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Short communication

An efficient one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch four component condensation

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Abstract

A straightforward and general method has been developed for the synthesis of polyhydroquinolines derivatives by simply combining aldehyde, ethyl acetoacetate, dimedone, and ammonium acetate in the presence of a catalytic amount of scandium triflate. This method is very easy, rapid, and high yielding reaction for the synthesis of polyhydroquinolines.

Keywords: Polyhydroquinoline; Hantzsch reaction; Scandium triflate

1. Introduction

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers, and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases [1]. The DHP heterocyclic ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic agents [2]. Despite their importance from a pharmacological, industrial, and synthetic point of view, comparatively few methods for their preparation have been reported. The classical method for the synthesis of 1,4-dihydropyridines is one-pot condensation of aldehydes with ethyl acetoacetate, and ammonia either in acetic acid or by refluxing in alcohols [3]. This method, however, involves long reaction times, harsh reaction conditions, and generally gives low yields of products. Although, a number of modified methods under improved conditions have been reported [4–10], many of them suffer from drawbacks such as unsatisfactory yields, high temperatures, and long reaction times, and the use of stoichiometric and/or relatively expensive reagents. Moreover, the main disadvantage of almost all existing methods [4–8] is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of polyhydroquinolines in terms of operational simplicity, reusability, economic viability, and greater selectivity.

2. Results and discussion

In recent years, scandium triflate has received considerable attention as a mild Lewis acid for an array of organic transformations [11] because the catalyst is quite stable in water and reusable. As part of a continuing effort in our laboratory toward the development of new methods in organic synthesis [12], we became interested in the possibility of developing a one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch a four component coupling reaction of aldehydes, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of a reusable scandium triflate catalyst at room temperature (Scheme 1).

We have examined other Lewis acids for this reaction (Table 1), $Sc(OTf)_3$ was found to be the most effective catalyst in terms of conversion and reaction rates. The Hantzsch condensation of dimedone, benzaldehyde, ethyl acetoacetate, and ammonium acetate in the presence of a catalytic amount of scandium triflate at room temperature results in the formation of 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenyl-3-quinolinecarboxyl acid ethyl ester in 92% yield (Scheme 1).

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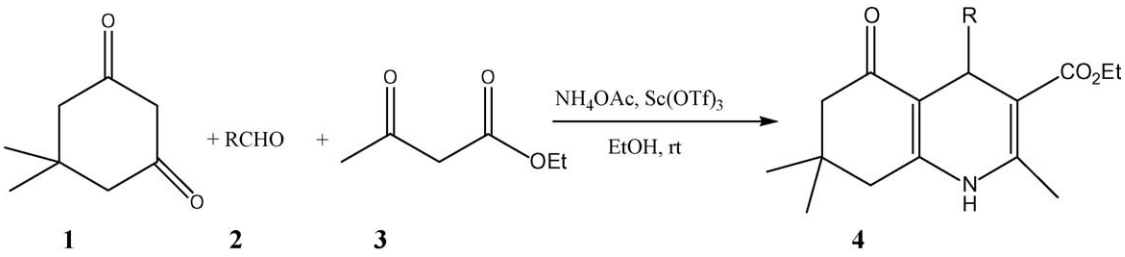

Scheme 1.

Table 1
The reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate: effect of catalysts[a]

Entry	Catalyst	Amount of catalyst (mol%)	Time (h)	Yield[b] (%)
1	None		24	30
2	None		24	52[c]
3	$AlCl_3$	100	24	48
4	$ZnCl_2$	100	24	42
5	$FeCl_3$	100	24	38
6	$Lu(OTf)_3$	20	24	64
7	$Nd(OTf)_3$	20	24	60
8	$Yb(OTf)_3$	10	5	85
9	$Y(OTf)_3$	10	6	77
10	$Sc(OTf)_3$	10	3	96
11	$Sc(OTf)_3$	5	4	93
12	$Sc(OTf)_3$	1	9	64

[a] All reactions were carried out in ethanol at room temperature.
[b] Isolated yields.
[c] Reaction was carried out at reflux temperature in ethanol.

The reaction is fairy general, clean, and efficient. The experimental procedure is very simple. The high yield transformation did not form any significant amounts of undesirable side products. Unlike previously reported methods, the present method does not require high temperatures to produce polyhydroquinoline derivatives. The results shown in Table 2 clearly indicate the scope and generally of the reaction with respect to various aromatic, aliphatic, heterocyclic, and unsaturated aldehydes.

Table 2
$Sc(OTf)_3$ catalyzed synthesis of polyhydroquinoline derivatives

Entry	R	Time (h)	Product	Yield[a] (%)
1	C_6H_5	4	**4a**	93
2	4-$MeOC_6H_4$	4	**4b**	95
3	4-$NMe_2C_6H_4$	6	**4c**	85
4	4-BrC_6H_4	4	**4d**	89
5	4-MeC_6H_4	6	**4e**	87
6	2-Furyl	2	**4f**	91
7	2-Thienyl	2	**4g**	86
8	$C_6H_5CH{=}CH$	5	**4h**	90
9	C_2H_5	5	**4i**	91
10	*n*-C_3H_7	6	**4j**	86

[a] Yields refer to isolated pure products. All products were characterized by comparison of their mp, IR, and ^{1}H NMR spectra with those of authentic samples (Refs. [4–10]).

3. Conclusion

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of polyhydroquinolines using scandium triflate as a reusable catalyst. The main advantages of this methodology are: (a) operational simplicity, (b) short reaction times, (c) high yields of products, and (c) the use of relatively non-toxic reagents and solvents.

