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Melamine trisulfonic acid as a highly efficient catalyst for the synthesis of polyhydroquinolines under solvent-free conditions

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Abstract

A highly efficient, simple and clean solvent-free protocol for the synthesis of polyhydroquinolines is described. The one-pot multi-component condensation reaction between arylaldehydes, dimedone (5,5-dimethylcyclohexane-1,3-dione), β-ketoesters and ammonium acetate in the presence of 2.5 mol% of melamine trisulfonic acid (MTSA) at 60 °C affords the title compounds in high yields (83-98%) and short reaction times (3-30 min).

Keywords: Polyhydroquinoline; melamine trisulfonic acid (MTSA); solvent-free; arylaldehyde; dimedone (5,5-dimethylcyclohexane-1,3-dione); β-ketoester.

Introduction

Quinolines and their derivatives have attracted much attention because a large number of natural products and drugs possess this heterocyclic unit [1-3]. Moreover, these compounds have various biological and pharmacological activities, such as antiviral, antidiabetic, antitubercle, antibacterial and antitumor properties [3-6]. In fact, the remarkable drug activity of quinoline derivatives not only attracted many chemists to synthesize this heterocyclic nucleus, but also became an active research area of continuing interest. Polyhydroquinolines, as an important class of quinolines, are synthesized by the one-pot multi-component condensation of arylaldehydes with dimedone (5,5-dimethylcyclohexane-1,3-dione), β-ketoesters and ammonium acetate [7-17]. Several catalysts have been reported

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to promote this transformation [7-17]. Although several catalysts for this transformation are known, newer catalysts continue to attract attention for their effectiveness and advantages in comparison with the others.

In recent years, the use of SO_3H-containing catalysts and reagents has gained considerable attention in organic synthesis, due to their unique properties such as enhanced reactivity as well as selectivity, efficiency, straightforward workup, easy availability of their starting materials, eco-friendly reaction conditions and ability to promote a wide range of reactions [18-31]. They are also non-toxic, non-corrosive and inexpensive. Melamine trisulfonic acid (MTSA) is certainly one of the most interesting SO_3H-containing catalysts, which has been efficiently promoted some organic transformations [26-31].

Solvent-free organic reactions have been applied as useful protocol in organic synthesis [32-34]. Solvent-free method is an efficient technique for various organic transformations instead of using harmful organic solvents. Performing these reactions under thermal or microwave conditions often leads to a remarkable decrease in reaction times, increased yields, easier workup, matching with the green chemistry protocols, and may enhance the regioselectivity and stereoselectivity of reactions [32-34].

Multi-component reactions (MCRs) have a significant role in combinatorial chemistry as they can prepare target compounds with higher efficacy and atom economy by formation of structural complexity in a single step from three or more reactants. Furthermore, MCRs present some advantages compared with conventional chemical reactions, e.g. simplicity and synthetic efficiency [35-37].

In this investigation, we report a simple, highly efficient and green solvent-free method for the synthesis of polyhydroquinolines by the one-pot multi-component condensation of arylaldehydes with dimedone, β-ketoesters and ammonium acetate using melamine trisulfonic acid (MTSA) as a recyclable SO_3H-containing catalyst.

Experimental

Generel

All chemicals were purchased from Merck, Aldrich or Fluka Chemical Companies. MTSA was synthesized according to the reported procedure [26,27]. All known compounds were identified by a comparison of their melting points and NMR data with those reported in the literature. The ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100

MHz) were run on Bruker Avance DPX FT-NMR spectrometers. Mass spectra were obtained with a Shimadzu GC–MS-QP 1100 EX model. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the preparation of polyhydroquinolines using MTSA

