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Conversion of a Thiohydantoin to the Corresponding Hydantoin via a Ring-Opening / Ring Closure Mechanism.

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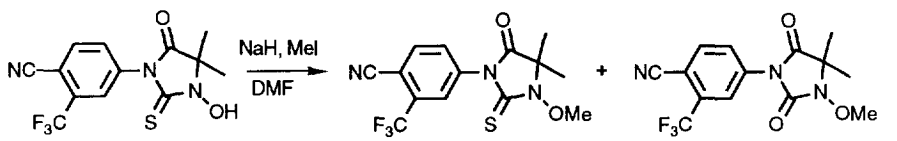
Abstract *: The treatment of activated N, N' disubstituted arylthiohydantoins with methyl or ethyl iodide and sodium methoxide in DMF at room temperature affords the corresponding hydantoins in good yield. The mechanism involves an unusual ring opening-ring closure sequence which can be exploited for a novel (thio) hydantoin to (thio) urea rearrangement.*

In the course of a programme aimed at the design of novel non-steroidal androgen receptor ligands[1,2], we came across an unexpected thiohydantoin to hydantoin conversion which may be of quite general utility : Attempts to methylate N-hydroxy thiohydantoin **1** with methyl iodide in DMF and sodium hydride as a base, yielded the expected N-methoxy derivative **2** (63%) along with a minor amount (12%) of the corresponding hydantoin **3**[3].



1 **2** **3**

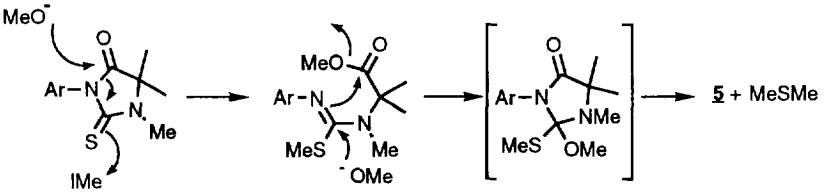
Attempts to extend these conditions to the general transformation of thiohydantoins to hydantoins (i.e. **4a** => **5a**) and investigations on the reaction conditions showed that, quite intriguingly, sodium hydride seemed indispensable. In its absence, starting material remained untransformed, even when powerful alkylating agents, like triethyloxonium tetrafluoroborate were used. It was finally found that methoxide must have been present in the reaction medium (via NaOH from partially hydrolyzed NaH and MeI). Indeed, addition of

MeONa (3 mmol) to a solution of thiohydantoin **4a**[1] (1 mmol) and MeI (4.8 mmol) in DMF (3 ml) at room temperature (slightly exothermic reaction), led cleanly and instantaneously to the hydantoin **5a** (90% isolated crystalline material).

4 a : R_1= CN, R_2= CF_3 b : R_1= R_2 = Cl c : R_1= OMe, R_2= H **5**

Ethyl iodide can advantageously replace methyl iodide (95% yield). Under similar conditions, compounds **4b** and **4c**[4] were transformed to **5b** and **5c** in 59% and 5% yield respectively, suggesting that electron-withdrawing substituents (EWG's) on the aromatic ring influence the reaction favorably, while electron-donating groups have a deleterious effect.

As methyl or ethyl iodide alone did not react with **4**, a mechanism involving opening and reclosure of the five-membered ring was postulated (Scheme) :



6 **7**

The observed substituent effect tends to support this hypothesis insofar EWG's on the aromatic ring will increase the electrophilic character of the carbonyl.

The tetrahedral intermediate **7** is similar to the one proposed by Fujisaki et al. in their synthesis of unsymmetrical sulfides from tetramethylthiourea, alkyl halides and alcohols in the presence of sodium hydride[5]. That ring opening is effectively occuring was demonstrated by reacting MeONa (0.42 mmol) with the functionnalized (thio)hydantoins **8** and **9**[6] (0.36 mmol) in DMF (1.5 ml) at r.t. for 30 minutes. The reaction afforded the rearranged compounds **10** and **11** in 74 and 77% isolated yields, respectively. Incidentally, this rearrangement constitutes a convenient access to novel, functionalized cyclic ureas and thioureas exemplified by compounds **11** & **10**.

8 X = S

9 X = O

10 X = S

11 X = O

Compound **10** remained untransformed in the presence of sodium methoxide and methyl iodide, confirming that S-methylation of the thiourea system in the arylthiohydantoins, is possible only after ring opening. Although the conversion described above is restricted to sufficiently activated N,N'-disubstituted thiohydantoins[7], the simplicity of reaction conditions make it a useful addition to the more general methods of thiocarbonyl to carbonyl transformations[8-14]. Thus, MnO_2 oxidation[8] and the trifluoroacetic anhydride method[9] were ineffective in transforming **4a** to **5a**. The cuprous chloride / sodium hydroxide system[10] gave only trace amounts of **5a**, whereas copper nitrate[11] or nitrosium tetrafluoroborate[12] led to poor isolated yields of the hydantoin (30 and 35% respectively), despite the complete consumption of the starting material. At last, the telluroxide method[13] (2 equivalents at room temp. for one week) led to 57% yield of **5a** from **4a** and 38% of **5c** from **4c.**

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4. Compounds **4b** and **4c** were prepared respectively from 3,4 dichloroaniline and 4 methoxyaniline according to the procedure described in ref.1.
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6. Compounds **8** and **9** were prepared from the corresponding alcohols (French Patent 2 715 402) by treatment with carbon tetrabromide-triphenylphosphine in methylene chloride, according to Weiss, R.G.; Snyder, E.I. *J. Org. Chem.* **1971**, *36*, 403-406.

