4-ALKOXYIMINOHYDANTOINS FROM O-ALKYLMANDELO-HYDROXAMIC ACIDS AND DICYCLOHEXYLCARBODIIMIDE

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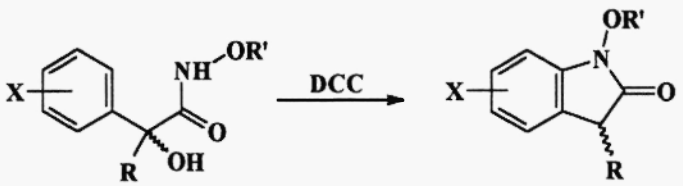
Abstract

The reaction of O-alkylmandelohydroxamic acids (**3a-d**) with dicyclohexylcarbodiimide produces 4-alkoxyiminohydantoins (**4a-d**), the structures of which were unambiguously confirmed by their spectral data, the hydrolytic conversion of **4a** to an imidazoline-2,4-dione (**5**) and the authentic synthesis of **5** by a one-pot reaction of (2-cyclohexylamino)phenylacetic acid (**6**), cyclohexylamine and 1,1'-carbonyldiimidazole.

Introduction

The dicyclohexylcarbodiimide-mediated cyclodehydration of N-alkoxy-2-aryl-glycolamides (**1**) has been shown [1] to provide an easy access to 1-alkoxy-indolin-2-ones (**2**), the heterocyclic skeleton of which is found in numerous bioactive compounds of natural and synthetic origin [2,3].



