Synthesis, dynamic $^1$H NMR and theoretical study of aryl-nitrogen single bond rotational energy barriers in highly functionalized $4H$-chromenes

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Abstract
The reactive intermediate was generated by reaction between 2,6-dimethylphenyl isocyanide and dialkyl acetylenedicarboxylates to react with $\beta$-diketones such as 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione to produce the dialkyl 2-(2,6-dimethylphenylamino)-5-oxo-5,6,7,8-tetrahydro-$4H$-chromene-3,4-dicarboxylate in fairly high yields 2a-c. The $^1$H NMR spectra of these compounds exhibited dynamic effects that are attributed to restricted rotation around the aryl-nitrogen single bond. The calculated rotational energy barrier ($\Delta G^\neq$) for their interconversion of these compounds equals (57.2, 54.0 and 55.7)$\pm2$ kJ.mol$^{-1}$, respectively. In addition, theoretical study on the basis of rotation around the aryl-nitrogen single bond was investigated using ab initio method at HF/6-31G level theory. The theoretical rotational energy barrier for these interconversion were in a good agreement with the experimental rotational energy emerged from dynamic$^1$H NMR data.

Keywords: Dynamic NMR, Restricted rotation, $4H$-Chromenes, Activation energy, CH Acids

Introduction
Multicomponent reactions (MCRs), defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been steadily gaining importance in synthetic organic chemistry.$^{1,2}$

Chromenes as a result of MCRs, have been the subject of the considerable chemical interest in the past decades because of their usefulness as biologically active agents.$^{3,4}$ Substituted $4H$-
chromens are a new class of anti-cancer compounds.\textsuperscript{5} Many studies have been reported on the synthesis of the chromene ring system.\textsuperscript{6,7} In continuing of our studies, the development of new route was made on heterocyclic systems, hence synthesis of highly functionalized pyranopyrimidines \textbf{1} accompanied by its dynamic \textsuperscript{1}H NMR was described in previous work (see Figure 1).\textsuperscript{8-13} Herein, we wish to report synthesis, dynamic \textsuperscript{1}H NMR and also theoretical study of highly functionalized 4\textit{H}-cromenes as a complementary investigation of rotation around the aryl-nitrogen single bond in compounds \textbf{2a-c}.

\textbf{Figure 1.} Synthesis of highly functionalized pyranopyrimidines.

\section*{Results and Discussion}

Initially, the 1:1 reactive intermediate was generated by reaction between 2,6-dimethylphenyl isocyanide and dialkyl acetylenedicarboxylates to react with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione to afford the dialkyl 2-(2,6-dimethylphenylamino)-5-oxo-5,6,7,8-tetrahydro-4\textit{H}-chromene-3,4-dicarboxylate \textbf{2} in fairly high yields.

The structures of \textbf{2a-c} were deduced from their elemental analysis, IR, \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate \textit{m/z} values, any initial fragmentation involve the loss of the ester moieties. The \textsuperscript{1}H and \textsuperscript{13}C NMR data for compounds \textbf{2a-c} are given in the experimental part. The \textsuperscript{1}H NMR spectrum of \textbf{2a} exhibits five singlets arising from Ar-Me\textsubscript{2} group (\textit{\delta}= 2.27), methoxy protons (\textit{\delta}= 3.67 and 3.72), NH (\textit{\delta}= 9.79) and methine protons (\textit{\delta}= 4.56) and multiplet for diastereotopic protons of 3 methylene (\textit{\delta}= 2.29–2.52) and Ar-H (\textit{\delta}= 7.11). The \textsuperscript{13}C NMR spectrum of \textbf{2a} showed eighteen distinct resonances in agreement with 4\textit{H}-chromene structure. The presence of one broad signal for the Ar-Me\textsubscript{2} group in the both \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of \textbf{2} is relevant to dynamic effect, as a result of restricted rotation around the \textit{N}-aryl bond in 25 \textdegree C.

Although we have not yet established the mechanism of the reaction between 2,6-dimethylphenyl isocyanide and dialkyl acetylenedicarboxylate in the presence of 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione, a possible explanation on the basis of the established chemistry \textsuperscript{1,13} of isocyanides has been proposed in Figure 2. It is reasonable to assume that \textbf{2} result from an initial addition of the aryl isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct by 1,3- cyclohexanedione. Then, the positively charged
ion might be attacked by the enolate anion of the 1,3-dicarbonyl compounds in a Michael addition process to afford the keteneimine 3. Under the reaction condition, 3 could be isomerized for generation of fused heterocyclic compound 2 (see Figure 2).

![Diagram of chemical reaction]

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield %</th>
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<tr>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>96</td>
</tr>
<tr>
<td>2b</td>
<td>H</td>
<td>Et</td>
<td>94</td>
</tr>
<tr>
<td>2c</td>
<td>Me</td>
<td>Me</td>
<td>93</td>
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</table>

**Figure 2.** Proposed mechanism for the reaction between 2,6-dimethyl phenyl isocyanide and dialkyl acetylenedicarboxylates and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione for generation of 4H-Chromene 2a-c.

