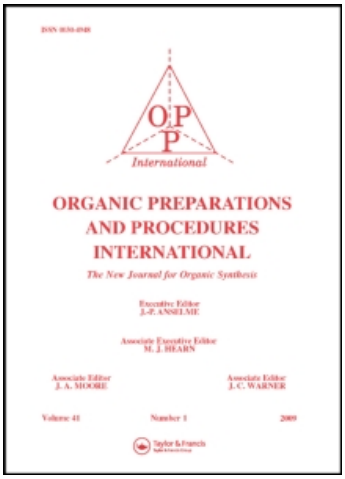

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A NEW, VERY SHORT PREPARATION OF 3-BENZOYLCYCLOHEXANONE, A KEY BUILDING BLOCK IN KETOPROFEN SYNTHESIS

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A NEW, VERY SHORT PREPARATION OF 3-BENZOYLCYCLOHEXANONE, A KEY BUILDING BLOCK IN KETOPROFEN SYNTHESIS

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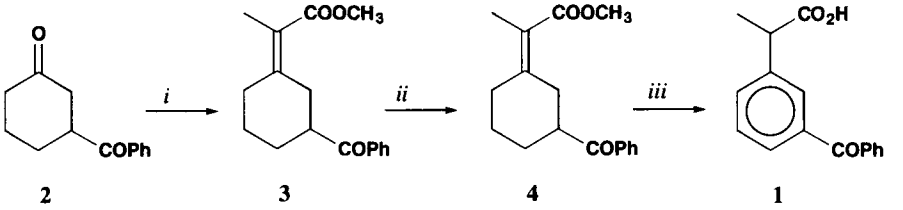
Non-steroidal antiinflammatory (NSAI) agents are one of the largest class of drugs both due to their high number and their therapeutic interest.[1] NSAI can be classified according their chemical structure and most of the more studied are α-arylpropionic acid derivatives. Ketoprofen **1** (Profenid®) is one of the most prominent modern anti-inflammatory drug,[2] and its synthesis has stimulated the interest of several researchers.[1] 3-Benzoylcyclohexanone **2** is a key building block of one of the most practical preparation of **1** (Eq. 1) reported by Sagami Chemical Research Center as a patent.[3] Compound **2** was first prepared from cyclohexenone and α-morpholinobenzyl cyanide with a tedious method,[3] while, Bennetau *et al.*[4] recently described a multistep, alternative route to **2** *via* 5-trimethylsilyl-3-cyclohexenone. Based in our previous experience in the chemistry of nitroalkanes[5] and in order to devise a new synthesis of the title compound, we now present a convenient, very short preparation of **2** using the easily available phenylnitromethane[6] **5** as starting material.

Our procedure (Fig. 1) starts by the conjugate addition of **5** to 2-cyclohexen-1one **6** on basic alumina as heterogeneous catalyst,[7] to give γ-nitro ketone **7** in 92% yield, which can be converted into the 1,4-diketone **2**, in 80% yield, by the Nef reaction.[8] The reaction is performed by addition of the corresponding nitronate to a mixture of methanol and concentrated sulfuric acid at -35°. Alternatively,

2 may be obtained in a one-pot reaction by conjugate addition of **5** to **6** on alumina followed by *in situ* oxidation with hydrogen peroxide[9] in methanol, in 70% overall yield.



2 **3** **4** **1**

i) $(EtO)_2POCHMeCO_2Et$, NaH, THF, r.t. *ii*) $CuCl_2$/LiF, DMF, reflux
iii) NaOH/MeOH, reflux, then Aromatization

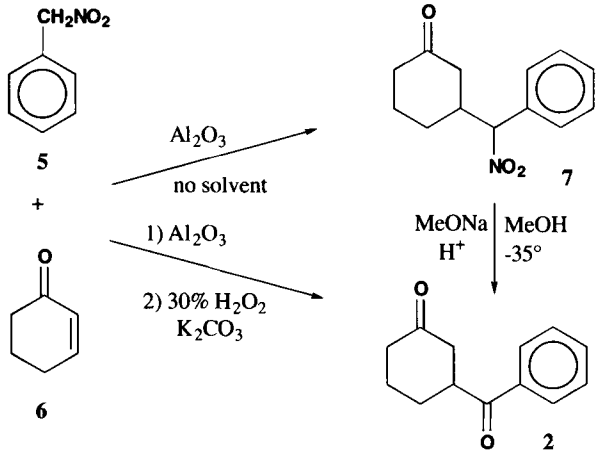


Figure 1

The principal advantages of the methodology presented here are the simple procedure using inexpensive chemicals in high yield and high purity, and a minimal number of steps.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded at 200 MHz on a Varian Gemini 200. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. Microanalyses were performed by using a C, H, N Analyzer Model 185 from Hewlett-Packard Co. All the products were monitored by GC, performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran glass (0.32 mm x 25 m), stationary phase OV1 (film thickness 0.4 - 0.45 nm).

