O- AND C-PRENYLATION OF trans-2-SULFUR-CONTAINING 3-ISOPROPENYLCYCLOPENTANONES

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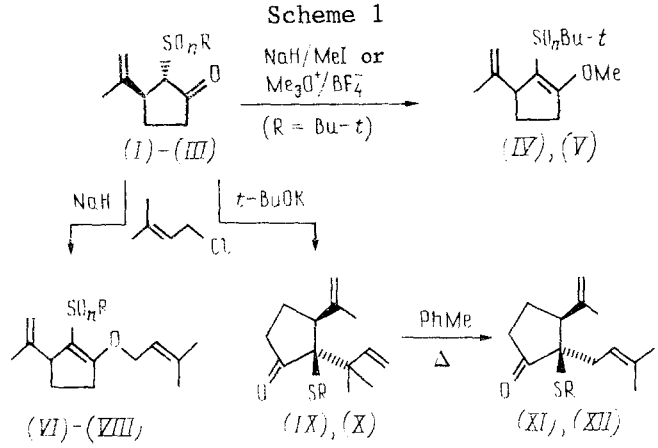
The conditions were found for the C-prenylation of the α,β derivatives of cyclopentanones indicated in the title.

Introduction of an anion-stabilized sulfur-containing group into the α position to the carbonyl group is presently a fairly widely used method [1], ensuring the controlled C-alkylation of various aldehydes and ketones, although in several cases it is complicated by the formation of undesirable O-alkyl regioisomers, cf. [2, 3]. We have previously reported [4] a simple synthesis of ketosulfides (I), (II), and sulfone (II) from the commercially available methylheptenone, which was undertaken in the course of a search for new approches to constructing molecules of cyclopentanoids [5], which are widely spread in nature, and which include monoterpenes of the iridane series [6]. The use of synthone blocks (I)-(III) for this purpose preliminarily requires finding of paths of their selective C-prenylation, and the present article is devoted to this objective.

Scheme 1



$n = 0$: R = Ph (I), (VI), (IX), (XI); R = Bu-*t* (II), (IV), (VII), (X), (XII).
$n = 2$: R = Bu-*t* (III), (V), (VIII).

The initially studied methylation of tert-butyl derivatives (II) and (III) by their deprotonation with NaH in a DMF medium (cf. [3]) and subsequent treatment with MeI, or in the case of (III) with the Meerwein salt, leads smoothly to vinyl ethers (IV) and (V), respectively. In a similar way, using prenyl chlorides, from ketones (I)-(III), the products of their O-alkylation (VI)-(VIII) were exclusively obtained under these conditions (see scheme 1).

At the same time, it was found that the t-BuOK initiated prenylation of ketosulfides (I) and (II) in the t-BuOH medium and makes it possible to suppress practically completely the undesirable O-alkylation process. Under the above conditions only products (IX) and (X) are preferentially formed in a S_N2' type reaction, although in the case of phenyl sulfide (I), the sought-for regioisomer (XI) was also found in the reaction mixture, but in an amount not higher than 20%. At the same time, it was found that the latter, and also its tert-butyl analog (XII) are readily formed under mild thermolysis conditions of their corresponding regioisomers (IX) and (X) as a result of the thus smoothly proceeding formally [1, 3]-sigmatropic rearrangement known for related objects, cf. [7].

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The structure of compounds (IV)-(XII) synthesized for the first time was confirmed by the physicochemical and elemental analysis data. In particular, in the PMR spectra of the methyl esters (IV) and (V) there are isolated signals of the CH_3O group, $\delta \approx 3.7$ ppm, and in the spectra of the prenyl derivatives (VI)-(VIII) – multiplet signals of the CH_2O group, located in the $\delta \approx 4.5$-4.6 ppm region. The relative configuration of the vicinal substituents in compounds (IX)-(XII) was determined from the experimental data on the recording of the Overhauser nuclear effect, by use of which, for example, for the pair of regioisomers (X) and (XII), the steric convergence was revealed for the proton at C^3 with the methine proton of HC=C of the vinyl and isopropylidene fragments of these molecules.

