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# 基于室温条件及无金属催化的多组分反应构建 4-氨基-2-烷基-6-苯基-5-腈基嘧啶分子骨架

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**摘要:** 以硫脲、苯甲醛、丙二腈和溴代脂肪烃为原料,在无金属催化及室温条件下,建立了可以较高产率制备 4-氨基-2-烷基-6-苯基-5-腈基嘧啶等嘧啶环系列化合物的 4 组分合成新方法,所得的合成新方法具有良好的普适性以及进一步推广应用的潜力.

**关键词:** 多组分反应; 室温; 无金属; 嘧啶
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## 0　引言

嘧啶环的骨架结构广泛存在于大量具有生物活性的天然产物之中,具有潜在的抗菌、HIV 蛋白酶抑制、抗逆转录酶以及抗坠体虫等生物活性[1-5].嘧啶杂环衍生物的合成方法较多,传统的合成工艺大多均需要通过多步反应才能获得相应的产物,致使存在产物产率低及工艺不适宜工业化生产等问题,而设计其简易的合成新工艺,是解决这一问题的关键[6-10].

多组分反应(Multicomponent Coupling Reactions,简称 MCRs)是将 3 种以上相对简单易得的原料同时进行“一锅煮”反应,不经中间体的分离,直接一步就可以获得结构复杂分子骨架的合成方法,具有高效性、高选择性、反应条件温和、操作简洁方便等优点,同时也能容易合成出常规方法难以合成的目标分子,因而 MCRs 被认为是合成分子多样性和复杂性的有效手段.近年来,MCRs 被进一步成功地应用于对嘧啶环分子骨架的合成构建,一定程度上克服了其相应传统合成工艺存在的诸多不足,不过,这类反应仍需在金属催化或较高温度(>70 ℃)下加热促进等条件下才能有效实现[11-14].

本课题组曾设计合成了一类非常具有潜在应用价值的嘧啶杂环衍生物,即 4-氨基-2-烷基-6-苯基-5-腈基嘧啶的系列化合物[15],本文在前期工作基础上,并借鉴国内外同行关于通过 MCRs 合成构建嘧啶环分子骨架的类似经验,拟进一步设计以无金属催化及温和的室温条件为基础的多组分合成新方法,用于合成构建 4-氨基-2-烷基-6-苯基-5-腈基嘧啶的嘧啶环系列化合物,所得化合物的结构均通过红外光谱(FT-IR)、核磁共振($^1$H NMR、$^{13}$C NMR)及高分辨质谱(HRMS)等分析手段进行了表征确定.

## 1　实验部分

### 1.1　试剂与仪器

所有的反应均在氮气保护下进行,溶剂均以标准方法处理.$^1$H NMR 及$^{13}$C NMR 分别在 Bruker AV400 和 Bruker AV100 型核磁共振仪上测试,内标为 TMS 或 $CDCl_3$,HRMS 在 Finnigan MAT 8430 型仪器上测试.柱层析所用硅胶规格是 300 ~ 400 目,板层析所用硅胶为 GF254 型,均为青岛海洋化工厂产品.实验所用试剂均为市售 G. R. 或 A. R. 级产品.

### 1.2　实验方法

在一个氮气保护并装有磁力搅拌子的反应管中,分别加入硫脲(**1**)0.5 mmol、丙二腈(**2**)0.5 mmol、芳香醛(**3**)0.5 mmol 及溴代烷烃(**4**)0.5 mmol,然后再加入 1 mL 的二氯甲烷(DCM)及 1 mmol 的二氮杂二环(DBU),于室温(约 25 ℃)下反应 1.5 h 后,蒸干溶剂,即可获得产物粗品.产物粗品进一步通过柱层析分离后(洗脱溶剂:石油醚/乙酸乙酯 = 6/1(体积比)),最终可获得纯的系列化 4-氨基-2-烷基-6-苯基-5-腈基嘧啶产物.反应方程式见 Scheme 1.

