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Hydantoins derived from ketopinic and 4-camphorcarboxylic acids

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Diastereospecific formation of hydantoins from ketopinic and 4-camphorcarboxylic acids under Bucherer-Bergs reaction conditions has been investigated. The easiness of this transformation provides a straightforward synthetic pathway to enantiopure conformationally rigid amino acids derivatives, as well as functionalized hydantoins, starting from inexpensive and easily available natural camphor.

Introduction

Specific arrangement of functional groups combined with rigidity of the conformationally restricted molecules enables, in favourable cases, key-in-the-lock fit combined with efficient intermolecular interaction. It is noteworthy that there are examples of improvements in performance achieved using this strategy, where better selectivity of the system coincided with higher activity and superior stability.

Hydantoins, also known as glycolylureas, are important moieties found in numerous natural products [1–3]. Hydantoin-based scaffolds often show interesting and significant pharmacological activities [1,4–9]. One the best-known example of such a derivative is 5,5-diphenylhydantoin (*phenytoin*), a commonly used antiepileptic (also anti-convulsant and cardiac antiarrhythmic) [4,5,10–12]. A wide range of hydantoin derivatives, such as 3-substituted-5-phenyl-5-pyridyl hydantoins, has been identified as effective and important cardiac antiarrhythmic agents [13]. This particular range of compounds have also shown good antidepressant, antimuscarinic and antiviral activities [5,6,14,15]. Recently, 5-substituted hydantoins have been reported to inhibit the binding of human immunodeficiency viruses to lymphocytes [16,17]. Substituted hydantoins are an important class of precursors to α-amino acids and pyruvic acids, which can be easily synthesized via alkaline degradation of the former [18–20].

The Bucherer-Bergs reaction is an important synthetic pathway to hydantoins using a wide range of aldehydes and ketones, including those with low reactivity of the carbonyl group [21,22].

The Nature itself perfected rigid biologically vital molecules over millions of years. However, such timescale is simply a luxury science and industry could not afford. Development of versatile synthetic pathways towards conformationally rigid molecules is therefore of paramount importance. We hereby report our approach towards selective synthesis of conformationally rigid bio-relevant molecules starting from readily available natural feedstocks.

Results and discussion

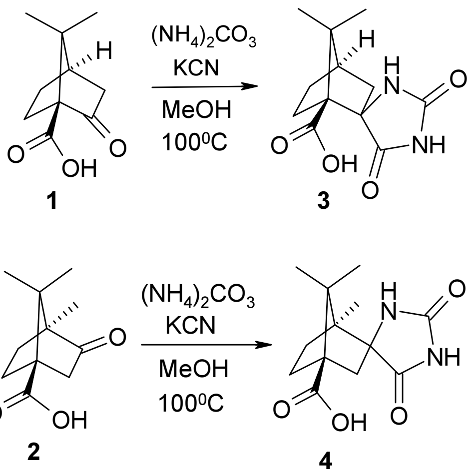
Camphor and its derivatives have attracted the interest of many organic chemists as an easily accessible and versatile starting material in the synthesis of chiral compounds. To the best of our knowledge, only the parent hydantoin of camphor has been previously reported, despite the fact that there is a huge variety of camphor derivatives containing carbonyl groups [23].

Herein, we have chosen ketopinic and 4-camphorcarboxylic acids, which contain carbonyl groups with slightly different reactivities, as the best substrates from the family of camphor derivatives for a study of regio- and diastereoselectivity of the formation of hydantoins under Bucherer-Bergs reaction conditions.

Camphor itself forms a mixture of diastereomeric hydantoins (7:3) under Bucherer-Bergs reaction conditions (KCN, $(NH_4)_2CO_3$, 120 °C, 10 atm, 5 h). The major product contains carboxamide carbonyl group in *endo* position, since the *endo* attack of cyanide anion on carbonyl group of camphor is preferable due to the steric hindrance of methyl group in bridge position [23].

