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STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. IX. REDUCTION OF THIENYL NITROÖLEFINS WITH LITHIUM ALUMINUM HYDRIDE[1]

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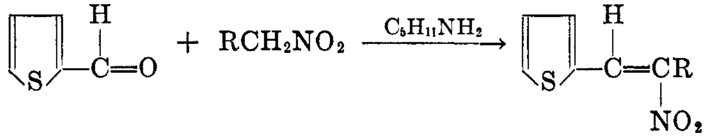
A new and *direct* synthesis of the pharmacologically active β-(2-thienyl)ethylamine (1, 2) and β-(2-thienyl)isopropylamine (2, 3), the thiophene analogue of Benzedrine, has been developed. The successful condensation of the readily available 2-thenaldehyde and various substituted 2-thenaldehydes (4) with nitromethane and 2-thenaldehyde with nitroethane to form the corresponding nitroölefins, was recently reported (5). These latter compounds have now been satisfactorily reduced to the desired saturated amines.

This was accomplished by the use of lithium aluminum hydride, shown to be an effective agent for reducing a nitroölefin to a saturated amine (6). This reagent is particularly suitable in view of the mild conditions which it affords for the reduction of the relatively unstable thienyl nitroölefins and the inherent capacity of thiophene and its derivatives to complicate catalytic hydrogenations.

It was found that the yield of 1-(2-thienyl)-2-nitropropene-1 was substantially increased by employing a Knoevenagel-Walter type catalyst (7) rather than alkali which was used as the condensing agent in the previous preparation (4), for the condensation of 2-thenaldehyde with nitroethane. Utilizing tenth-molar quantities of *n*-amylamine as the catalyst (8) it was found that the above unsaturated nitro compound was formed in 73% yields. Although the time of reaction in such a condensation is lengthy the actual operations are simple; the aldehyde, nitroparaffin, and catalyst are mixed together and allowed to stand for two weeks at the end of which time the mixture is taken up in hot alcohol and allowed to cool whereupon the solution deposits the crystalline product.

This method of condensation also made available the hitherto unknown 1-(2-thienyl)-2-nitrobutene-1. This product, obtained in 53% yields (conversion of 88%), was separated by distillation rather than by crystallization due to its low melting point. The above reactions may be indicated as follows:



(A)

$R = CH_3$ or C_2H_5

Not only has the method for preparing β-(2-thienyl)ethylamine and β-(2-thienyl)isopropylamine *via* the nitroölefins proven to be more direct than the procedures recorded in the literature, but the over-all yields show significant

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improvement. Table I contains a comparison of previous methods with the one presented in this paper.

Other new substituted thienylethylamines were also prepared according to this procedure. The transformations may be indicated as follows:

When R″ = H, R′ = H, CH_3, C_2H_5, C_3H_7, or Cl
When R′ = H, R″ = H, CH_3 or C_2H_5.

TABLE I

COMPARISON OF METHODS OF PREPARATION OF β-(2-THIENYL)ETHYLAMINE AND β-(2-THIENYL)ISOPROPYLAMINE

PRODUCT	REF.	METHOD	NO. OF STEPS[a]	YIELD[a], %
β-(2-Thienyl)ethylamine	(1)	Hofmann degradation of β-(2-thienyl) propionamide	6	15
	(2)	Amination of β-(2-thienyl)ethyl bromide with ammonia	4	6
	(11)	Reduction of 2-thienylacetonitrile with lithium aluminum hydride	6	17
		Reduction of ω-nitro-2-vinylthiophene with lithium aluminum hydride	3	33
β-(2-Thienyl)isopropylamine	(2)	Amination of β-(2-thienyl)isopropyl bromide with ammonia	4	6
	(3)	Amination of β-(2-thienyl)acetone with ammonium formate	4	—
		Reduction of β-(2-thienyl)-2-nitropropene-1 with lithium aluminum hydride	3	32

[a] Based on thiophene as the starting material.

The yields ranged from 50 to 70% for the above reductions; the thienyl nitroölefins, having either the 5-position on the ring or the β-position on the side chain alkylated, giving slightly higher yields (65–70%) than the unsubstituted compound (63%), while β-(5-chloro-2-thienyl)ethylamine was formed in a lower yield (50%). As was expected, no dehalogenated product was obtained in the latter case (9).

