THERMAL REARRANGEMENTS OF 3,3-SPIROALKYLATED PYRAZOLES: RING EXPANSION AND NOVEL CASES OF SEQUENTIAL 1,5-SHIFTS

Yao-pin Yen,* Shih-Feng Chen, Zan-Cheng Heng, Jen-Chieh Huang, Li-Chun Kao, Ching-Cheng Lai, and R. S. H. Liu

Abstract - A 3,3-spiro-(cyclopentyl)pyrazole containing electron withdrawing ester groups undergoes readily ring expansion in the form of the van Alphen-Huettel rearrangement. Subsequent post van Alphen-Huettel rearrangement involved a sequence of 1,5-shifts different from that suggested earlier. Reactive intermediates have been isolated and identified. The corresponding phenyl analog does not exhibit post van Alphen-Huettel rearrangement. A rationale for the different behavior is offered. X-Ray crystallography has been applied to differentiate between structurally similar product.

INTRODUCTION

1,5-Sigmatropic rearrangement of cyclopentadiene is a well known reaction that occupies an important chapter in symmetry correlation reactions. Pyrazoles are hetero-cyclopentadienes; hence, their propensity in undergoing 1,5-shift is also well known and continued to be of an interest. Such reactions, first studied by van Alphen, later were investigated in more detail by Huettel and coworkers. Henceforth, the common alkyl rearrangements of 3-hydrogen or 3-alkylated pyrazoles (1) to the adjacent C or N centers giving respectively the 4H-pyrazoles (2) or the 1H-pyrazoles (3) are known as the van Alphen-Huettel rearrangements.
Recent works, particularly those of Warkentin and coworkers, have shown that relative importance of the two 1,5-rearrangements and in some cases of possible formation of further rearrangement products is a sensitive balance between the structure and electronic properties of the substituents. Hence, it was shown that for 3-acyl-3-alkylpyrazoles, the acyl migration to the adjacent N-center is the exclusive process taking place below room temperature while corresponding migration of an alkyl group usually happens at >150°C. The 1,5-shift was shown to take place preferentially around the pyrazole ring rather than the cyclopentadiene ring in the 3,3-spiro-pyrazole (4). And thermal rearrangement of 5 gave an unexpected product (7) in addition to the expected alkylated product (6) (corresponding to 3). Since 7 was formed at the apparent expense of the C-alkylated product (8) (corresponding to 2), it was suggested without proof that formation of 7 was achieved via two subsequent 1,5-shifts originating from 8 (a post van Alphen-Huettel rearrangement). The involvement of ion-pair intermediates for cases capable of forming stable carbocation added a new dimension to the rearrangement.

In this paper, we would like to describe a study of thermal rearrangement and ring-expansion of 3,3-spiro-(cyclopentyl)pyrazoles. Because of our ability to isolate and identify the intermediates involved in secondary rearrangements in one system, we ascertained a new reaction pathway involved in the post van Alphen-Huettel rearrangement. These results are described below.

RESULTS AND DISCUSSION

Spiro-3H-pyrazoles (9a-c) were prepared following the procedure described in the literature. Each of
the three pyrazoles in benzene solution (2.40 × 10^{-2}M) was degassed and sealed in Pyrex tubes and heated in an oil bath. Product formation was monitored using analytical HPLC. The kinetic data (Table 1, EXPERIMENTAL) followed unimolecular processes rigorously. For structural characterization, products were isolated by column chromatography from mixtures obtained from scaled up runs and identified by comparison of GC-MS, IR, {\textsuperscript{1}}H NMR and {\textsuperscript{13}}C NMR with those of authentic or similar, known compounds, supplemented by X-Ray crystallography (see Figures 1-5). Compound (9a) was studied in most detail. Its results were discussed first.

