Reactions of 3-Acetyltropolone with Amines: Preparation of *N*-Alkyl-substituted 2-Acetyl-7-aminotropones and 3-Acetyl-2-aminotropones

Kimiaki IMAFUKU*, Akiko SHIMAZU

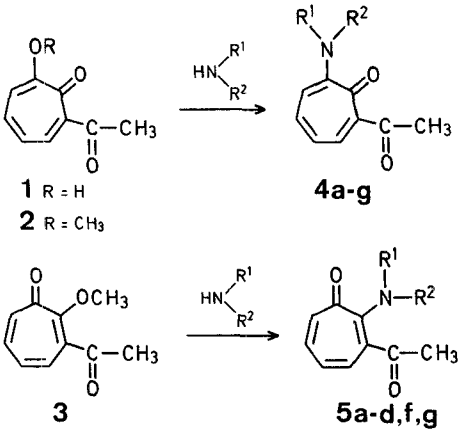
Department of Chemistry, Faculty of Science, Kumamoto University, Kurokami, Kumamoto 860, Japan

3-Acetyltropolone **(1)** is a useful starting material for the synthesis of heterocycle-condensed troponoid compounds. We have previously reported the reactions of 3-acetyltropolone **(1)**, 2-acetyl-7-methoxytropone **(2)**, and 3-acetyl-2-methoxytropone **(3)** with nucleophiles such as hydrazines[1,2,3], semicarbazide and thiosemicarbazide[4], hydroxylamine[5], guanidine[6], amidines[6], and *o*-phenylenediamine[7]. These nucleophiles have two nucleophilic functional groups. We now report the reaction of tropolone derivatives **1, 2,** and **3** with a variety of primary and secondary aliphatic amines having only one nucleophilic center.

In general, tropolones do not react with nucleophilic reagents. However, tropolones having a strongly electron-withdrawing group such as a nitro or nitroso group react with nucleophiles to give 2-substituted tropones[8].

When a suspension of 3-acetyltropolone **(1)** in aqueous 28% ammonia is allowed to stand at room temperature for a week, 2-acetyl-7-aminotropone **(4a)** can be isolated in 30% yield. The regioselectivity of this reaction may be attributed to the electron-withdrawing effect of the acetyl group. The analogous reaction with methylamine and ethylamine afford 2-acetyl-7-methylaminotropone **(4b)** and 2-acetyl-7-ethylaminotropone **(4c)** in 90 and 52% yields, respectively. The reactions of **1** with benzylamine, diethylamine, pyrrolidine, and morpholine also gave *N*-substituted 2-acetyl-7-aminotropones **(4d–g)** but the yields were low.

Tropolone methyl ethers are known to be reactive compounds. We found that the reaction of 2-acetyl-7-methoxytropone **(2)** with the above-mentioned amines affords the 2-acetyl-7-aminotropones **(4a–g)** in 28–92% yields, i.e., in yields which are generally better than those obtained from **1** and the amines. The isomeric 3-acetyl-2-methoxytropone **(3)** reacts with the same amines to afford the 3-acetyl-2-aminotropones **(5a–d, f, g)** in 20–61% yields, compounds **5b** in 11% yield, and compound **5c** in only 3% yield.



The I.R. spectra were taken on a JASCO IRA-1 spectrophotometer, the U.V. spectra on a Hitachi EPS-3T spectrophotometer. The ^{1}H-N.M.R. spectra were recorded with a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz).

2-Acetyl-7-aminotropones (4) and 3-Acetyl-2-aminotropones (5):

Method A; Compounds **4** from **1** and Amines:

2-Acetyl-7-aminotropone **(4a):** A suspension of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol) in aqueous 28% ammonia (10 ml) is allowed to stand at room temperature for a week. The mixture is then extracted with chloroform (3 × 30 ml), the extract washed with water (50 ml), dried with sodium sulfate, and evaporated. The residual product is recrystallized; yield: 122 mg (30%).

