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SHORT COMMUNICATIONS

First Synthesis of 5-(1-Ethoxyethoxy)-*N*-methyl-*N*-phenylthiophen-2-amine and Its Unexpected Alcoholysis

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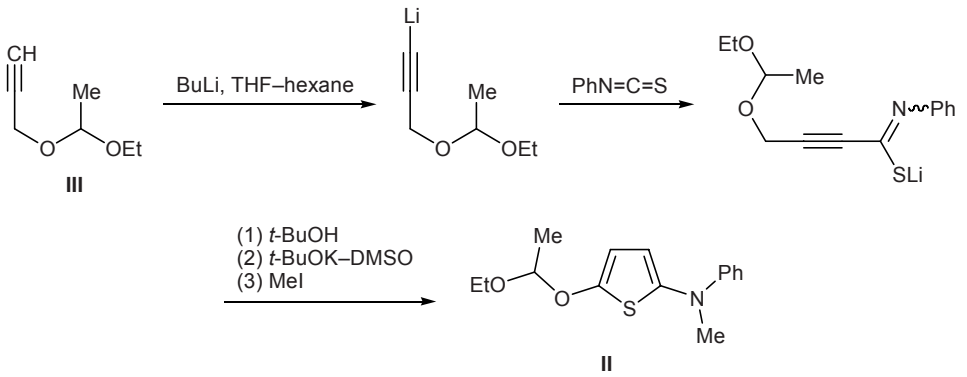
2-Hydroxythiophenes have long been known and studied in sufficient detail. They are usually prepared from α-metalated thiophene derivatives through the corresponding *tert*-butyl ethers or thienylboronic acids; in some cases they are formed as intermediate products in the synthesis of thiophene derivatives, e.g., via Paal cyclocondensation [1]. However, 2-hydroxythiophenes having a disubstituted amino group in position *5* were not described previously.

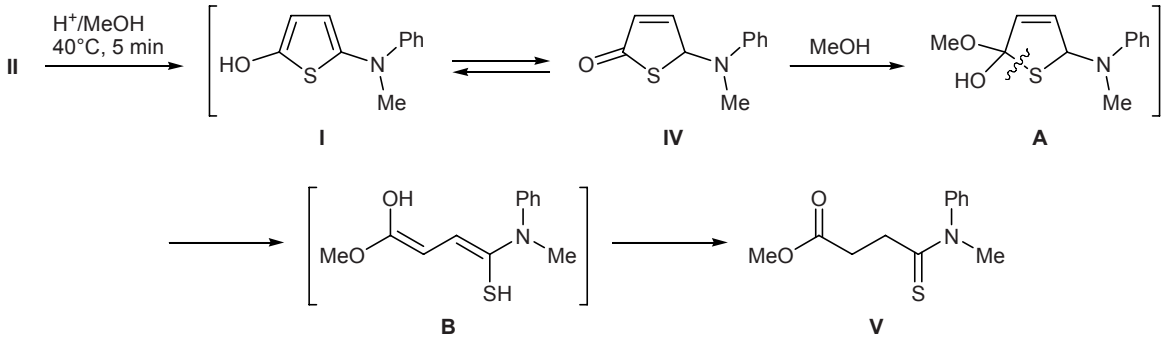
We recently proposed a new general approach to construction of thiophene ring on the basis of reaction of lithiated allenes and alkynes with isothiocyanates. It ensured synthesis of 3- or 5-substituted thiophen-2-amines in one preparative step and in good yield [2, 3]. 5-Substituted *N*,*N*-dialkyl- or *N*-alkyl-*N*-arylthiophen-2-amines are formed by cyclization of adducts of monolithiated terminal alkynes ($HC{\equiv}CCH_2R$, R = Me, *t*-Bu, OMe, $NAlk_2$) with isothiocyanates by the action of superbase (*t*-BuOH–*t*-BuOK–DMSO), followed by alkylation of cyclic intermediate at the nitrogen atom [3]. We also briefly reported on the synthesis of 3-(1-ethoxyethoxy)-*N*-methyl-*N*-phenylthiophen-2-amine by reaction of α-lithiated 1-(1-ethoxyethoxy)-allene with phenyl isothiocyanate; alcoholysis of this compound readily gives 3-hydroxy-*N*-methyl-*N*-phenylthiophen-2-amine which exists exclusively in the hydroxy form [4].

