Novel Synthesis of (1-Acetylindol-3-yl)methyl Acetate and Its Displacement Substitution Reactions (1)

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The acylation of gramine produces (1-acetyindol-3-yl) methylacetate from which the 3-alkoxy or thioacid derivatives have been synthesized.

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The utility of thioacid derivatives of 3-methylindole which have potential as plant growth regulators has been reported in our previous communication (3). Gramine (**1**) and its methiodide salt (**2**) are widely used in the synthesis of such compounds (4,5). Both **1** and **2** undergo a displacement substitution reaction at the reflux temperature of the solvent involved, as do thioacid derivatives of 3-methylindole (3). The reported procedures for these reactions involve various steps. We have found (1-acetylindol-3-yl) methylacetate (**5**) to be the most versatile intermediate for the synthesis of 3-substituted indole derivatives. The displacement substitution reaction on **5** can be conducted at room temperature in 10% sodium hydroxide solution and involves one step with a higher yield of product than previously reported.

Geissman and Armen (5) synthesized **5** by treating **1** with acetic anhydride in the presence of sodium acetate, but in poor yield. Leete and Marion (4) raised the yield in this reaction to 88%, but on recrystallization of the crude amorphous **5**, the yield decreased to 78%. Compound **3**

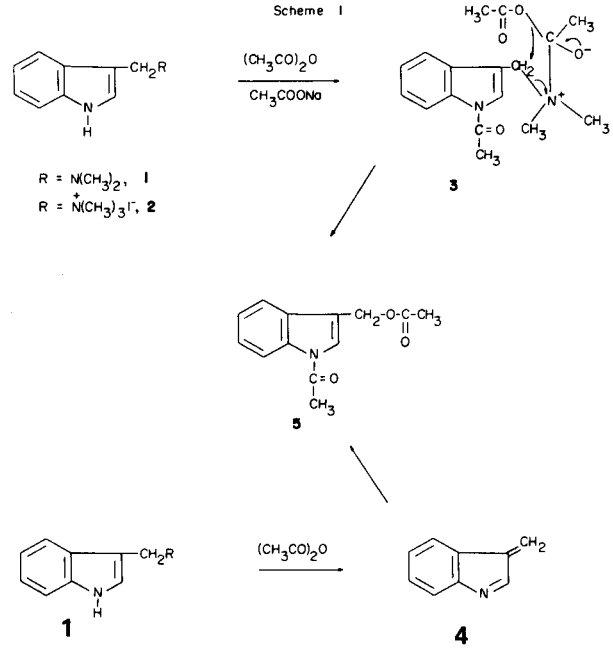


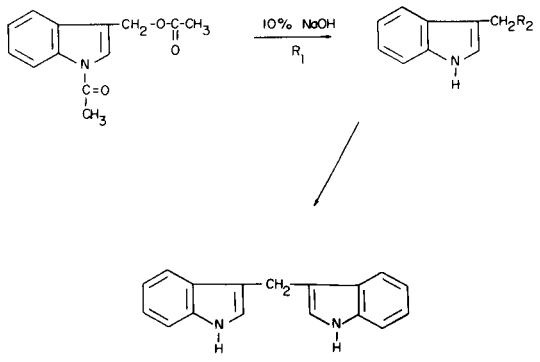
Table I

Physical Data for Compounds **5-10**

Compound	Yield %	MP °C	Molecular Formula	*Anal.* Calcd. (Found) C	H	N	IR (cm^{-1}) Potassium bromide
5	95	89-90 (a)	$C_{13}H_{13}O_3N$	67.53 (67.30	5.63 5.81	6.06 6.26)	3050, 2990, 2850, 1750, 1700, 1020, 1590, 1540, 1490, 1400, 1390, 1320, 1250, 1210, 1180, 1160, 1120, 1090, 1020, 950, 900, 850, 750
6	89	90-91 (b)	$C_{10}H_{11}NO$	74.53 (74.70	6.83 6.81	8.69 8.75)	3420, 3230, 3180, 3140, 3090, 3020, 2990, 2860, 1620, 1470, 1480, 1300, 1240, 1140, 1100, 750