2-Acetyl-7-methylaminotropone **(4b):** A suspension of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol) in aqueous 40% methylamine solution (10 ml) is allowed to stand at room temperature for a week. The mixture is worked up as described above; yield: 398 mg (90%).

2-Acetyl-7-ethylaminotropone **(4c):** A suspension of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol) in aqueous 70% ethylamine solution (8 ml) is allowed to stand at room temperature for 3 days. The mixture is worked up as described above; yield: 248 mg (52%).

2-Acetyl-7-benzylaminotropone **(4d):** A solution of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol) and benzylamine (268 mg, 2.5 mmol) in benzene (10 ml) is refluxed for 3 h in the presence of sodium acetate (200 mg). The mixture is washed with water (2 × 50 ml), dried with sodium sulfate, and evaporated. The residual product is recrystallized; yield: 63 mg (10%).

2-Acetyl-7-diethylaminotropone **(4e):** A mixture of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol), diethylamine (200 mg, 2.7 mmol), and methanol (10 ml) is allowed to stand at room temperature for a week. The solvent is then evaporated and the residue is chromatographed on a preparative Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate and recrystallized; yield: 25 mg (4.6%).

2-Acetyl-7-pyrrolidinotropone **(4f):** A mixture of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol), pyrrolidine (200 mg, 2.8 mmol), and methanol (10 ml) is allowed to stand at room temperature for a week and then worked up as described above; yield: 43 mg (7.9%).

2-Acetyl-7-morpholinotropone **(4g):** A solution of 3-acetyltropolone (**1**; 410 mg, 2.5 mmol) and morpholine (305 mg, 3.5 mmol) in benzene (20 ml) is refluxed for 4 h in the presence of sodium acetate (200 mg). The mixture is washed with water (2 × 50 ml) and dried with sodium sulfate. The solvent is removed and the residue is chromatographed on a preparative Wakogel B-10 plate (30 × 30 cm^2) with ethyl acetate and recrystallized; yield: 75 mg (13%).

Method B; Compounds **4** or **5** from **2** or **3**, respectively, and Amines: A suspension or solution of 2-acetyl-7-methoxytropone (**2**; 445 mg, 2.5 mmol) or 3-acetyl-2-methoxytropone (**3**; 445 mg, 2.5 mmol) is treated with the appropriate amine in the same manner as described for starting material **1** under Method A. Work-up as above affords the product **4** or **5**, respectively.

0039-7881/82/1232-1043 $ 03.00

Table 1. 2-Acetyl-7-aminotropones (**4**) prepared

4	R^1	R^2	Reaction conditions			Yield [%]	m.p. [°C] (Solvent)	Molecular formula[a]
			Substrate	Solvent	Temperature, Time			
a	H	H	1	—	r.t., 7 days	30	126–127°	$C_9H_9NO_2$
			2	—	r.t., 3 days	32	(benzene)	(163.2)
b	CH_3	H	1	—	r.t., 7 days	90	70–71°	$C_{10}H_{11}NO_2$
			2	—	r.t., 1 h	92	(hexane)	(177.2)
c	C_2H_5	H	1	—	r.t., 3 days	52	62–63°	$C_{11}H_{13}NO_2$
			2	—	r.t., 24 h	61	(hexane)	(191.2)
d	$-CH_2-C_6H_5$	H	1	C_6H_6/AcONa	reflux, 3 h	10	65.5–66.5°	$C_{16}H_{15}NO_2$
			2	C_6H_6/AcONa	reflux, 3 h	50	(benzene/hexane)	(253.3)
e	C_2H_5	C_2H_5	1	CH_3OH	r.t., 7 days	4.6	60–61°	$C_{13}H_{17}NO_2$
			2	CH_3OH	r.t., 24 h	28	(benzene/hexane)	(219.3)
f	$-(CH_2)_4-$		1	CH_3OH	r.t., 7 days	7.9	133–134°	$C_{13}H_{15}NO_2$
			2	CH_3OH	r.t., 1 h	62	(benzene/hexane)	(217.3)
g	$-CH_2-CH_2-O-CH_2-CH_2-$		1	C_6H_6/AcONa	reflux, 3.5 h	13	87–88°	$C_{13}H_{15}NO_3$
			2	C_6H_6/AcONa	reflux, 3 h	67	(benzene/hexane)	(233.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.29; H, ±0.20; N, ±0.16.

