monoperchlorate salt as white needles from ethanol, mp 218–220° dec.

Anal. Calcd for $C_9H_{17}ClN_2O_5$: C, 40.23; H, 6.38; N, 10.42. Found: C, 39.92; H, 6.42; N, 10.08.

1-(*N*-Methylbenzamido)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (5b). To an enriched mixture of **5a** (1.33 g, 6.3 mmol) in 10 ml of chloroform was added 1.4 g (10 mmol) of benzoyl chloride. After stirring for 4 hr at room temperature, the solution was poured into 10 ml of water. The chloroform was separated and discarded. The aqueous phase was washed once with 10 ml of chloroform. The aqueous layer was adjusted to pH 12 with 10% aqueous sodium hydroxide and extracted with two 15-ml portions of chloroform. The combined, dried (sodium sulfate), and filtered extracts were concentrated *in vacuo* leaving a yellow oil. This was dissolved in ether and treated with excess aqueous ethanolic perchloric acid. The dried precipitate was triturated with 5 ml of water, filtered, and washed with water to give the monoperchlorate of **5b** as a white solid, 0.5 g (50%): mp 224–226° dec; ir (KBr) 3.18 (w, C_6H_5), 5.78 (s, C=O), 6.14 (s, N-C=O), 9.26 μ (s, ClO_4^-).

Anal. Calcd for $C_{18}H_{26}N_3O_6Cl$: C, 51.98; H, 6.30; N, 10.10. Found: C, 52.24; H, 6.30; N, 9.89.

The monoperchlorate salt (149 mg, 0.36 mmol) was partitioned between 5 ml of 10% aqueous sodium hydroxide and 6 ml of chloroform. The combined, dried extracts were filtered and concentrated *in vacuo* to give 110 mg of a colorless, semicrystalline oil: nmr (CCl_4) δ 2.30 (s, 6, amine NCH_3), 3.05 (s, 3, amide NCH_3), 3.60 (s, 2, amide NCH_2), 7.35 (s, 5, aromatic), 2.30–3.30 (m, 8, amine NCH_2 and bridgehead CH); eims *m/e* 315 (M), 58 (B).

1-(*N*-Methylamino)methyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (6). Crude amino ketone **5a** (4 g) was reduced by the literature procedure.[6] The distillate that collected was saturated with sodium chloride and extracted with 25 ml of ether; the ether extracts contained 50 mg of **4**: nmr (identical with the published spectrum[6]); eims *m/e* 154 (M), 58 (B). Amino ketone **6** was recovered from the reaction solution by steam distillation as a white solid (0.85 g, 25%): mp 45–46°; ir (neat) 3.41 (s), 3.61 (s), 6.90, 6.99, 7.94 μ; nmr (C_6H_6) δ 1.30 (d, J = 3 Hz, 2, CH_2 bridge), 1.80 (m, 1, bridgehead CH), 2.20 (s, 6, NCH_3), 2.30 (s, 3, $NHCH_3$), 2.10–2.70 (m, 10, NCH_2); eims *m/e* 197 (M), 58 (B). The base was converted into the diperchlorate by treatment with excess perchloric acid. It crystallized from ethanol as white needles, mp 227–230° dec.

Anal. Calcd for $C_{11}H_{25}Cl_2N_3O_8$: C, 33.18; H, 6.33; Cl, 17.81; N, 10.55. Found: C, 33.32; H, 6.63; Cl, 18.00; N, 10.82.