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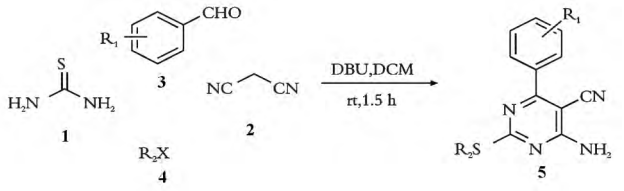


**Scheme1**　4-氨基-2-烷基-6-苯基-5-腈基嘧啶的 MCRs 合成路线

## 2　结果与讨论

### 2.1　MCRs 合成条件的优化

选用硫脲(1)、苯甲醛(2)、丙二腈(3a)和溴乙烷(4a)为原料来进行相应的"探针"实验,以获得其优化的合成反应条件. 结果发现,在室温条件下,无需辅以重金属催化剂,仅需加入一定量的碱性试剂就能有效催化反应生成相应的目标分子 5a. 同时,分别系统考察了各类碱性试剂(KOH、NaOH、$K_2CO_3$、$Cs_2CO_3$、$NaHCO_3$、$Et_3N$、*t*-BuOK、DABCO、KF、DBU 及吡啶)及溶剂(DCM、EtOH、DMSO、DMF、$CH_3CN$、甲苯、NMP、1,4-二氧六环、EtOH 及 DMAC)等因素对反应效果的影响,结果列于表 1.

**表 1**　4-氨基-2-烷基-6-苯基-5-腈基嘧啶的 MCRs 合成条件优化

| Entry | Base | Solvent | **5a**/% |
|---|---|---|---|
| 1 | KOH | EtOH | 31 |
| 2 | NaOH | EtOH | 33 |
| 3 | $K_2CO_3$ | EtOH | 54 |
| 4 | $Cs_2CO_3$ | EtOH | 21 |
| 5 | $NaHCO_3$ | EtOH | 12 |
| 6 | $Et_3N$ | EtOH | Trace |
| 7 | *t*-BuOK | EtOH | 9 |
| 8 | DBU | EtOH | 73 |
| 9 | DABCO | EtOH | 41 |
| 10 | KF | EtOH | 37 |
| 11 | Py | EtOH | Trace |
| 12 | DBU | DMSO | 49 |
| 13 | DBU | DMF | Trace |
| 14 | DBU | $CH_3CN$ | 58 |
| 15 | DBU | toluene | Trace |
| 16 | DBU | NMP | 36 |
| 17 | DBU | 1,4-dioxane | 44 |
| 18 | DBU | EtOH | 51 |
| 19 | DBU | DMAc | 17 |
| 20[a] | DBU | DCM | 83 |
| 21 | DBU | THF | 56 |
| 22[b] | DBU | DCM | 47 |
| 23[c] | DBU | DCM | 61 |
| 24[d] | DBU | DCM | 72 |
| 25[f] | DBU | DCM | 63 |

[a]In the presence of DBU(2 eq). [b]In the presence of DBU(0.5 eq). [c]In the presence of DBU(1 eq). [d]In the presence of DBU(3 eq). [f]In the presence of DBU(4 eq).

由表 1 可知,在以 DCM 为反应溶剂及 DBU(2.0 equiv)为碱性试剂的条件下,反应所得的产物 5a 的产率最佳,高达 83%(见表 1,entry 20),以此可作为优化的合成反应条件,用于下阶段工作中进行底物的普适性扩展. 此外,在反应过程中,碱剂 DBU 的用量会明显影响产物的产率(见表 1,entry 22 ~ 25),应该有效控制.

