Preparation of Spiro Hydroxy *S*-Methylisothioureas from Cyclic Ketones

Indrawan J. McAlpine and Robert W. Armstrong*

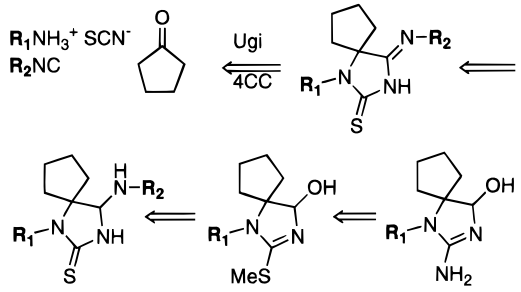
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

Received April 9, 1996

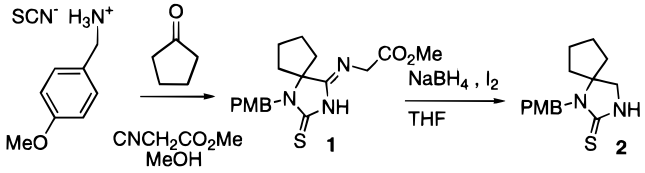
α-Hydroxyguanidines appear as a functionality in a number of natural products such as tetrodotoxin[1] and crambine B.[2] We were interested in synthesizing a blocked version of the spirohydroxyguanidinium portion of the natural products styloguanidine[3] and palau'amine.[4] A methodology was sought which would allow for the generation of this moiety starting from a ketone precursor under sufficiently mild conditions to be compatible with a multifunctional natural product intermediate. Ugi has reported the four-component condensation of a ketone, the thiocyanate salt of an amine, and an isocyanide to create 2-thiohydantoin 4-imines.[5] The ease of making 2-thiohydantoin 4-imines via an Ugi condensation and the fact that they are a single oxidation state away from hydroxyguanidines makes them attractive precursors for spirohydroxyguanidines.[6,7] Appropriate choice of amine such as *p*-methoxybenzylamine leads to an attractive protecting group on the 2-thiohydantoin 4-imine and consequently, also on the spirohydroxyguanidine. This overall concept is represented in Scheme 1.

The main issue in developing this methodology is converting the oxidation state of 2-thiohydantoin 4-imines to that of α-hydroxyguanidines. A masked version of α-hydroxyguanidines could be obtained if suitable conditions could be found for the reduction of 2-thiohydantoin 4-imines to the corresponding α-aminothiourea as represented by the second transformation in Scheme 1. Meyers has shown many examples of hydride reduction of oxazolines to carbinols using activators such as methyl triflate and iodine.[8,9] An example of the types of functionality amenable to these conditions includes a Boc-protected 1,3-imidazolidin-4-one which is reduced to the corresponding Boc-protected 1,3-imidazolidine.[10] We felt that this presented an opportunity to probe suitable reducing conditions. Here we report the synthesis of spiro hydroxy *S*-methylisothioureas using an Ugi four-component condensation followed by the reduction of the resultant spiro-2-thiohydantoin 4-imines using sodium cyanoborohydride and iodine as an activator of the amidine carbon.

Scheme 1



Scheme 2



To address the accessibility of this masked spirohydroxyguanidine, the spiro-2-thiohydantoin 4-imine **1** was prepared in 37% yield by adding methyl isocyanoacetate to a solution of cyclopentanone and the thiocyanate salt of *p*-methoxybenzylamine in methanol (Scheme 2). The thiocyanate salt is formed by heating the hydrochloride salt of the amine with potassium thiocyanate in methanol. Subjecting 2-thiohydantoin 4-imine **1** to standard hydride reductions using lithium aluminum hydride or sodium borohydride resulted only in the reduction of the methyl ester. By using conditions described by Meyers,[10] treatment of 2-thiohydantoin 4-imine **1** with sodium borohydride followed by activation with iodine resulted in the formation of the overreduced cyclic thiourea **2** in quantitative yield (Scheme 2). Attempts at effecting the single reduction to the aminal by using the less reactive sodium cyanoborohydride or running the reaction at a lower temperature resulted either in overreduction to the cyclic thiourea **2** or no reaction at all.

