COMMUNICATION

Novel and facile catalytic synthesis of 2,4-dioxopyrido[2,3-*d*]-pyrimidine derivatives in water

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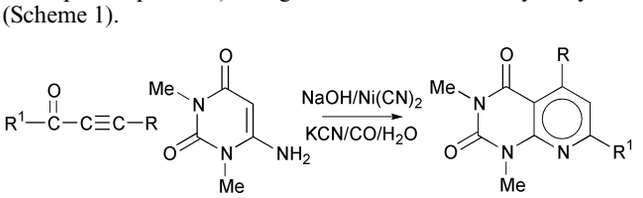
Reactions of 6-amino-1,3-dimethyluracil with substituted α-ketoalkynes using homogeneous nickel catalyst in aqueous alkaline medium, afford substituted 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives in quantitative yields under very mild conditions. A mechanism has been proposed for the reaction involving the nucleophilic attack of Ni(0) anion, formed *in situ* onto the triple bond of the substrate. All the synthesized pyrimidines were well characterized.

Introduction

The nickel catalyzed carbonylation of several α-ketoalkynes and α-haloalkynes using $Ni(CN)_2$ as a catalytic precursor, under phase transfer conditions, have been reported previously by our group.[1–3] Recently by working with a similar water-soluble nickel catalytic system *viz*. $Ni(CN)_2$–CO–KCN–NaOH, in the presence of excess cyanide ions, α-ketoalkynes were transformed regioselectively into δ-hydroxylactams in good yields,[4–6] while propargyl halides (prop-2-ynyl halides) and propargyl alcohols can be transformed into 4,6-dimethyl-5-cyano-2-pyrones[5] under the same reaction conditions. The homogeneous catalyzed processes using water as a solvent have several advantages over the phase transfer catalysis using organic solvents.

In view of the above and knowing that reports exist on the synthesis of pyrido[2,3-*d*]pyrimidines, with average to good yields in organic medium, and the potential pharmacological and biological activities[7–13] of pyrimidines, here we wish to report the novel and facile synthesis of some 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives in water as a reaction medium, under very mild conditions (room temperature and atmospheric pressure) using the same nickel catalytic system (Scheme 1).



Scheme 1

Results and discussion

The results obtained in the coupling and heterocyclization reaction of α-ketoalkynes with 6-amino-1,3-dimethyluracil in the presence and absence of the $Ni(CN)_2$–OH^-–CN^- system are shown in Table 1. Fig. 1 presents the molecular structure of 5-phenyl 1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4-dione determined by X-ray crystallography (compound **4**), as an example of the species obtained in this work.[14] The almost quantitative reaction product formation (Table 1) indicates a sequential process which involves coupling and heterocyclization similar to our earlier reports.[4,5] A plausible mechanism involving a nucleophilic attack[1,2,6] by the nickel(0) anion formed *in situ*,[6] onto the triple bond of substrate, thus promoting the activation of the remnant conjugated double bond. The studies with other unsaturated substrates are still in progress in order to clarify the general mechanism. It is interesting to note that the yields obtained (Table 1) with and without the catalytic system, indicate the gain in reactivity in the nickel catalyzed reactions. In the absence of this catalytic system, reaction takes a longer time period (10 h) to reach a maximum yield of up to ~30%. In the presence of this nickel catalyst the reaction terminates in 30 minutes, giving a maximum of ~98% of the desired pyrimidines.

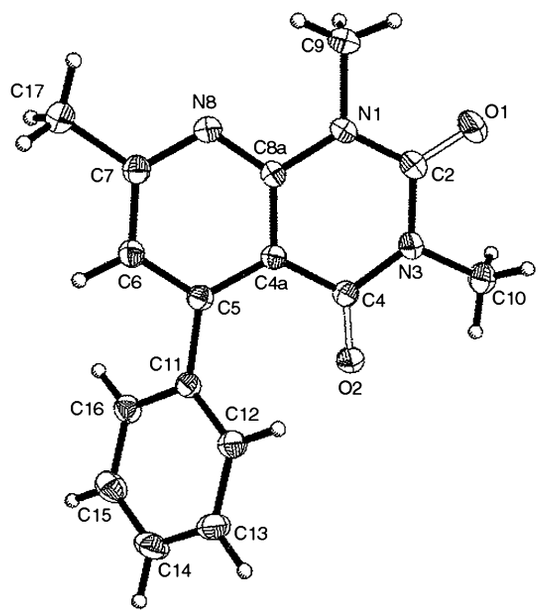


Fig. 1 Molecular structure of compound **4**

Conclusions

This contribution provides an easy way to prepare substituted pyrimidines. The nickel(0) anionic species seems to be the active catalytic species. The easy access to substituted ketoalkynes and 6-aminouracils or similar heterocycles renders this