Table 2. 3-Acetyl-2-aminotropones (**5**) prepared

5	R^1	R^2	Reaction conditions		Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]
			Solvent	Temperature, Time			
a	H	H	—	r.t., 3 days	30	101–102° (benzene)	$C_9H_9NO_2$ (163.2)
b	CH_3	H	—	r.t., 10 days	11	64–66° (hexane)	$C_{10}H_{11}NO_2$ (177.2)
c	C_2H_5	H	—	r.t., 7 days	3.0	111–113° (hexane)	$C_{11}H_{13}NO_2$ (191.2)
d	$-CH_2-C_6H_5$	H	C_6H_6/AcONa	reflux, 3 h	61	176–178° (benzene/hexane)	$C_{16}H_{15}NO_2$ (253.3)
f	$-(CH_2)_4-$		CH_3OH	r.t., 7 days	25	101–102° (benzene/hexane)	$C_{13}H_{15}NO_2$ (217.3)
g	$-CH_2-CH_2-O-CH_2-CH_2-$		CH_3OH	r.t., 24 h	20	116–118° (benzene/hexane)	$C_{13}H_{15}NO_3$ (233.3)

[a] See footnote a of Table 1.

Table 3. Spectral Data of Compounds **4** and **5**

Compound	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (CH_3OH) λ [nm] ($\log\varepsilon$)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
4a	3500, 3350, 1700, 1600	243 (2.34), 350 (3.82), 413 (3.99)	2.60 (s, 3H, CO—CH_3); 6.4 (br, 2H, NH_2); 6.5–7.4 (m, 3H, 4,5,6-H); 7.61 (dd, 1H, J=8.1, 1.4 Hz, 3-H)
4b	3310, 1700, 1600	248 (4.30), 350 (3.89), 425 (4.14)	2.59 (s, 3H, CO—CH_3); 3.12 (d, 2H, J=5.7 Hz, CH_3); 6.50 (d, 1H, J=9.6 Hz, 5-H); 6.74 (d, 1H, J=9.6 Hz, 6-H); 7.28 (dd, 1H, J=9.6, 1.4 Hz, 4-H); 7.63 (dd, 1H, J=9.6, 1.4 Hz, 3-H); 7.7 (br, 1H, NH)
4c	3280, 1690, 1595	248 (4.31), 352 (3.90), 415 (4.02)	1.38 (t, 3H, J=7.0 Hz, CH_3); 2.56 (s, 3H, CO—CH_3); 3.40 (m, 2H, CH_2); 6.4–7.7 (m, 5H, 3,4,5,6-H, NH)
4d	3280, 1695, 1595	248 (4.33), 352 (3.93), 415 (4.09)	2.54 (s, 3H, CO—CH_3); 4.50 (d, 2H, J=6.0 Hz, CH_2); 6.4–7.8 (m, 4H, 3,4,5,6-H); 7.25 (s, 5H_{arom}); 7.90 (br, 1H, NH)
4e	1690, 1605	260 (4.23), 374 (3.57), 470 (3.94)	1.24 (t, 6H, J=6.6 Hz, 2CH_3); 2.46 (s, 3H, CO—CH_3); 3.56 (q, 4H, J=6.6 Hz, 2CH_2); 6.2–7.9 (m, 4H, 3,4,5,6-H)

Table 3. (Continued)