3-(1-Nitrobenzyl)cyclohexanone (7).- A two-necked flask was equipped with a mechanical stirrer and charged with phenylnitromethane (**5**, 2.74 g, 0.02 mol) and cooled with an ice-water bath. 2-Cyclohexen-1-one (**6**, 1.92 g, 0.02 mol) was added and the mixture was stirred for 10 min. Chromatographic alumina (activity I, 5 g) was added and stirring was continued for 8 hrs at room temp. The mixture was extracted with Et_3O (3 x 30 mL) and the filtered extract was evaporated at reduced pressure. The crude product obtained (at least 90% pure by GC) was used as it is or purified by flash chro-

matography (EtOAc-cyclohexane, 3:7) to afford 4.28 g (92%) of the pure **7** as an oil.
IR (film): 1705 (CO); 1550 (NO_2).
^{1}H NMR ($CDCl_3$) δ 1.2-2.6 (m, 8H), 2.8-3.0 (m, 1H), 5.2 (dd, 1H, J = 1.7 and 10.8 Hz), 7.45 (m, 5H).
Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.02. Found: C, 67.20; H, 6.28; N, 6.20

3-Benzoylcyclohexanone (2).- Sodium (0.386 g, 0.0168 mol) was added to abs. MeOH (40 mL). The nitro derivative **7** (3.5 g, 0.015 mol) was then added in one portion, to generate the corresponding nitronate. The resulting solution was added in small portions during 30 min, to a mixture of MeOH (40 mL) and conc. H_2SO_4 (8 mL) at -35°. After 10 min, H_2O (100 mL,) was added and the solution was evaporated in order to remove MeOH. The solution was extracted with CH_2Cl_2 (100 mL), washed with 1% NaOH (40 mL), dried (Na_2SO_4) and evaporated to yield a crude product (89% pure by GC) which gave, after flash chromatography (EtOAc-cyclohexane, 3:7), 2.42 g (80%) of the pure **2** as an oil.
IR (film): 1708 and 1675 (CO) cm^{-1}.
^{1}H NMR ($CDCl_3$): δ 1.8-1.9 (m, 2H), 2.0-2.2 (m, 2H), 2.3-2.4 (m, 2H), 2.5 (dd, 1H, *J* = 4 and 14.4 Hz), 2.7 (dd, 1H, *J* = 10.7 and 14.4 Hz), 3.75-3.9 (m, 1H), 7.4-8.0 (m, 5H).
Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.00; H, 7.08

One-Pot Synthesis of 2.- Nitro compound **5** (2.74 g, 0.02 mol) and **6** (1.92 g, 0.02 mol) were mixed with cooling in an ice-water bath. After stirring for 10 min, chromatographic alumina (activity I, 5 g) was added and stirring was continued for 8 hrs at room temp. The mixture was then cooled to 0° and MeOH (70 mL), 30% aq. H_2O_2 (40 mL), and K_2CO_3 (14 g) were added. The mixture obtained was stirred overnight at room temp. The mixture was diluted with H_2O (3 x 60 mL) and brine (3 x 10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography afforded 2.83 g (70%) of the pure **2** an oil, with identical to that obtained above.

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ULTRASONICALLY ACCELERATED SYNTHESES OF FURAN-2,5-DICARBALDEHYDE FROM 5-HYDROXYMETHYL-2-FURFURAL

Submitted by (12/12/94)

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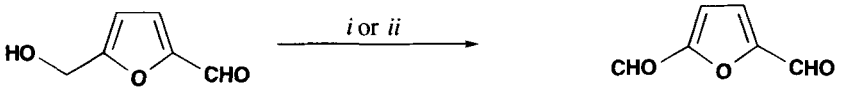
Furan-2,5-dicarbaldehyde (**2**) is an important starting compound for syntheses of annulene oxides,[1] mixed porfines[2] and various macrocycles.[3] Compound **2** has been synthesized from 2-diethoxymethylfuran,[4] 2,5-*bis*-hydroxymethylfuran[5] or furan-2,5-dicarbonitrile.[6] It may also be obtained by the regioselective oxidation of 5-hydroxymethyl-2-furfural **1** (HMF), which would be a good starting material, since it is easily accessible by the acid-catalyzed dehydration of carbohydrates.[7,8] van Reizendam *et al.*[9] oxidized **1** with lead tetracetate to yield dialdehyde **2** in poor yield. Chromium trioxide in pyridine[10] or nitrogen dioxide in DMSO[11] gave **2** in 70 and 76% yield respectively while oxidization of HMF with barium manganate leading to afforded **2** in 92% yield.[12]



i) DMSO-$K_2Cr_2O_7$, 100° or))) *ii*) $Me_3N{\bullet}NCl$-$CrO_3/Al_2O_3/CH_2Cl_2$, reflux or)))

We recently reported the synthesis of **2** from **1** using pyridinium chlorochromate with aluminium oxide[13] and from 5-(trialkylsilyl)oxymethyl-2-furfural using azobisisobutyronitrile-*NBS* pair.[14] We now describe two methods for the conversion of HMF to **2** accelerated by ultrasound, in satisfactory yields.

Following the published procedure,[15] we performed the oxidation of 5-hydroxy-methyl-2-furfural (**1**) with DMSO-potassium dichromate oxidative complex. However, only a 48% yield of the