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ORIGINAL PAPER

$FeNH_4(SO_4)_2{\cdot}12H_2O$ (alum)-catalyzed preparation of 1,4-dihydropyridines: improved conditions for the Hantzsch reaction

Ali A. Mohammadi · Armin Hadadzahmatkesh · Mohammad R. Asghariganjeh

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Abstract $FeNH_4(SO_4)_2{\cdot}12H_2O$ (alum) efficiently catalyzes the one-pot three-component reaction of dimedone, aldehydes, and 3-aminocrotonate to afford 1,4-dihydropyridines. The work-up is easy, and the products are obtained in good to excellent yields and high purity.

Keywords Hantzsch reaction · 1,4-Dihydropyridines · $FeNH_4(SO_4)_2{\cdot}12H_2O$ · Multi-component reactions

Introduction

The conventional synthesis of 1,4-dihydropyridines (1,4-DHPs) introduced by Hantzsch in 1881 involves one-pot condensation of an aldehyde, ammonia, and a ketoester in acetic acid [1]. Several methods have been developed to improve the efficiency of the Hantzsch reaction for synthesis of 1,4-DHPs, for example the use of microwaves [2], ionic liquids [3], high temperature [4], and acid catalysts, for example $Mg(ClO_4)$ [5], $CeCl_3{\cdot}7H_2O$/NaI [6], $Sc(OTf)_3$ [7], HY-Zeolite [8], and *p*-TSA [9].

1,4-Dihydropyridines have been reported to have diverse biological activity, for example anticonvulsant, antianxiety, antitumor, antidiabetic, antidepressive, analgesic, vasodilator, sedative, hypnotic, and anti-inflammatory activity [10], in addition to acting as a cerebral anti-ischemic agent in the treatment of Alzheimer's disease [11] and as a chemosensitizer in tumor therapy [12].

In continuation of our ongoing work on multi-component reactions (MCRs) [13–16], we now wish to report a facile and rapid one-pot three component reaction for preparation of DHP derivatives **4a**–**4k** from dimedone **1**, aldehydes **2a**–**2k**, and 3-aminocrotonates **3a**, **3b** using nontoxic and readily available $FeNH_4(SO_4)_2{\cdot}12H_2O$ as heterogeneous catalyst (Scheme 1).

Results and discussion

When a mixture of dimedone **1**, aldehyde **2a**, and 3-aminocrotonate **3a** in EtOH was stirred at r.t., the reaction was complete within 5 h. Work-up of the reaction mixture showed that dimethyl 1,4-dihydropyridine **4a** was prepared in 94% yield (Scheme 1).

Encouraged by this success, we extended this reaction of dimedone to a range of other aldehydes **2b**–**2k** and 3-aminocrotonates **3a**, **3b** under similar conditions, and 1,4-DHPs **4b**–**4k** were obtained in good yield [21]. The optimized results are summarized in Table 1.

In summary, we have described a successful strategy, an efficient and convenient green synthesis, for the preparation of some new 1,4-DHPs in a three-component cyclocondensation reaction of dimedone, aldehydes, and 3-aminocrotonate. The method has several advantages, including high yield of products, use of inexpensive, nontoxic, and readily available $FeNH_4(SO_4)_2{\cdot}12H_2O$ catalyst, and an easy experimental work-up procedure, that make it a useful process for synthesis of 1,4-dihydropyridines.

A. A. Mohammadi (✉) · A. Hadadzahmatkesh
Department of Chemistry, Sabzevar Branch,
Islamic Azad University, Sabzevar, Iran
e-mail: aliamohammadi@iaus.ac.ir

M. R. Asghariganjeh
Department of Chemistry, Omidieh Branch,
Islamic Azad University, Omidieh, Iran

Scheme 1

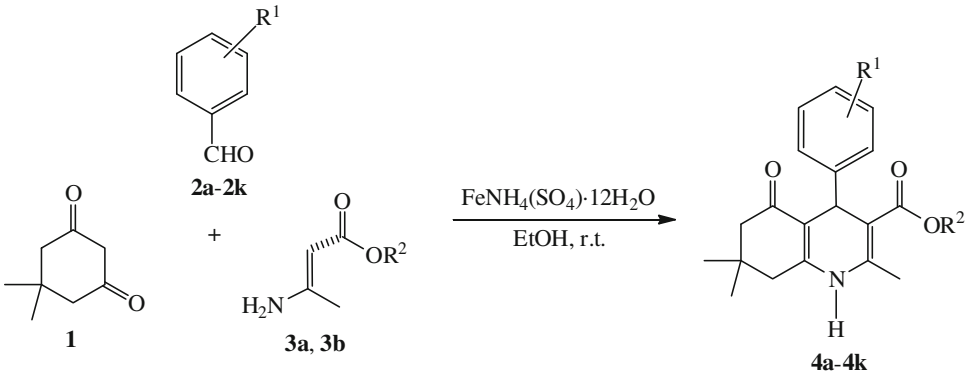

Table 1 $FeNH_4(SO_4)_2{\cdot}12H_2O$ (alum)-catalyzed synthesis of 1,4-dihydropyridines

Product	R^1	R^2	Time/ h:min	Yield/%	M.p./°C	Ref. m.p./°C
4a	H	Et	4:30	94	188–189	190 [17]
4b	*p*-Me	Et	4:30	93	268–269	270 [17]
4c	*p*-MeO	Et	4:00	92	255–257	256 [18]
4d	*p*-Cl	Et	4:45	93	243–245	243 [18]
4e	*p*-NO_2	Et	4:30	91	240–242	243 [18]
4f	*p*-F	Et	4:45	90	183–185	184–186 [9]
4g	*o*-Cl	Et	5:00	88	205–207	207–209 [19]
4h	H	Me	4:30	94	253–254	–
4i	*p*-Me	Me	4:30	92	271–273	272 [20]
4j	*m*-MeO	Me	5:00	93	258–259	–
4k	*p*-NO_2	Me	5:00	92	252–253	–

Reaction conditions: dimedone (1 mmol), aldehyde (1 mmol), 3-aminocrotonate (1 mmol), $FeNH_4(SO_4)_2{\cdot}12H_2O$ (20 mol%), 5 cm^3 EtOH, r.t.

