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The Synthesis of 3-[3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-5-pyrazolyl]-N-hydroxy-N-methylpropanamide, a Regioisomer of Tepoxalin

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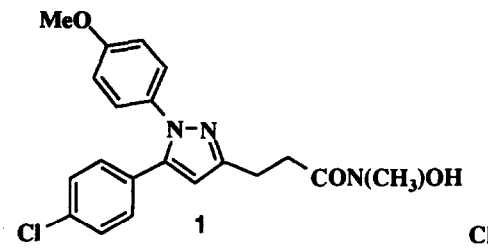
Abstract: Compound **2** was synthesized in 4 steps in 65% overall yield. Mechanistic studies of the key pyrazole forming step revealed a tetrahyrofuran intermediate (**10**) of the starting 1-(4-chlorophenyl)-6-hydroxyhexane-1,3-dione (**3**). This intermediate reverses the normal regioselectivity observed in additions of phenylhydrazines to aryl diketones.

During the course of our work with tepoxalin (**1**), we realized that small quantities of the 1,3 regioisomer, **2** could be produced in our processes.[1] It was therefore desirable to be able to regioselectively synthesize **2** in amounts adequate for biological profiling. In each of our previously reported syntheses, little if any of **2** was produced.[1,2,3] The synthesis which produced the most 1,3



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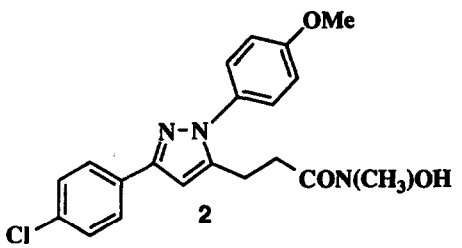
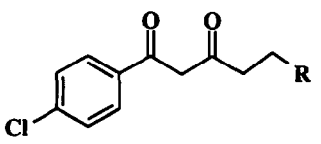


2

isomer involved the addition of 4-methoxyphenylhydrazine hydrochloride to 1-(4-chlorophenyl)-6-hydroxyhexane-1,3-dione **3** (Fig 1).[4] We felt it would be fruitful to examine the differences among

Figure 1

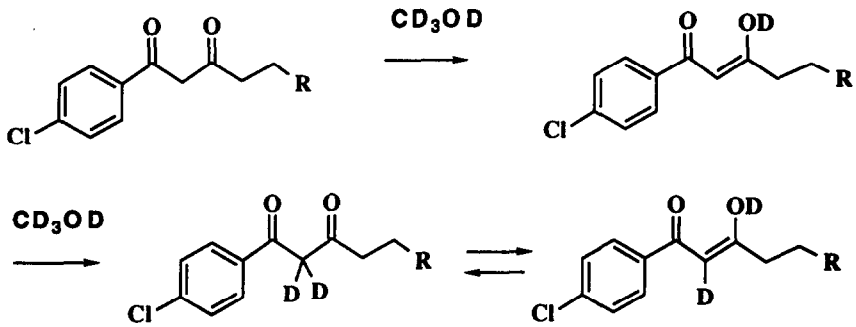


#	R	% 1,5 isomer	% 1,3 isomer
3	CH_2OH	85	15
4	CO_2H	>98	< 2
5	$CON(CH_3)OH$	92	8

the diketo intermediates (**3**,**4** and **5**) of these three syntheses in methanol, a standard solvent for these reactions.

Proton NMR spectra were run for **3**, **4** and **5** in deuteriomethanol. The NMR's showed **4** and **5** had completely exchanged the protons on the carbon between the carbonyls (Fig 2). This indicated a rapid exchange between the keto and enol forms of these compounds. Compound **3** however,