### 2.2　底物的普适性扩展

在获得优化的反应条件后,对反应底物的普适性进行了研究,结果如表 2 所示. 研究发现,各类苯甲醛($R_1$ = —$CH_3$,$CH_3O$—,$F^-$,$Cl^-$,$Br^-$,—$CF_3$等)均很好地参与了反应,且其产物收率不受各类取代基电子效应的影响(见表 2,entry 15 ~ 18);此外,各类溴代脂肪烃($CH_3Br$,$C_2H_5Br$,*n*-$C_3H_7Br$,*n*-$C_4H_9Br$,$(CH_3)_2CHBr$,$C_5H_{11}Br$)也能较好地参与反应. 总体而言,变换各类苯甲醛和溴代脂肪烃作为原料参与该 MCRs 反应时,所得的系列化 4-氨基-2-烷基-6-苯基-5-腈基嘧啶产物产率达到 62% ~ 94%,表明所构建的 MCRs 合成新方法在用于制备同类化合物时具有良好的普适性.

**表 2**　4-氨基-2-烷基-6-苯基-5-腈基嘧啶的底物扩展

| Entry | $R_1$ | $R_2$ | Product | Yield/% |
|---|---|---|---|---|
| 1 | H | Et | **5a** | 83 |
| 2 | 4-Me | $^n$Bu | **5b** | 85 |
| 3 | 2-Br | $^n$Pr | **5c** | 81 |
| 4 | 4-$CF_3$ | propyl | **5d** | 79 |
| 5 | 4-F | propyl | **5e** | 83 |
| 6 | 4-Me | propyl | **5f** | 89 |
| 7 | 4-Cl | dodecyl | **5g** | 71 |
| 8 | 4-MeO | butyl | **5h** | 91 |
| 9 | 4-Cl | butyl | **5i** | 81 |
| 10 | 4-Cl | propyl | **5j** | 82 |
| 11 | 4-MeO | propyl | **5k** | 94 |
| 12 | 2-Br | ethyl | **5l** | 76 |
| 13 | 4-MeO | isopropyl | **5m** | 62 |
| 14 | 4-F | pentyl | **5n** | 79 |
| 15 | 4-Me | ethyl | **5o** | 86 |
| 16 | 4-$CF_3$ | ehtyl | **5p** | 82 |
| 17 | 4-Cl | ethyl | **5q** | 84 |
| 18 | 4-F | ehtyl | **5r** | 86 |
| 19 | 2-Cl | propyl | **5s** | 73 |

### 2.3　产物表征

#### 2.3.1　4-氨基-2-乙硫基-6-苯基-5-腈基嘧啶(5a)

White solid; yield 83%; m. p.: 170 ~ 171℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 1.41 (t, $J$ = 7.2 Hz, 3H), 3.17 (m, $J$ = 7.2 Hz, 2H), 5.79 (s, 2H), 7.49 ~ 7.54 (m, 3H), 8.00 (d, $J$ = 6.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 14.5, 25.5, 83.0, 116.5, 128.7, 131.5, 135.8, 163.5, 167.3, 175.2; HRMS (ESI) calcd for $C_{13}H_{12}N_4S$ $[M+H]^+$: 257.086 1, found: 257.086 7.

2.3.2 **4-氨基-2-丁硫基-6-苯基-5-腈基嘧啶(5b)** White solid; yield 85%; m. p.: 151 ~ 152 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 0.95 (t, $J$ = 7.2 Hz, 3H), 1.48 (m, $J$ = 7.2 Hz, 2H), 1.73 (m, $J$ = 7.2 Hz, 2H), 2.43 (s, 3H), 3.17 (m, $J$ = 7.2 Hz, 2H), 5.70 (s, 2H), 7.11 (d, $J$ = 8.0 Hz, 2H), 7.92 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.7, 21.5, 22.0, 30.8, 31.3, 82.6, 116.7, 128.7, 129.4, 133.0, 142.1, 163.5, 167.0, 175.2; HRMS (ESI) calcd for $C_{16}H_{18}N_4S$ [M + H]$^+$: 299.133 0, found: 299.133 6.

