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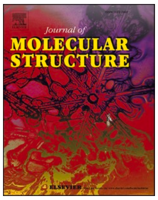

One-pot synthesis of 4,5,6-triacetoxyisoindole-1,3-dione derivatives by hydride transferring agent in Ac_2O: Explanation of the regioselectivity in the molecule by theoretical calculations

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ABSTRACT

Isoindole-1,3-dione derivatives containing an epoxy alcohol unit were synthesized. Epoxy alcohols were converted to the corresponding 1,2,3-triacetate derivatives in a one-pot manner using the NaBH4/Ac20 system for the first time and in high yield. C-3 selective ring-opening products were obtained with good yield and with stereospecificity with the $NaBH_4/Ac_2O$ system at 139–140 °C. The exact configuration of 2-methyl-1,3-dioxooctahydro-1H-isoindole-4,5,6-triyltriacetate was determined by X-ray diffraction analysis which was obtained from the reaction of epoxy alcohol by hydride transferring agent in acetic anhydride. On the other hand, theoretical computations were carried out to explain the regioselectivity in the ring opening reaction of epoxy alcohols. The results showed that the ring-opening reaction of epoxy alcohol proceeds in a thermodynamically controlled manner and regioselectivity occurs depending on the stability of the products.

1. Introduction

Epoxides have a high tendency to react due to polarization of the carbon-oxygen bond and ring strain. In addition, the *trans*-stereochemistry observed in the ring opening reaction makes it important to use epoxides in synthesis [1,2]. On the other hand, molecules containing 2, 3-epoxy alcohol units are synthetically useful materials in the synthesis of natural products and related molecules. Due to the asymmetry of epoxy alcohols, nucleophilic substitution at the C-2 or C-3 positions leads to the formation of regio-isomers.

Very recently, we examined the epoxide ring opening reactions of isoindole-1,3-dione derivatives containing epoxy alcohol units with nucleophiles such as Cl, Br and azide, and obtained C-2 type isomers regioselectively (Scheme 1). Additionally, we supported the experimental results with theoretical calculations [3].

On the other hand, the production of 1,2-diols from nucleophilic ring opening reactions of epoxides with water and acetylation reactions of these diols are important methods for the synthesis of polyhydroxy molecules. In this context, a method different from the literature was used for the acetylation reaction. One-pot catalytic conversion of epoxides to 1,2-diacetates with hydride transfer agents in acetic anhydride was carried out by Zadeh *et al.* (Scheme 2) [4,5].

Based on these studies, we decided to study for the first time the conversion of epoxy alcohols to acetates by hydride transfer. For this purpose, we focused on the reactions of isoindole-1,3-dione derivatives containing epoxy alcohol units with $NaBH_4$ in acetic anhydride. Here, we report the regiospecific and stereospecific synthesis via ring opening of isoindole-1,3-dione derivatives containing triacetoxy groups in the cyclohexane ring. Additionally, we explained the formation of C-3 type ring opening isomers with theoretical calculations.

2. Experimental

2.1. General

Chemicals were purchased from various companies and used directly without any purification. Column chromatography (Fluka Silica gel 60; 0.063 - 0.2 mm) weas used to purify the products after the reaction. Bruker 400 MHz NMR spectrometer (^{1}H NMR 400 MHz, ^{13}CNMR 100 MHz) was used for NMR analyses. Melting points of the products were determined with a GallenKamp MPD 350 capillary melting point device. Elemental analysis results were also recorded on the Leco CHNS-932

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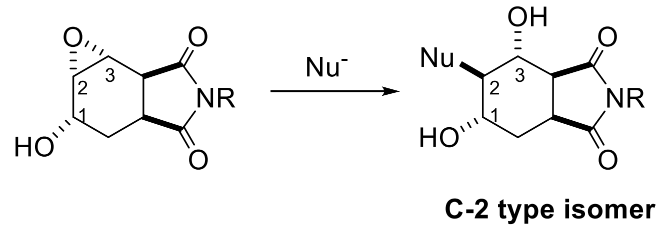
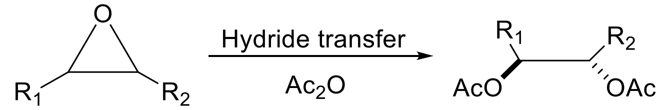


Scheme 1. The ring opening reaction of epoxy alcohol with nucleophile and formation of C-2 type isomer.



