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Short communication

# First catalytic synthesis of 7-ferrocenyl-2,4-dioxopyrido [2,3-*d*] pyrimidines derivatives in water

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**Abstract**

The reaction of 6-amino-1,3-dimethyluracil with substituted ferrocenyl-ketoalkynes using nickel cyanide as homogeneous catalyst precursor in aqueous alkaline medium, affords 5-substituted-7-ferrocenyl-dioxopyrido[2,3-*d*]pyrimidines derivatives, in moderate yields under mild conditions.


*Keywords:* Ferrocenylpyrimidines; Nickel; Catalysis; Cyclocarbonylation

## 1. Introduction

The substituted pyrimidines present very important potential pharmacological and biological activities [1–5], and there exist some reports on the synthesis of 2,4-dioxopyrido[2,3-*d*]pyrimidines derivatives in moderates yields in organic medium. These traditional syntheses of named compounds involve multi-step reaction sequences, stringent reaction conditions such as: high temperature, high pressures, the use of toxic solvents and long reaction times commonly resulting in low yields [6].

Recently, our group developed anionic catalytic species of Ni(0) [7] in water which induce the cyclocarbonylation reaction of alkynes, alkynyl-ketones and alkynyl-enones [8], affording lactones, lactams, pyrones, pyrimidines, naphthyridines and quinolinones in good yields [9–13]. These reactions are performed in a basic medium containing nickel cyanide, potassium cyanide under carbon monoxide.

Though many 5-substituted-2,4-dioxopyrido[2,3-*d*]pyrimidines derivatives are known, pyrimidines substituted by ferrocenyl group are still unknown. Considering that the ferrocene moiety has been readily applied for the drugs design, a synergistic effect between ferrocene and pyrimidines could be of interest. Here we wish to report the novel and facile synthesis of some 7-ferrocenyl-2,4-dioxopyrido[2,3-*d*]pyrimidines in water, by coupling and heterocyclization of ferrocenyl-α-ketoalkynes with 6-amino-1,3-dimethyluracil, in water as a reaction medium, under exceptionally mild conditions (room temperature and atmospheric pressure) using a nickel catalytic system *viz*. $Ni(CN)_2$/CO/KCN/NaOH.

## 2. Experimental

### 2.1. Materials and methods

Syntheses of 7-ferrocenyl-2,4-dioxopyrido[2,3-*d*]pyrimidines obtained by the reaction of ferrocenyl-α-ketoalkynes with 6-amino-1,3-dimethyluracil. The pyrimidine derivatives being characterized by the usual analytical spectroscopy, *e.g.* $^1$H and $^{13}$C NMR, IR, and mass spectrometry ($FAB^+$ and electronic impact), the structures of compounds 1-phenyl-3-ferrocenyl-propynone (**1a**), 7-ferrocenyl-5-phenyl-2,4-dioxopyrido[2,3-*d*] pyrimidine (**2a**) and 7-ferrocenyl-5-(3,5-dimethoxy-phenyl)-dioxopyrido[2,3-*d*]pyrimidine (**2b**) were unambiguously established by X-ray crystallography (Figs. 1, 2a and b and Table 1).

