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Rapid three-component synthesis of pyrimidine and pyrimidinone derivatives in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ as a mild and highly efficient catalyst

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Abstract Bismuth(III) nitrate pentahydrate is found as a mild and highly efficient catalyst for the rapid synthesis of 4-amino-5-pyrimidine carbonitrile and pyrimidinone derivatives via three-component reaction of aldehydes, *N*-unsubstituted amidines, and malononitrile or ethyl cyanoacetate under thermal aqueous conditions. The reaction protocol is rapid and simple which is followed by formation of the corresponding pyrimidine and pyrimidinone derivatives in good to excellent yields with high purity.

Keywords Bismuth(III) nitrate pentahydrate · Amidines · Malononitrile · 4-Amino-5-pyrimidine-carbonitrile and pyrimidinones

Introduction

The discovery of novel synthetic routes towards pyrimidines and dihydropyrimidinones (DHPMs) is an area of continuing interest for organic chemists. Pyrimidine derivatives have occupied an important position in natural and synthetic organic chemistry, due to their wide range of biological activities, particularly in cancer and virus research [1]. These compounds often play a fundamental role as analgesic [2], antihypertensive [3], antipyretic [4], and anti-inflammatory drugs [5], and as pesticides [6], herbicides, medications, and plant growth regulators [7]. Therefore, synthetic methodologies for the synthesis of novel pyrimidines or pyrimidine-fused compounds are of challenging interest to organic chemists [8]. Conventional organic syntheses are generally based on homogeneous catalysts. However, homogeneous reactions suffer disadvantages in separation, regeneration, and so forth. From the

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viewpoint of green chemistry, the use of heterogeneous catalysts is desirable. The consequential advantages of heterogeneous catalysts from the environmental and economic points of view are clearly understandable, because these procedures allow money to be saved and the production of waste material to be minimized [9]. Bismuth(III) nitrate pentahydrate is known as a heterogeneous catalyst and commercially available reagent and requires no special handling. It is a stable and non-toxic crystalline solid, insensitive to air, and requires no special care during its handling. This reagent can act as an effective Lewis acid, and it can be used successfully in the presence of commercially available solvents without any drying or treatment [10]. The use of bismuth nitrate derivatives as catalysts in organic synthesis has increased considerably over the years. A literature survey revealed that bismuth(III) nitrate pentahydrate has been used for conversion of thiocarbonyls to their carbonyl compounds [11], aromatic nitration [12], protection of carbonyl compound [13], Michael reactions [14], synthesis of coumarins [15], guanylation of thiourea [16], etc. In the course of our investigations to develop new synthetic methods for the preparation of nitrogen-containing heterocycles in the presence of environmentally friendly base and acid catalysts, in order to reduce the amount of toxic waste and byproducts arising from chemical processes [17–20], we have performed the synthesis of 4-amino-5-pyrimidinecarbonitrile and dihydro-5-pyrimidinonecarbonitrile derivatives through a three-component reaction in the presence of $Bi(NO_3)_3{\cdot}5H_2O$ as a Lewis acid.

Experimental

Melting points were determined on an Gallenkamp melting-point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 Fourier transform infrared (FT-IR) spectrometer. ^1H NMR and ^{13}C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. Mass spectra (MS) were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

General procedure for the preparation of pyrimidine and pyrimidinone derivatives

A mixture of the aldehyde (2 mmol), amidines hydrochloride (2 mmol), malononitrile or ethyl cyanoacetate (2 mmol), $Bi(NO_3)_3{\cdot}5H_2O$ (5 mol%) and a catalytic amount of Et_3N in CH_3CN (5 mL) was refluxed with stirring for the times reported in Table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC), and hexane/ethyl acetate was used as an eluent. After completion of the reaction, the catalyst was separated from the reaction mixture by centrifugation. The excess acetonitrile was removed by evaporation and then was poured into ice-cold water; the crude product was filtered, dried, and recrystallized from 96 % ethanol.