However, our attempt to obtain in a similar way 5-hydroxythiophen-2-amine **I** gave unexpected results [4]. Previously unknown 5-(1-ethoxyethoxy)-*N*-methyl-*N*-phenylthiophen-2-amine (**II**) was synthesized in 87% yield from lithiated 3-(1-ethoxyethoxy)prop-1-yne (**III**), phenyl isothiocyanate, and methyl iodide according to Scheme 1. Treatment of compound **II** with methanol in the presence of hydrochloric acid (with a view to remove acetal protection), instead of expected 2-[methyl(phenyl)amino]thiophen-2-ol (**I**) or its oxo tautomer **IV**, led to the formation of 76% of methyl 4-[methyl(phenyl)amino]-4-thioxobutanoate (**V**) as the first representative of 4-amino-4-thioxobu-

Scheme 1.



Scheme 2.



tanoic acid esters (Scheme 2). Neither hydroxy- (**I**) nor ketothiophene (**IV**) was detected in the reaction mixture.

Presumably, acid-catalyzed hydrolysis of the acetal moiety in compound **II** does not stop at the stage of formation of hydroxythiophene **I** but is followed by further transformations. The driving force of these transformations is the ability of more stable and reactive thiophen-2(5*H*)-one **IV** to take up methanol molecule at the carbonyl group; this process is accompanied by opening of the thiophene ring in intermediate **A** and tautomerization of open-chain intermediate **B**.

It should be noted that acid methanolysis [5] or hydrolysis [6] of analogous acetals of the pyrrole series, e.g., 2-(1-ethoxyethoxy)-5-methylsulfanyl-1*H*-pyrroles obtained according to the above scheme from 1-(1-ethoxyethoxy)hept-2-yne and isothiocyanate (by alkylation of the corresponding adduct and cyclization of the resulting 1-aza-1,3,4-triene in the presence of CuBr), smoothly affords 5-methylsulfanyl-1*H*-pyrrol-2-ols which exist as tautomeric 2,5-dihydro-1*H*-pyrrol-2-ones.

5-(1-Ethoxyethoxy)-*N*-methyl-*N*-phenylthiophen-2-amine (II). A solution of 7.68 g (60 mmol) of alkoxypropyne **III** in 45 ml of THF was cooled to –30°C, a solution of 56 mmol of butyllithium in 35 ml of hexane was added over a period of ~5 min (the mixture warmed up to 8°C), the mixture was cooled to 0°C, and 6.75 g (50 mmol) of phenyl isothiocyanate was added. The mixture was allowed to warm up to 18°C, and the subsequent reaction was accompanied by heat evolution (the temperature rose to 35°C). The mixture was stirred for 20 min at 28–35°C and cooled to –30°C, and a solution of 5 g of *tert*-butyl alcohol and 6 g of potassium *tert*-butoxide in 30 ml of DMSO was added. The mixture was heated for 10 min at 35°C and cooled to –10°C, 20 g of methyl iodide was added, and the mixture was heated for 20 min at 40°C, treated with a saturated aqueous solution of ammonium chloride, and extracted with three portions of diethyl ether. The extracts were combined, washed with water, and dried over potassium carbonate, the solvent was removed under reduced pressure, and the residue was distilled in a vacuum. Yield 12.0 g (87%), bp 180–185°C (~0.8 mm), n_D^{23} = 1.5660. ^{1}H NMR spectrum, δ, ppm: 1.23 t (3H, CH_2**Me**, ^3J = 7.09 Hz), 1.46 d (3H, CH**Me**, ^3J = 5.38 Hz), 3.24 s (3H, NMe), 3.59 d.q and 3.87 d.q (1H each, OCH_2, $^3J_{AB}$ = 9.29 Hz), 5.16 q (1H, OCHO, ^3J = 5.38 Hz), 6.14 d (1H, 3-H, $^3J_{3,4}$ = 3.91 Hz), 6.39 d (1H, 4-H, $^3J_{4,3}$ = 3.91 Hz), 6.79 m (1H, *p*-H), 6.82 m (2H, *o*-H), 7.19 m (2H, *m*-H). ^{13}C NMR spectrum, δ_C, ppm: 15.11 (CH_2**Me**), 20.03 (CH**Me**), 41.71 (NMe), 63.27 (OCH_2), 103.96 (OCHO), 108.71 (C^3), 114.46 (C^o), 118.82 (C^p), 119.85 (C^4), 128.89 (C^m), 142.07 (C^i), 149.52 (C^2), 155.62 (C^5). Found, %: C 64.98; H 6.81; N 5.03; S 11.51. $C_{15}H_{19}NO_2S$. Calculated, %: C 64.95; H 6.90; N 5.05; S 11.56.

