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ORIGINAL PAPER

A facile protocol for the synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives by a Hantzsch-type reaction

Kun Zhao · Min Lei · Lei Ma · Lihong Hu

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Abstract A facile and efficient protocol is described for the synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives in good yields by the condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehydes, and ammonium acetate under catalyst-free conditions. The advantages of this protocol are operational simplicity, mild reaction conditions, high yields, and little environmental impact.

Keywords Hantzsch-type reaction · Aldehyde · 3-Methyl-1*H*-pyrazol-5(4*H*)-one · Catalyst-free

Introduction

The Hantzsch reaction is a well-known, simple, and straightforward procedure for the synthesis of 1,4-dihydropyridines by the three-component condensation of an aldehyde, β-dicarbonyl compounds, and ammonium acetate [1–4]. 1,4-Dihydropyridines are an important heterocyclic motif in natural and synthetic organic chemistry owing to their wide spectra of biological activities [5–9], e.g., they act as vasodilator, bronchodilator, antitumor, hepatoprotective, and neuroprotective agents [10–12]. Furthermore, some 1,4-dihydropyridine derivatives are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of hypertension [13–16]. Because 1,4-dihydropyridines exhibit significant biological activity, their synthesis has received a lot of interest from organic and medicinal chemists.

In recent years, there have been several modifications of the Hantzsch synthesis of 1,4-dihydropyridine derivatives, e.g., the use of microwave irradiation [17, 18], ionic liquids [19], TMSCl-NaI [20], metal triflates [21, 22], molecular iodine [23, 24], SiO_2-$NaHSO_4$ [25], SiO_2-$HClO_4$ [26], ceric ammonium nitrate [27], phenylboronic acid [28], PTSA-SDS [29], and organocatalysts [30]. However, to the best of our knowledge, there have been no reports of using 3-methyl-1*H*-pyrazol-5(4*H*)-one instead of β-dicarbonyl compounds for the synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives by condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehydes, and ammonium acetate.

In connection with our ongoing research on the development of simple and efficient syntheses of heterocyclic compounds [31, 32], we carried out an investigation to develop an efficient and practical method for the one-pot synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives by the condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehydes, and ammonium acetate under catalyst-free conditions.

Results and discussion

Initially, we investigated the condensation reaction of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**, 6 mmol), benzaldehyde (**2a**, 3.3 mmol), and ammonium acetate (4.5 mmol)

K. Zhao · M. Lei (✉) · L. Hu (✉)
Shanghai Research Center for Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Shanghai 201203, People's Republic of China
e-mail: mlei@mail.shcnc.ac.cn

L. Hu
e-mail: simmhulh@mail.shcnc.ac.cn

L. Ma
School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China

Table 1 Optimization of reaction conditions

Entry	Catalyst/mol%	Solvent	Time/h	Yield of **3a**/%[a]
1	$ZnCl_2$ (10)	EtOH	5	88
2	$FeCl_3$ (10)	EtOH	5	85
3	$MgCl_2$ (10)	EtOH	5	84
4	$Yb(OTf)_3$ (5)	EtOH	3	90
5	$Cu(ClO_4)_2{\cdot}6H_2O$ (5)	EtOH	3	90
6	Vitamin B_1 (5)	EtOH	4	88
7	TsOH (10)	EtOH	4	88
8	NH_2SO_3H (10)	EtOH	4	86
9	None	EtOH	5	86
10	None	MeOH	8	85
11	None	THF	6	86
12	None	DMF	4	86[b]
13	None	MeCN	5	83

The reaction was carried out at reflux temperature

[a] Isolated yields

[b] The reaction was carried out at 100 °C

under different reaction conditions. The results are summarized in Table 1.

A series of catalysts and solvents were examined in the condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**), benzaldehyde (**2a**), and ammonium acetate under reflux conditions. As shown in Table 1, this reaction was complete in 3–5 h in the presence of different catalysts (Table 1). It was interesting to note that this three-component Hantzsch-type reaction could proceed smoothly under catalyst-free conditions in high yields (Table 1, entries 9–13). For economical and environmental reasons, EtOH was chosen as the reaction medium for all further reactions.

To explore the scope of this method, the reaction conditions were applied to a variety of aromatic aldehydes (Table 2).

The results in Table 2 indicate that the reaction was complete in 2–10 h and led to desired 1,4-dihydropyridines **3** in good yields (84–94%) (Scheme 1). Aromatic aldehydes carrying either electron-donating (**2b**, **2i**, **2j**, **2k**, and **2l**) or electron-withdrawing (**2c**, **2d**, **2e**, **2f**, **2g**, and **2 h**) substituents all reacted very well, giving excellent yields.