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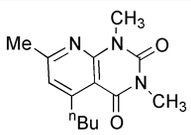
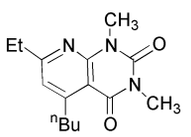
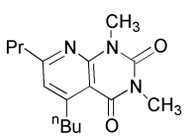
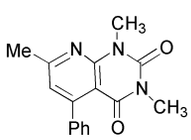
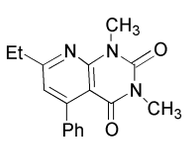
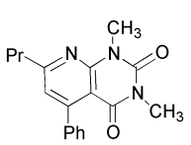
Table 1 Reaction of α-ketoalkynes with 6-amino-1,3-dimethyluracil by $Ni(CN)_2$–CO–KCN system in aqueous alkaline medium[a]

α-Ketoalkynes R–				
R	R^1	2,4-Dioxopyrido[2,3-*d*]pyrimidines	Yield (%) in the absence of catalyst	Yield (%) in the presence of catalyst
^{n}Bu	Me		27.6	98.6
		1		
^{n}Bu	Et		29.2	96.7
		2		
^{n}Bu	Pr		29.0	95.8
		3		
Ph	Me		20.1	97.0
		4		
Ph	Et		18.5	96.8
		5		
Ph	Pr		15.6	95.6
		6		

[a] Reaction conditions: without catalyst: keto alkyne (10 mmol), uracil (10 mmol) 5 M NaOH (50 mL), 15 mmol KCN, CO, 24 °C, reaction time 1–10 h. With catalyst: keto alkyne (10 mmol), uracil (10 mmol), $NiCN_2$ (2 mmol), 5 M NaOH (50 mL), CO (2–3 mL min^{-1}), 15 mmol KCN, 24 °C, reaction time 0.5 h.

nickel catalyzed route very attractive to variously substituted pyridopyrimidines.

Experimental

Synthesis of pyrimidines general procedure

A typical experiment was performed as follows. A 5 M NaOH solution (50 mL) was degassed and saturated with CO under atmospheric pressure for 30 min. To the solution was then added 2 mmol of $Ni(CN)_2{\cdot}4H_2O$ (366 mg, 2 mmol), the mixture was kept at room temperature overnight with stirring and slow bubbling of CO (2–3 mL min^{-1}) 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 α-ketoalkynes and the 6-amino-1,3-dimethyluracil compounds were added (10 mmol). The evolution of the reaction was followed by TLC. The reaction products were quantified by GC in a Hewlett Packard 5890 analyser with a HP 225 (10 m × 0.53 mm) packed column. At the end of the reaction, ethyl acetate was used to extract the product. The pure crystalline products were obtained following evaporation of the solvent after drying over $MgSO_4$.

5-*n*-Butyl-1,3,7-trimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (1)

The product was obtained as described in the general procedure in a 98.6% yield as a white solid. Mass spectrum EI: *m*/*z* = 261; IR (selected, cm^{-1}) 1703 and 1656 (C=O), 1597 (C=C), 1564 (C=N); ^{1}H-NMR δ_H(300 MHz; $CDCl_3$; TMS ppm): 6.8 (1H, s, CH), 3.66 and 3.42 (3H, s, CH_3), 3.15 (2H, t, CH_2), 2.51 (3H, s, CH_3), 1.56 (2H, q, CH_2), 1.41 (2H, m, CH_2), 0.92 (3H, t, CH_3); δ_C: 162.4 (C_7), 161.6 (C_1), 157.7 (C_2), 151.7 (C_4), 151.5 (C_6), 121.0 (C_5), 106.3 (C_3), 34.4 (C_{10}), 32.7 (C_{11}), 30.0 and 28.3 (C_8 and C_9), 24.8 (C_{14}), 22.9 (C_{12}), 14.0 (C_{13}).

5-*n*-Butyl-7-ethyl-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4-dione (2)

Yield = 96.7%, white solid. Mass spectrum, EI: *m*/*z* = 275; IR (selected, cm^{-1}) 1703 and 1656 (C=O), 1597 (C=C), 1562 (C=N); δ_H ppm: 6.79 (1H, s, CH), 3.68 and 3.42 (3H, s, CH_3), 3.16 (2H, t, CH_2), 2.77 (2H, q, CH_2), 1.39 (2H, m, CH_2), 1.28 (3H, t, CH_3), 0.92 (3H, t, CH_3); δ_C: 167.2 (C_7), 161.6 (C_1), 157.8 (C_2), 151.7 (C_4), 151.5 (C_6), 119.8 (C_5), 106.4 (C_3), 34.5 (C_{10}), 32.8 (C_{11}), 30.0 and 28.3 (C_8 and C_9), 22.9 (C_{12}), 14.0 (C_{14}), 13.0 (C_{13}).

5-*n*-Butyl-1,3-dimethyl-7-*n*-propylpyrido[2,3-*d*]pyrimidine-2,4-dione (3)

Yield = 95.8%, white solid. Mass spectrum EI: *m*/*z* = 289; IR (selected, cm^{-1}) 1703 and 1654 (C=O), 1597 (C=C), 1562 (C=N); δ_H ppm: 6.79 (1H, s, CH), 3.68 and 3.42 (3H, s, CH_3), 3.16 (2H, t, CH_2), 2.71 (2H, t, CH_2), 1.76 (2H, m, CH_2), 1.57 (2H, q, CH_2), 1.41 (2H, m, CH_2), 0.92 (3H, t, CH_3); δ_C: 167.2 (C_7), 161.6 (C_1), 157.6 (C_2), 151.8 (C_4), 151.2 (C_6), 120.4 (C_5), 106.5 (C_3), 40.3 (C_{16}), 34.5 (C_{10}), 32.9 (C_{11}), 30.0 and 28.2 (C_8 and C_9), 22.9 (C_{12}), 22.3 (C_{15}), 14.0 (C_{14}), 13.9 (C_{13}).

