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Original article

Using a warm dioxane/MeOH/$NaBH_4$ mixture as convenient medium for the selective chemical reduction of the C=C double bond in α,β-unsaturated systems

Uso de una mezcla dioxane/MeOH/$NaBH_4$ en caliente como un medio conveniente para la reducción química selectiva del doble enlace C=C en sistemas α,β-insaturados

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Abstract

Diversely substituted Knoevenagel products were subjected to reduction with $NaBH_4$ in MeOH/*p*-dioxane solution at 70 °C. Selectively reduction of their C=C double bond was achieved in all cases. Reduction conditions tolerated a variety of functional groups although simple aldolic or Claisen-Schmidt products showed to be less selective toward C=C reduction and on the contrary C=O bond was reduced under these reaction conditions. Additionally, selectivity of the $NaBH_4$-mediated chemical reduction was compared with the classical Raney-Nickel-mediated catalytic hydrogenation in order to find similarities and differences. Moreover, trying to explain the selective $NaBH_4$-mediated reductive process a plausible mechanistic pathway was proposed in this regard.

Keywords: Chalcones; Knoevenagel products; α,β-Unsaturated systems; Selective reductions; $NaBH_4$-mediate reductions; Catalytic hydrogenation.

Resumen

Productos de Knoevenagel diversamente sustituidos fueron sometidos a reducción con una solución de $NaBH_4$ en MeOH/*p*-dioxano a 70 °C. A través de este proceso, se alcanzó la reducción selectiva de sus dobles enlaces C=C en todos los casos. Las condiciones de reducción establecidas toleró una variedad de grupos funcionales, aunque productos simples de condensación aldólica o de Claisen-Schmidt mostraron menos selectividad hacia la reducción del doble enlace C=C, y por el contrario, condujo específicamente a la reducción de los grupos C=O. Adicionalmente, la selectividad de nuestras condiciones de reducción mediadas por $NaBH_4$ fue comparada con la clásica hidrogenación catalítica mediada por Raney-Nickel para encontrar algunas similitudes y diferencias. Así mismo, se propuso una secuencia de pasos mecanísticos, con el fin de intentar explicar el proceso de reducción selectiva mediada por $NaBH_4$.

Palabras clave: Chalconas; Productos de condensación de Knoevenagel; Sistemas α,β-insaturados; Reducciones selectivas; Reducciones mediadas por $NaBH_4$; Hidrogenación catalítica.

Introduction

The control of the selectivity remains as one of the main concerns in the synthetic organic chemistry (**Balcells, *et al.,*** 2016; **Ward,** 1999). Particularly, selective reduction of C=C double bonds in the presence of carbonyl and carboxyl functionalities (in α,β-unsaturated systems), is frequently a challenging aspect in synthetic organic strategies. For that, several approaches have been reported in that direction with varied grades of success (**Cornubert**

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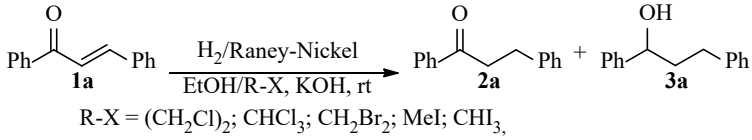
& Eggert, 1954; **Cornubert & Thomas,** 1954; **Hammond, *et al.,*** 2009; **Inoue, *et al.,*** 2002; **Chikashita, *et al.,*** 1987; **Felpin & Fouquet,** 2010; **Gutierrez, *et al.,*** 2010; **Zheng, *et al.,*** 2015; **Keess & Oestreich,** 2017; **Mori, *et al.,*** 2006; **Lipshutz, *et al.,*** 1998; **Wang, *et al.,*** 2016). In a classical procedure described by Cornubert *et al.*, the selective reduction of the C=C double bond in the α,β-unsaturated ketone (chalcone) **1a** was performed by means of a catalytic hydrogenation process in EtOH mediated by Raney-Nickel poisoned with halo-alkanes (R-X). Nevertheless, appreciable formation of the double-reduction side-product (i.e. saturated alcohol **3a**) also accompanied this process, Scheme 1 (**Cornubert & Eggert,** 1954; **Cornubert & Thomas,** 1954). When reaction was performed in absence of halo-alkanes, the double-reduction side-product **3a** was obtained exclusively (**Tucker,** 1950).



Scheme 1. Attempts to selective reduction of the C=C double bond in chalcone **1a** by catalytic hydrogenation using Raney-Nickel poisoned with halo-alkanes (R-X).

A modification to the above approach was performed by Hammond, *et al.*, replacing the reducing couple H_2/Raney-Nickel by ammonium formate/Pd/C, affording the expected product **2a** in better yield (**Hammond, *et al.,*** 2009). Alternatively, $NaBH_4$-based chemical reductions have also been performed but in most cases the carbonyl or both carbonyl and C=C double bond functionalities resulted in reduction (**Zeynizadeh & Shirini,** 2003; **Aramini, *et al.,*** 2000; **Mohamadi, *et al.,*** 2013).

As part of our current program on the synthetic utilization of chalcones and their analogues for the synthesis of diverse heterocyclic compounds (**Insuasty,** *et al.*, 2017; **Ramírez-Prada, *et al.,*** 2017; **Montoya, *et al.,*** 2016; **Insuasty, *et al.,*** 2016), herein, we wish to report two complementary approaches for the preparation of diverse α,β-reduced derivatives of synthetic interest mediated by the selective (catalytic and chemical) reduction of their α,β-C=C double bonds starting from their corresponding α,β-unsaturated precursors.

Materials and Methods

Melting points were determined on a Stuart SMP10 melting point apparatus and are uncorrected. FTIR spectra were recorded on a Shimadzu FTIR 8400 ATR technique. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrophotometer operating at 400 MHz and 100 MHz respectively, using $CDCl_3$ and DMSO-d_6 as solvents and tetramethylsilane (TMS) as internal standard. Mass spectra were run on a SHIMADZU-GCMS-QP-2010 Plus spectrometer (equipped with a direct inlet probe) operating at 70 eV. The starting indole was purchased from Merck (analytical grade reagent), and was used without further purification. The starting *N*-alkylindoles (i.e. 1-methyl, 1-butyl and 1-benzyl) were synthesized by *N*-alkylation reaction using iodomethane, 1-bromobutane and benzyl chloride, following the procedures described by (**Kong, *et al.,*** 2006). Synthetic details for the new and some representative known compounds are described as follow:

Selective reduction of the α,β-unsaturated C=C double bonds in chalcones 1 by catalytic hydrogenation

A mixture of chalcone **1** (1 gram), ethanol (5-10, mL), chloroform or DCM (0.5 mL) and Raney-Nickel (0.3 g) was stirred at room temperature under hydrogen pressure (20 psi) in a Parr apparatus for 15-20 min. The solid formed was completely dissolved by adding the adequate volume of ethyl acetate, the catalyst was removed by filtration and product recovered after removing the solvent mixtures under reduced pressure. No further purification was required to afford hydrogenated ketones **2**.