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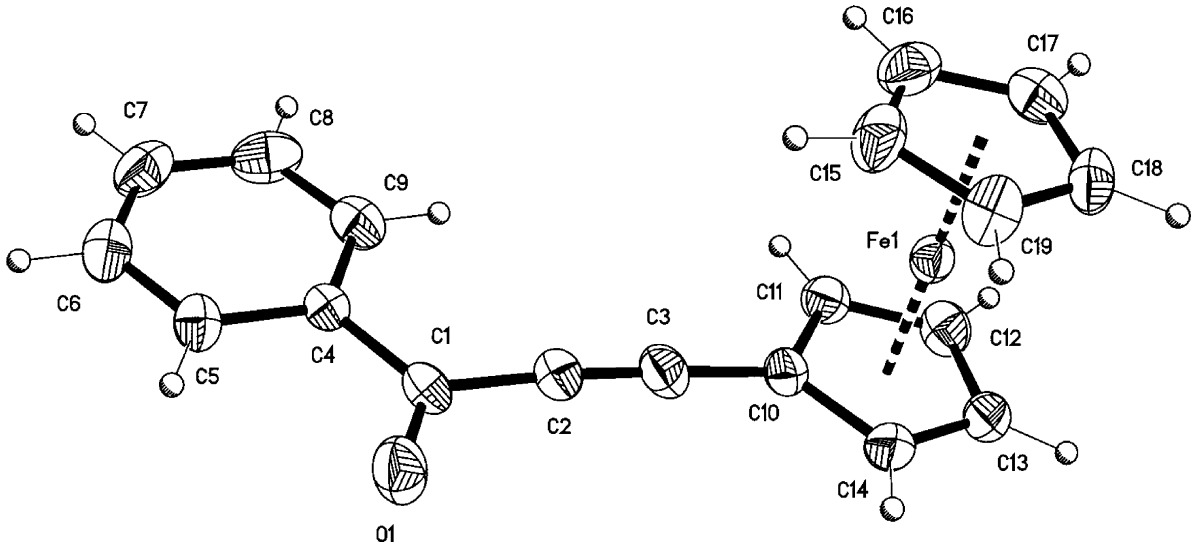



Fig. 1. 1-Phenyl-3-ferrocenyl-propynone.

### 2.2. Synthesis of ferrocenyl-α-ketoalkynes: general procedure

Ferrocenyl-α-ketoalkynes were synthesized by coupling ferrocenylethyne with acyl chlorides in dry argon atmosphere at room temperature according to the method reported in Ref. [14]. As shown in Scheme 1.

A mixture of ferrocenylethyne (420 mg, 2 mmol), $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol), and CuI (38 mg, 0.2 mmol) in anhydrous $Et_3N$ (100 mL), was stirred under argon for 30 min.

The appropriate acyl chloride (3 mmol) was added. The progress of the reaction was followed by GC in a Hewlett Packard 5890, with HP 225 (10 m × 053 mm) packed column. At the end of the reaction (3 h), aq. 2.5 M HCl (40 mL) was added to neutralize the $Et_3N$ and the mixture was diluted with an aqueous solution of $NaHCO_3$. Ethyl acetate was used to extract the product. After the usual workup, the organic solvent was removed at reduced pressure in arotatory evaporatorresulting ing the crude product which was crystallized from ethyl acetate/hexane mixture.

### 2.3. Synthesis of ferrocenyl-pyrimidines: general procedure

The 7-ferrocenyl-2,4-dioxopyrido[2,3-*d*]pyrimidines were synthesized by coupling of ferrocenyl-α-ketoalkynes with 6-amino-1,3-dimethyluracil. The general reaction is shown in Scheme 2.

Table 1
Crystal data and structure refinementor ferrocenyl-α-ketoalkyne (**1a**) and derivatives of 7-ferrocenyl-2,4-dioxopyrido[2,3-*d*]pyrimidines (**2a** and **2b**)

| | Compounds | | |
|---|---|---|---|
| | **1a** | **2a** | **2b** |
| Empirical formula | $C_{19}H_{14}FeO$ | $C_{25}H_{21}FeN_3O_2$ | $C_{27}H_{25}FeN_3O_4$ |
| Formula weight | 314.15 | 451.30 | 511.35 |
| Crystal system | Orthorhombic | Triclinic | Monoclinic |
| Space group | *Pbca* | *P*-1 | $P2_1/c$ |
| Crystal size (mm) | 0.298 × 0.182 × 0.022 | 0.316 × 0.124 × 0.026 | 0.286 × 0.282 × 0.056 |
| *a* (Å) | 10.449(1) | 9.8676(8) | 12.833(1) |
| *b* (Å) | 13.322(1) | 10.2006(9) | 11.797(1) |
| *c* (Å) | 20.852(2) | 11.481(1) | 15.580(1) |
| *α* (°) | 90 | 98.003(2) | 90 |
| *β* (°) | 90 | 112.788(2) | 104.89(1) |
| *γ* (°) | 90 | 101.350(2) | 90 |
| Volume ($Å^3$) | 2902.6(4) | 1014.4(8) | 2279.5(3) |
| *Z* | 8 | 2 | 4 |
| Density (calc.) ($Mg/cm^3$) | 1.438 | 1.477 | 1.490 |
| *μ* ($mm^{-1}$) | 1.033 | 0.772 | 0.703 |
| Reflections collected | 19865 | 8622 | 18810 |
| Independent reflections | 3328 | 3720 | 4179 |
| *R* | 0.1492 | 0.0669 | 0.0518 |
| GOF | 0.941 | 1.040 | 1.037 |
| *Δ*/*σ* (einsteen $Å^{-3}$) | 1.357/−0.455 | 0.435/−0.267 | 0.375/−0.175 |