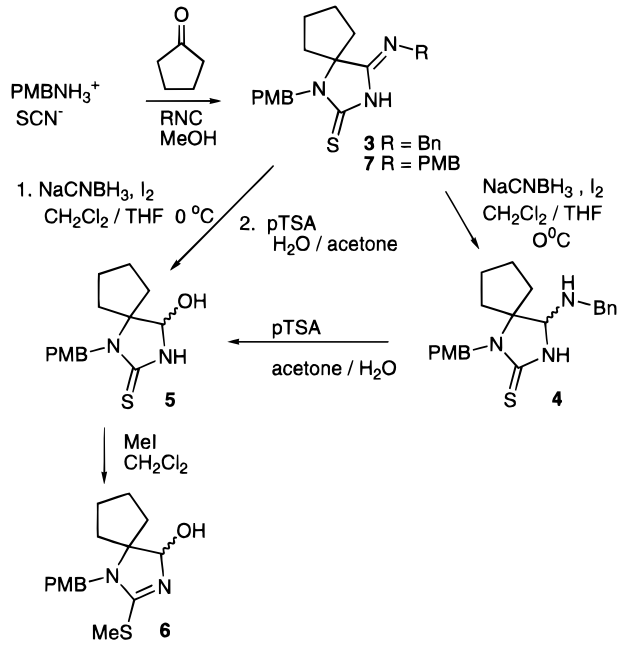
The mechanism of reduction might proceed via the association of iodide with the amidine nitrogen and resultant reduction of the amidine carbon yielding the α-amino thiourea. Assistance from the thiourea nitrogen may also result in elimination and subsequent reduction to the thiourea due to the lability of the glycylamino group. Therefore, using an electron-rich isocyanide in the 2-thiohydantoin 4-imine formation should lead to a more robust amino group which might in turn result in an aminal stable to further reduction. With this in mind, 2-thiohydantoin 4-imine **3** was prepared in 65% yield via an Ugi condensation using benzyl isocyanide in place of methyl isocyanoacetate (Scheme 3). Reduction with sodium cyanoborohydride and iodine in methylene chloride and tetrahydrofuran at 0 °C for 20 min was successful in giving a 40% yield of the desired α-benzylamino thiourea **4** (48% yield based on recovered thiohydantoin **3**) after chromatography. Prolonged exposure to the reduction conditions resulted in overreduction to the cyclic thiourea **2**. Conversion to the α-hydroxy thiourea **5** was accomplished in 68% yield by dissolving **4** in an acetone/water mixture with a catalytic amount of *p*-toluenesulfonic acid.[11]

(1) Goto, T.; Kishi, Y.; Takahashi, S.; Hirata, Y. *Tetrahedron Lett.* **1963**, *4*, 2105, 2115.
(2) Berlink, R. G. S.; Braekman, J. C.; Daloze, D.; Hallenga, K.; Ottinger, R.; Bruno, I.; Ricco, R. *Tetrahedron Lett.* **1990**, *31*, 6531.
(3) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133.
(4) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376.
(5) Interestingly, Ugi points out that 2-thiohydantoin 4-imines are formed in high yield only from ketones and not from aldehydes, whereas, hydantoin 4-imines are formed from aldehydes but not very well from ketones (see ref 6).
(6) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971; Vol. 20, pp 145−155.
(7) Ugi, I.; Rosendahl, F. R.; Bodesheim, F. *Justus Liebigs Ann. Chem.* **1963**, *666*, 54.
(8) Meyers, A. I.; Shimano, M. *Tetrahedron Lett.* **1993**, *34*, 4893.
(9) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607.
(10) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.

(11) The hydroxythiourea **5** is somewhat unstable and rearranges upon standing, presumably to the 4-hydroxy-2-imino-3,1-thiazaspiro-[4]nonane.