We propose a mechanism of the Hantzsch-type condensation as shown in Scheme 2. Initially, intermediate **4** is formed by Knoevenagel condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**) and aldehyde **2**, and **5** is formed by the condensation of 3-methyl-1*H*-pyrazol-5(4*H*)-one and ammonium acetate. Then, Michael addition of intermediate **5** to **4** leads to the intermediate **6**. Finally, intramolecular cyclization and dehydration affords the 1,4-dihydropyridine **3** (Scheme 2).

Table 2 Synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives

Entry	ArCHO **2**	Time/h	Product **3**	Yield/%[a]
1	C_6H_5CHO (**2a**)	5	**3a**	86
2	$4\text{-}MeC_6H_4CHO$ (**2b**)	5	**3b**	92
3	$4\text{-}ClC_6H_4CHO$ (**2c**)	4	**3c**	93
4	$3\text{-}NO_2C_6H_4CHO$ (**2d**)	3	**3d**	84
5	$4\text{-}NO_2C_6H_4CHO$ (**2e**)	2	**3e**	90
6	$4\text{-}CNC_6H_4CHO$ (**2f**)	2	**3f**	88
7	$2,4\text{-}Cl_2C_6H_3CHO$ (**2g**)	10	**3g**	86
8	$4\text{-}FC_6H_4CHO$ (**2h**)	5	**3h**	90
9	$4\text{-}(CH_3)_2NC_6H_4CHO$ (**2i**)	3	**3i**	94
10	$4\text{-}OH\text{-}3\text{-}CH_3OC_6H_3CHO$ (**2j**)	3	**3j**	92
11	$4\text{-}OHC_6H_4CHO$ (**2k**)	3	**3k**	88
12	$4\text{-}CH_3OC_6H_4CHO$ (**2l**)	6	**3l**	85

[a] Isolated yield

In conclusion, we have developed a simple and efficient synthesis of 4-aryl-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-*b*:4′,3′-*e*]pyridine derivatives by a three-component reaction of 3-methyl-1*H*-pyrazol-5(4*H*)-one, aromatic aldehydes, and ammonium acetate in EtOH under catalyst-free conditions. This method has the advantages of high yields, short reaction times, and simple manipulations, which make it a useful process for the synthesis of these heterocyclic compounds.

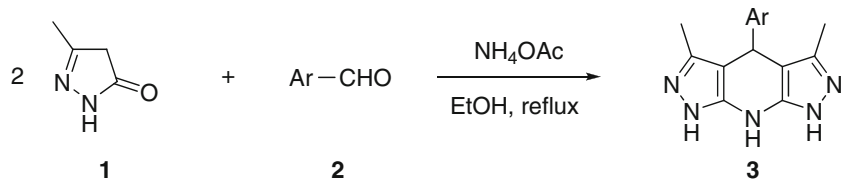
Experimental

Reagents and all solvents were analytically pure grade and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer at 400 MHz and 100 MHz, with TMS as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, coupling constants (J) in hertz. Melting points were determined with an X-4 apparatus and are corrected. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyzer, and their values were found to agree favorably with the calculated ones.

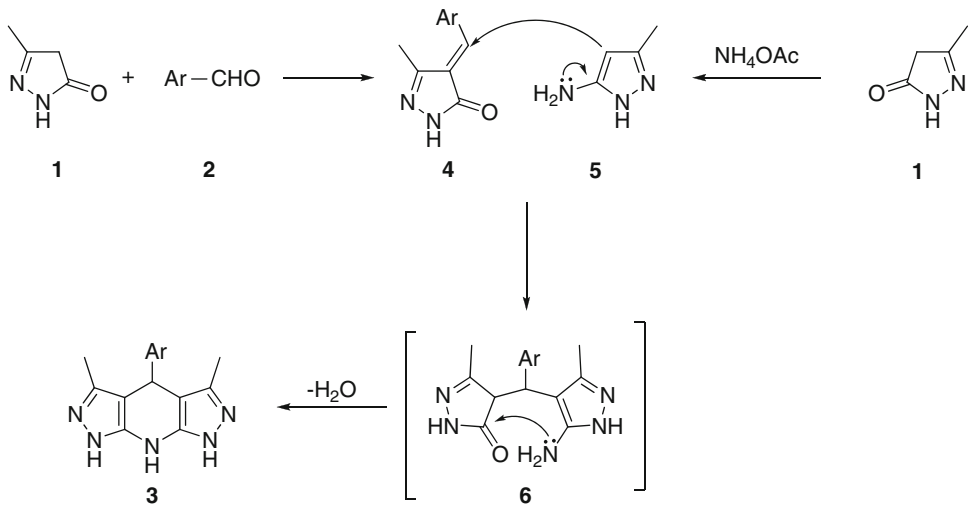
General procedure for the synthesis of compounds ***3a–3l***