**The diester spiral analog (9a).** Compound (9a) was found to rearrange cleanly within the temperature range of 64-92°C with an activation energy of 26.3 ± 0.1 kcal/mol and a log A value of 12.8 ± 0.1. In a preparative run, after heating a sample at 90°C for 40 min, the reaction was found to be complete. Only one major product (10a) was isolated in 70 % yield. Its structure was characterized by comparison of spectral data with other van Alphen-Huettel rearranged products and by its X-Ray crystal structure (Figure 1). A trace amount of a minor product (0.4 %) was also detected which was subsequently characterized to be 11a (see below). These products are those expected from the van Alphen-Huettel rearrangement involving ring expansion of the spiro-cyclopentyl ring. At 190°C (60 min), the rearranged product mixture was found to contain, again, primarily a single, but different product (12a, 69 % isolated yield) at the complete expense of 10a while the amount of 11a increased to 8 % (Scheme 1 and Table 2).

![Scheme 1](image)

**Table 2.** Experimental Reaction Conditions and Product Yields of the Thermal Reactions of Spiro-3H-Pyrazole (9a)

<table>
<thead>
<tr>
<th>Condition</th>
<th>10a Yield (%)</th>
<th>11a Yield (%)</th>
<th>12a Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 °C 40 min</td>
<td>70</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>190 °C 60 min</td>
<td>-</td>
<td>8</td>
<td>69</td>
</tr>
</tbody>
</table>
We were able to crystallize both of the isolated 11a and 12a. Their X-Ray crystal structures (Figures 2-3) removed any ambiguity in differentiating between them. Furthermore, the relative bond lengths clearly reflect the delocalized nature of the pyrazole rings for these two compounds, expectedly different from the localized structure of the isomeric (10a). Thus, that 11a and 12a are at the energy minima of the potential surface for 1,5-shifts can be readily rationalized by aromatic resonance stabilization.

**Figure 1.** ORTEP Plots of Dimethyl 4,5,6,7-tetrahydro-3aH-indazole-3,3a-dicarboxylate (10a)

**Figure 2.** ORTEP Plots of Dimethyl 4,5,6,7-tetrahydropyrazolo-[1,5-a]pyridine-2,3-dicarboxylate (11a)
To test whether 12a originated from 10a or not, we heated a sample of 10a at a lower temperature (160 °C for 5 h). While we readily confirmed that 12a (isolated yield 66 %) indeed originated from 10a, much to our surprise, another isomer of pyrazole was also formed (13a, 19 %) (Scheme 2). But 13a was an oil, thus its structure could not be elucidated by X-Ray crystallography. Fortunately, its spectral data were most informative. Its 13C NMR spectrum exhibits three vinyl signals at 124.4, 132.5 and 149.6 ppm and two carbonyl ester carbons at 153.9 and 161.1 ppm, linked respectively to N and C-atom. These data are consistent with 13a and not with the alternative structure (14a). The latter should have one C-signal at <100 ppm as in the structurally similar 5,6,7,7a-tetrahydro-3-methyl-7a-phenyl-4H-indazole (14b). Finally with an isolated sample of 13a, we found that upon heating (>160°C for 5 h), it was cleanly converted to 12a (89% yield).

Scheme 2

Figure 3. ORTEP Plots of Dimethyl 4,5,6,7- tetrahydroindazole-1,3-dicarboxylate (12a)
The sequence of reactions shown below summarizes the thermal reactions of 9a. Indeed similar to that proposed previously, the unexpected product (12a) originated from the van Alphen-Huettel product (10a). However, the course of this post van Alphen-Huettel rearrangement is apparently two consecutive 1,5-shifts to 13a followed by another N,N-1,5-shift to 12a. This is different from the proposed mechanism involving two 1,5-shifts with compound (14a) being the reactive intermediate.

