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Peculiar Features of the Willgerodt–Kindler Reaction of 1-Adamantylpropan-2-one and Its Derivatives

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Abstract—The Willgerodt–Kindler reaction of 1-(1-adamantyl)propan-2-one and its derivatives was studied by gas chromatography–mass spectrometry. The reaction time was found to be 3–4 times longer than in the case of alkyl aryl ketones due to considerable steric hindrances in the molecules of adamantyl ketones. The use of diglyme as solvent and sodium butyl xanthate as catalyst significantly shortened the reaction time and improved the yield to 92%.

Keywords: Willgerodt–Kindler reaction, 1-adamantylpropan-2-one, 3-(1-adamantyl)propanoic acid, sodium butyl xanthate

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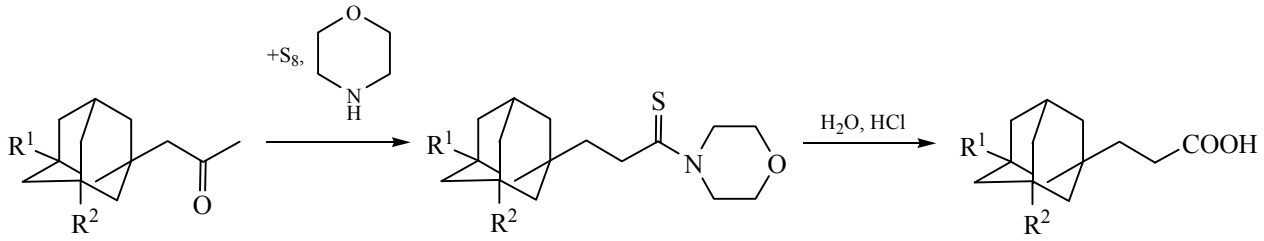
The Willgerodt–Kindler reaction is widely known as the method of synthesis of thioamides from alkyl aryl ketones [1–4], arylalkenes, and alkynes [5, 6]. Aliphatic ketones and aldehydes can also be involved in this reaction [7]. The reaction of acetophenone with morpholine and sulfur with formation of thiomorpholide has been studied most thoroughly [8, 9]. However, there are no published data on Willgerodt–Kindler reactions with ketones containing an adamantyl fragment. Therefore, we have studied the possibility of using this reaction to obtain adamantylcarboxylic acids as an alternative to the existing methods that are multistage, experimentally complex, and expensive. For example, a seven-stage procedure for the synthesis of 3-(1-adamantyl)propanoic acid from adamantan-1-ol has been described in [10]. Posterma et al. [11] proposed an analogous procedure with the use of adamantane-1-carbaldehyde as starting material. Nicolaou et al. [12] reported a two-stage method for the synthesis of adamantanecarboxylic acids via reaction of 1-bromoadamantane with methyl acrylate in the presence of azobis(isobutyronitrile) and tributyltin hydride, followed by hydrolysis. The main drawback of this method is high cost of tributyltin hydride. The procedures described in [13, 14] utilized sodium cyanide in the penultimate stage, which also restricts the application of these methods. Therefore, development of methods for the synthesis of 3-(1-adamantyl)propanoic acid by the Willgerodt–Kindler reaction of adamantylacetone is an important problem.

The Willgerodt–Kindler reaction of 1-(1-adamantyl)propan-2-ones **1a**–**1c** with sulfur and morpholine afforded the corresponding thiomorpholides which were hydrolyzed to obtain target 3-(1-adamantyl)propanoic acids **2a**–**2c** in 92–95% yield. It should be noted that in the reaction with compound **1c** after 16 h the reaction mixture contained a considerable amount (25%) of 3-[3-(morpholin-4-yl)-3-sulfanylidenepropyl]adamantan-1-ol. Therefore, the latter was subjected to alkaline hydrolysis to complete the transformation of the bromo derivative to the corresponding hydroxy derivative (Scheme 1).

We examined the effects of temperature, reaction time, and reactant ratio on the yield of 3-(1-adamantyl)-propanoic acids with a view to obtaining target compounds in acceptable yield and purity. The maximum conversion was attained with 2.2 equiv of morpholine and sulfur with respect to initial 1-(1-adamantyl)propan-2-one. The reaction required prolonged heating. After heating for 40 h at 160°C, the concentration of thiomorpholide in the reaction mixture was 62%, the conversion of **1** being 65%. Increase of the reaction time to 45 h did not raise the

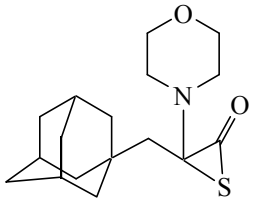
Scheme 1.



1a–**1c** **2a**–**2c**

1a, **2a**, $R^1 = R^2 = H$; **1b**, **2b**, $R^1 = R^2 = Me$; **1c**, $R^1 = H$, $R^2 = Br$; **2c**, $R^1 = H$, $R^2 = OH$.

conversion of ketone **1**, but the concentration of both thiomorpholide and intermediate compound **3** decreased; as result, the number and amount of by-products increased. This problem was solved by proper choice of the catalyst. Using sodium xanthate as catalyst, we succeeded in shortening the reaction time to a considerable extent and minimizing formation of by-products.



