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Unexpected formation of derivatives of cyclobutene and thiacyclobutane from the reaction between dilithiated benzylacetylene and isothiocyanates†

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Abstract—Reaction of dilithiated benzylacetylene PhCH(Li)-C≡C-Li with one equivalent of an isothiocyanate RN=C=S followed by successive addition of *t*-BuOH, a solution of *t*-BuOK in DMSO and methyl iodide gives exclusively a cyclobutene or a thietane derivative if R = *t*-Bu or Ph, respectively, and mixtures of the expected thiophene, the cyclobutene and thietane derivatives if R = Me. © 2001 Published by Elsevier Science Ltd.

Recently,[1] we reported on the synthesis of 2-*N*-mono or 2-*N*,*N*-disubstituted aminothio-phenes using methoxyallene $H_2C{=}C{=}CHOCH_3$, methylthioallene $H_2C{=}C{=}CHSCH_3$, 2-alkynes $CH_3C{\equiv}C$-R (R = alkyl) or 1-alkynes $HC{\equiv}C\text{-}CH_2R$ (R = H, alkyl, *O*-alkyl or $N(alkyl)_2$) and isothiocyanates RN=C=S (R = alkyl or aryl) as starting compounds. The general principle of our synthetic methods consists of metallating the acetylene or allene with a strongly basic reagent, allowing the intermediate to react with the isothiocyanate, forcing the adduct to undergo cyclization under strongly polar conditions and finally adding either water or an alkyl iodide. In all cases the expected thiophene derivatives were isolated in fair to good yields as the only identifiable cyclic products. Earlier,[2] it was shown that 1,3-dilithiated acetylenes RCH(Li)C≡C-Li react with one equivalent of an electrophile such as an alkyl halide or oxirane, dialkyl disulfide, trialkylchlorosilane, carbon disulfide or non-enolizable thiocarbonyl compound, exclusively, or predominantly at the most strongly basic propargylic site.

Using isothiocyanates as electrophiles and 1,3-dilithiated benzylacetylene **1** we hoped to synthesize 3-substituted 2-aminothiophenes **11**.

Benzylacetylene was treated with two molar equivalents of *n*-BuLi in THF–hexane mixtures, after which one molar equivalent of an isothiocyanate was added at low temperatures. All isothiocyanates reacted very smoothly. Subsequently *t*-BuOH (one equivalent) and a solution of *t*-BuOK (one equivalent) in DMSO (about 30 vol%) were successively added following the previously applied procedure for suchlike cyclizations (compare Ref. 1). Finally, a large excess of methyl iodide was introduced in the expectation that the *N*,*N*-disubstituted aminothiophene **11** would be formed.

However, reaction with methyl isothiocyanate gave, after final methylation with methyl iodide, cyclobutene derivative **8** (R = Me) as the main product (~65% rel.), whereas the expected thiophene **11** (R = Me) was present in minor amounts only (~15%), in addition to small amounts (~15%) of thiacyclobutane derivative **10**.

Using *t*-butyl isothiocyanate, and following the above mentioned succession of operations, the cyclobutene derivative **8** (R = *t*-Bu) was the only product (isolated yield ~65%), while in the case of phenyl isothiocyanate exclusively, the thietane derivative **10** (R = Ph) was

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† Dedicated to my teacher, Professor Dr. J. F. Arens, who recently became 86 years old.

