Research Article

Preparation of α -Bromoketones Involving the Reaction of Enol Triethyl Borates with N-Bromosuccinimide

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Received 4 December 2012; Accepted 31 December 2012

Academic Editor: Stojan Stavber

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The ketones (5 α - and 5 β -cholestan-3-one and (1S,7aS)-1-tert-butoxy-hexahydro-7a-methyl-1H-inden-5-one) were efficiently α -monobrominated by treatment of the corresponding enol triethyl borates with N-bromosuccinimide (NBS).

1. Introduction

Bromination of ketones is an important reaction in synthetic organic chemistry [1] because bromoketones obtained this way are common intermediates in the synthesis of biologically active compounds. The bromination reaction constitutes the first step of introducing a heteroatom to generate stabilized carbanions [2] and support conjugation of the carbonyl group.

In the classic procedures for α -bromination of ketones, hazardous molecular bromine is utilized [5–7]. N-bromosuccinimide (NBS) is a safer brominating reagent which can be used in milder reaction conditions. It has been reported that NBS brominates ketones in α position using radical initiators, such as azobisisobutyronitrile (AIBN) [8] or dibenzoyl peroxide [9]. Recently, methods of α -bromination using NBS in the presence of $\text{SiO}_2\text{-NaHSO}_4$ [10], trimethylsilyl trifluoromethanesulfonate (TMS-OTf) [11], ammonium acetate [12], and solvent-free reaction conditions have been developed [13–15]. Photochemical α -bromination ($\lambda = 200\text{--}600\text{ nm}$) has also been described [16].

2. Results and Discussion

Here, I report a new procedure for the preparation of α -bromoketones involving the reaction of enol triethyl borate with NBS (Scheme 1). The potassium enolate was prepared by treatment of the ketone with potassium

hexamethyldisilazide (KHMDs). Potassium enoxytriethylborate was easily obtained by reaction of the corresponding potassium enolate with triethylborane. The generation of potassium enoxytriethylborate required a low temperature (-78°C), while the reaction of potassium enoxytriethylborate with NBS occurred at room temperature. Anhydrous reaction conditions (argon atmosphere, anhydrous solvent, and reagents) are necessary.

As a model for examination of the α -bromination process, 5 α - and 5 β -cholestan-3-one and the indenone system [1, (1S,7aS)-1-tert-butoxy-hexahydro-7a-methyl-1H-inden-5(6H)-one], and some others were chosen.

The α -bromination method described in Scheme 1 showed high regioselectivity (Table 1). In addition, the yields of α -brominated compounds were superior (87% and 90%, respectively, for 5 α - (2) and 5 β -cholestan-3-one (3)). Furthermore, the tert-butoxy protecting group tolerated the described reaction conditions. Some examples (cyclopentanone and 2-methylcyclohexanone) gave a mixture of products. A likely mechanism of compound 1 reaction is outlined in Scheme 2. A separate experiment of cholestanone (3) with KHMDs and NBS yielded a mixture of various products.

The typical experimental procedure was as follows: to KHMDs (1.1 equivalent of 0.5 M solution in toluene) under argon at room temperature a solution of ketone (1 equivalent) in dry THF was added. The reaction mixture became turbid. After 0.5 hour, the reaction mixture was cooled to -78°C ,

SCHEME 1: (a) 1,1 equivalent of KHMDS, rt; (b) 1,1 equivalent of BET_3 , -78°C ; (c) 2 equivalents of NBS, rt.

TABLE 1: Results of α -bromination of ketones.

Entry	Starting material	Product	Yield	dr %
1	<p style="text-align: center;">(1)</p>	<p style="text-align: center;">(1A)</p>	55% ^a	100
2	<p style="text-align: center;">(2)</p>	<p style="text-align: center;">(2A)</p>	87% ^b	100
3	<p style="text-align: center;">(3)</p>	<p style="text-align: center;">(3A)</p>	90% ^c	100
4	<p style="text-align: center;">(4)</p>	<p style="text-align: center;">(4A)</p>	90% ^d	90 : 10
5	<p style="text-align: center;">(5)</p>	<p style="text-align: center;">(5A)</p>	85% ^e	50 : 50
6	<p style="text-align: center;">(6)</p>	<p style="text-align: center;">(6A)</p>	90% ^f	75 : 25

TABLE 1: Continued.

Entry	Starting material	Product	Yield	dr %
7	(7)	(7A)	30%	—
8	(8)	Mixture of products	—	—

^aThe selected spectral data of (1S,6R,7aS)-tert-butoxyhexahydro-6-bromo-7a-methyl-1H-inden-5-one (**1A**): mp (CH₂Cl₂/hexane) 88–91°C; IR (CHCl₃) $\nu_{\max}$ (cm⁻¹) 1725, 1193; ¹H NMR (400 MHz, CDCl₃): δ_{H} 4.81 (1H, dd, $J_1 = 6.7$, $J_2 = 12.8$ Hz, CH–Br), 3.52 (1H, dd, $J_1 = 7.5$, $J_2 = 8.8$ Hz, CH–OBu^t), 1.15 (9H, s, OC(CH₃)₃), 1.06 (3H, s, CH₃); ¹³C NMR (ppm): 201.3 (C), 78.6 (CH), 72.8 (C), 54.1 (C), 48.5 (CH₂), 45.1 (CH), 45.0 (C), 41.7 (CH₂), 32.1 (CH₂), 28.6 (CH₃ × 3), 25.4 (CH₂), 10.9 (CH₃); HRMS: calculated 325.0779, found 325.0779 for C₁₄H₂₃O₂BrNa.

