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SHORT COMMUNICATIONS

Unconventional Synthesis of Pyridines with Rare O- and S-Functionality from Lithiated Allenes and Isothiocyanates

N. A. Nedolya[1], L. Brandsma[2], N. I. Shlyakhtina[1], S. V. Fedorov[1], and L. V. Klyba[1]

[1]*Faworsky Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences, Irkutsk, 664033 Russia*
[2]*Utrecht University, the Netherlands*

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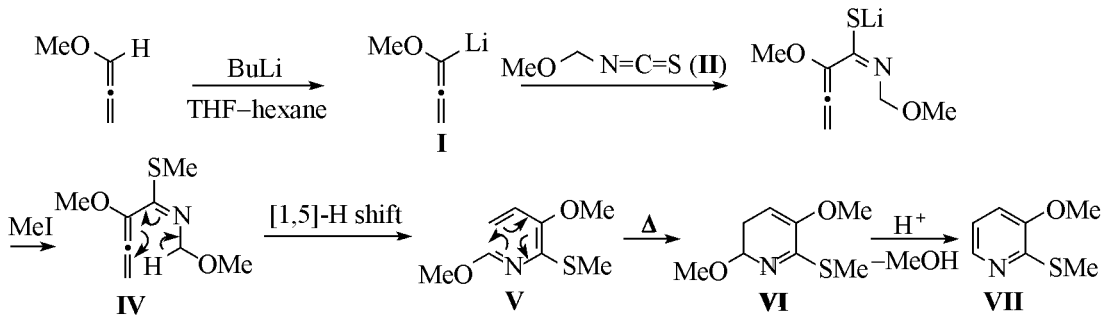
Reactions we discovered between heterocumulenes and unsaturated carbanions readily generated from accessible allenes and acetylenes of versatile structures treated with superbases were successfully developed into a fundamentally new strategy of synthesis of the basic heterocyclic systems (pyrroles, thiophenes, quinolines etc.) [1–3]. We established formerly [4–6] that reaction of lithiated alkoxyallenes with aliphatic (alkyl, cyanoalkyl) isothiocyanates furnished mixtures of 3-alkoxy-2-(alkylsulfanyl)pyrroles and 5-alkoxy-6-(alkylsulfanyl)-2,3-dihydropyridines, and the ratio of the products depended on the structure of the isothiocyanate. Therewith no aromatization of the arising 5-alkoxy-2,3-dihydropyridines was observed.

The use in reaction of 1-lithio-1-methoxyallene (**I**) of methoxymethyl isothiocyanate (**II**) led to an unexpected result. It turned out that on alkylation of adduct **III** the arising 2,3-butadienimidothioate **IV** even under the conditions of reaction (at uncommonly low temperature for sigmatropic rearrangements, –70°C ÷ 0°C) isomerized quantitatively into *N*-(1,3-butadienyl)iminoformate (**V**). The electrocyclization of the latter afforded in high yield (>70%) one more previously unknown and inaccessible (alkylsulfanyl)-2,3-dihydropyridine: 2,5-dimethoxy-6-(methylsulfanyl)-2,3-dihydropyridine (**VI**). The corresponding pyrrole whose formation may be expected in keeping with the previous results [4–6] was not found among the reaction products.

We found that dihydropyridine **VI** very easily underwent aromatization eliminating methanol. The process did not require catalyst and proceeded at room temperature (conversion 85% within ~1 month). In the presence of hydrochloric acid dihydropyridine



cleanly and quantitatively under mild conditions (Et_2O, ~35°C, 1.5–2 h) transformed into previously unknown 2-(methylsulfanyl)-3-methoxypyridine (**VII**).

Thus a new unconventional approach was found for building up a pyridine ring with rare substituents (OR, SR, etc). namely, a reaction of lithiated allenes with alkoxymethyl isothiocyanates. The reaction discovered fundamentally extends the limits of the approach we develop to the synthesis of heterocycles

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[3] and opens interesting opportunities for purposeful syntheses of new families of inaccessible pyridine systems, among them optically active molecules.

2,5-Dimethoxy-6-(methylsulfanyl)-2,3-dihydropyridine (VI). To a solution of 57.6 mmol of BuLi in 36 ml of hexane and 70 ml of THF cooled to –90°C under argon atmosphere was added 5 g (71.4 mmol) of methoxyallene. After 5–7 min of stirring of the mixture at –65÷–60°C it was cooled to –100°C, and in one portion was added 5.15 g (50 mmol) of methoxymethyl isothiocyanate. On raising the temperature to –70°C 20 g (138.9 mmol) of MeI was added, the reaction mixture was stirred for 15 min at room temperature, and then it was poured into water (100 ml). The reaction products were extracted into pentane, the organic fraction was dried with K_2CO_3, the solvent was removed on a rotary evaporator. The residue (light-yellow liquid) weighed 9.4 g (100%) and according to ^{1}H NMR spectrum was methyl-*N*-[1-(methylsufanyl)-2-methoxy-1,3-butadienyl]iminoformate (**V**); content of the main substance ~100% (GLC). ^{1}H NMR spectrum, δ, ppm: 7.97 s (1H, N=CH), 6.74 d.d (1H, CH=, *J* 17.4, 10.9 Hz), 5.39 d.d (1H, CH_2=, *trans*, *J* 17.4, 1.8 Hz), 5.08 d.d (1H, CH_2=, *cis*, *J* 10.9, 1.8 Hz), 3.82 s (3H, OMe), 3.68 s (3H, OMe), 2.19 s (3H, SMe).