The $^1$H NMR spectrum of 2 showed one single resonance arising from the Ar-Me$_2$ protons in CDCl$_3$ at 15 °C. It is appreciably broadened with respect to the two corresponding signals measured at ambient temperature, whereas the two single resonances of methoxy protons remain unchanged. The Ar-Me$_2$ protons coalesce at approximately −10 °C. Investigation of the $^1$H NMR spectra of 2 at variable temperatures allowed us to calculate the Gibbs free-energy barrier for the band rotation process. Using the expression $k = \pi \Delta v / \sqrt{2}$, first order rate constant ($k = 22.11 s^{-1}$) calculated for the N-aryl bond rotation in 2a at -10 °C (see Table 1). Application of the absolute rate theory with a transmission coefficient ($K$) of one, gave Gibbs free-energy barrier ($\Delta G^\neq$) of 57.2±2 kJ.mol$^{-1}$. All known sources of errors were estimated and included in employed equation. The available data were not suitable for obtaining meaningful values of $\Delta H^\neq$ and $\Delta S^\neq$, even though the errors in $\Delta G^\neq$ were not large. Effect of temperature on the rate constant was investigated on the basis of measurement of different chemical shift in a series of $^1$H NMR spectra at variable temperature. The result was too small so that changes in first order rate constant and also the Gibbs free-energy of barrier are negligible in comparison with the results obtained previously at -10 °C. In addition, the Gibbs free energies barrier equal 54.0 and 55.7±2 kJ.mol$^{-1}$ were also calculated for 2b and 2c respectively.
Table 1. Selected proton chemical shift and activation parameters for 2a-c

<table>
<thead>
<tr>
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<th>T/°C</th>
<th>C-Me δ/ppm</th>
<th>Δυ/Hz</th>
<th>k/s⁻¹</th>
<th>Tc/K</th>
<th>ΔG°/kJ.mol⁻¹</th>
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<tr>
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<td>25</td>
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<tr>
<td></td>
<td>-10</td>
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<tr>
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<tr>
<td>2c</td>
<td>25</td>
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<tr>
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<td>-10</td>
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<td>2.28</td>
<td>20</td>
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Rotational barrier of aryl-nitrogen single bond has also been calculated by ab initio method at HF/6-31G level of theory. All calculations have been performed by Gaussian 98 program package. Relative energy versus C₁C₂N₃C₄ (see Figure 3) as a dihedral angle is plotted in Figure 4 and energy Profile is also shown in Figure 5.

Figure 3. The performance of C₁C₂N₃C₄ dihedral angel in 4H-chromenes.

![Figure 3](image)

Figure 4. Relative energy in 4H-chromenes 2 (see Fig. 2) versus dihedral angels C₁C₂N₃C₄.

![Figure 4](image)

The corresponding structures, with respect to all points (a-h) in Figure 4 were drawn in Figure 6. The high jumps between abc and fgh points are corresponding to N-inversion. As can be seen, two weak intramolecular hydrogen bonds O···HC could be formed between both CO₂Me groups and the hydrogen atoms of CH₃ groups of aryl ring in structure d. Only one hydrogen
bond O···HC can be seen in structure f, because of the CO$_2$Me groups is approximately orthogonal to the phenyl ring, and there is not any possibility for intramolecular hydrogen bonding in this structure. On the basis of emerged results, from both Figures 4 and 5, the rotational energy barrier calculated around aryl-nitrogen single bond ($\Delta G^\# \cong 60$ kJ mol$^{-1}$). The result is in a good agreement with experimental rotational energy barrier which was obtained by dynamic $^1$H NMR data ($\Delta E^\# \cong 57.2 \pm 2$ kJ mol$^{-1}$).

![Dihedral Angle vs Energy Graph]

**Figure 5.** The profile energy of 4$H$-chromenes.

In conclusion, the reaction between 2,6-dimethylphenyl isocyanide and electron deficient acetylenic esters, such as dimethyl acetylenedicarboxylate (DMAD), in the presence of 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione provides a simple one-pot entry into the synthesis of polyfunctional 4$H$-chromene derivatives of potential interest. Dynamic $^1$H NMR study of compounds 2a-c confirmed a restricted rotation around the aryl-nitrogen single bond. In compound 2 with a non planar structure, rotational energy barrier around the aryl-nitrogen single bond, is less than compound 1 involving a planar structure. Furthermore, the obtained results from ab intio method at HF/6-31G level theory are in a good consistent with experimental dynamic $^1$H NMR data.
General Procedures. Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and on a Shimadzu IR-460 spectrometer, respectively. Elemental analysis for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. The $^1$H and $^{13}$C NMR spectra were measured on a Bruker DRX-500 AVANCE instrument with CDCl$_3$ as a solvent at 500.1 and 125.7 MHz, respectively. The Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. 2,6-Dimethylphenyl isocyanide, dialkyl acetylenedicarboxylates, 1,3-cyclohexanedicarboxylate, 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione
were obtained from Fluka and used without further purification. All theoretical calculations performed by Gaussian 98 program package.