Methyl 4-[methyl(phenyl)amino]-4-thioxobutanoate (V). Compound **II**, 11 g (40 mmol), was added to a solution of 1 ml of 30% hydrochloric acid in 30 ml of methanol. The mixture warmed up to 40°C. After 5 min, excess methanol and volatile products were distilled off under reduced pressure. The residue was dissolved in diethyl ether, the solution was washed with an aqueous solution of potassium carbonate, dried over K_2CO_3, and evaporated, and the residue was distilled in a vacuum. Yield 7.24 g (76%), greenish–yellow viscous liquid which rapidly crystallized, bp ~160°C (0.8 mm), mp 40–42°C. IR spectrum (KBr), ν, cm^{-1}: 3060 w, 3043 w, 2997 w, 2944, 2935, 2910, 1737 s (C=O), 1594, 1494 s, 1472, 1454, 1435, 1404, 1386, 1362, 1335 w, 1283, 1242, 1222, 1193, 1175, 1158, 1109, 1073 w, 1018, 998 w, 982, 951, 921, 836, 810 w, 778, 703 s, 654, 609 w, 566 w, 524 w. ^{1}H NMR spectrum, δ, ppm: 2.49 m (2H, CH_2C=O), 2.69 m (2H, CH_2C=S), 3.44 s (3H, OMe), 3.60 s (NMe), 7.10 m (2H, *o*-H), 7.25 m (1H, *p*-H), 7.53 m

(2H, *m*-H). ^{13}C NMR spectrum, δ_C, ppm: 34.76 (**C**H_2C=S), 38.48 (**C**H_2C=O), 46.98 (NMe), 52.78 (OMe), 126.95 (C^o), 129.84 (C^p), 131.36 (C^m), 146.61 (C^i), 174.10 (C=O), 204.57 (C=S). Signals in the NMR spectra were assigned using two-dimensional HSQC and HMBC techniques. Found, %: C 60.58; H 6.51; N 5.77; S 13.51. $C_{12}H_{15}NO_2S$. Calculated, %: C 60.73; H 6.37; N 5.90; S 13.51.

The IR spectra were recorded on a Bruker IFS-25 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 instrument at 400.13 and 100.61 MHz, respectively; two-dimensional NMR experiments were performed on a Bruker AV-400 spectrometer; chloroform-*d* was used as solvent, and the chemical shifts were determined relative to hexamethyldisiloxane as internal reference.

All operations were carried out under nitrogen. Liquid nitrogen was used as cooling agent. Tetrahydrofuran was purified by treatment with mechanically dispersed potassium hydroxide (~50 g/l), followed by distillation over $LiAlH_4$ in the presence of benzophenone under nitrogen. 3-(1-Ethoxyethoxy)prop-1-yne (**III**) was obtained in quantitative yield from ethoxyethene and prop-2-yn-1-ol in the presence of trifluoroacetic acid. Butyllithium (a ~1.6 M solution in hexane) and other reagents and solvents used in this work were commercial products.

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