Scheme 2. Conversion of epoxides to 1,2-diacetates with hydride transferring agents.

device.

2.2. Synthesis of acetate compounds

Epoxy alcohol compounds were dissolved in Ac_2O, $NaBH_4$ (2 eq.) was added at 0 °C and refluxed for 3–4 h. Then, the reaction was stopped by adding saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried with Na_2SO_4 and the solvent was removed in the evaporator. The mixture was purified by column chromatography.

2.3. Synthesis of aromatic compounds

Epoxy alcohol compounds were dissolved in Ac_2O, $NaBH_4$ (2 eq.) was added at 0 °C and stirred for 1 days at rt. Then, the reaction was stopped by adding saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were dried with Na_2SO_4 and the solvent was removed in the evaporator. The mixture was purified by column chromatography.

2-methyl-1,3-dioxooctahydro-1*H*-isoindole-4,5,6-triyl triacetate (4a): It was obtained as white solid mp 186–187 °C, $R_f = 0.31$ (40 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 (dd, *J* = 10.5, 5.4 Hz, 1H), 5.24 – 5.16 (m, 1H), 5.11 (s, 1H), 3.62 (t, *J* = 9.2 Hz, 1H), 3.45 – 3.33 (m, 1H), 3.19 – 3.06 (m,1H), 2.96 (dd, *J* = 10.6, 8.0 Hz, 3H), 2.40 – 2.27 (m, 1H), 2.15 – 2.04 (m, 4H), 1.98 (p, *J* = 4.6 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.60, 174.85, 169.88, 169.14, 168.56, 67.95, 67.18, 65.56, 40.20, 37.30, 24.66, 21.73, 20.78, 20.66, 20.46. FT-IR (KBr, cm^{-1}): 1742, 1706, 1431, 1369, 1245, 1207, 1044, 1008, 704. **HRMS**: (ESI), *m/z*: Calculated for $[M+Na]^+$ $C_{15}H_{19}NO_8$; 364,1111; Found: 364.1001.

2-methyl-1,3-dioxo-2,3,4,5,6,7-hexahydro-1*H*-isoindole-5,6-diyl diacetate (6a): It was obtained as white solid mp 97–99 °C, $R_f = 0.35$ (20 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 5.28 (dt, *J* = 11.1, 4.8 Hz, 1H), 3.01 (s, 3H), 2.82 – 2.60 (m, 2H), 2.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.10, 169.63, 138.36, 67.90, 24.06, 23.75, 20.91. FT-IR (KBr, cm^{-1}): 1734, 1694, 1439, 1376, 1254, 1226, 1201, 1049, 996, 967, 725. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{13}H_{15}NO_6$; 282,0899; Found: 282.0978.

2-methylisoindoline-1,3-dione (7a): It was obtained as white solid mp 134–136 °C, $R_f = 0.54$ (20 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 2H), 7.77 – 7.67 (m, 2H), 3.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.45, 133.85, 132.26, 123.15, 23.90. FT-IR (KBr, cm^{-1}): 2962, 2901, 1757, 1707, 1429, 1377, 1249, 1005, 714. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_9H_7NO_2$; 162,0477; Found: 162.0534.

2-ethyl-1,3-dioxooctahydro-1*H*-isoindole-4,5,6-triyl triacetate (4b): It was obtained as white solid mp 205–207 °C, $R_f = 0.34$ (40 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 5.38 – 5.34 (m, 1H), 5.18 (dd, *J* = 4.8, 2.9 Hz, 1H), 5.10 (ddd, *J* = 10.0, 4.6, 3.0 Hz, 1H), 3.54 – 3.43 (m, 2H), 3.30 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.07 (td, *J* = 8.5, 4.3 Hz, 1H), 2.28 (dt, *J* = 14.1, 4.5 Hz, 1H), 2.12 – 2.07 (m, 1H), 2.04 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.37, 174.48, 169.88, 169.06, 168.56, 68.15, 67.23, 65.57, 40.00, 37.28, 33.85, 21.69, 20.80, 20.67, 20.52, 13.08. FT-IR (KBr, cm^{-1}): 2938, 1765, 1742, 1698, 1402, 1366, 1347, 1217, 1201, 1029. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{16}H_{21}NO_8$; 356,1267; Found: 356.1334.

