

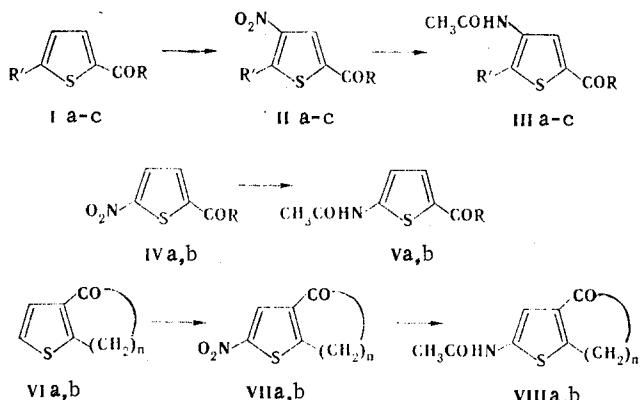
REDUCTIVE ACETYLATION OF NITRO KETONES OF THE THIOPHENE SERIES

Ya. L. Gol'dfarb, B. P. Fabrichnyi,
and I. F. Shalavina

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The action of reduced iron on solutions of nitro ketones of the thiophene series in a mixture of acetic acid and acetic anhydride gave the corresponding acetamido ketones, which can be used, for example, for the synthesis of diacetamidothiophenes (through the oximes).

It is known that several types of aminothiophene derivatives find application in organic synthesis. In particular, in a recently published review [1] devoted chiefly to methods for the synthesis of 2-aminothiophenes that contain electron-acceptor groups several possibilities for their use in the preparation of condensed systems were examined. Of the other methods that lead to the formation of 2- and 3-acylaminothiophenes and substituted derivatives, one should note cleavage of thiophene-2-carboxylic acid azides [2, 3], Beckmann rearrangement of acetylthiophene oximes (for example, see [4]), and the reductive acetylation of nitrothiophenes with Raney nickel in acetic anhydride [5] or with reduced iron in acetic acid and acetic anhydride [6, 7]. The methods mentioned above have certain limitations. An improved variant of the latter method, which makes it possible to obtain 2- and 3-acetamidothiophenes in good yields, was published in 1975.



I, II, III a R=CH₃, R'=H; b R=C₂H₅, R'=H; c R=CH₃, R'=i-C₄H₉; IV, V a R=CH₃; b R=C₂H₅; VI, VII, VIII a n=3; b n=4

To the best of our knowledge, this method has not been previously used for the reductive acetylation of nitro ketones of the thiophene series. Side reactions such as reduction of the carbonyl function to a methylene group [9] could occur under the conditions that we used for reductive acetylation with iron, whereas, from the point of view of our research, it seemed expedient to verify the possibilities of the indicated method for the preparation of acetamido ketones. We established that the action of iron on nitro ketones that contain a thiophene ring in a mixture of acetic acid and acetic anhydride makes it possible to synthesize 4- and 5-acetamidoacetylthiophenes in rather high yield (63-84%).* Except for 5-acetamido-2-acetylthiophene, which was previously obtained [11, 12], all of the acetamido ketones that we synthesized are new compounds that may find application in syntheses such as the preparation of diacetamidothiophenes (through the oximes).

*Our attempt to obtain acetamidoacetylthiophene from 4-nitro-2-acetylthiophene by the action of Zn dust in acetic acid and acetic anhydride by the method in [10] was unsuccessful.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1323-1325, October, 1982. Original article submitted January 22, 1982.

