Preparation and Spectral Properties of Benzylidene Diacetates

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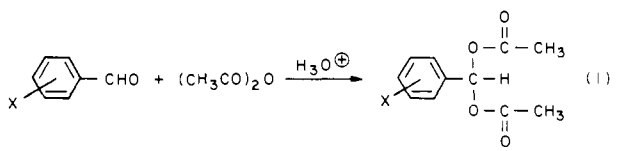
Aromatic aldehydes react with acetic anhydride in the presence of methanesulfonic acid, phosphoric acid, or sulfuric acid catalyst to afford benzylidene diacetates (acylals) in good to excellent yields. Overall, sulfuric acid is the most effective catalyst although better yields of diacetates are obtained from the more reactive aldehydes with methanesulfonic acid and/or phosphoric acid. This procedure produces higher yields of benzylidene diacetates than are obtained from the chromyl acetate oxidation of methylbenzenes. The infrared, NMR, and ultraviolet spectra of benzylidene diacetates are presented.

Although benzylidene diacetates (acylals, **1**) are well known (*1–9, 11–15*), there does not appear to be a systematic study of the experimental conditions which will generate optimum yields of products. Benzylidene diacetates (**1**), which are acetate esters of the hydrates of benzaldehydes, are prepared from the reaction of aromatic aldehydes with acetic anhydride in the presence of acid catalysts or from the reaction of methylbenzenes, acetic anhydride, chromyl acetate, and sulfuric acid (*7, 8, 11, 12*). The latter procedure gives fair to modest yields of acylals with 4-bromo- (48–60%), 4-cyano- (47–50%), 2-nitro- (37%), and 4-nitrotoluene (66%) (*8*). Benzylidene diacetates (**1**) are useful intermediates for preparing phenylmethanals (*4–6, 13*).



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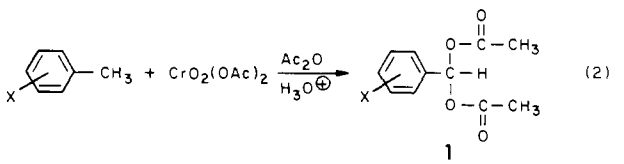

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During the course of our studies of the chromyl acetate oxidation of alkylaromatics, we have also explored the experimental conditions for preparing benzylidene diacetates (**1**) and triacetates from aromatic and heteroaromatic aldehydes using methanesulfonic acid, phosphoric acid, or sulfuric acid as catalyst. The slightly exothermic reaction was carried out at room temperature in an excess of acetic anhydride. The vigorous reaction among hydronium ion, aromatic aldehydes, and acetic anhydride was minimized by adding a solution of acid catalyst and anhydride to a solution of aromatic aldehyde and anhydride. This mode of addition appears to be especially beneficial for reactive aldehydes which are highly susceptible to acid catalyzed reactions.

Table I shows that sulfuric acid is generally a more effective catalyst than either methanesulfonic acid or phosphoric acid under these experimental conditions. It is the catalyst of choice except for alkoxyl substituted aromatic aldehydes where phosphoric acid appears to be more effective than methanesulfonic acid.

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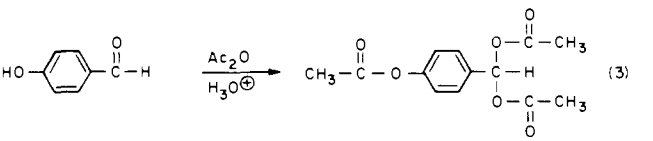
Table I also shows the yields of benzylidene diacetates (**1**) are influenced by the nature of the electron releasing and electron withdrawing groups and by their positions on the aromatic rings. In general, for aromatic aldehydes, the yields ranged from good to excellent in the sulfuric acid catalyzed reactions. Excellent yields are obtained from 1- and 2-naphthylmethanal and the heteroaromatic aldehydes (2-furylmethanal and 2-thienylmethanal) afforded fair yields of diacetates with phosphoric acid or methanesulfonic acid as catalyst.

Esterification of the hydroxyl group in 3-hydroxy-, 4-hydroxy-, and 3-methoxy-4-hydroxyphenylmethanal affords the corresponding triacetates.



(3)

Table I also summarizes the spectral properties of 17 benzylidene diacetates, two naphthylidene diacetates, and two heteroaromatic diacetates. The ultraviolet spectra of the acylals generally showed B-bands (benzenoid bands) with multiple peaks or fine structure in the region between 230 and 270 nm. NMR spectra showed benzene ring resonances in the δ 7.2–7.3 (τ 2.7–2.8) region, methyl groups in the ester as singlets in the δ 2.0 (τ 8.0) region, and benzylic hydrogens as singlets in the δ 7.5–8.1 (τ 1.9–2.5) region or as part of the multiplet for aromatic hydrogens.

