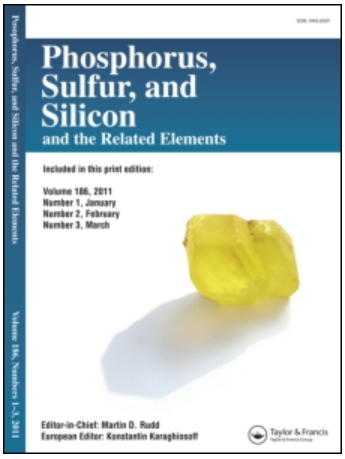

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Reductive Alkylation of Pentaphenylthiopyrylium Perchlorate: An Approach to Regiospecific Synthesis of Hexasubstituted 2H-Thiopyrans

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REDUCTIVE ALKYLATION OF PENTAPHENYLTHIOPYRYLIUM PERCHLORATE: AN APPROACH TO REGIOSPECIFIC SYNTHESIS OF HEXASUBSTITUTED 2H-THIOPYRANS

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Regiospecific synthesis of some new hexasubstituted 2H-thiopyrans was examined by reductive alkylation of pentaphenylthiopyrylium perchlorate and found to be in quantitative yields. Under our experimental conditions, the formation of unstable thiabenzene intermediates could be observed through detectable color changing during the addition of C-nucleophiles to thiopyrylium perchlorate. Moreover, the effect of phenyl groups on the 3,5-positions of thiopyrylium perchlorate on the regioselectivity were compared with other analogs having methyl groups on the same positions.

Keywords C-Nucleophile; pentaphenylthiopyrylium; reductive alkylation; 2H-thiopyrans

INTRODUCTION

Thiopyrylium salts with a large number of technological applications have been investigated extensively.[1] These salts are, in general, capable of accepting nucleophiles by addition at position 2, 4, or 6 giving the corresponding 2H- and 4H-thiopyran derivatives in agreement with HMO reactivity indices.[2] The earliest nucleophilic addition is the reaction of thiopyrylium with organometallic reagents. Contrary to the reaction with Grignard reagents, where no unambiguous evidence concerning the formation of thiabenzene intermediates is available, organolithium nucleophiles added selectively to thiopyrylium by the attack at sulfur to give colored unstable thiabenzene intermediates,[3] which undergo rearrangement to 2H- and 4H-thiopyrans adducts with an apparently unpredictable regioselectivity[4–6] (Scheme 1).

The results of a mechanistic investigation of the rearrangement indicate an intramolecular shift that involves a 1,2- or 1,4-migration of the sulfur substituents.[7] According to Scheme 1, if the R, R_1, and R_3 are all alkyl in structure **I**, the reaction proceeds rapidly

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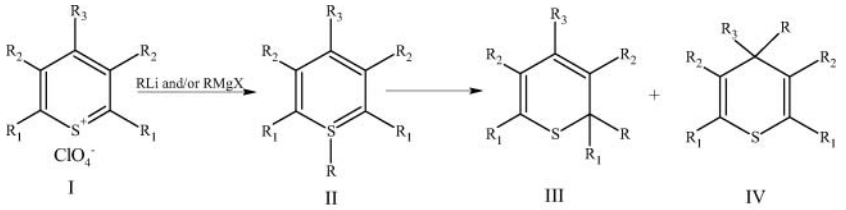

R_1=R_2=R_3=Ph: a) R=Me,X=Br b) R=Et,X=Br c) R=*n*-Bu d) R=*t*-Bu,X=Cl

Scheme 1

at room temperature unselectively. 2,4,6-Triphenylthiopyrylium salt (R_2=H) reacts less rapidly with organometallic reagents, and the reaction time takes into account the rearrangement of the intermediate.[8,9] Although the reaction shows good regioselectivity with organolithiums[8,9] (only 4H- or with more reactive reagents; only 2H-thiopyrans obtained), it exhibits different regioselectivity toward Grignard reagents. The involvement of bulky groups R_2, e.g., the replacement of a hydrogen atom by methyl, also increases the rate of rearrangement and alters the regioselectivity depending on the nature of the C-nucleophiles.[10] Following our studies on the chemistry and synthesis of thiopyrylium and thiopyrans derivatives,[11–15] and in order to obtain a better view on the competition of 2H- vs. 4H-thiopyran in the reaction of organometallics with thiopyrylium salts, herein we undertake a systematic examination of reductive alkylation of 2,3,4,5,6-pentaphenylthiopyrylium perchlorate in the presence of various alkyl C-nucleophiles. Such a model should provide further insight into the probable rearrangement and regioselectivity, and would also furnish an access to new steric crowding of thiopyrans.

RESULTS AND DISCUSSION

Treatment of a molar equivalent of an ethereal MeMgBr solution with 0.001 mol of pentaphenyl thiopyrylium perchlorate in dry ether under an argon atmosphere at room temperature gave a red solution that faded when stirred. Workup of the reaction mixture furnished 2-methyl-2,3,4,5,6-pentaphenyl-2H-thiopyran **IIIa** and 4-methyl-2,3,4,5,6-penatphenyl-4H- thiopyran **IVa** in the ratio of 3:1 according to ^{1}H NMR spectra. Based on the theory that 2H-thiopyrans are thermodynamically more stable and the 4H-thiopyrans are kinetic products, we decide to run this reaction under other temperature conditions. At –20°C, the same products were obtained in a new ratio of 2.5:1, while the reaction under reflux showed high regioselectivity and gave 2H-thiopyran **IIIa** as the sole product, though faster changing in color. Under identical experimental conditions, MeLi also exhibited the same behaviors, and the only difference was a small relative increase of the 4H-thiopyran. Addition of an equivalent ethereal solution of EtMgBr to 0.001 mol of pentaphenyl thiopyrylium perchlorate under the same conditions afforded only 2-ethyl-2,3,4,5,6-pentaphenyl-2H-thiopyan **IIIb**, though color changing from orange red to colorless, where no evidence for formation of 4H-isomer could be observed. When an equivalent of n-BuLi and t-BuMgCl ethereal solution was treated with 0.001 mol of pentaphenyl thiopyrylium perchlorate under the above conditions, the same results, as EtMgBr had, were obtained in which only 2-*n*-butyl-2,3,4,5,6-pentaphenyl-2H-thiopyran **IIIc** and 2-*t*-butyl-2,3,4,5,6-pentaphenyl-2H-thiopyran **IIId** could be isolated according to spectral data.

