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SHORT COMMUNICATIONS

First Synthesis of 2-Aminothiophen-3-ols

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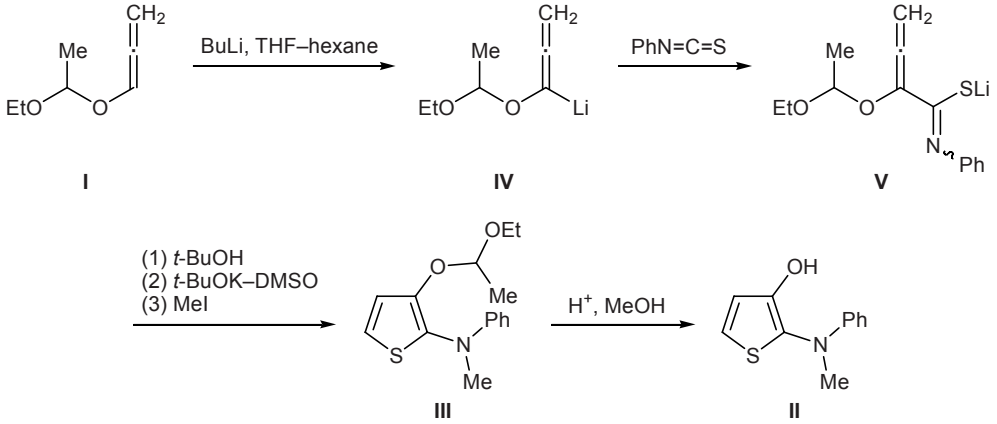
Development of new improved procedures for the synthesis of functionalized thiophene derivatives and discovery of their new important applications, e.g., in pharmacology (as medicines or their precursors), optoelectronics, and molecular electronics (as dyes, liquid crystalline photoswitches, organic transistors, conducting materials, etc.), continuously stimulate studies in the field of thiophene chemistry [1].

We recently reported on novel reactions of lithiated allenes and acetylenes with isothiocyanates, which lead to the formation of fundamental nitrogen- and sulfur-containing heterocycles [2], including 3- [2, 3] and 5-substituted thiophen-2-amines [2, 4] and thiophen-2(5*H*)-imines [5]. While continuing studies in this line, we found that the use of accessible 1-(1-ethoxyethoxy)allene (**I**) [6] as starting compound makes it possible to readily obtain previously unknown 2-[alkyl(aryl)amino]thiophen-3-ols **II** which exist almost exclusively as hydroxy tautomers [7]. In the present communication we describe the first example of the corresponding reaction sequence.

Precursors of 2-aminothiophen-3-ols **II**, *N*-alkyl-*N*-aryl-3-(1-ethoxyethoxy)thiophen-2-amines **III** (first representatives of aminothienyl acetals), were formed in a good yield (74%, Ar = Ph, R = Me) by reaction of α-lithiated 1-(1-ethoxyethoxy)allene (**IV**) with aromatic isothiocyanate (e.g., commercially available phenyl isothiocyanate), followed by treatment of adduct **V** first with *tert*-butyl alcohol and then with *t*-BuOK–DMSO and alkylation of cyclic intermediate at the nitrogen atom. The acetal protection is removed from thiophene **III** by methanolysis in the presence of hydrogen chloride (45–50°C, 5 min) to give 95% of 2-aminothiophen-3-ol **II**.

It should be noted that the alcoholysis process is not inhibited despite the presence in molecule **III** of an amino group capable of binding hydrogen chloride. Presumably, unlike aliphatic amines, less basic aromatic amines with mineral acids form considerably weaker salts, so that some amount of free acid is always present in equilibrium with the salt, and it is capable of catalyzing electrophilic process. As we showed previ-



ously [8], *N*-benzyl- and *N*,*N*-dimethylaniline hydrochlorides catalyze addition of propan-2-ol to butoxyethene with formation of the corresponding acetal. *N*-Aryl-*N*-hetarylamines are expected to give even weaker hydrochlorides; therefore, protolysis of acetal **III** was successful under fairly mild conditions. On the other hand, the acetal moiety in *N*,*N*-dialkyl-3-(1-ethoxyethoxy)thiophen-2-amines obtained from allene **I** and alkyl isothiocyanates remained unchanged under analogous conditions, whereas more severe conditions promoted profound decomposition.

