Chemistry of Heterocyclic Compounds, Vol.35, No. 2, 1999

CLEAVAGE OF 2-ISOXAZOLINE DERIVATIVES BY GRIGNARD REAGENTS IN THE PRESENCE OF TETRAISOPROPOXYTITANIUM

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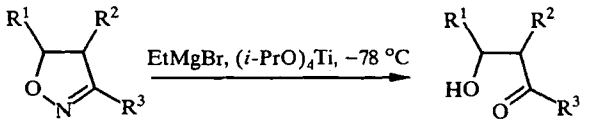
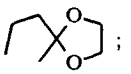
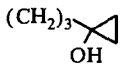
Isoxazoles cleave under conditions of the Grignard reaction with formation of enaminoketones [1-3]. The opening of the isoxaline ring by Grignard reagents is not known hitherto. We have observed that derivatives of 2-isoxazoline I-III react with ethylmagnesium bromide in the presence of tetraisopropoxytitanium to cause not only addition of ethylmagnesium bromide at the carboxyl group (in the cases of compounds I and II), which leads to formation of a three-membered carboring (Kulinkovich's cyclopropanization [4, 5]), but also leads to cleavage of the heterocyclic compound on the N—O bond with formation of the corresponding hydroxyketones IV-VI. In the absence of one of the reagents (ethylmagnesium bromide or tetraisopropoxytitanium), the cleavage of the isoxazoline ring is not observed over the temperature range from -78°C to +20°C.



I–III IV–VI

I, IV R^1 = Ph, R^2 = H; II, V R^1R^2 =  ;

III, VI R^1R^2 =  ; I, II $R^3 = (CH_2)_3COOMe$;

IV, V R^3 =  ; III, VI R^3 = Me

To ethylmagnesium bromide, prepared from 10 mmol of ethyl bromide in 20 ml of diethyl ether and cooled to -78°C, we added 1 mmol of tetraisopropoxytitanium in 15 ml of ether. Then we added by drops in 15-20 min 1 mmol of the corresponding isoxazoline derivative in 20 ml of THF. Over an hour, temperature of the reaction mixture was raised to 0°C, and then it was poured into 50 ml of 5% sulfuric acid cooled to 0°C. The organic layer was separated off and the aqueous part was extracted with ether. The extracts were washed with water, dried with Na_2SO_4, and evaporated. The reaction products were isolated by preparative chromatography on silica gel.

1-Hydroxy-6-(1-hydroxycyclopropyl)-1-phenylhexan-3-one (IV). Yield 40%. IR spectrum: 3380-3400, 3050, 1610, 1013 cm^{-1}. PMR spectrum ($CDCl_3$): 0,44 (2H, t, CH_2); 0,72 (2H, t, CH_2); 1,54 (2H, t, CH_2); 1,84 (2H, m, CH_2); 2,58 (2H, t, CH_2); 2,78 (1H, dd, J = 3,5; 17,0 Hz, CH_2); 2,98 (1H, dd, J = 8,5; 17,0 Hz, CH_2); 3,40 (1H, s, OH); 5,18 (1H, dd, J = 3,5; 8,5 Hz, 1-H); 7,06 (1H, s, OH); 7,36 ppm (5H, m, Ph). Found, %: C 72,21; H 8,08. $C_{15}H_{20}O_3$. Calculated, %: C 72,55; H 8,12.

Biological Chemistry Institute, Belarus National Academy of Sciences, Minsk 220141. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 277-278, February, 1999. Original article submitted December 15, 1998.

 0009-3122/99/3502-0231$22.00©1999 KluwerAcademic/Plenum

2-(4-(1-Hydroxycyclopropyl)-2-oxobutyl)-3,3-ethylenedioxycyclopentan-1-ol (V). Yield 12%. IR spectrum: 3400, 3050, 1710, 1190, 1160, 1105, 1020 cm^{-1}. PMR spectrum ($CDCl_3$): 0,44 (2H, t, CH_2); 0,74 (2H, t, CH_2); 1,24-1,98 (6H, m, CH_2); 2,40-2,78 (4H, m, CH_2); 3,08 (1H, dd, J = 6,0; 3,0 Hz, CH); 3,98 (4H, m, OCH_2, CH_2—O); 4,58 (1H, dd, J = 14,0; 6,0 Hz, CH); 5,00 (1H, w. s, OH); 6,72 ppm (1H, w. s, OH). Found, %: C 61,95; H 8,11. $C_{14}H_{22}O_5$. Calculated, %: C 62,20; H 8,20.

3-Acetylbicyclo[2.2.1]heptan-2-ol (VI). Yield 50%. IR spectrum: 3450, 1710, 1358 CM^{-1}. PMR spectrum ($CDCl_3$): 0,84-1,60 (5H, m); 1,82 (1H, dm, $C_{(7)}H$-*syn*, J_{gem} = 10,0 Hz); 2,18 (3H, s, CH_3); 2,28 (1H, w. s, CH); 2,38 (1H, d, J = 4,0 Hz, CH); 2,70 (1H, J = 7,2 Hz, CH); 2,04 (1H, w. s, OH); 4,09 ppm (1H, J = 7,2 Hz, CH). Found, %: C 70,18; H 9,18. $C_9H_{14}O_2$. Calculated, %: C 70,10; H 9,15.

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