Each diacetate infrared spectrum generally showed carbonyl group absorption in the 1755 cm^{-1} (5.70 μ) region and an asymmetric carbon–oxygen–carbon absorption of an ester at about 1225 cm^{-1} (8.15 μ) which is characteristic of an acetate (*10*). In most diacetates the characteristic infrared absorptions in the 2000–1667 cm^{-1} (5–6 μ) and 750–835 cm^{-1} (12.0–13.3 μ) regions for mono-, di-, and trisubstituted benzene absorptions were also observed.

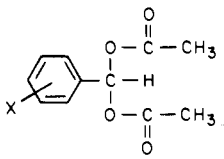
Experimental Section

General. Liquid aldehydes were distilled under reduced pressure and solid aldehydes were triturated with 2% sodium carbonate solution, filtered, dried, and recrystallized from ethyl alcohol or aqueous ethyl alcohol immediately before use. In all cases, the boiling points and melting points agreed with literature values. Reagent grade acetic anhydride, methanesulfonic acid (70%), phosphoric acid (85–86%), and sulfuric acid (95–96%) were used directly without special purification.

All melting points are uncorrected and were determined on a Thomas-Hoover apparatus. NMR spectra were taken on a Varian E-M360 instrument, infrared spectra were taken on a Beckman AccuLab 2 instrument, and ultraviolet spectra were taken on a Cary 14 or Beckman ACTA III spectrophotometer. Elemental analyses were performed by G. I. Robertson, Jr., Florsham Park, N.J.

Procedure. To a three-necked round-bottomed flask fitted with a dropping funnel and thermometer and containing 0.025 mol of aldehyde in 25 mL of acetic anhydride was added 0.0004 mol of acid catalyst in 4.95 mL of acetic anhydride. The reaction mixture was stirred during addition (30 min) and for 15 min after addition. The product mixture was poured, with stirring, into a beaker containing 75 g of ice and 75 mL of water. The solid was

Table I. Physical and Spectral Properties and Yields of Benzylidene Diacetates and Triacetates[a,b]



X	Catalysts, yield (%)			Mp, °C	Spectral data	
					^{1}H NMR[c] δ	UV[d] λ_{max} (ϵ_{max})
	H_2SO_4	H_3PO_4	CH_3SO_3H			
4-CH_3	76.1	89.2	72.4	81–82	2.05 (s, 6), 2.3 (s, 3), 7.20 (q, 4), 7.5 (s, 1)	223 (4650), 255 (219), 262 (259), 267 (188), 271 (113)
2-OCH_3	—[e]	81.9	79.9	74–75	2.0 (s, 6), 3.8 (s, 3), 6.7–7.30 (m, 4), 7.75 (s, 1)	223 (5063), 274 (3200), 280 (3000)
4-OCH_3	—[e]	52.1[f]	—[g]	64–65[h]	2.0 (s, 6), 3.7 (s, 3), 6.7–7.4 (m, 4), 7.4 (s, 1)	234 (4032), 255 (219), 273 (2280), 280 (2160), 291 (1080)
2-OC_2H_5	—[e]	86.1	—[g]	86–87	1.3–1.6 (t, 3), 2.0 (s, 6), 3.8–4.2 (q, 2), 6.7–7.5 (m, 4), 7.9 (s, 1)	275 (2840), 281 (2600)
3,4-(OCH_2O)–	—[e]	78.2	—[g]	75–76	2.0 (s, 6), 5.9 (s, 2), 6.6–7.4 (m, 4)	237 (5080), 286 (4360), 314 (320)
3-OH	77.2	—[e,g]	—[e,g]	75–76	2.05 (s, 6), 2.2 (s, 3), 7.1–7.5 (m, 5)	263 (597), 269 (511)
4-OH	97.9	—[e]	—[e]	89–90	2.05 (s, 6), 2.2 (s, 3), 7.0–7.5 (m, 4), 7.5 (s, 1)	253 (760), 259 (715)
4-OH, 3-OCH_3	91.8	—[e]	—[e]	79–80	2.1 (s, 6), 2.2 (s, 3), 3.8 (s, 3), 7.0–7.1 (m, 3), 7.55 (s, 1)	274 (2760), 281 (2640)
4-F	98	92.5	—[e]	50.5–51.5	2.05 (s, 6), 6.9–7.6 (m, 4), 7.5 (s, 1)	244 (110), 249 (210), 254 (320), 257 (330), 260 (390), 262 (440), 267 (425)
2-Cl	90.5	—[g]	—[e]	56–57	2.05 (s, 6), 7.1–7.6 (m, 4), 7.8 (s, 1)	254 (270), 262 (410), 269 (520), 275 (420)
3-Cl	86.5	88.5	—[g]	65–66	2.1 (s, 6), 7.35–7.5 (m, 5)	243 (135), 249 (180), 255 (270), 262 (405), 269 (565), 276 (485)
4-Cl	93.1	93.3	83.2	79–80	2.1 (s, 6), 7.4–7.6 (m, 5)	246 (355), 252 (355), 257 (370), 263 (365), 270 (235), 273 (160)
4-Br	92.4	86.9	90.3	91–92[i]	2.05 (s, 6), 7.2–7.7 (m, 5)	252 (285), 258 (345), 264 (365), 270 (240), 274 (150)
4-H	85.6	100	100	41–41.5[j]	2.0 (s, 6), 7.4–7.65 (m, 6)	252 (224), 255 (226), 263 (269), 268 (186)
2-NO_2	94.9	—[g]	—[g]	85.5–86.5[k,l]	2.1 (s, 6), 7.6–8.0 (m, 6)	225 (19 800), 258 (12 100)
3-NO_2	63.0	—[g]	—[g]	63–64[l,m]	2.15 (s, 6), 7.5–8.3 (m, 6)	215 (7640), 265 (7720)
4-NO_2	87.4	—[g]	—[g]	124–125[l,n]	2.15 (s, 6), 7.9 (q, 4), 7.7 (s, 1)	260 (10 300)
1-Naphthylidene	92.1	87.1	77.0	105–106	2.11 (s, 6), 7.4–8.1 (m, 8)	222 (8910), 270 (630), 281 (685), 292 (445)
2-Naphthylidene	91.2	77.7	—[g]	99.5–100	2.1 (s, 6), 7.2–8.0 (m, 8)	246 (4300), 268 (5200), 275 (5525), 284 (4000), 305 (490), 312 (375), 319 (325)
2-Furfurylidene	—[e]	69.8	25.4	50–51[o]	2.00 (s, 6), 6.2–7.4 (m, 3), 7.5 (s, 1)	
2-Thienylidene	—[g]	43.3	42.9	66–67	2.05 (s, 6), 6.9–7.4 (m, 3), 7.8 (s, 1)	