MTSA (0.009 g, 0.025 mmol) was added to a mixture of dimedone (0.141 g, 1 mmol), arylaldehyde (1 mmol), β-ketoester (1 mmol) and ammonium acetate (0.108 g, 1.4 mmol) in a test tube. The resulting mixture was firstly stirred magnetically at 60 °C, and after solidification of the reaction mixture, it was vigorously stirred with a small rod at the same temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature, CH_2Cl_2 (30 mL) was added, stirred for 2 min, and filtered to separate the catalyst (the product is soluble in CH_2Cl_2, but, the catalyst isn't soluble in this solvent). The filtrate was washed by H_2O (20 mL), and dried over Na_2SO_4. The solvent was evaporated to give the crude product which was purified by recrystallization from ethanol (95%) or column chromatography eluted with *n*-hexane/ethyl acetate. The recycled catalyst was washed by CH_2Cl_2, and used for the next run.

Selected spectral data of the polyhydroquinolines

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1a)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 3H), 1.00 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H), 2.01-2.20 (m, 2H), 2.29 (s, 3H), 2.38-2.50 (m, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 4.82 (s, 1H), 7.05 (m, 1H), 7.18 (t, *J* = 6.7 Hz, 2H), 7.21 (t, *J* = 6.5 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.5, 18.8, 26.8, 29.5, 32.6, 36.5, 50.6, 59.6, 103.4, 109.9, 113.5, 126.9, 128.8, 130.5, 146.0, 150.3, 167.0, 194.7.

Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1c)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (s, 3H), 0.99 (s, 3H), 1.10 (t, *J* = 6.9 Hz, 3H), 1.96 (d, *J* = 16.0 Hz, 1H), 2.16 (d, *J* = 16.1 Hz, 1H), 2.29 (s, 3H), 2.38-2.49 (m, 2H), 3.97 (q, *J* = 7.0 Hz, 2H), 4.84 (s, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 2H), 9.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.6, 18.8, 26.9, 29.5, 32.6, 36.2, 50.6, 59.5, 103.5, 110.1, 119.1, 130.2, 131.0, 145.8, 147.4, 150.0, 167.1, 194.7.

Methyl 4-(3-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1h)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.83 (s, 3H), 1.00 (s, 3H), 1.99 (d, *J* = 16.0 Hz, 1H), 2.18 (d, *J* = 16.1 Hz, 1H), 2.30 (s, 3H), 2.39-2.49 (m, 2H), 3.53 (s, 3H), 4.85 (s, 1H), 7.14-7.16 (m, 2H), 7.25-7.27 (m, 2H), 9.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.8, 26.8, 29.5, 32.6, 36.3, 103.1, 109.9, 121.6, 126.8, 129.1, 130.5, 130.6, 146.3, 150.3, 150.5, 167.5, 194.7.

Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1j)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (s, 3H), 1.00 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.96 (d, *J* = 16.0 Hz, 1H), 2.15 (d, *J* = 16.1 Hz, 1H), 2.27 (s, 3H), 2.37-2.49 (m, 2H), 3.66 (s, 3H), 3.97 (q, *J* = 7.0 Hz, 2H), 4.79 (s, 1H), 6.73 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3Hz, 2H), 8.99 (s, 1H); ^{13}C NMR (75MHz, DMSO-d_6): δ 14.6, 18.7, 26.9, 29.6, 32.6, 35.4, 50.6, 55.3, 59.4, 104.4, 110.7, 113.5, 128.8, 140.5, 145.1, 149.7, 157.7, 167.4, 194.7.

Methyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1n)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (s, 3H), 0.99 (s, 3H), 1.97 (d, *J* = 16.0 Hz, 1H), 2.15 (d, *J* = 16.1 Hz, 1H), 2.28 (s, 3H), 2.37-2.49 (m, 2H), 3.52 (s, 3H), 3.66 (s, 3H), 4.81 (s, 1H), 6.73 (d, *J* = 7.4 Hz, 2H), 7.05 (d, *J* = 7.4 Hz, 2H), 9.02 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.7, 26.9, 29.6, 32.6, 35.2, 50.7, 51.1, 55.3, 104.0, 110.7, 113.6, 128.7, 140.3, 145.4, 149.7, 157.7, 167.9, 194.7.