1 2

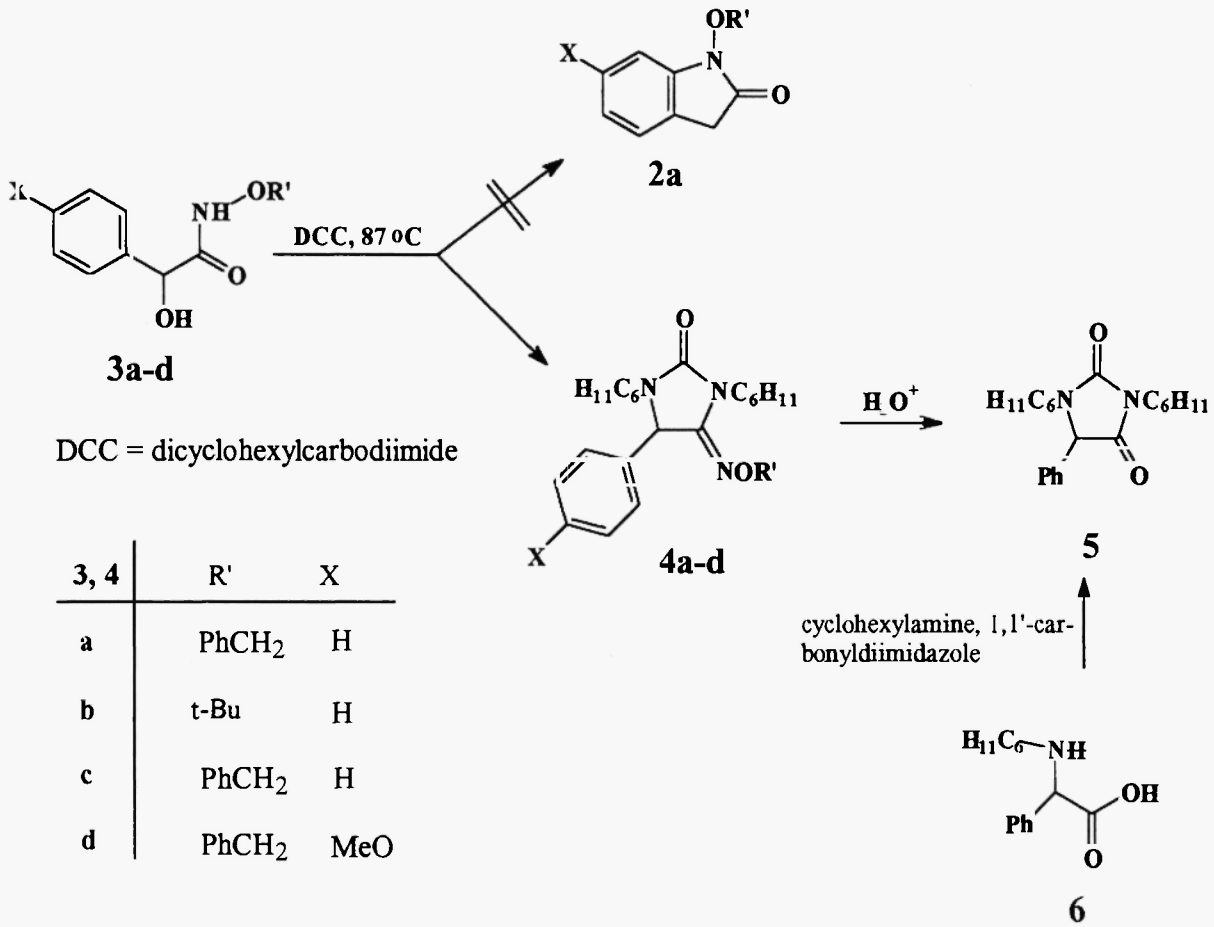
Scheme 1

As an extension of our studies on the chemistry of cyclic hydroxamic acids we expected the O-alkylmandelohydroxamic acids **3a-d,** i.e. **1** with R = H, to undergo an analogous cyclisation to the corresponding 3-*unsubstituted* 1-alkoxy-2-oxindoles **2a**. However, as outlined below, only the iminohydantoins **4a-d** could be isolated from the reaction of **3a-d** with dicyclohexylcarbodiimide.

Results and Discussion

When **3a-d** were allowed to react with two equivalents of DCC in boiling 1,1,2-trichloroethene, precipitation of dicyclohexylurea was observed within 12 hours. After filtration and decomposition of unconsumed DCC with acetic acid, nonpolar compounds were obtained, the elemental analysis data of which indicated the incorporation of the complete DCC entity into the molecule. The IR spectra of these compounds showed characteristic absorption bands at 1738-1725 (C=O) and 1670-1660 (C=N) cm^{-1} and the ^{1}H-NMR spectra exhibited a methine proton at δ = 4.77 ppm (H^5) suggesting the formation of 4-alkoxyiminohydantoins **4.**

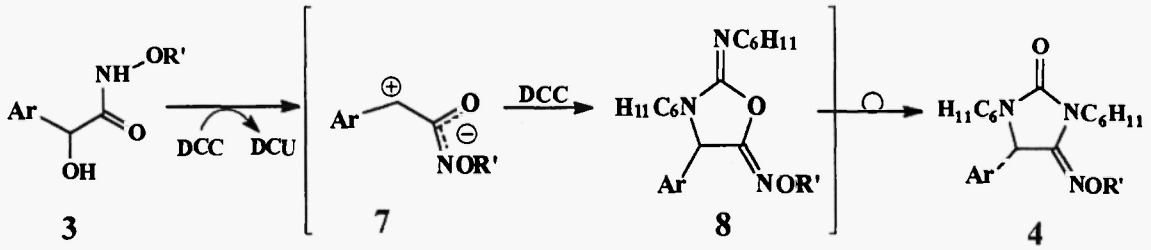
Unambiguous proof for structure **4** was obtained by the hydrolysis of **4a** with dilute hydrochloric acid leading to **5** which in turn could authentically be prepared by the reaction of (2-cyclohexylamino)phenylacetic acid **6** with cyclohexylamine and two equivalents of 1,1'-carbonyldiimidazole (Scheme 2). The intermediate formation of cyclohexyl isocyanate is probable.



