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Reactions of 2-Tosyloxy- and 2-Chlorotropones with Hydrazine, Methylhydrazine, and Phenylhydrazine

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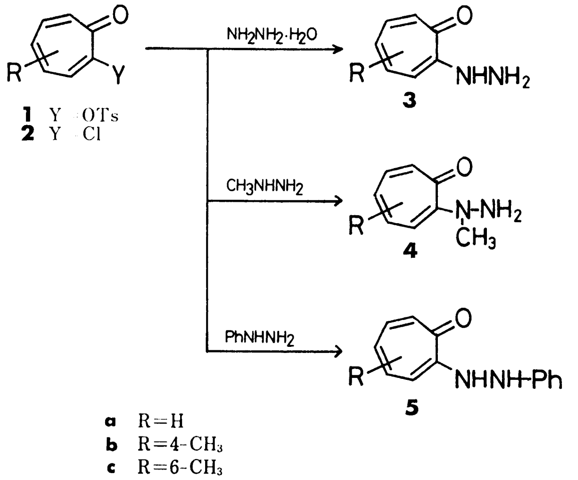
Synopsis. The reactions of 2-tosyloxytropones or 2-chlorotropones with hydrazine, methylhydrazine, and phenylhydrazine gave 2-hydrazinotropones, 2-(α-methylhydrazino)tropones, and 2-(β-phenylhydrazino)tropones, respectively. All the reactions are normal substitution at C-2 position of the tropone ring. No ciné reaction was observed. The reactivity of hydrazines decreases in the order: $NH_2NH_2 > CH_3NHNH_2 \gg PhNHNH_2$.

In troponoids, ciné substitution very often occurs besides normal substitution, especially when the leaving group is a tosyloxy or halogen group, rather than a methoxyl group.1) The reactions of tropolone methyl ethers with hydrazine afford 2-hydrazinotropones, which are useful as synthetic intermediates, by normal substitution at the C-2 atom. However, little is known about the reaction of 2-tosyloxytropones or 2-chlorotropones with hydrazine. We wish to report on the reactions of these reactive troponoids with hydrazine, methylhydrazine, and phenylhydrazine.



Scheme 1.

Results and Discussion

Reactions with Hydrazine. 2-Tosyloxytropone (**1a**) was refluxed with hydrazine hydrate in methanol for 30 min to afford 2-hydrazinotropone (**3a**)2) in 48% yield. 4- (**1b**) and 6-methyl-2-tosyloxytropone (**1c**) also gave the corresponding 4- (**3b**)3) and 6-methyl-2-hydrazinotropone (**3c**)3) in 31 and 41% yields, respectively.

In a similar manner, the reactions of 2-chlorotropones (**2a**—**c**) with hydrazine hydrate gave 2-hydrazinotropones (**3a**—**c**) in 92, 89, and 91% yields, respectively, all the reactions being normal substitution at the 2-position of tropones.

Reactions with Methylhydrazine. The reactions of 2-tosyloxytropones (**1a**—**c**) with methylhydrazine under reflux in methanol gave 2-(α-methylhydrazino)tropones (**4a**—**c**) in 31, 38, and 34% yields, respectively. The NMR spectrum of **4a** shows peaks at δ 3.29 (s, 3H) for CH_3 and δ 4.29 (br, 2H) for NH_2, indicating the presence of an α-methylhydrazino group. The spectra of **4b** and **4c** also show the presence of the α-methylhydrazino group (Table 1). The position of the *C*-methyl substituent in **4b** and **4c** were confirmed by alkaline hydrolysis to 4-methyltropolone.4)

