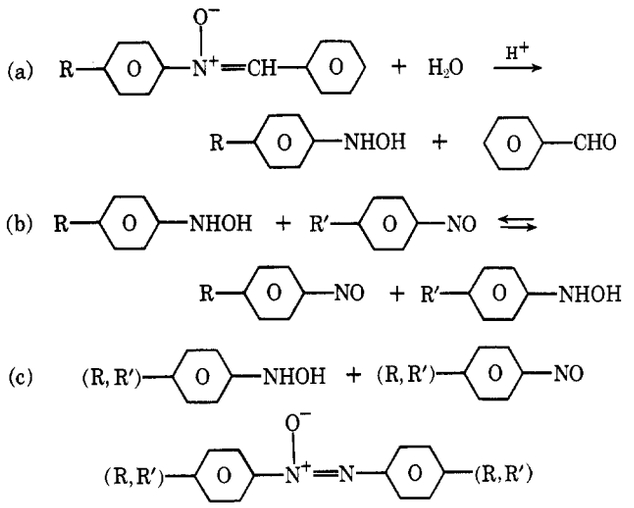
SCHEME II



hydroxylamine which then equilibrates with the phenylnitrosobenzene. The phenylhydroxylamines and phenylnitroso compounds then react irreversibly to give azoxy products (Scheme II). The kinetics and mechanism of the latter reactions have previously been investigated.[5a,b]

In order to examine the possibility that α-anilino-*N*-phenylnitrones[3] might react differently than **1**, α-*p*-toluidino-*N*-tolylnitrone (**3**) was treated with nitrosobenzene in chloroform in the dark for 5 days at ambient temperature. In addition to *p*-methylformanilide, azoxybenzene, 4,4′-dimethylazoxybenzene, and a mixture of 4- and 4′-methylazoxybenzene were formed. This suggests that the α-anilino-*N*-phenylnitrones react *via* a mechanism similar to α-phenyl-*N*-phenylnitrones (Scheme II).

Experimental Section

The aryl hydroxylamines were prepared by the procedure of Kamm.[6] Nitrosobenzene was purchased from the Aldrich Chemical Co. The other nitrosobenzenes were prepared using the procedure of Barrow.[7] α-*p*-Chlorophenyl-*N*-phenylnitrone and α-*p*-tolyl-*N*-phenylnitrone were synthesized using the reported methods.[8a,b]

α-*p*-Toluidino-*N*-*p*-tolylnitrone.—Using the procedure of Taylor,[3] a solution of *p*-methylnitrosobenzene (2.4 g, 0.92 mol) and *p*-methylmethylene aniline (3.6 g, 0.03 mol) in 70 ml of chloroform was stoppered and kept in the dark for 70 hr. The chloroform was removed under reduced pressure. The solid remaining was taken up and recrystallized from benzene, yield 1.9 g (35%), mp 129–130°.

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.71; N, 11.66. Found: C, 74.77; H, 6.79; N, 11.42.

The reaction below illustrates the general procedure used in the reactions of arylnitrones with the nitrosobenzenes.

Reaction of α-Phenyl-*N*-*p*-chlorophenylnitrone with Nitrosobenzene.—A solution of α-phenyl-*N*-*p*-chlorophenylnitrone (3.45 g, 0.015 mol) and nitrosobenzene (1.5 g, 0.015 mol) in 75 ml of chloroform was stoppered and placed in the dark for 70 hr. At the end of that time no nitrone remained as evidenced by glpc. Three products were formed. The products were separated by preparative glpc and found to be azoxybenzene, 4- and 4′-chloroazoxybenzene, and 4,4′-dichloroazoxybenzene by superimposing their ir spectra with the ir spectra of known samples. The three products were formed in the ratio of 0.9:1:0.9. Benzaldehyde was the only other product formed.

Reaction of α-*p*-Toluidino-*N*-*p*-tolylnitrone with Nitrosobenzene.—Using the procedure of Taylor and Buntrock,[3] a mixture of α-*p*-toluidino-*N*-*p*-tolylnitrone (0.48 g, 0.0002 mol) and nitrosobenzene (0.22 g, 0.002 mol) in 30 ml of chloroform was allowed to stand in the dark for 5 days. Analysis by glpc showed that the nitrone was 75% reacted. The four products found were *p*-methylformanilide, azoxybenzene, 4- and 4′-methylazoxybenzene, and 4,4′-dimethylazoxybenzene, formed in the ratio of 7:3:1.8:1.

