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SYNTHESIS OF ACETYLENIC KETONES

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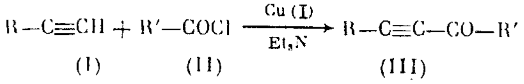
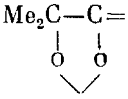
A general preparative method of synthesis of acetylenic ketones was developed based on acylation of terminal acetylenes with acid chlorides in the presence of Cu(I) chloride.

The high reactivity of acetylenic ketones in reactions with nucleophilic reagents makes them valuable starting compounds for synthesis of heterocyclic systems [1]. From them can be obtained aminovinyl ketones, β-diketones, and β-diols [2]. In connection with this we have continued our investigation of catalytic acylation of terminal acetylene compounds with acid chlorides (AC's) in the presence of Cu(I) chloride, since this reaction is a convenient way for obtaining acetylenic ketones [3-6]



$$\underset{(I)}{R{-}C{\equiv}CH} + \underset{(II)}{R'{-}COCl} \xrightarrow[Et_3N]{Cu(I)} \underset{(III)}{R{-}C{\equiv}C{-}CO{-}R'}$$

R = Me_2COMe, R' = i-Pr (a), t-Bu (b); R = $Me(n\text{-}C_6H_{13})COMe$, R' = i-Pr (c), t-Bu(d); R = $Me_2\cdot COMe$, R' = $MeCH(n\text{-}Bu)$ (e); $p\text{-}NO_2C_6H_4$ (f), $p\text{-}MeC_6H_4$ (g), α-naphthyl (h), R = $(CH_2)_5COMe$, R' = Ph (i), $p\text{-}NO_2C_6H_4$ (j); R = Me_2COMe, R' = Pr (k), $n\text{-}C_5H_{11}$ (ℓ), $n\text{-}C_6H_{13}$ (m), $n\text{-}C_7H_{15}$ (n), $n\text{-}C_8H_{17}$ (o), R = $Me_2C(OMe)C{\equiv}C$, R' = i-Pr (p), t-Bu (q); R =  $Me_2C{-}C{=}$, R' = t-Bu (r); R = $CH_2{=}C(Me)$, R' = t-Bu (s); R = $MeOCH_2$, R' = t-Bu (t); R = Ph, R' = i-Pr (u), t-Bu (v), $p\text{-}MeC_6H_4$ (w), α-naphthyl (x); R = $CH_2{=}CH$, R' = t-Bu (y).

Reaction was carried out in benzene, toluene, or CCl_4 at 20-70°C under a nitrogen flow. Solvent selection was determined by reaction conditions and by the possibility of separating the starting acetylenes from the reaction products under GLC control. As the base Et_3N (1.2-2 moles per 1 mole AC) was used. The amount of CuCl was varied from 0.05 to 2 mole per 1 mole of acetylene compound (Table 1).

Analysis of experimental data indicates that reaction of methyl ethers of acetylenic carbinols (Ia, c) with the AC's of branched aliphatic acids (IIa, b, e) proceeds vigorously in the presence of catalytic amounts of CuCl and the best solvents are benzene and toluene. Upon using CCl_4 the yields of ketones (IIIa, c, d) decrease.

Among the AC's of aromatic acids the most active is PhCOCl. Thus, reaction of the corresponding acetylene with PhCOCl proceeds exothermically and is complete in 1.5 h. The yield of ketone (IIIi) is 90.7%. For other aromatic AC's the reaction temperature must be increased to 50-75°C and the time necessary for complete reaction increased from 1-2 to 5-11 h. The same conditions are necessary for acylation of phenylacetylene with $p\text{-}MeC_6H_4\cdot COCl$ and the AC of 1-naphthoic acid.

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TABLE 1. Reaction Conditions and Properties of Acetylenic Ketones R—C≡C—COR'