7. Carbonyl stretching frequency may provide an approximate ranking of decreasing electrophilic potency : for **4a**, **4b** and **4c** it is respectively 1760, 1753 and 1749 cm^{-1}.

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Physical data for key compounds (Unless stated otherwise : IR in $CHCl_3$, ν in cm^{-1} ; ^{1}H-NMR in $CDCl_3$, 250 MHz, δ in ppm) : **4b** : m.p. 128-129°C ; IR : 1753 (carbonyl), 1595, 1570, 1496 (aromatics) ; ^{1}H-NMR : 1.54 (s, 6H, 4-diMe), 3.30 (s, 3H, NMe), 7.22 (dd, J=2.5 & 8.5, 1H, H-6'), 7.47 (d, J=2.5, 1H, H-2'), 7.56 (d, J=8.5, 1H, H-5') ; **4c** : m.p. 159-160°C ; IR : 1749 (carbonyl), 1612, 1591, 1515, 1497 (aromatics) ; ^{1}H-NMR : 1.54 (s, 6H, 4-diMe), 3.31 (s, 3H, NMe), 3.84 (s, 3H, OMe), 6.99 (AB, 2H, H-3'& H-5'), 7.22 (AB, 2H, H-2'& H-6') ; **5a** m.p. 157-158°C ; IR : 2238 (CN), 1780, 1727 (carbonyls), 1615,1574, 1505 (aromatics) ; ^{1}H-NMR : 1.53 (s, 6H, 4-diMe), 3.00 (s, 3H, NMe), 7.92 (d, J=8.5, 1H,5'-H), 7.99 (dd, J=8.5&2,1H, 6'-H), 8.14 (d, J=2, 1H, 2'-H) ; **5b** : m.p. 117-118°C ; IR : 1778, 1728 (carbonyls), 1596, 1570, 1480 (aromatics) ; ^{1}H-NMR ($CDCl_3$, 60 MHz) : 1.45 (s, 6H, 4-diMe), 2.93 (s, 3H, NMe), 7.33 (m, 2H, 5'-H & 6'-H), 7.58 (bs, 1H, 2'-H) ; **5c** : m.p. 93-94°C ; IR : 1772, 1713, 1687 (carbonyls), 1610, 1590, 1515 (aromatics) ; ^{1}H-NMR : 1.49 (s, 6H, 4-diMe), 2.97 (s, 3H, NMe), 3.82 (s, 3H, OMe), 6.96 (AA'BB', 2H, 3'-H & 5'-H), 7.30 (AA'BB', 2H, 2'-H & 6'-H) ; **8** : m.p. 142-143°C ; IR : 2237 (CN), 1761 (carbonyl), 1615, 1580, 1504, 1491 (aromatics) ; ^{1}H-NMR : 1.69 (s, 3H, 4-Me), 3.33 (s, 3H, NMe), 3.60 & 3.85 (2d's, J=11.5, 2H, 4-CH_2Br), 7.77 (dd, J= 2 & 8, 1H, 6'-H), 7.87 (d, J=2, 1H, 2'-H), 7.91 (d, J=8, 1H, 5'-H) ; **9** : m.p. 141-142°C ; IR : 2235 (CN), 1785, 1732 (carbonyls), 1616, 1582, 1505 (aromatics) ; ^{1}H-NMR : 1.65 (s, 3H, 4-Me), 3.02 (s, 3H, NMe), 3.54 (d, J=11.5, 1H, CH_2Br), 3.82 (d, J=11.5, 1H, 4-CH_2Br), 7.95 (m, 2H, H-5'& H-6'), 8.09 (bs, 1H, H-2') ; **10** : m.p. 135-136°C, IR : 2233 (CN), 1742 (ester), 1613,1571,1507 (aromatics) ; ^{1}H-NMR : 1.72 (s, 3H, 4-Me), 3.26 (s, 3H, NMe), 3.82 (s, 3H, OMe), 3.94 & 4.39 (2d, J=10, 2H, H-5), 7.81 (d, J=8.5, 1H, H-5'), 8.11 (dd, J=8.5&2, 1H, H-6'), 8.18 (d, J=2, 1H, H-2') ; **11**: m.p. 119-120°C ; IR : 2231 (CN), 1742, 1723 (carbonyls), 1616, 1565, 1508 (aromatic) ; ^{1}H-NMR : 1.67 (s, 3H, 4-Me), 2.94 (s, 3H, NMe), 3.81 (s, 3H, OMe), 3.65 & 4.17 (2d, J=9.5, 2H, 5-CH_2), 7.75 (d, J=8.5, 1H, 5'-H), 7.85 (dd, J=8.5 & 2, 1H, 6'-H), 7.98 (d, J=2, 1H, 2'-H).

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