ISOMERIZATION OF α-ACETYLENIC KETONES

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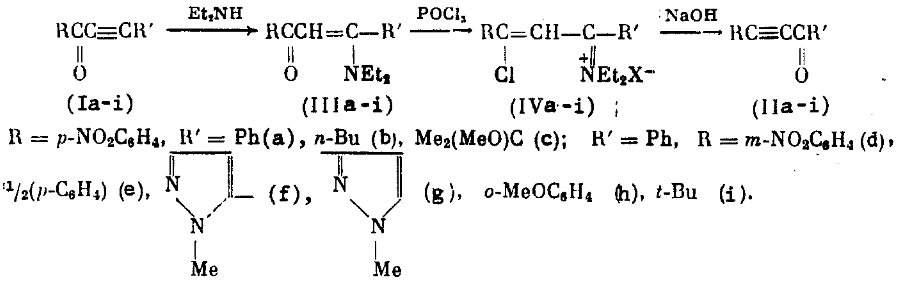
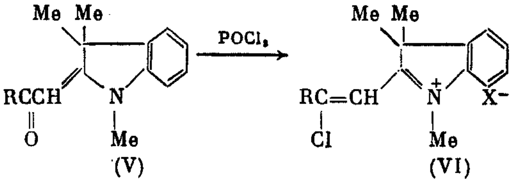
A method is suggested for isomerization of α-acetylenic ketones with migration of the oxo group from position 1 to position 3 and of the triple bond from position 2 to position 1 of the ketoacetylenic fragment; it consists of addition of Et_2NH at the triple bond of the ketone, conversion of the adduct to the imminium salt with $POCl_3$, followed by alkaline hydrolysis. The isomerization is achieved in one preparative stage without isolation of intermediate compounds.

Acetylenic ketones are used as key intermediates in the synthesis of β-diketones, enaminoketones, acetylenes, heterocyclic compounds, etc. The use of these compounds became especially important after a convenient method was found for their production from acid chlorides and terminal acetylenes [1, 2]. Nevertheless, owing to the relatively poor accessibility of many of the ethyl derivatives involved in this reaction, frequently one of the two isomeric acetylenic ketones $RCOC{\equiv}CR'$ (I) and $RC{\equiv}CCOR'$ (II) is considerably less accessible than the other. Inteconversion of ketones (I) and (II) would eliminate this difficulty. We have suggested that this isomerization is possible according to the scheme:



The first stage, addition of a secondary amine, has been well studied and is easily carried out [3]. Accounts have been published [4-6] for conversion of the 1,3,3-trimethyl-2-phenacylideneindolines (V), synthesized by acylation of the Fischer base, into γ-chlorindolenine salts (VI) with $POCl_3$, suggesting the possibility of preparing the iminium salts (IV) from enaminoketones (III):



(V) (VI)

Published data on the hydrolysis of imminium salts mainly refer to salts produced from methyl or methylene ketones and the Wilsmeier reagent, $RCCl{=}CR'{-}CH{=}\overset{+}{N}Me_2X^-$ [7-9]. On acid hydrolysis, these salts give labile β-chloroacroleins $RClC{=}CR'CHO$ which fragment in alkaline media to form $RC{\equiv}CR'$ acetylenes. Since the reactivity of the ketones with respect

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TABLE 1. α-Acetylenic Ketones RC≡CCOR' (II)