Compound	CuCl amount mole per 1 mole of (I)	Solvent	T, °C	Time, h	Yield, %	Bp, °C (p, mm Hg) Mp, °C (solvent)	n_D(°C)	Found/Calculated, %		Empirical formula
								C	H	
(IIIa)	0,1	CCl_4	20	3	48,8	* —	—	—	—	—
		Benzene	60	2	72,6					
(IIIb)	0,1	»	60	3	91,2	93–94(15)	1,4415(19)	72,40/72,49	9,99/9,96	$C_{11}H_{18}O_2$
(IIIc)	0,1	CCl_4	20	1	54,6	* —	—	—	—	—
(IIId)	0,1	CCl_4	20	1	64,5	* —	—	—	—	—
	0,05	Benzene	20	1	84,3	—	—	—	—	—
			40	1						
(IIIe)	0,1	Toluene	55	5	89,0	112–115(15)	1,4495(23)	74,40/74,24	10.32/10,54	$C_{13}H_{22}O_2$
(IIIf)	0,1	»	75	5	75,3	87–89 Petroleum benzine	—	62,97/63,15	5,14/5,30	$C_{13}H_{13}NO_4$
(IIIg)	0,1	»	75	7	77,9	131(2)	1,5350(21,5)	77,87/77,75	7,49/7,46	$C_{14}H_{16}O_2$
(IIIh)	0,1	Benzene	60	11	81,3	57–59 (Sublim.)	—	80.84/80,92	6,40/6,39	$C_{17}H_{16}O_2$
(IIIi)	0,1	Toluene	60	1,5	90,7	* —	—	—	—	—
(IIIj) **	0,1	»	70	4	64,8	73–75	—	66,54/66,65	6,18/6,29	$C_{16}H_{17}NO_4$
(IIIk)	2	»	45	6	71,4	92(15)	1,4450(20)	71,19/71,39	9,54/9,59	$C_{10}H_{16}O_2$
(IIIℓ)	2	»	45	7,5	61,3	113(20)	1,4490(18)	73.31/73,43	10,46/10,27	$C_{12}H_{20}O_2$

(IIIm)	2	»	45	5	58,0	100(2)	1,4530(18)	74,27 74,24	10,48 10,54	$C_{13}H_{22}O_2$
(IIIn)	2	»	20	7	49,2	110,5(2)	1,4505(21,5)	74,88 74,95	10,55 10,88	$C_{14}H_{24}O_2$
(IIIo)	2	»	45	6	52,9	121,5(2)	1,4525(21,5)	75,55 75,58	10,88 11,00	$C_{15}H_{26}O_2$
(IIIp)	0,1	»	20	1	50,0	74–76(0,5)	1,4950(20)	74,32 74,97	8,54 8,39	$C_{12}H_{16}O_2$
(IIIq)	0,1	»	20	1	63,7	82–83(1)	1,4895(18)	75,01 75,69	9,04 8,80	$C_{13}H_{18}O_2$
(IIIr)	0,1	»	55	6	50,0	49–51 Petroleum benzine	—	70,18 70,24	8,12 8,16	$C_{13}H_{18}O_3$
(IIIs)	0,1	Benzene	30	10	72,0	78(15)	1,4715(20)	79,34 79,95	9,43 9,39	$C_{10}H_{14}C$
(IIIt)	0,1	Toluene	50	20	49,0	88–89(20)	1,4430(21)	70,02 70,10	9,31 9,15	$C_9H_{14}O_2$
(IIIu)	0,05	Benzene	50	5	68,9	*** —	—	—	—	—
(IIIv)	0,05	»	50	4	91,9	*** —	—	—	—	—
(IIIw)	0,1	Toluene	65	17	63,6	65–67 (Sublim.)	—	87,09 87,24	5,26 5,49	$C_{16}H_{12}O$
(IIIx)	0,1	»	75	10	73,5	90–92 (Sublim.)	—	88,86 89,04	4,82 4,72	$C_{19}H_{12}O$
(IIIy)	1	»	50	2	62,0	75–78(11)		79,10 79,37	8,91 8,88	$C_9H_{12}O$

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*Described earlier in [5].

**For (IIIf): Found: N, 5.76%; calculated: N, 5.66%. For (IIIj): Found: N, 4.65%; calculated: N, 4.86%.

***In [6].

With AC's of acids of normal structure a secondary reaction is formation of ketene from the AC in the presence of Et_3N. In the presence of catalytic amounts of CuCl it predominates over acylation. We succeeded in obtaining acetylenic ketones (IIIk-o) only with a twofold excess of CuCl relative to the acetylene. Under these conditions Et_3N is completely bound in a complex with CuCl.

We have found that this complex can be used repeatedly in acylation of acetylenic compounds. After reaction termination the reaction mixture was poured off from the complex and subjected to the usual treatment. To the complex Et_3N and acetylene (Ia) were added and reaction was carried out again. This series of four experiments was carried out with the acetylene $Me_2C(OMe)C{\equiv}CH$ and the AC $C_5H_{11}COCl$. The yield of the corresponding ketone even increased from 61.3% in a first synthesis to 71.5% in the fourth, and decreasing the CuCl amount from 2 to 0.5 mole per 1 mole of acetylene decreases the yield of ketone (IIIℓ) to 45.6%.

Beside reacting individual AC's of acids of normal structure with $Me_2C(OMe)C{\equiv}CH$, a mixture of AC's obtained from industrial synthetic fatty acids (SFA-7, 9) was also used to give a mixture of ketones with yield of 80%.

With the goal of functionalization of acetylenic ketones and widening the area of their application we decided to test the proposed method for synthesis of diacetylene and vinylacetylene ketones.

