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# A Facile Synthesis of 2-Amino-5-cyano-4, 6-disubstitutedpyrimidines under MWI

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## Abstract

Microwave Assisted Organic Synthesis (MAOS) is energy efficient and effective tool to speed up the synthesis for drug discovery process. In the present study we report a novel protocol for the rapid, high throughput synthesis of mononuclear 2-amino-5-cyano-4,6-disubstituted pyrimidines, adaptable to parallel synthesis for compound libraries. The overall reaction time in hrs has been reduced to 25 - 50 minutes with improved yields.

**Keywords:** Microwave Assisted Organic Synthesis (MAOS), 2-Amino-5-Cyano-2, 6-Disubstitutedpyrimidines, *α*-Cyanoketene *S*,*S*-Acetals

## 1. Introduction

Mononuclear pyrimidines exhibit a wide range of medicinal activities and are isomeric with two other forms of diazine. Physiologically important nucleic acids bases as well as some vitamins are pyrimidine derivatives [1,2]. The major approach to the synthesis of mononuclear pyrimidines is the principal synthesis, involving the condensation of N-C-N fragment with an appropriate functionalized 3-carbon unit [3]. Various synthetic methods and reaction conditions have been employed for the synthesis of mononuclear pyrimidines in the literature [4-17].

The reported methods for the syntheses of mononuclear pyrimidines have one or the other limitations such as more number of steps, use of carcinogenic reagents like benzene, pyridine and lengthy reaction time. In many syntheses volatile organic solvents are used, which are detrimental to the environment and are to be recovered.

The generalized method for the synthesis of mononuclear pyrimidines is by the cyclocondensation of α-cyanoketene S,N-acetals with guanidine in DMF under reflux for 24 - 36 hr. The α-cyanoketene S,N-acetals were prepared through the nucleophilic displacement of the 3-methylthio group of the corresponding α-cyanoketene S,S-acetals with various amines [16].

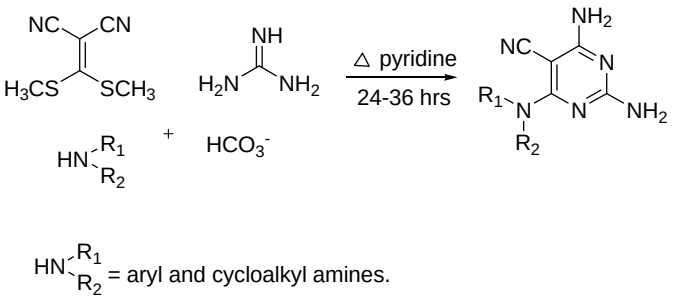
Tominaga *et al.* [18] have further improved on the synthesis of mononuclear pyrimidines by direct one pot synthesis through Multi Component Reaction (MCR) of *α*-Cyanoketenes *S*,*S*-acetals, appropriate amine and guanidine carbonate (Scheme 1). The solvent employed was pyridine and overall reaction time was 24 - 36 hr.

Microwave Assisted Organic Synthesis (MAOS) is an invaluable technology for drug discovery applications as it dramatically reduces reaction time, which makes it ideal for rapid reaction scouting and optimization, allowing rapid synthesis of large number of NCEs and their libraries. It is an efficient synthetic tool and its benefit has been well documented [19-22]. In continuation to our ongoing work on green chemical techniques [23], herein we report a novel, hitherto unreported protocol for the rapid synthesis of mononuclear 2-amino-5-cyano-4,6-disubstituted-pyrimidines under MWI. (Microwave Irradiation)