Registry No.—α-*p*-Toluidino-*N*-*p*-tolylnitrone, 33905-35-0; α-phenyl-*N*-*p*-chlorophenylnitrone, 5909-74-0; nitrosobenzene, 586-96-9.

(5) (a) Y. Ogata, M. Tsuchida, and Y. Takgi, *J. Amer. Chem. Soc.*, **79**, 3397 (1957). (b) G. A. Russell and E. J. Geels, *ibid.*, **87**, 122 (1965).

(6) O. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., p 445.

(7) F. Barrow and F. J. Thorneycroft, *J. Chem. Soc.*, 773 (1939).

(8) (a) R. E. Erickson and T. M. Myszkewicz, *J. Org. Chem.*, **30**, 4236 (1965). (b) S. L. Larsen, G. Schroll, S. O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

On the Friedel–Crafts Benzoylation and Acylation of Kojic Acid

LUISITO TOLENTINO AND JACQUES KAGAN*

Chemistry Department, University of Illinois at Chicago Circle, Chicago, Illinois 60607

Received June 16, 1971

Despite reports to the contrary, we believe that Friedel–Crafts acylation or aroylation reactions of kojic acid (**1**, 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one)[1] under Friedel–Crafts conditions are yet to be accomplished.

Woods reported that treatment of **1** with benzoyl chloride and aluminum chloride in carbon disulfide yielded 6-benzoylkojic acid (**2**), mp 188°.[2] Following the published procedure, we obtained a crystalline monobenzoylated product, mp 180–181°, mol wt 264 (mass spectrum), which gave a positive $FeCl_3$ test. That it was not the anticipated Friedel–Crafts product but rather the benzoate ester **3** (lit.[3] mp 180–181°) was demonstrated by comparing the nmr spectra of **1** and **3**, which showed the deshielding of the methylene protons from 4.50 to 5.20 ppm by the benzoate group, and which confirmed the presence of two pyrone ring protons (Table I). Although the signals for the phenyl protons overlapped that of the C-6 proton, the latter was clearly visible in the integration.

Woods' structural assignment for his benzoylated product rested largely on the results of a Clemmensen reduction, which yielded a product different from the starting material, and the reaction was therefore taken to represent the reduction of the benzoyl ketone. While it is entirely possible that Woods had actually obtained **2**, and that its synthesis was very sensitive to minor changes in reaction conditions, we also considered the possibility that he was dealing with **3** and that its reduction had taken an unforeseen course. Treatment of **3** in the conditions of the Clemmensen reduction[1] yielded some benzoic acid, probably resulting from hydrogenolysis.[3] A neutral fraction which we could not crystallize was also obtained. It was acetylated to yield a product, mp 91–92°. Its molecular weight of 168 (mass spectrum) and nmr ($CDCl_3$), which consisted

(1) A. Beelik, "Advances in Carbohydrate Chemistry," Vol. 11, M. L. Wolfrom, Ed., Wiley, New York, N. Y., 1956, p 145.

(2) L. L. Woods, *J. Amer. Chem. Soc.*, **74**, 1105 (1952).

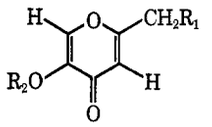
(3) A. Beelik and C. B. Purves, *Can. J. Chem.*, **33**, 1361 (1955).

TABLE I

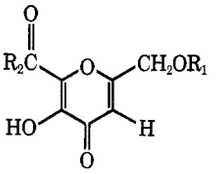
NMR SPECTRA OF KOJIC ACID DERIVATIVES[a]