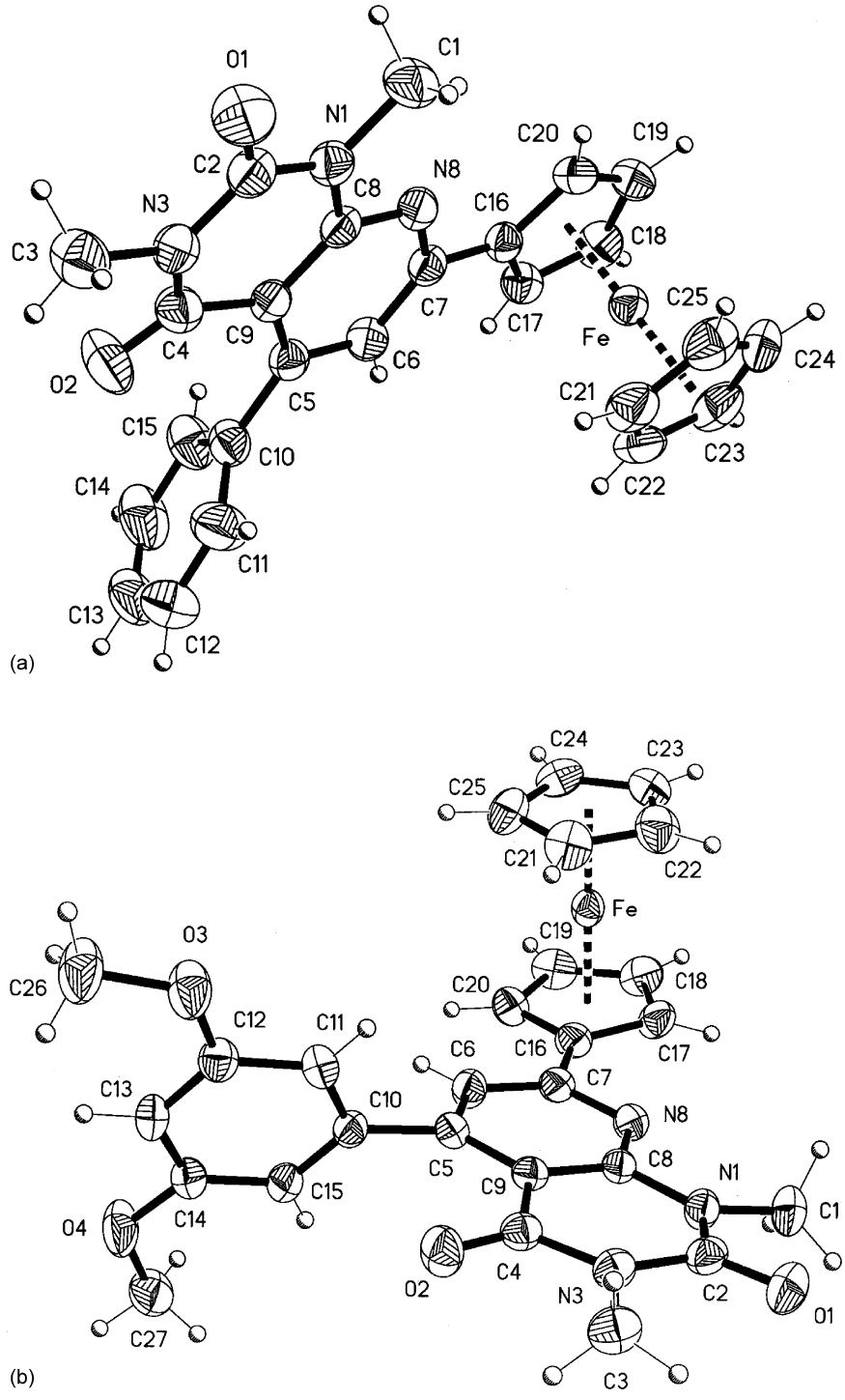
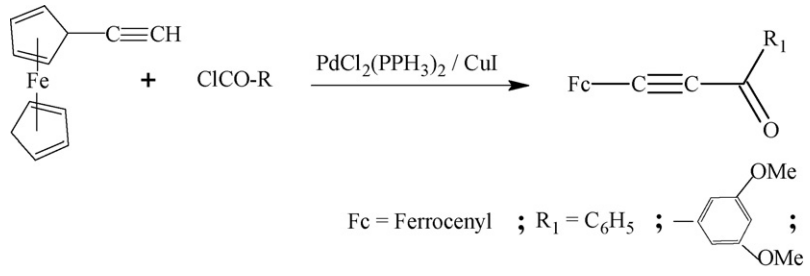
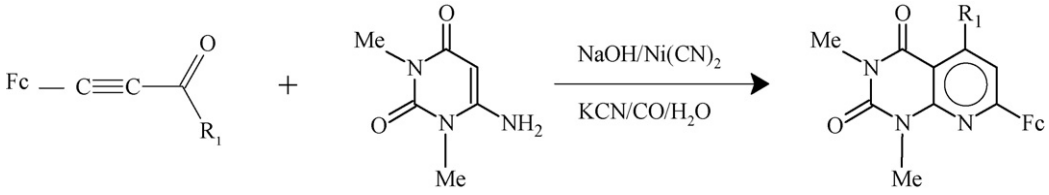