Due to the fact that the amines readily absorb carbon dioxide from the air to form the solid carbonates (1), the final distillations were carried out under nitrogen and the amines were analyzed as their hydrochlorides rather than in the uncombined state. Phenylthiourea derivatives were also prepared to further characterize the amines. The collected data on the compounds prepared are recorded in Table II.

A mixed melting point was taken of the hydrochloride of β-(2-thienyl)ethylamine prepared by the above method, with the one[2] obtained according to reference (1). There was no depression.

EXPERIMENTAL[3]

Preparation of intermediates. 2-Thenaldehyde and its alkylated and chlorinated derivatives were synthesized according to the previously described procedure (4). The thienyl nitroölefins were prepared as before (5) with the exceptions of 1-(2-thienyl)-2-nitropropene-1 and 1-(2-thienyl)-2-nitrobutene-1.

1-(2-Thienyl)-2-nitropropene-1. There were mixed together 20 g. (0.18 mole) of freshly distilled 2-thenaldehyde, 13.4 g. (0.18 mole) of freshly distilled nitroethane, and 1.56 g. (0.018 mole) of *n*-amylamine. The solution was stored in a dark place at room temperature. After one day an aqueous phase separated from the solution. At the end of 8 days there appeared a heavy deposit of crystals. After two weeks the mixture was taken up in hot ethyl alcohol and the solution was allowed to cool whereupon yellow crystals precipitated out. These were washed with 10 ml. of cold ethyl alcohol and dried. There were thus obtained 22.1 g. (73% yield) of 1-(2-thienyl)-2-nitropropene-1; m.p. 68.5°, which showed no depression when mixed with an authentic sample (5).

Anal. Calc'd for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28.
Found: C, 50.01; H, 3.89; N, 7.90.

1-(2-Thienyl)-2-nitrobutene-1. There were mixed together 20 g. (0.18 mole) of freshly distilled 2-thenaldehyde, 17.7 g. (0.18 mole) of freshly distilled 1-nitropropane, and 1.56 g. (0.018 mole) of *n*-amylamine. The solution was stored in a dark place at room temperature. After one day an aqueous phase separated from the solution but crystals failed to appear even after two weeks. At that time the reaction mixture was extracted with ether. The extract was washed with 6 *N* HCl, then with water and rectified after being dried over calcium sulfate. After a small pre-run of 1-nitropropane there was recovered 2.4 g. of 2-thenaldehyde b.p. 64–66°/4 mm. (88% conversion). Next, there was obtained 17.1 g. (52% yield) of 1-(2-thienyl)-2-nitrobutene-1, b.p. 120–122°/2.3 mm., m.p. 32°.

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.65.
Found: C, 52.63; H, 4.72; N, 7.44.

Reduction of the thienyl nitroölefins. All of the reductions were carried out utilizing the same procedure. As an example, the preparation of β-(2-thienyl)ethylamine is given:

In a 2-liter 3-necked flask, fitted with a reflux condenser, a mercury-sealed stirrer, and a dropping-funnel, were placed 8.0 g. (0.21 mole, a 20% excess) of lithium aluminum hydride, dissolved in 300 ml. of absolute ether. A solution of 15.5 g. (0.1 mole) of ω-nitro-2-vinylthiophene in 400 ml. of absolute ether was added dropwise at such a rate as to cause gentle reflux. Shortly after the addition terminated, a few ml. of water was cautiously introduced to decompose the excess hydride. There was added 500 ml. of a 20% aqueous solution of sodium potassium tartrate. The ethereal layer was separated and the aqueous layer extracted successively with two 100-ml. portions of ether. The combined extracts were dried over calcium sulfate and rectified, the vacuum-distillation bring carried out under nitrogen.

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[2] Courtesy of L. J. Oddo of this laboratory.

[3] The thiophene used in this investigation was obtained through the courtesy of Dr. G. A. Harrington of Socony-Vacuum Oil Company, and the nitroparaffins were placed at our disposal by the Commercial Solvents Corporation.