4. Experimental

NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low resolution mass spectra (CI, EI) were recorded on a Finnigan 4000 mass spectrometer. High resolution mass spectra (HRMS, EI, CI, ESI) were recorded on Finnigan MAT XL95 mass spectrometer. Melting points were recorded on Buchi R-535 apparatus and are uncorrected. The reactions were monitored by TLC, and visualized with UV light followed by development using 15% phosphomolybdic acid in ethanol. All solvents and reagents were purchased from Aldrich with high-grade quality, and used without any further purification. All yields refer to isolated products. All compounds are known and were identified by comparison with those of the authentic samples [4–10].

4.1. Typical procedure

To a mixture of benzaldehyde (106 mg, 1 mmol), dimedone (140 mg, 1 mmol), ethyl acetoacetate (130 mg, 1 mmol), ammonium acetate (77 mg, 1 mmol) in ethanol (5 mL), scandium triflate (25 mg, 5 mol%) was added at room temperature. The reaction mixture was stirred for 4 h (TLC) at room temperature then the resulting solid product was filtered, washed with water, and dried in vacuum to afford the crude product. A pure product was obtained by further recrystallization using ethanol as a solvent. The filtrate containing the catalyst could be evaporated under reduced pressure to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next reaction with only a modest loss in activity. The catalyst has been recovered and reused four times (reaction yields: 92%, 89%, 81%, and 72%).

4.2. Analytical and spectral data

1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenyl-3-quinolinecarboxyl acid ethyl ester (**compound 4a**): Mp

204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.07 (s, 3H), 1.18 (t, J = 7 Hz, 3H), 2.14–2.35 (m, 4H), 2.37 (s, 3H), 4.06 (q, J = 7 Hz, 2H), 5.06 (s, 1H), 5.79 (s, 1H), 7.06–7.34 (m, 5H); EIMS m/z 339 (M^+); HRMS calcd for $C_{21}H_{25}NO_3$ 339.1834, found 339.1836; **Compound 4b**: Mp 258–259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.07 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H), 2.12–2.28 (m, 3H), 2.33–2.38 (m, 4H), 3.74 (s, 3H), 4.07 (q, J = 7.2 Hz, 2H), 5.02 (s, 1H), 5.82 (s, 1H), 6.72–6.76 (m, 2H), 7.21–7.24 (m, 2H); HRMS calcd for $C_{22}H_{27}NO_4$ 369.1940, found 369.1941; **Compound 4c**: Mp 233–234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.08 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H), 2.10–2.26 (m, 3H), 2.29–2.36 (m, 4H), 2.87 (s, 6H), 4.08 (q, J = 7.2 Hz, 2H), 4.96 (s, 1H), 5.88 (s, 1H), 6.62 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H); HRMS calcd for $C_{23}H_{30}N_2O_3$ 382.2256, found 382.2258; **Compound 4d**: Mp 254–255 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.07 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 2.18–2.28 (m, 3H), 2.34–2.42 (m, 4H), 4.08 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 5.80 (s, 1H), 7.18 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H); HRMS calcd for $C_{21}H_{24}BrNO_3$ 417.0940, found 417.0942; **Compound 4e**: Mp 261–262 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.08 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H), 2.10–2.24 (m, 4H), 2.26 (s, 3H), 2.37 (s, 3H), 4.06 (q, J = 7.1 Hz, 2H), 5.03 (s, 1H), 5.73 (s, 1H), 7.02 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H); HRMS calcd for $C_{22}H_{27}NO_3$ 353.1991, found 353.1990; **Compound 4f**: Mp 248–249 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.10 (s, 3H), 1.25 (t, J = 7 Hz, 3H), 2.21–2.28 (m, 3H), 2.34–2.38 (m, 4H), 4.10–4.17 (m, 2H), 5.20 (s, 1H), 5.81 (s, 1H), 6.04 (s, 1H), 6.24 (s, 1H), 7.19 (s, 1H); $C_{19}H_{23}NO_4$ 329.1627, found 316.1629; **Compound 4g**: Mp 241–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.12 (s, 3H), 1.25 (t, J = 7.2 Hz, 2H), 2.27 (t, J = 3 Hz, 3H), 2.35–2.40 (m, 4H), 4.12 (q, J = 7.2 Hz, 2H), 5.45 (s, 1H), 5.89 (s, 1H), 6.80–6.88 (m, 2H), 7.03 (m, 1H); HRMS calcd for $C_{19}H_{23}NO_3S$ 345.1399, found 345.1398; **Compound 4h**: Mp 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.10 (s, 3H), 1.25–1.32 (m, 3H), 2.30 (t, J = 7.3 Hz, 3H), 2.33–2.40 (m, 4H), 4.1–4.21 (m, 2H), 4.71 (d, J = 7 Hz, 1H), 5.76 (s, 1H), 6.23 (d, J = 7 Hz, 2H), 7.21–7.32 (m, 5H); $C_{23}H_{27}NO_3$ 365.1991, found 365.1993; **Compound 4i**: Mp 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (t, J = 7.2 Hz, 3H), 1.12 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.37–1.47 (m, 2H), 2.15 (d, J = 7.2 Hz, 1H), 2.26 (d, J = 3.2 Hz, 2H), 2.32 (t, J = 7.2 Hz, 4H), 4.03 (t, J = 5 Hz, 1H), 4.16–4.20 (m, 2H), 5.56 (s, 1H); HRMS calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1835; **Compound 4j**: Mp 150–152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (t, J = 7.2 Hz, 3H), 1.07 (s, 6H), 1.10–1.38 (m, 6H), 2.12–2.34 (m, 7H), 4.02 (q, J = 6 Hz, 1H), 4.10–4.23 (m, 2H), 5.58 (s, 1H); HRMS calcd for $C_{18}H_{27}NO_3$ 305.1991, found 305.1992.

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