Revised Synthesis of *N,N'*-Dimethylbispidinone (4). In a 2000-ml round-bottomed flask were placed 44.3 g of paraformaldehyde, 18.7 g (0.2 mol) of methylamine acetate, and 1000 ml of methanol. To this magnetically stirred suspension was added a solution of 36 g (0.2 mol) of *N*-methyl-4-piperidone acetate in 100 ml of methanol in increments over a period of 14 days. The paraformaldehyde slowly dissolved during this time. After completion of addition, the solution was stirred at room temperature for an additional 32 days. Then the solvent was removed *in vacuo*, and the residual oil, dissolved in 150 ml of water, was extracted twice with 75-ml portions of chloroform. These extracts were discarded. To the aqueous phase was cautiously added 20 g of anhydrous sodium carbonate. The resulting suspension was filtered and extracted with five successive 200-ml portions of chloroform. The pH of the aqueous phase was maintained at 8.5–9.0 with 10% aqueous sodium carbonate. The chloroform extracts, containing starting materials and polymeric products, were discarded. The aqueous phase was concentrated at an oil pump to a volume of 50 ml, filtered, and made strongly alkaline with 10% aqueous sodium hydroxide. This suspension was extracted with five successive 90-ml portions of chloroform. Work-up of the combined extracts left 24.7 g of an amber oil. Distillation of this crude product gave 6.82 g (10%) of **4** which crystallized upon cooling; analytical data were identical with those of the extraction-purified sample (see above).

Registry No.—**3** acetate, 53210-06-3; **4**, 14789-54-9; 4 $HClO_4$, 53210-07-4; **5a**, 53210-08-5; **5b**, 53210-09-6; **5b** $HClO_4$, 53210-10-9; **5c**, 53210-11-0; **6**, 53230-02-7; **6** $2HClO_4$, 53230-03-8; *o*-nitrophenylsulfinyl chloride, 7669-54-7; methylamine acetate, 6998-30-7.

References and Notes

(1) Deceased July 14, 1974.
(2) NIH predoctoral trainee, University of Kansas, 1971–1974. Correspondence should be addressed to School of Pharmacy, University of Georgia, Athens, Ga. 30602.
(3) (a) H. Stetter and H. Hennig, *Chem. Ber.*, **88**, 789 (1955); (b) H. Stetter and R. Merten, *ibid.*, **90**, 868 (1947).
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2-(2-Imidazolyl)acetophenones. Preparation and Some Reactions

Antonius A. Macco, Erik F. Godefroi,* and Josephus J. M. Drouen

Department of Organic Chemistry, University of Technology, Eindhoven, The Netherlands

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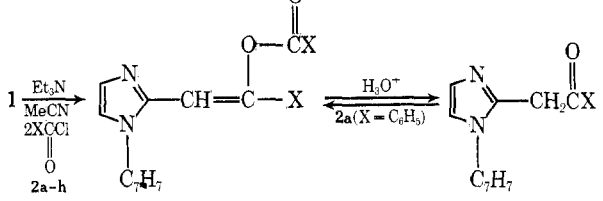
Imidazoles, in their behavior with acid chlorides, can be made to react in a number of ways. In the absence of N substituents, benzoylation[1] and acetylation[2] in inert solvents give rise to N-substituted derivatives. Imidazole with benzoyl chloride (BzCl) in aqueous alkali, instead, initially provides a 1,3-dibenzoyl cation which then suffers hydrolytic ring cleavage to give 1,2-dibenzoylaminoethylene.[3] N-Substituted imidazoles have also been shown to react with BzCl; on conducting the reaction in Et_3N-containing acetonitrile, 2-benzoyl derivatives are obtained.[4]

Interest in the electrophilic substitution pattern of 1,2-disubstituted imidazoles[5] prompted a study of the behavior of 1-benzyl-2-methylimidazole (**1**) with various benzoyl chlorides.[6] This showed that **1** with 2 equiv of various benzoyl chlorides in Et_3N-containing acetonitrile gave enol esters **3a–e** in essentially quantitative yield. Subsequent acid hydrolysis then provided 2-(2-imidazolyl)acetophenones **4a–e** (Scheme I). The present paper demonstrates the generality of the method.

Scheme I



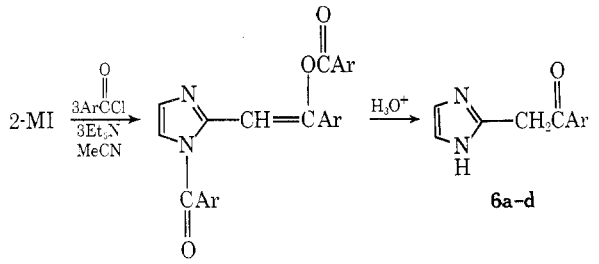
X: **a**, C_6H_5; **b**, *p*-$CH_3OC_6H_4$; **c**, *p*-$CH_3C_6H_4$; **d**, *p*-ClC_6H_4; **e**, *p*-$O_2NC_6H_4$; **f**, $(CH_3)_3C$; **g**, Cl_3C; **h**, C_2H_5O