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Synthesis of 1-methyl-1H-indole

In a 15 mL round-bottom flask, NaH (2 mmol) was added to a cold (0 °C) stirred solution of indole (1.0 mmol) in THF (5 mL). After 25 min, iodomethane (1.4 mmol) was added at 0 °C and the mixture was stirred at room temperature for 3 h. The solution was then quenched with a saturated solution of ammonium chloride (4 mL), and extracted with ethyl acetate (2 x 5 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (eluent: hexane/dichloromethane 40%), to provide the corresponding product as a yellow oil in 98% yield. FTIR (ATR): v = 3010 (C-H), 2946 (C-H), 2929 (C-H), 2900 (C-H), 2842 (C-H), 1570 (C=C), 1550 (C=C) cm^{-1}.

General procedure for the synthesis of 1-benzyl- and 1-butyl-1H-indoles

Triturated KOH (1.5 g, 27.3 mmol, 3.2 equiv) was added to a stirred solution of indole (1.0 g, 8.53 mmol, 1 equiv) in acetone (15 mL). After 20 min of stirring benzyl chloride (1.73 g, 13.6 mmol, 1.6 equiv) was added. The solution was stirred at room temperature until the indol was no longer detected by TLC. The insoluble materials were removed by filtration, and the acetone was concentrated under reduced pressure. The resulting oil was purified by flash chromatography (eluent: hexane/dichloromethane 1:1). The same procedure was followed by using 1-bromobutane instead benzyl chloride.

1-Benzyl-1H-indole. Yellow oil, 86 % yield. FTIR (ATR): v = 3005 (C-H), 2940 (C-H), 2889 (C-H), 1585 (C=C), 1560 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (s, 2H, CH_2Ph), 6.68 (d, J = 3.0 Hz, 1H), 7.05 – 7.53 (m, 9H), 7.79 (d, J = 7.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.2 (CH_2Ph), 101.8, 109.8, 119.6, 121.1, 121.8, 126.9, 127.7, 128.3, 128.8 (Cq), 128.9, 136.4 (Cq), 137.7 (Cq) ppm.

1-Butyl-1H-indole. Yellow oil, 82 % yield. FTIR (ATR): v = 3007 (C-H), 2956 (C-H), 2929 (C-H), 2872 (C-H), 1609 (C=C), 1483, 1463, 1456, 1315, 1242, 1199, 1012, 734, 713 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 8.4 Hz, 3H, CH_3), 1.51 (m, J = 15.1, 7.4 Hz, 2H, CH_2), 1.97 (m, J = 7.3 Hz, 2H, CH_2), 4.25 (t, J = 7.1 Hz, 2H, CH_2), 6.68 (s, 1H, =C-H), 7.24 (d, J = 2.8 Hz, 1H, ArH), 7.29 (t, J = 6.7 Hz, 1H, ArH), 7.40 (t, J = 6.0 Hz, 1H, ArH), 7.52 (d, J = 8.2 Hz, 1H, ArH), 7.83 (d, J = 7.8 Hz, 1H, =C-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.4 (CH_2), 32.5 (CH_2), 101.0, 46.2 (CH_2), 109.6, 119.3, 121.1, 121.4, 127.9, 128.7 (Cq), 136.1 (Cq) ppm.

General procedure for the synthesis of indole-oxo-propanenitriles

These compounds were obtained by adapting procedures described previously by (**Fadda, *et al.,*** 2014; **Cai, *et al.,*** 2018; **Chen, *et al.,*** 2013). In a 25 mL round-bottom flask coupled with a condenser and stir bar, a mixture of the corresponding indole (1.0 mmol), cyanoacetic acid (1.2 mmol) and acetic anhydride (2-3 mL) was stirred under heating in an oil bath at 105 °C for 1.5 h. During this time, the initial yellow solution turned dark-red and a precipitate was observed. After complete consumption of the starting indole (monitored by TLC), the solution was cooled to 0 °C overnight. The precipitate was filtrated and washed with methanol (2 x 1.0 mL). No further purification was required in any case.

3-(1H-Indol-3-yl)-3-oxopropanenitrile. This compound was obtained according to the above procedure from indole as beige solid, 79% yield, mp 243 °C. FTIR (KBr): v = 3225 (N-H), 2253 (CN), 1643 (C=O), 1581 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.47 (s, 2H, CH_2), 7.19-7.27 (m, 2H), 7.47-7.52 (m, 1H), 8.10-8.16 (m, 1H), 8.36 (s, 1H), 12.14 (s, 1H, NH) ppm. MS (70 eV): m/z (%) = 184 (23) $[M]^{+\bullet}$, 144 (100), 116 (27), 89 (26).

3-(1-Methyl-1H-indol-3-yl)-3-oxopropanenitrile. This compound was obtained according to the above procedure from 1-methyl-1*H*-indole as a brown solid, 73% yield, mp 153 °C. FTIR (ATR): v = 3110 (C-H), 2250 (CN), 1643 (C=O), 1581 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 7.31–7.48 (m, 3H), 7.81 (s, 1H), 8.27–8.37 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.6 (CH_2), 33.9 (CH_3), 110.1, 114.2 (Cq), 114.9 (CN), 122.3, 123.5, 124.2, 126.1 (Cq), 136.2, 137.5 (Cq), 180.5 (C=O).

3-(1-Benzyl-1H-indol-3-yl)-3-oxopropanenitrile. This compound was obtained according to the above procedure from 1-benzyl-1*H*-indole as a beige solid, 72% yield, mp 124 °C. IR (ATR): ν = 3105 (C-H), 2252 (CN), 1662 (C=O), 1602 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (s, 2H, CH_2CN), 5.41 (s, 2H, CH_2Ph), 7.21 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.30-7.40 (m, 6H), 7.85 (s, 1H), 8.37 (dd, *J* = 8.4, 1.7 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8 (CH_2), 51.1 (CH_2Ph), 110.6, 114.7 (Cq), 114.8 (CN), 122.5, 123.6, 124.4, 126.3 (Cq), 127.2, 128.5, 129.2, 135.1 (Cq), 135.2, 137.1 (Cq), 180.6 (C=O). Anal. Calcd. For $C_{18}H_{14}N_2O$ (274.32): C, 78.81; H, 5.14; N, 10.21. Found: C, 78.93; H, 5.35; N, 9.94.

3-(1-Butyl-1H-indol-3-yl)-3-oxopropanenitrile. This compound was obtained according to the above procedure from 1-butyl-1*H*-indole as a yellow solid, 81% yield, mp 108 °C. FTIR (ATR): ν = 2249 (C≡N), 1641 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.4 Hz, 3H), 1.38 (m, *J* = 7.4 Hz, 2H), 1.88 (m, *J* = 7.4 Hz, 2H), 3.88 (s, 2H), 4.18 (t, *J* = 7.2 Hz, 2H), 7.42 – 7.29 (m, 3H), 7.82 (s, 1H), 8.34 – 8.27 (m, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.6 (CH_2), 20.1 (CH_2), 29.7 (CH_2), 31.8 (CH_2), 47.2 (CH_2), 110.3, 114.2, 115.0 (Cq), 122.5, 123.4, 124.1, 126.3 (Cq), 135.1, 136.9 (Cq), 180.5 (C=O) ppm.