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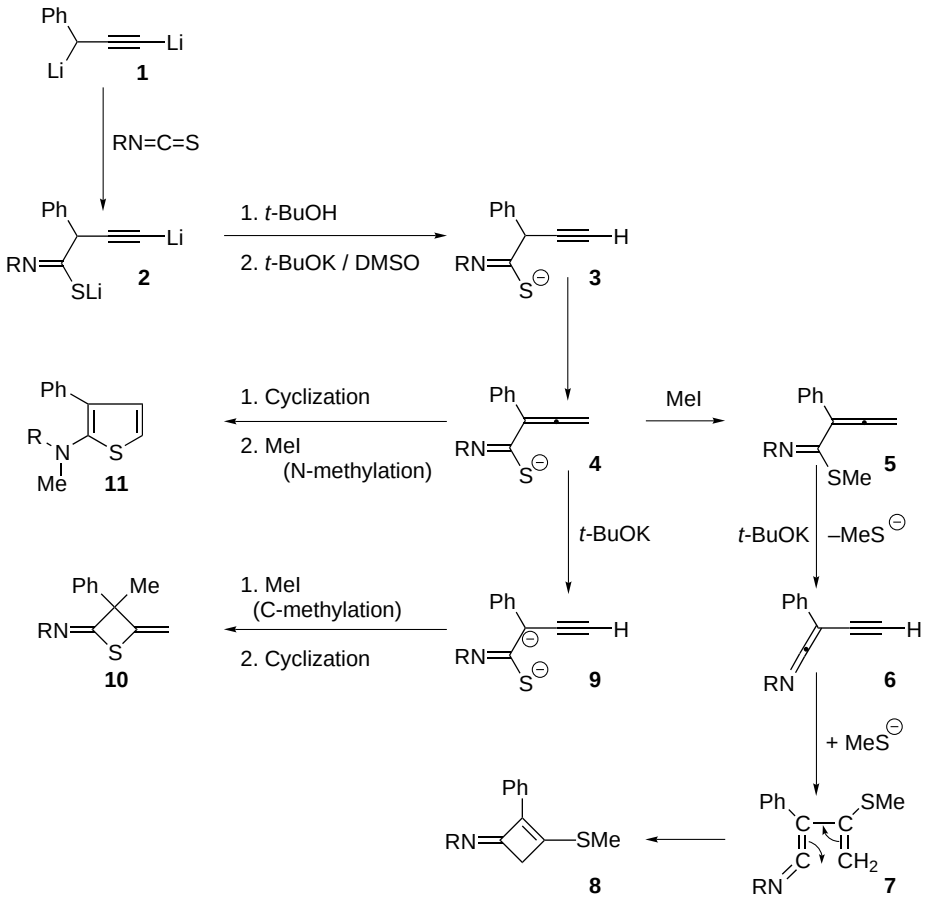

Scheme 1.

obtained in 77% yield. The structures of these products were derived by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy using NOESY, HMQC and HMBC experimental data. The product analogous to **8**, obtained in high yield from the reaction with *t*-BuN=C=S and *p*-F-C_6H_4-$CH_2C{\equiv}CH$, was isolated as fine crystalline needles. Its cyclobutene structure was established by X-ray determination.

Preliminary experiments with analogous dimetallated ring-substituted propargylbenzenes, 2-methyl-5-propargylthiophene, 1-methyl-2-propargylpyrrole and methyl 2-propynyl sulfide showed that the ratio of the thiophene, thietane and cyclobutene derivatives strongly depends on the R group in the isothiocyanate, the nature of the R group in the acetylene R-CH_2-C≡C-H and the reaction conditions (e.g. temperature of addition of the alkyl iodide, amounts of *t*-BuOH, *t*-BuOK and DMSO). Following our standard procedure[3] the reaction between dilithiated 2-methyl-5-propargylthiophene and MeN=C=S, *t*-BuN=C=S and PhN=C=S afforded the expected thiophene, cyclobutene and thietane derivatives, respectively, in good yields.

The mechanisms by which the three cyclic products are formed (depending on the isothiocyanate) are the subject of further investigations; some suggestions with regard to the pathways followed are put forward in Scheme 1. The isolation, in good yield, of allene **5** (R = Me) after addition of methyl iodide at temperatures in the region of −50°C suggests the occurrence of intermediate **4**, which in turn could be the result of a base-induced isomerization of **3** formed by protonation of **2**.

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3. To a mixture of 0.05 mol of benzylacetylene and 100 ml of THF was added at −100°C a solution of 0.11 mol of

n-BuLi in 68 ml of hexane. After stirring for 15 min at 10°C, the brown solution was cooled to −100°C and a mixture of the isothiocyanate (0.05 mol) and 10 ml of THF was added in one portion. The cooling bath was removed and the temperature allowed to rise to −40°C. After an additional 10 min the reaction mixture was cooled to −50°C and a mixture of 0.05 mol of *t*-BuOH and 5 ml of ether was added, followed (at −50°C) after a few minutes by a solution of 0.05 mol of *t*-BuOK in 40 ml of DMSO. The mixture was warmed to 20°C and then immediately cooled to 5°C. The alkyl iodide (0.15 mol) was introduced in one portion and the temperature allowed to rise. After warming for an additional 20 minutes at 40°C, a solution of 20 g of ammonium chloride in 100 ml of water was added and the product was isolated via extraction with ether, washing (four times) with water, drying over $MgSO_4$, removal of the solvent in vacuo and distillation of the remaining liquid in a high vacuum. The thietane **10** (R = Ph) and cyclobutene **8** (R = *t*-Bu) showed correct elemental analyses, while in the mass spectra the expected parent peaks were present. The ^{1}H NMR spectrum of **10** (R = Ph) showed inter alia two doublets around 5.26 ppm (=CH_2 protons) and a singlet at 1.93 ppm (C-Me). Characteristic signals for **8** (R = *t*-Bu) appeared at 3.57 (CH_2) and at 2.46 (SMe) ppm, respectively.