Fig 2

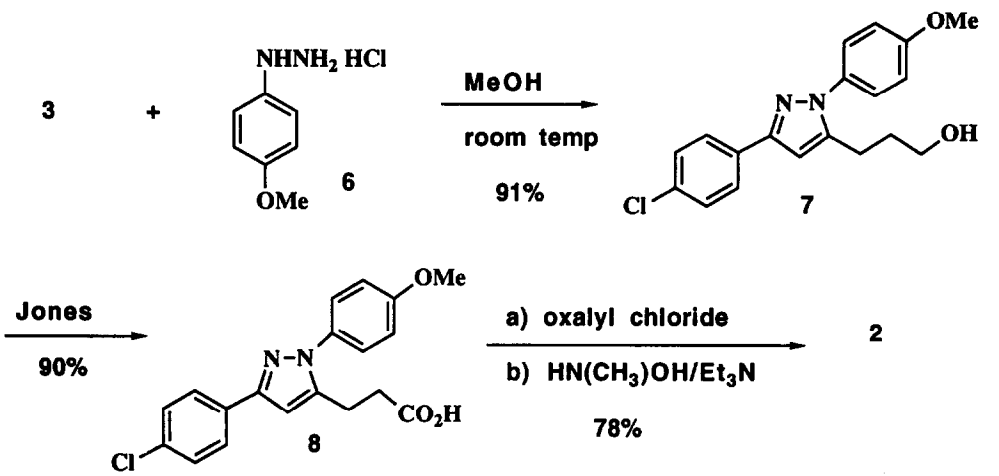


#	R	$t_{1/2}$
3	CH_2OH	5400 sec
4	CO_2H	< 120 sec
5	$CON(CH_3)OH$	< 120 sec

showed the enol tautomer with no exchange of the ene proton. We monitored the ^1H NMR spectrum of **3** over time and found that the $t_{1/2}$ for exchange at 26.5°C was 1.5 hours. We also found that by adding 1 equivalent of Et_3N complete exchange occurred as in **4** and **5**. We postulated that the enol form was responsible for formation of the 1,3 isomer, and thus, addition of 4-methoxyphenylhydrazine hydrochloride (**6**) to the enol form of **3** without base should give us a much higher percentage of the 1,3 isomer **7** than the standard reaction conditions.[5] When we combined **3** and **6** we found we reversed the regioselectivity and had a 15:1 mixture of 1,3 to 1,5 diphenylpyrazole isomers (Scheme 1). We had also isolated a 91% yield of **7** by crystallization.[6] Jones oxidation of **7** afforded **8** in 90% yield.[7] Compound **2** was synthesized in 78% yield by preparation of the acid chloride which was then added to a solution of N-methylhydroxylamine in methylene chloride at 0°C.[8,9]

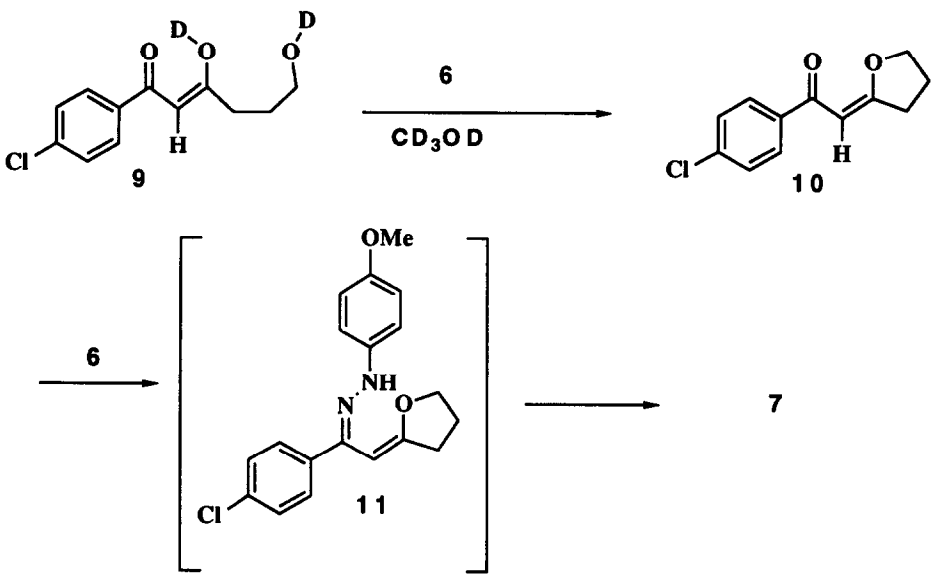
Since the conversion of **3** to **7** was carried out in methanol at room temperature it was amenable to direct NMR study. Compound **3** and **6** (0.5 mmole each) were dissolved in CD_3OD and proton spectra were taken every 15 minutes for the first 3 hours and every 3 hours after that. The initial reaction we observed was the formation of the (E)-2-(4-chlorobenzoylmethylene)tetrahydrofuran **10** (Scheme 2). This reaction is probably catalyzed by the hydrazine hydrochloride **6**.This reaction occurred at a faster rate than the deuterium exchange of the ene proton.[10] This closure had been