Compound	Yield, %	mp, °C (solvent)	Empirical formula	Found/Calculated, %			PMR spectrum* (δ, ppm)
				C	H	N	
(IIa)	62	148–149 [10] (toluene)	–	–	–	–	–
(IIb)	78	†	$C_{13}H_{13}NO_3$	67,58 67,52	5,89 5,67	5,84 6,06	0,93 t (3H, CH_3), 1,39 sextet (2H, C^6H_2), 1,71 quintet (2H, C^5H_2), 2,68t (2H, C^4H_2), 7.71 d and 8.22 d (4H, arom.)
(IIc)	47	49–50 (hexane)	$C_{13}H_{13}NO_4$	62,95 63,15	5,47 5,30	5,54 5,66	1,43 s (6H, $C(CH_3)_2$), 3,33 s (3H, OCH_3), 7,76d and 8,23 d (4H, arom.)
(IId)	80	151–152 (toluene)	$C_{15}H_9NO_3$	71,78 71,71	3.89 3,61	5,58 5.57	–
(IIe)	40	183–184 [11] (dichloroethane)	–	–	–	–	–
(IIf)	51	76,5–77,5 (hexane)	$C_{13}H_{10}N_2O$	74,06 74,27	4,61 4,79	13,44 13,32	4,08 s (3H, CH_3), 6,73 d (1H, C^4H), 7,59 d (1H, C^3H), 7,53–7,57 and 8,12–8,22 m (5H, Ph)
(IIg)	66	79–80 (hexane)	$C_{13}H_{10}N_2O$	74,28 74.27	4,94 4,79	13.11 13,32	3,98 s (3H, CH_3), 6,65 d (1H, C^4H), 7,39 d (1H, C^5H), 7,47–7,58 and 8,18–8,27 m (5H, Ph)
(IIh)	73	72,5–73,5 (hexane)	$C_{16}H_{12}O_2$	81,54 81,34	4,95 5,12	–	4,15 s (3H, OCH_3), 7,17–7,83 and 8,44–8,48 m (9H, arom.)
(IIi)	80	bp [12] 125–126 (7 mm)	–	–	–	–	–

*IR spectra (ν, cm^{-1}): 1650-1685 (C=O), 2210-2245 (C≡C).
†Viscous liquid.

to nucleophilic agents is lower than that of aldehydes, it might be expected that interaction of the salts (IV) with aqueous alkali under mild conditions would be limited to their hydrolysis and dehydrochlorination. However, it should be noted that under these conditions the indolenine salts (VI) undergo cleavage into monosubstituted acetylenes and trimethylindolinone [4-6].

We have found that the enaminoketones (III), produced in excellent yields by addition of Et_2NH to (I), react vigorously with evolution of heat with $POCl_3$. Unlike the analogous reaction of the phenacylideneindolinones (V) [4-6], neither a large excess of $POCl_3$ nor prolonged heating are necessary as a rule. The increased nucleophilic nature of the carbonyl oxygen atoms in (III) is apparently explained by the larger +M effect of the diethylamino group compared with that of the methylphenylamino group in (V), which is incorporated into a strained five-membered ring.

On treatment with 5% aqueous NaOH, the resulting imminium salts (IV) lose hydrogen chloride and are hydrolyzed into (II). Formation of fragmentation products as a side reaction was observed only during isomerization of the pyrazolylketone (If) into (pyrazolylethynyl)ketone (IIf). It is likely that the difference in reactivity of salts (IV) and (VI) is largely determined by the specific cyclical structure of the amine part of a molecule of (VI). Acid hydrolysis of the imminium salts (IV), as shown in the case of (IVa), requires heating for many hours in 15-20% HCl and yields chlorovinylketones which correspond in structure to the isomerized acetylenic ketones (II).

In spite of the fact that the process of isomerization of (I) into (II) consists of several chemical stages, it is simple and achieved in one preparative stage without isolating the intermediate enaminoketones (III) and imminium salts (IV) (see Experimental section).

TABLE 2. Enaminoketones $RCOCH{=}CNEt_2R'$ (III)