2-ethylisoindoline-1,3-dione (7b): It was obtained as white solid mp 78–79 °C, $R_f = 0.37$ (40 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.73 (m, 2H), 7.67 – 7.61 (m, 2H), 3.67 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.27, 133.84, 132.26, 123.13, 32.90, 13.94. FT-IR (KBr, cm^{-1}): 2962, 2901, 1757, 1707, 1429, 1377, 1249, 1005, 714. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{10}H_9NO_2$; 176.0633; Found: 176.0636.

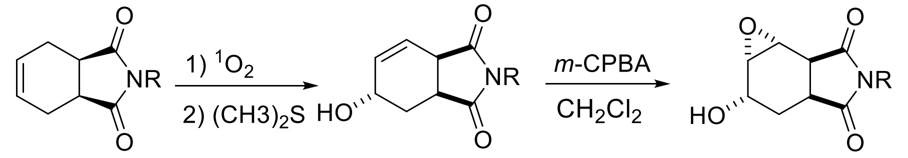
1,3-dioxo-2-phenyloctahydro-1*H*-isoindole-4,5,6-triyl triacetate (4c): It was obtained as white solid mp 176–178 °C, $R_f = 0.38$ (40 % Petroleum ether / EtOAc) ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.45 – 7.38 (m, 1H), 7.33 – 7.25 (m, 2H), 5.57 – 5.50 (m, 1H), 5.36 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.25 (ddd, *J* = 10.5, 4.8, 2.8 Hz, 1H), 3.61 – 3.51 (m, 1H), 3.36 (tt, *J* = 15.5, 7.8 Hz, 1H), 2.56 – 2.45 (m, 1H), 2.25 – 2.17 (m, 1H), 2.14 (s, 3H), 2.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.39, 173.72, 169.93, 169.08, 168.48, 131.60, 129.27, 128.71, 125.92, 68.44, 67.00, 65.44, 40.29, 37.67, 21.43, 20.87, 20.75, 20.68. FT-IR (KBr, cm^{-1}): 1735, 1707, 1371, 1377, 1227, 1193, 1110, 982. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{20}H_{21}NO_8$; 404,1267; Found: 404.1336.

1,3-dioxo-2-phenyl-2,3,4,5,6,7-hexahydro-1*H*-isoindole-5,6-diyl diacetate (6c): It was obtained as white solid. mp 184–186 °C, $R_f = 0.62$ (40 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.31 – 7.23 (m, 3H), 5.29 (t, *J* = 5.2 Hz, 2H), 2.85 – 2.73 (m, 2H), 2.72 – 2.61 (m, 2H), 2.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.13, 168.34, 138.44, 131.54, 129.11, 127.75, 125.90, 67.86, 24.21, 20.96. FT-IR (KBr, cm^{-1}): 1728, 1705, 1493, 1396, 1368, 1236, 1226, 1207, 791. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{18}H_{17}NO_6$; 344.1056; Found: 344.1128.

2-phenylisoindoline-1,3-dione (7c): It was obtained as white solid. mp 207–208 °C, $R_f = 0.53$ (20 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.74 – 7.68 (m, 2H), 7.47 – 7.40 (m, 2H), 7.39 – 7.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.29, 134.40, 131.79, 131.71, 129.12, 128.11, 126.59, 123.75. FT-IR (KBr, cm^{-1}): 2923, 2853, 1695, 1589, 1490, 1378, 1109, 876, 753. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{14}H_9NO_2$; 224,0633; Found: 224,0700.