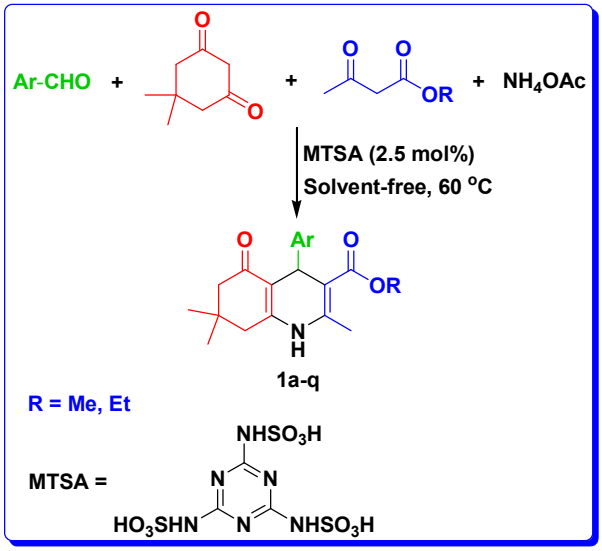
Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (1o)

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.10 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 2.16 (d, *J* = 16.4 Hz, 2H), 2.24-2.29 (Distorted AB system, 2H), 2.41 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 5.18 (s, 1H), 6.68 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6, 19.8, 27.5, 29.8, 33.1, 37.7, 41.3, 51.0, 60.5, 105.3, 111.4, 123.7, 129.4, 145.0, 146.6, 149.6, 154.9, 167.3, 195.9.

Results and discussion

To obtain the optimized reaction conditions, at first, the condensation of benzaldehyde with dimedone, ethyl acetoacetate and ammonium acetate was selected as a model reaction to provide the desired polyhydroquinoline (Scheme 1), and its behavior was studied in the presence of different molar ratios of MTSA at range of 25-110 ºC under solvent-free conditions; the respective results are summarized in Table 1. As it is shown in Table 1, the reasonable results were obtained when the reaction was

carried out using 2.5 mol% of the catalyst at 60 °C (Table 1, Entry 2).



Scheme 1. The preparation of polyhydroquinolines using MTSA.

Table 1. Effect of the catalyst amount and temperature on the model reaction

Entry	Mol% of MTSA	Temp. (°C)	Time (min)	Yield[a] (%)
1	1.5	60	15	81
2	2.5	60	6	95
3	5	60	6	90
4	7.5	60	6	80
5	2.5	25 (r.t.)	50	41
6	2.5	50	15	75
7	2.5	70	6	85
8	2.5	90	5	80
9	2.5	110	3	73

[a]Isolated yield

To assess the efficiency and generality of the catalyst, dimedone was reacted with ammonium acetate, β-ketoesters and various arylaldehydes; the corresponding results are displayed in Table 2. As Table 2 indicates, all aldehydes, including benzaldehyde and arylaldehydes bearing halogens, electron-donating substituents or electron-attracting substituents on their aromatic rings, afforded the desired products in high yields and short reaction times. Thus, MTSA was an efficient and general catalyst for the reaction.