Reaction of the methyl ether of the diacetylene carbinol $Me_2C(OMe)C{\equiv}CC{\equiv}CH$ with the AC i-PrCOCl or t-BuCOCl is complete in 30 min. However ketones (IIIp, q) were isolated with yields of 50.0 and 67.7%, respectively, due to their extensive resinification during distillation.

Vinylacetylene hydrocarbons are less active and reaction time increases to 10-20 h and the temperature to 50°C. Vinylacetylene successfully reacted with t-BuCOCl only in the presence of equimolar amounts of CuCl. It should be noted that this reaction can proceed in 18 h at 50°C upon using catalytic amounts of the chelate $[(CH_3)(C_6H_{13})C(OCH_3)C(NH){=}CHCOC(CH_3)_3]_2Cu$ [3]; however, the yield of ketone (IIIy) does not exceed 55.8%.

The low activity of vinylacetylenes is explained by the low solubility of the intermediate acetylides in the reaction mixture. This is confirmed by our experiments on acylation of acetylene. In spite of a wide variation of reaction conditions for acylation, we were not able to obtain ethynyl ketones with acetylene.

The presence in the IR spectra of ketones (IIIa-f) with absorption bands at 2210 cm^{-1} ($-C{\equiv}C-$) and 1680 cm^{-1} ($C{=}O$), and elemental analysis and GLC data confirm the structure of the previously unknown compounds.

EXPERIMENTAL

IR spectra were recorded in CCl_4 on a UR-20 spectrometer. GLC was carried out on Chrom-4 and Chrom-5 instruments with two columns: 120 × 0.4 cm, 0.5% PEGA on glass (0.2-0.25 mm), and 360 × 0.3 cm, 5% SE-30 on inerton AW, with nitrogen as carrier gas, at 110-160°C. Methyl ethers of mono- and diacetylene carbinols were obtained by the methods of [7, 8] and isopropenylacetylene by the method of [10]. CuCl was previously purified by washing with 5% H_2SO_4 and alcohol followed by drying under vacuum.

Reaction of the Acetylene $Me_2COMeC{\equiv}CH$ (Ia) with AC's (general methods). a) To a mixture of 2 g (0.02 mole) of CuCl in 100 ml of benzene with stirring in a nitrogen flow 19.6 g (0.2 mole) of acetylene (Ia), 40.0 g (0.4 mole) of Et_3N, and 25.3 g (0.21 mole) of t-Bu·COCl in 50 ml benzene was added. The mixture was stirred for 3 h at 60°C and cooled. Then 100 ml of water was added and extracted with benzene or ether. The organic layer was washed with dilute HCl, water, dried above $CaCl_2$, and by distillation ketone (IIIb) was isolated.

b) To the complex prepared from 19.8 g (0.2 mole) of CuCl and 11.2 g (0.11 mole) of Et_3N in 100 ml of toluene, 9.8 g (0.1 mole) of acetylene (Ia) and 11.6 g of $n\text{-}C_5H_{11}COCl$ was added. The mixture was stirred for 6 h at 45°C in a nitrogen flow. The toluene solution was poured off of the complex, treated as above, and by distillation ketone (IIIℓ) was isolated. The remaining complex was again introduced into a reaction.

Reaction conditions, yields, properties and results of elemental analysis of acetylenic ketones (IIIa-y) are shown in Table 1.

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HIGHER N-ACYL-L-AMINO ACID DERIVATIVES

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A preparative method is proposed for obtaining higher N-acylamino acids by reaction of free amino acids with fatty acid nitrophenyl esters. It was shown that these acids can transport positive ions through a liquid lipophilic medium. A direct method is proposed for obtaining fatty acid 4-nitrophenyl esters by boiling 4-nitrophenol and the fatty acid in xylene in a Soxhlet apparatus in the presence of an acid catalyst.

Higher N-acyl-L-amino acid derivatives possess lipophilic and hydrophilic properties which determine their practical applications [1, 2]. Their structure resembles that of N-acetylamino acids, which are metabolic products, and they are hydrolyzed by acylases [3] to amino and fatty acids that are metabolized by animals. The slow hydrolysis of N-acylamino acids may have practical applications in feeding ruminants, which rapidly decompose free amino acids [4] in their rumens, thus lessening the nutritional value of food. At present capsules containing food supplements, such as amino acids along with fatty acids, chitosan, and other fillers [4], are given to animals as protection against factors in the rumen.

There are many well-established methods for obtaining N-acylamino acids [5-8]. However, a comparative study of these methods [5] has shown that each one has some drawbacks. Moreover, none of them affords high product yields when a wide selection of acidic, neutral, and basic amino acids are used as starting materials, which limits their use. A seri-

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