Chemistry of Heterocyclic Compounds, Vol. 32, No. 7, 1996

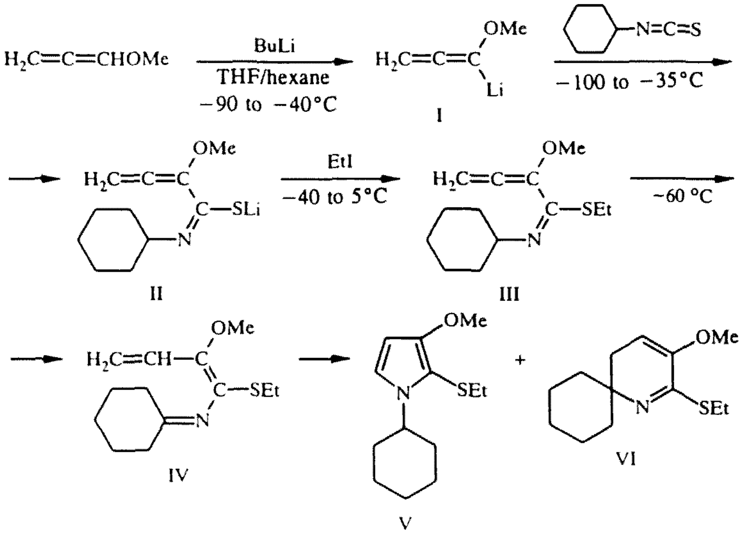
REACTION OF LITHIOALKOXYALLENES WITH ISOTHIOCYANATES: SYNTHESIS OF PYRROLES AND 5,6-DIHYDROPYRIDINES

N. A. Nedolya, L. Brandsma, and B. A. Trofimov

We have found a novel synthesis route for 2,3-disubstituted pyrroles and 5,6-dihydropyridines, starting from lithiated alkoxyallenes and organic isothiocyanates.

We know [1-4] that the reaction of organolithium compounds with isothiocyanates leads to thioamides.

For the first time we have shown that organic isothiocyanates and lithiated alkoxyallenes are suitable starting materials for synthesis of pyrroles and dihydropyridines. Thus the previously unknown 2-ethylthio-3-methoxy-N-cyclohexylpyrrole (V) is obtained in high yield, in a single preparative stage, via a novel reaction of cyclohexylisothiocyanate with 1-lithiomethoxyallene through the intermediate 1,3,4-(II,III) and 1,3,5-azatrienes (IV). The pyrrole V:dihydropyridine VI ratio in the mixture of reaction products is 1:9.



From the PMR spectrum, we observed facile isomerization of the initially formed 1,3,4-azatriene III to 1,3,5-azatriene IV. The pyrrole V and the dihydropyridine VI were isolated in pure form; their composition and structure were confirmed by elemental analysis and IR and PMR spectra.

EXPERIMENTAL

The PMR spectra were recorded on a Varian EM-390 spectrometer (90 MHz, ~20% solution in CCl_4, internal standard TMS). The IR spectra were recorded on a Specord IR-75 spectrometer in a thin layer and in a film. GLC analysis was

---

Irkutsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Irkutsk 664033. Preparative Organic Chemistry Group, Utrecht University, The Netherlands. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 32, No. 7, pp. 917-918, July, 1996. Original article submitted April 17, 1996.

0009-3122/96/3207-0781$15.00

performed on a Varian 3400 gas chromatograph (FID, 15 m capillary column, internal diameter 0.53 mm with 1.5 mm DB-5 coating, nitrogen as the carrier gas).

All the operations were done under a nitrogen atmosphere. We synthesized methoxyallene and cyclohexylisothiocyanate according to the methods in [5] and [6] respectively. Tetrahydrofuran was shaken with mechanically dispersed KOH (~50 g/liter) and distilled over $LiAlH_4$ in the presence of benzophenone under an N_2 atmosphere. *n*-Butyllithium (1.6 M solution in hexane) was provided by the Chemetall company (FRG). The rest of the reagents and solvents used in this work were also commercial products.

