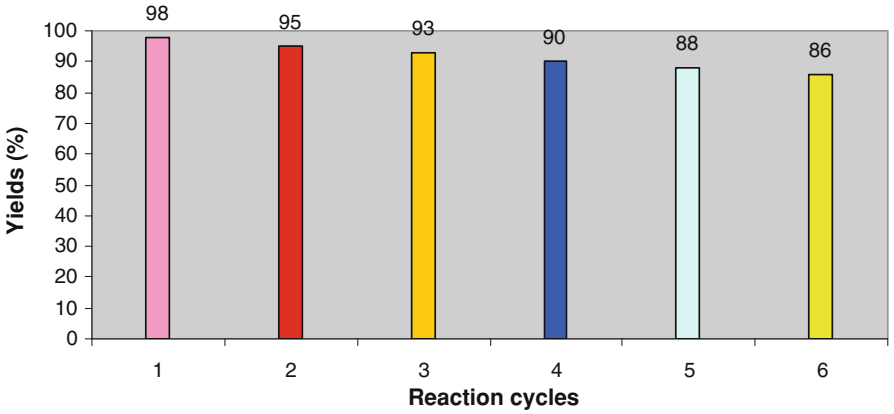


Fig. 4 Recycling of nano TiO_2–$HClO_4$ as catalyst in the preparation of 9,9-dimethyl-12-(4-chlorophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one

ones were described. The catalyst was reused several times without significant loss of its activity in the reactions. Simple reaction, easy work-up, and solvent-free conditions are advantages of these procedures.

Table 10 Comparison of results obtained by use of nano TiO_2–$HClO_4$ with results reported for other catalysts used for synthesis of 9,9-dimethyl-12-(4-chlorophenyl)-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one under thermal solvent-free conditions

Entry	Catalyst	Conditions	Time (min)	Yield (%)[a] [Ref.]
1	*p*-TSA (10 mol %)	[bmim]BF_4 (5 mL) Room temperature	120	85 [35]
2	*p*-TSA (2 mol %)	Solvent-free, 120 °C	35	86 [35]
3	Trityl chloride (7 mol %)	Solvent-free, 110 °C	45	90 [33]
4	Nano TiO_2–$HClO_4$ (5 mg)	Solvent-free, 90 °C	18	93 (this work)

[a] Yields are for isolated pure products and are based on the reaction of 4-chlorobenzaldehyde, 2-naphthol, and dimedone

Acknowledgments We are grateful to the University of Sistan and Baluchestan Research Council for partial support of this research.

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