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A New Convenient Synthetic Method for 3,4-Diaryl-2,6-piperidinediones

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A one-pot reaction for the preparation of 3,4-diaryl-2,6-piperidinediones through acid hydrolysis of the corresponding ethyl 3,4-diaryl-4-cyanobutyrates is described.

(Keywords: Heterocycles; Piperidinediones)

Ein neuer einfacher Syntheseweg für 3,4-Diaryl-2,6-piperidindione

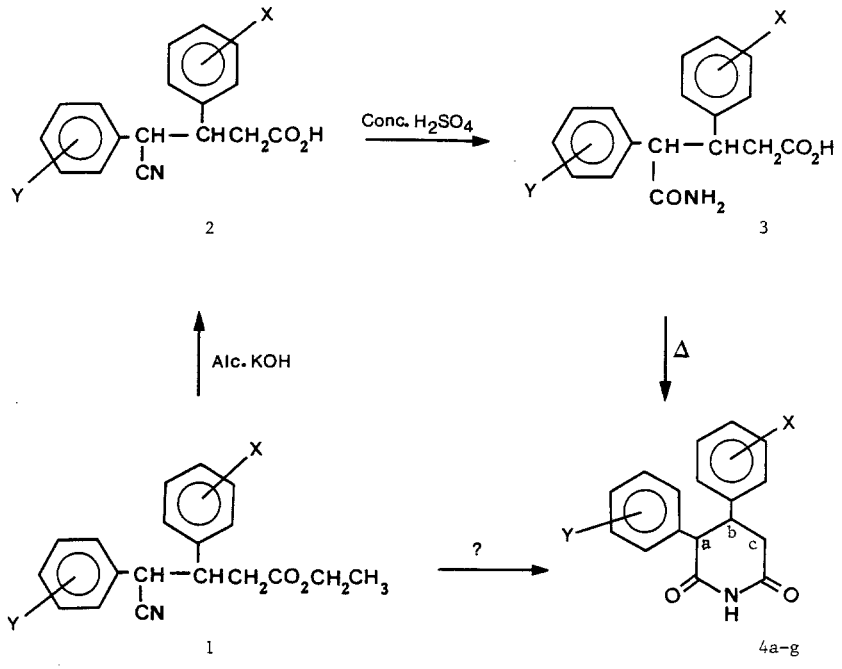
Durch saure Hydrolyse der entsprechenden Ethyl-3,4-diaryl-4-cyanobutyrate wurden in einem Schritt (Eintopfreaktion) die 3,4-Diaryl-2,6-piperidindione dargestellt.

Introduction

Meyer and *Hauser* [1] synthesized 3,4-diphenyl-2,6-piperidinediones by the reaction of ethyl cinnamate and disodiophenylacetamide in the presence of ammonium chloride. *Shandala* [2] and his co-workers reported the synthesis of related piperidinediones by condensation of ethyl cinnamate and arylacetamides in the presence of powdered sodium in boiling benzene, or by the reaction of cinnamaldehyde and arylacetamide [3] again using sodium in boiling benzene.

On the other hand, *Koelsch* [4] and *Cook* [5] have synthesized ethyl 3,4-diaryl-4-cyanobutyrates by *Michael* condensation of benzyl cyanide and ethyl cinnamates. It was shown that the hydrolysis of ethyl 3,4-diphenyl-4-cyanobutyrate (**1**) using alcoholic potash yielded 4-cyano-3,4-diphenylbutyric acid (**2**) [5] which was subsequently hydrolyzed using concentrated sulfuric acid to afford the amide **3**, which afforded 3,4-diphenyl-2,6-piperidinedione (**4**) when heated above its melting point. We report now that **4** can be prepared directly in a one-pot process by

Scheme 1



4	X	Y
a	4-Cl	H
b	H	4-Cl
c	H	4-Br
d	4-Br	H
e	4-Br	4-Br
f	4-Cl	4-Cl
g	H	H

acid hydrolysis of the corresponding ethyl 3,4-diaryl-4-cyanobutyrates (**1**) using aqueous sulfuric acid as shown in Scheme 1.

Results and Discussion

The biological significance [5] and the synthetic importance of the substituted 2,6-piperidinediones prompted us to prepare new derivatives. A convenient one-pot reaction for the synthesis of 3,4-diaryl-2,6-piper-

idinediones (**4 a–g**) is the acid hydrolysis of the corresponding ethyl 3,4-diaryl-4-cyanobutyrates (**1 a–g**).

The infrared spectra of **4 a–g** show a peak in the 3 320–3 370 cm^{-1} range due to the stretching vibration of the N—H bond, and two sharp peaks between 1 685 and 1 720 cm^{-1} which are characteristic for the stretching vibrations of the imide carbonyl groups [6].

Their nmr spectra exhibit a one-proton doublet between δ 3.88–4.31 representing the "a" methine proton with a coupling constant of ≈ 13 Hz. This large *J* value indicates that H_a and H_b are *trans* to each other. One-proton multiplet centered between 3.57 and 3.86 which corresponds to the "H_b" methyne proton is also observed. The methylene protons "c" appear as two doublets in the ranges of 2.44–3.87 and 2.94 and 3.24 ppm. The N—H proton is a broad singlet, exchangeable with D_2O. Finally, the aromatic moiety was indicated by a multiplet centered near 7.16 ppm.

Acknowledgement

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Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide pellets on a Pye-Unicam SP 300 instrument. ^{1}H-NMR spectra were measured on a Brucker WP 80-SY spectrometer using $CDCl_3$ solutions containing *TMS* as internal standard. Mass spectra were recorded on a 7070-E VG analytical organic mass spectrometer. Elemental analysis were carried out by M-H-W Laboratories, Phoenix, Arizona, U.S.A.