[a] All compounds gave satisfactory C and H analyses. [b] Recrystallized from aqueous ethyl alcohol. [c] Tetrachloromethane solvent. [d] Absolute ethyl alcohol solvent. [e] Benzylidene diacetate not isolated. [f] Recrystallized from ethyl acetate–petroleum ether. [g] Impure crystals with wide melting range. [h] Lit. 65–66 °C (*2*). [i] Lit. 94–95 °C (*7*). [j] Lit. 45.8 °C (*13*). [k] Lit. 86.3 °C (*13, 14*). [l] Higher temperatures might be necessary with phosphoric acid and methane sulfonic acid. [m] Lit. 66.5–67 °C (*14*). [n] Lit. 125–126 °C (*11, 14*). [o] Lit. 52–53 °C (*9*).

filtered, washed successively with cold water (25 mL), 2% aqueous sodium carbonate solution (25 mL), and cold water (25 mL), dried, and recrystallized from ethyl alcohol, aqueous ethyl alcohol, or ethyl acetate–petroleum ether.

Acknowledgment

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Literature Cited

(1) Adams, R., Fogler, M. F., Kreger, C. W., *J. Am. Chem. Soc.*, **44**, 1126 (1922).
(2) Andrulis, Jr., P. J., Dewar, M. J. S., Dietz, R., Hunt, R. L., *J. Am. Chem. Soc.*, **88**, 5473 (1966).

(3) Brady, O. L., Cosson, A. N., Roper, A. J., *J. Chem. Soc.*, **127**, 2427 (1925).
(4) Davey, W., Gwilt, J. R., *J. Chem. Soc.*, 204 (1950).
(5) Davey, W., Gwilt, J. R., *J. Chem. Soc.*, 3348 (1950).
(6) Davey, W., Gwilt, J. R., *J. Chem. Soc.*, 1384 (1955).
(7) Lieberman, S. V., Connor, R., "Organic Synthesis", Coll. Vol. II, Wiley, New York, N.Y., 1943, p 441.
(8) Nishimura, T., ref 7, Coll. Vol. IV, 1963, p 713.
(9) Scheibler, H., Sotschech, F., Friese, H., *Chem. Ber.*, **57**, 1443 (1924).
(10) Silverstein, R. M., Bassler, G. C., Morrill, T. C., "Spectrometric Identification of Organic Compounds", Wiley, New York, N.Y. 1974, p 262.
(11) Thiele, J., Winter, E., *Justus Liebigs Ann Chem.*, **311**, 356 (1900).
(12) Tsang, S. M., Wood, E. H., Johnson, J. R., ref 7, Coll. Vol. 3, 1955, p 641.
(13) Wegscheider R., Spath, E., *Monatsh. Chem.*, **30**, 825, 840 (1909).
(14) Van der Beek, P. A. A., *Recl. Trav. Chim. Pays-Bas*, **47**, 304 (1928).
(15) Van Peski, A. J., *Recl. Trav. Chim. Pays-Bas*, **40**, 117 (1922).