Formation of **3a–e** is surprising since, to our knowledge, a nonactivated 2-methyl group on a 1,2-disubstituted imidazole is reluctant to partake in electrophilic processes. 1,2-Dimethylimidazole, for example, undergoes hydroxymethylation at C-5 exclusively;[5] lithiation, previously reported to proceed solely at C-5,[7] has recently been shown to occur at both C-5 and at the C-2 methyl.[8] In the case at hand, formation of **3a–e** is to be ascribed to an irreversible O-aroylation of anionic intermediates serving to displace all prior equilibria in favor of a final conjugated system. O-Aroylation stems, *i.e.*, from minimal anion solvation in the polar, aprotic acetonitrile, a view consistent with the observation that **4a** with BzCl under the reaction conditions provides **3a**.

In the present work, the reactions of **1** with some acyl chlorides were examined. Acetyl chloride, under the reaction conditions, formed intractable product mixtures.

When lacking α hydrogens, acyl chlorides such as pivaloyl- and trichloroacetyl chloride (**2f,g**) and also ethyl chloroformate (**2h**) behaved as their aromatic counterparts. Compound **4f** resulted from acid treatment of **3f;** however, **4g** and **4h** were obtained directly from **1a.** The fact that optimal yields of **4h** required the use of at least 2 equiv of chloroformate ester leads us to suspect the intermediacy of enol esters which, being highly reactive, would be destroyed during the aqueous work-up.

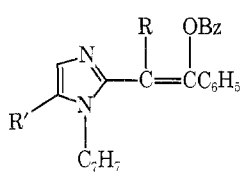
In a related study, treatment of 2-methylimidazole (2-MI) with 3 equiv each of aroyl chloride and Et_3N gave N-substituted enol esters **5a–d;** subsequent hydrolysis then gave the corresponding Imidazolylacetophenones **6a–d.**



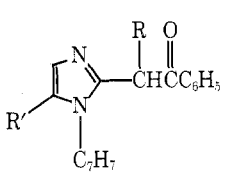
5a–d

(**a**, Ar = C_6H_5; **b**, Ar = p-$CH_3OC_6H_4$; **c**, Ar = p-$CH_3C_6H_4$; **d**, Ar = p-$O_2NC_6H_4$)

Methyl groups located at C-5 of an N-substituted imidazole do not respond to this benzoylation technique. For example, given two alternatives, BzCl reacted with the 2- rather than the 5-methyl substituent of 1-benzyl-2,5-dimethylimidazole[2] (**7b**) and gave enol ester **8a.** 1-Benzyl-5-methylimidazole[2] (**7a**), lacking a 2 substituent, underwent benzoylation at C-2 to yield 2-(1-benzyl-5-methylimidazolyl) phenyl ketone (**10**) in direct analogy with literature reports.[4] Higher homologs of **1a,** *i.e.,* 1-benzyl-2-ethylimidazole[5] (**7c**) and 1-benzyl-2-isopropylimidazole[5] (**7d**), were also examined. These experiments were suggested by our earlier results[5] which showed that the rate of hydroxymethylation at C-5 was enhanced by the presence of electron-donating groups at C-2. On going from 2-Me to 2-*i*-Pr, one would expect benzoylation to start occurring at C-5. This was not the case; BzCl with **7c** gave **8b** albeit in diminished yield, while **7d** failed to react altogether. Hydrolysis of **8a** and **8b** provided **9a** and **9b,** respectively.