Table 1 Synthesis of compounds **4a–s** and **5a–f** in the presence of base and acid catalysts

Compd. no.	Ar	R	Thermal conditions		Commercially available MgO		High surface area MgO		$Bi(NO_3)_3{\cdot}5H_2O$	
			Time (h)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	C_6H_5	Ph	6	78	60	83	20	85	5	86
4b	C_6H_5	NH_2	5	81	55	86	15	88	4	83
4c	4-MeC_6H_4	Ph	4	79	65	81	20	83	5	82
4d	4-MeC_6H_4	NH_2	5	64	60	84	22	86	7	86
4e	4-$MeOC_6H_4$	Ph	8	60	70	80	30	82	12	80
4f	4-$Me_2NC_6H_4$	Ph	12	78	90	80	40	83	15	83
4g		Ph	6	46	70	65	30	70	11	71
4h	4-ClC_6H_4	Ph	4	73	50	87	15	89	4	90
4i	4-ClC_6H_4	NH_2	3	82	45	90	13	91	4	90
4j	4-BrC_6H_4	Ph	4	80	58	84	18	87	5	85
4k	4-BrC_6H_4	NH_2	4	78	52	87	15	89	4	89
4l	4-FC_6H_4	NH_2	4	63	48	88	14	90	3	88
4m	4-FC_6H_4	Ph	4	66	45	91	12	92	3	91
4n	3-FC_6H_4	Ph	3	80	50	87	10	90	2	90
4o	3-FC_6H_4	NH_2	4	68	45	92	8	96	2	96
4p	3-FC_6H_4	Me	5	60	60	83	20	85	5	83
4q	4-$CF_3C_6H_4$	Ph	2	70	53	83	17	88	6	88
4r	4-$CF_3C_6H_4$	NH_2	4	72	50	87	15	90	4	92
4s	4-$CF_3C_6H_4$	Me	5	60	65	80	25	83	10	81
5a	C_6H_5	Ph	–	–	120	80	40	82	20	80
5b	4-ClC_6H_4	Ph	–	–	110	84	35	85	16	85
5c	3-FC_6H_4	Ph	–	–	100	84	33	86	15	82
5d	4-$CF_3C_6H_4$	Ph	–	–	110	82	36	84	16	81
5e	2,4-ClC_6H_3	Ph	–	–	105	86	33	88	14	89
5f	4-$NO_2C_6H_4$	Ph	–	–	100	87	33	89	13	89

*6-Oxo-2,4-diphenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**4a**)*

Yellow crystals; mp 105 °C. IR (KBr, υ_{max}/cm^{-1}): 3,329 (NH), 2,212 (CN), 1,691 (C=O), 1,617 (C=N), 1,542, 1,492 (C=C); ^1H NMR (300 MHz, DMSO-d_6): 9.62 (s, 1H, NH), 8.32–7.29 (m, 10H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 173.50, 168.29, 166.51, 138.96, 138.55, 130.72, 130.34, 129.40, 128.89, 128.66, 128.63, 120.88 (CN), 91.47 (C5). MS (*m*/*z*): 273 (M^+) (30), 245 (35), 170 (50), 142 (15), 120 (60), 104 (87), 77 (50), 53 (25). Anal. calcd. for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38 %. Found: C, 74.37; H. 3.92; N; 15.05 %.

*4-(4-Chlorophenyl)-6-oxo-2phenyl-1,6dihydro-5-pyrimidinecarbonitrile (**4b**)*

Yellow crystals; mp 210–212 °C. IR (KBr, υ_{max}/cm^{-1}): 3,478 (NH), 2,212 (CN), 1,690 (C=O), 1,617 (C=N), 1,542 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): 9.35 (s, 1H, NH); 8.31–7.33 (m, 9H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 173.29, 167.00, 164.95, 138.82, 137.23, 135.16, 130.81, 130.61, 128.76, 128.60, 128.54, 120.12 (CN), 91.37 (C5). MS (*m*/*z*): 307 (M^+) (40), 272 (45), 145 (60), 104 (60), 77 (55), 51 (35). Anal. calcd. for $C_{17}H_{10}ClN_3O$: C, 66.35; H, 3.28; N, 13.65 %. Found: C, 66.12; H. 3.08; N; 13.31 %.

