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ORIGINAL PAPER

Preparation of amidoalkyl naphthols by a three-component reaction catalyzed by 2,4,6-trichloro-1,3,5-triazine under solvent-free conditions

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Abstract An efficient one-pot synthesis of amidoalkyl naphthols is described. This involves the three-component reaction of 2-naphthol, aromatic aldehydes and amide or urea in the presence of a catalytic amount of 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) under solvent-free conditions.

Keywords Multicomponent reaction · 2-Naphthol · Aldehydes · Amide · 2,4,6-Trichloro-1,3,5-triazine

Introduction

Multicomponent reactions (MCRs) have become an efficient and powerful tool for the construction of complex molecules because of the fact that the products are formed in a one-pot reaction without isolation of intermediates or modification the reaction conditions [1–3]. MCRs are particularly useful to generate diverse chemical libraries of "drug-like" molecules for biological screening.

Compounds bearing 1,3-arrangement of amino and oxygenated functional groups are frequently found in biologically important natural products [4]. Furthermore, amidoalkyl naphthols can be converted to useful synthetic building blocks [5] and 1-aminomethyl-2-naphthols, which exhibit depressor and bradycardiac activity [6]. The preparation of amidoalkyl naphthols can be carried out by multicomponent condensation of aldehydes, 2-naphthol and amide or urea in the presence of Lewis or Brønsted acid catalysts such as chlorosulfonic acid [7], *p*-toluene sulfonic acid [8], $NaHSO_4 \cdot H_2O$ [9], $Fe(HSO_4)_3$ [10], $Sr(OTf)_2$ [11], iodine [12], heteropoly acid $K_5CoW_{12}O_{40} \cdot 3H_2O$ [13] and heterogeneous catalysts like cation-exchange resins [14], silica supported perchloric acid [15, 16], $FeCl_3 \cdot SiO_2$ [17], montmorillonite K10 clay [18], silica sulfuric acid [19] and sulfamic acid [20, 21]. However, some of the reported methods suffer from disadvantages such as long reaction time [13], the use of expensive reagents [11], low yields of products [20], high catalyst loading [19], corrosive reagents [7], strongly acidic conditions [15, 16], and the use of an additional microwave oven [10] or ultrasonic irradiation [19]. Therefore, to avoid these limitations, the discovery of a new, easily available catalyst with high catalytic activity and short reaction time for the preparation of amidoalkyl naphthols is still desirable.

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT, cyanuric chloride) has been used in organic synthesis because it is stable, non-volatile, inexpensive, commercially available and an easy-to-handle reagent [22, 23]. TCT has been utilized for many important organic transformations, including the ring opening of epoxides with thiols [24], direct conversion of carboxylic acids to amides [25], chemoselective transthioacetalization of aldehyde acetals and oxathioacetals [26], conversion of nitronate into nitrile oxide [27], the synthesis of homoallylic alcohols and amines [28], thiiranes [29], dihydropyridine glycoconjugates [30], α-amino nitriles [31], allylic chloride [32], α,α′-bis(substituted-benzylidene) cycloalkanones [33], 14-aryl or alkyl-14-*H*-dibenzo[*a,j*]xanthenes [34] and 1,8-dioxo-octahydroxanthene derivatives [35]. It is therefore of interest to examine the behavior of TCT as catalyst in the synthesis of amidoalkyl naphthols. To the best of our knowledge, the generality and applicability of TCT in the preparation of amidoalkyl naphthols are not known. In continuation of our work on the development of new

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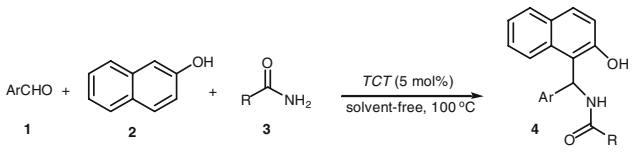


Scheme 1

synthetic methodologies [36–44], we herein describe a new, convenient synthesis of amidoalkyl naphthols by multicomponent reaction of 2-naphthol, aromatic aldehydes and amide or urea catalyzed by TCT under solvent-free conditions (Scheme 1).