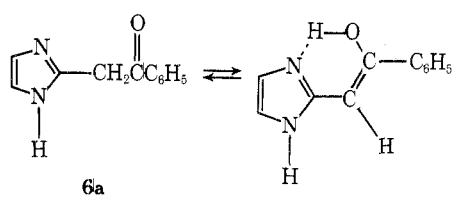


8a, 8b



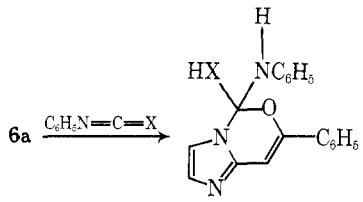
9a, R = H; R′ = CH_3
b, R = CH_3; R′ = H

The phenacylimidazoles as free bases exist as keto–enol mixtures. For the case of **4a** the enol content amounted to *ca.* 40% as arrived at by total integration of nmr signals at δ 4.42 ($CH_2C{=}O$) and 6.05 (HC=COH). Ir data for **6a** showed, in addition to a C=O band at 1680 cm^{-1}, also significant OH absorption. The possibility offered by intramolecular N···H···O bonding undoubtedly promotes enolization.



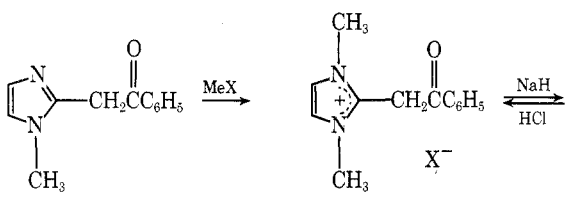
6a

The partial enolic character of **6a** is reflected in some of its reactions. On treatment with phenyl isocyanate and isothiocyanate, for example, 1:1 adducts were obtained; these, lacking C=O absorptions, were assigned structures **11a** and **11b.**

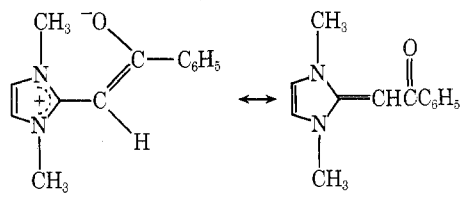


11a, X = O
b, X = S

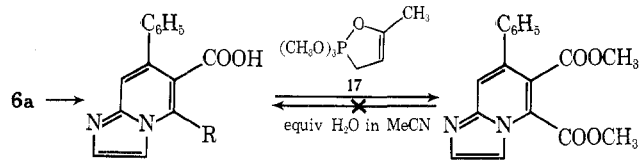
Zwitterions result on anionizing quaternary salts related to **4a.** Considerations of symmetry made us examine **13a,** which was prepared by treatment of **12**[6] with MeI. On addition of NaH to a THF solution of the cation, H_2 was evolved and a strongly basic, water-soluble, and relatively high-melting solid resulted. Ir inspection indicated no C=O absorption, while nmr considerations (equivalency of the imidazolyl protons and Me groups) showed the molecule to be symmetrical. These data all point to betaine **14** and minimize the contribution of ketene–aminal hybrid **15.** Protonation of **14** in alcoholic HCl regenerated quaternary salt **13b,** which was spectrally (ir and nmr) identical with **13a.**



12 **13a**, X = I
b, X = Cl

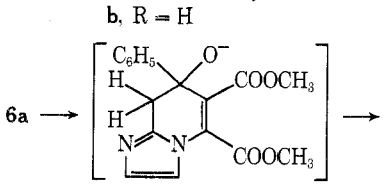


14 **15**

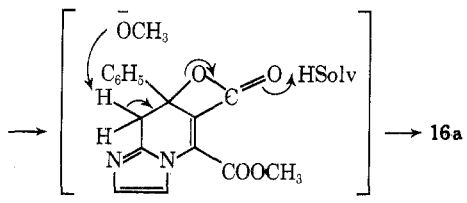


16a, R = $COOCH_3$
b, R = H

18



i



ii

Dimethyl acetylenedicarboxylate in MeOH or MeCN reacted with **6a** to give imidazo[1,2-*a*]pyridine **16a** (70 and 40%, respectively). The location of the COOH and $COOCH_3$ functions at C-5 and C-6, respectively, is based on the following. Esterification of **16a** with oxaphospholene **17**[9] gave diester **18**. The action thereon of 1 equiv of H_2O under the reaction conditions failed to regenerate **16a**, thus eliminating **18** from the reaction path leading to **16a**. Mechanistically, the key transition state in this transformation, namely i, resembles the one envisaged in Stobbe condensations,[10] in which monoesters of dicarboxylic acids are ultimately produced via γ-lactones. Whereas in the case at hand, γ-lactone formation is sterically unfavorable, a β-lactone such as ii is quite feasible. Subsequent CH_3O^--induced proton abstraction, facilitated by formation of an aromatic 10-π-electron system, then completes the process. A comparable rationale accounts for formation of **16b** from **6a** and ethyl propiolate.

