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Mendeleev Commun., 2004, 14(6), 304–306
Mendeleev Communications

One-pot diastereoselective synthesis of new racemic and achiral spirohydantoins

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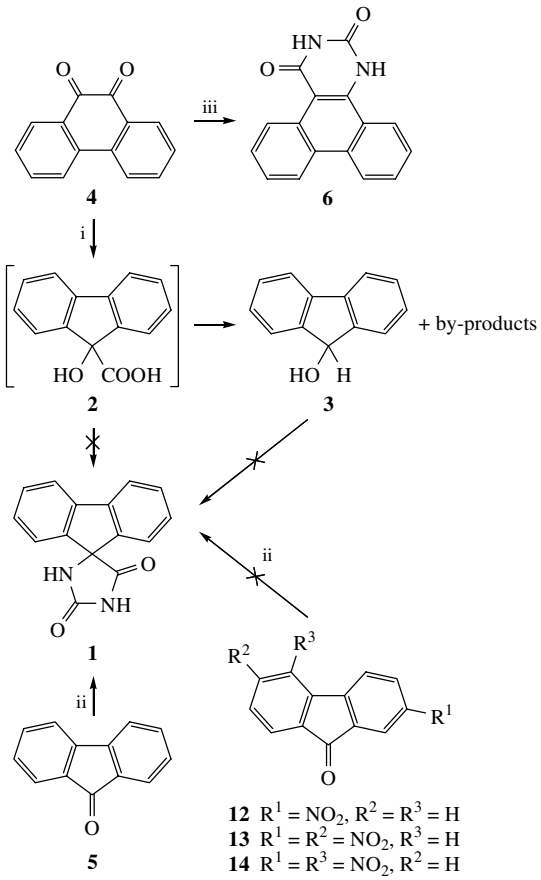
DOI: 10.1070/MC2004v014n06ABEH002014

An efficient and versatile method was used for the diastereoselective synthesis of achiral and racemic spirohydantoins based on ketones 4, 5, 7 and 10.

Hydantoins substituted at C-5 are important medicinal compounds. The most familiar derivative, 5,5-diphenylhydantoin (phenytoin), is extensively used as an anti-convulsant and cardiac antiarrhythmic.[1,2] Recently, fosphenytoin, a water-soluble phenytoin prodrug, has been introduced.[2,3] Other 5-substituted hydantoins have been reported to exhibit antiarrhythmic,[4] antidepressant[5] and antiviral activities[6,7] and inhibited binding of HIV to lymphocytes.[8] Furthermore, hydantoin derivatives are synthetically valuable, *e.g.*, as precursors to α-amino acid and pyruvic acid derivatives.[9–12] One-pot synthesis of phenytoin analogues was reported recently.[13] The aim of this study was one-pot preparation of hydantoin related to phenanthrene-9,10-dione **4** in the presence of urea in an alkali solution similar to benzilic acid rearrangement and final conversion to phenytoin analogues. However, expected spirohydantoin **1** even in a variety of conditions was not prepared. These results suggest that expected α-hydroxy acid **2** was formed but underwent decarboxylation fast to provide **3** and other by-products. The decarboxylated products were subsequently partially oxidised and converted into insoluble compounds. The use of potassium cyanide and ammonium carbonate, *i.e.*, Bucherer–Bergs reaction[14] for fluoren-9-one **5** led to the formation of target achiral spiro hydantoin **1** in 82% yield (Scheme 1).† Utilising this reagent for the preparation of substituted **1** when applied to 2-mono-, 2,6- and 2,7-dinitro fluorens **12**–**14** after several efforts,

† *Synthesis of hydantoin* **1** *from fluoren-9-one* **5**. *A typical procedure.*

3 g (17 mmol) of **5**, 2.16 g (33 mmol) of KCN and 6.38 g (66 mmol) of $(NH_4)_2CO_3$ were added to a solution of 50 ml of 50% EtOH in a 100 ml round-bottom flask equipped with a reflux condenser. The reaction mixture was stirred and heated to reflux at 50–65 °C on an oil bath for 24 h. Then, the reaction mixture was cooled to room temperature and filtered. The pH of the aqueous filtrate solution was adjusted to pH 2–3 by carefully adding conc. HCl to provide some more crystals. The crude material was several times recrystallised from 96% EtOH, 3.4 g (82%) of analytically pure white needle crystals of **1** was collected, mp > 300 °C [lit.,[16] 324–325 (decomp.)]. ^{1}H NMR ([$^2H_6$]acetone) δ: 10.1 (s, 1H), 7.45 (dd, 2H, *J* 0.9 and 0.9 Hz), 7.49 (dd, 2H, *J* 0.9 and 0.9 Hz), 7.54 (s, 1H), 7.56 (d, 2H, *J* 7.5 Hz), 7.86 (d, 2H, *J* 7.5 Hz), 2.9 (d, H_2O), 2.07 (s, [$^2H_6$]acetone). ^{13}C NMR ([$^2H_6$]DMSO) δ: 174.16, 157.66, 142.94, 140.68, 129.83, 128.35, 123.54, 120.73, 72.44. IR (KBr, ν/cm^{-1}): 3220 (m), 3150 (w), 3020 (m), 1770 (m), 1720 (vs), 1700 (vs), 1420 (m).