7	90	64-65 (c)	$C_{11}H_{13}NO$	75.43 (75.23	7.43 7.39	8.00 7.98)	3440, 3260, 3150, 3120, 3050, 3010, 2970, 2880, 1620, 1450, 1430, 1310, 1260, 1120 1090, 750
8	85	85-89	$C_{12}H_{12}N_2O$	72.00 (71.90	6.00 6.00	14.00 13.85)	3400, 3050, 3000, 2850, 2250, 1460, 1625, 1560, 1540, 1440, 1100, 750
9	92	107-109	$C_{11}H_{11}NO_2S$	59.72 (59.85	4.97 5.00	6.33 6.29)	3420, 3150, 3100, 3050, 1490, 1620, 1590, 1540, 1440, 1720, 1295, 750
10	80	115-117	$C_{12}H_{13}NO_2S$	61.40 (61.50	5.60 5.70	6.00 5.88)	3410, 3150, 3100, 3050, 1490, 1630, 1580, 1530, 1460, 1730, 1280, 750

(a) Lit (5) mp 90-90.5°. (b) Lit (5) mp 97-98°, (c) Lit (5) mp 63-64°.

Scheme II



II

R_1	R_2	Compound
$HOCH_3$	$-OCH_3$	**6**
$HOCH_2CH_3$	$-OCH_2CH_3$	**7**
$HOCH_2CH_2CN$	$-OCH_2CH_2CN$	**8**
$HSCH_2COOH$	$-SCH_2COOH$	**9**
$HSCH_2CH_2COOH$	$-SCH_2CH_2COOH$	**10**

had been suggested as a possible intermediate (5), but **4** is a more likely one (7-8). The same compound **5** has been synthesized in our laboratory by reacting **1** with acetic anhydride at reflux temperature (Scheme I) in the absence of sodium acetate. This procedure afforded the crystalline product in 95% yield without recrystallization. The reaction time has been significantly reduced to 45 minutes from the 4 hours previously reported (4,5).

Table II

Proton Magnetic Resonance Parameters

Compounds	Solvent	Parameters
(5)	DMSO-d_6	2.08 (s, 3H, CH_3CO-), 2.62 (s, 3H, $CH_3CON<$), 5.26 (s, 2H, $-CH_2$-O-CO-), 6.72-7.77 (5H of Indole ring), 10.4 (s, 1H, >NH).
(6)	DMSO-d_6	3.27 (s, 3H, $-OCH_3$), 4.6 (s, 2H, $-CH_2$-O-), 6.73-7.72 (5H of Indole ring), 10.4 (s, 1H, >NH).
(7)	Deuteriochloroform	1.13, 1.22, 1.30 (t, 3H, $-CH_3$); 3.44, 3.53, 3.61, 3.70 (Q, 2H, $-O-CH_2$); 4.68 (s, 2H, $-CH_2$-O-); 6.62-7.90 (5H of Indole ring); 9.9 (s, 1H, >NH).
(8)	Deuteriochloroform	2.44, 2.52, 2.60 (t, 2H, $-CH_2CN$); 3.57, 3.67, 3.73 (t, 2H, $-O-CH_2$-); 4.76 (s, 2H, $-CH_2$-O-); 6.90-7.96 (5H of Indole ring); 10.03 (s, 1H, >NH).
(9)	DMSO-d_6	3.00 (s, 2H, $-S-CH_2-COOH$), 3.96 (s, 2H, $-CH_2$-S-), 6.64-7.82 (5H of Indole ring), 10.2 (s, 1H, >NH).
(10)	DMSO-d_6	2.46-2.68 (m, 4H, $-S-CH_2-CH_2$), 4.02 (s, 2H, $-CH_2$-S-) 6.01-7.82 (5H of Indole ring), 10.3 (s, 1H, >NH).

