Stereoselective Synthesis of \(\textit{endo}\)-7-Halo-3-Oxo-2-Azabicyclo[4.1.0]Heptanes by Reductive Hydrodehalogenation of \(\textit{gem}\)-Dihalocyclopropanes

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Abstract: The reduction of \(\textit{7-gem}\)-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes with metallic zinc yielded stereoselective synthesis of novel heterocyclic \(\textit{endo}\)-7-halo-3-oxo-2-azabicyclo[4.1.0]heptanes in good to high yields without any evidence for the formation of corresponding \(\textit{exo}\)-isomers. The prepared heterocyclic compounds were characterized by various techniques and their stereochemistry was established on the basis of the values of the coupling constants for H-1, H-5, H-6 and H-7 by recording homonuclear spin-spin decoupled \(^1\)H NMR spectra. The developed protocol has many advantages such as simple reaction conditions, lower cost, high yields, and selective synthesis of novel heterocyclic cyclopropyl compounds present in a large number of biologically active natural products and pharmaceutical compounds.

Keywords: Cyclopropane derivatives, Heterocyclic compound, Monohydrodehalogenation, Reduction, Stereoselective synthesis,

1. INTRODUCTION

The heteroatom-substituted cyclopropane derivatives owing to their unique steric and electronic properties are used extensively in biomedicine and are also present in a wide range of biologically active natural and unnatural compounds [1-5]. Monohalocyclopropanes, in particular, are valuable synthetic intermediates which can be converted into a range of acyclic, carbocyclic and heterocyclic systems through the reactions such as ring opening, ring-enlargement and metallation [6]. Nevertheless, direct access of monohalocyclopropanes by the reaction of monohaloarene to alkene seems to be limited to a few methods [7, 8]; due to the poor selectivity and difficult synthesis of monohaloarenes. Whereas the addition of dihalocarbene to an alkene followed by subsequent reduction of the \(\textit{gem}\)-dihalo-cyclopropane into a monohaloarene via hydrodehalogenation is a simple and efficient approach for the preparation of these classes of compounds [9, 10]. In addition, the dichlorocyclopropanation [11, 12] followed by subsequent reduction [13] also found applications in the sphere of \(P\)-heterocycles. Although, a variety of reducing agents such as tributyltin hydride, lithium aluminium hydride, alkali metals in liquid ammonia, alkyl lithium followed by treatment with an alcohol, potassium dimethyl phosphate, Grignard reagents, diethyl phosphate in the presence of triethylamine, sodium dimethyl sulfoxide in DMSO, low-valent vanadium and diethyl phosphonate or triethyl phosphate, hydrindene hydrate and Raney nickel have been reported in the literature to accomplish this transformation [14-17]. However, most of the methods have certain drawbacks such as limited availability, toxicity and expensive nature of the reagents. Zinc in its zero valence state shows important properties and has been extensively used as a potential reductant in hydrodehalogenation reactions. Yamanaka \textit{et al.} [18] reported an efficient and simple methodology for the reduction of gem-dihalo-cyclopropanes to monohalo-cyclopropanes by using zinc powder in ethyl alcohol or amyl alcohol containing 10% of potassium hydroxide.

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1,2,3,4-Tetrahydropyridin-2-ones \(^1\), easily accessible from reaction of \(1\)-aza-1,3-butadiene with \(2\)-oxazolin-5-ones, are typical enamides containing pyridin-2-one ring, comprises of an important feature of many naturally occurring alkaloids and biologically active substances [19]. Cyclopropanation of these compounds with diazoacetates [20] and trimethylsilyldiazomethane [21] to prepare novel bicyclic heterocycles has been reported, however, to the best of our knowledge there is no literature report on the selective synthesis of monohalo-cyclopropanes of 1,2,3,4-tetrahydropyridin-2-one.

