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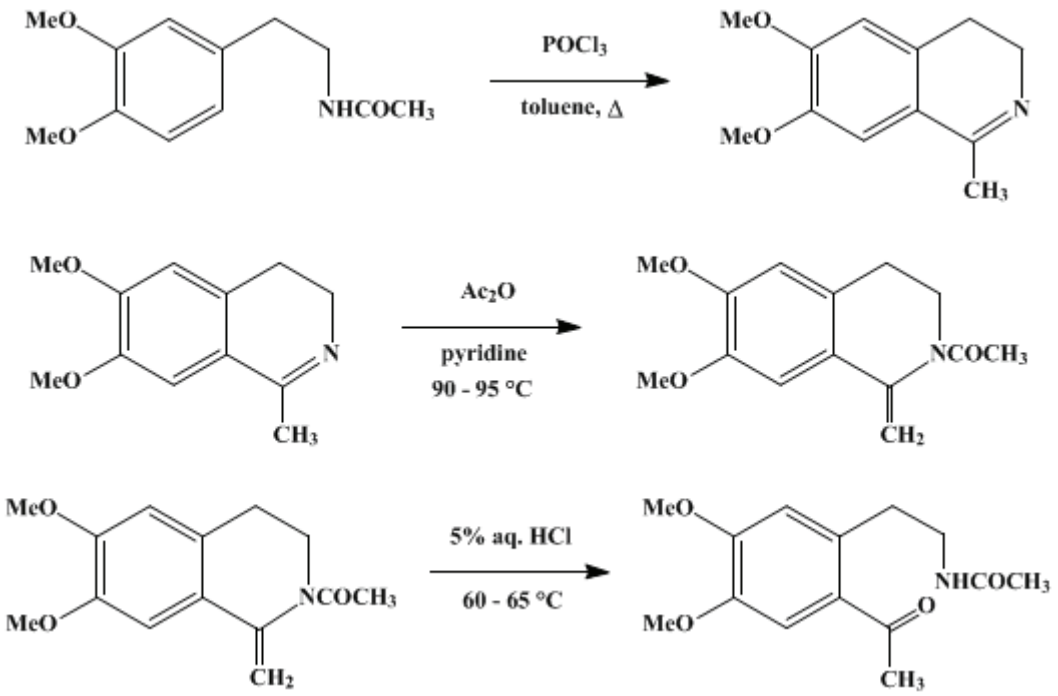
ACYLAMIDOALKYL ACETOPHENONES FROM SUBSTITUTED PHENETHYLAMINES: 2-(2-ACETAMIDOETHYL)-4,5-DIMETHOXYACETOPHENONE

[Acetamide, *N*-[2-(2-acetyl-4,5-dimethoxyphenyl)ethyl]-]



Submitted by A. Brossi, L. A. Dolan, and S. Teitel[1].
Checked by Hiroshi Itazaki and Wataru Nagata.

1. Procedure

Caution! Part A should be conducted in a hood to avoid inhalation of hydrogen chloride fumes.

A. 6,7-*Dimethoxy*-1-*methyl*-3,4-*dihydroisoquinoline*. A 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser protected by a calcium chloride tube, and a pressure-equalizing dropping funnel is charged with 54.0 g. (0.243 mole) of *N*-acetylhomoveratrylamine (Note 1) and 275 ml. of dry toluene (Note 2). The mixture is stirred, warmed to 40°, and treated with 86.4 g. (52.5 ml., 0.572 mole) (Note 3) of phosphorus oxychloride (Note 4), which is added over 1 hour (Note 5). After addition, the reaction mixture is stirred at reflux for 2 hours, then cooled with an ice bath for 4 hours. The resulting crystals are collected by filtration and dried overnight at 50° in a vacuum oven, giving 79.0–79.5 g. (Note 6) of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline dichlorophosphate, m.p. 148–152° (Note 7). This material is dissolved in 150 ml. of water (Note 8), and the solution is treated with 100 ml. of aqueous 40% sodium hydroxide (Note 9). The oil which separates is drawn off, and the aqueous solution is washed with three 20-ml. portions of chloroform. These extracts and the oil are combined, washed with 15 ml. of water, and dried over anhydrous sodium sulfate. Removal of chloroform with a rotary evaporator provides 47.0–48.0 g. (95–96%) of product, which is used without purification in Part B (Note 10).

