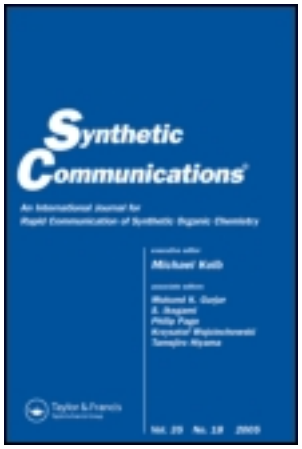

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Clean and Efficient Synthesis of Polyhydroquinoline Derivatives Under Solvent-Free Conditions Catalyzed by Morpholine

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Version of record first published: 14 Dec 2010.

To cite this article: Majid M. Heravi , Masoumeh Zakeri , Samira Pooremamy & Hossien A. Oskooie (2010): Clean and Efficient Synthesis of Polyhydroquinoline Derivatives Under Solvent-Free Conditions Catalyzed by Morpholine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:1, 113-120

To link to this article: http://dx.doi.org/10.1080/00397910903531862

Synthetic Communications®, 41: 113–120, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903531862

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CLEAN AND EFFICIENT SYNTHESIS OF POLYHYDROQUINOLINE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS CATALYZED BY MORPHOLINE

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A series of 1,4-dihydropyridines was obtained via a sequential Hantzsch condensation under solvent-free conditions catalyzed by morpholine in a one-pot reaction.

Keywords: Hantzsch reaction; morpholine; multicomponent; polyhydroquinoline

INTRODUCTION

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry, allowing the facile creation of several new bonds in one-pot reactions. Clearly, for multistep synthetic procedures, the number of reactions and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as small as possible. Therefore, in the past decade, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[1]

4-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogs of NADH coenzymes and an important class of drugs.[2] Current literature reveals that these compounds possess a variety of biological activities. For example, they can cure the disordered heart ratio as the chain-cutting agent of factor IV channel and also have calcium channel agonist–antagonist modulation activities.[3–7] Extensive studies have revealed that these compounds exhibit various medicinal functions such as neuroprotectant, platelet anti-aggregatory, and cerebral antischemic activity in the treatment of Alzheimer's disease and chemosensitizing activity in tumor therapy.[8] These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidates. Furthermore, the oxidation of these compounds to pyridines has also been extensively studied.[9] Thus, the synthesis of this heterocyclic nucleus is of much importance.

Received October 20, 2009.

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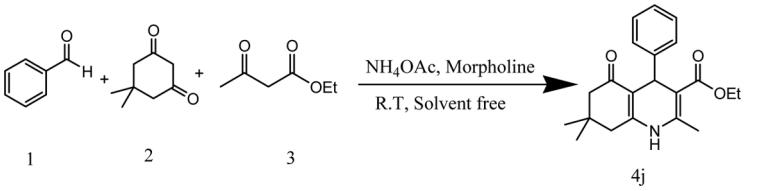


Scheme 1. Organocatalyzed unsymmetric Hantzsch reaction.

Polyhydroquinoline derivatives are important in the synthesis of various drug sources and have many classical methods such as conventional heating.[10,11] Progress in this field is remarkable, and new methods include microwave irradiation and ultrasound[12,13] as well as various catalysts such as trimethylsilyl chloride (TMSCl),[14] ionic liquid,[15–17] silica perchloric acid ($HClO_4$–SiO_2),[18] HY-zeolite,[19] montmorillonite K-10,[20] cerium(IV) ammonium nitrate,[21] iron(III) trifluoroacetate,[22] heteropoly acid,[23] $Sc(OTf)_3$.[24] and p-TSA.[25] Each of the methods for the Hantzsch reaction has its own merits, but some of the methods are plagued by the limitations of poor yield, longer reaction time, difficult workup, and effluent pollution. Moreover, there are a relatively limited number of reports on the synthesis of polyhydroquinoline derivatives compared to the synthesis of simple 4-substituted 1,4-DHP nucleus. Consequently, there is scope for further work toward increased variations of the subsistents in the product, mild conditions, and better yields.