The reaction clearly showed good regiospecificity, while in the latter case, no detectable color changing could be observed as it has been expected from pervious report.[3] Unusual behavior of Grignards MeMgBr and EtMgBr by typical color changing for the formation of thiabenzene, which could also be observed for analogous that having methyl groups in 3,5-positions,[10b]b may be expressed by the steric and electronic effect. Regiospecific formation of hexasubstituted 2H-thiopyrans and the disappearance of 4H-isomers in the case of pentaphenylthiopyrylium perchlorate, however, are contrast sharply with those analogs that contain methyl groups on the 3,5-positions.

In conclusion, our experimental findings revealed that the thermodynamically more stable hexasubstituted 2H-thiopyrans **IIIa–d** were easily prepared in high yields as the sole products of reductive alkylation of pentaphenylthiopyrylium perchlorate, whereas for other analogs having methyl groups on the 3,5-positions, the reaction did not show this regiospecificity.[10b]b Although the isolation of thiabenzene intermediate was not successful in any case, the characteristic color changing during the reaction showed that, with the exception of using t-BuLi, in all other cases the formation of hexasubstituted 2H-thiopyrans from the direct attack to 2- and 6-positions might be associated with a rearrangement of the corresponding thiabenzene intermediates.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. All yields refer to isolated products. Monitoring of the reactions was accomplished by TLC. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}HNMR spectra were recorded on 400 MHz Brucker using $CDCl_3$ as the solvent and TMS as the internal standard. Mass spectra were measured with a Varian MAT-311A spectrometer.

Syntheses

Pentaphenylthiopyrylium perchlorate was synthesized from the corresponding pyrylium perchlorate, which is prepared from benzaldehyde and desoxybenzoine by the method previously described.[16,17] The new hexasubstituted 2H-thiopyrans and 4H-thiopyran were synthesized by the reaction of Grignard reagents (RMgX; R=Me, Et, *t*-Bu; X=Br, Cl) and/or RLi (R=Me, Bu) with equimolar pentaphenylthiopyrylium perchlorate according to the reported method.[7,10b] The products were isolated by chromatography on neutral alumina and recrystallized from alcohol.

General Procedure

Addition of an equivalent ethereal solution of different organometallic reagents to 0.001 mol of pentaphenyl thiopyrylium perchlorate in dry diethyl ether (50 mL) under an argon atmosphere at the different temperature conditions (–20°C, 25°C, and reflux) was monitored by the color changing in the reaction mixture and TLC. After completion, when a red to orange solution faded upon stirring, the reaction was stopped by the addition of a saturated solution of NH_4Cl (20 mL). The ethereal phases were separated, dried over $CaCl_2$, and finally evaporated under vacuum. Then the residue was purified by PLC using petroleum ether or/and recrystallized from suitable alcohols.

2-Methyl-2,3,4,5,6-pentaphenyl-2H-thiopyran (IIIa). Yellow crystals, mp 205–206°C (from amyl alcohol); m/z 492 ($M^{\cdot+}$ 100%), 477 (4.50), 445 (61.00), 166 (4.60); UV, λ max ($CHCl_3$) nm (log ε): 355.4 (3.98), 249.6 (4.65); ^1H NMR (C_6D_6), δ: 1.51 (3H, s, Me), 6.43–7.31 (25H, m, ArH), yield 83%.

2-Ethyl-2,3,4,5,6-pentaphenyl-2H-thiopyran (IIIb). Yellow crystals, mp 145–146°C (from EtOH); m/z 506 ($M^{\cdot+}$ 100%), 477 (5.45), 445 (56.36), 352 (4.54), 166 (4.61); UV, λ max (EtOH) nm (log ε): 351 (4.21), 248.6 (4.96); ^1H NMR (C_6D_6), δ: 1.13–1.32 (3H, t, Me), 2.36–2.60 (2H, q,CH2), 6.76–7.39 (25H, m, ArH), yield 75%.

2-n-Butyl-2,3,4,5,6-pentaphenyl-2H-thiopyran (IIIc). Yellow crystals, mp 81–82°C (from EtOH); m/z 534 ($M^{\cdot+}$ 16.6%), 477 (41.90), 34 (100); UV, λ max (EtOH) nm (log ε): 345 (3.98), 246.6 (4.22); ^1H NMR (C_6D_6), δ: 0.84–1.47 (7H, m, n-Pr), 2.40–2.60 (2H, t, CH_2), 6.66–7.39 (25H, m, ArH), yield 73%.

2-t-Butyl-2,3,4,5,6-pentaphenyl-2H-thiopyran (IIId). Yellow crystals, mp 92–93°C (from EtOH); m/z 534 ($M^{\cdot+}$ <1%), 477 (100), 401 (14.76), 166 (5.71), 121 (6.95), 57 (10.47); UV, λ max (EtOH) nm (log ε): 332.2 (3.60), 263 (3.91); ^1H NMR (C_6D_6), δ: 1.13–1.19 (9H, s, Me), 6.26–8.31 (25H, m, ArH), yield 78%.

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