

## Note

### An efficient synthesis of novel 2-amino-4-aryl-6-ferrocenyl pyrimidines

G S Rashinkar, S B Pore, K B Mote & R S Salunkhe\*

Department of Chemistry, Shivaji University,  
Kolhapur 416004, India

E-mail: gsrchemsuk@yahoo.co.in

Received 16 April 2008; accepted (revised) 16 January 2009

A series of 2-amino-4-aryl-6-ferrocenyl pyrimidines have been synthesized using cyclocondensation of 3-aryl-1-ferrocenyl-2-propen-1-ones with guanidine hydrochloride in basic medium. The synthesized compounds have been tested for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

**Keywords:** Ferrocene, aminopyrimidines, ferrocenyl chalcones, antibacterial activity

The discovery of ferrocene<sup>1,2</sup> in 1951 sparked off a truly remarkable interdisciplinary research activity. Since then ferrocene and its derivatives have been immensely exploited for their potential applications in diverse fields such as homogeneous catalysis<sup>3</sup>, organic synthesis, supramolecular chemistry<sup>4</sup>, biosensors<sup>5</sup>, medicinal chemistry<sup>6-8</sup> and materials science<sup>9</sup>. It is now well established that ferrocene functionalized organic compounds often exhibit unexpected biological activity owing to different membrane permeation properties and anomalous metabolism<sup>10</sup>. Owing to the resemblance of ferrocene to benzene, the substitution of the latter by the former in a biologically active compound is expected to induce dramatic change in properties like charge distribution, solubility and hydrophobicity. The stability and non toxicity of ferrocenyl group in aqueous and aerobic media has made it an ideal candidate for use in drug designing. With this background, the incorporation of one or more ferrocene units into a heterocyclic ring has become a relevant strategy of research in the communities of both organometallic chemists and biologists in expanding the potential applications of heterocyclic compounds. The past few years have seen a tremendous boost in ferrocene functionalized heterocyclic chemistry, as an avalanche of research activity has been directed towards this end<sup>11-15</sup>.

Pyrimidine is a fundamental part of nucleic acids and has been associated with a number of biological activities<sup>16</sup>. Aminopyrimidine constitutes one of the important classes of pyrimidines and its various derivatives have displayed interesting antibacterial<sup>17</sup>, antitumor<sup>18</sup> and HIV-I inhibiting activity<sup>19</sup>. Also, the pyrimidine and aminopyrimidine structures are frequently occurring motifs in commercially available drugs such as anti-atherosclerotic aronixil, anti-histaminic thonzylamine, anti-anxiolytic buspirone, anti-psoriatic enazadrem, and other medicinally relevant compounds.

A survey of literature reveals that no synthesis of ferrocene functionalized aminopyrimidines has been reported though a number of reports have been published which describe the synthesis of various ferrocene functionalized heterocycles.

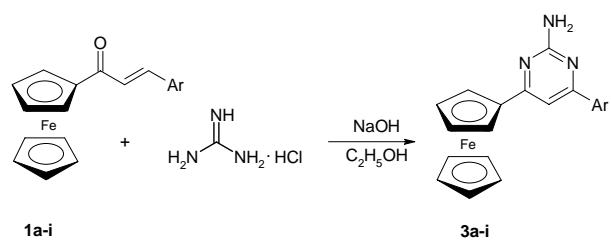
In this communication, is reported the synthesis of some novel 2-amino-4-aryl-6-ferrocenyl pyrimidines by the base induced condensation of various 3-aryl-1-ferrocenyl-2-propen-1-ones (ferrocenyl chalcones) with guanidine hydrochloride.

### Results and Discussion

As a trial case, a mixture 1-ferrocenyl-3-phenyl-2-propen-1-one (1 mmole), guanidine hydrochloride (1.5 mmole), NaOH (4.5 mmole) and 20 mL alcohol was refluxed on a waterbath. After completion of the reaction (monitored by TLC), the reaction mixture was poured into ice cold water (50 g). After stirring, the desired aminopyrimidine separated out which was filtered and dried. Purification by column chromatography over silica gel using pet ether - ethyl acetate mixture (9:1, v/v) as eluent afforded the corresponding 2-amino-6-ferrocenyl-4-phenyl pyrimidine in 71% yield.

Propelled by these encouraging results, the reactions were then performed between a variety of 3-aryl-1-ferrocenyl-2-propen-1-ones and guanidine hydrochloride (**Scheme I**) and the results are summarized in **Table I**.