TABLE 1. CHARACTERISTICS OF THE PRODUCTS

Compd	Mp/°C	ν^{CHCl_3}/cm^{-1}	λ_{max}^{MeOH}/nm (log ε)	δ^{CDCl_3}/ppm	Found (Calcd) %
4a	66—67	3320(NH) 1610(C=O)	259(4.17) 362(3.95) 418(3.85)	3.29(s, 3H, CH_3) 4.29(br, 2H, NH_2) 6.4—7.4(m, 5H)	C 63.73(63.98) H 6.82(6.71) N 18.83(18.66)
4b	89—91	3320(NH) 1585(C=O)	265(4.22) 363(3.93) 412(3.83)	2.37(s, 3H, *C*-CH_3) 3.21(s, 3H, *N*-CH_3) 4.62(br, 2H, NH_2) 6.4—7.3(m, 4H)	C 65.57(65.83) H 7.25(7.37) N 16.89(17.06)
4c	102.5—103	3300(NH) 1615(C=O)	260(4.24) 363(3.94) 411(3.86)	2.30(s, 3H, *C*-CH_3) 3.25(s, 3H, *N*-CH_3) 4.64(br, 2H, NH_2)	C 65.68(65.83) H 7.40(7.37) N 17.07(17.06)
5a	163—165	3290(NH) 1600(C=O)	249(4.48) 338(4.01) 404(4.07)	5.82(br, 1H, N**H**–Ph) 6.7—7.35(m, 10H) 8.25(br, 1H, N**H**–tropone)	C 73.63(73.56) H 5.64(5.64) N 12.90(13.20)
5b	193—196	3285(NH) 1600(C=O)	254(4.54) 341(4.03) 403(4.08)	2.34(s, 3H, CH_3) 5.77(br, 1H, N**H**–Ph) 6.5—7.3(m, 9H) 8.25(br, 1H, N**H**–tropone)	C 74.53(74.32) H 6.40(6.24) N 12.09(12.38)
5c	184—186	3290(NH) 1600(C=O)	252(4.55) 341(4.01) 401(4.05)	2.38(s, 3H, CH_3) 5.81(br, 1H, N**H**–Ph) 6.2—7.4(m, 9H) 8.20(br, 1H, N**H**–tropone)	C 74.12(74.32) H 6.36(6.24) N 12.27(12.38)

Heating of 2-chlorotropone (**2a**—**c**) with methylhydrazine afforded the same products (**4a**—**c**) in 69, 72, and 64% yields, respectively. Thus, all the reactions with methylhydrazine are normal substitution reactions, giving no abnormal substitution products.

Reactions with Phenylhydrazine. Heating of 2-tosyloxytropone (**1a**) with phenylhydrazine in methanol under reflux for 30 min gave no product in isolable amount. Prolonged reaction (8 h) afforded 2-(β-phenylhydrazino)tropone5,6) (**5a**) in only 18% yield. Similarly, both the reactions of 4- (**1b**) and 6-methyl-2-tosyloxytropone (**1c**) gave the corresponding 2-(β-phenylhydrazino)tropones (**5b** and **5c**) in 24 and 14% yields, respectively. Presence of the β-phenylhydrazino group was confirmed by the NMR spectra which show two peaks at δ 5.7—5.8 (br, 1H) for N**H**–Ph and δ 8.2—8.25 (br, 1H) for N**H**–tropone. Palladium-catalyzed hydrogenolysis of **5b** and **5c** yielded 4-7) and 6-methyl-substituted 2-aminotropones,3) respectively.

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This indicates that the reactions of **1b** and **1c** with phenylhydrazine are normal substitutions.

Furthermore, the reactions of 2-chlorotropones (**2a**—**c**) with phenylhydrazine gave normally-substituted 2-(β-phenylhydrazino)tropones (**5a**—**c**) in 10, 16, and 16% yields, respectively.

Reactivity of Hydrazines. The reactivity of hydrazines based on the product yields decreases in the following order:

$$NH_2NH_2 \gtrsim CH_3NHNH_2 \gg PhNHNH_2$$

In methylhydrazine, the reactivity enhancement by the +I effect of the methyl group is overcome by its steric effect. Thus, its reactivity might be comparable to that of hydrazine.

On the other hand, the reactivity of phenylhydrazine is considerably decreased by both the −I and steric effects of the phenyl group. The reactivity order is in line with the order of basicity (pK_a) of hydrazines:

$$NH_2NH_2\ (8.07)^{8)} > CH_3NHNH_2\ (7.87)^{8)} \gg PhNHNH_2\ (5.27)^{9)}$$

Experimental

Measurements. Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were taken on a JASCO IRA-1 spectrophotometer, and UV spectra on a Hitachi EPS-3T spectrophotometer. NMR spectra were recorded on a Hitachi R-24 spectrometer (60 MHz).