Fig. 2. (a) 7-Ferrocenyl-1,3-dimethyl-5-phenyl-pyrido-[2,3-*d*]pyrimidine-2,4-dione. (b) 7-Ferrocenyl-5-(3,5-dimethoxyphenyl)-1,3-pyrido-[2,3-*d*]pyrimidine-2,4-dione.

A typical experiment was performed as follows. A 5N NaOH solution (50 mL) was degassed and saturated with CO under atmospheric pressure for 30 min, 2 mmol of $Ni(CN)_2{\cdot}4H_2O$ (366 mg, 2 mmol) was added to the solution, the mixture was kept at room temperature overnight, with stirring and slow bubbling of CO (2–3 mL/min), until a pale yellow solution was obtained. Addition of 15 mmol of KCN (975 mg) resulted in a color change to orange. After stirring for 0.5 h the corresponding ferrocenyl-α-ketoalkynes and the 6-amino-1,3-dimethyluracil compounds were added (10 mmol). The evolution of the reaction was following by TLC. The products (ferrocenyl-α-ketoalkynes and ferrocenyl-pirido[2,3-*d*]pyrimidin-2,4-diones) were quantified by GC in a Hewlett Packard 5890 analyzer with a HP 225 (10 m × 0.53 mm) column packed. At the end of the reaction, ethyl acetate was used to extract the product. After evaporation of the solvent fol-




Scheme 1.




Scheme 2.

lowed by drying over $MgSO_4$, the pure crystalline products were obtained.

### 2.4. Product characterization

#### 2.4.1. 1-Phenyl-3-ferrocenyl-propynone (*1a*)

The product was obtained as described in the general procedure in a 62% yield as a yellow solid (mp 70 °C); mass spectrum EI: *m/z* (%) = 314 (100), 105 (24), 77 (19); IR (selected, $cm^{-1}$) 2179 (C≡C), 1624 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm) 4.27 (s, 5H cp-ring), 4.41 (s, 2H, cp-ring), 4.67 (s, 2H ring-cp), 7.50 (dd, 2H, 3,5-phenyl), 7.60 (d, 1H, 2,6-phenyl), 8.20 (d, 2H, 4-phenyl); $^{13}C$ NMR (75 MHz, $CDCl_3$, $\delta$ in ppm) 60.4 (*C*, cp-ring), 70.6 (*C*, cp-ring), 70.9 (*C*, cp-ring), 73.2 (*C*, cp-ring), 85.6 (Fc–*C*≡C), 96.7 (C≡*C*–CO), 128.6 (2*C*, 3,5-phenyl), 129.5 (2*C*, 2,6-phenyl), 133.8 (1*C*, 4-phenyl), 137.3 (1*C*, 1-phenyl), 177.7 (*C*=O).