Experimental Section

General. Melting points were determined on a Fisher-John block and are uncorrected. Nmr spectra (Varian A-60, TMS as internal standard) and ir data (Perkin-Elmer 337) were consistent with assigned structures. All enol esters and their hydrolysis products are listed in Tables I and II. The preparation of compounds serving as prototypes in these studies is given in detail.

Compound 3a. To a solution of 5.2 g (0.03 mol) of **1** in 30 ml of MeCN containing 6.7 g (0.066 mol) of Et_3N was added dropwise and below 10° 9.2 g (0.066 mol) of BzCl. After 2 hr at room temp, dilution with 100 ml of Et_2O and 300 ml of H_2O gave, on filtration, 11.2 g (98%) of **3a**: mp (C_6H_6) 144–146°; ir (KBr) 1730 cm^{-1} (C=O), 1660 cm^{-1} (C=C), 1240 cm^{-1} (C–O–C); nmr ($CDCl_3$) δ 8.40–8.15 (m, 2, arom H), 7.70–6.80 (m, 15, arom H), 6.67 (s, 1, CH=C), 5.17 (s, 2, $CH_2C_6H_5$).

2-[2-(1-Benzylimidazolyl)]acetophenone (4a). A solution of 2 g of **3a** in 20 ml of 3 *N* HCl was refluxed for 30 min. The solution was rendered basic, giving an oily product which was taken up in C_6H_6. Drying and evaporation of the organic phase gave crude **4a**; it was converted to the hydrochloride salt by treatment with *i*-PrOH/HCl. Yield: 1.1 g, which was recrystallized from *i*-PrOH–Et_2O to melt at 203–204°.

The free base, a yellow oil, had bp 190° (0.1 mm), which *slowly* solidified on standing to melt at *ca.* 70°.

Compound 5a. Gradual treatment of 36 g (0.45 mol) of 2-methylimidazole with 210 g (1.5 mol) of BzCl and 150 g (1.50 mol) of Et_3N in 500 ml of MeCN under conditions offered for **3a** gave 150 g (85%) of product: mp (C_6H_6) 172–173°; ir (KBr) 1710 cm^{-1} (ImC=O), 1740 cm^{-1} (C=C–O–C=O).

2-(2-Imidazolyl)acetophenone (6a). Compound **5a**, 60 g (0.152 mol), was held at reflux for 1 hr in 300 ml of a 2:1 mixture of HOAc:concentrated HCl. Solvent was then removed and was replaced by H_2O from which the BzOH was removed by scrubbing with C_6H_6. Introduction of $NaHCO_3$ to the aqueous phase admixed with *i*-Pr_2O gave, on prolonged stirring, slowly crystallizing tan **6a**: yield 77%; mp 112–114°; ir (KBr) 1680 cm^{-1} (C=O). The HCl salt, recrystallized from EtOH–Et_2O, had mp 252–253°.

2-(1-Benzyl-5-methylimidazolyl) Phenyl Ketone (10). The reaction of 5.2 g (0.03 mol) of 1-benzyl-5-methylimidazole[2] with 9.3 g (0.066 mol) of BzCl and 6.6 g (0.066 mol) of Et_3N in 30 ml of MeCN under conditions and work-up as offered for **3a** gave 6.7 g (81%) of **10**: mp (EtOH) 118–119°; ir (KBr) 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.12 (d, 3, Im-5CH_3).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.36; H, 5.82; N, 10.13.

The Reactions of 6a with Phenyl Isocyanate and Isothiocyanate. Compounds 11a and 11b. A solution of 1.86 g (0.01 mol) of **6a** and 1.2 g (0.01 mol) of C_6H_5NCO in 15 ml of THF was refluxed for 2 hr during which time **11a** started separating out. On filtration and recrystallization from aqueous DMF, it melted at 182–183°: yield 2.9 g (90%); ir (KBr) 3300–2300 cm^{-1} (NH, OH, C_6H_5), no carbonyl absorptions.

