Structure Determination of *N*-Methyl-tetrahydro-5*H*-indazol-5-ones

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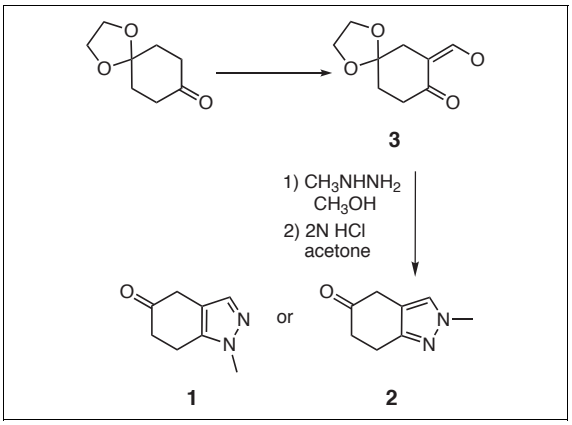

This paper communicates the (regio) synthesis and a convenient NMR structural assignment method for *N*-methyl-tetrahydro-*5H*-indazol-5-one isomers. The cyclization reaction of 7-(hydroxymethylene)-1,4-dioxaspiro[4,5]decan-8-one (**3**) with methylhydrazine yields, after de-protection predominately the N-2 methyl isomer **2**. Analysis of the product ratio and structural assignments are based on NMR data including NOE difference experiments and subsequently confirmed with X-ray crystallography. These findings are in sharp contrast with the literature. The experimental conditions used to optimize the synthesis of the individual isomers are discussed.

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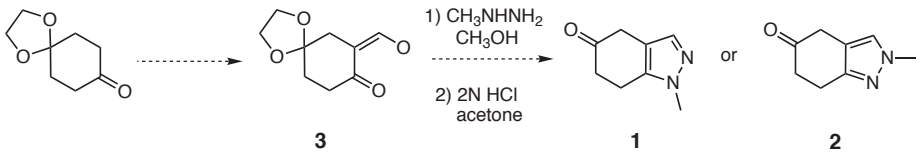
N-Alkyl-tetrahydroindazoles have long been of interest to synthetic organic chemists since first described by von Auwers [1]. Compounds comprised of these structures have been used throughout industry in many applications, ranging from anti-oxidants in rubber products [2], to intestinal bile acid transporters [3], to inhibitors of blood platelet aggregation [4] and thrombin [5]. Numerous synthetic approaches to tetrahydroindazoles have been described which produce substituted pyrazole regioisomers. In this paper we describe the structural characterization of the isomers of *N*-methyl-tetrahydro-5*H*-indazol-5-one using NMR methods. The structural assignments were confirmed using X-ray crystallography.

Scheme 1



For a medicinal chemistry lead optimization program we required the synthesis of both the *N*1-methyl and *N*2-methyl-tetrahydro-5*H*-indazol-5-ones. We initiated the general synthesis to the presumed N1-methyl β-ketone isomer based on a literature report [6]. The synthesis utilizes the key hydroxymethylidene ketal intermediate **3**, which is synthesized from commercially available 1,4-cyclohexanedione monoethylene ketal (Scheme 1). Indazolone isomer **1** was reported as the major product after condensation of **3** with *N*-methylhydrazine in methanol (0-65 ºC) and subsequent ketal removal.

Repeating the procedure exactly did give a major isomer; in our hands we found that keeping the initial temperature at -30 ºC was optimal to give this isomer at about 9:1 over the minor isomer. It was found, as reported, that the ratio of isomeric products changes to 1:1 in methanol at reflux [6]. However, after analysis of the reaction it remained unclear as to which ketal isomer represented the major product. The mixture of ketal isomers was deprotected at 60 ºC in equal volumes of acetone and 2 *N* HCl. The resulting keto isomers **1** and **2** were separated by silica gel chromatography. The major isomer was the first to elute in a 9:1 ratio over the minor

isomer. Both compounds are slightly orange solids that appear to be light and air sensitive. The mechanism for formation of each regioisomer is consistent with methyl-hydrazine condensation with either the hydroxymethylene (aldehyde) [1] or the dimethylamino methylidene moiety of cyclohexanedione [7]. The isomeric product ratio changes depending on the conditions used. At lower temperatures, the greater nucleophilicity of the methyl bearing nitrogen of hydrazine drives the reaction. As the temperature increases, that selectivity is lost. After careful ^{1}H NMR structural analysis the two N-methyl isomers **1** and **2**, the N2-methyl isomer **2** was assigned as the major product. In a similar system of N-methyl menthopyrazoles [8], the N2 isomer is also reported as the major isomer.