General procedure for the synthesis of the α,β-unsaturated α-cyanoketones 4

In a round-bottom flask coupled with a condenser and stir bar, a mixture of the oxopropanenitrile derivative (1.0 mmol), the corresponding aldehyde (1.2 mmol), triethylamine (TEA) (0.2 mL) and ethanol (4 mL) was stirred during 2 h at reflux, observing the formation of a yellow precipitate (corresponding to the α-cyanoketone **4**). When the starting oxopropanenitrile derivative was completely consumed, the solution was cooled to room temperature and the precipitate was filtrated and washed with methanol to provide the corresponding α-cyanoketone **4**. No further purification was required.

*(E)-2-Benzoyl-3-(2-bromophenyl)acrylonitrile **(4a)***. This compound was obtained according to the above procedure from benzoyl acetonitrile and 2-bromobenzaldehyde as an orange solid, 52% yield, mp 126 °C. FTIR (ATR): ν = 3015 (C-H), 2225 (CN), 1664 (C=O), 1251, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 2H), 8.35 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =113.7 (Cq), 115.8 (CN), 126.5 (Cq), 128.2, 128.9, 129.6, 130.2, 132.2 (Cq), 133.7, 133.8, 135.5 (Cq), 154.1, 188.7 (C=O) ppm.

*(E)-3-(2-Bromophenyl)-2-(1-methyl-1H-indole-3-carbonyl)acrylonitrile **(4d)***. This compound was obtained according to the above procedure from 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile and 2-bromobenzaldehyde as a yellow solid, 92% yield, mp 163 °C. FTIR (ATR): ν = 3018 (C-H), 2212 (CN), 1635 (C=O), 1581 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3H), 7.35 – 7.57 (m, 5H), 7.75 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.7 Hz, 1H), 8.35 (s, 1H), 8.44 – 8.54 (m, 1H), 8.58 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.0 (CH_3), 110.0, 113.9 (Cq), 114.1 (Cq), 117.8 (CN), 123.1, 123.5, 124.3, 126.1 (Cq), 127.4 (Cq), 128.0, 130.0, 132.8 (Cq), 132.9, 133.5, 137.2, 137.4 (Cq), 152.2, 178.6 (C=O) ppm. MS: (70 eV) *m/z* (%) = 366/364 (40/38) $[M]^{+\bullet}$, 285 (100), 236 (19), 158 (66), 152 (35). Anal. Calcd. For $C_{19}H_{13}BrN_2O$ (365.23): C, 62.48; H, 3.59; N, 7.67. Found. C, 62.22; H, 3.56; N, 8.00.

*(E)-3-(2-Bromophenyl)-2-(1H-indole-3-carbonyl)acrylonitrile **(4e)***. This compound was obtained according to the above procedure from 3-(1*H*-indol-3-yl)-3-oxopropanenitrile and 2-bromobenzaldehyde as a yellow solid, 95% yield, mp 249 °C. FTIR (ATR): ν = 3174 (N-H), 3012 (C-H), 2218 (CN), 1631 (C=O), 1579 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.26-7.35 (m, 2H) , 7.53 (t, 1H), 7.58 (d, 1H), 7.64 (t, 1H), 7.86 (d, 1H), 8.13 (d, 1H), 8.22 (d, 1H), 8.28 (s, 1H), 8.52 (s, 1H), 12.39 (s, 1H, NH) ppm. ^{13}C NMR (400 MHz, DMSO-d_6): δ =113.1 (Cq), 113.9, 115.9 (CN), 117.0, 121.8, 122.8, 123.1 (Cq), 125.0, 126.5, 128.7(Cq), 130.6 (Cq), 133.2 (Cq), 133.7, 134.8, 136.8 (Cq), 137.2, 151.0, 180.9 (C=O) ppm. MS: (70 eV) *m/z* (%) = 352/350 (22/22) $[M]^{+\bullet}$, 144 (100), 271 (41), 116 (37), 89 (62).

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(E)-2-(1-Benzyl-1H-indole-3-carbonyl)-3-(2-bromophenyl)acrylonitrile ***(4f)***. This compound was obtained according to the above procedure from 3-(1-benzyl-1*H*-indol-3-yl)-3-oxopropanenitrile and 2-bromobenzaldehyde as a yellow solid, 92% yield, mp 180 °C. FTIR (ATR): ν = 3018 (C-H), 2225 (CN), 1656 (C=O), 1517 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (s, 2H), 7.29 – 7.19 (m, 2H), 7.45 – 7.33 (m, 7H), 7.50 (td, *J* = 7.7, 1.2 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.19 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.36 (s, 1H), 8.63 – 8.46 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.2 (CH_2Ph), 110.5, 114.2 (Cq), 114.5 (Cq), 117,4 (CN), 123.1, 123.6, 124.4, 126.1 (Cq), 127.3, 127.6 (Cq), 128.0, 128.5, 129.2, 130.0, 132.7 (Cq), 132.9, 133.4, 135.1 (Cq), 136.6, 137.0 (Cq), 151.9, 178.3 (C=O) ppm. MS: (70 eV) *m/z* (%) = 442/440 (8/8) $[M]^{+\bullet}$, 361 (12), 234 (5), 91 (100).

(E)-2-(1-Benzyl-1H-indole-3-carbonyl)-3-(2-chloroquinolin-3-yl)acrylonitrile ***(4g)***. This compound was obtained according to the above procedure from 3-(1-benzyl-1*H*-indol-3-yl)-3-oxopropanenitrile and 2-chloroquinoline-3-carbaldehyde as a yellow solid, 89 % yield, mp 199 C. FTIR (KBr): ν = 3057, 2999, 2958 (C-H), 2245 (CN), 1649 (C=O), 1589 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (s, 2H), 7.30 – 7.27 (m, 2H), 7.44 – 7.33 (m, 6H), 7.73 – 7.64 (m, 1H), 7.93 – 7.84 (m, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.37 (s, 1H), 8.51 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.63 (s, 1H), 9.03 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.1 (CH_2), 110.4, 14.2 (Cq), 114.9 (Cq), 1117.2 (Cq), 122.9, 123.6, 124.4, 124.9 (Cq), 126.3 (Cq), 127.2, 127.3 (Cq), 127.9, 128.2, 128.4, 128.6, 129.0, 132.6, 134.8 (Cq), 136.3, 136.8 (Cq), 138.9, 147.6, 147.9 (Cq), 149.6 (Cq), 178.2 (C=O) ppm. MS: (70 eV) *m/z* (%) = 449/447 (3/10), 234 (7), 91 (100).