Ethyl 3,4-diaryl-4-cyanobutyrates (**1 a–g**); *General Procedure* [7]

Equimolar amounts of substituted benzyl cyanides and substituted ethyl cinnamates were added successively to a suspension of sodium ethoxide in dry ether (150 ml). The mixture was kept at room temperature for three to seven days and then poured into water (250 ml) and extracted with ether. The ether extract yielded a crude solid which after recrystallization from the appropriate solvent afforded ethyl 3,4-diaryl-4-cyanobutyrate. The alkaline aqueous layer was acidified with dilute sulfuric acid and extracted with ether and the organic layer was shaken with sodium hydrogen carbonate solution. Evaporation of the solvent yielded additional amounts of the desired product.

3,4-Diaryl-2,6-piperidinediones (**4**); *General Procedure*

To the corresponding cyanobutyrate **1** a solution of conc. H_2SO_4 and H_2O was added. After refluxing, the precipitate (if necessary after cooling and addition of H_2O) was collected and recrystallized (for details see Table 1).

3-(4-Chlorophenyl)-4-phenyl-2,6-piperidinedione (**4 a**)

IR (KBr): ν 3 370 (NH), 1 710 (C=O), 1 680 (C=O) cm. ^{1}H NMR ($CDCl_3$): δ = 2.66 (d, 1 H); 2.90 (d, 1 H); 3.83 (m, 1 H); 4.30 (d, 1 H); 7.30–7.40 (m, 9 H); 11.62 ppm (s, b, exchangeable; 1 H).

Table 1. *Diaryl-piperdinediones* **4**

Compd. No.	mmol of **1**	H_2SO_4 (ml)	H_2O (ml)	reflux (h)	cryst. from	yield (%)	m. p. (°C)	formula[a]
4 a	3.0	12.0	8.5	4	*Me*OH	82	212–214	$C_{17}H_{14}NO_2Cl$ (299.8)
4 b	1.5	4.1	6.5	2.5	*Et*OH	92	208–210	$C_{17}H_{14}NO_2Cl$ (299.8)
4 c	1.0	2.3	3.0	3	*Me*OH	78	239–240	$C_{17}H_{14}NO_2Br$ (344.2)
4 d	3.0	8.5	14.0	4	*Me*OH	66	209–211	$C_{17}H_{14}NO_2Br$ (344.2)
4 e	1.5	6.5	8.0	8	$CHCl_3$/ligroin	74	190–192	$C_{17}H_{13}NO_2Br_2$ (423.1)
4 f	2.0	5.5	8.0	10	*Et*OH/H_2O	73	213–215	$C_{17}H_{13}NO_2Cl_2$ (334.2)
4 g	3.0	12.0	8.4	3	*Me*OH	87	227–228[b]	$C_{17}H_{15}NO_2$ (265.3)

[a] Mass-spectra as well as elemental analyses are in full agreement with the proposed structures
[b] Lit. [2]: 225 °C

3-Phenyl-4-(4-chlorophenyl)-2,6-piperidinedione (**4 b**)

IR (KBr): ν 3 360 (NH); 1 710 (C=O); 1 685 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.56 (d, 1 H); 2.90 (d, 1 H); 3.49 (m, 1 H); 3.88 (d, 1 H); 6.79–6.87 (m, 9 H); 11.35 ppm (s, b, exchangeable, 1 H).

3-(4-Bromophenyl)-4-phenyl-2,6-piperidinedione (**4 c**)

IR (KBr): ν 3 370 (NH); 1 705 (C=O); 1 685 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.72 (d, 1 H); 2.94 (d, 1 H); 3.78 (m, 1 H); 4.31 (d, 1 H); 6.90–7.43 (m, 9 H); 11.05 ppm (s, b, exchangeable, 1 H).

3-Phenyl-4-(4-bromophenyl)-2,6-piperidinedione (**4 d**)

IR (KBr): ν 3 360 (NH); 1 705 (C=O), 1 680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.87 (d, 1 H); 3.24 (d, 1 H); 3.84 (m, 1 H); 4.24 (d, 1 H); 4.24 (d, 1 H): 7.04–7.47 (m, 9 H); 11.41 ppm (s, b, exchangeable, 1 H).

3,4-Di-(4-bromophenyl)-2,6-piperidinedione (**4 e**)

IR (KBr): ν 3 320 (NH); 1 720 (C=O); 1 680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.85 (d, 1 H); 3.01 (d, 1 H); 3.57 (m, 1 H); 4.27 (d, 1 H); 7.01–7.64 (d, 8 H); 11.32 ppm (s, b, exchangeable, 1 H).

3,4-Di-(4-chlorophenyl)-2,6-piperidinedione (**4 f**)

IR (KBr): ν 3 355 (NH); 1 720 (C=O); 1 690 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.44 (d, 1 H); 3.01 (d, 1 H); 3.86 (m, 1 H); 4.27 (d, 1 H); 7.01–7.31 (d, 8 H); 11.32 ppm (s, b, exchangeable, 1 H).

3,4-Diphenyl-2,6-piperidinedione (**4 g**)

IR (KBr): ν 3 360 (NH); 1 705 (C=O); 1 680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.87 (d, 1 H); 3.24 (d, 1 H); 3.84 (m, 1 H); 7.04–7.47 (m, 8 H); 11.21 ppm (s, b, exchangeable, 1 H).

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