2.3.3 **4-氨基-2-丙硫基-6-邻溴苯基-5-腈基嘧啶(5c)** White solid; yield 81%; m. p.: 148 ~ 149 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 0.95 (t, $J$ = 7.2 Hz, 3H), 1.67 (m, $J$ = 7.2 Hz, 2H), 3.04 (t, $J$ = 7.2 Hz, 2H), 5.73 (s, 2H), 7.24 ~ 7.36 (m, 3H), 7.61 ~ 7.63 (t, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 12.4, 21.6, 32.0, 85.2, 114.0, 120.2, 126.5, 129.1, 130.3, 132.4, 136.3, 161.4, 167.6, 174.6; HRMS (ESI) calcd for $C_{14}H_{13}N_4SBr$ [M + H]$^+$: 349.012 3, found: 349.012 5.

2.3.4 **4-氨基-2-丙硫基-6-对三氟甲基苯基-5-腈基嘧啶(5d)** White solid; yield 79%; m. p.: 206 ~ 207 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 1.06 (t, $J$ = 7.2 Hz, 3H), 1.78 (m, $J$ = 7.2 Hz, 2H), 3.15 (t, $J$ = 7.2 Hz, 2H), 5.84 (s, 2H), 7.78 (d, $J$ = 8.0 Hz, 2H), 8.09 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.4, 22.5, 33.1, 83.3, 115.9, 123.7 (q, $^1J$ = 270.8 Hz), 125.6 (q, $^3J$ = 3.7 Hz), 129.1, 133.0 (q, $^2J$ = 33.1 Hz), 139.1, 163.3, 165.9, 175.9; HRMS (ESI) calcd for $C_{15}H_{13}N_4SF_3$ [M + H]$^+$: 339.089 1, found: 339.089 3.

2.3.5 **4-氨基-2-丙硫基-6-对氟苯基-5-腈基嘧啶(5e)** White solid; yield 83%; m. p.: 163 ~ 164 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 1.05 (t, $J$ = 7.2 Hz, 3H), 1.77 (m, $J$ = 7.2 Hz, 2H), 3.14 (t, $J$ = 7.2 Hz, 2H), 5.76 (s, 2H), 7.19 (t, $J$ = 8.4 Hz, 2H), 8.03 (dd, $J_1$ = 5.2 Hz, $J_2$ = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.4, 22.6, 33.0, 82.6, 115.8 (d, $^2J$ = 21.9 Hz), 116.4, 131.0 (d, $^3J$ = 8.6 Hz), 164.7 (d, $^1J$ = 246.2 Hz), 166.0, 175.5; HRMS (ESI) calcd for $C_{14}H_{13}N_4SF$ [M + H]$^+$: 289.092 3, found: 289.093 1.

2.3.6 **4-氨基-2-丙硫基-6-对甲苯基-5-腈基嘧啶(5f)** White solid; yield 89%; m. p.: 154 ~ 155 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 1.05 (t, $J$ = 7.2 Hz, 3H), 1.78 (m, $J$ = 7.2 Hz, 2H), 3.15 (t, $J$ = 7.2 Hz, 2H), 5.77 (s, 2H), 7.31 (d, $J$ = 8.0 Hz, 2H), 7.91 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.4, 21.5, 22.7, 33.0, 82.7, 116.7, 128.7, 129.4, 133.0, 142.1, 163.5, 167.0, 175.2; HRMS (ESI) calcd for $C_{15}H_{16}N_4S$ [M + H]$^+$: 285.117 4, found: 285.118 0.

2.3.7 **4-氨基-2-十二烷硫基-6-对氯苯基-5-腈基嘧啶(5g)** White solid; yield 71%; m. p.: 120 ~ 121 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 0.88 (t, $J$ = 6.8 Hz, 3H), 1.25 (m, 16H), 1.43 (m, 2H), 1.72 (m, $J$ = 7.2 Hz, 2H), 3.14 (m, $J$ = 7.2 Hz, 2H), 6.01 (s, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.95 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 14.1, 22.7, 28.9, 29.2, 29.3, 29.4, 29.5, 29.6, 29.63, 29.7, 31.1, 31.9, 82.8, 116.4, 129.0, 130.1, 134.1, 137.8, 163.5, 165.9, 175.4; HRMS (ESI) calcd for $C_{23}H_{31}N_4SCl$ [M + H]$^+$: 431.203 6, found: 431.204 2.