Results and discussion

We first investigated the catalytic activities of various catalysts, which promoted the model reaction of 2-naphthol (1 mmol), 3-nitrobenzaldehyde (1 mmol) and acetamide (1.3 mmol) under solvent-free condition. In the course of this study, we found that TCT was the most effective catalyst producing amidoalkyl naphthol in higher yields than other catalysts, which furnished the product in lower yields (20–65%). In the absence of catalyst, the yield of the product was found to be very low. We also studied the model reaction catalyzed by TCT (5 mol%) at different temperatures. The reaction rate was increased as the reaction temperature was raised. When it was carried out at 100 °C, the maximum yield was obtained in a short reaction period (Table 1, entry 15). To evaluate the effect of catalyst concentration, the model reaction was carried out in the presence of different amounts of catalyst (1, 5, 10 and 20 mol%) at 100 °C. The results showed that 5 mol% of catalyst was sufficient to achieve a fairly high yield. With 1 mol% of TCT, a lower yield was observed under the same reaction period. This encouraged us to study the scope of the reaction under the optimized reaction parameters in the presence of 5 mol% of catalyst under solvent-free condition at 100 °C. The results of using TCT as a catalyst in the multicomponent reaction of 2-naphthol, aromatic aldehydes and amide or urea are summarized in Table 2.

A variety of aromatic aldehydes, 2-naphthol and different amides, including acetamide, benzamide and propenionamide, were submitted to these reaction conditions, and the desired products were obtained in good to excellent yields. This catalyst worked excellently with aromatic aldehydes bearing electron-donating substituents. It was shown that the aromatic aldehydes with electron-withdrawing groups reacted faster than the aromatic aldehydes with electron-donating groups, as would be expected. A reasonable explanation for this result has been suggested by Shaterian et al. [10]. The condensation of 2-naphthol with aldehydes under acid catalysts gave *ortho*-quinone methides (*o-QMs*). The generated *o-QM*s reacted with acetamide via the conjugated addition to afford 1-amidoalkyl-2-naphthols. Electron-withdrawing groups on the benzaldehydes in the *o-QM*s increase the rate of the 1,4-nucleophilic addition reaction because the alkene *LUMO* is at lower energy in the presence of electron-withdrawing groups compared with electron-donating groups. For *ortho*-substituted aromatic aldehydes such as 2-chlorobenzaldehyde, 2,4-dichlorobenzaldehyde and 2-nitrobenzaldehyde, a prolonged reaction time was required. Furthermore, this reaction was further explored for the synthesis of bis-amidoalkyl naphthol **6** by the four-compoponent reaction of

Table 1 Catalytic activity of various catalysts for the reaction of 2-naphthol, 3-nitrobenzaldehyde and acetamide

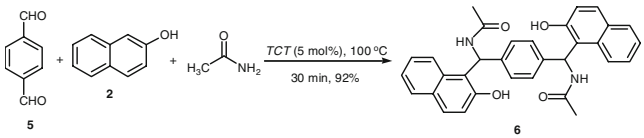
Entry	Catalyst	Temperature/°C	Time/min	Yield/%[a]
1	H_3BO_3 (10 mol%)	100	180	50
2	$H_2C_2O_4{\cdot}3H_2O$ (10 mol%)	100	60	25
3	*L*-Proline (10 mol%)	100	120	20
4	LaF_3 (10 mol%)	100	90	60
5	$NH_4Ce(NO_3)_2$ (10 mol%)	100	60	40
6	$C_{16}H_{35}$ N·H_2SO_4 (10 mol%)	100	60	30
7	$KAl(SO_4)_2{\cdot}12H_2O/SiO_2$ (10 mol%)	100	60	35
8	$(NH_4)_2PO_4{\cdot}12WO_3{\cdot}3H_2O$ (10 mol%)	100	120	65
9	*N*-Chlorosuccinimide	100	100	78
10	HBF_4/SiO_2 (10 mol%)	100	60	30
11	TCT (10 mol%)	100	40	95
12	TCT (5 mol%)	80	40	65
13	TCT (5 mol%)	120	40	92
14	TCT (1 mol%)	100	40	80
15	TCT (5 mol%)	100	40	95
16	TCT (20 mol%)	100	40	93

