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Three-component synthesis of 5:6 and 6:6 fused pyrimidines using KF–alumina as a catalyst

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ABSTRACT

A series of fused pyrimidine derivatives were synthesized by the three-component reaction of an aryl aldehyde, urea, or guanidine in ethyl alcohol/dioxane in presence of 1-methyl-1*H*-pyrrol-2(3*H*)-one **1**, 1-methylpiperidin-2-one **2**, 1-methylindolin-2-one **3,** or 1,3-dimethyl-dihydropyrimidine-2,4-dione **9** at 80 °C catalyzed by KF–Al_2O_3. For example, when 1-methyl-1*H*-pyrrol-2(3*H*)-one **1**, arylaldehyde **4**, and urea **5** were treated with KF–Al_2O_3 in ethyl alcohol at 80 °C for 3–5 h, we obtained pyrrolo[2,3-*d*]-pyrimidine derivatives in good yield.

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Inorganic solid supports as catalysts have been used increasingly in recent years for the synthesis of various biologically active molecules. Among these inorganic solid supports, potassium fluoride coated with alumina (KF–alumina) has been used as a versatile reagent for various reactions such as the Knoevenagel condensation,[1] the Henry reaction,[2] the Darzens reaction,[3] the Wittig reaction,[4] the Biginelli reaction,[5] and alkylation[6] and elimination[7] reactions. In this Letter, we report a simple three-component synthesis of 5:6 fused [*d*] pyrimidines such as pyrazolo[3,4-*d*]pyrimidines,[8] pyrrolo[2,3-*d*]pyrimidines[9] as well as 6:6 fused systems such as pyrido[2,3-*d*]pyrimidines.[10] These heterocycles represent the aglycons of the more common bicyclic nucleosides, and these heteroaromatic aglycons have been shown to possess a variety of biological activities, such as inhibitors of epidermal growth factor receptor (EGF-R) protein tyrosine kinases and their potential as a treatment for proliferate diseases involving mitogenic signaling from the EGF-R has been recognized.[11] Derivatives of pyrrolo[2,3-*d*]pyrimidines have also been evaluated for their anti-tumor activities.[12]

Reports of pyrrolo[2,3-*d*]pyrimidine derivatives and their synthesis are abundant in the literature.[13] However, none of the synthetic procedures provides a general route for the synthesis of the three types of fused pyrimidines described here. Thus, as part of our ongoing research on the development of new synthetic methods, we found that when 1-methyl-1*H*-pyrrol-2(3*H*)-one **1**, arylaldehyde **4** and urea/guanidine **5** were treated with KF–Al_2O_3 in ethyl alcohol at 80 °C for 3–5 h, we obtained pyrrolo[2,3-*d*]-pyrimidine derivatives **6a**–**e** in good yields (Scheme 1). Evidently, a sequence of reactions involving Biginelli-like condensation took place during formation of the product. This may be concluded from the fact that when condensation of 1-methyl-1*H*-pyrrol-2(3*H*)-one **1** and benzaldehyde was carried out, 3-benzylidene-1-methyl-1*H*-pyrrol-2(3*H*)-one was isolated as the product[13] thereby indicating that a condensation reaction is the first step in this three-component process.

In order to demonstrate the efficiency and the applicability of the method, the reaction of a series of arylaldehydes with **2** or **3** was carried out to give the corresponding products[14–17] **7a**–**e** and **8a**–**e** in good yields under identical reaction conditions (Table 1).

The scope of the reaction was also demonstrated by the synthesis of 7-pyrimido[4,5-*d*]pyrimidin-2-ones using 1,3-dimethyl-dihydropyrimidine-2,4-dione **9** as the starting material; the reaction proceeded at 100 °C in the presence of KF/alumina as catalyst in dioxane to yield the desired products in moderate yield **10a**–**e** (Scheme 2).

The product was also obtained in good yield when an alkyl or an electron-donating group was attached to the aromatic ring of **4**. Furthermore, the reaction shown in Scheme 2 proceeded only when dioxane was used as the solvent. The yield of this reaction was improved partially when a few drops of acetic acid were added.