2.3.8 **4-氨基-2-丁硫基-6-对甲氧苯基-5-腈基嘧啶(5h)** White solid; yield 91%; m. p.: 158 ~ 159 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 0.96 (t, $J$ = 7.2 Hz, 3H), 1.48 (m, $J$ = 7.2 Hz, 2H), 1.74 (m, $J$ = 7.2 Hz, 2H), 3.16 (m, $J$ = 7.2 Hz, 2H), 3.88 (s, 3H), 5.66 (s, 2H), 7.01 (d, $J$ = 8.8 Hz, 2H), 8.05 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 12.6, 21.0, 29.8, 30.3, 54.4, 80.9, 113.0, 116.0, 127.1, 129.5, 161.3, 162.7, 165.1, 173.8; HRMS (ESI) calcd for $C_{16}H_{18}N_4SO$ [M + H]$^+$: 315.128 0, found: 315.128 3.

2.3.9 **4-氨基-2-丁硫基-6-对氯苯基-5-腈基嘧啶(5i)** White solid; yield 81%; m. p.: 128 ~ 129 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 0.95 (t, $J$ = 7.2 Hz, 3H), 1.47 (m, $J$ = 7.2 Hz, 2H), 1.71 (m, $J$ = 7.2 Hz, 2H), 3.16 (m, $J$ = 7.2 Hz, 2H), 6.05 (s, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.95 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.6, 22.0, 30.8, 31.3, 82.8, 116.2, 128.9, 130.0, 134.2, 137.8, 163.6, 165.8, 175.5; HRMS (ESI) calcd for $C_{15}H_{15}N_4SCl$ [M + H]$^+$: 319.078 4, found: 319.078 6.

2.3.10 **4-氨基-2-丙硫基-6-对氯苯基-5-腈基嘧啶(5j)** White solid; yield 82%; m. p.: 182 ~ 183 ℃; $^1$H NMR (400 MHz, $CDCl_3$), $\delta$: 1.05 (t, $J$ = 7.2 Hz, 3H), 1.77 (m, $J$ = 7.2 Hz, 2H), 3.14 (m, $J$ = 7.2 Hz, 2H), 5.78 (s, 2H), 7.48 (d, $J$ = 8.4 Hz, 2H), 7.95 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$), $\delta_C$: 13.4, 22.6, 33.1, 82.7, 116.3, 129.0, 130.0, 134.1, 137.8, 163.4, 165.9, 175.6; HRMS (ESI) calcd for $C_{14}H_{13}N_4SCl$ [M + H]$^+$: 305.062 8, found: 305.061 9.

2.3.11　**4-氨基-2-丙硫基-6-对甲氧苯基-5-腈基嘧啶(5k)**　White solid; yield 94%; m. p.: 172 ~ 173 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.06(t, $J$ = 7.2 Hz, 3H), 1.78(m, $J$ = 7.2 Hz, 2H), 3.15(m, $J$ = 7.2 Hz, 2H), 3.88(s, 3H), 5.77(s, 2H), 7.01(d, $J$ = 8.4 Hz, 2H), 8.04(d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 13.4, 22.7, 33.0, 55.4, 81.9, 114.0, 117.0, 128.1, 130.5, 162.4, 163.6, 166.2, 175.0; HRMS(ESI) calcd for $C_{15}H_{16}N_4SO$ [M + H]$^+$: 301.112 3, found: 301.111 9.