#### 2.4.2. 1-(3,5-Dimethoxyphenyl)-3-ferrocenyl-propynone (*1b*)

The product was obtained in a 60% yield as orange-reddish crystals (mp. 93 °C); mass spectrum FAB+: *m/z* (%) = 374 (77), 375 (44), 136 and 154 (100); IR ($cm^{-1}$) 2195 (C≡C), 1634 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm) 3.87 (s, 6H, $OCH_3$), 4.28 (s, 5H, cp-ring), 4.41 (s, 2H, cp-ring), 4.67 (s, 2H, cp-ring), 6.70 (s, 1H, 4-phenyl), 7.34 (s, 1H, 2,6-phenyl); $^{13}C$ NMR (75 MHz, $CDCl_3$, $\delta$ in ppm) 55.7 ($OCH_3$), 60.3 (*C*, cp-ring), 70.5 (*C*, cp-ring), 70.9 (*C*, cp-ring), 73.2 (*C*, cp-ring), 85.6 (*C*≡C), 96.5 (C≡*C*), 106.3 (1*C*, 4-phenyl), 107.2 (2*C*, 2,6-phenyl), 139.3 (1*C*, 1-phenyl), 160.9 (2*C*, 3,5-phenyl), 177.2 (*C*=O).

#### 2.4.3. 7-Ferrocenyl-1,3-dimethyl-5-phenyl-pyrido[2,3-d] pyrimidine-2,4-dione (*2a*)

The product was obtained in a 50% yield as described in the general procedure as red crystals (mp 210 °C); mass spectrum IE: *m/z* (%) = 451 (100); IR ($cm^{-1}$) 1702, 1658 (C=O), 1589 (C=C), 1548 (C=N); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm) 3.36 (s, 3H, $CH_3N$), 3.81 (s, 3H, $CH_3N$), 4.11 (s, 5H, cp-ring), 4.56 (s, 2H, cp-ring), 5.04 (s, 2H, cp-ring), 7.02 (s, 1H, C=CH), 7.34 (m, 2H, 3,5-phenyl), 7.46 (d, 3H, 2,4,6-phenyl); $^{13}C$ NMR (75 MHz, $CDCl_3$, $\delta$ in ppm) 28.4 ($NCH_3$), 30.06 ($NCH_3$), 68.6 (*C*, cp-ring), 70.3 (*C*, cp-ring), 71.6 (*C*, cp-ring), 118.1 (C9), 120.2 (C6), 127.6 (C, phenyl), 127.9 (*C*, phenyl), 128.1 (*C*, phenyl), 129.2 (C5), 130.6 (C7), 137.6 [N(*C*=O)N], 152.1 [N(*C*=O)C], 160.9 (C=*C*N).