Coker, Mathre and Todd synthesized 3-indoleacetonitrile by treatment of **5** with potassium cyanide in hot ethanol and water under reflux conditions in 38% yield (6). We have treated **5** with either methanol, ethanol, 3-hydroxypropionitrile, mercaptoacetic acid or mercaptopropionic acid in 10% sodium hydroxide to yield **6-10** at room temperature in yields of 80-92%. All of the above reactions yielded **11** at reflux temperature. (Scheme II).

EXPERIMENTAL

Melting points were taken in open capillaries in a Buchi apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer 727 spectrophotometer. The macroanalyses were performed by Galbraith Laboratories in Knoxville, Tennessee (Table I). Nuclear magnetic resonance spectra were determined on a Varian FT-80 spectrometer using tetramethylsilane as an internal reference (Table II). Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

(1-Acetylindol-3-yl)methyl Acetate (**5**).

Gramine (**1**) 4 g (0.022 mole) was refluxed with 30.6 g (0.30 mole) of acetic anhydride for 45 minutes. The mixture was cooled in an ice water bath to 0-5°. Cold water (80 ml) was added to the mixture with constant stirring for 50 minutes at 0-5°. The resulting white crystalline precipitate was filtered, washed with water and dried *in vaccuo* over calcium chloride.

3-Methoxymethylindole (**6**) and 3-Ethoxymethylindole (**7**).

Compound **5** (5 g, 0.025 mole) in 30 ml of methanol or ethanol was stirred at room temperature with 17 or 15 ml of 10% sodium hydroxide solution for 45 minutes or 50 minutes. After cooling the reaction mixture in an ice water bath, ice water (80 ml) was added dropwise. The mixture was left overnight in the cold (0-5°). The fine yellow or white product thus obtained (**6** or **7**) was filtered under reduced pressure, dried and recrystallized from petroleum ether as colorless (**6**) or white (**7**) needles.

Indol-3-ylmethoxypropionitrile (**8**).

A mixture of **5** (5 g, 0.025 mole) and 30 ml of 3-hydroxypropionitrile was added dropwise to 20 ml of 10% sodium hydroxide with constant stirring. The reaction mixture was stirred for an additional 45 minutes, cooled and added dropwise to 80 ml of cold water and left overnight at 0-5°. The brown precipitated product was filtered, dried and recrystallized from ethanol.

Indole-3-ylmethylthioacetic Acid (**9**) and Indol-3-ylmethylthio-β-propionic Acid (**10**).

A mixture of **5** (5 g, 0.025 mole) in 20 ml of (0.22 mole) mercaptoacetic acid or 30 ml of (0.29 mole) mercaptopropionic acid was stirred for 20 minutes. To this mixture, 5 ml of 10% sodium hydroxide was added at 30-40°. The mixture was stirred at this temperature for 1 hour. After cooling, the reaction mixture was added dropwise to 20 ml of ice water with constant stirring. The white **9** or pink **10** precipitate was filtered, dried and recrystallized from benzene.

REFERENCES AND NOTES

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(2) To whom inquires should be addressed.

(3) R. Bennett, Jr., A. Maggiolo, T. Shah, *J. Heterocyclic Chem.*, **18**, 391 (1981).

(4) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).

(5) T. A. Geissman and A. Armen, *J. Am. Chem. Soc.*, **74**, 3916 (1952).

(6) J. N. Coker, O. B. Mathre and W. H. Todd, *J. Org. Chem.*, **28**, 589 (1963).

(7) R. J. Sundberg, "Chemistry of Indoles", Academic Press, New York, NY, 1970, p 93.

(8) W. A. Remers, "Heterocyclic Compounds", Vol. 25, W. J. Healihan, ed, John Wiley and Sons, New York, NY, 1979, p 357.