

A new report on one-pot synthesis of polyhydroquinolines using ti catalyst

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ABSTRACT

An efficient Hantzsch condensation of polyhydroquinoline derivatives was reported via a four component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of efficient organometallic catalyst of bis[7-tert-butyl-2-anilino]Ti complex in toluene. © 2015 Trade Science Inc. - INDIA

KEYWORDS

1, 4-Dihydropyridines;
Hantzsch condensation;
Catalyst.

INTRODUCTION

Heterocycles are used as scaffolds for creating pharmacophores to yield potent and selective drugs. Heterocycles are versatile class of nitrogen or oxygen containing bioactive moieties and continue to attract the attention of organic chemists due to its highly pronounced biological and physiological activities^[1-8].

1, 4-Dihydropyridines exhibit a variety of biological properties. They can cure the disordered heart ratio as a chain cutting agent of factor IV channel and also possess the calcium channel agonist-antagonist modulation activities^[9-11]. These compounds also behave as neuroprotectants, cerebral antiischaemic agents and chemosensitizers^[12,13].

In the past, many methods for synthesis of polyhydroquinoline derivatives have been reported, such as conventional heating^[14] refluxing in acetic acid^[15] and microwave irradiation and ultrasound^[16]. Ionic liquids^[17], have also been used to promote the reaction. Different other heating approaches for the syntheses of polyhydroquinoline derivatives have subsequently been reported^[18-20] recently, some other method for the

preparation of 1,4-dihydropyridines and the progress in this field is remarkable including recently the promotion of microwave^[21], TMSCl^[22], ionic liquids^[23,24]. However in spite of their potential utility some of the reported methods suffer drawbacks, these methods are associated with several shortcomings such as long reaction times, expensive reagents, harsh conditions, low-product yields, occurrence of several side products.

The possibility of performing multicomponent reactions under solvent-free conditions with a heterogeneous catalyst could enhance their efficiency from an economic as well as an ecological point of view. In recent years heterogeneous catalysts are gaining more importance due to environmental-economic factors. The catalyst is generally of low cost and can be easily handled or removed. In recent times, the progress in the field of solid-state organic reactions is gaining significance both from the mechanistic and synthetic point of view. Numbers of researches are available reporting solid-state reactions by grinding such as, Grignard reaction, Reformatsky reaction, Aldol condensation, and Dickmann condensation. Most of these reactions are carried out at room temperature, absolutely solvent-

Full Paper

free and use only a mortar and pestle. The usage of organometallic compounds will provide a broad exploration for new methods and techniques in organic synthesis.

Herein, we would like to report a convenient and efficient procedure for one-pot synthesis of polyhydroquinolines by four-component coupling reactions of aldehydes, ethyl acetoacetate, dimedone and ammonium acetate in the presence of catalyst of bis[7-tert-butyl-2-anilino]Ti catalyst in toluene.

EXPERIMENTAL

All Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. All yields refer to isolated products. The products were characterized by their spectral data. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ¹H NMR spectra were recorded on a Bruker 250-MHz spectrometer in chloroform as the solvent and TMS as internal standard. Elemental analysis was performed on a Thermo Finnigan EA1112 elemental analyzer. Bis[7-tert-butyl-2-anilino]Ti complex was prepared according to our previous report^[25].

Typical experimental procedure

A mixture of aldehyde (1 mmol), dimedone (1mmol), ethylacetoacetate (1 mmol), ammonium acetate (1.5 mmol) and Bis[7-tert-butyl-2-anilino]Ti complex (15 mol%) were added to toluene and the mixture was refluxed for the appropriate time, till the

reactant was disappeared (TLC). After completion, 10 mL dichloromethane was added to the reaction mixture; the catalyst was removed. The solvent was evaporated under reduced pressure on a rotary evaporator to give crude products were obtained. The crude products were purified by recrystallization from ethanol.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-aryl-5(6H)-oxoquinolin-3-carboxylate (4a)

IR (KBr): 3050, 2940, 1715, 1630, 1605, 1460, 1375, 1215, cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 0.94 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 1.14 (t, 3H, CH₂CH₃), 2.20 (m, 4H, 2CH₂), 2.36 (s, 3H, CH₃), 4.09 (q, 2H, CH₂CH₃), 5.02 (s, 1H, CH), 6.0 (s, 1H, NH), 7.05–7.26 (m, 5H, Ar). Mass (ES/MS): m/z 339.