^bData of 2 α -bromocholestan-3-one (**2A**) have been found to be identical with those reported [3].

^cThe selected spectral data of 4 β -bromocoprostan-3-one (**3A**): mp (CH₂Cl₂/hexane) 93–95°C; IR (CHCl₃) $\nu_{\max}$ (cm⁻¹) 1726, 1468, 555; ¹H NMR (400 MHz, CDCl₃): δ_{H} 4.98 (1H, d, $J = 12$ Hz, CH–Br), 2.95 (1H, m), 2.50 (1H, d, $J = 12$ Hz, CH₃), 1.08 (3H, s, CH₃), 0.90 (3H, d, $J = 7.7$ Hz, CH₃), 0.87 (3H, d, $J = 6.6$ Hz, CH₃), 0.69 (3H, s, CH₃); ¹³C NMR (ppm): 202.5 (C), 60.05 (CH), 56.4 (CH), 56.3 (CH), 54.2 (CH), 42.7 (C), 41.9 (CH), 39.9 (CH₂), 39.5 (CH₂), 38.3 (C), 36.7 (CH₂), 36.5 (CH₂), 36.1 (CH₂), 35.7 (CH), 35.6 (CH), 28.2 (CH₂), 27.9 (CH), 25.6 (CH₂), 25.1 (CH₂), 24.1 (CH₂), 23.8 (CH₂), 23.2 (CH₃), 22.8 (CH₃), 22.5 (CH₃), 21.2 (CH₂), 18.6 (CH₃), 12.0 (CH₃); HRMS: calculated 487.2551, found 487.2545 for C₂₇H₄₅OBrNa.

^dThe selected spectral data of 4 β -bromosmilagenin (**4A**): mp (CH₂Cl₂/hexane) 135–136°C; IR (CHCl₃) $\nu_{\max}$ (cm⁻¹) 1727, 1179; ¹H NMR (400 MHz, CDCl₃): 4.96 (1H, d, $J = 12.1$ Hz, CH–Br), 4.41 (1H, m, H16), 3.48 (1H, m, H26), 3.37 (1H, m, H26), 1.10 (1H, s, CH₃), 0.97 (1H, d, $J = 6.9$ Hz, CH₃), 0.80 (1H, s, CH₃), 0.79 (1H, d, $J = 6.0$ Hz, CH₃); ¹³C NMR (ppm): 202.2 (C), 109.2 (C), 80.7 (CH), 66.9 (CH₂), 62.2 (CH), 59.8 (CH), 56.2 (CH), 54.1 (CH), 42.0 (CH), 42.0 (CH), 40.7 (C), 40.0 (CH₂), 38.3 (C), 36.7 (CH₂), 36.5 (CH₂), 35.3 (CH), 31.7 (CH₂), 31.4 (CH₂), 30.2 (CH), 28.8 (CH₂), 25.5 (CH₂), 25.3 (CH₂), 23.2 (CH₃), 21.1 (CH₂), 17.1 (CH₃), 16.4 (CH₃), 14.4 (CH₃); HRMS: calculated 515.2137, found 515.2135 for C₂₇H₄₁O₃BrNa.

^eSpectral data identical with those from [4].

^fSpectral data identical with those from Spectra Database for Organic Compounds (SDBS), number 4818. Mixture of bromides **6A** in ratio 25 : 75, respectively, α -bromo : β -bromo; HRMS: calculated 253.0204, found 253.0201 for C₁₀H₁₅OBrNa.

SCHEME 2: Proposed mechanism of bromination reaction.

and BEt₃ (1.1 equivalent of 1.0 M solution in THF) was added. The reaction mixture then turned transparent. After 15 minutes, NBS (2 equivalents) in dry THF was added. The reaction mixture was allowed to reach room temperature, and stirring under argon was continued overnight. The organic solvent was evaporated. The residue was washed by 3N HCl solution and then extracted with CH₂Cl₂. The combined organic layers were washed with saturated NaHCO₃, dried over MgSO₄, and evaporated.

3. Conclusions

In conclusion, I have developed a mild and efficient method for the α -monobromination of ketones by treatment of their

enol triethylborates with NBS. The simple procedure, high yields, and regioselectivity of the products are the advantages of the described method.

Acknowledgments

The author would like to thank Prof. D. Covey from the Washington University School of Medicine in S. Louis, MO, USA, for lending one of the testing compound [(1S,7aS)-1-tert-butoxy-hexahydro-7a-methyl-1H-inden-5-one], Prof. J.W. Morzycki from the University of Białystok, Poland, for scientific support. The author also thanks Dr. L. Siergiejczyk for help in NMR spectra interpretation. Financial support from the University of Białystok within the project BST-124 is gratefully acknowledged.

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