Here we report a simple and efficient approach for the stereoselective synthesis of novel bicyclic \(7\)-halo-3-oxo-2-azabicyclo[4.1.0]heptanes \(^3\) by the monohydrodehalogenation of gem-dihalo-cyclopropanes \(^2\) by using Zn powder in alcoholic potassium hydroxide as reducing agent (Scheme 1). The prepared heterocyclic compounds have been characterized by several techniques like IR, \(^1\)H & \(^13\)C NMR and MALDI spectral analysis. The stereochemistry of the \(7\)-halo-3-oxo-2-azabicyclo[4.1.0]heptanes \(^3\) & \(^4\) was determined by homonuclear spin-spin decoupled \(^1\)H NMR spectral analysis and was assigned to be \(cis\) (endo) on the basis of the values of the coupling constants for H-1, H-5, H-6 and H-7.

2. EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The \(^1\)H NMR spectra were recorded on Bruker 300 MHz, 400 MHz spectrometers and chemical shift values were recorded in \(\delta\) units (parts per million) relative to Me\(_2\)Si as internal standard. IR spectra were recorded on a Perkin Elmer 1760X FTIR spectrometer in potassium bromide disc or neat thin film. Mass spectra were recorded on matrix assisted laser desorption ionization (MALDI) mass spectrometer at Instrumentation Centre of National Institute of Pharmaceutical Education and Research.

2.1. Materials

Cinnamaldehyde was purchased from Merck chemicals and distilled before use. All the amines used were commercially available and purchased from Aldrich. DL-\(\alpha\)-alanine and Zn dust were pur-
2.2. Reaction of 1,2,3,4-tetrahydropyridin-2-ones 1 with dibromocarbene (typical procedure) [23]

To a stirred solution of pyridone (0.03 mol) in dichloromethane (15 ml) was added bromoform (4 ml) and benzyl triethylammonium chloride was pur-
distilled before use. Benzyl triethylammonium chloride was pur-
died sodium sulphate. After removal of dichloromethane and

water layer was discarded and dichloromethane layer was dried on

to it resulted in 7-gem-dibromo-3-oxo-2-azabicyclo[4.1.0]

heptanes as white crystalline solid. The reaction times and the

yields of the products are mentioned in the Table 1. All the com-

pounds were characterized by IR and 1H & 13C NMR spectral analy-
sis. Spectral analysis data of the prepared compounds are given as

below:

Table 1. Dihalocyclopropanation of 1,2,3,4-tetrahydropyridin-2-ones 1.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>CH₃</td>
<td>72</td>
<td>85</td>
</tr>
<tr>
<td>2b</td>
<td>C₆H₁₁</td>
<td>72</td>
<td>83</td>
</tr>
<tr>
<td>2c</td>
<td>CH₃</td>
<td>96</td>
<td>30</td>
</tr>
<tr>
<td>2d</td>
<td>CH₂OC₆H₅(p)</td>
<td>96</td>
<td>32</td>
</tr>
<tr>
<td>2e</td>
<td>CIC₆H₅(p)</td>
<td>96</td>
<td>25</td>
</tr>
</tbody>
</table>

*Reaction conditions: substrate (0.03 mol), CH₂Cl₂ (15 ml), halohorm (3-4 ml), TEBA (0.001 mol), ice-cold, 50% NaOH solution (2.5 g) at rt; isolated yields.


2.3. Product Characterization Data

4-benzoylamino-7,7-dichloro-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2a (Table 1, entry 1): White crystalline solid. Mp 197-199 °C; IR (KBBr): 3270, 1690, 1648 cm⁻¹. 1H NMR (CDCl₃, δ) 1.50 (s, 3H), 2.87 (dd, 1H, J = 10 Hz, 8Hz, CH₃), 3.52 (d, 1H, J = 10 Hz, NCH), 7.12 (s, 1H, NCH₃), 7.12 (s, 1H, 7.29-7.50 (m, 8H), 7.68 (m, 2H); 13C NMR (CDCl₃, δ): 15.5 (CH₃), 21.6 (CH₄), 34.1 (CH₃), 35.0 (CH), 39.2 (CH), 55.0 (-CO), 124-127 (Ar-C), 162.0 (C=O), 169.0 (CO).