TABLE 1. Characteristics of the Synthesized Compounds

No.	Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
IIc	5-sec-Butyl-4-nitro-2-acetyl-thiophene	61-62 ^b	52,8	5,8	-	14,1	C ₁₀ H ₁₃ NO ₃ S	53,0	5,8	-	14,0	52
VIIa	Oxime ^c	129-132 ^d	-	-	11,5	-	C ₁₀ H ₁₄ N ₂ O ₃ S	-	-	11,6	-	82
	2-Nitro-4,5,6,7-tetrahydrobenzo[b]thiophen-4-one ^e	114-115 ^d	-	-	-	-	-	-	-	-	-	79
VIIb	Oxime	201-202 ^d	45,0	3,8	-	15,0	C ₈ H ₈ N ₂ O ₃ S	45,3	3,8	-	15,1	59
	2-Nitro-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-4-one	65-66 ^d	51,0	4,3	-	15,2	C ₉ H ₉ NO ₃ S	51,2	4,3	-	15,2	68
Va	Oxime	156-157 ^d	48,1	4,4	-	14,3	C ₉ H ₁₀ N ₂ O ₃ S	47,8	4,5	-	14,2	58
	5-Acetamido-2-acetylthiophene	272-273 ^{f,g}	-	-	-	-	-	-	-	-	-	79
IIIa	Oxime	223-225 ^d	-	-	13,9	-	C ₈ H ₁₀ N ₂ O ₂ S	-	-	14,1	-	80
	4-Acetamido-2-acetylthiophene	178-179 ^d	52,3	5,0	-	17,3	C ₈ H ₉ NO ₂ S	52,4	5,0	-	17,5	68
Vb	Oxime	179-180 ^d	-	-	14,3	-	C ₈ H ₁₀ N ₂ O ₂ S	-	-	14,1	-	74
	5-Acetamido-2-propionylthiophene	172-173 ^d	55,0	5,7	-	16,0	C ₉ H ₁₁ NO ₂ S	54,8	5,6	-	16,3	74
IIIb	Oxime	204-205 ^d	-	-	13,4	-	C ₉ H ₁₂ N ₂ O ₂ S	-	-	13,2	-	82
	4-Acetamido-2-propionylthiophene	102,5-103,5 ^h	55,0	5,6	-	16,2	C ₉ H ₁₁ NO ₂ S	54,8	5,6	-	16,3	67
IIIC	Oxime	150-153	-	-	13,1	-	C ₉ H ₁₂ N ₂ O ₂ S	-	-	13,2	-	85
	5-sec-Butyl-4-acetamido-2-acetothiophene	126-127 ^d	60,2	7,2	-	13,3	C ₁₂ H ₁₇ NO ₂ S	60,2	7,2	-	13,4	84
VIIIa	Oxime	189-190 ^d	-	-	11,0	-	C ₁₂ H ₁₈ N ₂ O ₂ S	-	-	11,0	-	63
	2-Acetamido-4,5,6,7-tetrahydrobenzo[b]thiophen-4-one	188,5-190 ^d	57,4	5,3	-	15,2	C ₁₀ H ₁₁ NO ₂ S	57,4	5,3	-	15,3	65
VIIIb	Oxime	225-226 ^d	-	-	12,2	-	C ₁₀ H ₁₂ N ₂ O ₂ S	-	-	12,5	-	90
	2-Acetamido-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophen-4-one	146-148 ^d	59,3	5,9	-	14,1	C ₁₁ H ₁₃ NO ₂ S	59,2	5,9	-	14,4	76
	Oxime	196-197 ^d	-	-	12,0	-	C ₁₁ H ₁₄ N ₂ O ₂ S	-	-	11,8	-	67

^aThe yields of the purified substances are presented.^bFrom cyclohexane. ^cObtained by oximation of nitro ketone IIc by the method presented for the oximation of acetamido ketones.^dFrom alcohol. ^eAccording to [14], this compound had mp 114-115°C. ^fAccording to the data in [11], this compound had mp 270-271°C (mp 271°C [12]).^gFrom acetic acid. ^hFrom a mixture of methylene chloride with hexane.

EXPERIMENTAL

Starting nitro ketones IIa,b and IVa,b were obtained by nitration of 2-acetylthiophene and 2-propionylthiophene and separation of the resulting mixtures into individual isomers by the method in [13]. Nitroketone VIIa [14] and the previously unknown IIc and VIIb were synthesized by nitration of the corresponding ketones by the method presented below.

Nitration of Ketones Ic, VIIa, and VIIb. A 0.06-mole sample of pulverized KNO₃ was added gradually with vigorous stirring at 0-3°C to a solution of 0.05 mole of the ketone in 80 ml of 98% sulfuric acid, and the reaction mass was stirred at 0°C for 30 min. It was then poured over ice, and the precipitate was removed by filtration, washed several times with water, dried, and recrystallized from alcohol.

The oximes of ketones VIa,b were similarly nitrated to give nitro ketone oximes VIIa,b. The constants of nitro ketones IIc and VIIa,b and their oximes are presented in Table 1.

Reductive Acetylation of Nitro Ketones IIa-c, IVa,b, and VIIa,b. A 6-g sample of powdered reduced iron was added to a solution of 0.02 mole of the nitro ketone in 100 ml of acetic acid and 15 ml of acetic anhydride, and the vigorously stirred mass was heated gradually

to 45-55°C on a bath. The reaction commenced at this temperature, the temperature rose rapidly (usually to 75-85°C), a light-colored precipitate formed, and the reaction mass thickened. Heating on the bath was resumed when the temperature began to decrease spontaneously. The reaction mass was stirred at 70-80°C for 8-10 h, after which it was cooled to 50-60°C and poured into 300-400 ml of water. The aqueous mixture was filtered immediately and the filtrate was diluted to approximately twice its original volume and allowed to stand in a refrigerator for 20-30 h. The precipitate was removed by filtration, washed with water, and dried. This procedure was used to isolate the bulk of the reaction product. To obtain an additional amount of product the mother liquor was evaporated *in vacuo* to a small volume, and dilute (1:5) hydrochloric acid was added to the dark viscous mass until it was acidic with respect to Congo red. The resulting solution was allowed to stand in a refrigerator for several hours, and the precipitate was removed by filtration and washed with water. The product was recrystallized.

In a number of cases the acetamido ketones were isolated by a simplified method: The reaction mass was diluted with water and filtered, and the filtrate was evaporated at reduced pressure until a precipitate began to form (at a volume of ~100 ml); the mixture was then acidified with dilute hydrochloric acid and allowed to stand in a refrigerator. The precipitate was then treated as indicated above.

The characteristics of acetamido ketones IIIa-c, Va,b, and VIIIA,b are given in Table 1.

The oximes of these acetamido ketones were obtained by refluxing them for 4 h with a 1.5-2-fold excess of hydroxylamine hydrochloride and sodium acetate in aqueous alcohol solutions. The crystalline oximes were isolated after the solutions were cooled for 10-15 h (see Table 1).

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