Compound	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (CH_3OH) λ [nm] ($\log\varepsilon$)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
4f	1675, 1595	248 (4.33), 352 (3.93), 415 (4.09)	1.8–2.3 (m, 4H, $2CH_2$); 2.48 (s, 3H, CO—CH_3); 3.4–3.8 [m, 4H, 2(N)—CH_2]; 6.21 (d, 1H, J = 10 Hz, 5-H); 6.45 (d, 1H, J = 10 Hz, 6-H); 7.01 (dd, 1H, J = 10, 1.2 Hz, 4-H); 7.80 (dd, 1H, J = 10, 1.2 Hz, 3-H)
4g	1690, 1600	260 (4.16), 380 (3.72), 450 (3.89)	2.46 (s, 3H, CO—CH_3); 3.3–3.5 [m, 4H, 2(N)—CH_2]; 3.7–3.9 [m, 4H, 2(O)—CH_2]; 6.4–7.7 (m, 4H, 3,4,5,6-H)
5a	3360, 3240, 1645, 1620	238 (4.22), 277 (3.80), 358 (3.65)	2.67 (s, 3H, CO—CH_3); 6.4–7.6 (m, 5H, 3,4,5,6-H, NH); 9.5 (br, 1H, NH)
5b	3280, 1695, 1580	248 (4.27), 356 (3.85), 425 (4.06)	2.80 (s, 3H, CH_3); 2.97 (d, 3H, J = 6.6 Hz, N—CH_3); 6.4–7.6 (m, 5H, 3,4,5,6-H, NH)
5c	3200, 1745, 1600	248 (4.31), 317 (3.46), 430 (2.80)	1.28 (t, 3H, J = 6.6 Hz, CH_3); 2.55 (s, 3H, CO—CH_3); 3.72 (q, 2H, J = 6.6 Hz, CH_2); 6.5–7.5 (m, 5H, 3,4,5,6-H, NH)
5d	3230, 1700, 1610	254 (3.71), 370 (2.93), 420 (2.97)	2.45 (s, 3H, CO—CH_3); 4.28 (d, 2H, J = 6.0 Hz, CH_2); 6.3–7.8 (m, 4H, 3,4,5,6-H); 7.22 (s, 5H_{arom}); 8.95 (br, 1H, NH)
5f	1640, 1595	250 (4.42), 394 (3.90), 450 (4.18)	1.8–2.1 (m, 4H, $2CH_2$); 2.48 (s, 3H, CO—CH_3); 3.4–3.7 [m, 4H, 2(N)—CH_2]; 6.1–7.7 (m, 4H, 3,4,5,6-H)
5g	1705, 1565	282 (4.18), 366 (3.91), 440 (3.65)	2.58 (s, 3H, CO—CH_3); 3.2–3.5 [m, 2H, 2(N)—CH_2]; 3.7–4.0 [m, 4H, 2(O)—CH_2]; 6.5–7.5 (m, 4H, 3,4,5,6-H)

The present work was supported in part by a Grant-in-Aid for Scientific Research (No. 56540308) from the Ministry of Education, Science, and Culture, Japan.

Received: May 25, 1982

* Address for correspondence.

[1] A. Yamane, M. Nagayoshi, K. Imafuku, H. Matsumura, *Bull. Chem. Soc. Jpn.* **52**, 1972 (1979).
[2] A. Yamane, K. Imafuku, H. Matsumura, *Bull. Chem. Soc. Jpn.* **53**, 1461 (1980).
[3] K. Imafuku, A. Yamane, H. Matsumura, *J. Heterocycl. Chem.* **17**, 1293 (1980).
[4] Z.-T. Jin, K. Imafuku, H. Matsumura, *Yuki Gosei Kagaku Kyokai Shi* **39**, 862 (1981).
[5] Y. Sudoh, Z.-T. Jin, K. Imafuku, H. Matsumura, *J. Heterocycl. Chem.* **19**, 525 (1982).
[6] Z.-T. Jin, K. Imafuku, H. Matsumura, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1037.
[7] K. Imafuku, A. Yamane, H. Matsumura, *J. Heterocycl. Chem.* **18**, 335 (1981).
[8] T. Nozoe, Y. Kitahara, K. Doi, T. Arai, *Tohoku Daigaku Hisui-yoeki Kagaku Kenkyusho Hokoku* **7**, 13 (1957); *C. A.* **53**, 18885 (1959).

0039-7881/82/1232-1045 $ 03.00