2-benzyl-1,3-dioxooctahydro-1*H*-isoindole-4,5,6-triyl triacetate (4d): It was obtained as white solid mp 133–135 °C, $R_f = 0.43$ (40 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.8 Hz, 2H), 7.34- 7.22 (m, 3H), 5.37 (t, *J* = 5.1 Hz, 1H), 5.22 – 5.15 (m, 1H), 5.11 (dd, *J* = 8.3, 4.1 Hz, 1H), 4.61 (q, *J* = 14.0 Hz, 2H), 3.35 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.20–3.12 (m, 1H), 2.44 – 2.27 (m, 1H), 2.18 – 2.05 (m, 4H), 2.00 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.31, 174.32, 169.84, 168.99, 168.61, 135.60, 129.40, 128.78, 128.14, 67.87, 67.09, 65.45, 42.64, 39.97, 37.27, 21.45, 20.79, 20.66, 19.69. FT-IR (KBr, cm^{-1}): 1768, 1738, 1710, 1400, 1370, 1242, 1203, 1116, 11,029, 986. **HRMS**: (ESI), *m/z*: Calculated for $[M+Na]^+$ $C_{21}H_{23}NO_8$; 440,1424; Found: 440.1313.

2-benzyl-1,3-dioxo-2,3,4,5,6,7-hexahydro-1*H*-isoindole-5,6-diyl diacetate (6d): It was obtained as white solid mp 115–117 °C, $R_f = 0.35$ (20 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, 5H), 5.21 (t, *J* = 4.7 Hz, 2H), 4.57 (s, 2H), 2.78 – 2.47 (m, 4H), 1.99 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.11, 169.18, 138.36, 136.40, 128.69, 128.65, 127.88, 67.87, 41.55, 24.08, 20.93. FT-IR (KBr, cm^{-1}): 1741, 1703, 1431, 1396, 1223, 1045, 704. **HRMS**: (ESI), *m/z*:



1a R = Me, **1b** R = Et
1c R = Ph, **1d** R = Bn

2a R = Me, **2b** R = Et
2c R = Ph, **2d** R = Bn

3a R = Me, **3b** R = Et
3c R = Ph, **3d** R = Bn

Scheme 3. Synthesis of epoxy alcohol compounds.

Calculated for $[M + H]^+$ $C_{19}H_{19}NO_6$; 358.1212; Found: 358.1285.

2-benzylisoindoline-1,3-dione (**7d**): It was obtained as white solid mp 108–110 °C, $R_f = 0.61$ (20 % Petroleum ether / EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.66 – 7.60 (m, 2H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.27 – 7.16 (m, 3H), 4.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.04, 136.37, 133.97, 132.16, 128.67, 128.61, 127.81, 123.34, 41.62. FT-IR (KBr, cm^{-1}): 1703, 1431, 1330, 1066, 1029, 896, 714. **HRMS**: (ESI), *m/z*: Calculated for $[M + H]^+$ $C_{15}H_{11}NO_2$; 238.0790; Found: 238.0858.

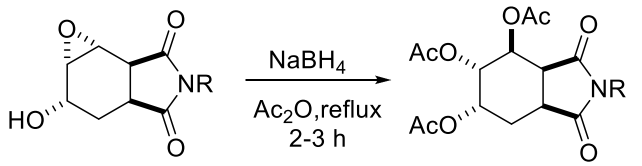
2.4. Crystal structure determination

For the crystal structure determination, single-crystal of the **4c** molecule was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). Graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and oscillation scans technique with Δ*w* = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F2>2σ(F2). Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software. The structures were solved by direct methods using SHELXS-2013 [6]., which allowed location of most of the heaviest atoms, with the remaining non-hydrogen atoms being located from difference Fourier maps calculated from successive full-matrix least squares refinement cycles on F2 using SHELXL-2013, All non-hydrogen atoms were refined using anisotropic displacement parameters. The hydrogen atoms were assigned with common isotropic displacement factors and included in the final refinement by using geometrical restrains. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for 4c: C20H21NO8, crystal system, space group: monoclinic, P21/n; (no:14); unit cell dimensions: *a* = 12.696(4), *b* = 8.550(3), *c* = 18.385(5) Å, α= 90, β = 106.674(4), γ = 90°; volume; 1911.8(2) Å3, *Z* = 4; calculated density: 1.401 g/cm3; absorption coefficient: 0.109 mm-1; F(000): 848; θ-range for data collection 1.7–25.2°; refinement method: full matrix least-square on F2; data/-parameters: 3376/265; goodness-of-fit on F2: 1.019; Data completeness; 1.00, final R-indices [$I > 2\sigma$ (I)]: R1 = 0.037, wR2 = 0.100; largest diff. peak and hole: 0.177and −0.188 eÅ-3.