Compound	Yield, %	mp, °C (solvent)	Empirical formula	Found/Calculated, %			PMR spectrum* (δ, ppm)
				C	H	N	
(IIIa)	93	125–126 (alcohol)	$C_{19}H_{20}N_2O_3$	70,38 70,35	6,34 6.21	8,75 8,64	1.16 br.m (6H, $2CH_3$), 3.30 br.m (4H, CH_2), 5,88 s (1H, =CH), 7,20–7.42 m (5H, Ph), 7,91 d 8,16 d (4H, arom.)
(IIIb)	95	94.5–95.5 (hexane)	$C_{17}H_{24}N_2O_3$	67,17 67,08	8,07 7,95	9,17 9,20	0.96 t (3H, C^7H_3), 1.24 t (6H, $NCH_2\underline{CH_3}$), 1,54 m (4H, C^5H_2, C^6H_2), 3.04 t (2H, C^4H_2), 3.39 q (4H, NCH_2); 5,58 s (1H, =CH), 7,92 d and 8.19 d (4H, arom.)
(IIIc)	85	91–92 (hexane)	$C_{17}H_{24}N_2O_4$	63,68 63,73	7,76 7.55	8,50 8.74	1,18 t (6H, $NCH_2\underline{CH_3}$), 1,55 s (6H, $C(CH_3)_2$), 3.24 s (3H, OCH_3), 3,70 q (4H, NCH_2), 5.79 s (1H, =CH), 7,98 d and 8,22 d (4H, arom.)
(IIId)	89	100–101 (alcohol)	$C_{19}H_{20}N_2O_3$	70,21 70,35	6,22 6.21	8,76 8.64	1.22 br.m (6H, CH_3), 3.30 br.m (4H, CH_2), 5,90 s (1H, =CH), 7.20–7.23, 7.40–7.52, 8,08–8.22 and 8.60–8.62 m (9H, arom.)
(IIIf)	91	53–54 (hexane)	$C_{17}H_{21}N_3O$	71,79 72,06	7,33 7.47	14,76 14,83	1,15 br.m (6H, $2CH_3$), 3.24 br.m (4H, CH_2), 3,99 s (3H, NCH_3), 5,77 s (1H, =CH), 6.6 d (1H, C^4H), 7,36 d (1H, C^3H), 7,20–7.30 and 7.40–7.45 m (5H, Ph)
(IIIg)	85	131–132 (hexane)	$C_{17}H_{21}N_3O$	72,07 72,06	7.58 7,47	14,69 14,83	1,12 br.m (6H, CH_3), 3.24 br.m (4H, CH_2), 3.91 s (3H, NCH_3), 6.32 s (1H, =CH), 6,62 d (1H, C^4H), 7.21–7,41 m (6H, C^5H), Ph)

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*IR spectra (ν, cm^{-1}): 1620-1630 (C=O).

EXPERIMENTAL

The PMR spectra were measured in $CDCl_3$ using Varian XL 200 and Jeol FX 90Q spectrometers and IR spectra were measured in $CHCl_3$ using a UR-20 apparatus. The course of the reaction was monitored by TLC using Silufol UV 254 plates.

The initial acetylenic ketones were produced by conventional methods [1, 2].

Isomerization of 1-(p-Nitrophenyl)-3-phenylpropyn-2-one-1 (Ia). A mixture of 5 g (Ia) and 1.6 g Et_2NH in 10 ml abs. dioxane was stirred for 1 h at 50°C, cooled, diluted with 10 ml dioxane, and 3.4 g $POCl_3$ added. The temperature of the reaction mixture rose spontaneously to ~35°C. Stirring was continued for 0.5 h, then the solution of the resulting imminium salt (IVa) was poured gradually into 500 ml 5% aqueous NaOH cooled to 10°C. The precipitate of (IIa) was filtered, washed with ice water, and dried; yield 3.1 g (Table 1).

Compounds (Ib-i) were isomerized similarly (Table 1); the time for Et_2NH addition was 1-2.5 h; the excess of $POCl_3$ (assuming a quantitative yield of (III) varied from 10 to 100%, liquids (II) were isolated by extraction with $CHCl_3$ followed by distillation.

3-(p-Nitrophenyl)-1-phenyl-3-chloropropen-2-one-1 (VII). To a dioxane solution of (IVa), produced as described earlier, were added 80 ml dil. HCl (1:1), followed by stirring for 22 h at 85°C; the precipitated (VII) was filtered. Obtained 5.0 g (87%) (VII), mp 129-130°C (acetone). Found: C 62.54; H 3.37; Cl 12.35%. $C_{15}H_{10}ClNO_3$. Calculated: C 62.62; H 3.50; Cl 12.32%. PMR spectrum (δ, ppm): 7.4 s (1H, =CH), 7.48-7.64 and 7.85-8.05 m (5H, Ph), 8.27 d and 7.91 d (4H, p-C_6H_4).

