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Synthesis of butyrolactones by nickel-catalyzed reductive cyanation of alkynols in water

José Luis García Gutiérrez,[a,*] Federico Jiménez-Cruz[a] and Noé Rosas Espinosa[b]

[a]*Instituto Mexicano del Petróleo. Eje Central Lázaro Cárdenas 15, México DF 07730, México*
[b]*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, México DF 04510, México*

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Abstract—One-pot catalytic synthesis of butyrolactones from alkynols under mild conditions is described here. The methodology involves the use of the $K_2[Ni(CN)_4]/NaBH_4$ system in presence of KCN and water. According to the experimental evidences, a possible mechanism pathway is suggested, which involves the nickel-catalyzed reductive cyanation of alkynol, followed by nitrile hydration, reduction of double bond and lactonization.

Lactones have deserved great interest in synthetic and natural products chemistry. These structures occur extensively in the natural world and their biological and pharmacological activities have been widely studied.[1] Several synthetic methods for lactones have been developed and reported during these last years.[1,2] A considerable number of these synthetic methods involves transition metal complexes as catalysts to accomplish the formation of carbon–carbon bonds by activation of unsaturated hydrocarbons by carbon monoxide and cyanide.[3,4] In seeking to develop new synthetic methods for heterocyclic organic compounds by using a novel nickel-based catalytic procedure, we have shown that α-ketoalkynes can be carbonylated in the presence of $Ni(CN)_2$ and carbon monoxide and basic aqueous medium under phase transfer conditions to give unsaturated hydroxybutyrolactones.[5] In addition, it was possible to obtain unsaturated hydroxybutyrolactams by working the same catalyst precursor in the presence of excess cyanide ions and aqueous phase.[6,7] Subsequently, it was reported the cascade conversion of propargyl halides or alcohols into 4,6-dimethyl-5-cyano-2-pyrone catalyzed by $Ni(CN)_2$ in presence of carbon monoxide and cyanide ions in water.[8] Likewise, it was shown that the reaction of 6-amino-1,3-dimethyluracil with substituted α-ketoalkynes affords substituted 2,4-dioxopyrido[2,3-*d*]pyrimidines derivatives.[9] Recently, the syntheses of substituted 1,8-naphthyridines and 2*H*-pyrano[3,2-*g*]quinolin-2-ones was carried out by the reaction of α-ketoalkynes with 6-aminonicotinamide and 7-amino-4-methyl-coumarin, respectively, by using the nickel system before indicated.[10] In this context, we wish to report the catalytic synthesis of butyrolactones from alkynols in good yield by the $K_2[Ni(CN)_4]/NaBH_4$ system, using an stoichiometric amount of KCN in water.

In Table 1 is showed the results of catalytic cyanation of alkynols with $K_2[Ni(CN)_4]/NaBH_4$/KCN system in water[11] (see Scheme 1). The 2,4-disubstituted-4-butyrolactones synthesis is carried out in good yield. It was observed that in absence of either $K_2[Ni(CN)_4]$ or $NaBH_4$ the reaction is not carried out and in the presence of internal alkynols a mixture of several product is obtained.

Likewise, $NiCl_2$ can act as precursor of active specie (Table 1, entry lc). The butyrolactone structures indicate that the cyanide anion is added on the internal acetylenic carbon. In addition, results of this reaction with 1-phenylhex-1-yn-3-one (1f) conducted to 2-phenyl-4-propyl-4-butyrolactone and the 4-keto-2-phenylheptanoic acid.[14] A lower yield of lactone is obtained when the substrate presents a keto group instead of alcohol group into its structure. This could be due to the lower amount of $NaBH_4$ used in the experimental conditions, which limited the reduction of the keto group and the

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* Corresponding author. Tel.: +52 55 9175 6646; fax: +52 55 9175 8429; e-mail: garciajl@imp.mx

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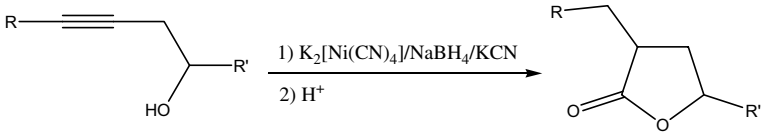
Table 1. Synthesis of butyrolactones from alkynols