[a] Isolated yields

Table 2 TCT-promoted synthesis of amidoalkyl naphthol derivatives

Entry	Aldehydes	R	Time/min	Yield/%[a]	R_f[b]	Mp/°C	
						Found	Reported
a	PhCHO	Me	50	93	0.39	243–245	245–246 [9]
b	4-MeC_6H_4CHO	Me	50	93	0.30	220–222	222–223 [9]
c	4-$MeOC_6H_4CHO$	Me	50	90	0.29	185–186	183–185 [10]
d	4-FC_6H_4CHO	Me	40	93	0.35	232–233	230–232 [10]
e	2-ClC_6H_4CHO	Me	60	92	0.33	210–212	213–215 [10]
f	4-ClC_6H_4CHO	Me	40	95	0.32	228–229	228–229 [13]
g	2,4-$Cl_2C_6H_3CHO$	Me	50	94	0.42	202–204	201–203 [15]
h	3,4-$Cl_2C_6H_3CHO$	Me	40	93	0.43	241–243	
i	3-BrC_6H_4CHO	Me	40	95	0.40	250–252	
j	4-BrC_6H_4CHO	Me	40	93	0.37	228–230	227–229 [9]
k	2-$NO_2C_6H_4CHO$	Me	60	95	0.38	210–212	212–215 [9]
l	3-$NO_2C_6H_4CHO$	Me	40	95	0.32	240–242	241–242 [9]
m	4-$NO_2C_6H_4CHO$	Me	40	93	0.32	246–248	248–250 [15]
n	PhCHO	Ph	23	92	0.80	240–241	242–243 [15]
o	4-MeC_6H_4CHO	Ph	25	93	0.77	215–216	216–217 [11]
p	4-FC_6H_4CHO	Ph	20	92	0.79	194–196	193–194 [20]
q	4-ClC_6H_4CHO	Ph	20	94	0.78	187–189	187–188 [11]
r	3-$NO_2C_6H_4CHO$	Ph	20	95	0.77	240–242	241–242 [11]
s	PhCHO	CH_2=CH	23	92	0.78	253–255	255–256 [11]
t	4-$MeOC_6H_4CHO$	CH_2=CH	25	93	0.54	220–222	222–223 [11]
u	4-ClC_6H_4CHO	CH_2=CH	20	94	0.70	210–212	213–215 [14]
v	3-$NO_2C_6H_4CHO$	CH_2=CH	20	95	0.68	253–254	255–256 [11]
w	PhCHO	NH_2	55	94	0.13	175–176	174–175 [11]
x	4-MeC_6H_4CHO	NH_2	60	93	0.11	118–120	117–118 [11]
y	4-ClC_6H_4CHO	NH_2	50	95	0.14	169–170	168–169 [14]
z	3-$NO_2C_6H_4CHO$	NH_2	45	92	0.13	180–181	179–180 [11]

[a] Yields refer to isolated products, [b] R_f values were examined by TLC with a mixture of ethylacetate: *n*-hexane (1:1) as the solvent system



Scheme 2

terphthalaldehyd*e* (**5**), acetamide and two equivalents of 2-naphthol (**2**) under similar conditions (Scheme 2). Unfortunately, with aliphatic aldehydes, a mixture of products was obtained and the desired product could not be isolated, consistent with literature precedent [9, 10, 13, 14]. On reaction of heterocyclic aldehydes such as pyridine-4-carboxaldehyde, indole-3-carboxaldehyde and furfural with 2-naphthol and acetamide under the same conditions, only trace amounts of the corresponding products were isolated.

In order to show the merit of TCT in comparison with other reported catalysts, we summarized some of the results for the preparation of *N*-[(2-hydroxy-naphthalen-1-yl)-phenylmethyl]-acetamide (**3a**) in Table 3, which shows that TCT is an equally or more efficient catalyst with respect to reaction time and yield than previously reported ones.

In conclusion, we developed a new application for 2,4,6-trichloro-1,3,5-triazine. By using this catalyst, a series of amidoalkyl naphthols were obtained in high yields via three-component reaction of 2-naphthol, aromatic aldehydes and amide or urea under solvent-free conditions. Further applications of TCT in organic transformation are currently in progress in our laboratories.

Experimental

Melting points were determined on a X-4 apparatus. Analytical thin-layer chromatography was performed on glass plates of silica gel GF_{254} of 0.2 mm thickness. IR spectra were obtained using a Shimadzu FTIR-8900 spectrometer. ^{1}H NMR spectra were recorded with a Varian Mercury Plus 400 spectrometer using TMS as an internal standard. Elemental analyses were performed on a Vario EL III

Table 3 Comparison of TCT with reported catalysts in synthesis of *N*-[(2-hydroxy-naphthalen-1-yl)-phenylmethyl]-acetamide (**3a**)