B. 2-*Acetyl*-6,7-*dimethoxy*-1-*methylene*-1,2,3,4-*tetrahydroisoquinoline*. A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser topped with a calcium chloride

drying tube, and a thermometer is charged with 110 ml. of acetic anhydride, 110 ml. of pyridine, and 45.0 g. (0.220 mole) of the dihydroisoquinoline prepared in Part A. The reaction mixture is stirred and heated at 90–95° for 30 minutes, stored at room temperature overnight, and concentrated by distillation at 50° using a rotary evaporator. The residue is diluted with 20 ml. of ethyl acetate, and another evaporation under reduced pressure gives material that can be crystallized from 75 ml. of ethyl acetate to yield 38.5–41.0 g. (72–77%) of product m.p., 106–107° (Note 11).

C. 2-(2-*Acetamidoethyl*)-4,5-*dimethoxyacetophenone*. A slurry of 31.0 g. (0.125 mole) of the methylene derivative obtained in Part B and 75 ml. of 5% hydrochloric acid is stirred and warmed on a steam bath to 60–65°. As soon as all the solid has dissolved, the solution is cooled with an ice bath to 30° and basified by slowly adding a solution of 6.25 g. of potassium carbonate in 12.5 ml. of water (Note 12). The crystalline precipitate is collected by filtration, washed with three 12.5-ml. portions of water, and air-dried, yielding 30.5–32.0 g. (91–93%) of the acetophenone, m.p. 123–125° (Note 13).

2. Notes

1. *N*-Acetylhomoveratrylamine[2] was prepared by adding 190 ml. of acetic anhydride to a stirred solution of 300 g. (1.80 moles) of β-(3,4-dimethoxyphenyl)ethylamine (Aldrich Chemical Company, Inc.) in 150 ml. of pyridine at such a rate that the temperature is maintained at 90–95° (*ca.* 1.5 hours is required). After the solution had been stored at room temperature overnight, the volatile material was evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to give 286–306 g. (78–83%) of acetylated product, m.p. 99–100°.
2. The checkers used reagent-grade toluene dried over Linde-type 5A molecular sieves.
3. The checkers obtained an identical result when the molar ratio of phosphorous oxychloride to substrate was reduced from 2.35 to 1.5.
4. The checkers obtained phosphorus oxychloride from Wako Pure Chemical Industries, Ltd., Japan and distilled it prior to use.
5. The reaction temperature increased gradually to reflux, at which time the rate of addition was adjusted to maintain reflux.
6. This weight varies with the amount of solvent remaining.
7. Analysis calculated for $C_{12}H_{15}O_2N \cdot HOPOCl_2$: C, 42.37; H, 4.74; N, 4.12; Cl, 20.85; P, 9.10. Found: C, 42.30; H, 4.92; N, 4.21; Cl, 19.08; P, 8.51. IR (KBr) cm.$^{-1}$: 2800, 1665, 1602, 1565, 1105; ^{1}H NMR (D_2O), δ (multiplicity, number of protons, assignment): 3.17 (s, 3H, N=CC*H*$_3$), 4.25 (s, 3H, OC*H*$_3$), 4.30 (s, 3H, OC*H*$_3$), 7.37 (s, 1H, aryl C*H*), 7.62 (s, 1H, aryl C*H*).
The submitters, working on a kilogram scale without purification of reagent or solvent and with no precaution against moisture, obtained 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride,[2] m.p. 202–203°, instead of the dichlorophosphate at this stage. The checkers obtained this hydrochloride by either treating the free base with hydrochloric acid or recrystallizing the dichlorophosphate from methanol–ethyl acetate.
8. The crystals dissolve gradually in water and, since dissolution is exothermic due to decomposition of the dichlorophosphoric acid, ice cooling is desirable.
9. Ice is added during neutralization to keep the temperature below 30°.
10. A pure sample may be prepared by crystallization from ether: m.p. 105–107°; UV (C_2H_5OH) nm. max. (ε): 227 (24,000), 270 (7360), 307 (6640); UV (0.01 *N* hydrochloric acid) nm. max. (ε): 244 (17,250), 302 (8740), 352 (8440); IR (KBr) cm.$^{-1}$: 1650 (C=N).
11. UV (C_2H_5OH) nm. max. (ε): 220 (30,750), 267 (13,200), 304 (7080); UV (0.01 *N* hydrochloric acid) nm. max. (ε): 232 (23,500), 276 (9345), 305 (6120); IR (KBr) cm.$^{-1}$: 880–910 (C=CH_2). A dimorphic form melts at 100–102°. A mixture of this material and the 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline described in (Note 10) melted below 90°.
12. The rate of addition is dependent on the amount of foaming. Ice is added periodically to keep the temperature below 35°.
13. The product can be used without further purification. Recrystallization from water gave an analytical specimen, m.p. 126–127°; UV (95% C_2H_5OH) nm. max. (ε): 231 (24,100), 274 (8750), 304 (5500); infrared (KBr) cm.$^{-1}$: 1673, 1633; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.92 (s, 3H, *H*a), 2.60 (s, 3H, *H*b), 2.68–3.17 (m, 2H, *H*g), 3.30–3.68 (m, 2H, *H*h), 3.93 (s, 6H, *H*c and *H*d), 6.68–7.07 (broad, 1H, *H*i), 6.80 (s, 1H, *H*e), 7.22 (s, 1H, *H*f).