It is interesting that 10a prefers the longer pathway of three 1,5-shifts to reach the final product. We suspect that the preference for the three consecutive “clockwise” 1,5-shifts rather than the two consecutive “counterclockwise” 1,5-shifts for the 10a to 12a is not controlled by thermal stability (or the lack of it) of the intermediate (14a) of the latter process. Rather, it is controlled by the conformation of the six-membered ring which makes 1,5-shifts across the ring-junction (the first step of the “counterclockwise” sequence) more difficult than the alternative “clockwise” 1,5-shift. However, it should be emphasized that the isolation of intermediate (13a) does not exclude a parallel route involving the unisolable 14a, especially in other analogous systems.

**Other spiro-3H-pyrazoles (9b and 9c).** For the hydrogen analog (9b), upon heating at 140°C for 30 min, the compound was converted completely to the final post van Alphen-Huettel product (12b) (95%). On the other hand, for the diphenyl analog (9c), a much higher temperature (230°C, 2 min) was required for the van Alphen-Huettel rearrangement (activation energy = 32.1 ± 0.9 kcal/mol and log A = 13.8 ± 0.6) giving products (10c) and (11c) (Scheme 3 and Table 3). Their structures were also confirmed by their X-Ray crystal structures (Figures 4-5). The observed difference in rates (R = H > R = CO₂Me > R = C₆H₅) are clearly not a reflection of relative migratory aptitude (however, see below for additional discussion) because all these cases involved the migration of the same alkyl group. Instead, it appears to be controlled by product stability. In the phenyl case, the first step of 1,5-shift yielded a product with the loss of resonance stabilization of a stilbene unit; the diester case, the loss of conjugation of one
of the two ester functional groups; and in unsubstituted 9b, no loss in resonance stabilization. These conclusions have since been confirmed by calculations.\textsuperscript{11}

**Scheme 3**

![Scheme 3](image)

**Table 3.** Experimental Reaction Conditions and Product Yields of the Thermal Reactions of Spiro-3\textit{H}-Pyrazoles (9b-c)

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>Condition</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>b</td>
<td>H</td>
<td>140 °C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 min</td>
<td>10 - - 95</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>230 °C</td>
<td>74 25 -</td>
</tr>
</tbody>
</table>

Furthermore, we found that prolonged heating of an isolated sample of the C-rearranged product (10c) at 230°C only resulted in its complete conversion to the N-rearranged product (11c). Interestingly, at the mid-point of this rearrangement (51 % conversion), we detected the presence of a small amount (0.11 %) of the spiro-reactant (9c). Apparently, the rearrangement of 10c to 11c involved reversion to the starting spiro structure.

**Figure 4.** ORTEP plot of 3,3a-Diphenyl 4,5,6,7-tetrahydro-3\textit{aH}-indazole (10c)
A few interesting points may be concluded from these observations. First, in this case no post van Alphen-Huettel rearrangement product was detected. We believe this is due to the fact that additional rearrangement would result in a further loss of resonance stabilization to give first, in the case of 10c, compound (15). It is apparently too high in energy. Second, the reaction pathway for 10c to 11c has been clarified. Conversion of 10c to 11c (and also 10a to 11a, previous section) involves a formal 1,3-sigmatropic reaction, a symmetry forbidden process. The sequence of consecutive symmetry allowed 1,5-shifts with intermediacy of 9c is therefore a logical alternative. The secondary rearrangement of 10c, and related compounds, provides a good measure of the migratory aptitude of the two substituents at the quaternary carbon. In the case of 10c, the result clearly shows the lower migratory aptitude of the phenyl group. Thus, it made reversion to the starting spiro-cyclopentyl system competitively possible. In the equivalent structure (10a), the ester group clearly migrates much more readily. This large difference in migratory aptitude for these two substituents is consistent with analogous examples in cyclopentadienes and other pyrazoles, favoring systems with electron deficient substituents.
In summary, because of our ability to isolate reaction intermediates in a van Alphen-Huettel rearrangement and another case of a post van Alphen-Huettel rearrangement, we were able to characterize the specific reaction pathways involved in different stages of the thermal rearrangements of the pyrazoles. A better understanding of relative product stability and migratory aptitude allowed us to rationalize the seemingly confusing and divergent pathways available to these compounds.