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.56; H, 5.10; N, 13.75.

In a related reaction, treatment of equimolar amounts of **6a** and C_6H_5NCS in refluxing MeCN for 2 hr gave 67% yield of **11b**: mp (*i*-PrOH) 161–163°; ir (KBr) 3300–2300 cm^{-1} (NH, SH, C_6H_5), no carbonyl absorptions.

Table I
Enol Esters 3f, 5a-d, and 8a,b[a]

Compd	Yield,[b] %	Mp, °C	Formula[c]
3f	58	124–126	$C_{21}H_{28}N_2O_2$
5a	85	172–173	$C_{25}H_{18}N_2O_3$
5b	80	177–178	$C_{28}H_{24}N_2O_6$
5c	68	197–198	$C_{28}H_{24}N_2O_3$
5d	95	223–224	$C_{25}H_{15}N_5O_9$
8a	61	151–152	$C_{26}H_{22}N_2O_2$
8b	67	125–126	$C_{26}H_{22}N_2O_2$

[a] For physical data of enol esters **3a–e** see table in ref 6. [b] Yields based on product melting within a few degrees of analytical material. [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds in this table.

Table II
Hydrolysis Products Derived from Esters (Table I)[a]

Compd	Yield, %	Mp, °C	Formula[b]
4f	74	54–55	$C_{16}H_{20}N_2O$
4g[c]	84	147 dec	$C_{13}H_{11}Cl_3N_2O$
4h[c]	47	176–177	$C_{14}H_{16}N_2O_2 \cdot HCl$
6a	83	252–253	$C_{11}H_{10}N_2O \cdot HCl$
6b	65	255–258	$C_{12}H_{12}N_2O_2 \cdot HCl$
6c	69	268–270	$C_{12}H_{12}N_2O \cdot HCl$
6d	76	233–237	$C_{11}H_9N_3O_3 \cdot HCl$
9a	70	207–209	$C_{19}H_{18}N_2O \cdot HCl$
9b	95	108–109	$C_{19}H_{18}N_2O$

[a] For physical data of compounds **4a–e** see ref 6. [b] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds in this table. [c] Obtained directly from **1** and **2g** and **2h**, respectively, under conditions identical with those given for **3a** (see Experimental Section).

Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.04; H, 4.76; N, 12.93.

Compound 13a. A solution of 20 g (0.10 mol) of **12**[6] in 75 ml of MeCN was treated cautiously at 30° with 18 g (0.13 mol) of MeI. The insoluble quaternary salt, 28.3 g (80%), was isolated after 24 hr: mp (MeOH) 240–241°; ir (KBr) 1685 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.88 (s, 2, Im 4- and 5-H), 5.57 (s, 2, CH_2), 3.98 (s, 6, Im 1- and 3-CH_3).

Anal. Calcd for $C_{13}H_{15}N_2OI$: C, 45.63; H, 4.42; N, 8.19. Found: C, 45.97; H, 4.41; N, 8.22.

Betaine 14. To 100 ml of a THF solution containing 1.75 g (0.06 mol) of 80% NaH in oil was added portionwise and with stirring 20 g (0.059 mol) of **13a** over a period of 0.5 hr. Stirring was continued until H_2 evolution ceased whereupon solvent was removed and replaced with 400 ml of $CHCl_3$. On removal of the insolubles the filtrate was again taken to dryness. C_6H_6 was then added to give, on stirring, solid **14**. This was isolated by filtration, giving on trituration with Me_2CO 8.3 g (66%) of betaine: mp of analytical sample (MeCN) 180–181°; nmr ($CDCl_3$) δ 8.09–7.80 (m, 2, 2 aromatic *o*-H), 7.53–7.25 (m, 3, 3 aromatic H), 6.79 (s, 2, Im 4- and 5-H), 5.10 (s, 1, C=CH), 3.57 (s, 6, Im 1- and 3-CH_3); ir (KBr) no carbonyl absorption.

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 73.02; H, 6.52; N, 13.02.