3, 4	R'	X
a	$PhCH_2$	H
b	t-Bu	H
c	$PhCH_2$	H
d	$PhCH_2$	MeO

Scheme 2

Although heterocyclisations involving full incorporation of the DCC entity in the ring are known from literature [4-7], the herein described reaction is, to the best of our knowledge, without precedent in the literature. The reaction mechanism can be rationalized by a 1,3-cycloaddition between DCC and the dipolar intermediate **7** [1,8], originating from an initially formed isourea by loss of dicyclohexylurea (DCU), to form cycloadduct **8**. Finally, Dimroth rearrangement of **8** leads to the 4-alkoxyiminohydantoin **4**.



Scheme 3

Conclusion

In conclusion, we described a novel cyclocondensation of O-alkylmandelohydroxamic acids with dicyclohexylcarbodiimide to give 4-alkoxyiminohydantoins **(4).** Since 4-iminohydantoins deserve attention due to their biological activities [9], future studies will be directed to the corresponding reactions of mandeloamides in order to explore whether this method can offer a general access to heterocycles of type **4**.

Acknowledgement
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Experimental

Melting points were taken in open capillary tubes and are uncorrected. The IR spectra were recorded on a Philips Unicam SP3 200 and Perkin Elmer 1420. The ^{1}H NMR spectra were recorded on a Varian XL 300 and a Bruker AMX 400 with TMS as the internal reference. Chromatographic separations were performed on ICN Silica 100-200, active, 60A, 10 x 2 cm ∅.

Starting materials

Compounds **3a-d** were prepared by the reaction of the appropriate mandelic acid with benzyloxyamine or tert-butoxyamine and 1,1'-carbonyldiimidazole according to [1b]. The yields and physical data of the novel **3b-d** are listed below.

N-tert-Butoxy-α-hydroxybenzeneacetamide (3b): 56%; mp 147 °C (diethyl ether). IR (KBr): 3400 (OH), 3220 (NH), 1645 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.20 (s, 9H, CH_3), 5.10 (s, 1H, CH-O), 7.43 (m, 5 aromatic H). Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.26; H, 7.74; N, 6.28.

N-Benzyloxy-4-chloro-α-hydroxybenzeneacetamide (3c): 62%; mp 131 °C (toluene). IR (KBr): 3500 (OH), 3200 (NH), 1652, 1639 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.80 (s, 2H, OCH_2), 5.03 (s, 1H, CH-O), 7.30 (m, 9 aromatic H). Anal. Calcd. for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.83; N, 4.80. Found: C, 61.53; H, 4.85; N, 4.73.

N-Benzyloxy-α-hydroxy-4-methoxybenzeneacetamide (3d): 54%; mp 131 °C (diethyl ether). IR (KBr): 3300 (OH), 3180 (NH), 1660 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.73 (s, 3H, OCH_3), 4.73 (s, 2H, OCH_2), 4.96 (s, 1H, CH-O). Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.41; H, 6.01; N, 5.13.

General procedure for the conversion of **3a-d** to the 4-alkoxyiminohydantoins **4a-d:**

A mixture of **3a-d** (5 mmoles) and dicyclohexylcarbodiimide (10 mmoles) in 30 ml anhydrous trichloroethene was refluxed for 12h. After removal of the dicyclohexylurea and addition of 20 ml diethyl ether the filtrate was treated with 10 ml acetic acid (50%) and vigorously stirred for 1h. The dicyclohexylurea resulting from the decomposition of uncomsumed DCC was removed and the filtrate was extracted twice with saturated sodium bicarbonate solution. The organic layer was dried over $MgSO_4$, evaporated in vacuo and the residue chromatographed. After elution with 100 ml dichloromethane pale yellow oily residues were obtained, which could be crystallized from 15 ml petroleum ether/diethyl ether (5:1) by standing in the refrigerator.