The H3 proton on **1** and **2** is located at δ 7.27 and δ 7.15, respectively (Figure 1). An N2-methyl substituted tetrahydroindazole would exhibit the C3 pyrazole proton at a higher field than the corresponding N1-methyl isomer; owing to the fact that an olefinic "like" proton is more shielded than the C3-proton of an imine [9].

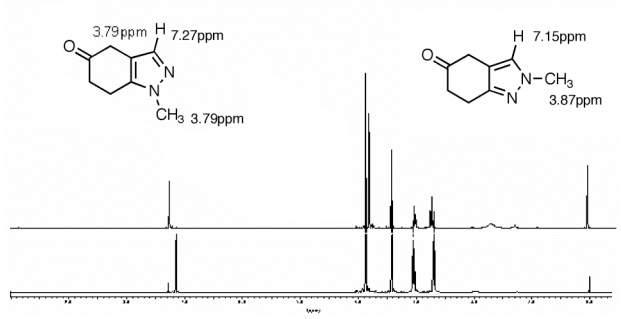


Figure 1

Further verification of these structural assignments was observed in the ^{13}C NMR spectra of **1** and **2**, where the same pattern was exhibited (Figure 2); the N1-methyl isomer has the lower field shift for the pyrazole C3-carbon (136.0 ppm) compared to the N2-methyl isomer with a C3 shift of 127.8 ppm [10]. Proton coupled ^{13}C spectra were also obtained in an attempt to find a three bond splitting pattern caused by spin lattice interactions of an N2 methyl substituent. Our results for **1** and **2** clearly show the expected doublet for the pyrazole proton (J = 184 Hz), but no fine quartets (J = 2.5 Hz) can be observed relating to the N2 methyl as described by Nagarajan [11].

The characterization of the two regioisomers can be readily made by ^{1}H and ^{13}C NMR when both compounds are available. Similar assignments have been reported using ^{15}N NMR, by directly comparing both isomers [12]. We were also interested in identifying a routine NMR technique to rapidly and accurately assign the correct indazole isomer even when only one isomer was available. A 1D NOE difference experiment on **2** resulted in a 5% enhancement at δ 7.15 when irradiating the N2-methyl at δ 3.87. This result clearly indicates that the methyl and the pyrazole C3-hydrogen are in close proximity to each other. In contrast, under the same conditions (irradiating the N1-methyl at δ 3.79) an NOE was not observed for **1**. Taken together, the NMR data described clearly supports the structural assignments made.

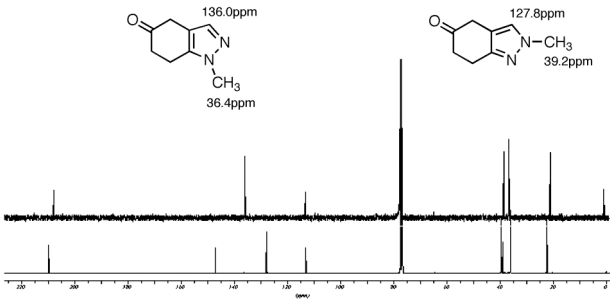
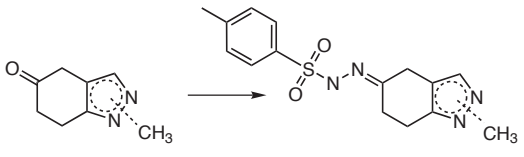


Figure 2

The structural assignments of the N-methyl-tetrahydroindazolones were further confirmed by X-ray crystallography. Suitable crystals of ketones **1** and **2** for defraction could not be obtained. Therefore, the toluenesulfonylhydrazone derivatives were prepared and crystallized (Scheme 2). The reaction of ketone isomer **2** and *p*-toluenesulfonyl hydrazide gave **7** as an off-white solid. The product was recrystallized from ethyl alcohol to produce colorless plates, which were suitable for X-ray structure determination [13]. Isomer **6** was obtained from ketone **1** in a similar fashion to give colorless blocks.

Scheme 2



The X-ray crystal structure data derived for each N-methyl-tetrahydroindazol-5-one isomer unequivocally confirms the NMR assignments of the methyl positions of the two regioisomers. Hydrazone **6** is the N1-methyl substituted product derived from isomer **1** (Figure 3), while hydrazone **7**, prepared from isomer **2**, is the N2-methyl isomer (Figure 4).