TABLE 3. Preparation of Initial Ketones (I)

Compound	Reaction conditions			Yield, %	mp, °C (solvent)	Empirical formula	Found/Calculated, %			PMR spectrum‡ (δ, ppm)
	method*	T, °C	time, h				C	H	N	
(Ia)	A	80	7	87	158–159 [13] (toluene)	–	–	–	–	–
(Ib)	B	60	7,5	63	34–35 (hexane)	$C_{13}H_{13}NO_3$	$\frac{67,83}{67,52}$	$\frac{5,92}{5,67}$	$\frac{5,90}{6,06}$	0,96 s (3H, CH_3), 1,43–1,73 m (4H, C^5H_2, C^6H_2), 2,53 t (2H, C^4H_2), 8,30 m (AB system) (4H arom.)
(Ic)	B	60	3	77	86–87 (hexane)	$C_{13}H_{13}NO_4$	$\frac{63,18}{63,15}$	$\frac{5,12}{5,30}$	$\frac{5,65}{5,66}$	1,60 s (6H, $C(CH_3)_2$), 3,45 s (3H, OCH_3), 8,30m (AB system) (4H, (arom.)
(Id)	A	80	8	90	130–131 [13] (toluene)	–	–	–	–	–
(Ie)	B	70	1	78	188–189 [13] (dichloroethane)	–	–	–	–	–
(If)	B	50	1	80	107–108 (hexane)	$C_{13}H_{10}N_2O$	$\frac{74,16}{74,27}$	$\frac{4,91}{4,79}$	$\frac{13,24}{13,32}$	4,21 s (3H, CH_3), 7.12 d (1H, C^4H), 7,5 d (1H, C^3H), 7,35–7.70 m (5H, Ph)
(Ig)	B	80	3	80	57–58 (hexane:toluene 1 : 1)	$C_{13}H_{10}N_2O$	$\frac{74,16}{74,27}$	$\frac{4,66}{4,79}$	$\frac{13,08}{13,32}$	4.02 s (3H, CH_3), 6,9 d (1H, C^4H), 7,36 d (1H, C^5H), 7,40–7,75 m (5H, Ph)
(Ih)	A	80	8	89	†	$C_{16}H_{12}O_2$	$\frac{81,29}{81,34}$	$\frac{5,25}{5,12}$	–	4,08 s (3H, CH_3), 7,10–8,25 m (9H, arom.)
(Ii)	A	80	4	90	bp, 95–96 (2 mm), [1]	–	–	–	–	–

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*In method A the CuCl catalyst was used in a 0.1:1 molar ratio with respect to reagent; in method B 2 g $Pd(PPh_3)_2Cl_2$ catalyst were used per mole of reagent.

†Viscous liquid.

‡IR spectra (ν, cm^{-1}): 1620-1690 (C=O), 2210-2220 (C≡C).

3-Diethylamino-1-(p-nitrophenyl)-3-phenylpropen-2-one-1 (IIIa). A mixture of 9.4 g (Ia) and 2.9 g Et_2NH in 20 ml benzene was stirred for 1 h at 50°C. Removal of the solvent by distillation yielded 11.3 g of chromatographically pure (IIIa) (Table 2).

A similar method was used to synthesize compounds (IIIb-d, f, g) which may be converted into the corresponding compounds (II) as described for the isomerization of (I).

1-(m-Nitrophenyl)-3-phenylpropyn-2-one-1 (Id). A mixture of 5.6 g m-nitrobenzoylchloride, 3.1 g phenylacetylene, 3.2 g Et_3N, and 0.3 g CuCl in 25 ml abs. toluene was stirred in a stream of Ar for 8 h at 80°C. The hot reaction mixture was filtered and the precipitate washed with hot toluene (50 ml). The combined filtrate was concentrated under vacuum to ~20 ml and cooled. The precipitated ketone (IId) was filtered; yield 6.8 g (Table 3).

Compounds (Ia-c, e-i) were obtained similarly.

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