4-Benzyloxyimino-1,3-dicyclohexyl-5-phenylimidazolidin-2-one (4a): 64%; mp 115 °C (petroleum ether). IR (KBr): 1725 (C=O), 1665 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.90-1.98 (m, 20 H, CH_2), 3.64 (m, 2H, CH), 4.97 (s, 2H, $NOCH_2$), 5.13 (s,1H, CH-O), 7.26 (m, 5 aromatic H), 7.33 (m, 5 aromatic H). Anal.Calcd. for $C_{28}H_{35}N_3O_2$: C, 75.38; H, 8.03; N, 9.39. Found: C, 75.47; H, 7.92; N, 9.43.

4-tert-Butoxyimino-1,3-dicyclohexyl-5-phenylimidazolidin-2-one (4b): 66%; mp 102 °C (petroleum ether). IR (KBr): 1730 (C=O), 1670 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.79-1.92 (m, 20 H, CH_2), 1,16 (s, 9 H, CH_3), 3.67 (m, 2H, CH), 5.13 (s, 1H, CH-O), 7.32 (m, 5 aromatic H). Anal. Calcd. for C_{25} H_{37} N_3O_2: C, 72.96; H, 9.33; N, 10.21. Found: C, 72.75; H, 9.17; N 10.04.

4-Benzyloxyimino-5-(4-chlorophenyl)-1,3-dicyclohexylimidazolidin-2-one (4c): 56%; mp 107 °C (petroleum ether). IR (KBr): 1738 (C=O), 1670 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.80-1.84 (m, 20H, CH_2), 3.66 (m, 2H, CH), 4.91 (q, 2H, J = 12.0 Hz, $NOCH_2$), 5.10 (s, 1H, CH-O), 7.22-7.32 (m, 10 aromatic H). Anal. Calcd. for $C_{28}H_{34}ClN_3O_2$: C, 70.1; H, 7.14; N, 8.75. Found: C, 70.23; H, 7.35; N, 8.68.

4-Benzyloxyimino-1,3-dicyclohexyl-5-(4-methoxyphenyl)imidazolidin-2-one (4d): 63 %; mp 84 °C (petroleum ether). IR (KBr): 1735 (C=O), 1660 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.79-1.82 (m, 20 H, CH_2), 3.63 (m, 2H, CH), 3.82 (s, 3H, OCH_3), 4.91 (q, 2H, J = 12.0 Hz, $NOCH_2$), 5.18 (s, CH-O), 6.86-7.31 (m, 9 aromatic H). Anal. Calcd. for $C_{29}H_{37}N_3O_3$: C, 73.23; H, 7.84; N, 8.83. Found: C, 73.46; H, 7.97; N, 8.98.

1,3-Dicyclohexyl-5-phenylimidazolidin-2,4-dione (5)

a) A suspension of **4a** (2 mmoles) in 20 ml 3 M HCl was vigorously stirred for 1 h at 80 °C. After stirring for 20 min at ambient temperature, the solvent was removed in vacuo and the residue extracted with 50 ml diethyl ether. The ethereal solution was dried over $MgSO_4$, evaporated and the residue chromatographed. Elution with 100 ml dichloromethane yielded **5** as a colourless oil which solidified on standing in the refrigerator. 77%; mp 102 °C (petroleum ether). IR (KBr): 1757 and 1695 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.82-2.24 (m, 20 H, CH_2), 3.82 (m, 2H, CH), 4.77 (s, 1H, H^5), 7.23-7.42 (m, 5 aromatic H). Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.07; H, 8.31; N, 8.23. Found: C, 74.03; H, 8.37; N, 8.22.

b) A mixture of (2-cyclohexylamino)phenylacetic acid (2 mmoles) [10], 1,1'-carbonyldiimidazole (4 mmoles), cyclohexylamine (2 mmoles) and 30 ml anhydrous toluene was refluxed for 6 h. The precipitate was filtered off, the filtrate evaporated in vacuo and the oily residue chromatographed. Elution with 100 ml dichloromethane afforded **5** in 56% yield.

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