(E)-3-(2-Chloroquinolin-3-yl)-2-(1-methyl-1H-indole-3-carbonyl)acrylonitrile ***(4h)***. This compound was obtained according to the above procedure from 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile and 2-chloroquinoline-3-carbaldehyde as a yellow solid, 70 % yield, mp 175 C. FTIR (KBr): ν = 2958, 2929 (C-H), 2225 (CN), 1645 (C=O), 1589 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 7.39 - 7.36 (m, 3H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H), 8.46 (dd, *J* = 6.7, 3.0 Hz, 1H), 8.65 (s, 1H), 9.00 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.0, 110.0, 114.1 (Cq), 114.9 (Cq), 117.7 (Cq), 123.1, 123.6, 124.4, 125.2 (Cq), 126.5 (Cq), 127.4 (Cq), 128.1, 128.5, 128.8, 132.8, 137.2, 137.4 (Cq), 138.9, 148.1, 148.3 (Cq), 149.9 (Cq), 177.9 (C=O) ppm.

(E)-2-(1-Butyl-1H-indole-3-carbonyl)-3-(2-chloroquinolin-3-yl)acrylonitrile ***(4i)***. This compound was obtained according to the above procedure from 3-(1-buthyl-1*H*-indol-3-yl)-3-oxopropanenitrile and 2-chloroquinoline-3-carbaldehyde as a yellow solid, 83 % yield, mp 147 C. FTIR (KBr): ν = 2951, 2929 (C-H), 2250 (CN), 1645 (C=O), 1525 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.4 Hz, 3H), 1.42 (m,2H), 1.92 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 2H), 7.47 – 7.36 (m, 3H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 8.36 (s, 1H), 8.51 – 8.44 (m, 1H), 8.65 (s, 1H), 9.02 (s, 1H) ppm. MS: (70 eV) *m/z* (%) = 415/413 (17/53), 378 (90), 200 (100), 144(58), 41 (33).

Methyl (E)-2-cyano-3-(4-methoxyphenyl)acrylate ***(12)***. This compound was obtained according to the above procedure from *p*-anisaldehyde (0.200 g, 1.47 mmol), methyl 2-cyanoacetate (0.220 g, 2.22 mmol), TEA (3 drops) under stirring at 70 °C for 2 h. The reaction produced a white solid, 95% yield, mp 64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3H), 3.86 (s, 3H), 7.37 (s, 4H), 7.72 (s, 1H). Other spectroscopic data for this compound were already reported in the literature. CAS 14479-58-4. https://pubchem.ncbi.nlm.nih.gov/substance/318298647#section=Top

(E)-2-Cyano-N-(2-iodophenyl)-3-phenylacrylamide ***(14)***. This compound was obtained starting from the (*E*)-2-cyano-3-phenylacrylic acid (0.300 g, 1.73 mmol) dissolved in 2.0 mL of thionyl chloride, the mixture was stirred at reflux for 1 h, after that, the excess of thionyl chloride was removed under reduced pressure. The acyl chloride (yellow solid) formed was dissolved in 5 mL of chloroform and 2-iodoaniline (0.380 g, 1.74 mmol) and TEA (5 drops) was added. The solution was stirred at room temperature by 2 h until the formation of a precipitate. The beige solid was filtered and dried at ambient, 62% yield,

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140-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (td, *J* = 7.7, 1.5 Hz, 1H), 7.44 (ddd, *J* = 8.4, 7.5, 1.4 Hz, 1H), 7.48 – 7.67 (m, 3H), 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.99 – 8.10 (m, 2H), 8.37 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.47 (s, 1H), 8.53 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 90.5 (Cq), 104.3(Cq), 116.6 (CN), 122.1, 126.9, 129.3, 129.4, 130.9, 131.7 (Cq), 133.2, 137.6 (Cq), 139.2, 154.0, 158.5 (C=O) ppm.

General procedure for the synthesis of partially-reduced compounds 5, 7, 9, 11, 13 and 15 via selective chemical $NaBH_4$-mediated reduction of the double bond C=C in their α,β-unsaturated precursors 4, 6, 8, 10, 12 and 14, respectively

In an Erlenmeyer with a stir bar, precursor **4**, **6**, **8**, **10**, **12** or **14** (0.2-1.0 g, 1.0 equiv.) was dissolved in a mixture dioxane/methanol (1:4) (5-10 mL). The solution was stirred at 70 °C, then, $NaBH_4$ (1.0 equiv.) was added portionwise until the starting material was no longer detected by TLC. The solution was cooled at room temperature and the solvent was removed under reduced pressure. Water was added to the reaction flask, and the solid formed was filtered, washed with water and with cold methanol to provide the corresponding product.

*2-(2-Bromobenzyl)-3-oxo-3-phenylpropanenitrile **(5a)***. This compound was obtained according to the above procedure from **4a** (0.200 g) as a yellow oil. FTIR (ATR): *v* = 3111, 2245 (CN), 1695 (C=O), 1257, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (dd, *J* = 13.8, 9.7 Hz, 1H), 3.58 (dd, *J* = 13.8, 5.9 Hz, 1H), 4.84 (dd, *J* = 9.7, 5.9 Hz, 1H), 7.21 (td, *J* = 7.7, 1.8 Hz, 1H), 7.77 – 7.31 (m, 6H), 8.17 – 7.97 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1 (CH_2), 39.2 (CH), 111.1, 116.6, 124.2, 128.1, 128.9, 129.1, 129.6, 132.3, 133.1, 134.7, 135.2, 189.9 (C=O) ppm.

*2-(2-Bromobenzyl)-3-(1-methyl-1H-indol-3-yl)-3-oxopropanenitrile **(5d)***. This compound was obtained according to the above procedure from **4d** (1.000 g) as a beige solid, mp 146 °C. FTIR (ATR): *v* = 3059 (C-H), 2249 (CN), 1641 (C=O), 1577 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (dd, *J* = 13.8, 9.5 Hz, 1H), 3.61 (dd, *J* = 13.7, 6.1 Hz, 1H), 3.89 (s, 3H), 4.53 (dd, *J* = 9.5, 6.1 Hz, 1H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 7.28 – 7.50 (m, 5H), 7.61 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.89 (s, 1H), 8.43 (ddd, *J* = 6.8, 3.0, 1.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.9 (NCH_3), 36.5 (CH_2), 40.4 (CH), 110, 114.1 (Cq), 117.9 (CN), 122.7, 123.5, 124.2 (Cq), 124.3, 126.5 (Cq), 128.1, 129.4, 132.4, 132.9, 135.8 (Cq), 136.2, 137.6 (Cq), 183.1 (C=O) ppm. MS: (70 eV) *m/z* (%) = 368/366 (2/2) $[M]^{+\bullet}$, 287 (9), 158 (100), 130 (17), 83 (61). Anal. Calcd. For $C_{19}H_{15}BrN_2O$ (367.25): C, 62.14; H, 4.12; N, 7.63. Found. C, 62.33; H, 4.11; N, 7.99.

