A Simple, Efficient, One-Pot Three-Component Domino Synthesis of Hantzsch Pyridines under Solvent-Free Condition

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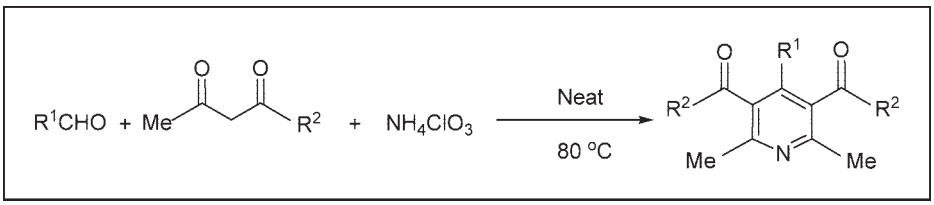

In this article, efficient and simple preparation of Hantzsch pyridine derivatives by reaction of various aldehydes and β-dicarbonyls in the presence of ammonium chlorate under solvent-free condition at 80°C is reported. The advantages of this system are the one-step procedure, high yields of the products, and the ability to carry out large-scale reactions.

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INTRODUCTION

Pyridine bases, as representative heteroaromatic ring compounds, are produced for applications in herbicides, insecticides, vitamins, nicotinic acid and nicotinic amide, pharmaceuticals, and adhesives [1]. For example, there are many bioactive pyridine compounds, such as the prosthetic pyridine nucleotide (NADP) [2], pyridoxine (vitamin B_6), and nicotine [3], and also many pharmaceuticals [4] and agrochemicals [5] possessing a pyridine nucleus. Pyridine is used as a basic solvent as well as a catalyst in industrially important organic reactions [6]. Thus, new construction methods for multisubstituted pyridines are still intriguing studies [7,8].

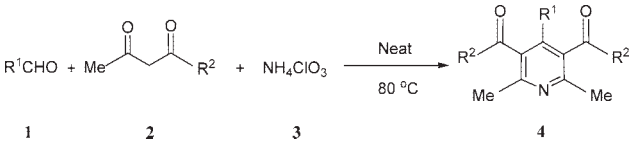
On the other hand, the synthesis of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic chemistry. These ubiquitous features always encourage synthetic chemist to explore improved protocols for the synthesis as well as the oxidation of 1,4-dihydropyridines. Oxidation of 1,4-dihydropyridines is one of the possible ways for the synthesis of the corresponding pyridines. Aromatization of 1,4-dihydropyridines has received considerable attention because of the fact that 1,4-dihydropyridine-based calcium channel blockers are oxidatively converted to pyridine derivatives by the action of cytochrome P-450 in the liver [9,10]. In addition, the corresponding pyridine derivatives show antihypoxic and anti-ischemic activities and are used in the treatment of atherosclerosis [11]. Additionally, dihydropyridines are often produced in a synthetic sequence and have to be oxidized to pyridines [12]. Numerous reagents and procedures have been recommended for this purpose, such as pyridinium chlorochromate (PCC) [13], N_2O_4 complex of 18-crown-6 [14], *tert*-butylhydroperoxide [15], photochemical oxidation [16], vanadium(V) salts [17], and biomimetic catalyzed oxidation [18].

Despite these intensive efforts, most of the reported oxidation procedures require long reaction time, use of the strong oxidants in large excess, and afford products with only modest yields. In particular, the aromatization reactions with these reagents lead to dealkylation of the 4-position or formation of side products.

It is well known in the protocol of green chemistry that its main objective is to perform reactions under solventless conditions using heterogeneous catalysts to generate environmentally friendly chemical transformations [19]. In addition, it is important to note that an ideal synthesis is considered as one in which a target molecule is produced quantitatively in one step, from available and inexpensive raw materials [20].

Ammonium acetate has been used for the synthesis of dihydropyridine [21] and pyridine derivatives. 4-Substituted Hantzsch 1,4-dihydropyridines were synthesized by replacing ammonium acetate with ammonia in a classical method, in which the products can be subsequently oxidized to corresponding pyridines. To the best of our knowledge, only two articles reported the continuous synthesis of Hantzsch pyridines by a mixture of bentonite clay, β-ketoester, aldehyde, and ammonium nitrate as the source of ammonia and oxidizing species [22,23]. These results are intriguing as they are somehow contradictory. In one of these reports [22], in the absence of solvent, the alkylated pyridine was isolated from the oxidation of 4-isopropyl dihydropyridine as the major product. On the other hand, dealkylated pyridine was isolated from the oxidation of 4-propyl or 4-phenyl dihydropyridines in substantial yield that this

Scheme 1



observation contrasts with the presented results in the second report [23], such as they do not mention the presence of this case of pyridine in the final mixtures.