S0022-3263(96)00657-3 CCC: $12.00

Scheme 3



In an attempt to optimize the yield of the reduction, 2-thiohydantoin 4-imine **7** was prepared in 73% yield using *p*-methoxybenzyl isocyanide. Reduction conditions were identical to that used for 2-thiohydantoin 4-imine **3** except the reaction was allowed to proceed for 1 h. Isolation of the corresponding α-(*p*-methoxybenzyl)amino thiourea was difficult as chromatography usually resulted in partial conversion to the α-hydroxy thiourea. Therefore, the crude material from the reduction of **7** was treated with catalytic *p*-toluenesulfonic acid in acetone and water to yield 48% of the α-hydroxy thiourea **5** on the basis of the two-step conversion (61% based on recovered starting 2-thiohydantoin 4-imine **7**). Treatment of **5** with iodomethane followed by basic workup gave the desired α-hydroxy *S*-methylisothiourea **6** in quantitative yield.

In conclusion, we have developed a mild synthetic route for building spiro α-hydroxy *S*-methylisothioureas from cyclic ketones via a 2-thiohydantoin 4-imine. We have shown that the reduction of 2-thiohydantoin 4-imine can be controlled by the appropriate choice of nitrogen substituent. The mild conditions of this procedure should be useful for the synthesis of spiroguanidines in the presence of additional functional groups.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained at room temperature. ^{1}H NMR chemical shifts are referenced to $CDCl_3$ (7.26 ppm), and those for ^{13}CMR to $CDCl_3$ (77.0 ppm). High-resolution mass spectroscopy (HRMS) was performed at UCLA. For EI, CI, and FAB methods, $2\sigma = 4$ ppm.

All water-sensitive reactions were conducted in oven- or flame-dried glassware under a nitrogen atmosphere. Solvents were distilled immediately prior to use: CH_2Cl_2 from P_2O_5, MeOH from magnesium metal, and THF from sodium benzophenone ketyl. Most commercially available reagents were distilled before use including methyl isocyanoacetate and cyclopentanone. Benzyl isocyanide and 4-methoxybenzyl isocyanide were prepared by standard methods described in ref 6. Thin-layer chromatography (TLC) was performed on silica gel-coated plates (0.25 mm thickness for analytical and preparative TLC) and visualized by UV light and/or *p*-anisaldehyde or ninhydrin staining. After all aqueous extractions of crude reaction products, the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* before further treatment.

General Procedure for Spiro 2-thiohydantoin 4-imine Formation. To a solution of the 4-methoxybenzylamine hydrochloride (100 mg, 0.575 mmol) in methanol (3 mL) was added potassium thiocyanate (55 mg, 0.570 mmol), and the mixture was heated to 60 °C for 1 h. The reaction mixture was passed over a cotton plug to remove the KCl. To the filtrate was then added distilled cyclopentanone (50 μL, 0.570 mmol) followed by isocyanide (1.1 equivalent) and the reaction was allowed to stir at room temperature for 18 h. The methanol was removed *in vacuo*, and the remaining residue was subjected to chromatography using a gradient of hexane and ethyl acetate.

1-(4-Methoxybenzyl)-4-(methylacetoimino)-1,3-diazaspiro[4.4]nonane-2-thione (1). Chromatography afforded **1** in 37% yield as a white powder: mp 187−188 °C; IR (KBr pellet) 3233, 2957, 1749, 1611, 1516, 1235 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.25 (d, J = 9.0 Hz, 2H), 6.8 (d, J = 9.0 Hz, 2H), 6.5 (bs, 1H), 4.9 (s, 2H), 4.3 (bs, 2H), 3.7 (s, 3H), 3.7 (s, 3H), 1.9 (m, 4H), 1.8 (m, 4H); ^{13}C NMR (101 MHz) δ 194.9, 182.2, 169.8, 158.8, 129.5, 128.4, 113.8, 77.7, 55.2, 52.6, 46.4, 43.7, 36.1 26.5; HRFAB calcd for $C_{18}H_{23}N_3O_3S$ [(M + H)$^+$] 362.1532, found 362.1538.

1-(4-Methoxybenzyl)-4-(benzylimino)-1,3-diazaspiro[4.4]-nonane-2-thione (3). Chromatography afforded **3** in 65% yield as a white powder: mp 227−229 °C; IR (KBr pellet) 3253, 2957, 1611, 1515, 1244 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.3 (m, 7H), 6.8 (d, J = 9.0 Hz, 2H), 4.9 (s, 2H), 4.7 (s, 2H), 3.8 (s, 3H), 1.9 (m, 4H), 1.7 (m, 4H); ^{13}C NMR (101 MHz) δ 158.9, 137.0, 129.7, 128.9, 128.5, 128.0, 127.9, 114.0, 77.6, 55.3, 47.4, 46.6, 36.8, 26.6; HRFAB calcd for $C_{22}H_{25}N_3OS$ [(M + H)$^+$] 380.1810, found 380.1797.