*2-(2-Bromobenzyl)-3-(1H-indol-3-yl)-3-oxopropanenitrile **(5e)***. This compound was obtained according to the above procedure from **4e** (0.500 g) as a white solid, mp 246 °C. FTIR (ATR): *v* = 3259 (N-H), 3028, 2247 (CN), 1666 (C=O), 1579 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.34-3.37 (m, 2H), 5.06 (t, 1H), 7.21-7.29 (m, 3H), 7.38 (t, 1H), 7.52 (t, 2H), 7.64 (d, 1H), 8.18 (d, 1H), 8.61 (s, 1H), 12.27 (s, 1H) ppm. ^{13} C NMR (100 MHz, DMSO-d_6): δ =35.4 (CH_2), 39.9 (CH), 112.5, 113.7 (Cq), 118.4 (CN), 121.5, 122.5, 123.6, 124.2 (Cq), 125.4 (Cq), 127.8, 128.4, 129.3 (Cq), 131.6, 132.7, 136.0 (Cq), 136.8, 184.3 (C=O) ppm. MS: (70 eV) *m/z* (%) = 354/352 (2.9/2.5) $[M]^{+\bullet}$, 144 (100), 273 (43), 116 (23), 89 (13).

*3-(1-Benzyl-1H-indol-3-yl)-2-(2-bromobenzyl)-3-oxopropanenitrile **(5f)***. This compound was obtained according to the above procedure from **4f** (0.300 g) as a white solid, mp 146 °C. FTIR (ATR): *v* = 3059 (C-H), 2250 (CN), 1671 (C=O), 1568 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.34 (dd, *J* = 13.7, 9.8 Hz, 1H), 3.55 (dd, *J* = 13.6, 6.0 Hz, 1H), 4.50 (dd, *J* = 9.7, 6.0 Hz, 1H), 5.29 – 5.45 (m, 2H), 7.12 – 7.27 (m, 3H), 7.33 – 7.47 (m, 8H), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.89 (s, 1H), 8.42 – 8.50 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.1 (CH_2), 40.7 (CH), 51.1 (CH_2Ph), 110.4, 114.5 (Cq), 117.6 (CN), 122.8, 123.7, 124.2 (Cq), 124.4, 126.7 (Cq), 127.6, 128.1, 128.7, 129.3, 129.4, 132.4, 132.9, 134.7 (Cq), 135.3, 135.6 (Cq), 137.3 (Cq), 183.6 (C=O) ppm. MS: (70 eV) *m/z* (%) = 444/442 (8/8) $[M]^{+\bullet}$, 234 (15), 149 (8), 91 (100). Anal. Calcd. For $C_{25}H_{19}BrN_2O$ (443.34): C, 66.44; H, 4.24; N 6.87. Found. C, 66.61; H, 4.33; N, 6.91.

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*3-(1-Benzyl-1H-indol-3-yl)-2-((2-chloroquinolin-3-yl)methyl)-3-oxopropanenitrile **(5g)***. This compound was obtained according to the above procedure from **4g** as a white solid, mp 198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.44 (dd, *J* = 13.8, 9.3 Hz, 1H), 3.70 (dd, *J* = 13.5, 6.1 Hz, 1H), 4.63 – 4.53 (m, 1H), 5.34 (s, 2H), 7.24 – 7.15 (m, 2H), 7.43 – 7.28 (m, 6H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.89 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 8.41 (dd, *J* = 8.3, 1.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.3 (CH_2), 40.3 (CH), 51.2 (CH_2Ph), 110.5, 114.3 (Cq), 117.5 (Cq), 122.7, 123.8, 124.5, 126.6 (Cq), 127.3 (Cq), 127.5, 127.6, 127.7, 127.9 (Cq), 128.1, 128.8, 129.3, 130.8, 134.6 (Cq), 135.4, 137.3 (Cq), 140.6, 147.1(Cq), 150.1 (Cq), 182.8 (C=O) ppm. MS: (70 eV) *m/z* (%) = 451/449 (0.1/0.3), 234 (14), 91 (100).

*2-((2-Chloroquinolin-3-yl)methyl)-3-(1-methyl-1H-indol-3-yl)-3-oxopropanenitrile **(5h)***. This compound was obtained according to the above procedure from **4h** as a white solid, mp 210 °C. FTIR (ATR): *v* = 2987, 2943, 2910 (C-H), 2243 (CN), 1663 (C=O), 1537 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (dd, *J* = 14.0, 9.2 Hz, 1H), 3.75 (dd, *J* = 13.0, 4.6 Hz, 1H), 3.86 (s, 3H), 4.62 (dd, *J* = 9.1, 6.3 Hz, 1H), 7.36 (d, *J* = 3.7 Hz, 3H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.88 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 8.23 (s, 1H), 8.38 (dd, *J* = 6.6, 2.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.8 (NCH_3), 33.9 (CH_2), 39.8 (CH), 110.0, 114.0 (Cq), 117.7 (Cq), 122.6, 123.7, 124.4, 126.4 (Cq), 127.3(Cq), 127.5, 127.6, 128.1(Cq), 128.2, 130.8, 136.2, 137.6 (Cq), 140.6, 147.2(Cq), 150.2 (Cq), 182.3 (C=O) ppm. MS: (70 eV) *m/z* (%) = 375/373 (0.1/0.3), 158 (100), 77 (29).

*3-(1-Butyl-1H-indol-3-yl)-2-((2-chloroquinolin-3-yl)methyl)-3-oxopropanenitrile **(5i)***. This compound was obtained according to the above procedure from **4i** as a white solid, mp 154 °C. FTIR (ATR): *v* = 3022, 2959, 2883 (C-H), 2258 (CN), 1678 (C=O), 1567 (C=C) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 6.8 Hz, 3H), 1.41 – 1.28 (m, 2H), 1.92 – 1.77 (m, 2H), 3.49 (dd, *J* = 13.1, 9.0 Hz, 1H), 3.75 (dd, *J* = 13.8, 5.4 Hz, 1H), 4.16 (t, *J* = 6.5 Hz, 2H), 4.69 – 4.50 (m, 1H), 7.43 – 7.30 (m, 3H), 7.57 (t, *J* = 6.9 Hz, 1H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.91 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 8.25 (s, 1H), 8.43 – 8.32 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 20.1 (CH_2), 31.7 (CH_2), 33.9 (CH_2), 39.9 (CH), 47.3 (CH_2), 110.3, 113.9 (Cq), 117.7 (Cq), 122.7, 123.6, 124.3, 126.6, 127.6, 127.7, 128.1, 128.1 (Cq), 130.9, 135.3 (Cq), 136.4 (Cq), 137.0 (Cq), 140.7, 147.1 (Cq), 150.1 (Cq), 182.5 (C=O) ppm; MS: (70 eV) m/z (%)= 415 (5), 380(21), 200 (100), 144(26).