In conclusion, we have developed a convenient method for the synthesis of 5:6 and 6:6 fused pyrimidine derivatives through a three-component reaction catalyzed by KF/alumina having wide applicability, thus providing a general method for the synthesis of potentially biologically active heterocycles.

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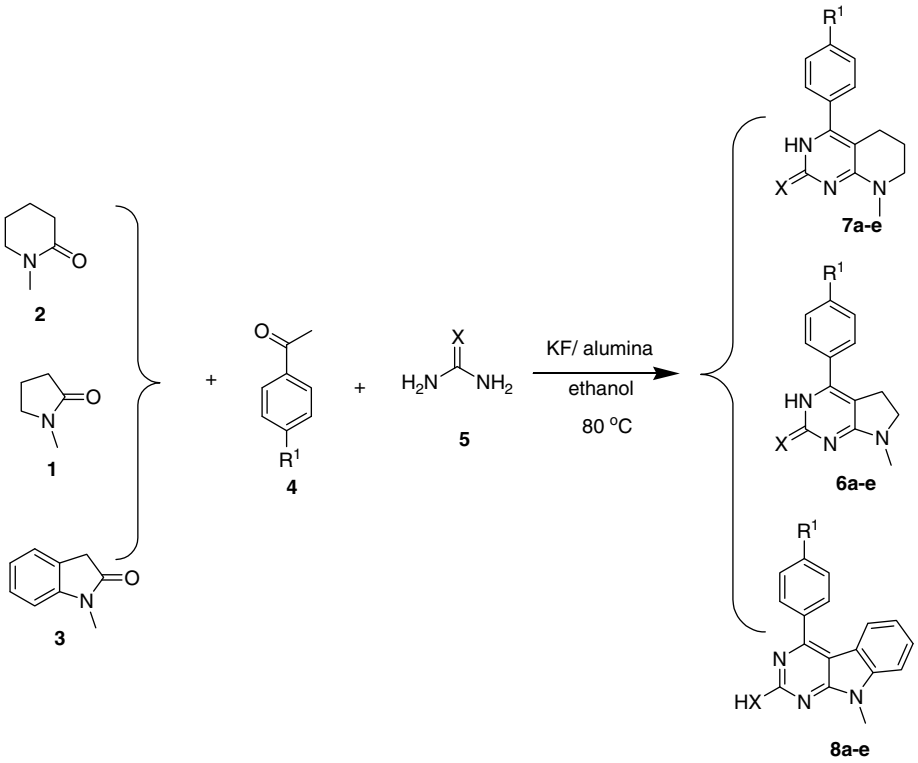

Scheme 1. Synthesis of substituted fused pyrimidines.

Table 1
Substituted fused pyrimidines

Entry	R^1	X	Yield (%)
6a	H	O	86
6b	CH_3	O	76
6c	NH_2	O	70
6d	NO_2	NH	81
6e	CH_3	NH	92
7a	H	NH	77
7b	CH_3	O	81
7c	NH_2	NH	83
7d	NO_2	O	60
7e	CH_3	NH	66
8a	H	NH	87
8b	CH_3	O	78
8c	NH_2	NH	76
8d	NO_2	O	68
8e	H	O	75
10a	OH	NH	50
10b	CH_3	O	59
10c	NH_2	O	55
10d	NO_2	NH	54
10e	NO_2	O	60

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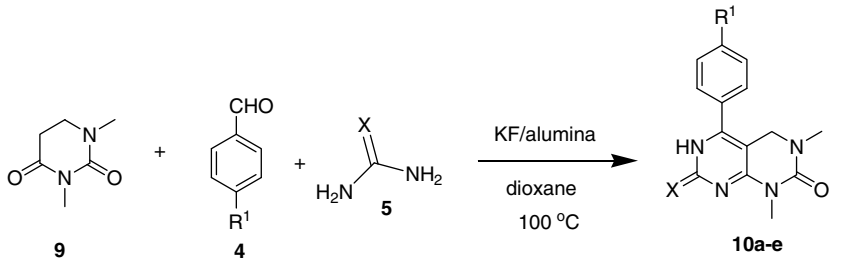

Scheme 2. Synthesis fo pyrimido[4,5-*d*]pyrimidines **10a**–**e**.