*4-(3-Fluorophenyl)-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**4c**)*

White crystals; mp 105 °C. IR (KBr, υ_{max}/cm^{-1}): 3,329 (NH), 2,212 (CN), 1,691 (C=O), 1,617 (C=N), 1,542, 1,492 (C=C). H NMR (300 MHz, DMSO-d_6): 9.35 (s, 1H, NH); 8.32–7.36 (m, 9H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6) 169.92, 166.81, 163.48, 162.30 (d,$^{1}J_{=C-F}$ 241.50 Hz), 140.27 (d,$^{3}J_{=C-F}$ 7.50 Hz), 137.01, 131.48, 130.88 (d,$^{3}J_{=C-F}$ 7.50 Hz), 128.76, 128.74, 125.03, 119.13 (CN), 117.58 (d,$^{2}J_{=C-F}$ 21 Hz),115.59 (d,$^{2}J_{=C-F}$ 22.50 Hz), 92.79 (C5). MS (*m*/*z*): 291 (M^+) (60), 263 (65), 188 (90), 160 (25), 138 (20), 104 (75), 77 (80), 51 (35). Anal. calcd. for $C_{17}H_{10}FN_3O$: C, 70.10; H, 3.46; N, 14.43 %. Found: C, 69.86; H, 3.22; N; 14.05 %.

*6-Oxo-2-phenyl-4-[4-(trifluoromethyl)phenyl]-1,6-dihydro-5-pyrimidinecarbonitrile (**4d**)*

Yellow crystals; mp 125 °C. IR (KBr, υ_{max}/cm^{-1}): 3,503 (NH), 2,212 (CN), 1,641(C=O), 1,592 (C=N), 1,567 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6) 9.55 (s, 1H, NH), 8.32–7.44 (m, 9H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 172.72, 166.83, 165.04, 142.64, 139.06, 131.81 (q, $^{2}J_{=C-F}$ 22.50 Hz), 130.01, 129.58, 128.01 (q, $^{1}J_{=C-F}$ 270.75 Hz, CF3), 125.86 (q, $^{3}J_{=C-F}$ 3.75 Hz), 120.04 (CN), 91.91 (C5). MS (*m*/*z*): 341 (M^+) (60), 313 (65), 238 (80), 221 (15), 194 (10), 172 (10), 145 (40), 104 (85), 77 (90), 51 (50). Anal. calcd. for $C_{18}H_{10}F_3N_3O$: C, 63.35; H, 2.95; N, 12.31 %. Found: C, 63.01; H. 2.90; N; 12.18 %.

*4-(2,4-Dichlorophenyl)-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**4e**)*

Yellow crystals; mp 110 °C. IR (KBr, υ_{max}/cm^{-1}): 3,379 (NH), 2,212 (CN), 1,690 (C=O), 1,617 (C=N), 1,542, 1,492 (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): 9.37 (s, 1H, NH), 8.20–7.41 (m, 9H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 171.84, 167.26, 166.29, 138.94, 137.19, 134.59, 132.82, 132.13, 130.64, 129.51, 129.42, 128.78, 127.88, 119.15 (CN), 94.13 (C5). MS (*m*/*z*): 341 (M^+) (90), 313 (75), 238 (85), 221 (60), 194 (25), 171 (20), 145 (65), 104 (80), 77 (90), 51 (40). Anal. calcd. For $C_{17}H_9Cl_2N_3O$: C, 59.67; H, 2.65; N, 12.28 %. Found: C, 59.35; H. 2.56; N; 12.14 %.