*Methyl 2-cyano-3-(4-methoxyphenyl)propanoate **(13)***. This compound was obtained according to the above procedure from **12** (0.150 g) as a colorless oil. FTIR (ATR): *v* = 3008 (C-H), 2232 (CN), 1721 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 – 3.03 (m, 2H), 3.73 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.83 (d, *J* = 3.9 Hz, 6H), 6.90 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.1 (CH_2), 39.8 (CH), 53.9 (OCH_3), 55.3 (OCH_3), 114.3, 116.1 (CN), 127.2 (Cq), 130.1, 159.2 (Cq), 166.1 (C=O) ppm.

*2-Cyano-N-(2-iodophenyl)-3-phenylpropanamide **(15)***. This compound was obtained according to the above procedure from **14** (0.120 g) as a white solid, mp 224 °C. FTIR (ATR): *v* = 3223 (N-H), 3068, 2221 (CN), 1662 (C=O), 1568 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3. 22 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.40 (dd, *J* = 13.3. 8.8 Hz, 1H), 4.36 (dd, *J* = 9.0, 6.4 Hz, 1H), 7.06 (td, *J* = 7.6, 1.7 Hz, 1H), 7.48 – 7.26 (m, 7H), 7.92 (dd, *J* = 7.8, 1.4 Hz, 1H), 10.11 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 36.1 (CH_2), 40.4 (CH), 97.1 (Cq), 118.3 (CN), 127.7, 128.0, 128.9, 129.0, 129.3, 129.6, 137.0 (Cq), 139.0 (Cq), 139.6, 164.3 (C=O) ppm.

The synthesis of the remaining known compounds have previously been reported elsewhere.

Results and discussion

Searching for diverse precursors to be used as starting material for the synthesis of new heterocyclic compounds, we required to obtain a variety of α,β-reduced ketone- and ester-derivatives. Selective reduction of the C=C double bond from their corresponding α,β-

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unsaturated precursors was chosen as the more expeditious approach. Firstly, looking for a simple, cheap, selective and quantitative gram-scale yield of the desired partially-reduced ketone **2a**, Scheme 1, we performed an adaptation of the Cornubert´s procedure for the selective reduction of chalcone **1a** as model reaction, using chloroform as catalyst-poisoning agent (**Cornubert & Eggert,** 1954; **Cornubert & Thomas,** 1954). Despite several synthetic variants were evaluated (i.e. adjusting the Raney-Nickel catalyst ratio, reaction times, volume of chloroform used as poisoning agent and hydrogen pressure, among others), not much success was achieved. Mixtures of the expected product **2a** along with the undesired doubly reduced product **3a** were obtained in all cases.

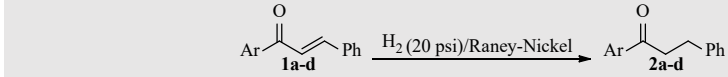
Finally, we found that controlling the volume of EtOH used as solvent was critical to achieve better results. Thus, in our alternative approach the minimum as possible volume of EtOH was used to dissolve the starting chalcones **1a-d**. Afterwards, the catalytic hydrogenation of the saturated ethanolic solutions of **1a-d** in the presence of Raney-Nickel poisoned with $CHCl_3$ at room temperature under (20 psi) pressure, afforded the desired ketones **2a-d** in almost quantitative yields, **table 1**. A gentle warming was required in some cases to get saturated solutions of chalcones **1**. Alternatively, the use of DCM instead $CHCl_3$ also worked well.

As mentioned above, we discovered that the control of the volume of solvent (i.e. EtOH) dramatically improved the selectivity towards the partially hydrogenated keto-derivatives **2**, in comparison with the previous approaches where larger volumes of EtOH were used (**Cornubert & Eggert,** 1954; **Cornubert & Thomas,** 1954; **Tucker,** 1950). This finding is supported by the experimental fact that products **2** were less soluble in the reaction media than the starting chalcones **1**. Thus, products **2** precipitated from the saturated ethanolic solutions as quickly as they were formed avoiding the subsequent reduction of their carbonyl groups. To confirm the above suggestion, a controlled experiment using chalcone **1a** and a large volume of EtOH was performed. In this case no solid precipitated and contrary formation of the dense-oily saturated alcohol **3a** turned into the main product of the reaction mixture.

At this stage, it is worth to mention that attempts to extend the above approach to Knoevenagel cyano-keto derivatives **4** did not work. Alternatively, after several assays we found that trying the Knoevenagel adducts **4** with $NaBH_4$ in a *p*-dioxane/MeOH mixture at 70 °C afforded the expected partially-reduced products **5** in satisfactory yields, **table 2**.

Structures of the new obtained compounds **4** and **5** were confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectra. Particularly, a comparative analysis of the ^{13}C NMR spectra for the starting α-cyanoketone **4d** and its corresponding partially-reduced product **5d** confirmed the efficacy of the established $NaBH_4$-metiated selective-reductive conditions, **figure 1**. The appearing of two new aliphatic carbon atom signals at high field (i.e. 40.36 and 36.5 ppm) in spectrum for **5d**, the disappearing of the =C signal at 152.21 ppm in the spectrum for **4d** and the presence of the carbonyl (C=O) signals in both spectra at (178.6 and 183.1) ppm for **4d** and **5d**, respectively, are in agreement with the selectivity of the reduction process.

Table 1. Selective reduction of the α,β-unsaturated C=C double bonds in chalcones **1**.[a,b]



2a	2b	2c	2d
(93%)	(95%)	(97%)	(98%)

[a]Reaction conditions: Chalcone **1** (1.0 gram), Raney-Nickel (0.3 g), EtOH (5-10 mL), $CHCl_3$ or DCM (0.5 mL), rt, 15-20 min. [b]For more details see Materials and Methods section.

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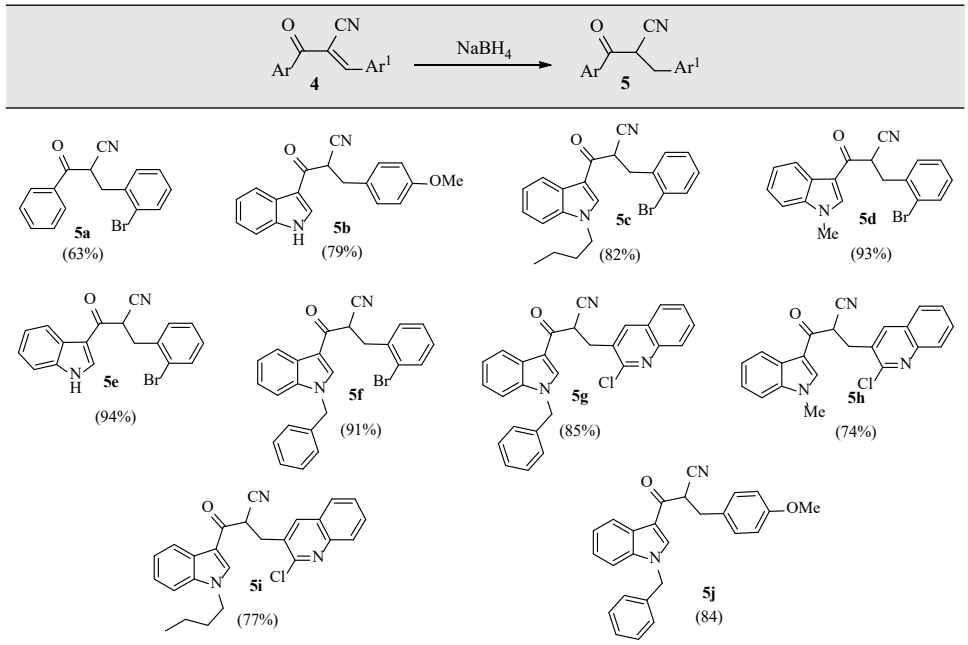
Table 2. Selective reduction of the C=C double bonds in α,β-unsaturated α-cyanoketones **4**.[a,b,c]