EXPERIMENTAL

The melting points were determined on a Koffler block. The IR spectra (ν, cm^{-1}) of the solutions in $CHCl_3$ were measured on a UR-20 spectrophotometer. The PMR spectra (δ, ppm, J, Hz) were obtained on a Bruker WM-250 spectrometer in $CDCl_3$ solutions. The mass spectra were obtained on a Varian MAT CH-6 mass spectrometer at 70 eV. The R_f values are given for a stationary layer of Silufol brand SiO_2 in a hexane–ether (9:1) system.

3-Isopropenyl-1-methoxy-2-tert-butylthiocyclopent-1-ene (IV). A solution of 0.2 g (0.94 mmole) of (II)* and 30 mg (1.25 mmoles) of NaH in 2 ml of DMF was stirred for 40 min at 40°C (Ar), and then was cooled in the course of 5 min to ~25°C, and treated in one portion with 0.16 g (1.13 mmoles) of CH_3I. The reaction mixture was held for 5 min at ~25°C and was then decomposed with ether and water. The aqueous layer was separated and extracted with ether. By the usual treatment of the combined organic layer, ~0.3g of a material was obtained, which was chromatographed on 10 g of SiO_2. A gradient elution from hexane to ether (up to 10% of the latter) gave 30 mg of the initial (II) and 0.13 g (72%) of (IV) in the form of a colorless oil. R_f 0.44. IR spectrum: 900, 1050, 1125, 1165, 1250, 1335, 1370, 1460, 1625, 1645, 2850-3000, 3080. PMR spectrum: 1.23 s (9H, CH_3), 1.56 br.s (3H, CH_3), 1.7 and 2.1 m (2H, HC^4), 2.52 d.t (2H, HC^5, J = 7 and 1.5), 3.30 m (1H, HC^3), 3.69 s (3H, CH_3), 4.64 and 4.71 br.s (2H, H_2C=C). Found, %: C 68.90; H 9.74; S 13.89. M^+ 226. $C_{13}H_{22}OS$. Calculated, %: C 68.97; H 9.80; S 14.16; mol. mass 226.4.

3-Isopropenyl-1-methoxy-2-tert-butylsulfonylcyclopent-1-ene (V). A suspension of 0.18 g (0.74 mmole) of (III) [4] and 30 mg (1.25 mmoles) of NaH in 2 ml of DMF was stirred at 50°C (Ar) for 1 h, was then cooled in the course of 5 min to ~25°C and treated in one portion with 0.16 g (1.08 mmoles) of $(CH_3)_3O^+BF_4^-$. The reaction mixture was held for 5 min at ~25°C and was then decomposed with ether and water. The aqueous layer was separated and extracted with ether. By the usual treatment of the combined organic layer, ~0.3 g of a product was obtained, which was chromatographed on 10 g of SiO_2. Elution with ether gave 0.16 g (84%) of (V) in the form of colorless crystals, mp 98-100°C (ether–hexane). IR spectrum: 880, 920, 1020, 1035, 1100, 1130, 1200, 1280, 1340, 1445, 1600, 1630, 2880-3000, 3060. PMR spectrum: 1.34 s (9H, CH_3), 1.78 br.s (3H, CH_3), 1.8 and 2.2 m (2H, HC^4), 2.7 m (2H, HC^5), 3.54 d.t (1H, HC^3, J = 10 and 2), 3.84 s (3H, CH_3), 4.79 and 4.90 br.s (2H, H_2C=C). Found, %: S 12.05. M^+ 258. $C_{13}H_{22}O_3S$. Calculated, %: S 12.41; mol. mass 258.4.

