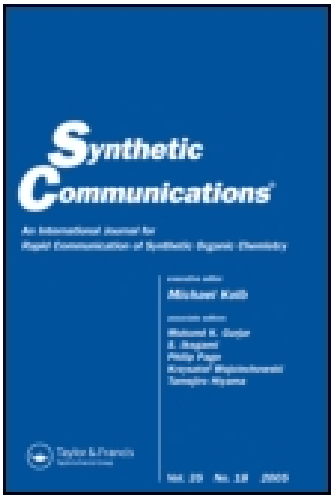

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SOLVENT-FREE SYNTHESIS OF DIHYDROPYRIDINES AND ACRIDINEDIONES VIA A SALICYLIC ACID–CATALYZED HANTZSCH MULTICOMPONENT REACTION

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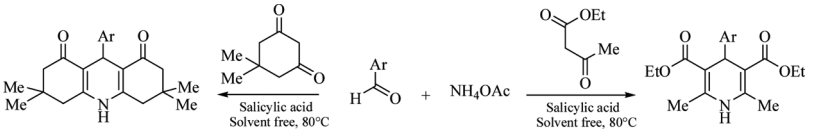
GRAPHICAL ABSTRACT



Abstract *A multicomponent Hantzsch synthesis of 1,4-dihydropyridines and acridinediones from commercially available aldehydes, ammonium acetate, and ethyl acetoacetate or dimedone, in the presence of salicylic acid as an efficient catalyst, in good yield and short reaction time is reported.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Acridinediones; 1,4-dihydropyridines; Hantzsch; multicomponent; salicylic acid

INTRODUCTION

Hantzsch 1,4-dihydropyridines (1,4-DHPs) constitute a class of compounds with many derivatives, especially among natural products and bioactive agents.[1] 1,4-DHP derivatives have been found to be commercially useful molecules as calcium channel blockers.[2–4] A number of these calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure.[5,6]

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Cerebrocrast, a dihydropyridine derivative, has been introduced as a neuroprotective agent.[7] Together with calcium channel blocker and neuroprotective activity, a number of dihydropyridine derivatives have been found to be vasodilatory, antihypertensive, bronchodilatory, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective, antidiabetic, and antiplatelet aggregation agents.[8–12]

For these reasons, dihydropyridine compounds not only have attracted the attention of chemists to synthesize but also represent an interesting research challenge. Numerous methods have been reported for the synthesis of 1,4-DHP derivatives, because of the biological importance associated with these compounds. The classical method involves the three-component coupling of an aldehyde with β-ketoester and ammonia in acetic acid or in refluxing alcohol.[13,14] However, these methods suffer from several drawbacks such as a long reaction time, an excess of organic solvent, lower product yields, and harsh refluxing conditions. Therefore, it is necessary to develop more efficient and versatile methods for the preparation of 1,4-DHPs, and the progress in this area is remarkable, including the use of microwaves,[15] ionic liquids,[16] refluxing at hight temperature,[17] TMSCl-NaI,[18] metal triflates,[19] and I_2.[20]

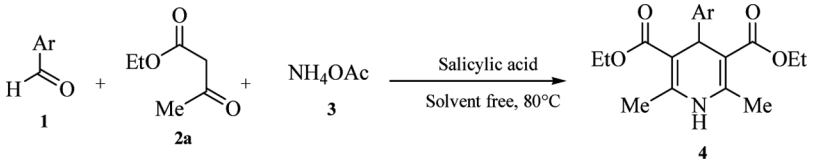
Also, other efficient methods for the synthesis of polyhydroquinoline derivatives have been described, such as the recent use of microwaves,[21] heterogeneous catalyst,[22] SiO_2-$HClO_4$,[23] silica gel–sulfonic acid,[24] tetrabutylammonium hydrogen sulfate,[25] ZnO,[26] ceric ammonium nitrate,[27] $ZrCl_4$,[28] [2-MPyH]OTf,[29] gadolinium triflate,[30] and solid-phase organic synthesis (SPOS) techniques.[31]

With a 1,4-DHP parent nucleus, acridine-1,8-diones have been developed recently, as a family of efficient laser dyes[32] that are structurally similar to NADH.[33] Acridinedione dyes have also been used as photoinitiators for polymerization of acrylates and methyl acrylates[34] and photosensitizers for the onium salt decomposition.[35] Many acridinediones have been synthesized by the reactions of aldehydes with 2 equivalents of 1,3-dicarbonyl compounds via various methods.[36]

RESULTS AND DISCUSSION

As a continuation of our studies of multicomponent reactions,[37] we report in this communication a novel and efficient synthesis of Hantzsch dihydropyridines by a modified Hantzsch procedure (Scheme 1) using salicylic acid as catalyst under different conditions.