[a]Reaction conditions: Knoevenagel adduct **4** (0.2-1.0 gram, 1 equiv.), $NaBH_4$ (1 equiv.), *p*-dioxane/MeOH (1:4) (5-10 mL), 70 °C. [b]For more details see Materials and Methods section. [c]The synthesis of the starting indoles and cyanoindoles as precursors for cyanochalcones **4b-j** is described in the Materials and Methods section.

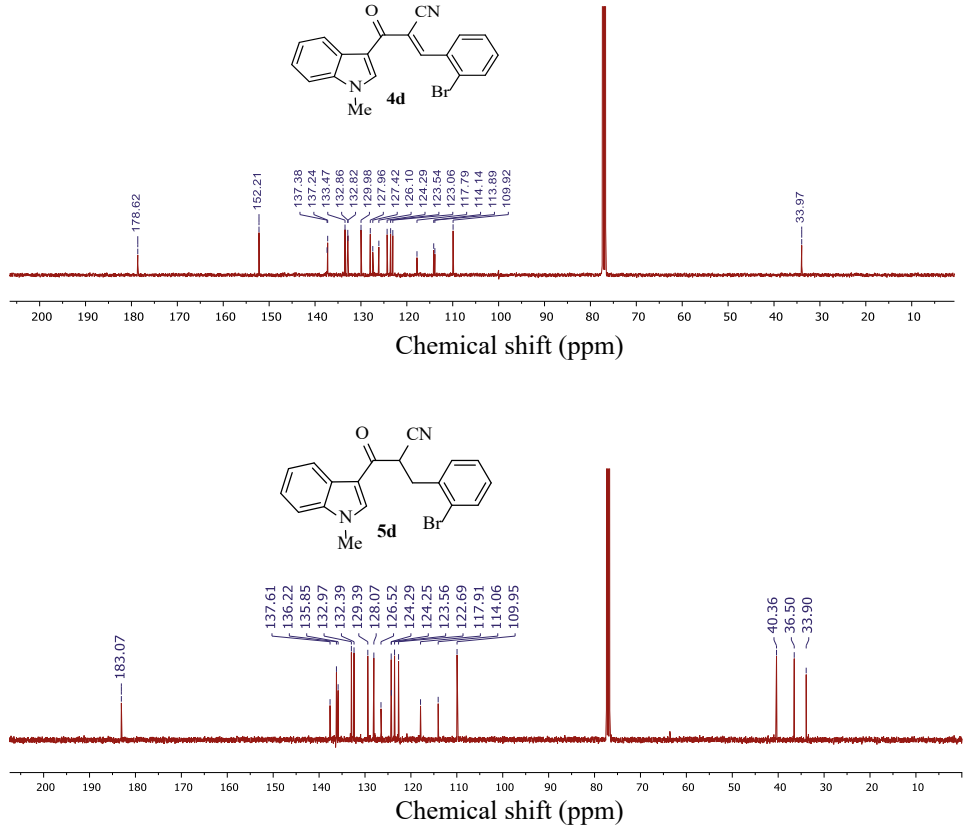


Figure 1. Comparative ^{13}C NMR spectra for α-cyanoketone **4d** and its partially-reduced product **5d**

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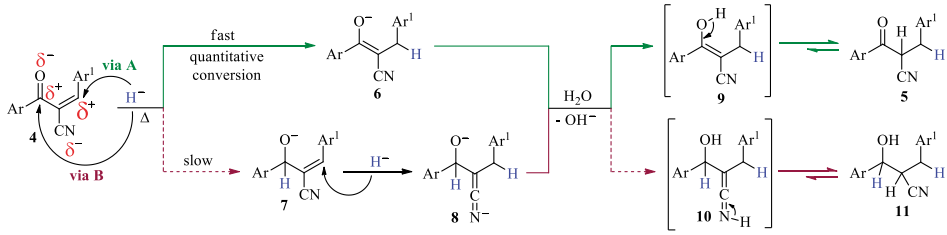
Interestingly, when the above reactions were performed at room temperature mixtures of **5** and their corresponding doubly reduced side-hydroxyl products **11** (i.e. alcohol analogues type **3**), were obtained. A suggested mechanistic sequence for the selective formation of products **5** and alternatively, for the double reduced side-hydroxyl products **11** is drawn in Scheme 2.

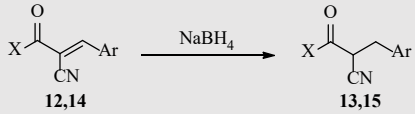


Scheme 2. Suggested mechanistic sequence for the selective formation of the partially-reduced products **5**

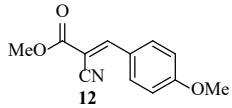
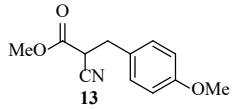
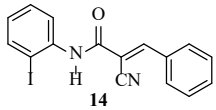
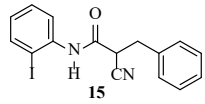
In principle, the presence of two electron-withdrawing functional groups (i.e. CN and C=O) is the responsible of the higher electrophilicity of the β-carbon atom than the carbonyl C=O group. Apparently, a higher temperature also increases the electrophilicity of such β-carbon atom in **4**, as well as, the reactivity of the hydride anion (i.e. less selectivity), for a faster Michael type addition of H^- (**via A**) than that for the carbonyl H^- addition (**via B**), affording preferably the enolate species **6**. This species should prevent the subsequent reduction of the carbonyl group toward the hydroxyl-compound **11** as happened in the formation of alcoholic derivatives **3**, showed in Scheme 1. Then, the work-up by adding water to the reaction crude (after removing the solvent under reduced pressure), supplied the required protons to recover selectively the target ketonic tautomer **5**. We assume that using lower temperatures reduces the electrophilicity of the β-carbon atom in **4** and hence, increases the chance that H^- attack the β-carbon atom but also the carbonyl group in **4** through a mixture of species **6** and **7**, respectively. A further β-addition of H^- over species 7 (through species **8**), followed by the usual aqueous work-up afforded the detected and isolated mixture of products **5** and the doubly reduced cianohydroxyl side-product **11**.

