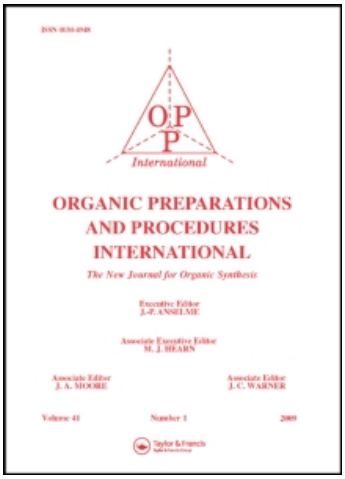


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

HYDROXYCYCLOHEXANONES FROM THE REACTION OF α-BENZOYLCINNAMONITRILES WITH ETHYL ACETOACETATE. A LITERATURE CORRECTION

M. Quinteiro[a]; J. Chicharro[a]; N. Martin[a]; J. A. Cillar[a]; C. Seoane[a]; J. L. Soto[b]
[a] Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid, SPAIN
[b] Departamento de Química Orgánica, Facultad de Química, Universidad de Alcalá, Madrid, SPAIN

To cite this Article Quinteiro, M. , Chicharro, J. , Martin, N. , Cillar, J. A. , Seoane, C. and Soto, J. L.(1986) 'HYDROXYCYCLOHEXANONES FROM THE REACTION OF α-BENZOYLCINNAMONITRILES WITH ETHYL ACETOACETATE. A LITERATURE CORRECTION', Organic Preparations and Procedures International, 18: 2, 85 — 93
To link to this Article: DOI: 10.1080/00304948609356826
URL: http://dx.doi.org/10.1080/00304948609356826

ORGANIC PREPARATIONS AND PROCEDURES INT. 18(2), 85-93 (1986)

HYDROXYCYCLOHEXANONES FROM THE REACTION OF α-BENZOYLCINNAMONITRILES WITH ETHYL ACETOACETATE. A LITERATURE CORRECTION

M. Quinteiro, J. Chicharro, N. Martin

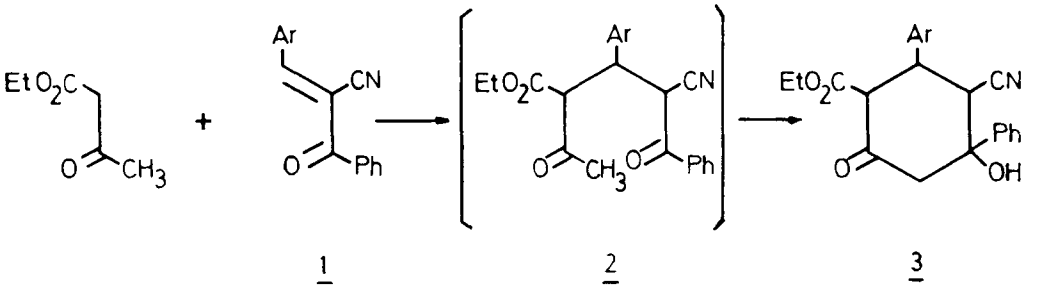
J. A. Cillar, C. Seoane and J. L. Soto*

Departamento de Química Orgánica,
Facultad de Química, Universidad Complutense,
28040-Madrid, SPAIN
and
Departamento de Química Orgánica,
Facultad de Química, Universidad de Alcalá,
Madrid, SPAIN

α-Benzoylcinnamonitriles have been previously used as starting materials for the preparation of nitrogen heterocycles, such as pyridones[1,2] and pyridothiones[3] by reaction with cyanoacetamide and cyanothioacetamide. Oxygen heterocycles, such as pyrans[4,5] and furans[6] have also been prepared by reaction with malononitrile or ethyl cyanoacetate and hydrogen cyanide. Reaction of hydrazine hydrochloride with α-benzoylcinnamonitrile affords a pyrazole derivative,[7] while other compounds such as phenylhydrazine,[8] hydrazine hydrate,[8] hydroxylamine,[9] and semicarbazide[10] result in retro-Knoevenagel or retro-Michael cleavage. This paper, describes the reaction of ethyl acetoacetate as the active methylene compound with α-benzoylcinnamonitriles. In this case no heterocycles result and hydroxycyclohexanones are obtained instead (Scheme 1).