CCDC-2,328,688 (4c) number contains the supplementary crystallographic data. These data are provided free of charge via the joint CCDC/FIZ Karlsruhe deposition service www.ccdc.cam.ac.uk/structures .

3. Result and discussion

In our previous work [3,7,8] epoxy alcohols 3a-d were obtained by using bicyclic imides 1a-d as the key compound. Bicyclic imides 1a-d were reacted with singlet oxygen in CH_2Cl_2 to give hydroperoxide. The resulting hydroperoxide was then reduced with dimethyl sulfide and converted to alcohols 2a-d. Thus, isoindole-1,3-dione derivatives containing allyl alcohol unit were obtained. Epoxidation of molecules containing allyl alcohol units with per acid gave *syn*-epoxy alcohols 3a-d (Scheme 3). All compounds were purified by column chromatography and their structures were assigned by using ^1H and ^{13}C NMR spectra.



3a R = Me, **3b** R = Et
3c R = Ph, **3d** R = Bn

4a R = Me, **4b** R = Et
4c R = Ph, **4d** R = Bn

Scheme 4. Synthesis of triacetate compounds **4a-d.**

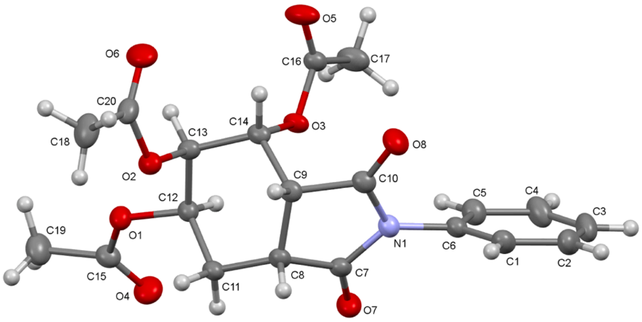


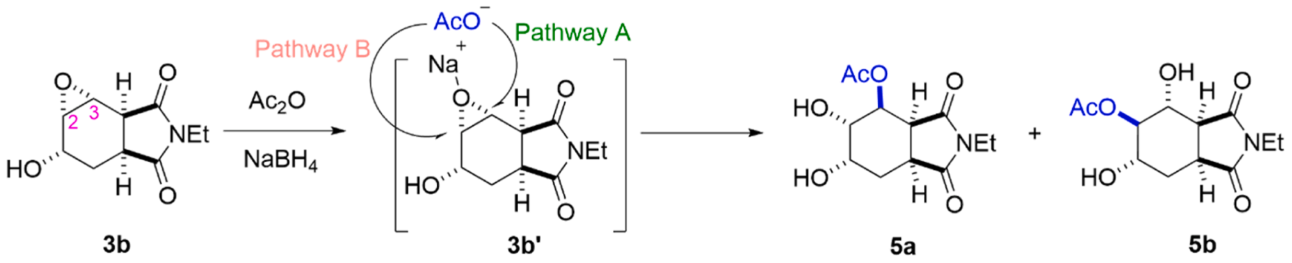
Fig. 1. X-ray structure of the molecule **4c**. Thermal ellipsoids are drawn at the 40 % probability level.

On the other hand, although it is known in the literature that epoxides are converted to the corresponding trans-diacetates in the presence of $NaBH_4/Ac_2O$, the ring opening reaction of epoxy alcohols in the presence of $NaBH_4/Ac_2O$ has not been reported in the literature. Starting from this point, we decided to examine the ring opening reactions of epoxy alcohols in the presence of $NaBH_4/Ac_2O$. For this purpose, the synthesized epoxy alcohol compounds were dissolved in Ac_2O, $NaBH_4$ was added at 0 °C and refluxed for 2–3 h (Scheme 4).

The ^1H NMR spectrum recorded from the mixture showed that the epoxide ring was opened and triacetate molecule were formed. Although two regio-isomers were expected, only one isomer was obtained

Table 1
Selected geometric parameters (Å, °) for the molecule **4c**.