Entry	Substrate	Entry	Product	% Yield
1a	3-Butyn-1-ol	2a	2-Methyl-4-butyrolactone	74
1b	4-Pentyn-2-ol	2b	2,4-Dimethyl-4-butyrolactone	87
1c	5-Hexyn-3-ol	2c	4-Ethyl-2-methyl-4-butyrolactone	93
1c	5-Hexyn-3-ol	2c	4-Ethyl-2-methyl-4-butyrolactone	95[a]
1d	6-Heptyn-4-ol	2d	2-Methyl-4-propyl-4-butyrolactone	85
1e	2-Butyne-1,4-diol	2e	2-Hydroxymethyl-4-butyrolactone	58[b]
1f	1-Phenyl-hex-1-yn-3-one[c]	2f	2-Phenyl-4-propyl-4-butyrolactone	5
1f	1-Phenyl-hex-1-yn-3-one[c]	2g	4-Keto-2-phenylheptanoic acid	89[d]

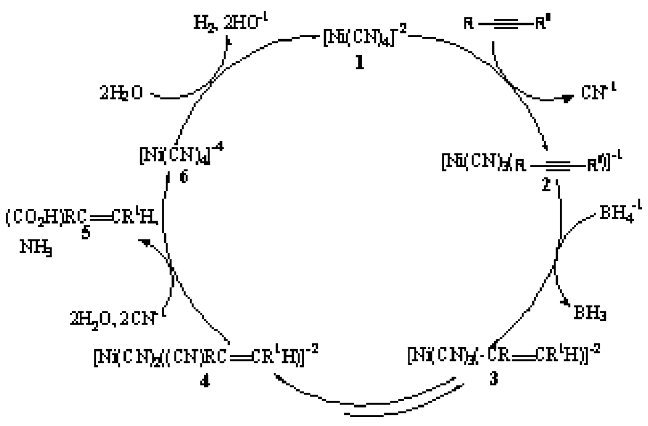
[a] $NiCl_2$ was used.
[b] Sample contained hydroxycarbonyl products; the ratio of lactone:hydroxycarbonyl product was about 1:1.
[c] α-Ketoalkyne was used.
[d] Isolated from the first extraction with ether.



Scheme 1.

subsequent lactonization. It is also noted that during the cyanide addition a double bond is formed, which is reduced before the lactonization.

According to prior observations, a series of successive steps is suggested: reduction of alkynol, cyanation, hydration of the nitrile group, reduction of double bond and lactonization (see Scheme 2). It is know that several Ni(II) salts, that is, chloride and cyanide, in the presence of excess cyanide ions in water generates the specie 1.[15] This specie can react with an alkyne by the displacement of cyanide ions to give the specie 2. In this way the activated alkyne, by its π-coordination at the nickel atom, is susceptible to a nucleophilic addition of hydride specie. Subsequently, the formed σ-vinyl complex, specie 3, can undergo a reductive elimination to give the specie 4. In recently publications, the Ni(0) fragment [(dippe)Ni] has been found to π-coordinate to the CN bond of several organic nitriles and undergo reversible insertion into the R–CN bond.[16–18] Thus, a interconversion between the species 3 and 4 should be consider in the mechanism pathway.[19] It is possible that the nickel also catalyze the hydration of the nitrile to 2,3-unsaturated acid, specie 5, as the triple bond case.[20] The before step is followed by a double bond reduction with $NaBH_4$ to give the respective 4-hydroxy acid. Lactonization of this latter specie gives the butyrolactone. Finally, the tetracyanonickel(II) (specie 1) is regenerated by the oxidation of the tetracyanonickel(0) (specie 6) with water according to the literature.[15]



Scheme 2.

In conclusion, a novel and simple method for the catalytic synthesis of 2,4-disubstitutedbutyrolactones is reported. It is suggested that the reaction is catalyzed by cyanonickel(II) specie, which is regenerated via its reoxidation with water. Apparently, the key step in the process is the reductive elimination of the cyanide and the vinyl attached on nickel atom. The preparation of butyrolactones by this method can apply to α-ketoalkynes as substrates.