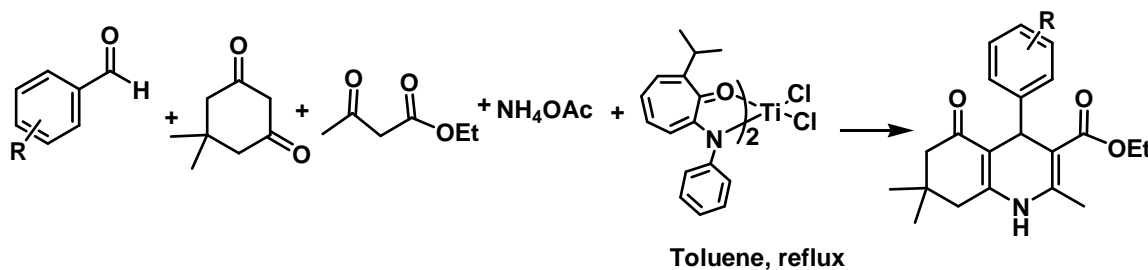
Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(2-chlorophenyl)-5(6H)-oxoquinolin-3-carboxylate(4c)

IR (KBr): 3065, 2957, 1725, 1644, 1614, 1467, 1386, 1227, cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 0.97 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 1.22 (t, 3H, CH₃), 2.03-2.22 (m, 4H, 2CH₂), 2.40 (s, 3H, CH₃), 4.07 (q 2H, CH₂), 4.63 (s, 1H, CH), 7.12-7.29 (m 4, ArH), 7.60 (s, 1H, NH). Mass (ES/MS): m/z 373.

RESULT AND DISCUSSION

Scheme 1 demonstrates the four component one step synthesis of a series of polyhydroquinoline derivatives procedure.

It can be seen that the one pot condensation of



Scheme 1 : An efficient one-pot synthesis of polyhydroquinolines at reflux temperature

series of aldehyde with dimedone, ethylacetoacetate and ammonium acetate leading to 4H-pyrimidine derivatives gives 90-95% yield under the catalytic effect of bis[7-tert-butyl-2-anilino]Ti complex. The results are summarized in TABLE1.

We also performed the model reaction of benzal-

dehyde with dimedone, ethylacetoacetate and ammonium acetate catalyzed by Ti catalyst used toluene as a solvent with stirring at room temperature. The condensation was carried out during 4 h. with 63% yield. It is clear that the reflux temperature could enhance the yield as well as accelerate the reaction since the

TABLE 1 : Synthesis of polyhydroquinoline by Ti catalyst

Sr. No.	Ar	Time (h)	Yield %	M. P. °C
a	C ₆ H ₅	1	93	225-227
b	4-Me.C ₆ H ₄	2	90	265-268
c	2-Cl. C ₆ H ₄	1	93	208-210
d	3-Cl. C ₆ H ₄	1	92	230-232
e	4-Cl. C ₆ H ₄	0.5	94	245-246
f	4-OH. C ₆ H ₄	2	91	238-240
g	4-OMe. C ₆ H ₄	3	92	258-260
h	4-NO ₂ . C ₆ H ₄	0.5	94	240-242
i	4-OH, 3-OMe.C ₆ H ₃	4	91	208-210
j	2-OMe	3	91	248-250

yield obtained and reaction time were 93% and 1h respectively at reflux condition. We also examine the reactions using electron donating and withdrawing substituted aryl aldehyde such as halogen, methoxy and nitro group. In all cases the corresponding to 4H-pyrimidine derivatives were obtained in excellent yields. The results are given in TABLE1. As can be seen, the reaction proceeds quickly when aldehyde containing electron releasing group is used, while the aldehyde with electron withdrawing groups needs more reaction time to complete the reaction. However, chemical yield is still excellent.

Due to heterogeneous nature of the catalyst, some additional studies were performed to test the reusability of the catalytic system. Model reaction was carried out over three cycles using the same catalytic system, which was recovered simply by filtering. Reused catalytic system was found to be efficient, without much loss in product yield.

CONCLUSION

In summary, we have we have developed a simple and efficient method for the synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a heterogeneous organometallic Ti catalyst in toluene. Excellent yield, short reaction time and easier work-up due to heterogeneity of the catalyst are some advantageous of the present method.

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