Ketopinic (**1**) and 4-camphorcarboxylic acid (**2**) form hydantoins in much milder reaction conditions (at a lower pressure and temperature) and faster than camphor does. Unlike camphor, which gives a mixture of diastereomeric hydantoins, the keto acids **1** and **2** give only one isomer – a product of cyanide ion attack from *endo* side of the norbornane skeleton (Scheme 1).

The NOE interaction between protons of amide group (N*H*CO) and methyl group (C*H*$_3$) at C-8 atom of camphor skeleton confirms the suggested structures of hydantoins (**3** and **4**).



Scheme 1. Hydantoins formation from *β*- and *γ*-keto carboxylic acids.

The presence of carboxyl groups at the bridgehead positions in *β*- and *γ*-keto acids **1** and **2** ensures easy and diastereospecific formation of corresponding hydantoins due to synergistic pre-organisation of reacting species.

Conclusions

In conclusion, we have studied the diastereospecific formation of hydantoins from ketopinic and 4-camphorcarboxylic acids under Bucherer-Bergs reaction conditions. The easiness of this transformation opens a straightforward synthetic pathway to enantiopure derivatives of bridgehead norbornane carboxylic acids. The described route provides a model procedure for the preparation of other interesting norbornane-based functionalized compounds.

Experimental part

All the starting materials were purchased from Acros, Merck, Aldrich and Fluka chemicals. All solvents were distilled before use [26]. All experiments, unless otherwise stated, were carried under a nitrogen atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded on a 'Mercury 400' Varian and Bruker AM 400 (400 MHz) spectrometers. Tetramethylsilane was used as the internal standard. IR spectra were obtained on a Perkin Elmer BX II spectrometer. ν_{max} (cm^{-1}) values in IR spectra are given for the main absorption bands. Mass spectra ware recorded on an Agilent 1100 LSMS SL instrument with chemical ionization.

General method of hydantoins preparation.

A solution of 5 mmol of keto acid **1** or **2** in 10 mL of ethanol in steel autoclave (ca. 100 mL of total volume), containing a magnetic stirrer, was quickly charged with a solution of 4.80 g (50 mmol) of ammonium carbonate in 20 mL of water and 1.30 g (20 mmol) of potassium cyanide in 10 mL of distilled water. The autoclave was sealed and left to stir at 10 bar pressure of CO_2 and 100 ºC for 4 h. The reaction mixture was then cooled to room temperature, transferred into a round bottom flask, and evaporated. The residue was dissolved in 10 mL of water and acidified to pH = 4. The resulting solid product was filtered and washed with small amount of cold water.

Hydantoin of 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylic acid (3)

Yield: 65%. Mp: 245 ºC (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.08 (s, 3H), 1.17 (s, 3H), 1.25–1.35 (m, 1H), 1.60–1.80 (m, 4H), 1.95–2.07 (m, 1H), 2.55–2.60 (m, 1H), 7.52 (br s, 1H), 10.65 (br s, 1H). 12.35 (br s, 1H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 21.0, 21.2, 25.6, 26.0, 43.0, 45.4, 50.2, 62.5, 68.5, 157.2, 173.0, 177.8. MS (CI): m/z 253.3 (M+H). $C_{12}H_{16}N_2O_4$ (252.3): calcd C 57.13, H 6.39, N 11.10; found C 57.10, H 6.45, N 11.06.

Hydantoin of 4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptane-1-carboxylic acid (4)

Yield: 69%. Mp: 265 ºC (dec.). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.77 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 1.30–1.40 (m, 1H), 1.45–1.60 (m, 1H), 1.90–2.10 (m, 3H), 2.28 (d, J = 15,6 Hz, 1H), 7.51 (br s, 1H), 10.68 (br s, 1H), 12.25 (br s, 1H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ = 11.3, 18.9, 19.6, 27.5, 29.7, 44.3, 53.3, 55.5, 56.2, 69.3, 156.9, 174.4, 177.6. MS (CI): m/z 267.3 (M+H). $C_{13}H_{18}N_2O_4$ (266.3): calcd C 58.64, H 6.81, N 10.52; found C 58.60, H 6.87, N 10.49.

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