Compd	Solvent	$-CH_2R$	H-3	H-6	Phenyl	CH_3CO	OCH_3	OH
1	DMSO-d_6	4.50	6.60	8.10				5.68
								9.09
3	DMSO-d_6	5.20	6.60	*b*	7.70–8.20[b]			9.30
4	$CDCl_3$	2.27	6.23	7.73		2.27		
5	$CDCl_3$	2.30	6.27	7.80				
	DMSO-d_6	2.34	6.32	8.08				9.05
6	$CDCl_3$	5.12	6.55	*b*	7.30–8.20[b]	2.32		
7	$CDCl_3$	4.93	6.53	7.92		2.17		
						2.33		
8	$CDCl_3$	5.03	6.68	*b*	7.40–8.40[b]	2.20		
9	$CDCl_3$	5.28	6.68	*b*	7.30–8.40[b]			
	DMSO-d_6	5.41	7.20	8.85	7.50–8.40[b]			
12	$CDCl_3$	4.93	6.50	7.87		2.17		
	DMSO-d_6	5.00	6.53	8.20		2.13		9.00
13	DMSO-d_6	4.35	6.36	8.18			3.69	5.70
14	$CDCl_3$	4.95	6.49	7.65		2.17	3.80	
15	DMSO-d_6	4.67	7.70	8.13				9.26
16	DMSO-d_6	4.40	6.55	8.74	7.60–8.40			5.84

[a] Values in parts per million relative to internal TMS. [b] The phenyl signals overlapped H-6.



1, R_1 = OH; R_2 = H
3, R_1 = $OCOC_6H_5$; R_2 = H
4, R_1 = H; R_2 = $OCOCH_3$
5, R_1 = R_2 = H
6, R_1 = $OCOC_6H_5$; R_2 = $COCH_3$
7, R_1 = $OCOCH_3$; R_2 = $COCH_3$
8, R_1 = $OCOCH_3$; R_2 = COC_6H_5
9, R_1 = $OCOC_6H_5$; R_2 = COC_6H_5
12, R_1 = $OCOCH_3$; R_2 = H
13, R_1 = OH; R_2 = CH_3
14, R_1 = $OCOCH_3$; R_2 = CH_3
15, R_1 = Cl; R_2 = H
16, R_1 = OH; R_2 = COC_6H_5



2, R_1 = H; R_2 = C_6H_5
10, R_1 = H; R_2 = CH_3
11, R_1 = $COCH_3$; R_2 = CH_3

of three singlets at 7.73 (1 H), 6.23 (1 H) and 2.27 ppm (6 H), suggested the 2-methyl-5-acetoxypyrone structure **4**. This assignment was confirmed by comparison with an authentic sample prepared from allomaltol (**5**), which was itself conveniently obtained by Clemmensen reduction of **1**.[4,5] No reaction was observed when **3** was exposed to thionyl chloride in hexane as described.[1,6] At room temperature **3** did not react with acetyl chloride in benzene, while acetylation took place upon heating, yielding **6**, mp 86–87°. It is therefore probable that Woods' product, mp 182°, was again his starting material. Finally, work-up of the Meerwein–Ponndorf–Verley reduction of **3**, which was carried out as described,[1] yielded crystalline starting material and we did not observe Woods' product, mp 114–115°.

Woods and Dix later noticed that benzoylation of diacetyl kojic acid (**7**) with benzoyl chloride in trifluoroacetic acid yielded a product, mp 143°, which was different from that obtained through benzoylation of **1** followed by acetylation as described above.[7] As no structural explanation had been offered, we repeated the benzoylation of **7**, which gave us a product, mp 145–146°, probably identical with that obtained by Woods and Dix. It was identified as 2-acetoxymethyl-5-benzoxy-4*H*-pyran-4-one (**8**) by its nmr ($CDCl_3$) which showed two pyrone ring protons (one of them overlapped by the phenyl), one acetyl, and the methylene at 4.90 ppm. The alternate 2-benzoxymethyl-5-acetoxy-4*H*-pyran-4-one (**6**) formulation was ruled out by the nmr. Synthesis of **8** and direct comparison confirmed the assignment.

The ring benzoylation to **2** was also claimed by Woods[8] in the reaction of **1** with benzoic acid or ethyl benzoate in the presence of trifluoroacetic acid. The values reported for the products, mp 188 and 186–187°, respectively, agree with that of **3**, which is the product obtained by us when the published procedures were followed.

Woods also reported[1] on the stannic chloride catalyzed benzoylation of **1**, without clarifying the nature of the crystalline product(s).[9] In our hands, benzoylation in these conditions yielded the diester **9**, mp 133–134°, which could survive the described acidic treatment.