*4-(4-Nitrophenyl)-6-oxo-2-phenyl-1,6-dihydro-5-pyrimidinecarbonitrile (**4f**)*

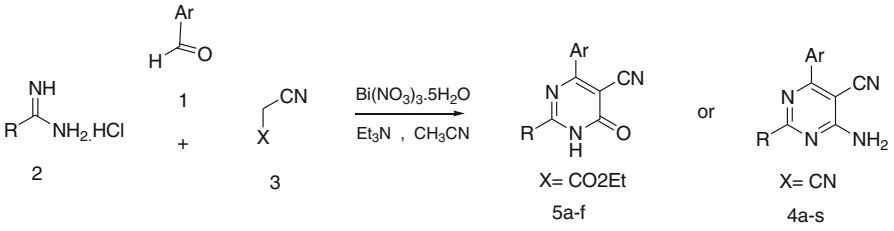
Brown crystals; mp 105 °C. IR (KBr, υ_{max}/cm^{-1}): 3,379 (NH), 2,212 (CN), 1,680 (C=O), 1,592 (C=N), 1,517 (C=C). ^1H NMR (300 MHz, DMSO-d_6): 9.52 (s, 1H, NH); 8.34–7.44 (m, 9H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): 172.53, 166.16, 165.03, 148.47, 144.81, 138.95, 130.74, 130.14, 128.54, 123.88, 120.04 (CN), 91.91 (C5). MS (*m*/*z*): 318 (M^+) (10), 215 (10), 176 (15), 136 (70), 103 (7), 77 (75), 63 (90), 45 (40). Anal. calcd. For $C_{17}H_{10}N_4O_3$: C, 64.15; H, 3.17; N, 17.60 %. Found: C, 64.03; H. 3.02; N; 17.45 %.

Results and discussion

The versatility of the bismuth(III) nitrate pentahydrate reagent encouraged us to study its utility for the Knoevenagel condensation and Michael addition. We have observed that $Bi(NO_3)_3{\cdot}5H_2O$ can be utilized efficiently for the synthesis of 4-amino-5-pyrimidinecarbonitrile and dihydro-5-pyrimidinonecarbonitrile derivatives with three-component reaction of aromatic aldehydes **1**, malononitrile or ethyl cyanoacetate **2**, and amidines **3** in acetonitrile at reflux, and in the presence of an equivalent amount of bismuth(III) nitrate pentahydrate for a short experimental time in good to excellent yields with high purity (Scheme 1).

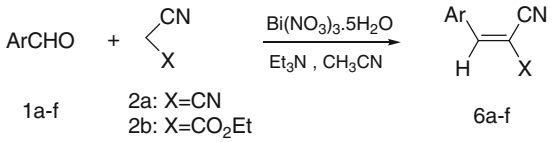
To optimize the reaction conditions for preparing compounds **4** and **5**, the effect of catalysts under different reaction conditions was investigated. We examined three-component reactions of aromatic aldehydes **1**, malononitrile or ethylcyanoacetate **2**, and amidines **3** in different solvents, such as water, ethanol, and acetonitrile at the thermal condition without catalyst and in the presence of catalysts, such as magnesium oxide MgO [commercial MgO (CM-MgO), high surface area MgO (HSA-MgO)] and bismuth(III) nitrate pentahydrate. As shown in Table 1, thr yield of the reaction is markedly affected by the catalyst and solvent, and optimum results were obtained when reactions were treated in acetonitrile and in the presence of bismuth(III) nitrate pentahydrate. We also optimized the quantity of catalyst, the best results being obtained when the reaction was carried out in the presence of 5 mol% catalyst.