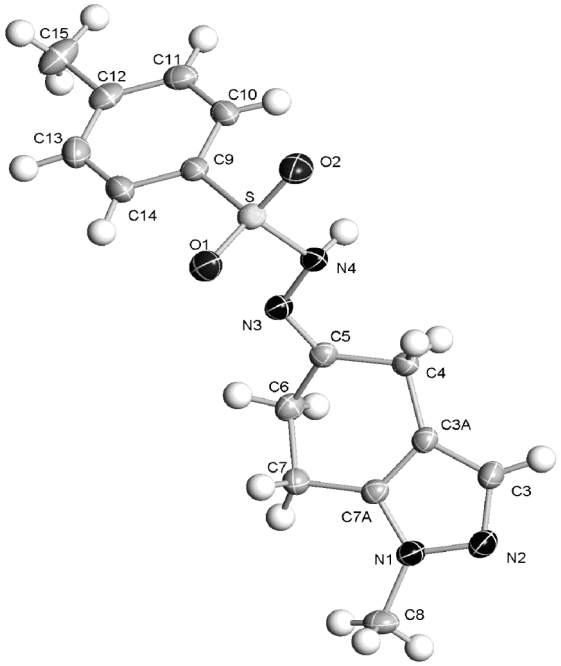


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Figure 3. Ortep drawing of compound **6**.

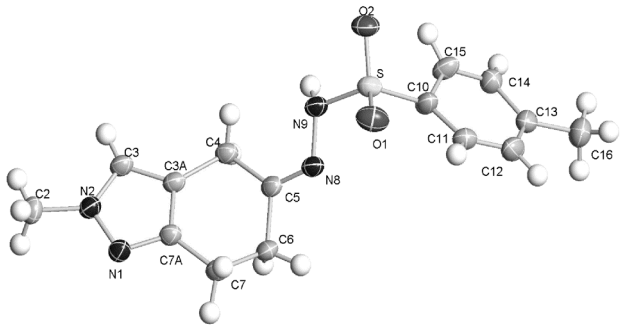

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Figure 4. Ortep drawing of compound **7**.

In conclusion, this paper describes an NMR method to correctly assign the individual N1/N2-methyl tetrahydroindazole isomers. The NMR methods described provide efficient methods to accurately assign isomers of *N*-methyl-tetrahydro-5*H*-indazol-5-ones when both regioisomers are available. An NOE difference experiment can also reveal an N2-methyl tetrahydroindazole, while the N1-methyl isomer is more difficult to detect. The condensation of ketal **3** with methylhydrazine and subsequent deprotection clearly provide a high yielding regioselective route to the N2-methyl isomer **2**.

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EXPERIMENTAL

NMR studies were performed on a 400 MHz Bruker DRX system using TMS as an internal standard. Mass spectra data were collected on a Bruker Esquire 2000 LC-MS system. Melting points are uncorrected. Elemental analysis were performed by Quantitative Technologies, Inc., 291 Route 22 East, Whitehouse, NJ 08888.

7-(Hydroxymethylene)-1,4-dioxaspiro[4,5]decan-8-one (**3**)

A mixture of NaH (60%, 19.2 g, 0.48 mol), ethyl formate (59.2 g, 0.80 mol), and 100 mL EtOH in 500 mL dry THF was charged with 1,4-cyclohexanedione monoethylene ketal (62.5 g, 0.40 mol) in 200 mL dry THF slowly over 90 minutes at 0 °C. After 1 h at 25 °C, the mixture was refluxed 2 h and then cooled. After dilution with ether, the mixture was extracted with 1 *N* NaOH. The aqueous layer was acidified to pH 4 with conc. HCl and then extracted with methylene chloride. After drying ($MgSO_4$), the solvent was removed to yield a dark oil that crystallizes upon standing to give 66.7 g (90%) of 7-(hydroxymethylene)-1,4-dioxaspiro[4,5]decan-8-one (**3**); mp 72-74 °C; ^{1}H nmr (deuteriochloroform): δ 1.87 (dd, J = 6.9 Hz, 2H), 2.56 (m, 4H), 4.00 (s, 4H), 8.52 (s, 1H), 14.40 (bs, 1H); MS (*m/e*) 185 (M+).