Catalyst/solvent/temperature/°C	Catalyst load	Time/h	Yield/%	Ref.
$Fe(HSO_4)_3$/solvent-free/85	5 mol%	1.08	83	[10]
$K_5CoW_{12}O_{40}{\cdot}3H_2O$/solvent-free/125	1 mol%	2.00	90	[13]
Montmorillonite K-10/solvent-free/125	0.1 g/mol	1.50	89	[18]
$HClO_4{\cdot}SiO_2$/solvent-free/125	100 mg	6.50	82	[16]
$Sr(OTf)_2/CHCl_3$/60	10 mol%	10.00	90	[11]
I_2/solvent-free/125	5 mol%	5.50	85	[12]
p-TSA/solvent-free/125	10 mol%	6.00	89	[8]
$FeCl_3{\cdot}SiO_2$/solvent-free/120	25 mg/mol	0.18	86	[17]
TCT/solvent-free/100	5 mol%	0.83	93	This work

CHNOS Elemental Analyzer, and their results agreed favorably with the calculated values.

General procedure for the synthesis of amidoalkyl naphthols

A mixture of 1 mmol 2-naphthol, 1 mmol aromatic aldehyde and 1.3 mmol amide or urea and 0.05 mmol TCT was heated at 100 °C. After completion of the reaction (monitored by TLC), the mixture was diluted with 20 cm^3 ethyl acetate, washed with 20 cm^3 water, and the aqueous layer was then extracted with 2 × 10 cm^3 ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum to obtain a product in almost pure form. Further purification was carried out by short-column chromatography on silica gel eluting with ethyl acetate/*n*-hexane (1/4 v/v).

N-[(3,4-Dichloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, **4h**, $C_{19}H_{15}Cl_2NO_2$)
White solid, Mp 241–243 °C; $R_f = 0.44$ (ethylacetate:hexane = 1:1); IR (KBr): $\bar{\nu} = 3,386$, 3,143, 1,627, 1,577, 1,508, 1,473, 1,400, 1,384, 1,330, 1,276, 1,249, 1,091, 1,068, 821, 767, 669 cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.97$ (s, 3H), 6.99–7.01 (m, 2H), 7.19 (d, $J = 8.4$ Hz, 1H), 7.27 (t, $J = 7.2$ Hz, 1H), 7.35–7.41 (m, 2H), 7.48 (d, $J = 8.4$ Hz, 1H), 7.76–7.81 (m, 3H), 8.53 (d, $J = 7.6$ Hz, 1H), 10.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 23.5$, 47.7, 110.0, 118.4, 119.0, 123.4, 127.3, 128.5, 129.1, 129.3, 129.4, 130.5, 131.3, 132.8, 144.9, 149.3, 153.7, 153.9, 170.2 ppm.

N-[(3-Bromo-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (Table 2, **4i**, $C_{19}H_{16}BrNO_2$)
White solid, Mp 250–252 °C; $R_f = 0.41$ (ethylacetate:hexane = 1:1); IR (KBr): $\bar{\nu} = 3,406$, 3,168, 3,066, 1,647, 1,577, 1,515, 1,438, 1,400, 1,384, 1,336, 1,280, 1,207, 1,188, 987, 812, 756 m^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.97$ (s, 3H), 7.08 (d, $J = 7.2$ Hz, 1H), 7.19 (t, $J = 7.2$ Hz, 2H), 7.26 (t, $J = 7.6$ Hz, 1H), 7.31–7.40 (m, 4H), 7.76–7.81 (m, 3H), 8.59 (d, $J = 8.4$ Hz, 1H), 10.00 (s, 1H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 23.2$, 48.1, 118.9, 119.1, 122.2, 123.2, 123.7, 125.89, 127.3, 129.1, 129.3, 129.7, 130.2, 130.3, 130.9, 132.8, 146.3, 153.9, 170.2 ppm.

N-[{4-[Acetylamino-(2-hydroxy-naphthalen-1-yl)-methyl]-phenyl}-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (**6**, $C_{32}H_{28}N_2O_4$)
White solid, Mp 267–269 °C; $R_f = 0.21$ (ethylacetate:hexane = 1:1); IR (KBr): $\bar{\nu} = 3,386$, 3,143, 1,685, 1,637, 1,577, 1,473, 1,400, 1,276, 1,195, 1,091, 945, 821, 669 cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.91$ (s, 6H), 7.02–7.77 (m, 18H), 8.40 (d, $J = 8.0$ Hz, 2H), 9.98 (s, 2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 23.2$, 48.7, 119.2, 119.3, 123.3, 124.8, 127.0, 129.2, 129.4, 130.1, 133.0, 153,8, 128.5, 142.9, 170.3 ppm.

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