In the Vilsmeier–Haack reaction progress, Jutz et al. [24] have demonstrated that the cyclization of the intermediate iminium salts formed by the multiple iminoalkylations of certain alkenes, in the presence of ammonium acetate, leads to the formation of substituted pyridines and naphthyridines. Thomas and Asokan [25] envisaged that a similar ammonium acetate-induced cyclization of the intermediates formed by the treatment of α-hydroxyketenedithioacetals would afford a useful method for the synthesis of substituted pyridines with moderate yields.

In this research, we report that the ammonium chlorate can be used as both ammonia and oxidizing agent source for the direct synthesis and oxidation of Hantzsch 1,4-dihydropyridines to pyridines.

RESULTS AND DISCUSSION

As a part of our current studies on multicomponent reaction (MCR) involving synthesis of dihydropyrimidinones [26] and our interest in the chemistry of dihydropyridines [18], we have investigated the one-pot synthesis of pyridine derivatives (Scheme 1).

The synthetic method for the preparation of substituted pyridine derivatives (**4**) was relatively easy and simple, and the compounds could be obtained in one step. The optimized reaction conditions were subsequently applied to the reaction between various aliphatic or aromatic aldehydes and β-dicarbonyls in the presence of ammonium chlorate in solvent-free conditions at 80°C. In all cases, the desired pyridine derivatives were obtained in high to excellent yields. Both electron-rich and electron-deficient aromatic aldehydes as well as heterocyclic ones worked well. Aliphatic aldehydes afforded equally good results. Many of the pharmacologically significant substitution patterns can be introduced with good efficiency (Table 1).

In a typical procedure, 2 mmol of aldehyde, 4 mmol of β-dicarbonyl, and 3 mmol of ammonium chlorate were mixed in solvent-free conditions at 80°C for 40–300 min. After work-up, the corresponding pyridines were isolated with excellent yields (**4a**–**4s**). One advantage of this method is its large-scale applicability. Pyridines were prepared on a 50-mmol scale, and the results were comparable with the small-scale experiments.

According to the literature, the thermal decomposition of NH_4ClO_3 begins at 50°C, which possibly includes equilibrium formation of ammonia and chloric acid according to Scheme 2 [28]. This process is probably accelerated by water formed in reaction. Thus, formed ammonia acts as a nitrogen nucleophile in Hantzsch dihydropyridine synthesis while chloric acid as an actual oxidant. However, it cannot be excluded that the product, substituted pyridine, is formed by the oxidation of intermediates different than 1,4-dihydropyridines.

Based on the evidences from the reaction and previous suggestions on such a system as shown in Scheme 1, our rationalization about the proposed mechanism includes thermal decomposition of ammonium chlorate to NH_3 and $HClO_3$ that these lead to Hantzsch dihydropyridine synthesis and its oxidation of the products with chloric acid to corresponding pyridines.

CONCLUSIONS

In conclusion, we have developed a simple and efficient synthetic protocol for the synthesis of a wide variety of Hantzsch pyridine derivatives under solvent-free conditions. Mild reaction conditions, cost efficiency, simplicity in operation, and large-scale applicability are some significant features of this protocol.

EXPERIMENTAL

All chemicals were purchased from Merck, Fluka, and Sigma-Aldrich chemical companies. The reactions were monitored by TLC. The products were isolated and identified by comparison of their physical and spectral data with authentic samples. IR spectra were recorded on FTIR JASCO-680. The ^{1}H NMR spectra were obtained on a Brüker-instrument DPX-300 MHz and melting points determined on a Barnstead Electrothermal (BI 9300) apparatus.

General procedure for the preparation of the Hantzsch pyridines. All reactions were carried out in a 25-mL round bottomed flask equipped with a magnetic stirring bar. A mixture of aldehyde (2 mmol), β-dicarbonyl (4 mmol), and ammonium chlorate (3 mmol) was heated at 80°C. After completion of the reaction, as monitored by TLC, the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The solvent was evaporated off, and the crude product was purified by silica gel plate or silica gel column (eluent: *n*-hexane–EtOAc). The products were characterized by IR, ^{1}H NMR, and *via* comparison of their melting points with the reported ones.