As shown in **Table I**, both the substituted phenyl ring and heterocyclic ring containing ferrocenyl chalcones reacted efficiently with guanidine hydrochloride to yield the title compounds. In all the cases, the reaction proceeded smoothly to give

**Scheme I**

ferrocenyl substituted 2-aminopyrimidines in moderate to good yield.

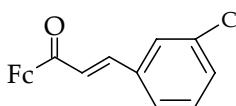
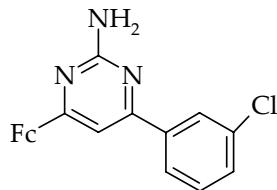
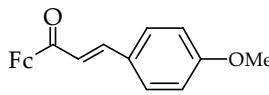
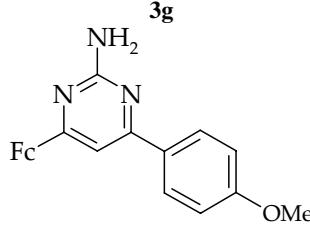
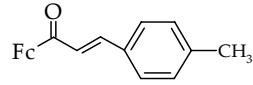
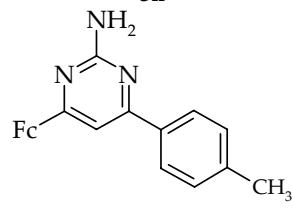
Molecular formulae for **3a-i** were determined from microanalysis (CHN) and confirmed by mass spectroscopy. The IR spectra of synthesized compounds displayed characteristic peaks in the region 3150-3500 (NH stretching), 1500-1575 (C=C stretching) and 1600-1650  $\text{cm}^{-1}$  (C=N stretching)

**Table I** — Reaction of various 3-aryl-1-ferrocenyl-2-propen-1-ones with guanidine hydrochloride in ethanol

Entry	Chalcone	Product	Yield (%) <sup>a</sup>	Time (hr)
1			71	10
2			64	11
3			67	12
4			72	07
5			74	12
6			65	08

*— Contd*

**Table I** — Reaction of various 3-aryl-1-ferrocenyl-2-propen-1-ones with guanidine hydrochloride in ethanol—*Contd*

Entry	Chalcone	Product	Yield (%) <sup>a</sup>	Time (hr)
7			68	10
8			62	14
9			64	12

<sup>a</sup> Isolated yieldsFc =  $C_5H_5FeC_5H_4$ 

indicating the formation of the desired compounds. The <sup>1</sup>H NMR data of synthesized compounds confirm the supposed structures in a straightforward manner.

### Biological evaluation

The compounds **3a-i** were screened for their antibacterial activity *in vitro* against *Staphylococcus aureus* and *Escherichia coli* by disc diffusion method. Surprisingly, none of the compounds **3a-i** showed any significant activity (data not shown). The other biological activities such as antimalarial and antihypertensive are being tested and the results will be presented in the future.

### Experimental Section

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on Perkin-Elmer spectrum one FTIR spectrophotometer using KBr pellets. <sup>1</sup>H NMR spectra were recorded on Varian (300 MHz) instrument using  $CDCl_3$  as solvent and TMS as internal reference. Mass spectra were recorded on a Shimadzu QP2010 GCMS with an ion source temperature of 200°C.

3-Aryl-1-ferrocenyl-2-propen-1-ones **1a-i** were prepared by base catalyzed Claisen-Schmidt condensation of 1-acetyl ferrocene with different aldehydes following the literature procedure<sup>20</sup>. All other chemicals were obtained from the local suppliers and were used as received.

### General procedure for the preparation of 2-amino-4-aryl-6-ferrocenyl pyrimidines, **3a-i**

A mixture of 3-aryl-1-ferrocenyl-2-propen-1-one (1 mmole), guanidine hydrochloride (1.5 mmole), sodium hydroxide (4.5 mmole) and 20 mL ethanol was refluxed for the required time (**Table I**). The mixture was poured into ice cold water after completion of the reaction. The formed solid was separated by filtration, dried and purified by column chromatography over silica gel with the solvent system ethyl acetate/petroleum ether.

### Spectroscopic data of synthesized compounds

#### 2-Amino-6-ferrocenyl-4-phenyl pyrimidine, **3a**

Brown solid; m.p. 143–45°C; IR(KBr): 3455, 3355, 2924, 1630  $cm^{-1}$ ; <sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):  $\delta$  4.09 (s, 5H), 4.47 (s, 2H), 4.96 (s, 2H), 5.09 (bs, 2H), 7.06

(s, 1H), 7.23 (s, 3H), 7.45 (s, 2H); MS (EI): *m/z* 355 ( $M^+$ ). Anal. Calcd for  $C_{20}H_{17}N_3Fe$ : C, 67.62; H, 4.82; N, 11.82. Found: C, 67.53; H, 4.86; N, 11.85%.