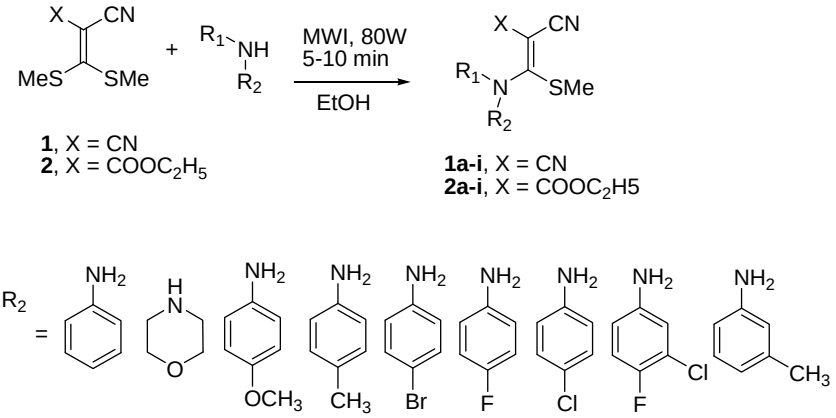
## 2. Results and Discussion

The *α*-cyanoketene *S*,*S*-acetals such as di-(methylthio) methylene malononitrile **1** and ethyl-2,2-di(methylthio)methylene cyanoacetate **2** were prepared as per reported method [16]. The *α*-cyanoketene *S*,*S*-acetals **1** and **2** were converted to corresponding *S*,*N*-acetals by reacting with appropriate primary as well as secondary amine in ethanol under microwave at 80 W (Scheme 2). Secondary amine being more reactive underwent nucleophilic

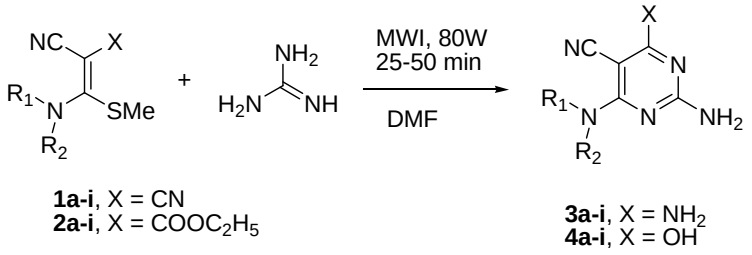
 




**Scheme 1. MCR of *α*-cyanoketenes *S,S*-acetals, amine and guanidine carbonate.**




**Scheme 2. Synthesis of *α*-cyanoketene *S,N*-acetals (1a-i, 2a-i)E.**




**Scheme 3. Synthesis of target compounds.**

substitution with *α*-cyanoketene *S,S*-acetals in 5 minutes. Also the amines possessing substitution like halogens as well as electron donating groups such as methyl and methoxy completed the displacement in shorter time (5 minutes) when compared with unsubstituted amine owing to its resonance effect.

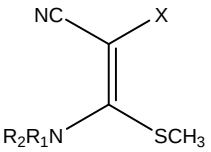
There was not much difference in the reaction rate between the amines bearing substitution at *meta* and *para* positions. The overall reaction time were 5 - 10 minutes. The best yields were obtained for **1c**, 96%. Over all yields were in the range of 84% - 96% (**Table 1**).

In the subsequent step condensation of guanidine with *α*-cyanoketene *S,N*-acetals for the synthesis of title compounds were investigated. The reaction involved one-pot cyclocondensation of functionalized *α*-cyanoketene *S,N*-acetals with guanidine in the dimethylformamide. Initially guanidine as a free base was generated *in situ* from its salt form by treating with sodium hydride in DMF under microwave irradiation for 1 minute at 20W. Once the free base was generated, *α*-cyanoketene *S,N*-acetals was added and subjected to MWI for 25 - 50 minutes at 80 W to afford the title 2-amino-5-cyano-4,6-disubstituted-pyrimidines (Scheme 3). The reaction was completed in just few minutes instead of the 18 hrs required under conventional heating. The products were obtained in high yield (76% - 90%), purity (>95%). (**Table 2**)

In comparison to the conventional heating method, microwave heating affords more advantages such as high yield, reduced reaction time, low cost, and simplicity in reaction progress, reduced pollution and higher product