1-(4-Methoxybenzyl)-4-[(4-methoxybenzyl)imino]-1,3-diazaspiro[4.4]nonane-2-thione (4). Chromatography afforded **4** in 73% yield as a white powder. mp 211−214 °C; IR (KBr pellet) 3247, 2955, 1613, 1514, 1245, 1179 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.3 (d, J = 9.0 Hz, 2H), 7.2 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 5.6 (bs, 1H), 5.0 (s, 1H), 4.6 (d, J = 5.0 Hz, 1H), 3.8 (s, 3H), 1.90−1.95 (m, 2H), 1.75−1.80 (m, 4H), 1.63−1.68 (m, 2H); ^{13}C NMR (101 MHz) δ 195.3, 182.0, 159.4, 158.9, 129.8, 129.5, 128.9, 128.5, 114.3, 113.9, 77.5, 55.3, 55.2, 46.5, 36.5, 26.7; HRFAB calcd for $C_{23}H_{27}N_3O_2S$ [(M + H)$^+$] 410.1892, found 410.1902.

1-(4-Methoxybenzyl)-1,3-diazaspiro[4.4]nonane-2-thione (2). To a solution of **1** (19 mg, 0.052 mmol) in THF (2 mL) was added an excess of $NaBH_4$ which was stirred for 30 min. To this mixture was added dropwise a solution of iodine (15 mg, 0.059 mmol) in THF (0.5 mL) and the reaction was allowed to stir for 10 h. The reaction mixture was quenched with 1 N HCl and then poured into saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phase was dried and evaporated to give **2** (15 mg) as a yellow solid in quantitative yield: mp 148−151 °C; IR (KBr pellet) 3219, 2954, 1613, 1513, 1453, 1245 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.3 (d, J = 9.0 Hz, 2H), 6.8 (d, J = 9.0 Hz, 2H), 4.7 (s, 2H), 3.8 (s, 3H), 3.4 (s, 2H), 1.65−1.75 (m, 4H), 1.5−1.6 (m, 4H); ^{13}C NMR (101 MHz) δ 183.2, 158.6, 130.6, 128.1, 113.7, 73.8, 56.1, 55.1, 45.5, 34.7, 22.7; HRFAB calcd for $C_{15}H_{20}N_2OS$ [(M + H)$^+$] 277.1369, found 277.1375.

1-(4-Methoxybenzyl)-4-(benzylamino)-1,3-diazaspiro[4.4]-nonane-2-thione (5). To a solution of **3** (30 mg, 0.079 mmol) in CH_2Cl_2 (2 mL) was added an excess of $NaCNBH_3$, and the reaction was left to stir for 10 min. The reaction mixture was cooled to 0 °C and a solution of iodine (20 mg, 0.079 mmol) in THF (1 mL) was added dropwise. After 20 min at 0 °C, the reaction was quenched with 1 N HCl solution and then poured into saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic phase was dried and evaporated. The crude residue was subjected to preparative TLC using 1:1 hexanes/ethyl acetate and gave **5** (12 mg) as a yellow oil in 40% yield and **3** (5 mg) in 13% yield: IR (neat) 3215, 2960, 1729, 1612, 1514, 1455, 1249 cm^{-1}; ^{1}H NMR (360 MHz) δ 7.3 (m, 7H), 6.8 (d, J = 9.0 Hz, 2H), 5.0 (d, J = 16.0 Hz, 1H), 4.5 (d, J = 16.0 Hz, 1H), 4.1 (s, 1H), 3.9 (d, J = 13.0 Hz, 1H), 3.8 (d, J = 13.0 Hz, 1H), 3.8 (s, 3H), 2.0 (m, 1H), 1.5−1.7 (m, 7H); ^{13}C NMR (101 MHz) δ 181.7, 158.7, 139.3, 130.6, 128.5, 128.3, 128.0, 127.3, 113.9, 76.3, 76.0, 55.2,

49.5, 45.9, 34.9, 28.3, 23.8, 22.6; HRFAB calcd for $C_{22}H_{27}N_3OS$ [$(M + H)^+$] 382.1961, found 382.1953.