In order to confirm the reactivity of bismuth(III) nitrate pentahydrate ($Bi(NO_3)_3{\cdot}5H_2O$) in the mentioned reactions, we separately studied Knoevenagel



Scheme 1 Three-component reaction of aromatic aldehydes **1**, malononitrile or ethyl cyanoacetate **2**, and amidines **3** in the presence of $Bi(NO_3)_3{\cdot}5H_2O$

Table 2 Knoevenagel condensation of aldehydes with malononitrile or ethyl cyanoacetate catalyzed by $Bi(NO_3)_3{\cdot}5H_2O$ in CH_3CN



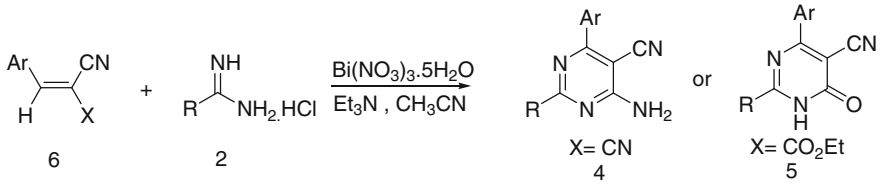
Compound	Ar	X	Time (s)	Yield (%)
6a	C_6H_5	CN	5	94
6b	C_6H_5	CO_2Et	70	92
6c	4-ClC_6H_4	CN	2	97
6d	4-ClC_6H_4	CO_2Et	20	93
6e	4-$O_2NC_6H_4$	CN	2	98
6f	4-$O_2NC_6H_4$	CO_2Et	25	92

condensations of malononitrile or ethyl cyanoacetate as active methylene compounds with aromatic aldehydes **1a–f**. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Our observations are reported in Table 2.

We also separately studied the Michael addition of arylidenemalononitriles or arylidene cyanoacetate **6** with amidines in the presence bismuth(III) nitrate pentahydrate. As shown in Table 3, the rates of these reactions are fast.

The one-pot and sequential steps reaction is often referred to as a tandem or cascade reaction in which reagents and catalysts are mixed together and experimental conditions are set up in such a way as to promote the reaction cascade. Thus, the arylidenemalononitrile or arylidenecyanoacetate **6** containing the electron-poor C=C double bond is quantitatively produced by fast Knoevenagel

Table 3 Michael additions of compounds 6 with amidines in the presence of $Bi(NO_3)_3{\cdot}5H_2O$



Compound	Ar	R	Time (min)	Yield (%)
4a	C_6H_5	C_6H_5	4	91
4b	C_6H_5	NH_2	6	92
5a	C_6H_5	C_6H_5	18	96
5b	4-ClC_6H_4	C_6H_5	15	96
4h	4-ClC_6H_4	C_6H_5	2	97
4i	4-ClC_6H_4	NH_2	4	94

addition of malononitrile to an aromatic aldehyde in the presence bismuth(III) nitrate pentahydrate. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatizetion to afford the 4-amino-5-pyrimidinecarbonitrile and dihydro-5-pyrimidinone carbonitrile derivatives. Structures **4a–s** were established on the basis of infrared (IR), which showed the presence of a C=N group in the region of 2,235–2,238 cm^{-1} and two sharp bands at 3,500–3,450 and 3,390–3,380 cm^{-1}, due to the asymmetric and symmetric vibrations of NH_2 group. The ^1H and ^{13}C NMR spectroscopic data were comparable with the reported data [17]. The structures of **5a–f** were determined on the basis of their elemental analyses, mass spectra, ^1H and ^{13}C NMR data, and IR spectral data.

Conclusion

In summary, $Bi(NO_3)_3{\cdot}5H_2O$ is reported as an efficient Lewis acid for the synthesis of 4-amino-5-pyrimidinecarbonitrile and pyrimidinones derivatives in a three-component reaction containing aldehydes, amidin systems, or malononitrile or ethyl cyanoacetate. Advantages of the strategy include mild reaction temperature, easy recovery, and reusability of the catalyst with consistent activity and short reaction times.

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