2.3.12　**4-氨基-2-乙硫基-6-邻溴苯基-5-腈基嘧啶(5l)**　White solid; yield 76%; m. p.: 131 ~ 132 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.38(t, $J$ = 7.2 Hz, 3H), 3.13(m, $J$ = 7.2 Hz, 2H), 5.76(s, 2H), 7.33 ~ 7.44(m, 3H), 7.69(d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 13.4, 24.5, 85.2, 114.0, 120.2, 126.6, 129.1, 130.4, 132.5, 136.3, 161.5, 167.7, 174.5; HRMS(ESI) calcd for $C_{13}H_{11}N_4SBr$ [M + H]$^+$: 334.996 6, found: 334.998 4.

2.3.13　**4-氨基-2-异丙硫基-6-甲氧苯基-5-腈基嘧啶(5m)**　White solid; yield 62%; m. p.: 197 ~ 198 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.44(d, $J$ = 6.4 Hz, 6H), 3.72(m, $J$ = 6.8 Hz, 1H), 3.88(s, 3H), 5.80(s, 2H), 7.01(d, $J$ = 8.4 Hz, 2H), 8.05(d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 22.9, 36.2, 55.5, 81.8, 114.0, 117.0, 128.1, 130.5, 162.4, 163.6, 166.3, 174.8; HRMS(ESI) calcd for $C_{15}H_{16}N_4SO$ [M + H]$^+$: 301.112 3, found: 301.113 3.

2.3.14　**4-氨基-2-戊硫基-6-对氟苯基-5-腈基嘧啶(5n)**　White solid; yield 79%; m. p.: 135 ~ 136 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 0.91(t, $J$ = 7.2 Hz, 3H), 1.33 ~ 1.45(m, 2H), 1.74(m, $J$ = 7.2 Hz, 3H), 3.15(t, $J$ = 8.4 Hz, 4H), 5.78(s, 2H), 7.19(t, $J$ = 8.4 Hz, 2H), 8.03(dd, $J_1$ = 5.2 Hz, $J_2$ = 8.8 Hz, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 13.9, 22.2, 28.9, 31.0, 31.1, 82.6, 115.8(d, $^2J$ = 21.8 Hz), 116.4, 131.0(d, $^3J$ = 9.0 Hz), 131.8(d, $^4J$ = 2.5 Hz), 164.7(d, $^4J$ = 247.0 Hz), 166.0, 175.5; HRMS(ESI) calcd for $C_{16}H_{17}N_4SF$ [M + H]$^+$: 317.123 6, found: 317.124 0.

2.3.15　**4-氨基-2-乙硫基-6-对甲苯基-5-腈基嘧啶(5o)**　White solid; yield 86%; m. p.: 200 ~ 201 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.40(t, $J$ = 7.2 Hz, 3H), 2.43(s, 3H), 3.17(m, $J$ = 7.2 Hz, 2H), 5.82(s, 2H), 7.31(d, $J$ = 7.6 Hz, 2H), 7.92(d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 14.5, 21.5, 25.5, 82.7, 116.7, 128.7, 129.4, 133.0, 142.1, 163.6, 167.1, 175.0; HRMS(ESI) calcd for $C_{14}H_{13}N_4S$ [M + H]$^+$: 270.093 9, found: 270.094 1.

2.3.16.　**4-氨基-2-乙硫基-6-对三氟甲基苯基-5-腈基嘧啶(5p)**　White solid; yield 82%; m. p.: 239 ~ 240 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.41(t, $J$ = 7.2 Hz, 3H), 3.17(m, $J$ = 7.2 Hz, 2H), 5.78(s, 2H), 7.78(d, $J$ = 8.0 Hz, 2H), 8.09(d, $J$ = 8.4 Hz, 2H), $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 14.4, 25.5, 83.3, 116.0, 123.7(q, $^1J$ = 270.9 Hz), 125.7(q, $^3J$ = 3.6 Hz), 129.1, 133.0(q, $^2J$ = 32.9 Hz), 139.1, 163.3, 165.9, 175.8; HRMS(ESI) calcd for $C_{14}H_{11}N_4F_3S$ [M + H]$^+$: 325.073 5, found: 325.074 1.