Thus, the condensation of 1 equiv. of benzaldehyde **1a** with 2 equiv. of ethyl acetoacetate **2a** and 4 equiv. of NH_4OAc in the presence of 20 mol% of salicylic acid resulted in the formation of Hantzsch 1,4-dihydropyridine **4a** (Scheme 1). The



Scheme 1.

Table 1. Salicylic acid–catalyzed Hantzsch synthesis of 1,4-dihydropyridine **4a** under different conditions[a]

Entry	Solvent	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)
1	EtOH	20	Reflux	18	45
2	CH_3CN	20	Reflux	18	54
3	THF	20	Reflux	18	84
4	—	20	80	2	89
5	—	10	80	2	85
6	—	5	80	2	75

[a]All reactions were performed using benzaldehyde (1 equiv.), ethyl acetoacetate (2 equiv.), and ammonium acetate (4 equiv.).
[b] Isolated yields.

reaction was performed in refluxed ethanol, and the product was isolated by the usual workup in 45% yield only (Table 1, entry 1).

Several other solvents have been also used for this condensation, such as CH_3CN and tetrahydrofuran (THF). When the reaction was performed in CH_3CN, a moderate yield was obtained even with a prolonged reaction time, probably a result of poor catalyst solubility, although the yield was comparable to that of EtOH. The product yield was increased to 84% when THF was used (entry 3). However, the reaction under solvent-free conditions gave better results within 2 h (Entry 4).

To optimize the reaction conditions further, the catalyst amount effect was investigated with the optimum solvent, and the best result was obtained with 20 mol% of salicylic acid (entries 5 and 6).

Thus, the optimal reaction conditions for this transformation were determined to be 20 mol% of the catalyst under solvent-free condition at 80 °C.

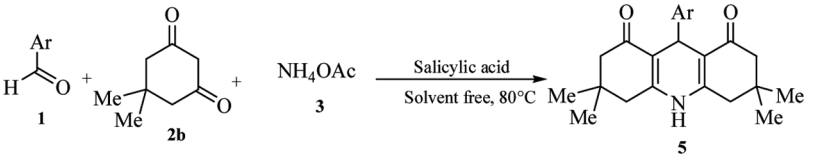
With the optimized conditions in hand, the substrate scope of this reaction was probed. In general, all the examined aldehydes could furnish the expected heterocycles in good to excellent yields, and the results are summarized in Table 2. Changes to the substituents seemed not to have any striking effect on the yield values.

All reactions were clean and efficient under solvent-free conditions, and the products were obtained within 2 h in good yields.

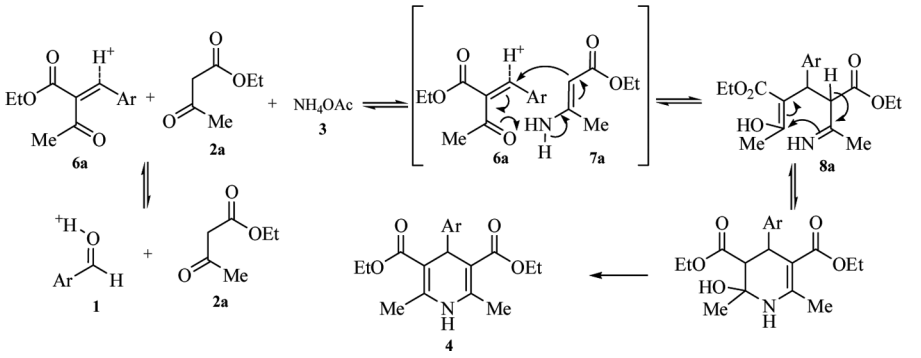
Table 2. Salicylic acid–catalyzed Hantzsch synthesis of 1,4-dihydropyridines **4a–f** under optimized conditions[a]

Entry	1,4-DHP	Ar	Time (h)	Yield[b] (%)
1	**4a**	C_6H_5-	2	89
2	**4b**	4-OH-C_6H_4-	2	65
3	**4c**	4-CH_3O-C_6H_4-	2	68
4	**4d**	4-Br-C_6H_4-	2	71
5	**4e**	Styryl-	2	64
6	**4f**	2-Furyl	2	88

[a]All reactions were performed using aldehyde (1 equiv.), ethyl acetoacetate (2 equiv.), ammonium acetate (4 equiv.), and salicylic acid (0.2 equiv.) at 80 °C.
[b] Isolated yields.



Scheme 2.



Scheme 3.

A mechanism for the formation of compounds **4** is outlined in Scheme 3. The Michael addition of **6a** with enaminoester **7a**, which are formed in situ from the condensation reactions of ethyl acetoacetate **2a** with aromatic aldehydes **1** and ammonium acetate **3**, respectively, give the intermediate **8a**. Intramolecular cycloaddition and subsequent dehydration afford compounds **4**.