We now turn to the Friedel–Crafts acetylation of **1** to **10**. Woods' first report on the matter concerned the reaction with acetic anhydride and zinc chloride at

(4) The reduction of an amino- or hydroxymethyl to a methyl group is not without precedent in the γ-pyrone series. For example see (a) R. L. Miller, B. E. Tate, R. P. Allingham, and H. Rutner, Belgian Patent 625,114 (1963); *Chem. Abstr.*, **60**, 10651 (1964); (b) B. E. Tate, U. S. Patent 3,171,842 (1965); *Chem. Abstr.*, **62**, 16201 (1965); (c) I. Ichimoto, K. Fujii, and C. Tatsumi, *Agr. Biol. Chem.*, **29**, 325 (1965); (d) B. E. Tate and R. P. Allingham, U. S. Patent 3,365,469 (1968); *Chem. Abstr.*, **69**, 10360 (1968).

(5) A similar reduction of a benzoxymethyl to a methyl group was reported by Beelik and Purves.[3]

(6) The product reported by Woods and purported to be 2-chloromethyl-5-hydroxy-6-benzoyl-4*H*-pyran-4-one melted at 185–187°, very close to his starting material (188°).

(7) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **24**, 1126 (1959).

(8) L. L. Woods, *ibid.*, **27**, 696 (1962).

(9) No melting point was reported for the twice-recrystallized material which was submitted to analysis. Its resemblance to the product, mp 128–130°, which was obtained by subsequent acid treatment, is therefore unknown.

elevated temperature.[10] The product, mp 106°, was soon shown by Hurd and Sims[11] to be the diacetate **7**. A later report[12] described the acetylation with acetic anhydride and phosphoric acid at 150°, which was claimed to yield **10**, mp 156.5°, *via* its monoacetate **11**, mp 119–120°. We did not obtain this material, but found instead a product, mp 135–137°, mol wt 184, which was the monoacetate **12** as shown by its nmr (Table I). It behaved as described by Woods, who may have been dealing with an impure sample. He reported that reflux in water converted it into a product, mp 156.5°; reflux of **12** in water hydrolyzed it into kojic acid, mp 155–157°, in agreement with Hurd and Sims,[11] who observed complete hydrolysis of the diacetate **7** when refluxed in water. Complete O acetylation of Woods' compound was reported to yield a product, mp 98–99°; acetylation of **12** (performed more conveniently by complete acetylation of **1** with acetyl chloride) yielded the diacetate **7**, mp 101–102°. Finally, Clemmensen reduction of **12** would now be expected to yield **5**, mp 150–152°, in a reaction analogous to that of **3**, and the product obtained by Woods melted at 147–149°.

A synthesis of 6-acetylkojic acid (**10**), mp 136°, was also claimed by Eiden,[13] who treated **1** with acetic acid in the presence of hydrogen chloride. In our hands the synthesis led to the acetate **12**, and the proposed structures for the thio derivatives[13] must be corrected accordingly.[14] This result is analogous to that described by Ichimoto and Tatsumi, who acetylated **1** with acetic acid and zinc chloride.[15]

Woods also reported the synthesis of diketones when kojic acid or its derivatives were treated with diethyl oxalate in the presence of trifluoroacetic acid.[16] The foregoing results with ethyl benzoate made the claim doubtful, and we found that no reaction took place when **1** was treated as indicated, thus explaining the melting point and yield of Woods' material. A "reductive acetylation" had been performed on that material, yielding a product, mp 103–104°. We found that **1** yielded the diacetate **7**, mp 102–103°, when treated with zinc and acetic anhydride as indicated. A similar observation was made with the methyl ether **13**, which did not react with diethyl oxalate and which yielded the acetate **14**, mp 124–125°, in the presence of zinc and acetic anhydride.[17]

The products obtained by Woods and Dix,[18] after treatment of **1**, **13**, or chlorokojic acid (**15**) with carbon monoxide and hydrogen chloride in trifluoroacetic acid, and the starting materials had very close melting points and had nmr spectra not readily explained by the proposed structures. We found no reaction when the published procedures were followed and the nmr spectra must therefore be reinterpretated in terms of showing the hydroxyl protons in DMSO,[19] rather than ab-