3-(1-Ethoxyethoxy)-*N*-methyl-*N*-phenylthiophen-2-amine (III). (1-Ethoxyethoxy)allene (**I**), 16 g (125 mmol), was added in one portion to a solution of 112 mmol of butyllithium in a mixture of 70 ml of hexane and 90 ml of tetrahydrofuran, cooled to –100°C. The mixture warmed up to –55°C and was stirred for 10 min at −65 to −60°C and cooled to –90°C, 13.5 g (100 mmol) of phenyl isothiocyanate was added, and the mixture was stirred for 20 min at −65 to −60°C. A solution of 10 ml of *tert*-butyl alcohol in 15 ml of diethyl ether was added, and a suspension of 14 g (125 mmol) of potassium *tert*-butoxide in 50 g of DMSO was then added. When the temperature reached –13°C (~10 min), 40 g (282 mmol) of methyl iodide was added, and the mixture was heated for 20 min at 35–45°C, cooled to 20°C, treated with a saturated aqueous solution of NH_4Cl, and extracted with diethyl ether (2×50 ml). The extracts were combined, washed with five portions of water, and dried over potassium carbonate, the solvent was removed under reduced pressure, and the residue (30.07 g) was distilled in the presence of ~2 ml of diethylamine. Yield 20.41 g (74%), purity 100% (GLC), bp ~160°C (0.8 mm), n_D^{20} = 1.5700. ^{1}H NMR spectrum, δ, ppm: 7.17 t (2H, *m*-H, ^3J = 8.06 Hz), 6.94 d (1H, 4-H, $^3J_{4,5}$ = 6.04 Hz), 6.83 d (1H, 5-H, $^3J_{5,4}$ = 6.04 Hz), 6.76 m (3H, *o*-H, *p*-H), 5.13 q (1H, OCHO, ^3J = 5.27 Hz), 3.71 d.q and 3.42 d.q (1H each, OCH_2, $^2J_{AB}$ = 9.27 Hz), 3.22 s (3H, NMe), 1.31 d (3H, CHC**H**$_3$, ^3J = 5.27 Hz), 1.12 t (3H, CH_2C**H**$_3$, ^3J = 7.07 Hz). ^{13}C NMR spectrum, δ_C, ppm: 149.84 (C^3), 147.29 (C^2), 132.93 (C^i), 128.70 (C^m), 120.60 (C^5), 119.62 (C^4), 118.19 (C^p), 113.54 (C^o), 101.50 (OCHO), 62.25 (OCH_2), 40.32 (NMe), 20.45 (CH**C**H_3), 15.00 (CH_2**C**H_3). Found, %: C 65.03; H 6.74; N 5.13; S 11.40. $C_{15}H_{19}NO_2S$. Calculated, %: C 64.95; H 6.90; N 5.05; S 11.56.

2-[Methyl(phenyl)amino]thiophen-3-ol (II). One drop of 30% hydrochloric acid and 3.5 g (12.6 mmol) of thiophene **III** were added to 50 ml of methanol cooled to –10°C, and the mixture was heated for 5 min at 45–50°C. A few drops of a saturated aqueous solution of potassium carbonate were added, and methanol and volatile alcoholysis products were removed on a rotary evaporator. The residue was a brown liquid which was treated with 30 ml of water and extracted with two portions of diethyl ether. The extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to isolate 2.45 g (95%) of compound **II** containing 96% of the main substance (GLC). IR spectrum, ν, cm^{-1}: 3462 s (OH), 3104 v.w, 3063 v.w, 3036 v.w, 2993 v.w, 2939 v.w, 2879 v.w, 2813 v.w, 1598 v.s, 1580 v.s, 1498 v.s, 1474, 1449, 1421, 1399, 1336, 1322, 1295, 1282, 1253, 1182 s, 1169, 1121, 1088, 1042, 979 s, 875, 843, 814, 753 s, 728 s, 693 s, 669, 645, 569, 547, 514, 452. ^{1}H NMR spectrum, δ, ppm: 7.22 t (2H, *m*-H, ^3J = 8.73 Hz), 6.98 d and 6.70 d (1H each, 4-H, 5-H, ^3J = 6.0 Hz), 6.83 t (1H, *p*-H, ^3J = 8.16 Hz), 6.75 m (2H, *o*-H), 4.90 br.s (1H, OH), 3.21 s (3H, NMe). ^{13}C NMR spectrum, δ_C, ppm: 148.94 (C^3), 148.15 (C^i), 129.27 (C^m), 125.94 (C^2), 120.84 (C^5), 119.22 (C^4), 118.10 (C^p), 113.94 (C^o), 40.86 (NMe). Found, %: C 64.55; H 5.31; N 6.74; S 15.33. $C_{11}H_{11}NOS$. Calculated, %: C 64.36; H 5.40; N 6.82; S 15.62.