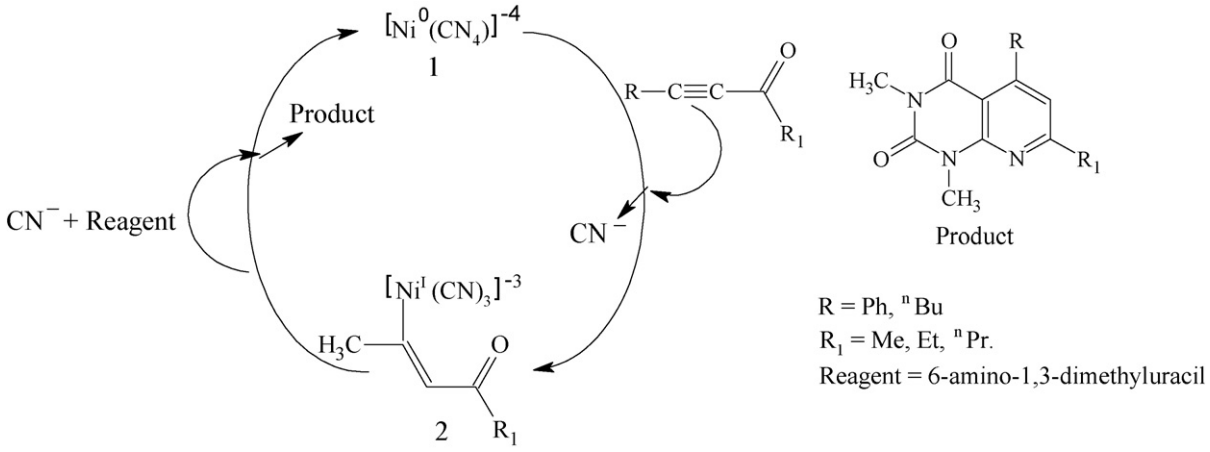
#### 2.4.4. 7-Ferrocenyl-5-(3,5-dimethoxyphenyl)-1,3-dimethyl-pyrido[2,3-d]pyrimidine-2,4-dione (*2b*)

The product was obtained as described in the general procedure in a 56% yield as dark red crystals (mp 208 °C); IE: *m/z* (%) = 511 (100), 446 (85); IR ($cm^{-1}$) 1705, 1659 (C=O), 1589 (C=C), 1548 (C=N); $^1H$ NMR (300 MHz, $CDCl_3$, $\delta$ in ppm) 3.39 (s, 3H, $CH_3N$), 3.82 (s, 3H, $CH_3N$), 3.91 (s, 6H, $OCH_3$), 4.21 (s, 5H, cp-ring), 4.51 (s, 2H, cp-ring), 4.75 (s, 2H, cp-ring), 6.62 (s, 1H, 4-phenyl), 7.30 (s, 2H, 2,6-phenyl), 8.10 (s, 1H, C=CH); $^{13}C$ NMR (75 MHz, $CDCl_3$, $\delta$ in ppm) 28.6 ($NCH_3$), 30.3 ($NCH_3$), 55.6 ($OCH_3$), 69.2 (*C*, cp-ring), 70.5 (*C*, cp-ring), 72.6 (*C*, cp-ring), 84.5 (1*C*, 4-phenyl), 102.3 (2*C*, 2,6-phenyl), 105.5 (C9), 120.6 (C6), 139.7 (1*C*, 1-phenyl), 151.6 (C5), 151.82 (C7), 154.5 [N–(*C*=O)N], 157.4 (2*C*, 3,5-phenyl), 161.4 [N(*C*=O)].

## 3. Results and discussion

It should be mentioned here that previously our group has reported [13,15] the synthesis of 5-substituted-2,4-dioxo[2,3-*d*]pyrimidines for which nucleophilic Michael's type attack of Ni(0) anion ($NiCN_4^{-4}$), (1) onto the conjugated triple bond of the α-ketoalkyne yielding the species (2) as is shown in the Scheme 3.

The species (1) is obtained when an excess of KCN is added to an alkaline solution of $Ni(CN)_2$ in CO atmosphere. It is known that the presence of carbon monoxide in the media attains an equilibria which involves different carbonylic species in the




Scheme 3.

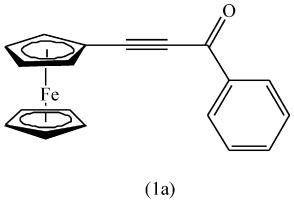
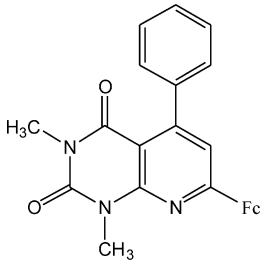
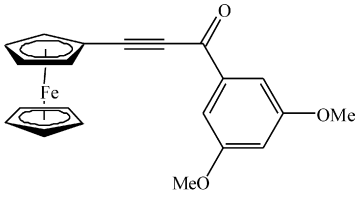
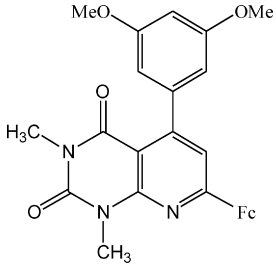
solution [7].