To study the generality of our methodology toward other 1,3-dicarbonyl compounds, the synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones **5a–f** was also explored. The reactions of different aldehydes **1** (1 equiv.) with 5,5-dimethylcyclohexane-1,3-dione (dimedone) **2b** (2 equiv.), ammonium acetate (4 equiv.), and salicylic acid (0.2 equiv.) were performed under the optimized solvent-free conditions to afford a series of the corresponding acridinediones

Table 3. Salicylic acid–catalyzed Hantzsch synthesis of acridinediones **5a–f** under optimized conditions[a]

Entry	Product	Ar	Time (h)	Yield[b] (%)
1	**5a**	C_6H_5-	3	82
2	**5b**	2-CH_3-C_6H_4-	5	67
3	**5c**	4-CH_3O-C_6H_4-	3	73
4	**5d**	4-Cl-C_6H_4-	5	85
5	**5e**	4-$(CH_3)_2N$-C_6H_4-	3	88
6	**5f**	2-Thienyl	3	90

[a]All reactions were performed using aldehyde (1 equiv.), dimedone (2 equiv.), ammonium acetate (4 equiv.), and salicylic acid (0.2 equiv.) at 80 °C.

[b] Isolated yields.

(Scheme 2). The results summarized in Table 3 showed the high efficiency for the one-pot multicomponent reaction.

All the products prepared from this method were characterized by their spectral data and known compounds by comparison with reported data. The advantages of the present protocols are the shorter reaction times and mild reaction conditions. Because of the high reactivity of the reagents, the products are obtained in good yields.

SUMMARY

In summary, we have found that salicylic acid is extremely useful and highly efficient for the synthesis of 1,4-DHPs and acridinediones by means of three-component condensations of an aldehyde, 1,3-dicarbonyl compound, and ammonium nitrate in a one-pot condensation. This method is applicable to a wide range of substrates, including aromatic, α, β-unsaturated, and heterocyclic aldehydes, and provides a variety of biologically relevant compounds in good yields under solvent-free conditions. The mildness of the conversion, experimental simplicity, compatibility with various functional groups, efficient yields, short reaction times, and easy workup procedure make this procedure attractive for synthesizing a variety of these derivatives.

EXPERIMENTAL

Typical Experimental Procedure for the Synthesis of 1,4-Dihydropyridines 4a–f or Acridinediones 5a–f

A mixture of aldehyde (1 mmol), ammonium acetate (4 mmol), ethyl acetoacetate or dimedone (2 mmol), and salicylic acid (20 mol%) was magnetically stirred at 80 °C under solvent-free conditions for the appropriate time indicated in Tables 2 and 3. After complete conversion as indicated by thin-layer chromatography (TLC), the reaction mixture was cooled and poured onto crushed ice, and the separated solid was filtered.

Diethyl 4-(Phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4a)

Mp 156–158 °C; lit.[38a] 158–160;^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (t, $J = 7.1$ Hz, 6H), 2.33 (s, 3H), 2.32 (s, 6H), 4.11 (q, $J = 7.1$ Hz, 4H), 5.01 (s, 1H), 5.97 (s, 1H), 7.11–7.32 (m, 5H);^{13}C NMR (62.9 MHz, $CDCl_3$): δ: 14.1, 19.5, 39.4, 59.3, 104.1, 127.5, 128.8, 135.7, 144.1, 145.9, 167.8; FT-IR (KBr): 3334, 1690, 1654, 1494, 1243, 1127, 721 cm^{-1}.

9-(2-Methylphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-1,8-(2H,5H)-acridinedione (5b)

Mp > 300 °C;^{1}H NMR (250 MHz, $CDCl_3$): δ: 1.20 (s, 6H, CH_3), 1.34 (s, 6H), 2.32 (s, 3H), 2.38 (d, $J = 16.2$ Hz, 2H), 2.44 (d, $J = 16.2$ Hz, 2H), 2.51 (d, $J = 16.2$ Hz,

2H), 2.60 (d, $J = 16.2$ Hz, 2H), 3.94 (s, 1H), 7.15–7.23 (m, 5H), 9.37 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ: 18.3, 26.7, 29.4, 32.3, 39.3, 40.2, 40.4, 50.7, 51.4, 114.3, 125.4, 128.0, 129.4, 135.9, 146.5, 148.7, 195.6; FT-IR (KBr): 3371, 3317, 3193, 2958, 1654, 1608, 1461, 1369, 1211, 1157 cm^{-1}. Anal. calcd. for $C_{24}H_{29}NO_2$: C, 79.30; H, 8.04; N, 3.85. Found: C, 79.45; H, 8.00; N, 3.84.

SUPPORTING INFORMATION

Full experimental detail and ^{1}H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's Web page.

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