Reaction of equimolar amounts of ethyl acetoacetate and the corresponding α-benzoylcinnamonitrile (1) leads in absolute

ethanol and piperidine as the catalyst at room temperature or under reflux, to 5-hydroxycyclohexanones (3) through Michael addition and spontaneous cyclization of the resulting 1,5-diketone (2). Adducts 2 could also cyclize by nucleophilic attack of the oxygen at the cyano group leading to 2-amino-4H-pyrans as it happens in somewhat similar adducts.[4,5] On the other hand, 1,5-diketones with electron-withdrawing substituents can be cyclized in certain cases to 4H-pyrans and cyclohexanone ring.[11] In our case the reaction leads to the cyclohexanone ring (3) as the only product and in good yield.



1 2 3

Scheme 1

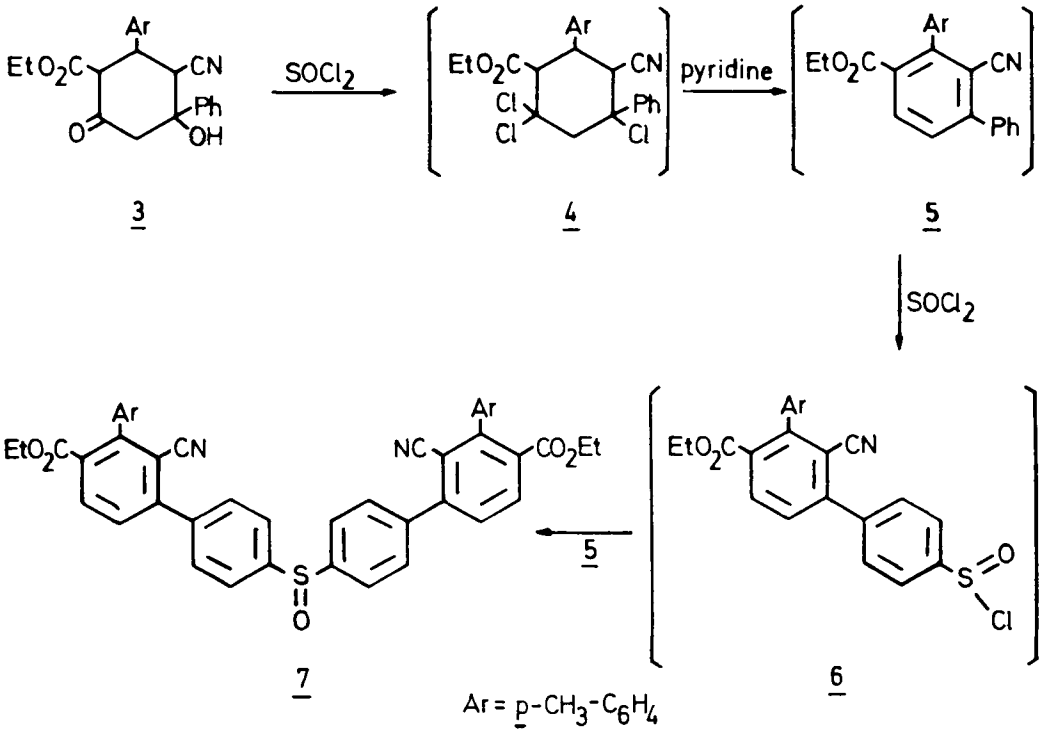
Spectroscopic data of compounds 3 confirm their structure, the OH group showing a strong band at 3340 cm^{-1} and a singlet at δ 6.46 in the ^{1}H-NMR spectra which disappears on addition of TFA. ^{13}C-NMR spectra clearly show two carbonyl groups at 201.72 and 167.25 ppm due to the exocyclic C=O and the ethoxycarbonyl group respectively. The only methyl group appears at 13.54 ppm, which in the "off resonance" spectra is observed as a quartet. The ring carbon atoms appear at chemical shifts in agreement with calculated values and "off resonance" splitting for the proposed structure (3): C_2 at 61.24 ppm and C_5 at 75.97 ppm. C_3 and C_4 appear as two very close signals at 45.48 and

44.74 ppm. C_6 gives rise to a signal at 52.45 ppm, and the carbon of the cyano group appears at 117.80 ppm. A paper recently[12] assigned the open-chain structure 2 to the product resulting from the reaction of ethyl acetoacetate and α-benzoylcinnamonitrile using triethylamine as the catalyst. Using this catalyst both in absolute ethanol and 96% ethanol, we always obtained the same cyclohexanone (3) as described above.