EXPERIMENTAL

General information. Melting point were determined on Yamaco micro melting points apparatus and are uncorrected. IR spectra were obtained on a Perkin Elmer 2000 spectrophotometer in KBr. \(^1\)H NMR spectra were determined on a Bruker AC-250 spectrometer in CDCl\(_3\) with TMS as an internal standard. High performance liquid chromatography (HPLC) was performed on a Dynamax Chromatograph equipped with Dynamax SD-200 pump and controller and a Water 486 detector.

Materials. The dimethyl 3,3-cyclopentyl-3\(H\)-pyrazole-4,5-dicarboxylate (9a), and 3,3-cyclopentyl-3\(H\)-pyrazole (9b) were prepared according to published procedures.\(^8\) 3,3-Cyclopentyl-4,5-diphenyl-3\(H\)-pyrazole (9c) was prepared in sequence of reactions similar to those of 3,3-dimethyl-4,5-diphenyl-3\(H\)-pyrazole.\(^{13}\) Hence, only characterization data are listed below.

3,3-Cyclopentyl-4,5-diphenyl-3\(H\)-pyrazole (9c)

Product (9c) was prepared following the literature\(^{13}\) procedure and recrystallized from n-hexane; yield 26 %; mp 134-135\(^\circ\)C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 1.86-2.02 (m, 6H), 2.28-2.35 (m, 2H), 7.13-7.43 (m, 8H), 7.70-7.74 (m, 2H); IR (KBr): 3056, 2969, 2870, 1454, 771, 710 cm\(^{-1}\); MS m/z (%): 274 (M\(^+\), 8), 246 (68), 218 (45), 217 (100), 203 (27), 202 (34), 178 (36); Anal. Calcd for C\(_{19}\)H\(_{18}\)N\(_2\): C, 83.21; H, 6.57; N, 10.22. Found: C, 83.33; H, 6.49; N, 10.19.

General Procedure for Thermal Rearrangement of 3\(H\)-pyrazoles (9a-c)

For preparative purpose, thermal rearrangement was carried out by heating a solution (1.5 mL, 2.40 \(\times\) \(10^{-2}\) M) of the appropriate 3\(H\)-pyrazole in benzene in a sealed pyrex tube. After the rearrangement of reactant was complete (\(>\)95 %), the products were isolated by flash column chromatography on silica gel using the solvent mixtures: n-hexane/EA = 3/1 or n-hexane/EA = 5/1 for 10a and 11a.
Characterization data of the products are listed below.

**Dimethyl 4,5,6,7-tetrahydro-3aH-indazole-3,3a-dicarboxylate (10a)**

Yield 70 %; mp 94.5-95.5°C (ethanol); ¹H NMR (CDCl₃) δ: 1.16-1.50 (m, 2H), 1.77-1.97 (m, 2H), 2.23-2.50 (m, 2H), 3.08-3.13 (m, 2H), 3.68 (s, 3H), 3.96 (s, 3H); ¹³C NMR (CDCl₃) δ: 21.1, 27.5, 28.7, 35.3, 52.8, 53.1, 70.3, 159.8, 164.4, 167.6, 180.3; IR (KBr): 2955, 2860, 1754, 1720, 1562, 1443, 1367, 1219, 1091 cm⁻¹; MS m/z (%): 238 (M⁺, 7), 206 (53), 179 (100), 163 (26), 147 (55), 135 (25), 119 (3), 91 (45); Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.61; H, 5.87; N, 11.55.