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Synthesis of Potential Specific Inhibitors of Certain Amino Acid Decarboxylases

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A number of potential specific inhibitors of amino acid decarboxylases were synthesized by subjecting amino acids and their derivatives to Dakin–West reaction conditions. In some cases the Dakin–West conditions were modified. Pyridine and imidazole were found to be suitable as bases in the Dakin–West reaction.

The Dakin–West reaction (*3*) on α-amino acids yields 1-substituted-1-*N*-acetamidopropanones. The acetamidopropanone obtained from histidine as well as the aminopropanone (obtained by the hydrolysis of the acetamidopropanone) have been shown to be specific inhibitors of histidine decarboxylase (*7–9*).

This report is a continuation of our attempts (*6–8*) to synthesize active-site-directed reversible inhibitors of enzymes utilizing amino acids as substrates.

Potential inhibitors of specific amino acid decarboxylases were synthesized by subjecting selected amino acids and their derivatives to Dakin–West reaction conditions. In some cases the Dakin–West reaction was modified to obtain the desired products (Tables I–III) (Figure 1).

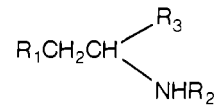
L-Cysteine (I) underwent Dakin–West reaction to give 4-acetylthio-3-acetamido-2-butanone (II) (Table I). Acid hydrolysis of II afforded 4-mercapto-3-amino-2-butanone hydrochloride (III). Treatment of compound II with trifluoroacetic anhydride yielded the oxazole IV (Table II) along with a small amount of the free mercaptooxazole V (4-mercaptomethyl-2,5-dimethyloxazole), identified by its NMR spectrum.

L-Cysteine hydrochloride monohydrate was dehydrated to cysteine hydrochloride (*1*) which in turn was converted quantitatively to *S*-benzhydrylcysteine (*4*) (VI). Compound VI upon treatment with Ac_2O and pyridine gave 4-diphenylmethylthio-3-acetamido-2-butanone (VII). *S*-Triphenylmethylcysteine (VIII) was obtained from L-cysteine hydrochloride (*13*) and converted to 4-triphenyl-methylthio-3-acetamido-2-butanone (IX).

DL-Methionine (X) gave the normal Dakin–West product XI. The acetamido ketone XI was converted to the corresponding oxazole XII.

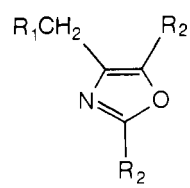
The Dakin–West reaction on L-proline (XIII) or *N*-acetyl-L-proline (obtained in 95% yield from XIII, Ac_2O, and pyridine) or *N*-trifluoroacetyl-L-proline (XIV) was unsuccessful. Compound

Table I

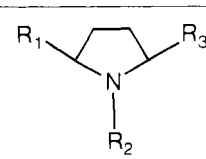


Compound	R_1	R_2	R_3
II	CH_3COS	$COCH_3$	$COCH_3$
III	HS	H·HCl	$COCH_3$
VI	$(C_6H_5)_2CHS$	H	COOH
VII	$(C_6H_5)_2CHS$	$COCH_3$	$COCH_3$
VIII	$(C_6H_5)_3CS$	H	COOH
IX	$(C_6H_5)_3CS$	$COCH_3$	$COCH_3$
XI	CH_3SCH_2	$COCH_3$	$COCH_3$
XIX	CH_3COOCO	$COCH_3$	$COCH_3$
XXIII	C_6H_5	$COCF_3$	COOH
XXIV	$[C_6H_5$	$COCF_3$	$CO]_2O$
XXVI	C_6H_5	$COCF_3$	$COOC_6H_5$
XXVIII	C_6H_5	$COCH_3$	$COCH_3$
XXIX	H	$COCH_3$	$COCH_3$

Table II



Compound	R_1	R_2
IV	CH_3COS	CH_3
V	HS	CH_3
XXII	CH_3SCH_2	CH_3
XX	CH_3COOCO	CH_3
XXI	HOOC	CH_3
XXV	C_6H_5	CF_3



Compound	R_1	R_2	R_3
XIV	H	$COCF_3$	COOH
XV	[H	$COCF_3$	$CO]_2O$
XVII	=O	$COCH_3$	$COCH_3$

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