2.3.17　**4-氨基-2-乙硫基-6-对氯苯基-5-腈基嘧啶(5q)**　White solid; yield 84%; m. p.: 191 ~ 192 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.40(t, $J$ = 7.2 Hz, 3H), 3.16(m, $J$ = 7.2 Hz, 2H), 5.85(s, 2H), 7.48(d, $J$ = 8.4 Hz, 2H), 7.96(d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 14.5, 25.5, 82.8, 116.3, 129.0, 130.4, 134.1, 137.9, 163.5, 166.0, 175.4; HRMS(ESI) calcd for $C_{13}H_{11}N_4SCl$ [M + H]$^+$: 291.047 1, found: 291.048 2.

2.3.18　**4-氨基-2-乙硫基-6-对氟苯基-5-腈基嘧啶(5r)**　White solid; yield 86%; m. p.: 159 ~ 160 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.40(t, $J$ = 7.2 Hz, 3H), 3.16(t, $J$ = 7.2 Hz, 2H), 5.81(s, 2H), 7.19(td, $J$ = 2.4 Hz, $J$ = 8.8 Hz, 2H), 8.01 ~ 8.05(m, 2H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 14.5, 25.5, 82.7, 115.8(d, $^2J$ = 21.7 Hz), 116.4, 131.0(d, $^3J$ = 8.9 Hz), 131.9(d, $^4J$ = 2.6 Hz), 163.5, 164.7(d, $^4J$ = 246.2 Hz), 175.3; HRMS(ESI) calcd for $C_{13}H_{11}N_4SF$ [M + H]$^+$: 275.076 7, found: 275.076 9.

2.3.19　**4-氨基-2-丙硫基-6-邻氯苯基-5-腈基嘧啶(5s)**　White solid; yield 73%; m. p.: 134 ~ 135 ℃; $^1$H NMR(400 MHz, $CDCl_3$), $\delta$: 1.03(t, $J$ = 7.2 Hz, 3H), 1.75(m, $J$ = 7.2 Hz, 2H), 3.11(t, $J$ = 6.8 Hz, 2H), 5.80(s, 2H), 7.38 ~ 7.45(m, 3H), 7.51(d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR(100 MHz, $CDCl_3$), $\delta_C$: 13.4, 22.6, 33.1, 86.4, 115.1, 127.0, 130.2, 130.3, 131.3, 132.2, 135.4, 162.5, 167.4, 175.7; HRMS(ESI) calcd for $C_{14}H_{13}N_4SCl$ [M + H]$^+$: 305.062 8, found: 305.063 9.

## 3　结论

首先,选择以简单易得的硫脲、苯甲醛、丙二腈和溴代脂肪烃为原料,在无金属催化及室温条件下,

实现了新的4组分合成方法,该法具有条件温和、原料易得以及环境友好性等优点.然后,将所构建的合成新方法用于制备4-氨基-2-烷基-6-苯基-5-腈基嘧啶的嘧啶环系列化合物,所得目标产物的产率为62%~94%,表明其在用于制备该类化合物时具有良好的普适性,具有进一步推广应用的潜力.

## 4 参考文献


[1] Bhojgude S S, Biju D A. Arynes in transition-metal-free multicomponent coupling reactions [J]. Angewandte Chemie International Edition, 2012, 51(7): 1520-1522.

[2] Alexander D, Wang Wei, Wang Kan. Chemistry and biology of multicomponet reactions [J]. Chemical Reviews, 2012, 112(6): 3083-3135.

[3] Junichiro Y, Atsushi D. C-H bood functionalization: emerging synthetic tools for natural products and pharmaceuticals [J]. Angewandte Chemie International Edition, 2012, 51(36): 8960-9009.