**Table 1. Physical Data of *α*-cyanoketene *S,N*-acetals (1a-i, 2a-i).**




| Comp.No. | X | $NR^1R^2$ | M.P. (˚C) | Reaction time (min) at 80 W | Yield | Comp. No | X | $NR^1R^2$ | M.P. (˚C) | Reaction time (min) at 80 W | Yield |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | CN | $C_6H_5NH$ | 170 - 172 | 10 | 90 | **2a** | $COOC_2H_5$ | $C_6H_5NH$ | 82 - 83 | 10 | 95 |
| **1b** | CN | 4-morpholinyl | 150 - 152 | 5 | 85 | **2b** | $COOC_2H_5$ | 4-morpholinyl | 93 - 94 | 5 | 91 |
| **1c** | CN | 4-$CH_3OC_6H_4NH$ | 148 - 150 | 10 | 96 | **2c** | $COOC_2H_5$ | 4-$CH_3OC_6H_4NH$ | 96 - 98 | 10 | 86 |
| **1d** | CN | 4-$CH_3C_6H_4NH$ | 140 - 141 | 5 | 94 | **2d** | $COOC_2H_5$ | 4-$CH_3C_6H_4NH$ | 112 - 114 | 10 | 87 |
| **1e** | CN | 4-Br-$C_6H_5NH$ | 122 - 124 | 10 | 92 | **2e** | $COOC_2H_5$ | 4-Br-$C_6H_5NH$ | 120 - 121 | 10 | 84 |
| **1f** | CN | 4-F-$C_6H_4NH$ | 135 - 137 | 5 | 88 | **2f** | $COOC_2H_5$ | 4-F-$C_6H_4NH$ | 128 - 130 | 5 | 95 |
| **1g** | CN | 4-Cl-$C_6H_4NH$ | 160 - 162 | 10 | 86 | **2g** | $COOC_2H_5$ | 4-Cl-$C_6H_4NH$ | 140 - 142 | 5 | 92 |
| **1h** | CN | 3-Cl,4-F-$C_6H_5NH$ | 139 - 141 | 5 | 91 | **2h** | $COOC_2H_5$ | 3-Cl,4-F-$C_6H_5NH$ | 151 - 153 | 5 | 90 |
| **1i** | CN | 3-$CH_3C_6H_4NH$ | 106 - 108 | 10 | 88 | **2i** | $COOC_2H_5$ | 3-$CH_3C_6H_4NH$ | 95 - 96 | 10 | 94 |

purity. Hence, the synthetic methodology reported herein is a very efficient method for the parallel library synthesis of 2-amino-5-cyano-4,6-disubstitutedpyrimidines.

## 3. Experimental

All reagents and chemicals used were of LR grade and purchased from standard vendors and used as received. Microwave synthesizer; (Questron Technologies Corp., Canada; model-ProM) having monomode open-vessel was used for the synthesis. The $^1$H NMR spectra were recorded in $CDCl_3$ using NMR Varian Mercury YH-300 MHz spectrometer and chemical shifts are given in units as per million, downfield from TMS (tetramethylsilane) as an internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP2010 spectrometer. The Ultraviolet absorption spectra were determined in methanol on JASCO (Japan) V-530, UV-Visible double beam spectrophotometer. The IR spectra of the synthesized compounds were recorded on Perkin Elmer (USA) spectrum BX.FT-IR in potassium bromide discs.

### 3.1. The *α*-Cyanoketene *S,S*-Acetals were Prepared as Per Literature Method

#### 3.1.1. Synthesis of *α*-Cyanoketene *S,N*-Acetals (1a-i, 2a-i)

A mixture of appropriate *α*-cyanoketene *S,S*-acetal **1** or **2** (0.02 mol) and 0.02 mol of aromatic amine in 10 ml of ethanol was subjected to microwave irradiation at 80 W for 5 - 10 minutes. The progress of the reaction was monitored by TLC. Upon completion the mixture was cooled and the crystals obtained were filtered, washed with chilled ethanol and air dried. The compounds were pure for all practical purpose.

#### 3.1.2. Synthesis of 2,4-Diamino-5-Cyano-6-(Phenylaminopyrimidine (3a-I & 4a-i)

To the benzene washed suspension of sodium hydride (50%) (0.01 mol) in DMF (10 ml), guanidine nitrate (0.01 mol) was added and subjected to microwave irradiation at 20 W for 1 min. The solution was filtered and to the filterate *α*-cyanoketene *S,N*-acetals **(1a-i, 2a-i)** (0.01 mol) was added. The flask was subjected to MWI at 80 W for 25 - 50 min. The progress of reaction was monitored by TLC for every 5 minutes. On completion of reaction, the reaction mixture was cooled to RT and poured into ice water (50 ml). The solid precipitate obtained was filtered and dried. The crude product was recrystallized from DMF-ethanol to obtain the desired product.