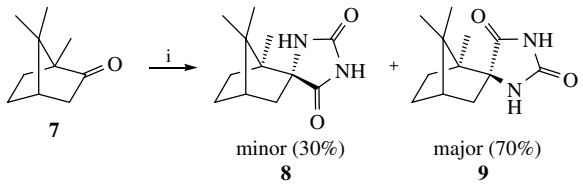


Scheme 1 *Reagents and conditions*: i, NH_2CONH_2, EtOH or $HO(CH_2)_2OH$, NaOH, H_2O, 2–24 h, reflux; ii, KCN, $(NH_4)_2CO_3$, EtOH/H_2O, 50–65 °C, 48 h, reflux; iii, KCN, $(NH_4)_2CO_3$, EtOH/H_2O, 50–65 °C, 12 h, reflux.

e.g., refluxing for 12–48 h and changing the solvent system such as DMF/H_2O and dioxane/H_2O failed. In the other effort the reaction of phenanthrene-9,10-dione **4** with KCN, $(NH_4)_2CO_3$ in EtOH/H_2O after 12 h reflux led to the synthesis of 1-*H*-1,3-diazatriphenylene-2,4-dione **6** (Scheme 1).‡

This efficient and versatile reagent was used for the synthesis of diastereoselective chiral 5,5-spirohydantoins **9** and **8** related to 1,7,7-trimethylbicyclo[2,2,1]heptan-2-one [(+)-camphor] **7** (Scheme 2).§ Herein we report on a synthesis entry to new spirohydantoins by employing KCN and $(NH_4)_2CO_3$ in the EtOH/H_2O solvent system on (+)-camphor. The mixture of diastereoisomers **9** and **8** was obtained in 40% yield. The ratio of **9** to **8** was ~7:3. This is best ascertained by monitoring the total integral for two characteristic methyl signals for each isomer. Thus, the ratio of the combined integral for the peaks at $\delta = 0.99$ and 0.8 for **9** to the combined integral for the peaks at $\delta = 0.85$ and 0.79 for **8** was 7 to 3 by ^{1}H NMR. The ^{13}C NMR spectrum of the recrystallised compound in [$^2H_6$]DMSO showed 24 peaks, mp 260–265 °C (decomp.), $[\alpha]_D^{20} = +166.6°$ (*c* 1.012, DMSO).

Examination of the MINDO/3 model of **8** and **9** indicated more interactions for **8** in contrast to **9**.[15] These interactions are predominantly accounted for the steric hindrance of the carbonyl group C(11)–O(18) in the presence of hydrogen attached to C(8) (Figure 1). A comparable type of steric hindrance is characteristic of unsuccessful application of this reagent when applied to the premade thermochromic dianthraquinone compound, which could act as an intelligent material. Since there will inevitably be a very negative entropy of activation due to the loss of translational freedom in preparation of corresponding mono and dihydantoin **15** compounds (Figure 2).



Scheme 2 *Reagents and conditions*: i, KCN, $(NH_4)_2CO_3$, EtOH/H_2O, 50–65 °C, 24 h, reflux.

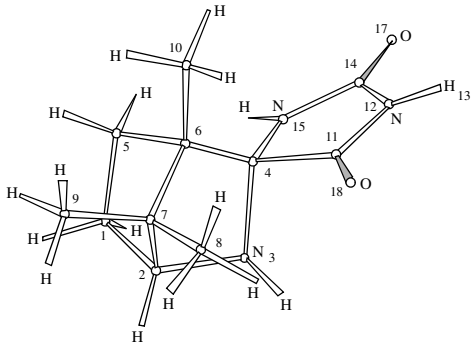


Figure 1 MINDO/3 model of **8** [shows steric hindrance of the carbonyl group C(11)–O(18) in the presence of hydrogens attached to C(8)].

In contrast to the dianthraquinone, 6-methoxy-3,4-dihydro-2*H*-naphthalene-1-one **10** with KCN, $(NH_4)_2CO_3$ in the EtOH/H_2O solvent system led to the formation of racemic **11** (Scheme 3).¶

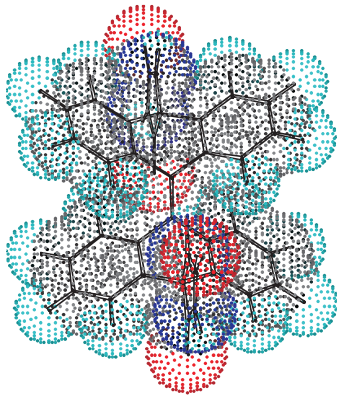


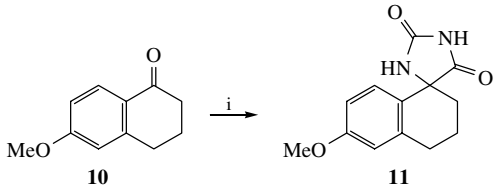
Figure 2 Dot surface model for thermochromic dianthraquinone **15** [points to an extremely negative entropy of activation (CS Chem 3D 5.0)].