O3-C16	1.347(2)	O2-C20	1.348(3)
O1-C15	1.346(3	O8-C10	1.201(3)
C4-C5	1.380(3)	O5-C16	1.188(2)
N1-C6	1.434(2)	N1- C10	1.393(3)
N1-C7	1.393(2)	O7-C7	1.207(2)
C9-C8	1.531(3)	C9-C10	1.504(3)
C7-N1-C6	124.8(2)	C7-N1-C10	112.4(2)
C6-N1-C10	122.8(2)	N1-C7-O7	124.6(2)
C13-C12-C11	111.9(2)	O7-C7-C8	128.0(2)
N1-C7-C8	110.3(2)	O1-C15-O4	123.9(2)
C12-C13-C14	95.14(7)	N1-C7-C8-C11	152.3
N1-C7-C8-C9	21.3	C8-C9-C14-C13	45.4
C14-C9-C8-C11	−37.0	C14-C9-C10-N1	−103.6



Scheme 5. The reaction mechanism of the nucleophilic addition reaction of AcO⁻ to epoxy alcohol **1.**

according to the ^{1}H and ^{13}C NMR spectrum of the crude product. However, which isomer was formed could not be determined from the NMR spectra of the compound. Although it was determined from the NMR spectra of the triacetate molecules **4** that a single isomer was formed, the exact configuration of the molecule was determined by X-Ray analysis of the molecule **4c** and it was determined that the C-3 type isomer was formed (Fig. 1). In these reactions, C-3 regioselective ring-opening products were obtained. Thus, epoxy alcohols were converted into the corresponding 1,2,3-triacetate derivatives in a single step by the hydride transfer method.

The exact conformation and structure of the 1,3-dioxo-2-phenyl-octahydro-1*H*-isoindole-4,5,6-triyl triacetate (**4c**) was confirmed by X-ray diffraction analysis. The molecule **4c** was crystallized monoclinic P2$_1$/n space group in racemic form, and only one enantiomer is seen in the asymmetric unit (Fig. 1). Selected geometric parameters are given in Table 1. It consists of fused cyclohexane and heterocylic pyrrolidine rings with substituted -OAc, phenyl and carbonyl oxygen atoms. Here, the cyclohexane ring in the chair shape, which is the most stable conformer. In this cycle C—C single bonds are in the range of 1.513–1.532(3) Å. The pyrrolidine rings are in envelope conformation. Maximum deviation from meanplane of C9/C10/N1/C7 for atom C8 is 0.142 Å. OAc units are *cis-trans* manner with respect to each other and the bond lengths of O1-C12 1.447(3) Å, O3-C13 1.443 Å and O3-C14 1.445 Å, respectively. C9-H•••O5 [*D*•••*A* = 3.302(3) Å] *H*-bond is an important intermolecular interaction. Although there is a phenyl ring in the structure, there are no possible stacking π-π interactions in the crystal lattice. vdW interactions contribute to the formation of a stable structure.

Once the exact configuration was determined, the formation of the C-3 type isomer was a surprise for us. This result shows that reaction conditions are an important factor in terms of regioselectivity. Because in our previous study, [3] the opening reaction of epoxy alcohols with nucleophiles was carried out at low temperature (at 0–25 °C) and C-2 type isomers were obtained. Thus, it was observed that the reactions proceeded in a kinetically controlled manner depending on the transition state of regioselectivity. Unlike the previous study, the ring opening reaction with acetate ion was carried out at high temperature (at 139–140 °C) and C-3 type isomer was obtained. When both results are evaluated, it clearly shows that the reaction conditions significantly affect the regioselectivity. Therefore, it was decided to perform theoretical calculations to explain the formation of C-3 type isomers and compare with the results of the previous study. The results of the theoretical calculations show that the regioselectivity depends on the product stability and the reaction proceeds in a thermodynamically controlled manner.

Examining the predicted reaction mechanism, the acetate anion (AcO⁻) can bind to the C-2 or C-3 carbons of the epoxy alcohol **3** by nucleophilic attack (Scheme 5). With the nucleophilic attack of the AcO⁻ on the C-2 carbon of epoxy alcohol **3**, shown as pathway B, the product **5b** is formed, while with its attack on the C-3 carbon, denoted as pathway A, the product **5a** is obtained (Scheme 5). In order to better understand the regioselectivity in the ring opening of epoxy alcohol **3** with AcO⁻ and NaBH$_4$, we have also performed theoretical computations. For this aim, the geometry optimization and harmonic vibrational frequency computations for all stationary point structures were performed using density functional theory, the B3LYP functional [9] with 6–31+*G*(d,p) basis set [10]. Note that for the TS between A and B, we use the notation A/B throughout the article. All computations were carried out with the Gaussian 09 software [11].