**Dimethyl 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-2,3-dicarboxylate (11a)**

Yield 0.4 %; mp 65-66°C (n-hexane); ¹H NMR (CDCl₃) δ: 1.87-1.98 (m, 2H), 2.04-2.15 (m, 2H), 3.04 (t, 2H, J= 6.3 Hz), 3.83 (s, 3H), 3.94 (s, 3H), 4.19 (t, 2H, J= 6.3 Hz); ¹³C NMR (CDCl₃) δ: 19.3, 22.6, 23.1, 48.6, 51.6, 52.5, 110.5, 143.1, 144.8, 162.7, 163.0; IR (KBr) 2961, 1736, 1717, 1303, 1077 cm⁻¹; MS m/z (%): 238 (M⁺, 22), 207 (94), 177 (22), 163 (16), 135 (10), 57 (29); Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.41; H, 5.84; N, 11.94.

**General Procedure for Thermal Rearrangement of 10a**

Dimethyl 4,5,6,7-tetrahydro-3aH-indazole-3,3a-dicarboxylate (10a) (1.5 mL × 2.50 × 10⁻² M) in benzene was degassed, sealed in pyrex tube and heated in an oil bath at 160°C for 4 h. The reaction mixture was concentrated in vacuo and the products were isolated by flash column chromatography on silica gel using the solvent mixtures: n-hexane/EA = 9/1 for 12a and 13a. Characterization data of 12a and 13a are listed below.

**Dimethyl 4,5,6,7-tetrahydroindazole-1,3-dicarboxylate (12a)**

Yield 66 %; mp 152-154°C (ethanol); ¹H NMR (CDCl₃) δ: 1.69-1.90 (m, 4H), 2.74 (t, 2H, J = 6.3 Hz), 2.98 (t, 2H, J = 6.1 Hz), 3.93 (s, 3H), 4.06 (s, 3H); ¹³C NMR (CDCl₃) δ: 21.2, 21.9, 22.0, 24.1, 52.0, 54.7, 122.3, 143.8, 144.8, 150.3, 162.5; IR (KBr) 2955, 1767, 1730, 1442, 1312, 1257, 1205, 1139, 806, 765 cm⁻¹; MS m/z (%): 238 (M⁺, 76), 206 (73), 179 (100), 147 (25), 135 (39), 59 (25); Anal. Calcd for C₁₁H₁₄N₂O₄: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.44; H, 6.03; N, 11.69.

**Dimethyl 4,5,6,7-tetrahydroindazole-2,3-dicarboxylate (13a)**

Yield 19 %; bp 65°C/0.25 torr; ¹H NMR (CDCl₃) δ: 1.77-1.85 (m, 4H), 2.63 (t, 2H, J = 6.0 Hz), 2.71 (t,
2H, J = 6.3 Hz), 3.91 (s, 3H), 4.02 (s, 3H); $^{13}$C NMR (CDCl$_3$) δ: 20.6, 22.2, 22.4, 23.4, 52.7, 55.0, 124.4, 132.4, 149.6, 153.9, 161.1; IR (neat) 2926, 2854, 1764, 1733, 1439, 1358, 1299, 1059, 804 cm$^{-1}$; HRMS calcd for C$_{11}$H$_{14}$N$_2$O$_4$: 238.09536. Found: 238.09545.

**4,5,6,7-Tetrahydroindazole (12b)**

Yield 95%; mp 78-79°C (petroleum ether); $^1$H NMR (CDCl$_3$) δ: 1.69-1.80 (m, 4H), 2.52 (t, 2H, J = 5.8 Hz), 2.65 (t, 2H, J = 5.7 Hz), 7.27 (s, 1H), 11.06 (br s, 1H); $^{13}$C NMR (CDCl$_3$) δ: 20.3, 21.9, 23.0, 23.4, 114.7, 131.5, 143.0; IR (KBr) 3160, 2931, 2852, 1443, 1342, 1087, 964, 854, 796 cm$^{-1}$; MS m/z (%): 122 (M$^+$, 35), 94 (100), 81 (4), 67 (7); HRMS calcd for C$_7$H$_{10}$N$_2$: 122.0843. Found: 122.0841.