Treatment of hydroxycyclohexanones (3) with sulfuric acid or phosphorus pentoxide to obtain the dehydrated product was unsuccesful. However, reaction of 3 with thionyl chloride in pyridine, led to an unexpected result. The reaction, carried out either at room temperature or under reflux, yielded a product with a molecular formula $C_{46}H_{36}N_2O_5S$ (M^+, 728; C, 75.42; H, 4.71; N, 4.12 and S, 4.48). The IR spectra show the characteristic peaks of ethoxycarbonyl and methyl protons together with aromatic protons, and the ^{13}C-NMR spectra is in agreement with a symmetric structure 7 (Scheme 2) in which the CN, CO_2Et and CH_3 carbon atoms appear at expected chemical shifts.

Scheme 2 represents a possible mechanism for the formation of this product, involving substitution of the hydroxyl group by a chlorine atom and gem-dihalogenation of the carbonyl group by thionyl chloride; gem-dihalogenations of this kind by thionyl chloride have previously been reported in the literature.[13,14] Dehydrohalogenation of intermediate 4 by pyridine would yield 5, which upon electrophilic substitution with excess of thionyl chloride, would then affords sulphinyl

chloride 6. Aromatic electrophilic substitutions by thionyl chloride to diaryl sulfoxides are also Known in the literature.[15-18] Reaction of 6 with another molecule of 5 could finally afford sulfoxide 7.



Scheme 2

EXPERIMENTAL SECTION

Melting points were determined with a Büchi apparatus in capillary tubes and are uncorrected. The IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 599 spectrophotometer. The ^{1}H-NMR spectra were measured with a Varian T-60 A and the ^{13}C-NMR spectra with a Varian FT-80 A. A Varian MAT-711 was used for the mass spectra. Microanalysis were performed by Centro Nacional de Química Orgánica de Madrid. The reactions were monitored by TLC, performed on silica gel

plates with toluene/ethyl acetate as the eluent. α-Benzoylcinnamonitriles were prepared by the method described by Kauffmann[19] by Knoevenagel condensation of benzoylacetonitrile with aromatic aldehydes.

3-Aryl-4-cyano-2-ethoxycarbonyl-5-hydroxy-5-phenylcyclohexanones (3). General procedures.

a) To a suspension of 1.5 mmole of the appropiate α-benzoylcinnamonitrile in 15 ml of absolute ethanol, 1.5 mmole of ethyl acetoacetate and a few drops of piperidine were added. The mixture was heated to reflux for 1-3 hrs and a solid separated. When TLC showed that the starting materials were consumed, the reaction mixture was allowed to cool at room temperature and the precipitate was collected and recrystallized from ethanol.

b) When the reaction was carried out at room temperature, the reaction mixture was stirred for a week and the hydroxycyclohexanones that separated were collected. The precipitate must be collected at time intervals during the reaction to allow the reaction to continue.

4-Cyano-2-ethoxycarbonyl-5-hydroxy-3,5-diphenylcyclohexanone (3a) was obtained in 82% yield by method a) in 2.5 hrs, and 82% yield by method b), mp. 240-243º (dec.).

Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.73; H, 5.79; N, 3.86
Found: C, 72.33; H, 5.86; N, 3.79

IR: 3340, 2240, 1740, 1715, 1600, 1585, 1290, 1270, 1240 cm^{-1}.
^{1}H-NMR (DMSO-d_6): δ 7.0-7.6 (m, 10 H, arom.), 6.5 (s, br. 1 H, OH), 2.55-4.3 (m, 7 H, 3 CH, 2 CH_2), 0.93 (t, 3 H, CH_3).

^{13}C-NMR (DMSO-d_6): δ 201.72 (C=O), 167.25 ($\underline{C}O_2Et$), 144.06, 138.72, 128.33-124.76 (aromatic carbons), 117.80 (CN), 75.97 (C_5), 61.24 (C_2), 52.45 (C_6), 45.48 (C_3 or C_4), 44.74 (C_4 or C_3), 13.54 (CH_3).