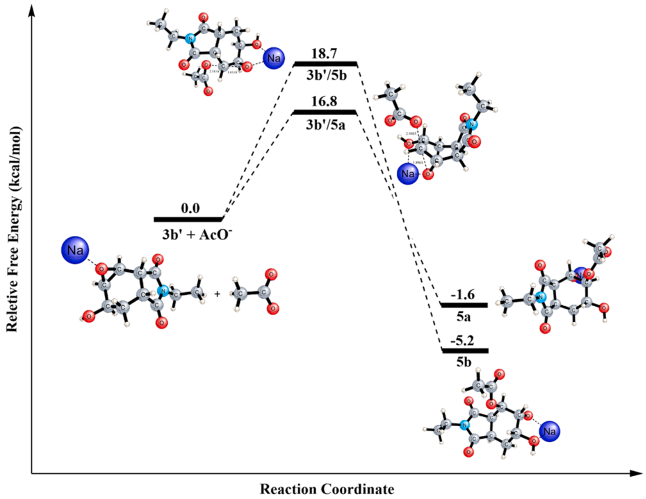
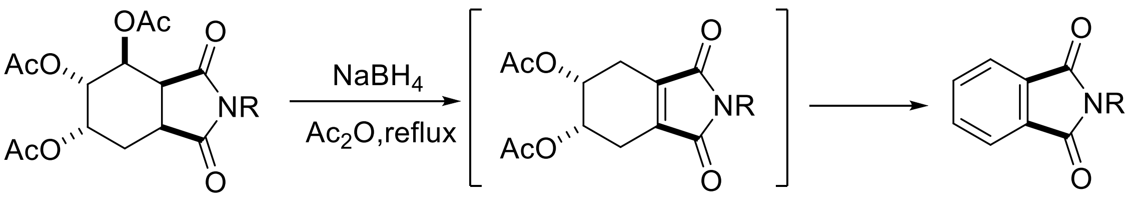


Fig. 2. Relative free energy profile (at 413.15 K) for the reaction of epoxy alcohol **3** with AcO⁻ and NaBH$_4$ at the B3LYP-6–31+*G*(d,p) level.

According to the computational results, the computed free energy barriers for the **3b'/5a** and **3b'/5b** are 18.7 and 16.8 kcal/mol, respectively, while the computed reaction free energies for **5a** and **5b** are −5.2 and −1.6 kcal/mol, respectively. These results indicate that the relevant reaction takes place under thermodynamic control, and in the nucleophilic addition reaction of AcO⁻ to epoxy alcohol **3**, AcO⁻ prefers the C-3 carbon in regioselectivity. Our results are in good agreement with experimental findings Fig. 2.