Experimental

Melting points were measured in open capillary tubes on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu QP 1100 BX mass spectrometer. IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a Bruker 300 DRX Avance instrument at 300 and 75 MHz.

General procedure for preparation of 1,4-dihydropyridines ***4a–4k***

To a mixture of 1 mmol dimedone, 1 mmol aldehyde, and 1 mmol 3-aminocrotonate in 5 cm^3 EtOH was added 0.1 g $FeNH_4(SO_4)_2{\cdot}12H_2O$ (20 mol%), and the reaction was stirred at r.t. for the time indicated in Table 1. After completion of the reaction (monitored by TLC, ethyl acetate–*n*-hexane, 1:1), water was added to the reaction mixture, and the resulting solid was separated by filtration. The crude product was recrystallized form ethanol.

The catalyst is very inexpensive and nontoxic. The catalyst in the aqueous phase can be recovered by removing the water under vacuum, then washing with acetone and ethanol and drying at room temperature. It can be recycled and used in subsequent reactions without reduction in activity.

Methyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate (**4h**, $C_{20}H_{23}NO_3$)
White powder; m.p.: 253–254 °C; IR (KBr): $\bar{\nu}$ = 3,203, 3,016, 2,918, 1,707 (C=O), 1,626 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.13 (d, 1H, J = 12.7 Hz, CH_2), 2.27 (d, 1H, J = 13.2 Hz, CH_2), 2.32 (d, 1H, J = 15.2 Hz, CH_2), 2.41 (s, 3H, CH_3), 2.43 (d, 1H, J = 13.2 Hz, CH_2), 3.64 (s, 3H, OCH_3), 5.13 (s, 1H, CH), 7.12 (d, 1H, J = 7.2 Hz, Ar), 7.26 (t, 2H, J = 7.5 Hz, Ar), 7.32 (d, 2H, J = 7.5 Hz, Ar), 8.14 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 19.25, 27.36, 29.86, 32.85, 36.56, 40.17, 40.43, 40.72, 40.81, 41.03, 51.13, 105.21, 110.78, 126.15, 128.14, 128.19, 145.41, 147.68, 149.85, 168.43, 195.88 ppm; MS: *m*/*z* (%) = 325 (M^+, 35), 248 (100), 77 (25), 51 (25), 39 (25).

Methyl 1,4,5,6,7,8-hexahydro-4-(3-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (**4j**, $C_{21}H_{25}NO_4$)
White powder; m.p.: 258–259 °C; IR (KBr): $\bar{\nu}$ = 3,203, 3,022, 2,888, 1,707 (C=O), 1,621 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 0.89 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.01 (d, 1H, J = 7.8 Hz, CH_2), 2.07 (d, 1H, J = 15.5 Hz, CH_2), 2.12 (d, 1H, J = 7.2 Hz, CH_2), 2.29 (d, 1H, J = 8.5 Hz, CH_2), 2.94 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.93 (s, 1H, CH), 6.85–7.02 (m, 4H, Ar), 8.98 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 19.18, 27.43, 29.93, 32.83, 35.65, 39.58, 39.85, 40.14, 40.42, 40.70, 40.98, 41.27, 51.10, 51.21, 55.40, 102.99, 109.91, 126.24, 126.44, 127.55, 130.31, 132.87, 146.38, 150.23, 150.32, 167.57, 194.86 ppm; MS: *m*/*z* (%) = 355 (M^+, 65), 340 (25), 248 (100), 57 (40), 41 (30).

Methyl 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxoquinoline-3-carboxylate (**4k**, $C_{20}H_{22}N_2O_5$) White powder; m.p.: 252–253 °C; IR (KBr): $\bar{\nu} = 3{,}204$, 3,016, 2,963, 1,712 (C=O), 1,612 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 1.03$ (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.11 (d, 1H, $J = 9.4$ Hz, CH_2), 2.34 (d, 1H, $J = 16.1$ Hz, CH_2), 2.50 (d, 1H, $J = 14.2$ Hz, CH_2), 2.56 (s, 3H, CH_3), 2.69 (d, 1H, $J = 9.5$ Hz, CH_2), 3.74 (s, 3H, OCH_3), 5.18 (s, 1H, CH), 7.62 (d, 2H, $J = 8.4$ Hz, Ar), 8.30 (d, 2H, $J = 8.4$ Hz, Ar), 9.51 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 19.24$, 27.25, 29.87, 33.02, 37.28, 50.91, 51.68, 102.93, 109.91, 124.10, 129.47, 146.51, 147.31, 151.02, 155.67, 167.78, 195.21 ppm; MS: *m*/*z* (%) = 370 (M^+, 60), 340 (25), 248 (100), 83 (40), 55 (80), 39 (85).

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