### 2-Amino-6-ferrocenyl-4-(furan-2-yl)pyrimidine, 3b

Reddish brown solid; m.p. 122-24°C; IR (KBr): 3323, 3187, 2923, 1645  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.10 (s, 5H), 4.45 (s, 2H), 4.96 (s, 2H), 5.03 (bs, 2H), 6.56 (s, 1H), 7.06 (s, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.58 (s, 1H); MS (EI): *m/z* 345 ( $M^+$ ). Anal. Calcd for  $C_{18}H_{15}N_3OFe$ : C, 62.63; H, 4.37; N, 12.17. Found: C, 62.48; H, 4.30; N, 12.05%.

### 2-Amino-6-ferrocenyl-4-(2-thienyl) pyrimidine, 3c

Red solid; m.p. 198-200°C; IR (KBr): 3395, 3304, 2925, 1621  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.09 (s, 5H), 4.44 (s, 2H), 4.94 (s, 2H), 5.02 (bs, 2H), 7.01 (s, 1H), 7.23 (s, 1H), 7.44 (d, *J* = 2.8 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H); MS (EI): *m/z* 361 ( $M^+$ ). Anal. Calcd for  $C_{18}H_{15}N_3SFe$ : C, 59.84; H, 4.18; N, 11.63. Found: C, 59.80; H, 4.22; N, 11.57%.

### 2-Amino-6-ferrocenyl-4-(3-nitrophenyl) pyrimidine, 3d

Orange solid; m.p. 210-12°C; IR (KBr): 3324, 3193, 2924, 1643  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.11 (s, 5H), 4.50 (s, 2H), 4.98 (s, 2H), 5.10 (bs, 2H), 7.13 (s, 1H), 7.65 (m, 1H), 8.32 (d, *J* = 7.9 Hz 1H), 8.38 (d, *J* = 7.5 Hz 1H), 8.87 (s, 1H); MS (EI): *m/z* 400 ( $M^+$ ). Anal. Calcd for  $C_{20}H_{16}N_4O_2Fe$ : C, 60.02; H, 4.02; N, 13.99. Found: C, 60.14; H, 4.08; N, 13.87%.

### 2-Amino-6-ferrocenyl-4-(4-nitrophenyl) pyrimidine, 3e

Reddish brown solid; m.p. 130-32°C; IR (KBr): 3391, 3198, 2923, 1625  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.10 (s, 5H), 4.48 (s, 2H), 4.98 (s, 2H), 5.09 (bs, 2H), 7.23 (s, 1H), 8.32 (d, *J* = 6.4 Hz, 2H), 8.47 (d, *J* = 6.5 Hz, 2H); MS (EI): *m/z* 389 ( $M^+$ ). Anal. Calcd for  $C_{20}H_{16}N_4O_2Fe$ : C, 60.02; H, 4.02; N, 13.99. Found: C, 59.93; H, 4.10; N, 14.07%.

### 2-Amino-4-(3-chlorophenyl)-6-ferrocenyl pyrimidine, 3f

Brown solid; m.p. 98-100°C; IR (KBr): 3324, 3193, 2924, 1643  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.09 (s, 5H), 4.45 (s, 2H), 4.96 (s, 2H), 5.08 (bs 2H), 7.04-8.01 (m, Ar-H); MS (EI): *m/z* 389 ( $M^+$ ).

Anal. Calcd for  $C_{20}H_{16}N_3ClFe$ : C, 61.14; H, 4.13; N, 10.78. Found: C, 61.07; H, 4.06; N, 10.72%.

### 2-Amino-4-(4-chlorophenyl)-6-ferrocenylpyrimidine, 3g

Red solid; m.p. 182-84°C; IR (KBr): 3404, 3333, 2923, 1645  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  4.09 (s, 5H), 4.46 (s, 2H), 4.95 (s, 2H), 5.04 (bs, 2H), 7.06 (s, 1H), 7.45 (d, *J* = 6.2 Hz, 2H), 7.96 (d, *J* = 6.7 Hz, 2H); MS (EI): *m/z* 389 ( $M^+$ ). Anal. Calcd for  $C_{20}H_{16}N_3ClFe$ : C, 61.14; H, 4.13; N, 10.78. Found: C, 61.10; H, 4.18; N, 10.84%.

