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Application of Copper Catalysis in a One-Pot Procedure for 1-Alkyl-3-methoxy-2-methylthiopyrroles Starting from Methoxyallene and Alkyl Isothiocyanates

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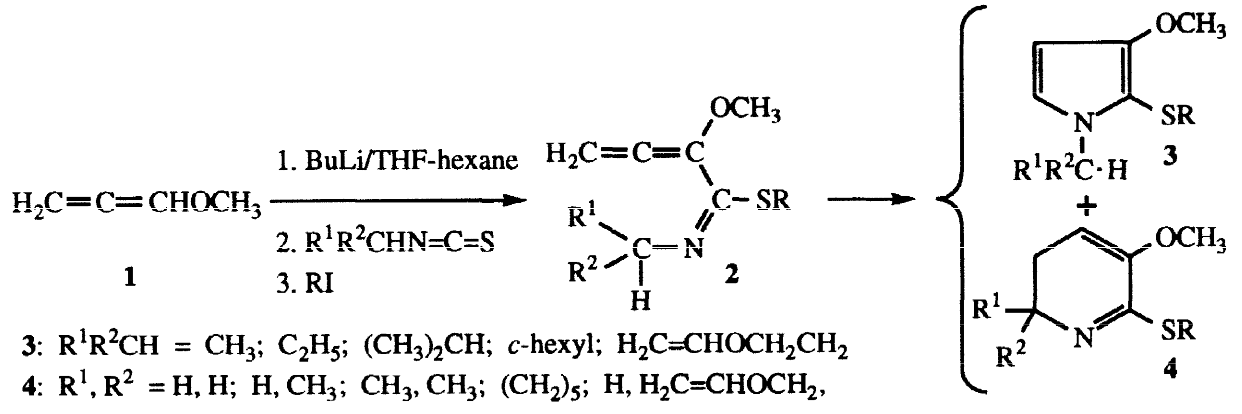
Abstract: 1-Alkyl-3-methoxy-2-methylthiopyrroles are obtained with high purities and in high yields by Cu(I)halide-catalyzed cyclization of the products from addition of 1-lithiomethoxyallene to alkyl isothiocyanates and subsequent methylation.

Methoxyallene $CH_3OCH{=}C{=}CH_2$, readily available by base-catalyzed isomerization of methyl propargyl ether[1-3] has been used as starting compound in a wide variety of syntheses (for a recent review see[4]).



3: R^1R^2CH = CH_3; C_2H_5; $(CH_3)_2CH$; *c*-hexyl; $H_2C{=}CHOCH_2CH_2$
4: R^1, R^2 = H, H; H, CH_3; CH_3, CH_3; $(CH_2)_5$; H, $H_2C{=}CHOCH_2$,

We recently reported the simultaneous formation of 2,3-dihydropyridines **4** and derivatives of pyrrole **3** by heating of the Schiff's bases **2** obtained by quenching of the adducts from 1-lithio-methoxyallene and alkyl isothiocyanates with alkyl iodide[5]. These cyclizations proceeded without any added catalyst. The ratio of **3** and **4** strongly depended upon the alkyl group of the isothiocyanate. Starting with $CH_3N{=}C{=}S$ the major product (~80 rel.%) was the pyrrole derivative, but in the cases of *c*-C_6H_{11}–N=C=S and $(CH_3)_2CH$–N=C=S the 2,3-dihydropyridines predominated.

We here report the specific formation of pyrrole derivatives **3** by treatment of **2** with a catalytic amount of

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copper(I)bromide or iodide at 20 to ~45 °C. The synthesis of **3** can be carried out in a one-pot procedure with good to excellent yields. The nickel(II) catalysts $NiCl_2$.dppf and $NiCl_2$.dppp and the palladium catalysts $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ showed no significant activity in qualitative experiments.

EXPERIMENTAL PROCEDURE

Methoxyallene (0.12 mol) was added at −100 °C in one portion to a mixture of 70 ml of THF and 65 ml (0.10 mol) of hexane solution of *n*-BuLi. After allowing the temperature to rise to −70 °C, the solution was cooled to −90 °C and a mixture of 0.10 mol of ethyl isothiocyanate and 15 ml of THF was added portionwise over 5 min while maintaining the temperature between −70 and −80 °C. After an additional 10 min (at −70 °C) 0.14 mol of methyl iodide was added and the temperature was allowed to rise to +10 °C. The solution was divided in two equal parts: one of them was treated with water and after the usual work-up the product was distilled *in vacuo*, affording a 1 : 3 mixture of **3** and **4** ($R = Me, R^1 = Me, R^2 = H$) in ~75% yield. The mixture was separated into the components by shaking the ethereal solution with cold, 2 M hydrochloric acid and treating the acidic layer with aqueous potassium hydroxide. Extraction with ether and distillation gave the pure (99%) dihydropyridine **4** ($R = Me, R^1 = Me, R^2 = H$), b.p. 90 °C/2 mm Hg, n^{20}_D 1.5376 in ~50% yield. NMR-spectrum (300 MHz, CD_3Cl: 1.90, 2.15 (m, H-3), 2.18 (s, SMe), 3.47 (m, H-2), 3.49 (s, OMe) and 4.92 (dd, H-4) ppm.

To the other part copper(I)bromide (1.5 g) or copper(I)iodide (2.5 g) was added with efficient stirring. The mixture was stirred for half an hour at 15-20 °C, after which the temperature was raised to 45 °C. After stirring for an additional 60 min at 40-50 °C a solution of 10 g of potassium cyanide and 15 g of ammonium chloride in 100 ml of water was added. The mixture was vigorously stirred for ~20 min under air after which the layers were separated and the aqueous phase was extracted twice with ether. The dried extracts were concentrated *in vacuo* and the remaining liquid distilled through a short Vigreux column. The compound **3**, R = Me, R^1R^2CH = Et, b.p ~70 °C/0.5 mm Hg, n^{20}_D 1.5390, was obtained in ~80% yield. NMR-spectrum (90 MHz, CCl_4): 1.35 (t, Me), 2.20 (s, SMe), 3.70 (s, OMe), 3.92 (q, NCH_2), 5.70 (d, H-4) and 6.47 (d, H-5) ppm.

Other pyrrole derivatives **3** were obtained in yields of at least 70% overall. The physical and spectral data of the intermediate **2** and pyrrole **3** having R = Me and R^1R^2CH = Me, corresponded with the data published recently[5].

The investigations are being continued with other terminally (e.g. *t*-Bu–CH=C=CHLi) and non-terminally ($CH_2=C=C(Li)CH_3$) lithiated allenes. In these cases pyrrole derivatives were obtained in satisfactory yields, whereas in the absence of copper catalysts *only* 2,3-dihydropyridines were formed at more elevated temperatures

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