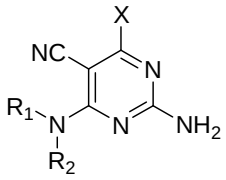
### 3.2. Representative Data of Target Compounds

**2,4-Diamino-5-cyano-6-(phenylamino)pyrimidine 3a**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 5.01(2H, s, $NH_2$ at 4); 5.13(2H, s, $NH_2$ at 2); 5.34(1H, s, N*H* 6); 7.11 - 7.62 (5H, m, ArH). IR (KBr) cm$^{-1}$: 3479, 3317$_{[\gamma NH]}$, 2210$_{[\gamma CN]}$. *m/z*

**Table 2. Physical data of 2-amino-5-cyano-4,6-disubstitutedpyrimidines (3a-i, 4a-i).**



| Com. No. | X | —N(R1)(R2) | Yield (%) | M.P. (˚C) (Solv. of recryst)* | Reaction time (Min) at 80 W |
|---|---|---|---|---|---|
| **3a** | $NH_2$ | $C_6H_5NH$ | 84 | 268 - 270 D - E | 25 |
| **3b** | $NH_2$ | 4-morpholinyl | 82 | 226 - 227 D - E | 35 |
| **3c** | $NH_2$ | 4-$CH_3OC_6H_4NH$ | 88 | 259 - 262 D - E | 40 |
| **3d** | $NH_2$ | 4-$CH_3C_6H_4NH$ | 78 | 253 - 254 D - E | 45 |
| **3e** | $NH_2$ | 4-Br $C_6H_5NH$ | 80 | 249 - 251 D - E | 40 |
| **3f** | $NH_2$ | 4-$FC_6H_4NH$ | 89 | 245 - 247 D - E | 35 |
| **3g** | $NH_2$ | 4-$ClC_6H_4NH$ | 81 | 2425 - 244 D - E | 30 |
| **3h** | $NH_2$ | 3-Cl,4F-$C_6H_5NH$ | 79 | 227 - 229 D - E | 35 |
| **3i** | $NH_2$ | 3-$CH_3C_6H_4NH$ | 76 | 264 - 266 D - E | 30 |
| **4a** | OH | $C_6H_5NH$ | 81 | 280 - 281 D - E | 40 |
| **4b** | OH | 4-morpholinyl | 80 | 257 - 258 D - E | 45 |
| **4c** | OH | 4-$CH_3OC_6H_4NH$ | 84 | 270 - 272 D - E | 50 |
| **4d** | OH | 4-$CH_3C_6H_4NH$ | 79 | 276 - 278 D-E | 45 |
| **4e** | OH | 4-Br $C_6H_5NH$ | 87 | 266 - 267 D-E | 35 |
| **4f** | OH | 4-$FC_6H_4NH$ | 88 | 259 - 261 D - E | 30 |
| **4g** | OH | 4-$ClC_6H_4NH$ | 85 | 247 - 250 D - E | 45 |
| **4h** | OH | 3-Cl,4F-$C_6H_4NH$ | 82 | 278 - 280 D - E | 35 |
| **4i** | OH | 3$CH_3C_6H_4NH$ | 90 | 260 - 263 D - E | 35 |

*Solv.of recryst. D = Dimethylformamide, E = Ethanol.

226 ($M^+$). Anal. Calcd. for $C_{11}H_{10}N_6$: C, 58.40; H, 4.46; N, 37.15; found C, 58.76; H, 4.76; N, 37.43.