$$Ni^{II}(CN)_2 \overset{HO/CN^-/CO}{\rightleftharpoons} [Ni^{II}(CN)_2(CO)_2] \overset{CO}{\rightleftharpoons} [Ni^{I}(CN)(CO)_3]$$
$$\overset{CO}{\rightleftharpoons} [Ni^{0}(CN)(CO)_3]^{-1} \overset{CN^-}{\rightleftharpoons} [Ni^{0}(CN)_4]^{-4}$$

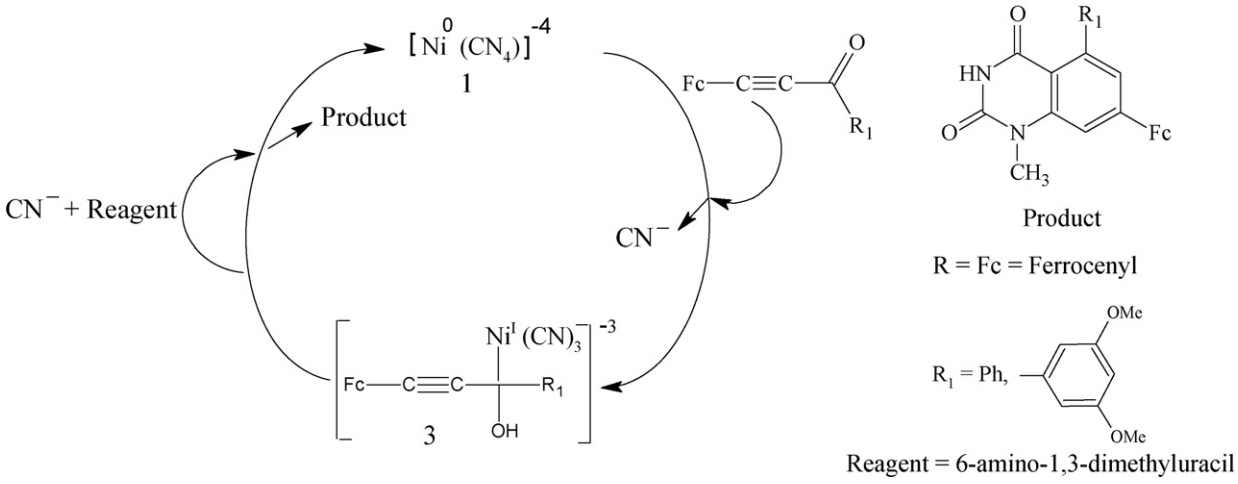
In addition, the presence of carbon monoxide in the system results in a reductive atmosphere, which promotes low oxidation states of nickel in the reaction. In the present work we evaluate the influence of the ferrocenyl group as *R* in the same reaction and we obtained the 5-substituted-7-ferrocenyl-dioxopyrido[2,3-*d*]pyrimidines shown in Table 2.

In this case, the preference for nucleophilic attack is in the carbonylic part of the ketoalkyne. It seems that the triple bond conjugates with the ferrocenyl group because the know electron donor effect of this moiety [16,17]. However the very important steric effect generated by the bulky (Fc) group determines the addition to the keto side (species 3). The possible reaction pathway involved in this process is shown in Scheme 4.

Table 2
Synthesis of 7-ferrocenyl-1,3-dimethyl-5-phenyl-pyrido-[2,3-*d*]pyrimidine-2,4-dione (**2a**), and 7-ferrocenyl-5-(3,5-dimethoxyphenyl)-1,3-pyrido-[2,3-*d*]pyrimidine-2,4-dione (**2b**)[a], by a reaction of cyclocarbonylation of ferrocenyl-α-ketoalkynes with 6-amino-1,3-dimethyluracil

| Ferrocenyl-α-ketoalkynes | 7-Ferrocenyl pyrimidines | Yield (%) | Reaction time (h) |
|---|---|---|---|
|  (1a) |  (2a) | 62 | 10 |
|  (1b) |  (2b) | 60 | 12 |

[a] *Reactions conditions*: ferrocenil-α-ketoalkynes (3.14 g, 10 mmol), 6-amino-1,3-dimethyluracil (1.57 g, 10 mmol), 5N NaOH solution (50 mL), $Ni(CN)_2{\cdot}4H_2O$ (366 mg, 2 mmol), KCN (975 mg, 15 mmol), CO atmospheric pressure and room temperature.