[4] Beingessner R L, Deng B-L, Fanwick P E, et al. A regioselective approach to trisubstituted 2 (or 6)-arylaminopyrimidine-5-carbaldehydes and their application in the synthesis of structurally and electronically unique G∧C base precursors [J]. J Org Chem, 2008, 73(3): 931-939.

[5] Payton M, Geuns-Meyer S D. Discovery of a potent, selective, and orally bioavailable pyridinyl-pyrimidine phthalazine aurora kinase inhibitor [J]. J Med Chem, 2010, 53(17): 6368-6377.

[6] Mukhopadhyay C, Das P, Butcher R J. An expeditious and efficient synthesis of highly functionalized [1,6]-naphthyridines under catalyst-free conditions in aqueous medium [J]. Org Lett, 2011, 13(17): 4664-4667.

[7] Danel K, Pedersen E B, Nielsen C. Synthesis and anti-HIV-1 activity of novel 2,3-dihydro-7*H*-thiazolo [3,2-*a*] pyrimidin-7-ones [J]. J Med Chem, 1998, 41(2): 191-198.

[8] Horvath A, Vasvari-Debreczy L, Dessy F, et al. Nitrogen bridgehead compounds. Part 18. New antiallergic 4*H*-pyrido [1,2-*a*] pyrimidin-4-ones. Part I [J]. J Med Chem, 1982, 25(10): 1140-1145.

[9] Bennett L R, Blankley C J, Fleming R W. Antihypertensive activity of 6-arylpyrido [2,3-*d*] pyrimidin-7-amine derivatives [J]. J Med Chem, 1981, 24(4): 382-389.

[10] Blankley C J, Bennett L R, Fleming R W, et al. Antihypertensive activity of 6-arylpyrido [2,3-*d*] pyrimidin-7-amine derivatives. 2, 7-Acyl amide analogs [J]. J Med Chem, 1983, 25(3): 403-411.

[11] Wang Zitao, Wang Yang, Zhang Wenxiong, et al. Efficient one-pot synthesis of 2,3-dihydropyrimidinthiones via multicomponent coupling of terminal alkynes, elemental sulfur, and carbodiimides [J]. J Am Chem Soc, 2009, 131(42): 15108-15109.

[12] Cevher A, Alan K B, Esra C, et al. An efficient one-pot multicomponent approach to 5-amino-7-aryl-8-nitrothiazolo [3,2-*a*] pyridines [J]. Tetrahedron, 2011, 67(49): 9522-9528.

[13] Soleimani E, Ghorbani S, Ghasempour H R. Novel isocyanide-based three-component reaction: a facile synthesis of substituted 1*H*-chromeno [2,3-*d*] pyrimidine-5-carboxamides [J]. Tetrahedron, 2013, 69(39): 8511-8515.

[14] Rong Liangce, Xia Sheng, Yin Shan, et al. An efficient multicomponent reaction for synthesis of 4-amino-6-aryl-2-alkylthiopyrimidine-5-carbonitrile derivatives [J]. Researches on Chemical Intermediates, 2013, 39(8): 3699-3707.

[15] Wang Tao, Liu Shu, Zheng Caihua, et al. New 3,7-dihydro-4*H*-pyrazolo [3′,4′:2,3] pyrido [4,5-*d*] pyrimidin-4-ones [J]. J Chem Research, 2008, 11: 619-621.


# The Room-Temperature Metal-Free Muticomponent Synthesis of 4-Amino-2-Alkylsulfanyl-6-Aryl-5-Cyanopyrimidines


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**Abstract:** New four-component tandem reactions of malononitrile, halohydrocarbon, thiourea and aromatic aldehyde have been successfully developed only at room temperature and under metal-free conditions, in good to excellent yields of 4-amino-6-aryl-5-cyanopyrimidines.



**Key words:** multicomponent reactions; room temperature; metal-free; pyrimidine

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