(10) L. L. Woods, *J. Amer. Chem. Soc.*, **70**, 2608 (1948).
(11) C. D. Hurd and R. J. Sims, *ibid.*, **71**, 2440 (1949).
(12) L. L. Woods, *ibid.*, **75**, 3608 (1953).
(13) F. Eiden, *Arzneim.-Forsch.*, **10**, 947 (1960).
(14) It is interesting to note that a similar treatment of 2-hydroxymethyl-3-hydroxy-4*H*-pyran-4-one yielded the chloromethyl derivative.[4a]
(15) I. Ichimoto and C. Tatsumi, *Bull. Univ. Osaka Prefect., Ser. B*, **13**, 53 (1962); *Chem. Abstr.*, **61**, 14627*f* (1964).
(16) L. L. Woods, *Trans. Kans. Acad. Sci.*, **66**, 59 (1963); *Chem. Abstr.*, **59**, 7624*e* (1963).
(17) Woods' sample, mp 102°, may have been the acetate in impure form.
(18) L. L. Woods and P. A. Dix, *J. Org. Chem.*, **26**, 1028 (1961).
(19) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

normal aldehyde protons. Judging from these results and our own synthesis with zinc and acid, one would have believed that the borohydride reduction performed by Woods and Dix[18] had converted **1** into **5**, mp 167°. However, we observed no reaction when **1** was treated with sodium borohydride.

Experimental Section

Benzoylation of Kojic Acid with $AlCl_3$.—Woods' procedure[2] was repeated with 14.2 g of **1**. The crude product was recrystallized twice from EtOH to yield 4.2 g of **3**: mol wt 246 (mass spectrum); mp 179–180° (lit.[1] mp 180–181°); ir (Nujol) 3264, 1732, 1640 cm^{-1}. No other product was found when either **1** or **3** was treated as above with excess BzCl.

Clemmensen Reduction of *O*-Benzoylkojic Acid (3).—Woods' procedure was repeated with 4 g of **3** and 30 g of Zn amalgam.[20] The filtrate obtained after a 7-hr reflux period was evaporated to yield a brown oil, which was dissolved in C_6H_6 and washed with Na_2CO_3 and with H_2O. Acid treatment of the aqueous phase yielded 0.712 g of benzoic acid, mp 121–123°, identified by direct comparison. The C_6H_6 solution was evaporated under vacuum and yielded a dark brown oil which did not crystallize. It was treated with excess Ac_2O–pyridine and was chromatographed over silica gel. Elution with $CHCl_3$–EtOAc (1:1) gave 0.2 g of **4**, mol wt 168 (mass spectrum), mp 91–92°, after recrystallization from CCl_4.

2-Benzoxymethyl-5-acetoxy-4*H*-pyran-4-one (6).—No reaction was observed (melting point and nmr) when a mixture of 1 g of **3** and 3 ml of AcCl in 20 ml of C_6H_6 was allowed to stand for 24 hr at room temperature. When the above mixture was refluxed for 2 hr and evaporated under vacuum a solid was obtained, which was recrystallized twice from EtOH to yield 0.26 g of **6**, mp 86–87°.

Reaction of 3 with $SOCl_2$.—A mixture of 1 g of **3** and 3 ml of $SOCl_2$ in 15 ml of hexane was stirred for 24 hr at room temperature. After filtration, the solid was washed with hexane. It was identical with the starting material (melting point and nmr).

Meerwein–Ponndorff–Verley Reduction of 3.—A mixture of 2 g of **3** and 3 g of $Al[OCH(CH_3)_2]_3$ in 40 ml of 2-propanol was refluxed for 8 hr. After removal of the solvent, the residue was acidified with 10 ml of concentrated HCl and 50 ml of H_2O was added. Extraction with C_6H_6 yielded a solid which was boiled with 100 ml of H_2O for 15 min and recrystallized from EtOH to yield 0.301 g, mp 186–188°, identical with starting material.[21]

Reduction of Kojic Acid to Allomaltol (5).—The procedure used for the reduction of hydroxymaltol to maltol[4a] was followed. It yielded 60% of **5**, mol wt 125 (mass spectrum), subliming near 130°, mp (capillary) 150–152° (lit.[1] mp 166°).

Acetylallomaltol (4).—A mixture of 0.1 g of **5** and 78 mg of AcCl in 25 ml of $CHCl_3$ was refluxed for 3 hr. The product was recrystallized twice from CCl_4 to yield 0.1 g of crystals, mp 92–93° identical with the product of the Clemmensen reduction of **3**.