4-benzoylamino-7,7-dibromo-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2b (Table 1, entry 1): White crystalline solid. Mp 202-204 °C; IR (KBBr): 3270, 1689, 1648 cm⁻¹. 1H NMR (CDCl₃, δ): 1.50 (s, 3H, CH₃), 2.87 (dd, 1H, J = 10 Hz, 8Hz, CH₃), 3.52 (d, 1H, J = 10 Hz, NCH), 7.12 (s, 1H, NCH₃), 7.12 (s, 1H, NH), 4.73 (d, 1H, J = 8Hz, ArCH), 7.28-7.48 (m, 8H, ArH), 7.70 (m, 2H, ArH). 13C NMR (CDCl₃, δ): 13.5 (CH₃), 21.6 (CH₄), 33.5 (CH₃), 39.9 (CH), 45.6 (-CO), 124-127 (Ar-C), 162.0 (C=O), 168.0 (CO).

4-Benzoylamino-2-cyclohexyl-7,7-dichloro-4-methyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2c (Table 1, entry 2): White crystalline solid. Mp 210-212 °C; IR (KBBr): 3270, 1689, 1646 cm⁻¹. 1H NMR (CDCl₃, δ): 1.21-1.76 (m, 13H, cyclohexyl-CH₂), 2.87 (dd, 1H, J = 10 Hz, 8Hz, CH₃), 3.52 (d, 1H, J = 10 Hz, NCH), 7.12 (s, 1H, NCH₃), 7.12 (s, 1H, NH), 4.73 (d, 1H, J = 8Hz, ArCH), 7.28-7.48 (m, 8H, ArH), 7.70 (m, 2H, ArH). 13C NMR (CDCl₃, δ): 13.5 (CH₃), 21.6 (CH₄), 33.5 (CH₃), 39.9 (CH), 45.6 (-CO), 124-127 (Ar-C), 161.5 (C=O), 164.0 (CO).

4-Benzoylamino-2-cyclohexyl-7,7-dibromo-4-methyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2d (Table 1, entry 2): White crystalline solid. Mp 214-217 °C; IR (KBBr): 3270, 1689, 1645 cm⁻¹. 1H NMR (CDCl₃, δ): 1.21-1.76 (m, 13H, cyclohexyl-CH₂), 2.86 (dd, 1H, J = 10 Hz, 8H, CH₃), 3.45 (s, 1H, cyclohexyl-H, CH₃), 3.53 (d, 1H, J = 10 Hz, NCH), 4.73 (d, 1H, J = 8Hz, ArCH), 7.12 (s, 1H, NH), 7.27-7.50 (m, 8H, ArH), 7.68 (m, 2H, ArH). 13C NMR (CDCl₃, δ): 13.5 (CH₃), 15.2 (CH₂), 20.3 (CH₃), 21.2-24.7 (cyclohexyl-CH₂), 28.8 (CH₂), 30.4 (CH₃), 31.5 (CH₂), 38.5 (CH₃), 55.4 (-CO), 124-129 (Ar-C), 161.5 (C=O), 164.2 (CO).

4-benzoylamino-7,7-dichloro-2,5-diphenyl-4-methyl-3-oxo-2-azabicyclo[4.1.0]heptane 2e (Table 1, entry 3): White crystalline solid. Mp 190-191 °C; IR (KBBr): 3270, 1690, 1645 cm⁻¹. 1H NMR (CDCl₃, δ): 1.65 (s, 3H), 3.05 (dd, 1H), 4.13 (d, 1H), 4.82 (d, 1H), 7.25-7.51 (m, 14H), 7.71 (m, 2H). 13C NMR (CDCl₃, δ): 15.8 (CH₃), 23.7 (CH₃), 38.7 (CH₃), 55.0 (-CO), 125-128 (Ar-C), 161.2 (C=O), 165.0 (CO).

4-benzoylamino-7,7-dibromo-2,5-diphenyl-4-methyl-3-oxo-2-azabicyclo[4.1.0]heptane 2e' (Table 1, entry 3): White crystalline solid. Mp 200-201 °C; IR (KBBr): 3270, 1690, 1647 cm⁻¹. 1H NMR (CDCl₃, δ): 1.65 (s, 3H, CH₃), 3.04 (dd, 1H, J=7Hz, CH), 4.13 (d, 1H, J=9.8 Hz, ), 4.82 (d, 1H, J = 7Hz, ArCH), 7.25-7.51 (m, 14H,
ArH and NH3), 7.72 (m, 2H, ArH), 1.65 (s, 3H, CH3), 4.12 (d, 2H), 7.25-7.52 (m, 13H), 7.72 (m, 2H). 13C NMR (CDCl3, δ): 15.2 (CH2), 20.3 (CH), 35.3 (CH3), 40.2 (CH), 55.0 (-C), 115.6-125.0 (Ar-C), 162.0 (C=O), 164.0 (CO).