1,3,7-Trimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4-dione (4)

Yield = 97.0%, white solid. Mass spectrum EI: *m*/*z* = 281; IR (selected, cm^{-1}) 1706 and 1660 (C=O), 1593 (C=C), 1560 (C=N); δ_H ppm: 6.85 (1H, s, CH), 7.43–7.24 (5H, m, phenyl), 3.75, 3.35 and 2.60 (3H, s, CH_3); δ_C: 162.7 (C_7), 160.7 (C_1), 154.4 (C_2), 151.6 (C_4 and C_6), 139.4 (C10), 128.1 (C_{11}), 127.7 (C_{13}), 121.8 (C_5), 105.6 (C_3), 30.1 and 28.4 (C_8 and C_9), 18.2 (C_{14}). X-Ray crystallographic data of compound **4** are reported.

7-Ethyl-1,3-dimethyl-5-phenylpyrido[2,3-*d*]pyrimidine-2,4-dione (5)

Yield = 96.8%, white solid. Mass spectrum EI: *m*/*z* = 294; IR (selected, cm^{-1}) 1706 and 1658 (C=O), 1593 (C=C), 1556 (C=N); δ_H ppm: 6.86 (1H, s, CH), 7.43–7.28 (5H, m, phenyl), 3.82 and 3.35 (3H, s, $3CH_3$), 2.86 (2H, q, CH_2), 1.34 (3H, t, CH_3); δ_C: 165.5 (C_7), 160.7 (C_1), 154.5 (C_2), 151.6 (C_4 and C_6), 139.6 (C_{10}), 128.0 (C_{11}), 127.8 (C_{12} and C_{13}), 120.7 (C_5), 105.8 (C_3), 31.6 (C_{15}), 30.0 and 28.4 (C_8 and C_9), 13.0 (C_{14}).

1,3-Dimethyl-5-phenyl-7-propylpyrido[2,3-*d*]pyrimidine-2,4-dione (6)

Yield = 95.6%, white solid. Mass spectrum EI: *m*/*z* = 309; IR (selected, cm^{-1}) 1708 and 1660 (C=O), 1591 (C=C), 1556 (C=N); δ_H ppm: 6.85 (1H, s, CH), 7.43–7.26 (5H, m, phenyl), 3.77 and 3.35 (3H, s, CH_3), 2.80 (2H, t, CH_2), 1.82 (2H, m, CH_2), 1.00 (3H, t, CH_3); δ_C ppm: 166.4 (C_7), 160.7 (C_1), 154.3 (C_2), 151.6 (C_4 and C_6), 139.5 (C_{10}), 128.0 (C_{11}), 127.8 (C_{12} and 13), 121.3 (C_5), 105.7 (C_3), 40.4 (C_{16}), 30.0 and 28.4 (C_8 and C_9), 24.8 (C_{14}), 22.2 (C_{15}), 13.9 (C_{14}).

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14 X-Ray data of compound (**4**): Empirical formula = $C_{16}H_{15}N_3O_2$; Formula weight = 281.31; Crystal system = Monoclinic; Space group = $P2_1/n$; a = 12.422(2) Å; b = 7.912(1) Å; c = 14.483(1) Å, β = 106.89(1)°; V = 1362.0(3) $Å^3$; z = 4; Density (cal) = 1.372 Mg m^{-3}; Absorption Coeff. = 0.093 mm^{-1}; Crystal size = 0.92 × 0.48 × 0.14 mm; θ range = 1.5–25.0°; Reflections collected 2525; Independent reflections = 2408 (*R*int = 0.0273): refinement method = full matrix least square on F^2; S = 1.019; R = 0.054; R_w = 0.126; Max/min $\nabla\rho/e$ $Å^{-3}$ = 0.219/−0.308; O(1)–C(2) 1.207(4); O(2)–C(4) 1.218(4); N(1)–C(2) 1.367(4); N(1)–C(8A) 1.391(4); N(1)–C(9) 1.466(4); N(3)–C(2) 1.389(4); N(3)–C(10) 1.474(4) N(8)–C(8A) 1.333(4); N(8)–C(7) 1.341(4); C(2)–N(1)–C(8A) 123.2(2); C(2)–N(1)–C(9) 116.1(3); C(9)–N(1)–C(8A) 120.6(3); C(2)–N(3)–C(10) 115.5(3); C(8A)–N(8)–C(7) 117.3(2); N(8)–C(8A)–N(1) 115.0(2); N(8)–C(7)–C(17) 116.5(3). CCDC number 159634.