2-Acetoxymethyl-5-benzoxy-4*H*-pyran-4-one (8).—A solution of 2 g of **7** and 1.5 ml of benzoyl chloride in 10 ml of CF_3COOH was refluxed for 1 hr. It was poured over ice and the solid was recrystallized from EtOH to yield 0.503 g of **8**: mp 145–146° (lit.[3] mp 144°); ir ($CHCl_3$) 1730, 1640, and 1620 cm^{-1}. The product was identical with a sample prepared by Schotten–Baumann benzoylation of **1** followed by acetylation.[3]

Benzoylation of Kojic Acid with $SnCl_4$.—Woods' procedure[2] was followed exactly. The solid obtained after NaOH treatment was recrystallized twice from EtOH and yielded 5.9 g of **9**, mp 133–134°, identical with a sample prepared in 84% yield by a brief treatment of **1** with benzoyl chloride in pyridine at −5°.[22] Treatment of 5 g of **9** with HCl as described[2] and recrystallization of the product from EtOH yielded 2.5 g of starting material, mp 131–132°.

Benzoylation of Kojic Acid with CF_3COOH.—Woods' procedure[8] was repeated exactly. After recrystallization from EtOH, **3** was obtained in 27% yield, mp 179–180°. The same

(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Interscience, New York, N. Y., 1969, p 1287.
(21) There must be two crystalline forms of **3**. The melting point of the sample obtained here agreed with Woods' values, but it was lowered to 179–180° by further recrystallizations from EtOH.
(22) J. H. Looker, T. T. Okamoto, E. R. Magnson, D. L. Shaneyfelt, and R. J. Prokop, *J. Org. Chem.*, **27**, 4349 (1962).

result was found when the reaction was run with 2 equiv of benzoic acid.

Acetylation of Kojic Acid with H_3PO_4.—Woods' procedure[12] was followed exactly and gave **12** (20% yield after recrystallization from MeOH), mol wt 184 (mass spectrum), mp 135–137° (lit.[1] mp 136–137°), positive $FeCl_3$ test.

Hydrolysis of Acetylkojic Acid (12).—A solution of 200 mg of **12** in 20 ml of H_2O was refluxed for 24 hr. Nmr of the product showed it to be a mixture of **1** (43%) and **12** (57%).

Diacetylkojic Acid (7).—A solution of 2 g of **1** and 2.8 g of AcCl in 50 ml of $CHCl_3$ was refluxed for 8 hr. The product was recrystallized from MeOH to yield **7** in 88% yield, mp 101–102° (lit.[1] mp 102°), negative $FeCl_3$ test.

Acetylation of Kojic Acid with HCl.—Through a refluxing solution of 5 g of **1** in 25 ml of AcOH, HCl was bubbled for 4 hr. After concentration under vacuum, the product was recrystallized from EtOH to yield 4.7 g of **12**, mp 135–136°, identical with the sample prepared above.

Treatment of Kojic Acid with Diethyl Oxalate and CF_3COOH.—Woods' procedure[16] was followed exactly. After recrystallization from EtOH, the starting material was recovered in 26% yield, mp 155–157°.

Treatment of Kojic Acid with Zn and Ac_2O.—The above material (1.6 g) was treated with 2.6 g of Zn dust and 9 ml of Ac_2O.[16] After standing at room temperature for 48 hr and work-up, there was obtained 0.380 g of **7**, mp 102–103°.

Treatment of 5-*O*-Methylkojic Acid (13) with Diethyl Oxalate and Acetylation Reaction.—Woods' procedure[16] was followed using 0.935 g of **13**.[23] After recrystallization from EtOH, the starting material was recovered in 50% yield, mp 162–164°. A portion (0.366 g) was treated with 3 g of Zn dust and 10 ml of Ac_2O at room temperature for 18 hr. After work-up, there was obtained 0.193 g of **14**, mp 124–125°.

Formylation Reactions.—The published procedure[18] was applied to 5 g of **1**, 3 g of **13**, and 1 g of **15** to yield 1.62, 0.95, and 0.61 g of product, respectively. These were found to be unreacted starting materials by nmr and melting point determinations.

$NaBH_4$ Reduction of Kojic Acid.—The published procedure was repeated with 2 g of **1**, substituting $NaBH_4$ for KBH_4. The solid (0.8 g) obtained after work-up and recrystallization from EtOH was identical with the starting material (nmr and melting point).