Compound 16a. A solution of 1.86 g (0.01 mol) of **6a** in 15 ml of MeOH was treated with 1.4 g (0.01 mol) of dimethyl acetylenedicarboxylate. The temperature rose to 47° as yellow product was deposited. The material was collected by filtration after 24 hr, giving 2.05 g (70%) of fluffy needles: mp (aqueous MeOH) 227–228°; ir (KBr) 1670 (COOH), 1740 cm^{-1} (COOMe); nmr ($CDCl_3$) δ 8.1–7.2 (m, 7, aromatic H), 6.4 (s, 1, C 8-H), 3.2 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 65.01; H, 4.15; N, 9.68.

Esterification of 16a to 18. One gram (0.052 mol) of oxaphospholene **17**[9] was introduced dropwise and with cooling into a suspension of 1.5 g (0.05 mol) of **16a** in 20 ml of CH_2Cl_2; after 1 hr the clear solution was scrubbed with H_2O, 10% $NaHCO_3$, and H_2O, respectively, to leave, on drying and evaporation, 1.55 g (95%) of

diester **18**: mp (C_6H_6–petroleum ether) 181–182°; ir (KBr) 1710 cm^{-1} (COOMe); nmr ($CDCl_3$) δ 4.55 (s, 3, CH_3), 4.40 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.85; H, 4.76; N, 9.06.

Compound 16b. Under conditions corresponding to those offered for **16a**, equivalent amounts of **6a** and ethyl propiolate provided 0.6 g (25%) of acid **16b**: mp (aqueous EtOH) 233–234°; ir (KBr) 1660 cm^{-1} (COOH).

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.38; H, 4.23; N, 11.76. Found: C, 70.59; H, 4.44; N, 11.84.

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Registry No.—**1**, 13750-62-4; **2a**, 98-88-4; **2g**, 76-02-8; **2h**, 541-41-3; **3a**, 52083-14-4; **3f**, 52855-65-9; **4a**, 52083-19-9; **4a** HCl, 52855-66-0; **4f**, 52855-67-1; **4g**, 52855-68-2; **4h** HCl, 52855-69-3; **5a**, 52855-70-6; **5b**, 52855-71-7; **5c**, 52855-72-8; **5d**, 52855-73-9; **6a**, 52855-74-0; **6a** HCl, 52855-75-1; **6b** HCl, 52855-76-2; **6c** HCl, 52855-77-3; **6d** HCl, 52855-78-4; **7a**, 52726-21-3; **7b**, 52726-27-9; **7c**, 39269-64-2; **8a**, 52855-81-9; **8b**, 52855-84-2; **9a HCl**, 52855-82-0; **9b**, 52855-85-3; **10**, 52855-83-1; **11a**, 52855-79-5; **11b**, 52855-80-8; **12**, 52083-24-6; **13a**, 52855-86-4; **14**, 52855-87-5; **16a**, 52855-88-6; **16b**, 52855-90-0; **17**, 26192-22-3; **18**, 52855-89-7; 2-methylimidazole, 693-98-1; phenyl isocyanate, 103-71-9; phenyl isothiocyanate, 103-72-0; dimethyl acetylenedicarboxylate, 762-42-5; ethyl propiolate, 623-47-2; *p*-methoxybenzoyl chloride, 100-07-2; *p*-methylbenzoyl chloride, 874-60-2; *p*-nitrobenzoyl chloride, 122-04-3.

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Allylic Rearrangement of 17α-Vinyl-17β-hydroxy Steroids