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13. *General reaction procedure:* Synthesis of **6a**: A dry 100 mL flask was charged with benzaldehyde **4** (8 mmol), urea **5** (8 mmol), 1-methylpyrrolidin-2-one **1** (8 mmol), KF/Al_2O_3 (1 g), and EtOH (30 mL). The mixture was stirred at 80 °C for 5–8 h. The reaction mixture, after completion (monitored by TLC), was cooled to room temperature, the solvent was evaporated in vacuum, and the crude product was purified by silica gel column chromatography using CH_2Cl_2 and methanol (9:1) as eluent to obtain an off-white solid **6a**. Mp = 254–256 °C. IR (KBr) 1785 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.01 (t, J = 7.4 Hz, 2H), 2.52 (s, 3H, CH_3), 2.61 (t, J = 7.4 Hz, 2H), 7.23–7.31 (m, 5H, aromatic), 11.26 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 30.5, 36.4, 57.5, 107.1, 126.5, 127.7, 129.1, 134.2, 135.1, 156.5, 160.3. MS (CI) m/z = 228.12 (M+1). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 69.18; H, 5.77; N, 18.49. Found: C, 69.21; H, 5.71; N, 18.52.
14. Compound **7b**: IR (KBr) 1778 cm^{-1}. Mp >300 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 1.42 (m, 2H), 1.91 (t, J = 7.1 Hz, 2H), 2.37 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.56 (t, J = 7.1 Hz, 2H), 7.02–7.21 (m, 4H, aromatic), 11.15 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 21.7, 24.3, 25.1, 35.1, 45.7, 105.6, 126.1, 128.7, 130.9, 133.2, 137.7, 156.2, 159.6. MS (CI) m/z = 256.14 (M+1). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.65; H, 6.68; N, 16.56.
15. Compound **8e**: IR (KBr) 3451 cm^{-1}. Mp >300 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 3.65 (s, 3H, CH_3), 6.15 (s, 2H, NH_2) 7.21–7.23 (m, 1H, aromatic), 7.24–7.30 (m, 4H, aromatic), 7.32–7.35 (m, 2H, aromatic), 7.44 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 44.6, 102.4, 111.3, 119.1, 120.5, 122.5, 127.6, 127.9, 128.5, 129.1, 131.8, 133.5, 136.7, 162.7, 163.7. MS (CI) m/z = 275.13. Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.53; H, 5.184; N, 20.62.
16. Compound **10d**: IR (KBr) 1675 cm^{-1}. Mp = 252–253 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.41 (s, 3H, CH_3) 2.68 (s, 6H, CH_3), 3.92 (s, 2H, CH_2), 7.01 (d, J = 7.0 Hz, 2H, aromatic), 7.15 (d, J = 7.2 Hz, 2H, aromatic), 11.36 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 24.6, 29.7, 38.0, 46.5, 103.6, 126.2, 128.5, 131.6, 134.1, 138.2, 154.9, 156.4, 158.6. MS(CI) m/z = 283.13 (M−1). Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.47; H, 5.77; N, 19.61.
17. Compound **10e**: IR (KBr) 1680, 3385 cm^{-1}. Mp = 257–258 °C ^1H NMR (DMSO-d_6, 400 MHz) δ ppm 2.67 (s, 6H, CH_3), 3.95 (s, 2H, CH_2), 7.56 (d, J = 7.2 Hz, 2H, aromatic), 8.18 (d, J = 7.2 Hz, 2H, aromatic), 11.57 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 29.8, 36.9, 46.5, 102.6, 120.9, 126.9, 134.2, 140.3, 147.5, 155.7, 156.2, 159.1. MS (CI) m/z = 316.10 (M+1). Anal. Calcd for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 53.43; H, 4.26; N, 22.11.