Reaction of 1-Lithiomethoxyallene (I) with Cyclohexylisothiocyanate and Ethyl Iodide. Methoxyallene (0.08 moles) was added rapidly to a solution of 0.05 moles *n*-BuLi in 60 ml dry THF and ~33 ml hexane, cooled down to −90°C. After the temperature of the reaction mixture was raised to −40°C, it was again cooled down to −100°C and over the course of a few seconds a solution of 0.05 moles cyclohexylisothiocyanate in 10 ml THF was introduced. After stirring for ~10 min at a temperature of −40°C, 0.07 moles ethyl iodide were added to the reaction mixture (a bright-yellow suspension). When the temperature was raised to 5°C, ~50 ml cold water was added to the reaction mixture with vigourous stirring. The organic layer was removed, and the aqueous layer was extracted three times with pentane. The extracts were dried with potassium carbonate (~10 min). The solvent was removed. Obtained: 9.2 g (77%) of material (a light yellow mobile liquid, n_D^{20} 1.5575), according to the PMR spectrum corresponding to 1,3,5-azatriene IV [5.85, 5.75 (1H, 2d, CH=), 5.00, 4.72 (2H, 2dd, CH_2=), 3.55 (3H, s, OMe), 1.65 (10H, m, cyclohexyl), 1.25 (3H, t, CH_2CH_3), 2.46 (2H, q, SCH_2)] with pyrrole V impurity [6.53 (1H, d, 5-H), 5.75 (1H, d, 4-H)].

Heating the reaction product to 190°C quantitatively leads to a mixture of pyrrole V (~12%) and 5,6-dihydropyridine VI (~88%) (PMR, GLC), bp 180°C (15 mm Hg).

Approximately 30 ml pentane was added to a mixture of pyrrole V and dihydropyridine VI. The solution was treated with a cold ~3.7% solution of hydrochloric acid and the layers were separated. The aqueous layer was first extracted with pentane (four times), the combined organic fraction was treated with a small amount of concentrated aqueous KOH solution (until neutral reaction), and the organic layer was dried with potassium carbonate. After removal of the solvent, 2-ethylthio-3-methoxy-N-cyclohexylpyrrole (V) was obtained (yield 1.3 g, 11%). PMR spectrum: 6.58 (1H, d, 5-H), 5.50 (1H, d, 4-H), 3.68 (3H, s, OMe), 1.60 (11H, m, C_6H_{11}), 1.12 (3H, t, CH_2CH_3), 2.47 (2H, q, SCH_2). Found, %: C 64.92, H 8.51, N 6.27, S 13.69. $C_{13}H_{21}NOS$. Calculated, %: C 65.27, H 8.79, N 5.86, S 13.39.

The acidic aqueous layer was neutralized with a concentrated aqueous KOH solution and extracted with ether (four times). After removal of the solvent, 2-ethylthio-3-methoxyspiro[5.5]-1-azaundeca-1,3-diene (VI) was obtained with purity 90.4% (GLC). Yield, 7.5 g (63%). IR spectrum: 470, 490, 520, 570, 610, 680, 710, 760 shoulder, 800, 850, 910, 935 shoulder, 950, 960 shoulder, 1020, 1040, 1050, 1060 shoulder, 1110, 1140, 1150, 1180, 1210, 1240, 1260, 1340, 1360, 1440, 1570, 1640, 2850, 2920, 2980 shoulder, 3050 cm^{-1} weak. PMR spectrum: 4.78 (1H, t, 4-H), 2.10 (2H, d, 5-H), 3.55 (3H, s, OMe), 1.23 (3H, t, CH_2CH_3), 2.80 (2H, q, SCH_2), 1.40, 1.70 (10H, 2m, $(CH_2)_5$]. Found, %: C 64.95, H 8.99, N 6.11, S 13.55. $C_{13}H_{21}NOS$. Calculated, %: C 65.27, H 8.79, N 5.86, S 13.39.

REFERENCES

1. K. A. Petrov and L. N. Andreev, Usp. Khim., **38**, 41 (1969).
2. L. Brandsma, Studies in Organic Chemistry. 34. Preparative Acetylenic Chemistry (Second Ed.), Elsevier, Amsterdam–Oxford–New York–Tokyo (1988), pp. 100, 108, 299.
3. L. Brandsma and H. Verkruijsse, Preparative Polar Organometallic Chemistry. Vol. 1, Springer-Verlag, Berlin–Heidelberg–New York–London–Paris–Tokyo (1987), pp. 34, 152, 190, 219, 221, 224, 226, 233.
4. L. Brandsma, Preparative Polar Organometallic Chemistry, Vol. 2, Springer-Verlag, Berlin/Heidelberg/New York–London–Paris–Tokyo–Hong Kong–Barcelona (1990), pp. 9, 30, 32, 35, 36, 73.
5. L. Brandsma and H. Verkruijsse, Studies in Organic Chemistry. 8. Synthesis of Acetylenes, Allenes, and Cumulenes. A Laboratory Manual, Elsevier, Amsterdam–Oxford–New York (1981), p. 92.
6. B. A. Trofimov, N. A. Nedolya, V. V. Gerasimova, and M. G. Voronkov, Sulfur Lett., **8**, 73 (1988).