**3,3a-Diphenyl-4,5,6,7-tetrahydro-3aH-indazole (10c)**

Yield 75%; mp 151-153°C (ether); $^1$H NMR (CDCl$_3$) δ: 1.47-1.64 (m, 2H), 1.80-1.91 (m, 2H), 2.13-2.26 (m, 2H), 2.91-2.99 (m, 1H), 3.17-3.24 (m, 1H), 7.09-7.38 (m, 8H), 7.70-7.74 (m, 2H); 13C NMR (CDCl$_3$) δ: 21.4, 26.6, 29.5, 34.6, 67.9, 125.3, 126.5, 127.1, 127.6, 127.8, 128.4, 129.5, 129.9, 130.5, 130.8, 132.5, 179.0, 183.2; IR (KBr) 3055, 2949, 2860, 1582, 1518, 1496, 1448, 1337, 772, 693 cm$^{-1}$; MS m/z (%): 274 (M$^+$, 32), 246 (81), 217 (54), 202 (20), 170 (38), 143 (87), 129 (100), 115 (29), 103 (36), 77 (29); Anal. Calcd for C$_{19}$H$_{18}$N$_2$: C, 83.18; H, 6.61; N, 10.21; Found: C, 82.90, H; 6.70; N, 10.35.

**2,3-Diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine (11c)**

Yield 11%; mp 142-144°C (ether/n-hexane); $^1$H NMR (CDCl$_3$) δ: 1.82-1.96 (m, 2H), 2.07-2.82 (m, 2H), 2.80 (t, 2H, J = 6.3 Hz), 4.28 (t, 2H, J = 6.1 Hz), 7.18-7.35 (m, 8H), 7.43-7.47 (m, 2H); $^{13}$C NMR (CDCl$_3$) δ: 20.2, 22.4, 23.2, 47.9, 116.3, 124.8, 126.1, 126.7, 127.1, 127.9, 128.2, 129.6, 130.9, 133.6, 137.9, 148.2; IR (KBr) 3048, 2950, 2863, 1600, 1542, 1496, 1431, 1347, 760 cm$^{-1}$; MS m/z (%): 274 (M$^+$, 100), 273 (42), 245 (10), 115 (8); Anal. Calcd for C$_{19}$H$_{18}$N$_2$: C, 83.18; H, 6.61; N, 10.21; Found: C, 82.90, H; 6.75; N, 10.09; HRMS calcd for C$_{19}$H$_{18}$N$_2$: 274.1470. Found: 274.1467.

For kinetic runs, benzene solutions of an appropriate pyrazole sealed in pyrex tubes were heated in a constant temperature bath. Aliquots were taken for periodic analysis by HPLC. Conditions for analysis were: hplc, Partisil-10 column, 25 cm × 4.6 mm, solvent hexane: ether = 3 : 1. Selected rate constants are listed in Table 1.
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<th>Compound</th>
<th>T (°C)</th>
<th>$10^4 \times k$ (s$^{-1}$)</th>
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<tbody>
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<td>9a</td>
<td>64</td>
<td>0.52 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>1.31 ± 0.14</td>
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<td>76</td>
<td>2.42 ± 0.05</td>
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<td></td>
<td>82</td>
<td>3.81 ± 0.01</td>
</tr>
<tr>
<td></td>
<td>92</td>
<td>11.09 ± 0.52</td>
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<tr>
<td>9c</td>
<td>130</td>
<td>2.03 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>136</td>
<td>3.50 ± 0.29</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>5.34 ± 0.32</td>
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<td></td>
<td>144</td>
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</tr>
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<td>151</td>
<td>14.44 ± 0.30</td>
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</table>

ACKNOWLEDGMENT

The authors gratefully acknowledge the National Science Council of the Republic of China for financial support and Dr. Y. J. Lee for helpful discussions.

REFERENCES


10. Conceptually a single 1,3-shift could have achieved the same results. But we believe the long accepted suprafacial 1,5-shifts for cyclopentadienes should apply here.

11. Molecular simulation using Cerius program. For example, relation energies of **9c** and **10c** were found to be 88.7 and 96.0 kcal/mol.