‡ *Synthesis of 1H-1,3-diazatriphenylene-2,4-dione* **6**. A comparable procedure as used for **1** was applied, but the reaction mixture was refluxed for 12 h. The crude material was purified by preprative TLC and several times recrystallised from 96% EtOH; 1.7 g (57%) of pure spangle crystals of **6** were collected; mp 188 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 12.31 (s, 1H), 11.56 (s, 1H), 8.65 (t, 2H, *J* 9.07 Hz), 7.98 (d, 1H, *J* 7.84 Hz), 7.86 (d, 1H, *J* 7.86 Hz), 7.65 (d, 1H, *J* 7.27 Hz), 7.62 (d, 1H, *J* 7.66), 7.57 (t, 1H, *J* 7.38), 7.52 (t, 1H, *J* 7.34 Hz), 3.4 (H_2O), 2.4 (DMSO). ^{13}C NMR ([$^2H_6$]DMSO) δ: 155.09, 134.40, 127.57, 127.32, 127.07, 126.29, 125.83, 125.12, 123.83, 123.89, 122.05, 121.44, 119.73, 119.45, 119.00. IR (KBr, ν/cm^{-1}): 3270 (m), 3450 (w), 3150 (m), 3080 (m), 1750 (s), 1715 (s), 1610 (m).

§ *Synthesis of hydantoins* **8** *and* **9** *from 1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one [(+)-camphor].* The crude material was several times recrystallised from 96% EtOH; 1.3 g (40%) of pure white needle crystals of **8** and **9** were collected; mp 260–265 °C (decomp.), $[\alpha]_D^{20} = +166.6°$ (*c* 1.012, DMSO). The ratio of **8** to **9** was ~3:7. IR (KBr, ν/cm^{-1}): 3200 (m), 3050 (w), 2975 (m), 2925 (m), 1760 (s), 1710 (vs), 1400 (m).

For **8**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 10.74 (s, 1H), 8.13 (s, 1H), 2.05 (s, 1H), 1.81 (d, 1H, *J* 2.5 Hz), 1.79 (d, 2H, *J* 5 Hz), 1.66 (d, 2H, *J* 5 Hz), 1.55 (d, 1H, *J* 5 Hz), 0.85 (s, 6H), 0.79 (s, 3H). ^{13}C NMR ([$^2H_6$]DMSO) δ: 179.18, 157.15, 58.68, 52.50, 46.76, 45.06, 40.41, 37.18, 36.36, 31.50, 25.95, 15.55.

For **9**: ^{1}H NMR ([$^2H_6$]DMSO) δ: 10.74 (s, 1H), 8.0 (s, 1H), 2.07 (s, 1H), 1.815 (d, 1H, *J* 2.5 Hz), 1.76 (d, 2H, *J* 5 Hz), 1.72 (dd, 2H), 1.57 (d, 1H, *J* 5 Hz), 0.85 (s, 6H), 0.79 (s, 3H). ^{13}C NMR ([$^2H_6$]DMSO) δ: 179.44, 156.72, 56,78, 54.76, 48.49, 35.05, 26.50, 25.95, 25.01, 15.45, two peaks are combined with DMSO signals.



10 **11**

Scheme 3 *Reagents and conditions*: i, KCN, $(NH_4)_2CO_3$, EtOH/H_2O, 80 °C, 24 h, reflux.

This study was supported in part by the Research Committee of Guilan University.

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¶ *Synthesis of hydantoin* **11** *from 6-methoxy-1,2,3,4-tetrahydronaphthalene* **10**. A similar procedure as used for **1** was applied, but the reaction mixture was refluxed for 72 h. The crude material was purified by preparative TLC and several times recrystallised from 96% EtOH to give 0.6 g (33%) of pure white needle crystals of **11**; mp 210 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 10.74 (s, 1H), 8.43 (s, 1H), 6.95 (d, 1H, *J* 8.56 Hz), 6.77 (d, 1H, *J* 8.61 Hz), 6.69 (s, 1H), 2.06 (d, 1H, *J* 10.01 Hz), 1.80 (dd, 1H, *J* 9.1 Hz), 1.72 (s, 1H), 1.66 (dd, 2H, *J* 9.7 and 14.5 Hz), 3.7 (s, 3H), 2.71 (t, 2H, *J* 6.1 Hz), 2.02 (p, 2H, *J* 9.72, 7.06 and 4.06 Hz), 1.86 (t, 1H, *J* 11.38, 9.4 and 2.67 Hz), 1.77 (p, 1H, *J* 7.19, 6.96, 3.36 and 2.72 Hz), 3.3 (H_2O), 2.4 (DMSO). ^{13}C NMR ([$^2H_6$]DMSO) δ: 174.53, 161.2, 139.62, 138.76, 132.9, 128.64, 111.12, 66.22, 56.13, 31.41, 26.32. IR (KBr, ν/cm^{-1}): 3270 (m), 3150 (s), 3050 (w), 2920 (m), 2850 (w), 1770 (m), 1715 (s), 1700 (s), 1600 (m), 1420 (m).

Received: 16th August 2004; Com. 04/2339