Registry No.—**1**, 501-30-4; **2**, 33777-41-2; **3**, 33777-42-3; **4**, 25552-08-3; **5**, 644-46-2; **6**, 33777-43-4; **7**, 26209-93-8; **8**, 33777-44-5; **9**, 33886-26-9; **10**, 33777-45-6; **11**, 33777-46-7; **12**, 25552-08-3; **13**, 6269-25-6; **14**, 33777-49-0; **15**, 7559-81-1; **16**, 33777-51-4.

Acknowledgments.—We are grateful to the National Science Foundation for some financial support of this work and J. K. thanks the Department of Organic Chemistry, University of Geneva, for its hospitality (1971–1972).

(23) K. N. Campbell, J. F. Ackerman, and B. K. Campbell, *J. Org. Chem.*, **15**, 221 (1950)

Synthesis of *cis*- and *trans*-3-Chloroazetidinones. II. Direct Acylation of Imines

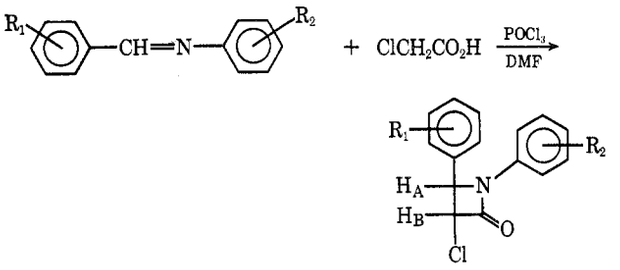
DAVID A. NELSON

Organic Chemicals Production Research, The Dow Chemical Company, Midland, Michigan 48640

Received October 12, 1971

Diaryl-3-halo-2-azetidinones have been prepared by the addition of haloacetic acid and phosphoryl chloride, in dimethylformamide (DMF), to imines,[1] and the authors indicated that single isomers, not mixtures, were obtained. The similarity of the chloroketene reaction with this procedure prompted a more thorough investigation of the haloacetic acid–phosphoryl chloride method.

Examination of the final products from ten reactions (Tables I and II), performed with the haloacetic acid–



phosphoryl chloride conditions,[1] indicated that both cis and trans β-lactams were formed. The coupling constants of vicinal protons in 3-chloro-2-azetidinones, $J(\text{cis}) > J(\text{trans})$, were used to distinguish the isomers.[2]

Since the isomer distribution differed from the original investigation,[1] the reaction was further examined in order to define the disparity. The nearly equal distribution of cis and trans isomers suggested that isomerization may have occurred. No isomerization occurred in refluxing DMF with either *cis*- or *trans*-**1**. However, in the presence of phosphoryl chloride and chloroacetic acid, isomerization was noted. An equilibrium mixture was established within 7 hr, starting from pure *cis*-**1**, and 22 hr from pure *trans*-**1**. This mixture contained 53% *cis*-**1** and 47% *trans*-**1** in both cases. When *cis*-**1** was subjected to these conditions for 2 hr, only 18% *trans*-**1** was formed; however, when *trans*-**1** was refluxed in the reagents for 2 hr, no *cis*-**1** was detected. This small amount of isomerization cannot fully account for the product distribution within the 2-hr reaction time.

Stereochemical evidence was obtained which favored direct acylation of the imine followed by ring closure. Since it is known that acyl chlorides can be formed from carboxylic acids with DMF–phosphoryl chloride,[3] chloroacetyl chloride was added to a solution of benzalaniline in DMF at 80°. The product was **1** (45% cis, 55% trans). No β-lactam was formed at 25°. A ketene mechanism was disfavored since chloroacetyl chloride addition to a DMF solution of benzalaniline and triethylamine at 25° gave only *trans*-**1**. Similar cycloadditions performed in benzene gave only *trans*-**1**.[4]

The proposed intermediate **11** was prepared by the direct acylation of benzalaniline with chloroacetyl chloride. No β-lactam was formed when **11** was stirred in DMF at 25°. However, mixed isomers of **1** (55% cis, 45% trans) were obtained when **11** was added to refluxing DMF. These results compare quite well with the results from the preparative reaction (see Table I). The treatment of **11** with triethylamine in either DMF or benzene at 25° yielded only *trans*-**1**. No β-lactam was observed when **11** was refluxed in benzene. Thus, the possibility of solvent participation, *i.e.*, DMF, cannot be neglected. The zwitterionic intermediate **12**, previously proposed for haloketene

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