A mixture of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**1**, 6 mmol), aromatic aldehyde (**2a–2l**, 3.3 mmol), and ammonium acetate (4.5 mmol) in 5 cm^3 EtOH was heated to reflux under stirring for the given time (Table 2). After completion (by TLC), the reaction mixture was cooled to room

Scheme 1



Scheme 2



temperature, then 5 cm^3 water was added to the mixture and stirred for 5 min. The solid was filtered and recrystallized from EtOH/H_2O (3:1) to afford the pure products **3**.

1,4,7,8-Tetrahydro-3,5-dimethyl-4-phenyldipyrazolo-[3,4-b:4′,3′-e]pyridine (**3a**, $C_{15}H_{15}N_5$)
White solid, m.p.: 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.07$ (s, 6H), 4.82 (s, 1H), 7.10–7.20 (m, 5H), 11.29 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.85$, 33.22, 104.67, 125.85, 127.93, 128.17, 140.23, 143.83, 161.55 ppm; IR (KBr): $\bar{\nu} = 2{,}921.6$, 1,602.6, 1,533.1, 1,490.7, 1,446.4, 1,218.8, 835.0, 709.7 cm^{-1}; MS (ESI): $m/z = 288$ ($[M + Na]^+$).

1,4,7,8-Tetrahydro-3,5-dimethyl-4-(4-methylphenyl)-dipyrazolo[3,4-b:4′,3′-e]pyridine (**3b**, $C_{16}H_{17}N_5$)
White solid, m.p.: 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.06$ (s, 6H), 2.23 (s, 3H), 4.78 (s, 1H), 7.01 (s, 4H), 11.31 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.85$, 20.98, 32.82, 104.83, 127.83, 128.74, 134.65, 140.14, 140.73, 161.53 ppm; MS (ESI): $m/z = 302$ ($[M + Na]^+$).

4-(4-Chlorophenyl)-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridine
(**3c**, $C_{15}H_{14}ClN_5$)
White solid, m.p.: 254–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.08$ (s, 6H), 4.83 (s, 1H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 8.4$ Hz, 2H), 11.34 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.79$, 32.69, 104.32, 128.06, 129.84, 130.49, 140.15, 142.79, 161.42 ppm; IR (KBr): $\bar{\nu} = 2{,}921.6$, 1,602.6, 1,529.3, 1,488.8, 1,440.6, 1,093.4, 1,014.4, 844.7 cm^{-1}; MS (ESI): $m/z = 322$, 324 ($[M + Na]^+$).

1,4,7,8-Tetrahydro-3,5-dimethyl-4-(3-nitrophenyl)-dipyrazolo[3,4-b:4′,3′-e]pyridine (**3d**, $C_{15}H_{14}N_6O_2$)
White solid, m.p.: 286–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.12$ (s, 6H), 5.01 (s, 1H), 7.53 (t, $J = 7.8$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.98 (s, 1H), 8.02 (d, $J = 7.8$ Hz, 1H), 11.38 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.76$, 33.02, 103.79, 121.20, 122.42, 129.70, 135.10, 140.25, 146.28, 148.05, 161.36 ppm; MS (ESI): $m/z = 333$ ($[M + Na]^+$).

1,4,7,8-Tetrahydro-3,5-dimethyl-4-(4-nitrophenyl)-dipyrazolo[3,4-b:4′,3′-e]pyridine (**3e**, $C_{15}H_{14}N_6O_2$)
White solid, m.p.: >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.10$ (s, 6H), 4.98 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 8.12 (d, $J = 8.4$ Hz, 2H), 11.38 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.77$, 33.42, 103.73, 123.44, 129.26, 140.17, 146.05, 152.21, 161.31 ppm; IR (KBr): $\bar{\nu} = 2{,}967.9$, 2,750.6, 1,604.5, 1,510.0, 1,442.5, 1,346.1, 1,176.4, 728.9 cm^{-1}; MS (ESI): $m/z = 333$ ($[M + Na]^+$).