4-Benzylamino-2-p-chlorophenyl-7,7-dichloro-4-methyl-3-oxo-2-azabicyclo[4.1.0]heptane [2e] (Table 1, entry 5): White crystalline solid. Mp 244-252 °C (IR (KBr): 3270, 1690, 1646 cm⁻¹. 1H NMR (CDCl3, δ): 1.65 (s, 3H, CH3), 4.12 (d, 1H), 4.82 (d, 1H), 7.25-7.52 (m, 13H), 7.72 (m, 2H). 13C NMR (CDCl3, δ): 14.9 (CH3), 21.3 (CH), 35.5 (CH3), 40.2 (CH), 54.5 (-C), 116.0-125.0 (Ar-C), 162.0 (C=O), 165.1 (CO).

2.4. Reduction of 7-gem-dibromo-3-oxo-2-azabicyclo[4.1.0]heptane (General Method)

The 7-gem-dibromo-3-oxo-2-azabicyclo[4.1.0]heptane (1 mmol) was added to 15 ml of ethanol containing potassium hydride (26.7 mmol, 1.5 g) and zinc (46.1 mmol, 3 g) and the mixture was stirred at 80 °C for the time given in Table 3. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered and solvent was removed under vacuum. The residue thus obtained was dissolved in dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulphate and solvent was removed in vacuo. The residue thus obtained was purified by column chromatography on silica using n-hexane/ethyl acetate (8:2) as eluent. The results of these experiments are summarized in Table 2. All the products were fully characterized by their physical and spectral analysis and the data obtained are given as follows:

2.5. Product Identification Data

4-Benzylamino-7-endo-bromo-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane [4a]: white crystalline solid, mp 250-251 °C (recrystallized with benzene). IR (KBr): 3270, 1689, 1650 cm⁻¹. 1H NMR (CDCl3, δ): 1.21-1.80 (m, 13H, CH6H10OH and CH3), 2.04 (dd, 1H, J = 7.2 Hz, 8.0 Hz, 8.8 Hz, ArCH), 2.91 (dd, 1H, J = 5.2 Hz, 8.8 Hz, CHBr), 3.34 (dd, 1H, J = 5.2, 8.0Hz, NCH), 2.94 (m, 1H, NCH6H10OH), 4.65 (dd, 1H, J = 7.2 Hz, ArCH), 5.76 (s, 1H, NH), 7.64-7.75 (m, 10H, ArH). 13C NMR (CDCl3, δ): 15.2 (CH2), 21.3 (CH), 37.7 (CH3), 40.5 (CH), 55.0 (-C), 122-127 (Ar-C), 160.5 (C=O), 163.0 (CO). MS m/z 437 (M⁺+1). Anal Caled for C26H23N2O2Br: C, 72.46, H, 6.69, N, 6.41, Cl, 8.11. Found: C, 72.46, H, 6.65, N, 6.37, Cl, 8.18.

4-Benzylamino-7-endo-chloro-2-cyclohexyl-4-methyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane [3b]: white crystalline solid, mp 270-285 °C (recrystallized with benzene). IR (KBr): 3282, 1692, 1644 cm⁻¹. 1H NMR (CDCl3, δ): 1.21-1.80 (m, 13H, CH6H10OH and CH3), 2.04 (dd, 1H, J = 7.2 Hz, 8.0 Hz, 8.8 Hz, ArCH), 2.91 (dd, 1H, J = 5.2 Hz, 8.8 Hz, CHBr), 3.34 (dd, 1H, J = 5.2, 8.0Hz, NCH), 2.94 (m, 1H, NCH6H10OH), 4.65 (dd, 1H, J = 7.2 Hz, ArCH), 5.76 (s, 1H, NH), 7.64-7.75 (m, 10H, ArH). 13C NMR (CDCl3, δ): 12.5-15.5 (cyclohexyl-CH2), 20.2 (CH), 21.6 (CH2), 22.3 (CH3), 23.0 (CH3), 30.5 (CH2), 32.5 (CH), 34.9 (CH), 40.5 (CH), 55.0 (-C), 125-128 (Ar-C), 161.5 (C=O), 164.0 (CO). MS m/z 481, 483 (M⁺+1). Anal Caled for C26H23N2O2Cl: C, 72.47, H, 5.38; N, 6.50; Cl, 8.23. Found: C, 72.44; H, 5.30; N, 6.56; Cl, 8.30.