**General procedure (Exemplified by 2a)**

To a stirred solution of (0.112 g, 1 mmol) 1,3-cyclohexadione and (0.15 g, 1 mmol) dimethyl acetylendicarboxylate in 6 mL CH₂Cl₂, a mixture of (0.131 g, 1 mmol) 2,6-dimethylphenyl isocyanide in 2 mL CH₂Cl₂ was added, dropwise, at −10 °C over 5 minutes. (The isocyanides are toxic compounds but the toxicity of them are less than cyanides, nevertheless the isocyanides take into the lungs by inhalation and contact with skin, therefore this work was carried out inside the polyethylene glove bags under completely air-cleaner condition). The reaction mixture was then allowed to warm up at room temperature and stand to rest on a base for 5 days. The solvent was then removed under reduced pressure and solid residue 2a was washed with 2×5 mL cold diethyl ether.

**Dimethyl 2-(2,6-dimethylphenylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (2a).** Pale yellow powder, yield 96% (0.37 g), mp 96-98 °C, IR (KBr) (νmax, cm⁻¹): 3450 (NH), 1597, 1678 and 1717 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ = 2.27 (6H, s, ArMe₂), 3.67 and 3.72 (6H, 2s, 2 OMe), 2.29-2.52 (6H, m, 3 CH₂), 4.56 (1H, s, CH), 7.11 (3H, m, Ar- H) 9.79 (1H, br s, NH…O=C) ppm. ¹³C NMR (CDCl₃): δ = 17.94 (ArMe₂), 19.82, 26.93 and 34.79 (3 CH₂), 36.73 (CH), 51.25 and 52.38 (2 OMe), 74.32 (N=C=C), 113.21 (O=C=C), 127.11, 128.02, 134.16 and 136.01 (4 C arom), 158.26 (O-C=C), 165.15 (N-C=C), 169.73 and 173.22 (2 C=O of ester), 196.13 (C=O) ppm. MS (m/z, %): 385 (M⁺, 5), 362 (100), 264 (7), 293 (13). Anal. Calc. for C₂₁H₂₃NO₆ (385): C, 65.44; H, 6.01; N, 3.63%; Found: C, 65.16; H, 5.85; N, 3.70%.

**Diethyl 2-(2,6-dimethylphenylamino)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (2b).** Yellow powder, yield 94% (0.39 g), mp 99-101 °C, IR (KBr) (νmax, cm⁻¹): 3405 (NH), 1600, 1680 and 1732 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ = 1.25 and 1.13 (6H, m, 2 OCH₂CH₃), 2.30 (6H, s, ArMe₂), 1.97–2.49 (6H, m, 3 CH₂), 4.11 and 4.24 (4H, m, 2 OCH₂CH₃), 4.55 (1H, s, CH), 7.11 (3H, m, Ar- H) 9.83 (1H, br s, NH…O=C) ppm. ¹³C NMR (CDCl₃): δ = 17.94 (ArMe₂), 19.82, 26.93 and 34.79 (3 CH₂), 36.73 (CH), 51.25 and 52.38 (2 OMe), 74.32 (N-C=C), 113.21 (O-C=C), 127.11, 128.02, 134.16 and 136.01 (4 C arom), 158.26 (O-C=C), 165.15 (N-C=C), 169.73 and 173.22 (2 C=O of ester), 196.13 (C=O) ppm. MS (m/z, %): 413 (M⁺, 3), 399 (18), 368 (3), 340 (100), 338 (5), 309 (5). Anal. Calc. for C₂₃H₂₇NO₆ (413): C, 66.81; H, 6.58; N, 3.39%; Found: C, 66.54; H, 6.61; N, 3.43%.

**Dimethyl 2-(2,6-dimethylphenylamino)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (2c).** Pale yellow powder, yield 93% (0.38 g), mp 100-103 °C, IR (KBr) (νmax, cm⁻¹): 3450 (NH), 1610, 1685 and 1740 (C=O) cm⁻¹. ¹H NMR (CDCl₃): δ = 1.00 and 1.02 (6H, s, CMe₂), 2.17 and 2.22 (4H, s, 2 CH₂), 2.22 (6H, s, ArMe₂) 3.66 and 3.75 (6H, s, 2 OCH₃), 4.53 (1H, s, CH), 7.07 (3H, m, Ar- H) 9.76 (1H, br s, NH…O=C) ppm. ¹³C NMR (CDCl₃): δ = 18.42 (2 ArCH₃), 27.08 and 29.34 (2 C-Me), 32.34 and 34.58 (2 CH₂), 40.57 (CMe₂), 50.53 (CH), 53.10 and 53.44 (2 OMe), 74.28 (N-C=C), 112.23 (O-C=C), 127.50, 128.00, 134.17 and 136.98(4 C arom), 158.40 (O-C=C), 163.55 (N-C=C), 168.71 and 173.65 (C=O) ppm...
of ester) and 196.10 (C=O) ppm. MS (m/z, %): 413 (M+, 5), 398 (12), 368 (3), 354 (22), 293 (100), 105 (5). Anal. Calc. for C_{23}H_{27}NO_6 (413): C, 66.83; H, 6.53; N, 3.39%; Found: C, 66.73; H, 6.48; N, 3.29%.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the University of Sistan & Baluchestan.

References