Douglas O. Olsen and James H. Babler*

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

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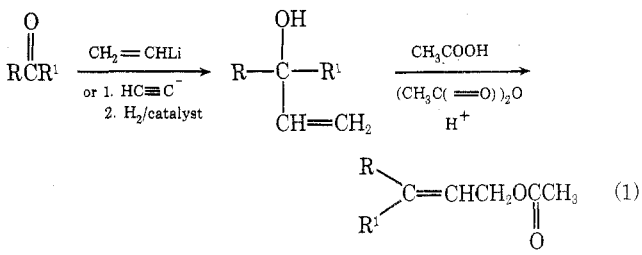
It is well known that generation of a cationic center at C-17 in steroids can promote the 1,2 shift of the C-18 methyl group (the Kägi–Miescher rearrangement).[1] For example, Morrow, Culbertson, and Hofer reported[2] 17-methyl-18-nor-17α-pregna-5,13,20-trien-3β-ol (**1a**) as a by-product of the acid-catalyzed isomerization of 17α-pregna-5,20-diene-3β,17-diol (**4a**). This same group also reported[2] that the direct acid-catalyzed conversion of the latter compound (**4a**) to pregna-5,17(20)-diene-3β,21-diol (**5a**) proceeded erratically (with generally 8–15% yield). They demonstrated, however, that allylic rearrangement of 17α-pregna-5,20-diene-3β,17-diol 3-acetate (**4b**) using thionyl chloride in an ether–pyridine mixture, followed by treatment of the rearranged chloride **6b** with potassium acetate (and subsequent saponification) was a good alternative to the direct one-step acid-catalyzed process.

In an effort to facilitate allylic rearrangements of the type cited above and avoid the unnecessary formation of an intermediate allylic halide (*e.g.*, **6** and **11**), we decided to examine the behavior of 17α-vinyl-17β-hydroxy steroids in a mixture of acetic acid–acetic anhydride containing a strong acid catalyst. Earlier we had reported[3] such reaction conditions as the key step in a method for the bishomologation of simple ketones to functionalized trisubstituted olefins (eq 1).



(1)

The first system we examined was 3-methoxy-19-nor-17α-pregna-1,3,5(10), 20-tetraen-17-ol (**8**), obtained in 97% yield by the addition of vinyllithium to estrone methyl ether (**7**). Subsequent acid-catalyzed rearrangement of alcohol **8** in a mixture of acetic acid and acetic anhydride proceeded smoothly, affording 3-methoxy-19-norpregna-1,3,5(10),17(20)-tetraen-21-ol acetate (**9**) in approximately 65% yield after purification *via* column chromatography. The identity of this rearranged allylic acetate (**9**) was confirmed by nmr analysis as well as comparison of its melting point and infrared spectrum with the corresponding physical properties previously reported[4] for this same compound, which had been synthesized from the corresponding bromide (**11**) as outlined in Scheme II. The only other component in our crude rearrangement product was a relatively nonpolar substance, subsequently shown by nmr analysis to be a mixture of aromatic ethers.

To further demonstrate the utility of our rearrangement conditions, we used as our next substrate 17α-pregna-5,20-diene-3β,17-diol (**4a**), prepared in approximately 80% yield by the addition of vinyllithium to dehydroisoandrosterone acetate (**3b**). As expected, the rearrangement afforded pregna-5,17(20)-diene-3β,21-diol diacetate (**5b**) in >60% yield after purification *via* column chromatography. As in the previous system examined, a mixture of at least two unsaturated compounds (determined by the vinyl patterns observed on its nmr spectrum) was formed during the reaction. Since the rearrangement we report proceeded in high yield to afford the desired allylic acetates (**5b** and **9**) and the elimination by-products failed to separate on silica gel tlc, we made no further effort to characterize them.

Experimental Section[5]

3-Methoxy-19-nor-17α-pregna-1,3,5(10),20-tetraen-17-ol (8). Treatment of a solution of 702 mg (2.47 mmol) of 3-methoxyestra-1,3,5(10)-trien-17-one (**7**) in 15 ml of anhydrous tetrahydrofuran with 3.0 ml of 2.5 *M* vinyllithium–tetrahydrofuran solution[6] at room temperature for 30 min, using experimental conditions similar to those described for the preparation of diol **4a**, afforded crude alcohol **8** contaminated by hydrocarbon impurities evidently present in the vinyllithium reagent. The product was purified *via* chromatography on 50 ml of Florisil (60–100 mesh). Elution with hexane–25% ether afforded 746 mg (97%) of crystalline alcohol **8**: mp 110–112° (lit.[4] mp 114–115°); λ_{max} (KBr) 3560, 3495, 1617, 1508, 1255, 1142, 1025, 930 and 910 cm^{-1}; δ_{TMS} ($CDCl_3$) 6.42–5.07