4-Benzylamino-7-endo-bromo-2,5-diphenyl-4-methyl-3-oxo-2-azabicyclo[4.1.0]heptane [3c]: white crystalline solid, mp 264-265 °C (recrystallized with benzene). IR (KBr): 3300, 3010, 1689, 1651 cm⁻¹. 1H NMR (CDCl3, δ): 1.64 (s, 3H, CH3), 2.22 (m, 2H), 3.43 (m, 2H), 4.88 (d, 1H, J = 7.6 Hz, 7.6 Hz), 5.79 (s, 1H, 7.26-7.66 (m, 15H). 13C NMR (CDCl3, δ): 15.2 (CH2), 21.5 (CH), 31.9 (CH), 37.2 (CH), 40.5 (CH), 55.0 (-C), 121.5-126.0 (Ar-C), 164.0 (C=O), 166.5 (CO). MS m/z 437 (M⁺+1). Anal Caled for C26H23N2O2Cl: C, 72.47, H, 5.38; N, 6.50; Cl, 8.23. Found: C, 72.44; H, 5.30; N, 6.56; Cl, 8.30.
3. RESULTS AND DISCUSSION

The cyclopropanation of a variety of 1,2,3,4 tetrahydropyridones with dihalocarbene (dibromo or dichloro) generated from haloform (bromoform or chloroform) and 50% sodium hydroxide in two-phase system by using the catalytic amount of benzyltriethylammonium chloride (TEBA) afforded the corresponding 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes 2 as white crystalline solids in high yields (Scheme 2). The results of these experiments are summarized in Table 1.

Next, we studied the reductive monohydrodehalogenation of the synthesized 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes 2. At first we performed the reaction with 4-benzoylaminono-7-gem-dichloro-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2a using Zn and KOH in the presence of ethanol as solvent at room temperature. The reaction was found to be very slow and yielded a very poor yield of the desired monohalocyclopropane. However, when the reaction temperature was raised to 80 °C, the same could be completed within 3h and afforded 72 % yield of the 4-benzoylamino-7-endochloro-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 3a, after purifying the compound by column chromatography (silica gel). The structure of 4-benzoylamino-7-endochloro-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 3a was assigned on the basis of elemental and spectral analysis. The IR (KBr) spectra showed bands characteristic of NH and amido groups respectively in the region 3269 cm⁻¹ and 1645 cm⁻¹, 1H NMR spectra showed bands of NH and amido groups respectively in the region 3269 cm⁻¹, 1645 cm⁻¹ in IR spectra and values of coupling constants of H-1, H-5, H-6 and H-7 in homonuclear spin-spin decoupled ¹H NMR spectra again revealed the cis (endo) configuration of the product was established on the basis of the coupling constants of H-1, H-5, H-6 and H-7, which were determined by recording homonuclear spin-spin decoupled ¹H NMR spectra (Fig. 1). The configuration of protons H-1, H-6, H-7 was found to be cis to each other, thus the stereochemistry of the product was assigned as endo. The MALDI spectra of the compound showed (M⁺+1) at m/e 369 and the presence of another peak at m/e 371 of roughly 3:1 intensity indicating the presence of chlorine atom.

The cyclopropanation of a variety of 1,2,3,4 tetrahydropyridones with dihalocarbene (dibromo or dichloro) generated from haloform (bromoform or chloroform) and 50% sodium hydroxide in two-phase system by using the catalytic amount of benzyltriethylammonium chloride (TEBA) afforded the corresponding 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes 2 as white crystalline solids in high yields (Scheme 2). The results of these experiments are summarized in Table 1.