Materials. All the known compounds were prepared according to the methods described: **1a**, mp 155.5—156.5 °C (lit,[10] 159—159.5 °C); **1b**, mp 114—118 °C (lit,[11] 117—118 °C); **1c**, mp 165—167 °C (lit,[11] 168—169 °C); **2a**, mp 66—67 °C (lit,[12] 66—67 °C).

*4- (**2b**) and 6-Methyl-2-chlorotropone (**2c**).* 4- (**2b**) and 6-methyl-2-chlorotropone (**2c**) were prepared by the reaction of the corresponding tosylates (**1b** and **1c**) with concentrated hydrochloric acid in dioxane according to the most advantageous method reported.[13,14] **2b**, mp 49—50 °C (lit,[7] 49—51 °C); **2c**, mp 59—60 °C (lit,[7] 60—61 °C).

Reactions with Hydrazine. A mixture of **1** or **2** (1 mmol) and 80% hydrazine hydrate (3 mmol, 185 mg) in methanol (5 ml) was refluxed for 30 min on a water-bath. The reaction mixture was diluted with water and extracted with chloroform. The extract was chromatographed on a Wakogel B-10 plate (30×30 cm^2) with ethyl acetate to afford the corresponding 2-hydrazinotropone (**3**) (from benzene–hexane). **3a**, mp 91—93 °C (lit,[2] 95—96 °C); **3b**, mp 120—123 °C (lit,[3] 124 °C); **3c**, mp 122—124 °C (lit,[3] 134—135 °C).

Reactions with Methylhydrazine. The active troponoid (**1** or **2**) (1 mmol) reacted with methylhydrazine (3 mmol, 138 mg) in methanol (5 ml) to give the corresponding 2-(α-methylhydrazino)tropone (**4**) (from benzene–cyclohexane). Characteristic data are given in Table 1.

*Alkaline Hydrolysis of 4- (**4b**) and 6-Methyl-2-(α-methylhydrazino)tropone (**4c**).* *a*) **4b** (15 mg) was heated on a water-bath for 2 h with 10% potassium hydroxide/ethanol–water (1:1) (4 ml). The reaction mixture was neutralized with 2 M hydrochloric acid and extracted with chloroform. The extract was dried over sodium sulfate, giving pale yellow crystals (11 mg, 88%) by evaporation of chloroform. The crystals were recrystallized from petroleum ether to afford 4-methyltropolone. Mp 73—76 °C (lit,[4] 76—77 °C). *b*) Alkaline hydrolysis of **4c** (210 mg) also gave 4-methyltropolone. Yield 120 mg (69%).

Reactions with Phenylhydrazine. A mixture of **1** or **2** (1 mmol) and phenylhydrazine (3 mmol, 324 mg) in methanol (5 ml) was refluxed for 8 h and worked up to afford the corresponding 2-(β-phenylhydrazino)tropone (**5**) (from ethyl acetate) (Table 1). Compound (**5a**) has been reported (mp 175 °C[5] and 163 °C[6]).

*Hydrogenolysis of 4- (**5b**) and 6-Methyl-2-(β-phenylhydrazino)tropone (**5c**).* *a*) **5b** (0.5 mmol, 113 mg) in acetic acid (100 ml) was stirred for an hour under hydrogen atomosphere in the presence of 5% palladium–charcoal (100 mg). After removal of the catalyst, the reaction mixture was diluted with water, neutralized with solid sodium carbonate, and extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate, and chromatographed on a Wakogel B-10 plate (20×20 cm^2) with chloroform to give 2-amino-4-methyltropone. Yield 27 mg (40%); mp 120—121 °C (lit,[7] 122—123 °C). *b*) In a similar manner, hydrogenolysis of **5c** (0.5 mmol, 113 mg) gave 2-amino-6-methyltropone. Yield 32 mg (47%); mp 110—112 °C (lit,[3] 111—112 °C).

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