3-Isopropenyl-1-(3-methylbut-2-en-1-yl)oxy-2-phenylthiocyclopent-1-ene (VI). A suspension of 0.14 g (0.60 mmole) of (I)† and 20 mg (0.83 mmole) of NaH in 2 ml of DMF was stirred (Ar) for 45 min at ~25°C, and was treated at ~25°C in the course of 5 min with a solution of 80 mg (0.76 mmole) of prenyl chloride in 1 ml of DMF. The reaction mixture was held for 25 min at ~25°C and then diluted with ether and decomposed with water. The aqueous layer was separated and extracted with ether. By the usual treatment of the combined organic layer ~0.2 g of a product was obtained which was chromatographed on 10 g of SiO_2. Elution with hexane gave 0.13 g (72%) of (VI) in the form of a colorless oil. R_f 0.41. IR spectrum: 900, 1020, 1045, 1125, 1240, 1320, 1380, 1440, 1480, 1580, 1625, 1640, 2860-3000, 3080. PMR spectrum: 1.65, 1.67, and 1.76 br.s (9H, CH_3), 1.7, 2.2, and 2.6 m (4H, CH_2), 3.3 m (LH, HC^3), 4.60 d (2H, CH_2O, J = 7.5), 4.62 and 4.74 br.s (2H, H_2C=C), 5.37 br.t (1H, HC=C, J = 7.5), 71.-7.3 m (5H, C_6H_5). Found, %: S 10.25. M^+ 300. $C_{19}H_{24}OS$. Calculated, %: S 10.67; mol. mass 300.5.

*Compound (II) was used in the investigation with an admixture of ~15% of the cis isomer, see [4].

†Compound (I) was used in the investigation with an admixture of ~15% of the cis isomer, see [4].

3-Isopropenyl-1-(3-methylbut-2-en-1-yl)oxy-2-tert-butylthiocyclopenten-1-ene (VII). In a similar way, from 0.47 g (2.21 mmoles) of (II), 80 mg (3.33 moles) of NaH, and 0.28 g (2.68 mmoles) of prenyl chloride, and 4 ml of DMF, ~0.6 g of a product was obtained, which was chromatographed on 30 g of SiO_2. Elution with hexane gave 0.43 g (69%) of (VII) in the form of a colorless oil. R_f 0.56. IR spectrum: 900, 1020, 1125, 1160, 1250, 1330, 1380, 1460, 1620, 1650, 1680, 2870-3000, 3080. PMR spectrum: 1.31 s (9H, CH_3), 1.63, 1.68, and 1.74 br.s (9H, CH_3), 1.7 and 2.1 m (2H, HC^4), 2.55 br.t (2H, HC^5, J = 8.5), 3.4 m (1H, HC^3), 4.5 m (2H, CH_2O), 4.71 and 4.78 br.s (2H, $H_2C{=}C$), 5.37 br.t (1H, HC=C, J = 6.5). High resolution mass spectrum for m/z 212 $[M - C_5H_8]^+$. Found: 212.12241. $C_{12}H_{20}OS$. Calculated: 212.12338.

3-Isopropenyl-1-(3-methylbut-2-en-1-yl)oxy-2-tert-butylsulfonylcyclopent-1-ene (VIII). In a similar way, from 0.3 g (1.23 mmoles) of (III), 40 mg (1.67 mmoles) of NaH, and 0.19 g (1.82 mmoles) of prenyl chloride in 5 ml of DMF, ~0.5 g of a product was obtained, which was chromatographed on 30 g of SiO_2. Gradient elution hexane to ether (up to 40% of the latter) gave 0.3 g (78%) of (VIII) in the form of colorless crystals, mp 61-62°C (hexane). IR spectrum: 920, 1010, 1040, 1110, 1130, 1230, 1290, 1350, 1380, 1450, 1610, 1640, 2860-3000, 3080. PMR spectrum: 1.33 s (9H, CH_3), 1.67, 1.76, and 1.79 br.s (9H, CH_3), 1.7 and 2.2 m (2H, HC^4), 2.7 m (2H, HC^5), 3.50 d.t (1H, HC^3, J = 10.5 and 2), 4.55 m (2H, CH_2O), 4.78 and 4.89 br.s (2H, $H_2C{=}C$), 5.37 br.t (1H, HC=C, J = 7). Found, %: C 65.32; H 9.13. M^+ 312. $C_{17}H_{28}O_3S$. Calculated, %: C 65.35; H 9.03; mol. mass 312.5.