1-Methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-one (**1**) and 2-methyl-2,4,6,7-tetrahydro-5*H*-indazol-5-one (**2**)

To a solution of 7-(hydroxymethylene)-1,4-dioxaspiro[4,5]-decan-8-one (**3**) (10 g, 54.5 mmol) in 200 mL MeOH at -30 °C was added methylhydrazine (3.0 mL, 56.5 mmol). The reaction was warmed to ambient temperature and concentrated to yield an amber oil that was dissolved in 100 mL acetone and 100 mL 2 *N* HCl. The solution was heated to 60 °C for 2 hours, concentrated, then neutralized with $NaHCO_3$. After extraction with methylene chloride and drying ($MgSO_4$), the isomers were seperated on silica gel with 70% ethyl acetate/hexanes. The first eluting isomer was triturated with diethyl ether to yield 2.94 g (36%) of 2-methyl-2,4,6,7-tetrahydro-5*H*-indazol-5-one (**2**); mp 87-90 °C; ^{1}H nmr (deuteriochloroform) δ 2.69 (dd, J = 6.9 Hz, 2H), 3.05 (dd, J = 7.1 Hz, 2H), 3.42 (s, 2H), 3.87 (s, 3H), 7.15 (s, 1H); ^{13}C nmr (deuteriochloroform) δ 22.27, 35.91, 38.84, 39.55, 112.93, 127.80, 147.10, 209.63; MS (*m/e*) 151 (M+).

Anal. Calcd. for $C_8H_{10}N_2O{\cdot}1.1H_2O$: C, 56.53; H, 7.23; N, 16.48. Found: C, 56.47; H, 7.01; N, 16.17.

The second eluting isomer was also triturated with diethyl ether to yield 0.33 g (4%) of 1-methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-one (**1**). mp 86-89 °C; ^{1}H nmr (deuteriochloroform): δ 2.71 (dd, J = 6.9 Hz, 2H), 3.00 (dd, J = 7.0 Hz, 2H), 3.41 (s, 2H), 3.79 (s, 3H), 7.27 (s, 1H); ^{13}C nmr (deuteriochloroform) δ 20.42, 36.02, 36.06, 37.99, 113.34, 136.03, 136.19, 208.64; MS (*m/e*) 151 (M+).

4-Methyl-*N*'-(1-methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-yl-idene)benzenesulfonohydrazide (**6**).

An oven dried flask was charged with 1-methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-one (**1**) (0.3 g, 2 mmol) and *p*-toluene-sulfonyl hydrazide (0.39 g, 2.09 mmol) followed by MeOH (10 mL). The resulting mixture was stirred at ambient temperature for 1 hr then filtered, washed with MeOH, ether and dried to furnish 0.4 g (63%) of 4-Methyl-N'-(1-methyl-1,4,6,7-tetrahydro-5*H*-indazol-5-ylidene)benzenesulfonohydrazide (**6**). Recrystallized from ethyl alcohol to afford quality crystals; mp 168.3 °C; ^{1}H nmr (dimethyl sulfoxide -d_6) δ 2.38 (s, 3H), 2.46 (dd, J = 6.6 Hz, 2H), 2.72 (dd, J = 6.6 Hz, 2H), 3.35 (s, 2H), 3.64 (s, 3H), 7.19 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 10.24 (s, 1H); MS (*m/e*) 319 (M+).

Anal. Calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.38; H, 5.60; N, 17.54.

4-Methyl-*N*'-(2-methyl-2,4,6,7-tetrahydro-5*H*-indazol-5-ylidene)-benzenesulfonohydrazide (**7**).

An oven dried flask was charged with 2-methyl-2,4,6,7-tetra-hydro-5*H*-indazol-5-one (**1**) (1.5 g, 10 mmol) and *p*-toluene-sulfonyl hydrazide (1.95 g, 10.48 mmol) followed by MeOH (60 mL). The resulting mixture was stirred at ambient temperature for 1 hr then filtered, washed with MeOH, ether and dried to give 2.8 g (88%) of 4-Methyl-*N*'-(2-methyl-2,4,6,7-tetrahydro-5*H*-indazol-5-ylidene)benzenesulfonohydrazide (**7**). Recrystallized from ethyl alcohol to afford quality crystals; mp 165.2 °C; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 2.38 (s, 3H), 2.43 (dd, J = 6.6 Hz, 2H), 2.62 (dd, J = 6.6 Hz, 2H), 3.39 (s, 2H), 3.73 (s, 3H), 7.39 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.75 (d, J = 8.2 Hz, 2H), 10.20 (s, 1H); MS (*m/e*) 319 (M+).

Anal. Calcd. for $C_{15}H_{18}N_4O_2S$: C, 56.58; H, 5.70; N, 17.60. Found: C, 56.03; H, 5.47; N, 17.50.

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