### 2-Amino-6-ferrocenyl-4-(4-methoxyphenyl) pyrimidine, 3h

Red solid; m.p. 140-42°C; IR (KBr): 3323, 3280, 2924, 1602  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.87 (s, 3H), 4.09 (s, 5H), 4.44 (s, 2H), 4.95 (s, 2H), 5.04 (bs, 2H), 7.00 (d, *J* = 5 Hz, 2H), 7.23 (s, 1H), 7.97 (d, *J* = 5 Hz, 2H); MS (EI): *m/z* 385 ( $M^+$ ). Anal. Calcd for  $C_{21}H_{19}N_3OFe$ : C, 65.47; H, 4.97; N, 10.91. Found: C, 65.30; H, 4.90; N, 11.06%.

### 2-Amino-6-ferrocenyl-4-(4-methyphenyl) pyrimidine, 3i

Red solid; m.p. 138-40°C; IR (KBr): 3308, 3179, 2923, 1626  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.42 (s, 3H), 4.09 (s, 5H), 4.45 (s, 2H), 4.96 (s, 2H), 5.05 (bs, 2H), 7.14 (s, 1H), 7.29 (d, *J* = 6.4 Hz, 2H), 7.89 (d, *J* = 6.8 Hz, 2H); MS (EI): *m/z* 369 ( $M^+$ ). Anal. Calcd for  $C_{21}H_{19}N_3Fe$ : C, 68.31; H, 5.18; N, 11.37. Found: C, 68.39; H, 5.15; N, 11.31%.

## Conclusion

A novel series of 2-amino-4-aryl-6-ferrocenyl pyrimidines were synthesized in moderate to good yields. The synthesized compounds might be able to work as important intermediates, ligands for transition metal ions and potential new drugs. Further work is in progress with respect to symmetry and stereochemical aspects of the charge distribution in such type of compounds.

## Acknowledgments

The authors gratefully acknowledge the KLE society, Belgaum for biological evaluation of the synthesized compounds and financial support from the Department of Science and Technology, Government of India through FIST programme.

**References**

- 1 Kealy T J & Pauson P L, *Nature*, **168**, **1951**, 1039.
- 2 Miller S A, Tebboth J A & Tremaine J F, *J Chem Soc*, **1952**, 632.
- 3 Roth B, Strelitz J Z & Rauckman B S, *J Med Chem*, **23**, **1980**, 379.
- 4 Kaifer A E & de Mendoza J, *Comprehensive Supramolecular Chemistry Vol. 1*, (Elsevier, Oxford) **1996**, 701.
- 5 Yao T & Rechnitz G A, *Biosensors*, **3**, **1987**, 307.
- 6 Kopf-Maier P & Kopf H, *Chem Rev*, **87**, **1987**, 1137.
- 7 Biot C, Delhaes L, N'Diaye C M, Maciejewski L A, Camus D & Dive D, *Bioorg Med Chem*, **7**, **1999**, 2843.
- 8 Epton R, Marr G & Rogers G K, *J Organomet Chem*, **10**, **1976**, C42.
- 9 Zhu H, Lin H, Guo H & Yu L, *Mat Sci Eng B*, **138**, **2007**, 101.
- 10 Fang J, Jin Z, Li Z & Liu W, *J Organomet Chem*, **674**, **2003**, 1, and references cited therein.
- 11 Fu N, Yuan Y, Pang M, Wang J & Peppe C, *J Organomet Chem*, **672**, **2003**, 52.
- 12 Braga D, Addario D & Polito M, *Organometallics*, **23**, **2004**, 2810.
- 13 Zhou W, Ji S & Shen Z, *J Organomet Chem*, **691**, **2006**, 1356.
- 14 Joksović M, Ratković Z, Vukićević M & Vukićević R D, *Synlett*, **16**, **2006**, 2581.
- 15 Mochida T, Shimizu F, Shimazu H, Okawaza K, Sato F & Kuwahara D, *J Organomet Chem*, **692**, **2007**, 1834.
- 16 Sayle K L, Bentley J, Boyle F T, Calvert A H, Cheng Y, Curtin N J, Endicott J A, Golding B T, Hardcastle I R & Jewsbury P, *Bioorg Med Chem Lett*, **13**, **2003**, 3079.
- 17 Chandrasekaran S & Nagarajan S, *Il Farmaco*, **60**, **2005**, 279.
- 18 Cocco M T, Congiu C, Lilliu V & Onnis V, *Bioorg Med Chem*, **14**, **2006**, 366.
- 19 Gadhachanda V R, Wu B, Wang Z, Kuhen K L, Caldwell J, Zondler H, Walter H, Havenhand M & He Y, *Bioorg Med Chem Lett*, **17**, **2007**, 260.
- 20 Wu X, Wilairat P & Go M, *Bioorg Med Chem Lett*, **12**, **2002**, 2299.