4-Hydroxy-1-(4-methoxybenzyl)-1,3-diazaspiro[4.4]-nonane-2-thione (6) from 5. To a solution of **5** (12 mg, 0.031 mmol) in acetone (1 mL) and water (1 mL) was added *p*-TSA (5 mg, 0.026 mmol). After 10 h of stirring, the reaction mixture was poured into a saturated $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried and evaporated. The crude residue was subjected to preparative TLC using ethyl acetate and gave **6** (6 mg) as a yellow oil in 68% yield: IR (KBr pellet) 3323, 3205, 2970, 2460, 2401, 1619, 1514, 1465 cm^{-1}; ^1H NMR (360 MHz) δ 7.3 (d, J = 9.0 Hz, 2H), 7.0 (s, 1H), 6.8 (d, J = 9.0 Hz, 2H), 5.0 (d, J = 16.0 Hz, 1H), 4.8 (s, 1H), 4.6 (d, J = 16.0 Hz, 1H), 3.8 (s, 3H), 2.0 (m, 1H), 1.5−1.7 (m, 7H); ^{13}C NMR (101 MHz) δ 181.5, 158.7, 130.0, 128.1, 113.8, 84.2, 55.2, 45.6, 33.2, 27.5, 23.4, 22.4; HREI calcd for $C_{15}H_{20}N_2O_2S$ [$(M + H)^+$] 292.1246, found 292.1241.

4-Hydroxy-1-(4-methoxybenzyl)-1,3-diazaspiro[4.4]-nonane-2-thione (6) from 4. To a solution of **4** (27 mg, 0.067 mmol) in CH_2Cl_2 (2 mL) was added iodine (18 mg, 0.071 mmol), and the reaction mixture was then cooled to 0 °C. After 15 min, an excess of $NaCNBH_3$ was added, and the reaction mixture was stirred for 1 h. The mixture was then quenched with 1 N HCl solution and poured into a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL), and the combined organic phase dried and evaporated. The crude residue was passed over a silicia gel plug using ethyl acetate, and the resulting solution was evaporated. The residue was dissolved in acetone (2 mL) and water (1 mL), and *p*-TSA (5 mg, 0.026 mmol) was added. The reaction mixture was stirred for 6 h at rt and then was poured into a saturated $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phase was dried and evaporated. The residue was subjected to preparative TLC to give **6** (9 mg, 0.033 mmol) as a yellow oil in 48% yield. The spectral data matched that of the previous procedure.

4-Hydroxy-2-(methylthio)-1-(4-methoxybenzyl)-1,3-diazaspiro[4.4]non-2-ene (7). To a solution of **6** (6 mg, 0.022 mmol) in CH_2Cl_2 (2 mL) was added excess MeI (10 μL, 0.161 mmol). The reaction mixture stirred for 14 h at rt after which the solution was poured into saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic phase was dried and evaporated to give **7** (7 mg) as a yellow oil in quantitative yield: IR (neat) 3176, 2960, 1729, 1612, 1249, 1033 cm^{-1}; ^1H NMR (360 MHz) δ 7.2 (d, J = 9.0 Hz, 2H), 6.9 (d, J = 9.0 Hz, 2H), 5.1 (s, 1H), 4.3 (s, 2H), 3.8 (s, 3H), 2.5 (s, 3H), 2.3 (m, 1H), 1.5−1.7 (m, 7H); ^{13}C NMR (101 MHz) δ 167.0, 158.7, 130.6, 127.7, 113.9, 93.8, 55.2, 44.7, 34.5, 29.7, 27.0, 23.6, 22.5, 13.9; HREI calcd for $C_{16}H_{22}N_2O_2S$ [$(M + H)^+$] 306.1402, found 306.1402.

Acknowledgment. This work was made possible by financial support from UCLA and NIH grant GM51095. I.J.M. was supported on an NSF Fellowship.

Supporting Information Available: ^1H NMR and ^{13}C NMR data for reported compounds (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO960657W