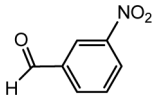
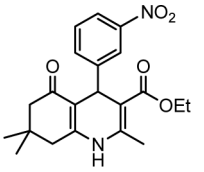
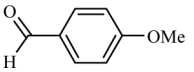
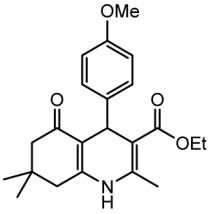
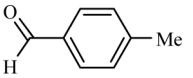
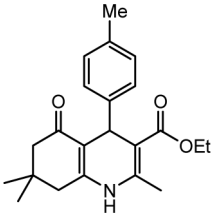
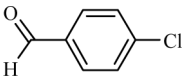
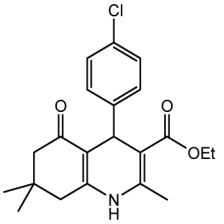
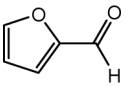
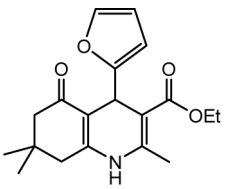
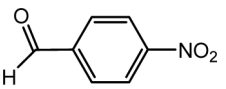
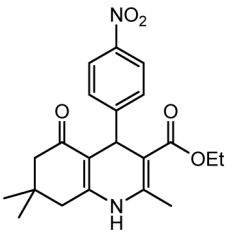
Small organic molecules such as morpholine, L-proline, and its derivatives are readily commercially available catalysts and have been used in various transformations with excellent yields.[26] More recently, morpholine, a cheap and facile weak base ($pK_b = 5.51$), has been used as the catalyst in sequential aldol and Michael addition reactions of aromatic aldehydes with 2′-hydroxyacetophenone.[27]

Therefore, we were interested in exploiting the activity of morpholine as well as other small organocatalysts in the synthesis of polyhydroquinoline derivatives through the Hantzsch reaction. Our results demonstrate that morpholine is a very effective, environmentally friendly catalyst for the four-component condensations of dimedone, ethylacetoacetate, aromatic aldehyde, and ammonium acetate to form polyhydroquinoline at room temperature under solvent-free conditions in excellent yields (Scheme 1).

RESULTS AND DISCUSSION

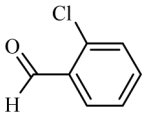
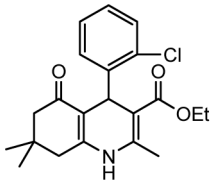
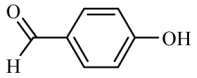
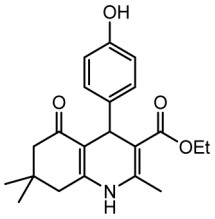
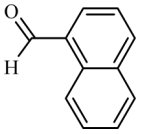
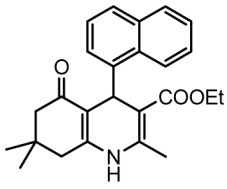
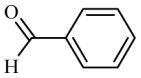
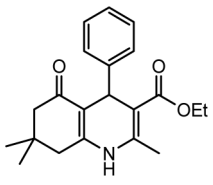
First, the mixture of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate was chosen as the model reaction (Scheme 1). The scope and generality of this four-component, one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch reaction is illustrated with different aldehydes (Table 1). This method has the ability to tolerate a variety of functional groups such as hydroxyl, methoxy, methyl, nitro, and halide under the reaction conditions. Both electron-rich and electron-deficient aldehydes as well as heterocyclic aldehyde (furfural) worked well, leading to excellent yields of products. The structures of all the products were established from their spectral data.

Table 1. Morpholine-catalyzed synthesis of polyhydroquinoline derivatives

Entry	Aldehydes	Products	Time (min)	Yield (%)[a]	Mp (°C) Found	Mp (°C) Lit.	Ref.
1		**4a** 	90	86	176–179	177–178	11
2		**4b** 	75	90	256	255–257	25
3		**4c** 	65	92	259–260	261–262	18
4		**4d** 	60	95	246	245–246	16
5		**4e** 	70	88	247–248	248–249	18
6		**4f** 	85	85	241–243	242–244	16

(*Continued*)

Table 1. Continued

Entry	Aldehydes	Products	Time (min)	Yield (%)[a]	Mp (°C) Found	Mp (°C) Lit.	Ref.
7		**4e** 	65	85	206–209	208–210	11
8		**4h** 	80	90	232–234	232–234	16
9		**4i** 	75	85	198–200	198–200	28
10		**4j** 	60	95	203–205	202–204	25

[a]The yields refer to isolated products by GC.

We also carried out the reactions without any catalyst. In these cases, the polyhydroquinoline derivatives were isolated in poor yields (10–20%), and the major product isolated was a dimedone, aldehyde adduct. While using morpholine (3 mol%) as catalyst, the reaction gave a yellow product in 90% yield in 60 min. By changing the amount of the catalyst from 3 mol% to 5 mol% and 10 mol%, the reaction resulted in the formation of **4j** in 95 and 85% yields, respectively. Thus, the use of just 5 mol% of morpholine was chosen as a quantitative catalyst to push the reaction forward with maximum yield of the product.