Scheme 4.

Additionally, no products of this reaction were obtained in the absence of CO atmosphere or in the absence of $Ni(CN)_2/HO^-$ system.

## 4. Conclusion

It was found that the reaction between 6-amino-1,3-dimethyluracil and substituted ketoalkynes (in the presence of catalytic promoter) depends on the nature of the alkynyl substituent. With weak electronic donor groups (as *n*-butyl and Ph) yields 5-substituted pyrimidines *via* the 1,4 Michael's type condensation [15], however with strong donor groups (as ferrocenyl moiety), the nucleophilic attack (by the Ni(0) anion formed *in situ*) seems to be at the carbonylic group of ynone, resulting finally in 7-substituted pyrimidine derivatives. Systematic work on this reaction, different subtituents groups are in progress.

## References

[1] M. Barvian, D.H. Boschelli, J. Cossrow, E. Dobrusin, A. Fattaey, A. Fritsch, D. Fry, P. Harvey, J. Med. Chem. 43 (2000) 4606.
[2] A. Gangjee, O. Adair, S.F. Queener, J. Med. Chem. 42 (1999) 2447.
[3] J.M. Hamby, C.J.C. Connolly, M.C. Schroeder, R.T. Winters, H.D.H. Showalter, R.L. Panek, J. Med. Chem. 40 (1997) 2296.
[4] M. Sielecki, J.F. Boylan, P.A. Benfield, G.L. Trainor, J. Med. Chem. 43 (2000) 1.
[5] Patent WO 2005/090344. Novel dichloro-phenyl-pyrido[2,3-*d*]pyrimidine derivates, their manufacture and use as pharmaceutical agents.
[6] I. Devi, B.S.D. Kumar, P.J. Bhuyan, Tetrahedron Lett. 44 (2003) 8307.
[7] N. Rosas, A. Cabrera, P. Sharma, H. Arzoumanian, J. Mol. Catal. 156 (2000) 1038.
[8] N. Rosas, J.L. Arias, A. Cabrera, Recent Research Trends in Organometallic Chemistry, Publishers Research Editors India, 2005, pp. 65–86.
[9] N. Rosas, P. Sharma, I. Arellano, M. Ramírez, D. Pérez, S. Hernández, A. Cabrera, Organometallics 24 (2005) 4893.
[10] A. Cabrera, J.L. Arias, P. Sharma, N. Rosas, Recent Research Trends in Organometallic Chemistry, Publishers Research Editors India, 2005, pp. 33–64.
[11] H. Arzoumanian, M. Jean, D. Nuel, A. Cabrera, J.L. García, N. Rosas, Organometallics 14 (1995) 5438.
[12] H. Arzoumanian, M. Jean, D. Nuel, N. Rosas, Organometallics 16 (1997) 2726.
[13] N. Rosas, P. Sharma, A. Cabrera, G. Pénieres, J.L. García, L.A. Maldonado, Heterocycles 60 (2003) 2631.
[14] Y. Juxing, W. Xiaojun, L. Yongmin, W. Xiaoli, C. Baohua, M. Yongxiang, Synthesis 3 (2004) 331.
[15] N. Rosas, P. Sharma, C. Alvarez, A. Cabrera, R. Ramírez, H. Arzoumanian, J. Chem. Soc., Perkin Trans. 1 (2001) 2341.
[16] L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, H.-L. Hou, Acc. Chem. Res. 36 (2003) 659.
[17] P Sharma, J.G. Lopez, C. Ortega, N. Rosas, A Cabrera, C. Alvarez, A. Toscano, E. Reyes, Inorg. Chem. Commun. 9 (2006) 82.