cis-3-Isopropenyl-2-(2-methylbut-3-en-2-yl)-2-phenylthiocyclopentan-1-one (IX) and cis-3-Isopropenyl-2-(3-methylbut-2-en-1-yl)-2-phenylthiocyclopentan-1-one (XI). A solution of 0.14 g (0.6 mmole) of (I), 90 mg (0.86 mmole) of prenyl chloride and 80 mg (0.71 mmole) of t-BuOK in 3 ml of t-BuOH was stirred at ~25°C (Ar) for 6 h, and then treated with ether and water. The aqueous layer was separated and extracted with ether. By the usual treatment of the combined organic extract, ~0.2 g of a product was obtained, which was chromatographed on 10 g of SiO_2. Elution with a hexane–ether (97:3) mixture gave in order of elution 0.1 g (55%) of (IX) and 30 mg (17%) of (XI).

Compound (IX) – light-yellow oil, R_f 0.29. IR spectrum: 910, 925, 1020, 1130, 1160, 1370, 1380, 1420, 1470, 1635, 1730, 2880-3010, 3090. PMR spectrum: 1.36 and 14.1 s (6H, CH_3), 1.8-2.5 m (4H, CH_2), 2.03 br.s (3H, CH_3), 3.20 d.d (1H, HC^3, J = 12 and 6), 4.93 and 5.14 br.s (2H, $H_2C{=}C$), 5.0-5.2 m (2H, $\underline{H}_2C{=}CH$), 6.13 d.d (1H, $\underline{HC}{=}CH_2$, J = 20 and 10), 7.2-7.5 m (5H, C_6H_5). Found, %: C 75.45; H 8.13; S 10.28. M^+ 300. $C_{19}H_{24}OS$. Calculated, %: C 75.95; H 8.05; S 10.67; mol. mass 300.5.

Compound (XI) – colorless oil, R_f 0.21. IR spectrum: 900, 975, 1000, 1080, 1160, 1220, 1315, 1330, 1400, 1455, 1620, 1640, 1725, 2860-3000, 3080. PMR spectrum: 1.59, 1.64, and 1.99 br.s (9H, CH_3), 1.7-3.1 m (7H, CH_2, HC^3), 4.80 br.t (1H, HC=C, J = 6), 5.0 and 5.12 br.s (2H, $H_2C{=}C$), 7.2-7.5 m (5H, C_6H_5). Found, %: C 76.18; H 8.36; S 10.24. M^+ 300. $C_{19}H_{24}OS$. Calculated, %: C 75.95; H 8.05; S 10.67; mol. mass 300.5.

A solution of 0.22 g of (XI) in 2 ml of toluene was boiled (Ar) for 13 h, and then was evaporated under vacuum, and the residue was chromatographed on 10 g SiO_2. Elution with a hexane–ether (9:1) mixture gave 90 mg (41%) of (IX), which was identical (TLC, IR, PMR) to the above-described sample of this sulfide.