Remarkably, the established approach showed to be robust and a miscellaneous of cyanoester **12**, cyanamide **14**, ketoester **16**, diester **18** and diketone **20** derivatives, were also selectively reduced, as shown in **tables 3 and 4**.

Table 3. Selective reduction of the C=C double bonds in α,β-unsaturated α-cyanoester **12** and α-cyanamide **14**.[a,b]



12,14 **13,15**

Entry	Precursor	Product
1	 **12**	 **13** (65%)
2	 **14**	 **15** (80%)

[a]Reaction conditions: α-cyano-derivatives **12/14** (0.2-1.0 gram, equiv.), $NaBH_4$ (1 equiv.), *p*-dioxane/MeOH (1:4) (5-10 mL), 70 °C. [b]For more details see Materials and Methods.

Rev. Acad. Colomb. Cienc. Ex. Fis. Nat. 45(177):1232-1245, octubre-diciembre de 2021
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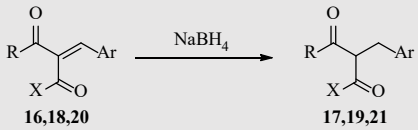
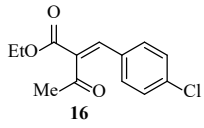
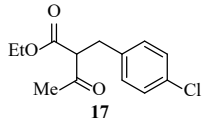
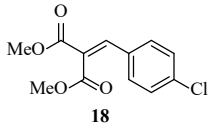
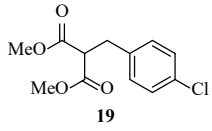
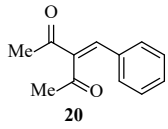
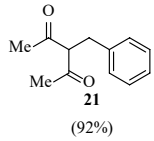
Table 4. Selective reduction of the C=C double bonds in α,β-unsaturated α-ketoester **16**, 1,3-diester **18** and 1,3-diketone **20**.[a,b]

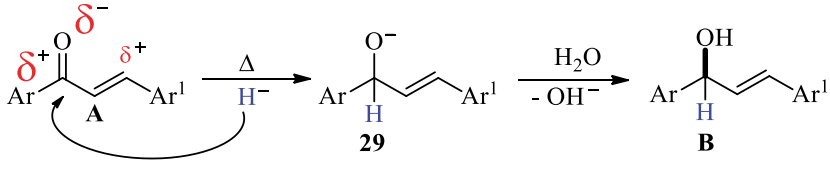


Entry	Precursor	Product
1	 **16**	 **17** (82%)
2	 **18**	 **19** (87%)
3	 **20**	 **21** (92%)

[a]Reaction conditions: Dicarbonyl compounds **16**/**18**/**20** (0.2-1.0 gram, 1 equiv.), $NaBH_4$ (1 equiv.), *p*-dioxane/MeOH (1:4) (5-10 mL), 70 °C. [b]For more details see Materials and Methods.

Noteworthy, when this approach was applied to simple Claisen-Schmidt condensation products (i.e. chalcones **1e**, **23**, **25** and *bis*-chalcone **27**), their corresponding hydroxyl-derivatives **22**, **24**, **26** and **28**, respectively, were obtained as unique isolated products, without affecting their C=C double bonds, **table 5**.

A suggested mechanistic sequence for the selective reduction of the carbonyl (C=O) groups for the above simple ketonic devivatives **A** (i.e. **1e**, **23**, **25** and **27**) is drawn in Scheme 3.



A = **1e**, **23**, **25** or **27**; **B** = **22**, **24**, **26** or **28**

Scheme 3. Suggested mechanistic sequence for the selective reduction of the carbonyl (C=O) groups in simple ketonic devivatives **A** (i.e **1e**, **23**, **25** and **27**)

In this case, the absence of the second electron-withdrawing group in simple ketones **A**, in comparison with precursors **4**, causes a lower electrophilicity of the β-carbon atom than that of the carbonyl C=O carbon atom in structure **A**. In this sense, the nucleophilic attack by H^- ion is produced preferably over the carbonyl C=O carbon atom producing the alkoxy intermediate **29**. Subsequently, by performing the work-up as usual, afforded the corresponding isolated allylic alcohols **B** (i.e. **22**, **24**, **26** or **28**) as shown in Scheme 3.

In summary, we implemented two complementary approaches for the selective reduction of the C=C functionality in diverse α,β-unsaturated precursors. In general, poisoned Raney-Nickel-mediated catalytic hydrogenation under controlled volume of EtOH worked

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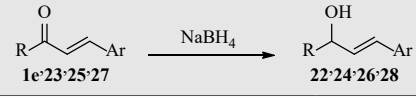
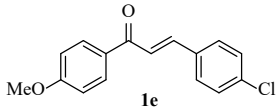
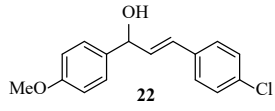
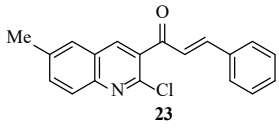
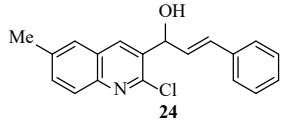
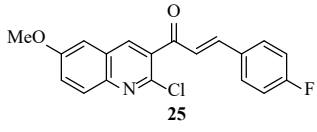
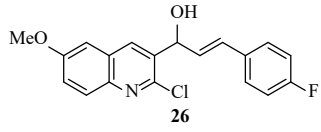
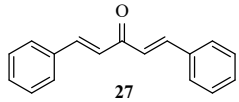
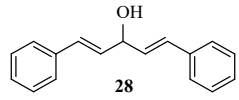
Table 5. Selective reduction of the C=O double bond in α,β-unsaturated ketones **1e**, **23**, **25** and **27**.[a,b]



1e,**23**,**25**,**27** **22**,**24**,**26**,**28**

Entry	Precursor	Product
1	 **1e**	 **22** (90%)
2	 **23**	 **24** (79%)
3	 **25**	 **26** (85%)
4	 **27**	 **28** (81%)

[a]Reaction conditions: Chalcone **1e**, **23**, **25** or **27** (0.2-1.0 gram, 1 equiv.), $NaBH_4$ (1 equiv.), *p*-dioxane/MeOH (1:4) (5-10 mL), 70 °C. [b]For more details see Materials and Methods.

well for ordinary chalcones **1**, while warm *p*-dioxane/MeOH/$NaBH_4$-mediated chemical reduction was the best reductive conditions for Knoevenagel condensation adducts **4**, **12**, **14**, **16**, **18** and **20**, affording the respective partially reduced products in almost quantitative to excellent yields. The fact that it was possible to reduce, in a selective way, the carbonyl group on some chalcone derivatives is also highlighted in this approach. Moreover, trying to explain the selective $NaBH_4$-mediated reductive process a plausible mechanistic pathway was proposed in this regard.

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Authors contribution

RA, design of the study; ACG, experimental procedures; RA and ACG, analysis of the results and writing of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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