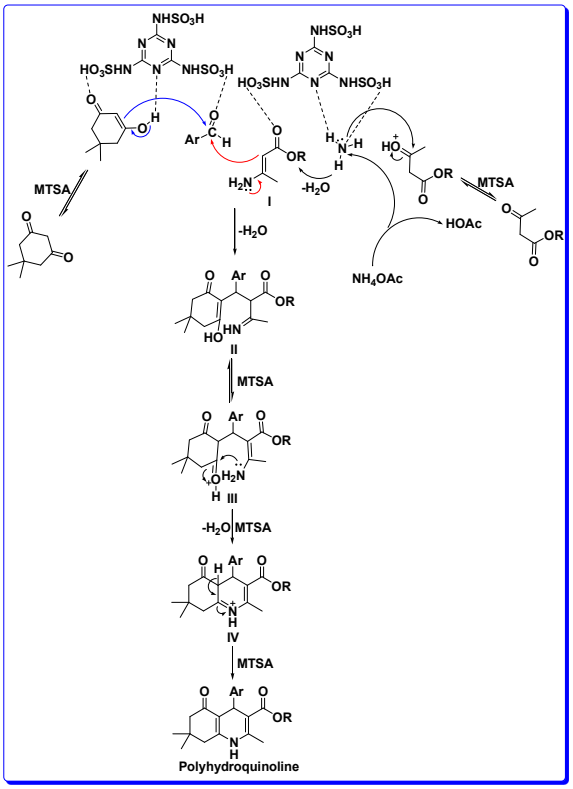
Table 2. The synthesis of polyhydroquinolines using MTSA

Ar/R/Product	Time (min)/ Yield[a] (%)	M.p. °C (Lit.)
C_6H_5/Et/1a	6/95	204-206 (203-205) [11]
C_6H_5/Me/1b	8/90	258-260 (258-260) [13]
p-BrC_6H_4/Et/1c	5/95	254-256 (255-257) [11]
m-BrC_6H_4/Et/1d	7/93	238-240 (235-237) [11]
p-ClC_6H_4/Et/1e	5/95	245-247 (245-246) [14]
m-ClC_6H_4/Et/1f	7/94	233-234 (231-233) [38]
o-ClC_6H_4/Et/1g	8/92	205-207 (208-210) [38]
m-BrC_6H_4/Me/1h	10/93	225-227 (221-223) [15]
p-ClC_6H_4/Me/1i	3/94	223-225 (220-222) [12]
p-$MeOC_6H_4$/Et/1j	8/89	257-259 (255-257) [15]
p-MeC_6H_4/Et/1k	6/93	254-256 (256-258) [15]
p-HOC_6H_4/Et/1l	11/98	229-231 (234-236) [15]
p-$Me_2NC_6H_4$/Et/1m	30/88	258-260 (262-263) [14]
p-$MeOC_6H_4$/Me/1n	10/95	255-257 (257-259) [15]

p-$O_2NC_6H_4$/Et/1o	10/85	245-247 (242-244) [10]
m-$O_2NC_6H_4$/Et/1p	13/83	179-180 (177-178) [14]
o-$O_2NC_6H_4$/Et/1q	5/85	202-204 (205-207) [39]

[a]Isolated yield

In a proposed mechanism (Scheme 2), we suggest that, at first, dimedone is converted to its enol form using MTSA. On the other hand, the activated β-ketoester (by the catalyst) and ammonia (resulted from ammonium acetate) gives enamine **I**. Afterward, the enol and enamine **I** react with the activated aldehyde (by MTSA) to afford intermediate **II** and one molecule H_2O. **II** is converted to **III** by tautomerization, and intermediate **III** affords **IV** by intramolecular nucleophilic attack of the NH_2 group to the activated carbonyl group and then removing one molecule H_2O. Finally, polyhydroquinonine is formed by tautomerization of **IV**.



Scheme 2. The proposed mechanism for the reaction

In fact, the catalyst not only activates carbonyls to accept nucleophilic attack, and amine as well as enamine groups for nucleophilic attack by its SO_3H groups, but also can collect and arrange the starting materials by dual hydrogen-bonding. For these reasons, a small amount of the catalyst (2.5 mol%) was sufficient to promote the reaction efficiently. It should be mentioned that in the steps in which MTSA gives a proton to activate carbonyl groups, the proton is transferred to the catalyst in another steps. The mechanism is confirmed by the literature [10,11,14,15].

Conclusion

In summary, we have developed a new solvent-free protocol for the synthesis of polyhydroquinolines using MTSA. The advantages of this method are efficiency, generality, high yield, short reaction time, cleaner reaction profile, simplicity, recyclability of the catalyst, ease of product isolation, and good compliance with the green chemistry protocols.

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