4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)benzonitrile (**3f**, $C_{16}H_{14}N_6$)
White solid, m.p.: 286–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.09$ (s, 6H), 4.93 (s, 1H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 11.39 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.77$,

33.49, 103.76, 108.72, 119.61, 129.08, 132.19, 140.26, 149.91, 161.36 ppm; MS (ESI): $m/z = 313$ ($[M + Na]^+$).

4-(2,4-Dichlorophenyl)-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridine (**3g**, $C_{15}H_{13}Cl_2N_5$)
Yellow solid, m.p.: >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.95$ (s, 6H), 5.06 (s, 1H), 7.33 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.4$ Hz, 1H), 7.47 (d, $J = 2.1$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 1H), 11.08 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 15.62$, 36.37, 107.01, 131.71, 133.56, 136.19, 137.10, 138.41, 143.80, 145.18, 165.75 ppm; IR (KBr): $\bar{\nu} = 2{,}746.1$, 1,602.6, 1,571.7, 1,533.1, 1,469.5, 1,384.6, 790.6 cm^{-1}; MS (ESI): $m/z = 366$, 368 ($[M + Na]^+$).

4-(4-Fluorophenyl)-1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridine (**3h**, $C_{15}H_{14}FN_5$)
White solid, m.p.: 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.08$ (s, 6H), 4.83 (s, 1H), 7.03 (t, $J = 8.9$ Hz, 2H), 7.15 (dd, $J_1 = 5.9$ Hz, $J_2 = 8.4$ Hz, 2H), 11.35 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.79$, 32.57, 104.61, 114.74 ($J = 21$ Hz), 129.67 ($J = 7.9$ Hz), 139.81 ($J = 2.8$ Hz), 140.10, 160.88 ($J = 240$ Hz), 161.44 ppm; MS (ESI): $m/z = 306$ ($[M + Na]^+$).

4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)-N,N-dimethylaniline (**3i**, $C_{17}H_{20}N_6$)
Red solid, m.p.: 240–242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.07$ (s, 6H), 2.81 (s, 6H), 4.73 (s, 1H), 6.59 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 11.38 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.86$, 32.38, 40.91, 105.25, 112.74, 128.37, 131.65, 137.00, 149.08, 161.63 ppm; MS (ESI): $m/z = 331$ ($[M + Na]^+$).

2-Methoxy-4-(1,4,7,8-tetrahydro-3,5-dimethyldipyrazolo-[3,4-b:4′,3′-e]pyridin-4-yl)phenol (**3j**, $C_{16}H_{17}N_5O_2$)
Yellow solid, m.p.: 262–264 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.06$ (s, 6H), 3.65 (s, 3H), 4.76 (s, 1H), 6.56 (d, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 6.76 (s, 1H), 11.03 (brs, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.89$, 32.90, 56.09, 105.07, 112.80, 115.34, 120.41, 134.82, 140.00, 144.92, 147.44, 161.45 ppm; IR (KBr):$\bar{\nu} = 3{,}191.6$, 2,503.1, 1,610.3, 1,585.2, 1,484.9, 1,259.3, 1,224.6, 1,130.1, 788.7 cm^{-1}; MS (ESI): $m/z = 334$ ($[M + Na]^+$).

4-(1,4,7,8-Tetrahydro-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridin-4-yl)phenol (**3k**, $C_{15}H_{15}N_5O_2$)
White solid, m.p.: 268–270 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.06$ (s, 6H), 4.73 (s, 1H), 6.61 (d, $J = 8.6$ Hz, 2H), 6.93 (d, $J = 8.6$ Hz, 2H), 11.02 (brs, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.86$, 32.42, 105.14, 114.96, 128.80, 133.90, 140.13, 155.58, 161.54 ppm; MS (ESI): $m/z = 304$ ($[M + Na]^+$).

1,4,7,8-Tetrahydro-4-(4-methoxyphenyl)-3,5-dimethyldipyrazolo[3,4-b:4′,3′-e]pyridine (**3l**, $C_{16}H_{17}N_5O$)
Yellow solid, m.p.: 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.07$ (s, 6H), 3.69 (s, 6H), 4.77 (s, 1H), 6.77 (d, $J = 8.5$ Hz, 2H), 7.04 (d, $J = 8.5$ Hz, 2H), 11.16 (brs, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 10.83$, 32.41, 55.41, 104.98, 113.57, 128.86, 135.68, 140.10, 140.16, 157.64 ppm; MS (ESI): $m/z = 318$ ($[M + Na]^+$).

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