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11. *Experimental procedure*: all materials were obtained from commercial suppliers and used without further purification. 5-Hexyn-3-ol, 6-heptyn-4-ol and 1-phenylhex-1-yn-3-one were synthesized according to published methods.[12,13] A typical experiment was performed as follows: in a round-bottom flask were mixed 1 mmol of $K_2[Ni(CN)_4]$, 10 mmol KCN and 10 mmol of $NaBH_4$, then 12.5 mL of water was added yielding an orange solution that was stirred and heated at 393 K. To this solution was then added 10 mmol of α-alkynol **1a**–**f** and the stirring continued at 393 K for 12 h. At the end of the reaction, ethyl ether (2×20 mL) was used to eliminate the impurities. The aqueous phase was acidified with diluted HCl at pH ~ 1 (Caution! HCN is generated). Ethyl ether (2×20 mL) was used to extract the product. Evaporation of the solvent after drying over Na_2SO_4 gave the lactone. Spectral data for **2a**–**g**: *2-methyl-4-butyrolactone* (**2a**). IR (KBr) cm^{-1}: 1767 (C=O). ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.20 (3H, d, CH_3); 1.82 (1H, m, CH); 2.45 (2H, m, CH_2); 4.17 (2H, m, CH_2–O). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 15.45 CH_3; 30.99 CH; 34.50 CH_2; 66.73 C–O; 180. 79 C=O. *2,4-Dimethyl-4-butyrolactone* (**2b**). IR (KBr) cm^{-1}: 1764 (C=O). ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.08 (3H, dd, CH_3); 1.23 (3H, dd, *CH_3*–CH–O); 1.92 (1H, m, CH); 2.45 (2H, m, CH_2); 4.43 (1H, m, CH–O). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 15.90 CH_3; 21.23 *CH_3*–CH–O; 34.13 CH; 39.28 CH_2; 75.32 C–O; 180.48 C=O. *4-Ethyl-2-methyl-4-butyrolactone* (**2c**). IR (KBr) cm^{-1}: 1763 (C=O); ^1H NMR (300 MHz, $CDCl_3$) ppm: 0.98 (3H, dd, *CH_3*–CH_2); 1.09 (3H, dd, CH_3); 1.32 (2H, m, CH_3–*CH_2*); 1.93 (1H, m, CH); 2.45 (2H, m, CH_2); 4.47 (1H, m, CH–O). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 11.30 *CH_3*–CH_2; 15.90 CH_3; 22.30 CH_3–*CH_2*; 35.0 CH; 39.20 CH_2; 74.11 CH–O; 180. 6 C=O. *2-Methyl-4-propyl-4-butyrolactone* (**2d**). IR (KBr) cm^{-1}: 1763 (C=O); ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.0 (3H, dd, *CH_3*–CH_2–CH_2); 1.10 (3H, dd, CH_3); 1.20 (2H, m, CH_3–*CH_2*–CH_2); 1.31(2H, m, CH_3–CH_2–*CH_2*); 1.90 (1H, m, CH); 2.41 (2H, m, CH_2); 4.41 (1H, m, CH–O). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 10.21 *CH_3*–CH_2–CH_2; 13.20 CH_3–*CH_2*–CH_2; 16.01 CH_3; 22.11 CH_3–CH_2–*CH_2*; 35.12 CH; 39.10 CH_2; 73.27 CH–O; 180.7 C=O. *2-Hydroxymethyl-4-butyrolactone* (**2e**). IR (KBr) cm^{-1}: 1767 (C=O); 3504 (OH). ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.88 (1H, qn, CH); 2.50 (2H, m, CH_2); 4.15 (2H, m, CH_2–O); 4.20 (2H, m, CH_2–O); 7.85 (br, OH). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 49.29 CH; 34.56 CH_2; 66.82 CH_2–O; 62.88 CH_2–OH; 182. 88 C=O. *2-Phenyl-4-propyl-4-butyrolactone* (**2f**). IR (KBr) cm^{-1}: 1765 (C=O); ^1H NMR (300 MHz, $CDCl_3$) ppm: 0.96 (3H, t, *CH_3*–CH_2–CH_2); 1.26 (2H, m, CH_3–*CH_2*–CH_2); 1.53 (2H, m, CH_3–CH_2–*CH_2*); 2.08 (1H, m, CH); 2.35 (2H, m, CH_2); 4.29 (1H, m, CH–O); 7.15 (7H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 10.42 *CH_3*–CH_2–CH_2; 13.34 CH_3–*CH_2*–CH_2; 23.65 CH_3–CH_2–*CH_2*; 36.45 CH; 40.10 CH_2; 74.87 CH–O; 127.6 C_o; 127.4 C_m; 128.3 C_p; 136.1 C_{ip} 177.5 C=O. *4-Keto-2-phenylheptanoic acid* (**2g**). IR (KBr) cm^{-1}: 1709 (C=O); 1720 (CO_2H); 1685. ^1H NMR (300 MHz, $CDCl_3$) ppm: 0.87 (3H, t, CH_2); 1.59 (2H, h, CH_3–*CH_2*–CH_2); 2.39 (2H, m, CH_3–CH_2–*CH_2*); 2.69 (1H, dd, *CH_aH_b*); 3.30 (1H, dd, CH); 4.12 (1H, dd, *CH_aH_b*); 7.27 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$) ppm: 13.6 CH_3; 17.1 CH_3–*CH_2*–CH_2; 44.6 CH_3–CH_2–*CH_2*; 45.8 CH_2; 46.1 CH; 127.6 C_o; 127.8 C_m; 128.8 C_p; 137.5 C_{ip}; 177.7 CO_2H; 208.4 C=O.
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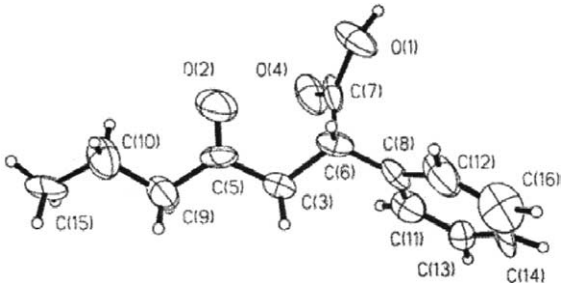
14. *X-ray data of 4-keto-2-phenylheptanoic acid* **2g**: empirical formula = $C_{13}H_{14}O_3$; formula weight = 218.2; crystal system = monoclinic; space group = $P2_1/n$; a = 15.075(3) Å; b = 5.5890(10) Å; c = 15.595(3) Å, β = 112.98(3)°; V = 1209.7(6) $Å^3$; z = 4; density (calcd) = 1.198 Mg m^{-3}; absorption coefficient = 0.085 mm^{-1}; crystal size = 0.17 × 0.11 × 0.10 mm; 2θ range = 7.0–45.0°; reflections collected 4473; independent reflections = 3519 (R int = 12.03%): refinement method = full matrix least square on F^2; R = 21.36%; Rw = 20.88%; Largest and mean Δ/σ = 5.026, 0.243;



O(1)–C(7) 1.336(22); C(3)–C(5) 1.515(24); O(4)–C(7) 1.253(29); C(6)–C(7) 1.477(37); C(9)–C(10) 1.491(23); O(2)–C(5) 1.202(23); C(3)–C(6) 1.551(26); C(5)–C(9) 1.501(27); C(6)–C(8) 1.500(25); C(8)–C(12) 1.373(31); C(10)–C(15) 1.474 (38); C(5)–C(3)–C(6) 110.6(15); O(2)–C(5)–C(9) 122.2(17); C(3)–C(6)–C(7) 109.6(15); C(7)–C(6)–C(8) 107.3(19); C(6)–C(8)–C(11) 122.1(16); O(2)–C(5)–C(3) 121.1(18); C(3)–C(5)–C(9) 116.8(15); C(3)–C(6)–C(8) 112.4(14); O(1)–C(7)–O(4) 117.5(24); O(4)–C(7)–C(6) 127.6(17); O(6)–C(8)–C(12) 120.8(18). Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary Publication No. CCDC 256739.

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