3

We also found that the conversion of 1-(1-adamantyl)propan-2-one can be increased to ~68% by carrying out the reaction in the absence of a solvent (16 h). Further increase of the reaction time (to 25 h) did not improve the conversion to an appreciable extent because of considerable thickening of the reaction mixture. Therefore, to improve the conversion of the initial adamantyl ketones, all reactions were subsequently carried out in diglyme at 160°C using butyl xanthate as catalyst.

The effect of the reaction time on the yield of the corresponding thiomorpholide was studied by GC/MS (see table). It should be noted that the Willgerodt–Kindler reaction with 1-adamantylpropan-2-ones takes, on the average, 3–4 times more time than analogous reactions with alkyl aryl ketones. After 8 h, the concentration of thiomorpholide was 55%. The other substituted adamantylpropan-2-ones behaved similarly. Most probably, this is related to reduced reactivity of 1-(1-adamantyl)propan-2-one in the Willgerodt–Kindler reaction, which strongly depends on spatial accessibility of the carbonyl group. The presence of a substituent in position *3* of the adamantyl fragment does not affect the reactivity of adamantyl alkyl ketones to an appreciable extent. Presumably, the reaction is low sensitive to electronic properties of substituents in the adamantyl fragment. A more important factor is likely to be the position of the carbonyl oxygen atom with respect to the adamantyl fragment. Sterically hindered 1-(1-adamantyl)propan-1-one showed very low reactivity: after 20 h, only 11% of thiomorpholide was formed. It is steric factor that is responsible for the low reactivity of 1-(1-adamantyl)-propan-1-one in this reaction.

The mechanism of the Willgerodt–Kindler reaction was the subject of numerous studies; however, there is still no consensus on this topic. On the basis of

Composition of the reaction mixtures[a] according to the GC/MS data

Reaction time, h	Conversion of 1-(1-adamantyl)-propan-2-one, %	Concentration, wt %		
		thiomorpholide	enamine	**3**
2	20.0	18.0	0.5	6.0
4	40.0	32.0	0.8	10.0
6	58.0	42.0	1.5	12.0
8	70.0	55.0	1.5	13.5
10	75.0	58.0	2.0	15.0
16	85.0	71.0	2.0	8.8
24	92.0	88.0	0.9	6.3
32	98.0	91.0	0.8	5.3
40	99.0	94.0	0.5	4.2
45	99.5	98.0	0.2	0.2

[a] The reaction was carried out in the presence of 0.5 wt % of sodium butyl xanthate in diglyme.

experimental data, mechanisms involving enamines, thioketones, thiols, and unsaturated hydrocarbons as intermediates were proposed [1, 15–21]. In order to elucidate the transformation path we used GC/MS data. The chromatograms of the reaction mixture contained four major peaks corresponding to initial 1-adamantylpropan-2-one, two intermediate compounds, and final thiomorpholide. The intermediate compounds were identified as enamine (retention time 8.9 min) whose concentration ranged from 2 to 0.9% and (assumingly) compound **3** (*m*/*z* 307).

In order to confirm the above assumption, the Willgerodt–Kindler reaction of 1-(1-adamantyl)propan-2-one was carried out at a temperature not exceeding 130°C. After hydrolysis, the reaction mixture contained 20% of 1-adamantylacetic acid, which suggests intermediate formation of compound **3** with a high degree of probability. The concentration of enamine in the reaction mixture did not exceed 2%, while the concentration of **3** reached its maximum value (13.5%) after 8 h and then dropped down to 0.2% (after 45 h). These findings conform to the classical Willgerodt–Kindler reaction scheme proposed in [15]. The reaction begins with the formation of enamine which rapidly takes up sulfur. Another version implies migration of the oxygen atom to the methyl group and subsequent addition of morpholine and sulfur to form intermediate **3**.

In summary, we have studied the Willgerodt–Kindler reaction of 1-adamantylpropan-2-one and its derivatives and shown the possibility of using this reaction to obtain 3-(1-adamantyl)propanoic acids.

EXPERIMENTAL

The mass spectra were recorded on a Varian Saturn-2100 GC/MS instrument. The IR spectra were measured on a Thermo Electron Nicolet-6700 spectrometer with Fourier transform. The ^{1}H NMR spectra were recorded on a Varian Mercury Plus BB spectrometer (300 MHz) relative to hexamethyldisiloxane as internal standard.

Morpholine and diglyme were dried over potassium hydroxide and then distilled. 1-Adamantylpropan-2-ones **1a**–**1c** were synthesized according to the procedure developed by us previously [22].