**2,4-Diamino-5-cyano-6-(4-morpholinyl)pyrimidine 3b**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 3.54 - 3.76(4H, m, -NH($CH_2$-)2); 3.84-4.12 (4H, m, O-($CH_2$-)2]; 6.51(2H, s, $NH_2$ at 4); 6.69(2H, s, $NH_2$ at 2). IR (KBr) $cm^{-1}$: 3466, 3358$_{[\gamma NH]}$, 2216$_{[\gamma CN]}$. *m/z* 220($M^+$). Anal. Calcd. for $C_9H_{12}N_6O$: C, 49.08; H, 5.49; N, 38.16; found C, 49.32; H, 5.68; N, 38.29.

**2,4-Diamino-5-cyano-6-[(4-methoxyphenyl)amino]pyrimidine 3c**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 3.73(3H, s, $OCH_3$); 4.0 - 4.31(4H, s, $NH_2$ at 2 and 4); 6.85 - 7.33 (4H, m, Ar-*H*). IR (KBr) $cm^{-1}$: 3416, 3374 $_{[\gamma NH]}$, 2208 $_{[\gamma CN]}$. *m/z* 256($M^+$). Anal. Calcd. for $C_{12}H_{12}N_6O$: C, 56.24; H, 4.72; N, 32.79; found C, 56.35; H, 4.45; N, 32.93.

**2,4-diamino-5cyano-6-[(4-methylphenyl)amino]pyrimidine 3d**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 3.4(3H, s, $ArCH_3$ at 6); 6.6(4H, m, $NH_2$ at 2 and 4); 8.4(4H, m, ArH at 6). IR (KBr) $cm^{-1}$: 3474, 3289, 3153$_{[\gamma NH]}$, 2188$_{[\gamma CN]}$. *m/z* 240($M^+$). Anal. Calcd. for $C_{12}H_{12}N_6$: C, 59.99; H, 5.03; N, 34.98 ; found C, 59.84; H, 5.34; N, 34.87.

**2,4-diamino-5-cyano-6-[(4-chlorophenyl)amino]pyrimidine 3g**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 3.4(3H, s, $ArCH_3$ at 6); 6.6(4H, m, N$H_2$ at 2 and 4); 8.4(1H, s, ArH at 6). IR (KBr) $cm^{-1}$: 3324, 3178$_{[\gamma NH]}$, 2190$_{[\gamma CN]}$. *m/z* 260($M^+$). Anal. Calcd. for $C_{11}H_9N_6Cl$: C, 50.68; H, 3.48; N, 32.24; found C, 50.43; H, 3.62; N, 32.26.

**2-amino-4-hydroxy-5-cyano-6-(4-morpholinyl)pyrimidine 4b**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 2.9[s, -N($CH_2$-)2]; 3.8[s, O-($CH_2$-)2]; 6 (2H, s, $NH_2$ at 2); 7.4( s, 1H, OH at 4). IR (KBr) $cm^{-1}$: 3357, 3115$_{[\gamma NH]}$, 2922$_{[\gamma C\text{-}H]}$, 2182$_{[\gamma CN]}$, 1628$_{[\gamma CONH]}$. *m/z* 221($M^+$). Anal. Calcd. for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66; found C, 48.74; H, 5.44; N, 31.34.

**2-amino-4-hydroxy-5-cyano-6-[(4-flurophenyl)amino]pyrimidine 4f**

$^1$HNMR (400 MHz, DMSO-$d_6$): δ 4.2(2H, s, $NH_2$ at 4); 5.07(1H, s, OH); 6.72(5H,m, Ar-H ). IR (KBr) $cm^{-1}$: 3476, 3296$_{[\gamma NH]}$, 2916.12$_{[\gamma C\text{-}H]}$, 2211$_{[\gamma CN]}$ 1654, 1618$_{[\gamma CONH]}$. *m/z* 245($M^+$). Anal. Calcd. for $C_{11}H_8N_5OF$: C, 53.88; H, 3.29; N, 28.56; found C, 53.73; H, 3.08; N, 28.32.

## 4. Conclusions

We have described a new, rapid and a versatile approach by MAOS for the synthesis of 2-amino-5-cyano-4,6-disubstitutedpyrimidines in a highly efficient way. Further work is in progress with respect to diversity oriented synthesis of mononuclear pyrimidines and their biological screening.

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