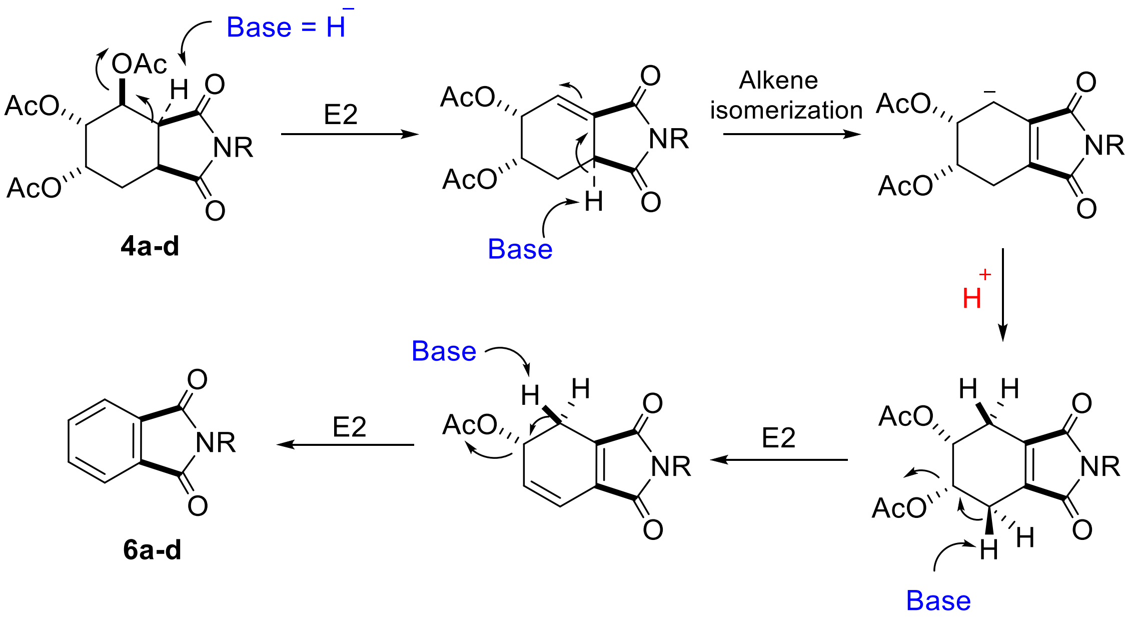
On the other hand, it was determined that second products were formed in the reaction medium as the reaction time prolonged. As a result of the spectrum analysis, it was determined that the products formed were secondary products of triacetates.

Secondary products were observed in all groups linked to the nitrogen atom. It was determined that these secondary products were phthalimide derivatives from the NMR spectra of the molecules. Especially in the reaction of the two compounds with NaBH$_4$, diacetates **6a** and **6c**, the precursor compounds of the phthalimide derivative, were obtained. The structures of compounds **6a** and **6c** were assigned by spectroscopic methods. The symmetry in the compounds **6a** is clearly seen from ^{1}H and ^{13}C NMR. The methyl protons of acetate resonate as singles at δ = 2.08 ppm. Protons at carbons C-5 and C-6 to which acetoxy groups are attached appear as quasi-triplets at δ = 5.28 ppm. Due to the symmetry in molecule **6a**, in the ^{13}C NMR spectrum, acetate carbonyl carbons, carbonyl carbons in the imide ring and olefinic carbons have a single signal group at δ = 170.10, 169.63, 138.36 ppm respectively, and



4 **6** **7**

Scheme 6. Elimination of triacetate compounds **4a-d** in the presence of NaBH$_4$.



4a-d

Scheme 7. Proposed mechanism for the formation of phthalimide derivatives **6a-d**.

a total of 7 lines support the structure of the molecule **6a**. Additionally, it was determined that the resulting diacetates were converted into phthalimide derivatives when reacted with NaBH$_4$ in acetic anhydride (Scheme 6).

After determining the structures of the secondary products and their precursor compounds, the formation mechanisms of both the precursor compounds and the resulting products are discussed in relation to the product structures. We propose that the reaction proceeds *via* the mechanism given in Scheme 7.

4. Conclusions

In conclusion, we studied the reaction of isoindole-1,3-dione **3** with NaBH$_4$/Ac$_2$O system and performed an efficient synthesis of new derivatives of isoindole-1,3-dione with triacetoxy functional groups at the 4,5,6-position of the cyclohexane ring in isoindole-1,3-dione structure. It is envisaged that this method will have the potential to be widely used to arrive at molecules containing triacetoxy groups from related epoxy alcohols in one step. Furthermore, we have performed C-3 type ring opening reaction of epoxy alcohols under mild conditions. In this context, we have explained regioselectivity of epoxy alcohols **3** by theoretical computations. It was determined that regioselectivity depends on the stability of the product formed and the reactions proceed in a thermodynamically controlled manner. Phthalimide derivatives **6** formed depending on the reaction time are secondary products of triacetates. Additionally, the formation mechanism of the secondary product phthalimide derivatives formed in the reactions is discussed and the formation mechanism is proposed.

CRediT authorship contribution statement

Ozlem Gundogdu: Writing – original draft, Investigation. **Abdurrahman Atalay:** Software, Formal analysis. **Ertan Şahin:** Software, Formal analysis. **Yunus Kara:** Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2024.138767.

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