4-Cyano-2-ethoxycarbonyl-5-hydroxy-3-(p-methylphenyl)-5-phenylcyclohexanone (3b) was obtained in 83% yield by method a) in 2.5 hrs, and in 88% yield by method b), mp. 242-244º.

Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.21; H, 6.10; N, 3.71
Found: C, 73.14; H, 6.17; N, 3.68

IR: 3340, 2240, 1740, 1715, 1515, 1500, 1290, 1280, 1265, 1240, 1230 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.0-7.7 (m, 9 H, arom.), 6.55 (s, br. 1 H, OH), 2.4-4.3 (m, 7 H, 3 CH, 2 CH_2), 2.25 (s, 3 H, CH_3), 0.95 (t, 3 H, CH_3).
^{13}C-NMR (DMSO-d_6): δ 202.21 (C=O), 167.54 ($\underline{C}O_2Et$), 144.29, 140.82, 136.91-124.93 (aromatic carbons), 118.14 (CN), 76.12 (C_5), 61.46 (C_2), 60.20 (CH_2 ester), 53.53 (C_6), 44.50 (C_3 or C_4), 45.69 (C_4 or C_3), 20.59 (CH_3), 13.77 (CH_3 ester).
MS: m/e (relative intensity): 377 (M^+,2), 286 (3), 247 (4), 234 (18), 232 (9), 217 (7), 202 (3), 189 (5), 171 (8), 160 (6), 145 (8), 143 (13), 115 (7), 106 (9), 105 (100), 77 (19).

4-Cyano-2-ethoxycarbonyl-3-(p-chlorophenyl)-5-hydroxy-5-phenylcyclohexanone (3c) was obtained in 67% yield by method a) in 2.5 hrs and 71% yield by method b), mp. 242-243º.

Anal. Calcd. for $C_{22}H_{20}NO_4Cl$: C, 66.42; H, 5.03; N, 3.52; Cl, 8.93
Found: C, 66.39; H, 4.85; N, 3.46; Cl, 8.68

IR: 3340, 2240, 1730, 1710, 1660, 1640, 1590, 1490, 1280, 1265, 1240, 1040 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.1-7.7 (m, 9 H, arom.), 6.5 (s, 1 H, OH), 2.5-4.2 (m, 7 H, 3 CH, 2 CH_2), 0.96 (t, 3 H, CH_3).

4-Cyano-2-ethoxycarbonyl-5-hydroxy-3-(p-methoxyphenyl)-5-phenylcyclohexanone (3d) was obtained in 86% yield by method a) in 2.5 hrs and 85% yield by method b), mp. 237-238º.

Anal. Calcd. for $C_{23}H_{23}NO_5$: C, 70.23; H, 5.85; N, 3.56
Found: C, 69.94; H, 6.04; N, 3.70

IR: 3340, 2240, 1740, 1720, 1610, 1585, 1520, 1300, 1260, 1250, 1030 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 6.8-7.6 (m, 9 H, arom.), 6.45 (s, 1 H, OH), 2.5-4.2 (m, 10 H, 3 CH, 2 CH_2, OCH_3), 1.0 (t, 3 H, CH_3).
^{13}C-NMR (DMSO-d_6): δ 202.16 (C=O), 167.55 ($\underline{C}O_2Et$), 158.64, 130.81, 144.29, 129.33-124.91 (aromatic carbons), 118.14 (CN), 76.03 (C_5), 61.62 (C_2), 60.17 (CH_2), 54.93 (OCH_3), 52.54 (C_6), 45.84 (C_3 or C_4), 44.14 (C_4 or C_3), 13.79 (CH_3).

4-Cyano-2-ethoxycarbonyl-5-hydroxy-3-(p-nitrophenyl)-5-phenylcyclohexanone (3e) was obtained in 62% yield by method a) in 45 min. and 81% yield by method b), mp. 222-223º.

Anal. Calcd. for $C_{22}H_{20}N_2O_6$: C, 64.71; H, 4.90; N, 6.86
Found: C, 65.00; H, 4.95; N, 7.20

IR: 3340, 2250, 1750, 1720, 1600, 1520, 1350, 1290, 1250, 1240, 1150, 1140 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 7.1-8.0 (m 9 H, arom.), 6.6 (s, 1 H, OH), 2.6-4.3 (m, 7 H, 3 CH, 2 CH_2), 0.95 (t, 3 H, CH_3).