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Similarity, reduction of 4-benzoylaminono-7-gem-dibromo-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 2a' was carried out using Zn and KOH in the presence of ethanol under similar reaction conditions. The product was separated from the reaction mixture by usual work-up procedure followed by column chromatography on silica gel. The structural assignment of the product 4-benzoylaminono-7-endobromo-2,4-dimethyl-3-oxo-5-phenyl-2-azabicyclo[4.1.0]heptane 3a' was again determined by elemental as well as spectral data. The presence of characteristics bands of NH and amido groups respectively in the region 3269 cm⁻¹, 1685, 1647 cm⁻¹ in IR spectra and values of coupling constants of H-1, H-5, H-6 and H-7 in homonuclear spin-spin decoupled ¹H NMR spectra again revealed the cis (endo) configuration of

![Fig. 1. Structural assignment of 3a.](image-url)
the 3a' (Fig. 2). Further, the MALDI spectra of the compound showed (M+1) at m/e 413 and the presence of another peak at m/e 415 of roughly equal intensity indicated the presence of bromine atom.

Next, the reaction was extended by using a variety of 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes 2 as substrates under described reaction conditions. All the substrates were selectively reduced to the corresponding 7-halo-3-oxo-2-azabicyclo[4.1.0]heptanes and afforded endo isomers 3 exclusively without any evidence of the formation of exo isomer 4 and 3-oxo-2-azabicyclo[4.1.0]heptanes 5 which could arise from the complete reduction of 7-gem-dibromo-3-oxo-2-azabicyclo[4.1.0]heptanes. Results of these experiments are presented in Table 2. In general, gem-dihalocyclopropanes having alkyl group on ring nitrogen were found to be more reactive and afforded products in high yield within short reaction times.

4. CONCLUSION

In summary, we have developed a simple yet efficient approach for the synthesis of novel heterocyclic compounds 7-halo-3-oxo-2-azabicyclo[4.1.0]heptanes with endo-selectively in high yields using dihalocyclopropanation of 1,2,3,4-tetrahydropyrimidinones followed by their reduction with metallic zinc under very mild reaction conditions. The reaction was found to be highly stereoselective and afforded the corresponding endo-products exclusively without any evidence for the formation of exo-isomers.

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REFERENCES


Table 2. Reductive monohydrodechlorination of 7-gem-dihalo-3-oxo-2-azabicyclo[4.1.0]heptanes 2.*

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R</th>
<th>Reaction Time (h)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>CH₂</td>
<td>3.5</td>
<td>72</td>
</tr>
<tr>
<td>3a'</td>
<td>CH₂</td>
<td>3.0</td>
<td>75</td>
</tr>
<tr>
<td>3b</td>
<td>C₂H₅</td>
<td>4.0</td>
<td>64</td>
</tr>
<tr>
<td>3b'</td>
<td>C₂H₅</td>
<td>4.0</td>
<td>67</td>
</tr>
<tr>
<td>3c</td>
<td>C₂H₅</td>
<td>5.0</td>
<td>59</td>
</tr>
<tr>
<td>3c'</td>
<td>C₂H₅</td>
<td>5.0</td>
<td>63</td>
</tr>
<tr>
<td>3d</td>
<td>CH₂OClC₂H₅</td>
<td>6.5</td>
<td>54</td>
</tr>
<tr>
<td>3d'</td>
<td>CH₂OClC₂H₅</td>
<td>6.0</td>
<td>58</td>
</tr>
<tr>
<td>3e</td>
<td>ClC₂H₅</td>
<td>6.0</td>
<td>56</td>
</tr>
<tr>
<td>3e'</td>
<td>ClC₂H₅</td>
<td>6.5</td>
<td>59</td>
</tr>
</tbody>
</table>

*aReaction condition: substrate (1 mmol), Zn-powder (46.1 mmol), KOH (26.7 mmol), ethanol (15 ml) at 80 °C; b Isolated yields.

![Fig. 2](image-url) Structural assignment of 3a'.