1-(1-Adamantyl)propan-2-one (1a). A solution of 43 g (0.2 mol) of 1-bromoadamantane in 260 mL of methylene chloride was cooled to –10°C, and 61.9 g (0.23 mol) of aluminum bromide was added. The mixture was stirred for 0.5 h, 44 mL (40 g, 0.42 mol) of isopropenyl acetate was added over a period of 2 h, and the mixture was stirred for 0.5 h, poured onto 200 g of ice, and made weakly alkaline reaction by adding sodium carbonate (106 g, 1 mol) and sodium metabisulfite (38 g, 0.2 mol). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (3×50 mL). The extracts were combined with the organic phase, the solvent was distilled off, and the residue was distilled under reduced pressure. Yield 31.9 g (83%), bp 110–112°C (4 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.50–1.80 m (12H, CH_2), 1.94 s (3H, CH), 2.10 s (3H, CH_3), 2.16 s (2H, CH_2CO).

1-(3,5-Dimethyladamantan-1-yl)propan-2-one (1b) was synthesized in a similar way from 48.6 g (0.2 mol) of 1-bromo-3,5-dimethyladamantane. Yield 37.1 g (91%), bp 125–127°C (4 mm). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.83 s (6H, CH_3), 1.51–1.82 m (12H, CH_2), 1.94 s (3H, CH), 2.11 s (3H, CH_3), 2.15 s (2H, CH_2CO).

1-(3-Bromoadamantan-1-yl)propan-2-one (1c) was synthesized in a similar way from 58.8 g (0.2 mol) of 1,3-dibromoadamantane. Yield 41.1 g (76%), bp 155–156°C (4 mm), n_D^{20} = 1.5360. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.48–2.08 m (14H, CH_2, CH), 2.31 s [2H, $C\underline{H}_2C(O)CH_3$], 2.26 s [3H, $CH_2C(O)C\underline{H}_3$].

3-(1-Adamantyl)propanoic acid (2a). A mixture of 19.2 g (0.1 mol) of 1-(1-adamantyl)propan-2-one, 6.4 g (0.2 mol) of sulfur, 17.4 g (0.2 mol) of morpholine, 50 mL of diglyme, and 0.5 g (0.0029 mol) of sodium butyl xanthate was stirred for 45 h at 160°C. The solvent was distilled off, the residue was cooled and poured into 200 mL of water, and the precipitate was filtered off. The resulting thiomorpholide was hydrolyzed by heating for 20 h in concentrated aqueous HCl. The mixture was cooled, 30 g of sodium hydroxide was added, the mixture was extracted with benzene to remove impurities, and aqueous HCl was then added to pH 1–3. The product was extracted with diethyl ether, the solvent was removed from the extract, and the residue was distilled under reduced pressure. Yield 19.8 g (95%), bp 175–178°C (4 mm), mp 151°C. IR spectrum, ν, cm^{-1}: 904, 988, 1029, 1107, 1148, 1187, 1216, 1244, 1304, 1336, 1713 (COOH), 2850 (CH), 2914, 3434 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22–1.45 m (14H, CH_2, $C\underline{H}_2CH_2COOH$), 2.16–2.22 t (4H, CH, $CH_2C\underline{H}_2COOH$, J = 8.3 Hz), 11.90 br.s (1H, COOH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 208 (2) $[M]^+$, 206 (2), 190

(3), 189 (2), 135 (10), 134 (100), 106 (12), 105 (4), 93 (12), 91 (9), 79 (12), 45 (4), 41 (3).

3-(3,5-Dimethyladamantan-1-yl)propanoic acid (2b) was synthesized in a similar way from 20.8 g (0.1 mol) of 1-(3,5-dimethyladamantan-1-yl)propan-2-one. Yield 22.0 g (93%), mp 84–87°C. IR spectrum, ν, cm^{-1}: 902, 980, 1034, 1107, 1148, 1187, 1216, 1244, 1304, 1336, 1718 (COOH), 2850 (CH), 2915, 3438 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.85 s (6H, CH_3), 1.23–1.51 m (14H, CH_2, $C\underline{H}_2CH_2COOH$), 2.02–2.10 m (4H, CH, $CH_2C\underline{H}_2COOH$), 11.95 br.s (1H, COOH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 237 (47) $[M]^+$, 236 (100), 163 (49), 162 (18), 149 (26), 133 (10), 122 (6), 121 (24), 107 (21), 105 (8), 95 (15), 93 (14), 91 (11), 45 (10), 41 (9).

3-(3-Hydroxyadamantan-1-yl)propanoic acid (2c) was synthesized in a similar way from 20.8 g (0.1 mol) of 1-(3-hydroxyadamantan-1-yl)propan-2-one. The hydrolysis of thiomorpholide was carried out in the presence of sulfuric acid. Yield 20.6 g (92%), mp 175–178°C. IR spectrum, ν, cm^{-1}: 902, 980, 1034, 1107, 1148, 1187, 1216, 1244, 1304, 1336, 1713 (COOH), 2849 (CH), 2915, 3435 (OH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.22–1.45 m (14H, CH_2, $C\underline{H}_2CH_2COOH$), 2.01–2.10 m (4H, CH, $CH_2C\underline{H}_2COOH$), 4.36 s (1H, OH), 11.90 br.s (1H, COOH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 224 (23) $[M]^+$, 208 (14), 207 (100), 206 (18), 151 (49), 150 (18), 149 (70), 133 (10), 122 (6), 121 (24), 107 (21), 105 (8), 95 (15), 93 (14), 91 (11), 45 (10), 41 (9).

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