Spectral and physical data for selected compounds

Diethyl 4-(2,4-dichlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (4i). mp: 58–60°C, R_f (*n*-hehaxe/EtOAc, 5:1) = 0.55. IR (KBr): υ (cm^{-1}) = 2982, 2905, 1720, 1585, 1472, 1412, 1375, 1264, 1242, 1143, 1105, 1051, 837, 758; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.05 (t, 6H), 2.11 (s, 6H), 3.89 (q, 4H),

Table 1

The one-pot synthesis of pyridine derivatives.[a]

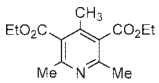
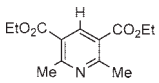
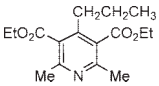
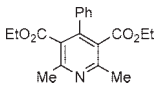
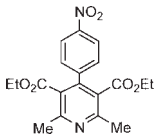
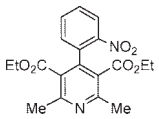
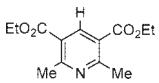
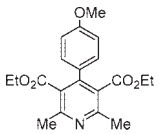
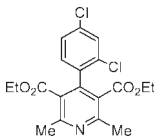
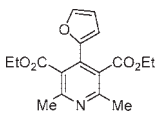
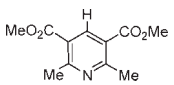
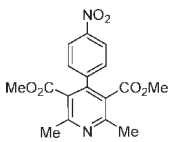
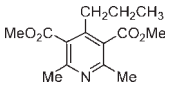
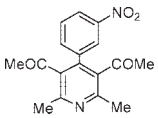
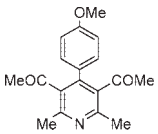
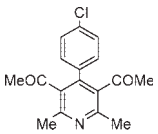
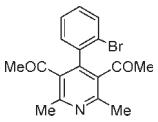
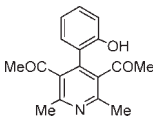
Entry products	R^1	R^2	Products	Time (min)	Yields[b] (%)	mp (°C)
4a	CH_3	OEt		70	90	Oily [27b]
4b	$(CH_3)_2CH$	OEt		75	95	70–72 [27e]
4c	$CH_3(CH_2)_2$	OEt		60	90	Oily [27a]
4d	C_6H_5	OEt		50	94	62–63 [27b]
4e	4-NO_2—C_6H_4	OEt		75	89	113–115 [27b]
4f	2-NO_2—C_6H_4	OEt		180	94	75–76 [27f]
4g	C_6H_5—$CHCH_3$	OEt		80	95	70–72 [27d]
4h	4-CH_3O—C_6H_4	OEt		40	94	49–50 [27a]
4i	2,4-$(Cl)_2$—C_6H_3	OEt		130	91	62–64
4j	2-Furyl	OEt		85	96	39–41 [27c]
4k	H	OMe		200	92	100–102 [27h]
4l	4-NO_2—C_6H_4	OMe		200	97	90–93 [27g]

Table 1
(*Continued*)

Entry products	R^1	R^2	Products	Time (min)	Yields[b] (%)	mp (°C)
4m	$CH_3(CH_2)_2$	OMe		180	85	Oily [27h]
4n	3-NO_2-C_6H_4	Me		300	92	125–127 [27i]
4o	4-CH_3O-C_6H_4	Me		200	87	163–164 [27i]
4p	4-Cl-C_6H_4	Me		250	80	174–176 [27i]
4q	2-Br-C_6H_4	Me		160	89	190–192
4r	2-OH-C_6H_4	Me		130	90	140–142

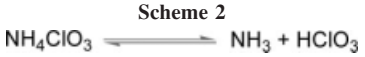
[a] Characterized by spectral analysis and comparison with these reported in the literature [27].
[b] Isolated yields.

6.91 (q, 1H), 7.06–7.13 (m, 2H). Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53; found: C, 57.5; H, 4.7; N 3.4.

3,5-Diacetyl-4-(2-bromophenyl)-2,6-dimethylpyridine (4q). mp: 190–192°C, R_f (CCl_4/EtOAc, 5:1) = 0.57. IR (KBr): υ (cm^{-1}) = 2975, 2900, 1695, 1620, 1456, 1405, 1378, 1260, 1225, 1140, 1110, 1045, 720; ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.10 (s, 6H), 2.59 (s, 6H), 6.91–7.34 (m, 4H). Anal. Calcd. for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05; found: C, 58.8; H, 4.5; N, 3.9.

3,5-Diacetyl-4-(2-hydroxyphenyl)-2,6-dimethylpyridine (4r). mp: 140–142°C, R_f (CCl_4/EtOAc, 5:1) = 0.52. IR (KBr): υ (cm^{-1}) = 3410, 3015, 2985, 2920, 1690, 1615, 1585, 1470, 1402, 1320, 1265, 1172, 1115, 1040, 905, 812, 740; ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.95 (s, 6H), 2.50 (s, 6H), 4.01 (br, 1H), 6.80–7.42 (m, 4H). Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; found: C, 71.9; H, 5.9; N, 4.8.

Scheme 2



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