Iminoformate **V** was heated to ~40°C, the reaction of electrocyclization proceeded with self-heating to 150°C. On completion of reaction the product was distilled in a vacuum. Yield of dihydropyridine **VI** 6.8 g (73%), content of the main substance 99% (GLC), bp 85–90°C (1 mm Hg), n_D^{20} 1.5365. ^{1}H NMR spectrum, δ, ppm: 5.02 d (1H, H^4, *J* 5.9 Hz), 4.61 d.d (1H, NCH, *J* 13.4, 6.1 Hz), 3.59 s (3H, OMe), 3.55 s (3H, OMe), 2.32 s (3H, SMe), 2.29 m (2H, H^3). ^{13}C NMR spectrum, δ, ppm: 160.41 (C^6), 147.87 (C^5), 97.06 (C^4), 90.46 (NCHO), 54.69 (OMe), 54.59 (OMe), 26.61 (C^3), 11.41 (SMe). Mass spectrum, *m/z* (I_{re} *%): 187 (72) [M]*$^{+\cdot}$, 172 (100) [*M*–Me]$^+$, 156 (20) [*M*–MeO]$^+$, 155 (10) [*M*–MeOH]$^{+\cdot}$, 140 (40) [*M*–MeS]$^+$. Found, %: C 51.62; H 7.21; N 6.91; S 16.80. $C_8H_{13}NO_2S$. Calculated, %: C 51.31; H 7.00; N 7.48; S 17.12. *M* 187.

2-(Methylsulfanyl)-3-methoxypyridine (VII). A solution of 1.75 g (9.36 mmol) of dihydropyridine **VI** and 2.5 g 30% HCl in 25 ml of Et_2O was stirred for 1.5 h at boiling of ether, then the mixture was neutralized with KOH solution, the organic fraction was dried with K_2CO_3, and ether was removed under reduced pressure. Yield 1.04 g (72%), bp 82–84°C (1.5 mm Hg), n_D^{20} 1.5742. ^{1}H NMR spectrum, δ, ppm: 8.07 d.d (1H, H^6, *J* 3.8, 2.3 Hz), 6.96 m (1H, H^4), 6.95 m (1H, H^5), 3.88 s (3H, OMe), 2.53 s (3H, SMe). ^{13}C NMR spectrum, δ, ppm: 152.37 (C^3), 149.58 (C^2), 140.89 (C^6), 119.10 (C^5), 114.65 (C^4), 55.58 (OMe), 12.03 (SMe). Mass spectrum, *m/z* (I_{re} *%): 155 (100) [M]*$^{+\cdot}$, 140 (75) [*M*–Me]$^+$, 124' (12) [*M*–MeO]$^+$, 122 (65) [*M*–HS]$^+$, 108 (32) [*M*–MeS]. Found, %: C 54.31; H 5.42; N 8.77; S 20.32. C_7H_9NOS. Calculated, %: C 54.17; H 5.84; N 9.02; S 20.66.

^{1}H and ^{13}C NMR spectra were registered on spectrometers Bruker DPX-400 at operating frequencies 400 and 100 MHz respectively, and Bruker DPX-250 at operating frequencies 259 for ^{1}H and 62.9 MHz for ^{13}C respectively; 5–10% solutions in $CDCl_3$, internal reference TMS. Mass spectra were measured at ionizing voltage 60 V on GC-MS instrument LKB-2091 equipped with direct injection of sample into an ion source at temperature of the latter 120 and 250°C, capillary column 30 m long, stationary phase SE-54, vaporizer temperature 250°C, oven temperature programmed from 60 to 250°C at a rate 16 deg/min. GLC analysis was carried out on gas chromatograph Varian 3400 equipped with flame-ionization detector, capillary column 15 m long, internal diameter 0.53 mm with 1.5 μ coating with DB-5, carrier gas nitrogen. Methoxyallene was obtained by procedure from [7]. Methoxymethyl isothiocyanate was obtained by boiling methoxy(chloro)methane with KSCN in pentane in ~65% yield.

REFERENCES

1. Nedolya, N.A., *Novel Chemistry Based on Isothiocyanates and Polar Organometallics*, Utrecht: Utrecht University, 1999.
2. Brandsma, L., Nedolya, N.A., Tarasova O.A., and Trofimov, B.A., *Khim. Geterotsikl. Soed.*, 2000, no. 11, pp. 1443–1463.
3. Brandsma, L., *Eur. J. Org. Chem.*, 2001, no. 24, pp. 4569–4581.
4. Nedolya, N.A., Brandsma, L., and Trofimov B.A., *Khim. Geterotsikl. Soed.*, 1996, no. 7, pp. 917–918.
5. Nedolya, N.A., Brandsma, L., and Trofimov B.A., *Zh. Org. Khim.*, 1996, vol. 66, no. 12, pp. 2042–2043.
6. Nedolya, N.A., Brandsma, L., Tarasova O.A., Verkruijsse, H.D., and Trofimov, B.A., *Tetrahedron Lett.*, 1998, vol. 39, no. 16, pp. 2409–2410.
7. Brandsma, L. and Verkruijsse, H.D., *Synthesis of Acetylenes, Allenes and Cumulenes*, Amsterdam: Elsevier, 1981.