TABLE II

REDUCTION OF THIENYL NITROÖLEFINS WITH LITHIUM ALUMINUM HYDRIDE

STARTING MATERIAL	AMINE			HYDROCHLORIDE							PHENYLTHIOUREIDE				
	Product	Yield, %	B.P.[a] °C/MM.	M.P.,[a] °C.	Analysis						M.P.,[a] °C.	Analysis			
					Calc'd			Found				Calc'd		Found	
					C	H	N	C	H	N		C	H	C	H
ω-Nitro-2-vinylthiophene	β-(2-Thienyl)ethylamine	63	76–78/7.0[b]	200–202[c]	44.03	6.16	8.56	44.15	6.23	8.53	109.5–110[d]	59.50	5.38	59.25	5.16
1-(2-Thienyl)-2-nitropropene-1	β-(2-Thienyl)isopropylamine	65	62–65/1.5[e]	143–144.5[f]	47.31	6.81	7.88	47.10	6.59	8.19	98–99	60.83	5.83	60.65	5.91
1-(2-Thienyl)-2-nitrobutene-1	1-(2-Thienyl)-2-aminobutane	69	74–76/6.0	92–93	50.11	7.36	7.31	50.26	7.18	7.20	96.5–97	62.03	6.25	62.02	5.90
5-Methyl-2-(ω-nitrovinyl)thiophene	β-(5-Methyl-2-thienyl)-ethylamine	67	79–81/5.5	180.5–182	47.31	6.81	7.88	47.30	6.71	7.92	119–120	60.83	5.83	61.00	6.02
5-Ethyl-2-(ω-nitrovinyl)-thiophene	β-(5-Ethyl-2-thienyl)-ethylamine	70	84–86/2.8	168–171	50.11	7.36	7.31	49.95	7.28	7.42	84–84.5	62.03	6.25	62.20	6.41
5-Propyl-2-(ω-nitrovinyl)thiophene	β-(5-Propyl-2-thienyl)-ethylamine	70	87–89/2.0	[g]	52.53	7.84	6.81	52.45	7.93	6.89	66–67	63.11	6.62	62.95	6.46
5-Chloro-2-(ω-nitrovinyl)-thiophene	β-(5-Chloro-2-thienyl)-ethylamine	50	70–74/1.2	215–217	36.37	4.58	7.07	36.20	4.44	7.17	87–88	52.61	4.41	52.50	4.58

[a] All melting and boiling points are uncorrected. [b] Reported (2) as 88–90°/13.0 mm. [c] Same as listed in ref. (1). [d] Same as recorded in ref. (11). [e] Reported as 94–96°/15.0 mm. (2). [f] Listed as 139–141° (2). [g] Starts to char at 140°. No definite m.p. was obtained.

In this way there was obtained 8 g. (63% yield) of β-(2-thienyl)ethylamine, b.p. 76–78°/7.0 mm.

Preparation of derivatives. The hydrochlorides were prepared by treating the amine, in absolute ether, with alcoholic hydrogen chloride. They were recrystallized by solution in warm, absolute alcohol, with the addition of absolute ether until the solution became cloudy, followed by boiling until the solution became clear, and subsequent cooling.

The phenylthioureides were prepared by treatment of the amines with an equal amount of phenylisothiocyanate. The reactants were shaken together for a few minutes, cooled, and washed successively with petroleum ether and 50% alcohol. They were recrystallized from 95% alcohol (10).

SUMMARY

1. Lithium aluminum hydride is shown to be an effective reducing agent for nitroölefins in the thiophene series.

2. The amine-catalyzed condensations of 2-thenaldehyde with nitroethane and 1-nitropropane are described.

3. A new and direct method is presented for the synthesis of β-(2-thienyl)-ethylamine and β-(2-thienyl)isopropylamine.

4. The following amines, together with their hydrochlorides and phenylthioureides, none of which is listed in the literature, are reported, *viz.*, β-(5-methyl-2-thienyl)-, β-(5-ethyl-2-thienyl)-, β-(5-propyl-2-thienyl)-, and β-(5-chloro-2-thienyl)-ethylamine and 1-(2-thienyl)-2-aminobutane.

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