Scheme 1



previously described using a triphenylphosphine carbontetrahalide complex.[11] Compound **10** showed characteristic resonances at 6.5 (1H, t, J = 1.5 Hz) and 4.3 (2H, t, J = 7 Hz).[12] We postulate that **6** then adds to **10** to generate **11** which then closes to **7** at a rate faster than or equal to the rate of formation of **11**.

Scheme 2



In conclusion, we have demonstrated a synthesis of our title compound which completely reverses our previously reported regioselectivity. This synthesis proceeds through a benzoylmethylenetetrahydrofuran which is formed *in situ.*

References and Notes

(1) Wachter M.; Ferro M. U.S. Patent 4,826,868, **1989.**

(2) Murray, W.; Wachter, M., Barton, D., Forrero-Kelly, Y. *Synthesis* **1991**,18 .

(3) Murray, W.; Hadden. *J. Org. Chem.* **1992**, *57*, in press.

(4) See reference 1

(5) Standard conditions include 1 - 2 equivalents of Et_3N or pyridine.

(6) Compound **3** (2.4 g, 0.01 moles) was dissolved in methanol (60 mL). To this solution was added 4-methoxyphenyl hydrazine hydrochloride (1.75 g, 0.01 moles). The solution was stirred for 12 h at room temp. The solvent was removed in vacuo leaving a tan residue. The residue was crystallized from acetone to afford 3.1 g (91%) of **3** as a white solid mp 87-88°C; NMR (DMSO d_6) 1.73 (2H, m) , 2.66 (2H, t, J = 8 Hz), 3.41 (2H, t, J = 8 Hz), 3.83 (3H, s), 6.78 (1H, s), 7.08 (2H, d, J = 8.5 Hz), 7.45 (4H, m), 7.85 (2H, d, J = 8.5 Hz); Mass spec (DCI) m/z 343 (M+H).

(7)Compound **7** (1.71g, 0.005 moles) was dissolved in acetone (40 mL) and added to a stirred solution of 2N $H_2Cr_2O_7$ (7 mL, 0.0075 moles) at 10 °C. The mixture was stirred for 30 min.and the solution was decanted away from the solids. The solution was concentrated in vacuo, dissolved in 200 mL EtOAc, washed 3X with water, dried over Na_2SO_4, filtered and concentrated in vacuo. Crystallization from ether/ hexanes afforded 1.61g (90%) of **8** as a beige solid. mp 151-152°C; NMR (DMSO d_6) 2.61 (2H, t, J = 8 Hz), 2.84 (2H, t, J = 8 Hz), 3.83 (3H, s), 6.80 (1H, s), 7.09 (2H, d, J = 8.5 Hz), 7.48 (4H, m), 7.83 (2H, d, J = 8.5 Hz), 12.24 (1H, br s); Mass spec (DCI) m/z 357 (M+H).

(8) See ref 2 for experimental conditions.

(9) mp 127-128°C, NMR (DMSO d_6) 2.43 (2H, t, J = 8 Hz), 2.88 (2H, t, J = 8 Hz), 3.20 (3H, br s) 3.83 (3H, s), 6.68(1H, s), 7.09 (2H, d, J = 8.5 Hz), 7.42 (4H, m), 7.75 (2H, d, J = 8.5 Hz); Mass Spec (DCI) m/z 386 (M+H).

(10) The exocyclic methylene proton appears at approximately the same rate that the enol ene proton dissappears.

(11) Detty, M. R. *J. Org. Chem.* **1979**, *44*, 2073.

(12) Resonances for (E)-2-(4-methylbenzoylmethylene)tetrahydrofuran are described in reference 11.

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