We then continued to optimize the model process by detecting the efficiency of several classic solvents chosen as the medium for comparison (Table 2). Among the tested solvents, such as ethanol, water, acetonitrile, and chloroform, and a solvent-free system, the latter gave the best result.

The effect of temperature was also studied by carrying out the model reaction in the presence of morpholine (5 mol%) at 25, 40, and 60 °C under solvent-free conditions 5, 6, and 7 (Table 2). The reaction under solvent-free conditions and at room

Table 2. Reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate: effect of solvent and temperature

Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	C_2H_5OH	Reflux	30	85
2	H_2O	Reflux	180	45
3	CH_3CN	Reflux	40	82
4	$CHCl_3$	Reflux	90	75
5	Solvent-free	25	60	95
6	Solvent-free	40	30	90
7	Solvent-free	60	20	92

temperature was found to be the best for the synthesis of polyhydroquinoline derivatives, and the products were obtained in excellent yields. In this green chemistry approach, the reaction times were increased but the yield of products was also increased to a remarkable extent.

CONCLUSION

In conclusion, we have developed a simple, rapid, efficient, and green method for the synthesis of a variety of polyhydroquinoline derivatives via an improved Hantzsch reaction catalyzed by small organic molecules. The reaction conditions are mild, and the reaction gives excellent yields of products. This method does not involve the use of volatile organic solvents and thus is an environmentally friendly process.

EXPERIMENTAL

All of the products are known compounds and were identified by comparison of their physical and spectroscopic data with those reported in literature.

Melting points were measured with an Electrothermal Engineering LTD 9200 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer RX1 Fourier transform–IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AQS Avance 300-MHz spectrometer using tetramethylsilane (TMS) as an internal standard ($CDCl_3$ solution). The progress of reactions was monitored by thin-layer chromatography (TLC) using n-hexane/EtOAc (3:2 v/v) as eluent.

General Procedure

In a typical experimental procedure, aldehyde **1** (1 mmol), dimedone **2** (1 mmol), acetoacetate ester **3** (1 mmol), ammonium acetate (1.5 mmol), and morpholine (0.05 mmol) were taken in a 10-ml, round-bottomed flask and stirred with a magnetic stirrer until all reactants were consumed (TLC). Then the mixture was poured into the water and the precipitate solid was washed with water two or three times and purified by recrystallization from absolute ethanol to obtain pure yellow crystalline polyhydroquinoline.

The structure of the products was confirmed by IR and ^{1}H NMR spectra and comparison with authentic samples prepared by reported methods.

Data

Compound 4b. Mp: 256 °C; IR (KBr) (ν max): 3276, 3204, 3076, 2957, 1701, 1648, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.93 (3H, s), 1.06 (3H, s), 1.20 (3H, $J = 7.2$ Hz, t), 2.10–2.26 (4H, m), 2.35 (3H, s), 3.72 (3H, s), 4.05 (2H, $J = 7.2$ Hz, q), 4.99 (1H, s), 6.37 (1H, s), 6.74–6.77 (2H, $J = 8.7$ Hz, d), 7.23–7.25 (2H, $J = 8.7$ Hz, d).

Compound 4c. Mp: 259–260 °C; IR (KBr) (ν max): 3277, 3204, 3076, 2958, 1702, 1647, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (3H, s), 1.07 (3H, s), 1.24 (3H, $J = 7.2$ Hz, t), 2.17 (3H, s), 2.25–2.28 (4H, m), 2.35 (3H, s), 4.07 (2H, $J = 7.2$ Hz, q), 5.01 (1H, s), 5.81 (1H, s), 7.01–7.05 (2H, m), 7.16–7.20 (2H, m).

Compound 4d. Mp: 246 °C; IR (KBr) (ν max): 3275, 3204, 3075, 2962, 1705, 1647, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (3H, s), 1.07 (3H, s), 1.18 (3H, t, $J = 7.1$ Hz), 2.15–2.30 (4H, m), 2.38 (3H, s), 4.03 (2H, $J = 7.1$ Hz, q), 5.03 (1H, s), 6.80 (1H, s), 7.13–7.17 (2H, m), 7.22–7.26 (2H, m).

Compound 4h. Mp: 232–234 °C; IR (KBr) (ν max): 3416, 3281, 3076, 2959, 1687, 1614, 1484 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (3H, s), 1.07 (3H, s), 1.22 (3H, $J = 7.2$ Hz, t), 2.17–2.3 (4H, m), 2.37 (3H, s), 4.07 (2H, q), 4.65 (1H, s), 4.98 (1H, s), 5.58 (1H, s), 6.62 (2H, $J = 8.5$ Hz, d), 7.16 (2H, $J = 8.5$ Hz, d).

ACKNOWLEDGMENT

We are grateful to Azzahra University Research Council for partial support of this work.

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