Bis (4"-methyl-2'-cyano-4'-ethoxycarbonyl-4-|1,1':3,1"|-terphenyl) sulfoxide (7).- Compound 3b (1 g) was disolved in the minimum amount of pyridine and 6 ml of thionyl chloride was added to the solution. The reaction mixture was then heated to reflux for 15 min. and then cooled to room temperature and allowed to stand in the refrigerator for 12 hrs. The precipitate that separates was collected and washed with a large amount of water. The collected solid was then refluxed with norite in ethanol and recrystallized from this solvent to yield 0.2 g (21%) of a white solid, mp. 300º.

Anal. Calcd. for $C_{46}H_{36}N_2O_5S$: C, 75.82; H, 4.95; N, 3.85; S, 4.40

Found: C, 75.42; H, 4.71; N, 4.12; S, 4.48

IR: 2220, 1740, 1610, 1590, 1555, 1530, 1510, 1390, 1370, 1340, 1315, 1285, 1190 cm^{-1}. ^{1}H-NMR (DMSO-d_6):δ 7.0-7.4 (m, 20 H, arom.), 3.95 (q, 4 H, 2 CH_2), 2.3 (s, 6 H, 2 CH_3), 0.9 (t, 6 H, 2 CH_3).

^{13}C-NMR (DMSO-d_6): δ 162.93 (COO), 148.48, 144.35, 143.2, 138.91, 134.1, 131.8, 129.7, 128.8, 128.7, 128.6, 127.8, 124.39, 119.86 (aromatic carbons), 115.53 (CN), 110.33 (C-CN), 61.52 (CH_2), 20.72 (CH_3), 13.21 (CH_3).

MS: m/e (relative intensity): 728 (M^+,21), 727 (38), 726 (68), 635 (8), 326 (11), 204 (29), 203 (14), 202 (100), 201 (46), 200 (79), 199 (61), 198 (36), 102 (6), 101 (22), 100 (20), 99 (9).

REFERENCES

1. C. Seoane, J.L. Soto and M.P. Zamorano, Heterocycles, 14, 639 (1980).
2. C. Seoane, J.L. Soto and M.P. Zamorano, J. Heterocyclic Chem., 18, 309 (1981).
3. M.J. Rubio, C. Seoane and J.L. Soto, Ann., 213 (1984).
4. M. Quinteiro, C. Seoane and J.L. Soto, J. Heterocyclic Chem., 15, 57 (1978).
5. J.L. Soto, C. Seoane, N. Martín and M. Quinteiro, Heterocycles, 22, 1 (1984).
6. V.J. Arán and J.L. Soto, Synthesis, 513 (1982).
7. S. Cusmano and V. Sprio, Gazz. Chim. Ital., 82, 199 (1952).
8. S. Cusmano, ibid., 81, 380 (1951).
9. S. Cusmano, V. Sprio and F. Trapani, ibid., 82, 98 (1952).
10. S. Cusmano and V. Sprio, ibid., 82, 191 (1952).
11. J. Wolinsky and H.S. Hauer, J. Org. Chem., 34, 3169 (1969).
12. N.N. Abed, E.A.Z. Hafez, I. Elsakka and M.H. Elnagdi, J. Heterocyclic Chem., 21, 1261 (1984).
13. M.S. Newman and P.K. Sujeeth, J. Org. Chem., 43, 4367 (1978).
14. A. Schonberg, O. Schutz and S. Nickel, Ber., 61, 1375 (1928).
15. S. Oae and C. Zalut, J. Am. Chem. Soc., 82, 5359 (1960).
16. S. Smiles and R.L. Rossignol, J. Chem. Soc., 745 (1908).
17. G. Glaros and S. Sullivan, Synth. Comm., 6, 495 (1976).
18. L.N. Nikolenko and N.I. Krizhechkovskaya, J. Gen. Chem. USSR, 33, 3664 (1963).
19. H. Kauffmann, Ber., 50, 527 (1917).

(Received August 5, 1985; in revised form September 25, 1985)