The IR spectra were recorded on a Bruker IFS-25 spectrometer from samples prepared as thin films. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400.13 and 100.61 MHz, respectively, using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. Signals in the ^{13}C NMR spectra were assigned using HSQC two-dimensional heteronuclear correlation technique; two-dimensional NMR experiments were performed on a Bruker AV-400 instrument. Gas–liquid chromatography was performed on a Varian 3400 chromatograph equipped with a flame ionization detector and a DB-5 capillary column, 15 m×0.53 mm, film thickness 1.5 μm; carrier gas nitrogen.

All operations were carried out under nitrogen. Liquid nitrogen was used as cooling agent. Tetrahydrofuran was purified by treatment with finely dispersed potassium hydroxide (~50 g/l), followed by distillation over $LiAlH_4$ in the presence of benzophenone under nitrogen. 1-(1-Ethoxyethoxy)allene (**I**) was prepared according to the procedure described in [6]. Butyllithium (a ~1.6 M solution in hexane) and the other reagents and solvents used in this work were commercial products.

REFERENCES

1. *Comprehensive Heterocyclic Chemistry III*, Katritzky, A.R., Ramsden, C.A., Scriven, E.F.V., and Taylor, R.J.K., Eds., Amsterdam: Elsevier, 2008, vol. 3, pp. 625, 741, 843, 931.
2. Nedolya, N.A., *Ph.D. Thesis of Utrecht University*, Utrecht, The Netherlands, 1999; Brandsma, L., Nedolya, N.A., Tarasova, O.A., and Trofimov, B.A., *Khim. Geterotsikl. Soedin*., 2000, p. 1443; Brandsma, L., *Eur. J. Org. Chem*., 2001, p. 4569; Brandsma, L. and Nedolya, N.A., *Synthesis*, 2004, p. 735.
3. Brandsma, L., Nedolya, N.A., Tarasova, O.A., Klyba, L.V., Sinegovskaya, L.M., and Trofimov, B.A., *Dokl. Ross. Akad. Nauk*, 1997, vol. 357, p. 350; Tarasova, O.A., Klyba, L.V., Vvedensky, V.Yu., Nedolya, N.A., Trofimov, B.A., Brandsma, L., and Verkruijsse, H.D., *Eur. J. Org. Chem*., 1998, p. 253; Brandsma, L., Vvedensky, V.Yu., Nedolya, N.A., Tarasova, O.A., and Trofimov, B.A., *Tetrahedron Lett*., 1998, vol. 39, p. 2433; Brandsma, L., Tarasova, O.A., Vvedenskii, V.Yu., de Jong, R.L.P., Verkruijsse, H.D., Klyba, L.V., Nedolya, N.A., and Trofimov, B.A., *Russ. J. Org. Chem*., 1999, vol. 35, p. 1228; Tarasova, O.A., Brandsma, L., Nedolya, N.A., and Dmitrieva, G.V., Abstracts of Papers, *Mezhdunarodnaya konferentsiya po khimii geterotsiklicheskikh soedinenii, posvyashchennaya 90-letiyu so dnya rozhdeniya professora A.N. Kosta* (Int. Conf. on the Chemistry of Heterocyclic Compounds, Dedicated to 90th Anniversary of Prof. A.N. Kost), Moscow, 2005, p. 316.
4. Tarasova, O.A., Nedolya, N.A., Vvedensky, V.Yu., Brandsma, L., and Trofimov, B.A., *Tetrahedron Lett*., 1997, vol. 38, p. 7241.
5. Nedolya, N.A., Brandsma, L., Schlyakhtina, N.I., Lazarev, I.M., Albanov, A.I., Zinchenko, S.V., and Klyba, L.V., *Arkivoc*, 2001, part (ix), p. 12.
6. Hoff, S., Brandsma, L., and Arens, J.F., *Recl. Trav. Chim. Pays–Bas*, 1968, vol. 87, p. 916.
7. Brandsma, L., Tarasova, O.A., Nedolya, N.A., and Trofimov, B.A., Abstracts of Papers, *XX Vserossiiskaya konferentsiya po khimii i tekhnologii organicheskikh soedinenii sery* (XXth All-Russian Conf. on the Chemistry and Technology of Organic Sulfur Compounds), Kazan, 1999, p. 105.
8. Nedolya, N.A., *Cand. Sci. (Chem.) Dissertation*, Irkutsk, 1982; Nedolya, N.A. and Trofimov, B.A., *Zh. Org. Khim*., 1985, vol. 21, p. 271.