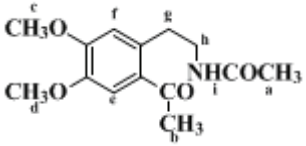
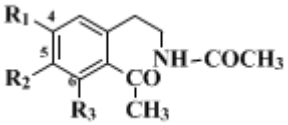
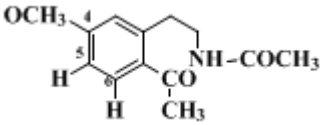
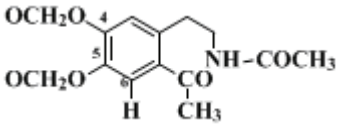
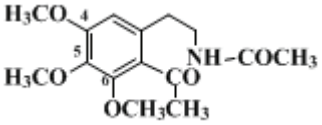


TABLE I
SUBSTITUTED ACETAMIDOETHYL ACETOPHENONES[3]

	Melting Point	Ultraviolet C_2H_2OH nm. max (ε)
$R_1 = OCH_3$, $R_2 = R_3 = H$		
	86°	221 (14,700), 269 (13,600)
R_1, $R_2 = OCH_2O$, $R_3 = H$		
	120°	230 (36,500), 273 (5200), 307 (5460)
$R_1 = R_2 = R_3 = OCH_3$		
	58°	222 (14,700), 263 (16,250)

3. Discussion

This procedure provides a facile method for converting substituted 1-methyl-3,4-dihydroisoquinolines into the corresponding 2-(2-acetamidoethyl)acetophenones, which are useful intermediates in the synthesis of 1-(substituted phenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines.[4,5] The sequence is uncomplicated and affords, in excellent yield, a product that requires no further purification. In addition to the examples in Table I, this method has been utilized for the synthesis of other substituted acetophenones,[4,3,6] as well as related benzophenones and a heptanophenone.[7] The latter two classes of compounds have also been obtained by ring opening of 2-ethyl-1-phenyl- or 2-ethyl-1-hexyl-6,7-dialkoxy-3,4-dihydroisoquinolinium iodides with benzoyl chloride.[8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 268

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-(2-Acetamidoethyl)-4,5-dimethoxyacetophenone

2-(2-acetamidoethyl)acetophenones

1-(substituted phenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines

potassium carbonate (584-08-7)

hydrogen chloride,
hydrochloric acid,
hydrochloride (7647-01-0)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether (60-29-7)

acetic anhydride (108-24-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

Acetophenone (98-86-2)

benzoyl chloride (98-88-4)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

toluene (108-88-3)

methylene (2465-56-7)

β-(3,4-dimethoxyphenyl)ethylamine (120-20-7)

phosphorous oxychloride

6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline dichlorophosphate

dihydroisoquinoline

6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride

dichlorophosphate

dichlorophosphoric acid

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (4721-98-6)

heptanophenone (1671-75-6)

Acetamide, N-[2-(2-acetyl-4,5-dimethoxyphenyl)ethyl]- (57621-03-1)

N-acetylhomoveratrylamine (6275-29-2)

2-Acetyl-6,7-dimethoxy-1-methylene-1,2,3,4-tetrahydroisoquinoline (57621-04-2)