cis-3-Isopropenyl-2-(2-methylbut-3-en-2-yl)-2-tert-butylthiocyclopentan-1-one (X). In a similar way as described above for (IX), from 0.65 g (3.06 mmoles) of (II), 0.48 g (4.59 mmoles) of prenyl chloride and 0.51 g (4.54 mmoles) of t-BuOK in 5 ml of t-BuOH, ~1 g of a product was obtained, which was chromatographed on 40 g of SiO_2. Elution with hexane gave 0.65 g (76%) of (X) in the form of a colorelss oil, R_f 0.56. IR spectrum: 900, 920, 1025, 1140, 1280, 1380, 1410, 1440, 1635, 1730, 2880-3000, 3070. PMR spectrum: 1.22 and 1.38 s (6H, CH_3), 1.36 s (9H, CH_3), 1.6-2.5 m (4H, CH_2), 1.89 br.s (3H, CH_3), 3.04 d.d (1H, HC^3, J = 12 and 5), 4.84 and 5.07 br.s (2H, $H_2C{=}C$), 5.0 m (2H, $\underline{H}_2C{=}CH$), 6.03 d.d (1H, $\underline{HC}{=}CH_2$, J = 17 and 11). The high resolution mass spectrum for m/z 224 $[M - C_4H_8]^+$. Found: 224.12299. $C_{13}H_{20}OS$. Calculated: 224.12338.

cis-3-Isopropenyl-2-(3-methylbut-2-en-1-yl)-2-tert-butylthiocyclopentan-1-one (XII). In a similar way as described above for (XI), from 0.65 g (2.32 mmoles) of (X) in 3 ml of toluene, ~0.7 g of a product was obtained, which was chromatographed on 30 g of SiO_2. Elution with hexane gave 0.36 g (55%) of (XII) in the form of a colorless oil, R_f 0.48. IR spectrum: 900, 1025, 1100, 1140, 1280, 1380, 1410, 1440, 1585, 1640, 1670, 1730, 2860-

3000, 3080. PMR spectrum: 1.32 s (9H, CH_3), 1.5-3.2 m (7H, CH_2, HC^3), 1.61, 1.65, and 1.84 br.s (9H, CH_3), 4.84 and 4.97 br.s (2H, $H_2C{=}C$), 4.87 br.t (1H, HC=C, J = 6.5). Found, %: C 72.90; H 10.33; S 11.13. M^+ 280. $C_{17}H_{28}OS$. Calculated, %: C 72.80; H 10.06; S 11.43; mol. mass 280.5.

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MONO- AND DI-(2-NITROGUANIDINO)BENZENES AND SOME OF THEIR AMINO AND NITRO DERIVATIVES

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A method was developed for the synthesis of mono- and di-(2-nitroguanidino)benzenes and some of their amino and nitro derivatives, based on the reaction of aniline and phenylenediamines with S-methylisothionitrourea, followed by oxidation of the aminophenyl-2-nitroguanidines or by nitration of aryl-2-nitroguanidines. It was shown that o-phenylenediamine reacts with S-methylisothionitrourea to form 2-nitraminobenzimidazole.

As known, aryl-2-nitroguanidines exhibit biological activity [1]. The main method for their synthesis comprises the reaction of arylamines with 1-methyl-1-nitroso-2-nitroguanidine (MNNG) [1-3]. Unfortunately, this method cannot be regarded as suitable for the preparation of aryl-2-nitroguanidines, since, on the one hand, aromatic amines, having strong electron-acceptor substituents, especially in the o- and p-position to the amino group undergo this reaction with difficulty or not at all, while on the other hand, MNNG displays strong carcinogenic properties.

We therefore studied the possibility of preparation of aryl-2-nitroguanidines based on the action of aniline and o-, m-, and p-phenylenediamines with S-methylisothionitrourea (MITNU). The phenylenediamines were selected because the formation of aminophenyl-2-nitroguanidines from them opens a new path for preparing various aryl 2-nitroguanidines, including those having strong electron-acceptor properties, in particular, the nitro groups.

It was found that MITNU undergoes the reaction with the arylamines studied relatively readily, at temperatures of 60-80°C, whereby the yield and structure of the compounds thus formed are dependent on both the conditions of carrying out the reaction and the structure of the amine used. Heating of MITNU with aniline, and also with p- and m-phenylenediamines

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