

Letter to the Editor

## [3,3] Sigmatropic Rearrangement of 3-Alkynyladenines

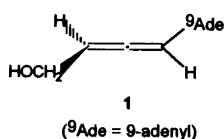
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Sigmatropic rearrangement reactions constitute an important class of carbon–carbon bond-forming transformations.<sup>1,2</sup> The [3,3] subclass (e.g. the Cope rearrangement) may involve heteroatoms, such as in the Claisen rearrangement (with oxygen), and proved to be versatile in constructing polyfunctional compounds in a stereochemically controlled way.<sup>3</sup> There is little evidence of such a rearrangement among purines. Ranganathan *et al.*<sup>4</sup> reported a few cases involving the O-6 and N-1 atoms of hypoxanthine, while Shimizu and Miyaki<sup>5</sup> have pursued some introductory studies on the alkyl migration and N-3→N-9 rearrangement properties of purines. We became particularly interested in this field owing to the antiretroviral and adenosine deaminase inhibiting adenallenes (*R*-enantiomer: **1**, Scheme 1) featuring a unique allenic moiety.<sup>6,7</sup> The challenging synthesis of an axially chiral allene from a centrally chiral alkyne on a purine substrate prompted us to investigate the [3,3] sigmatropic rearrangement of 3-alkynyladenines.

Adenine was alkylated with propargyl bromide in DMF in either the absence or presence of potassium carbonate to afford nearly exclusively pure 3- (**2**) and 9-propargyladenine (**3**), respectively, in accordance with literature data for analogous cases.<sup>8–11</sup> However, the site of alkylation was also corroborated in selective INEPT experiments<sup>12,13</sup> irradiating the methylene protons of the propargyl moiety to obtain signals at C-2 and C-4, and C-4 and C-8 atoms, respectively. Allenes **4** and **5** were prepared in a base-catalysed reaction from the corre-

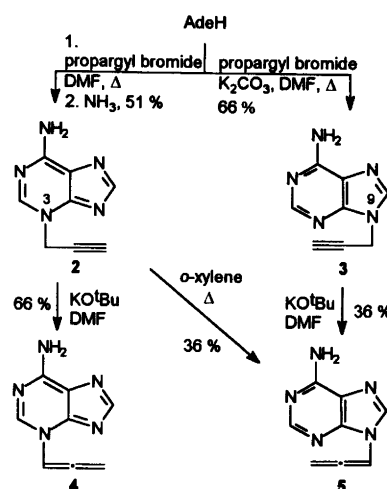


Scheme 1

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sponding alkyne, **2** and **3**, respectively (Scheme 2). Then we pursued systematic studies on the thermal behaviour of these compounds. By gradually increasing the temperature we have observed the transformation of **2** to **5** (36% on a preparative scale, at 150°C in *o*-xylene, 1.5 h), along with a very small amount of **3** (0.3%). Performing this experiment with compounds **3–5**, no significant transformations could be observed. These facts clearly suggest an N-3→N-9 [3,3] sigmatropic rearrangement of 3-propargyladenine (**2**) to 9-allenyladenine (**5**), accompanied by a minor alkyl migration (**2**→**3**).

The above transformations can be understood by comparing the heats of formation for the compounds involved (Table 1). The energy differences between the respective 3- and 9-substituted adenines are in good agreement with those of the 3*H*- and 9*H*-tautomeric forms of adenine (48.6 kJ mol<sup>-1</sup>)<sup>14</sup> and 2*H*- and 1*H*-pyrrole (54.4 kJ mol<sup>-1</sup>),<sup>15</sup> respectively. The calculations were extended to all ring-substituted propargyladenines



Scheme 2

Table 1. Calculated heats of formation for compounds 2–7.

| Compd. | Site of alkylation | $\Delta H_f$ (AM1)/kJ mol <sup>-1</sup> |
|--------|--------------------|---|
| 2      | N-3                | 673.6                                   |
| 3      | N-9                | 626.3                                   |
| 4      | N-3                | 660.7                                   |
| 5      | N-9                | 608.3                                   |
| 6      | N-1                | 715.9                                   |
| 7      | N-7                | 657.7                                   |

Table 2. Melting points and <sup>1</sup>H-NMR data of compounds.

| Compd. | M.p./°C     | <sup>1</sup> H-NMR data in DMSO-d <sub>6</sub><br>( $\delta$ in ppm; $J$ in Hz)   |
|--------|-------------|---|
| 2      | 194–196     | 3.54 (t, 1H, <sup>4</sup> J=2.5, C≡CH); 5.17 (d, 2H, <sup>4</sup> J=2.5, CH <sub>2</sub> ); 7.77 (s, 1H, H-8*); 7.99 (s, 2H, NH <sub>2</sub> ); 8.41 (s, 1H, H-2*)  |
| 3      | 206–208     | 3.46 (t, 1H, <sup>4</sup> J=2.5, C≡CH); 5.03 (d, 2H, <sup>4</sup> J=2.5, CH <sub>2</sub> ); 7.27 (s, 2H, NH <sub>2</sub> ); 8.16 (s, 1H, H-8*); 8.19 (s, 1H, H-2*)  |
| 4      | 260–265     | 5.50 (dd, 1H, <sup>4</sup> J=10; <sup>2</sup> J=3, HCH); 6.31 (dd, 1H, <sup>4</sup> J=17; <sup>2</sup> J=3, HCH); 6.61 (dd, 1H, <sup>4</sup> J=17; <sup>2</sup> J=10, CH); 7.09 (s, 3H, H-8*, NH <sub>2</sub> ); 8.09 (s, 1H, H-2*) |
| 5      | 170–175     | 5.80 (d, 2H, <sup>4</sup> J=7 Hz, CH <sub>2</sub> ); 7.36 (s, 2H, NH <sub>2</sub> ); 7.45 (t, 1H, <sup>4</sup> J=7, CH); 8.18 (s, 1H, H-8*); 8.20 (s, 1H, H-2*)   |
| 8      | ~180 (dec.) | 4.08 (s, 2H, CH <sub>2</sub> OH); 5.20 (s, 2H, CH <sub>2</sub> N); 5.25 (bs, 1H, deut., CH <sub>2</sub> OH); 7.78 (s, 1H, H-8*); 8.05 and 8.12 (2 × bs, 2 × 1H, deut., NH <sub>2</sub> ); 8.42 (s, 1H, H-2*)                        |
| 9      | ~188 (dec.) | 4.50 (s, 2H, methylene); 5.52 (bs, 1H, CH <sub>2</sub> OH); 5.58 (s, 2H, methylene); 7.30 (bs, 2H, NH <sub>2</sub> ); 8.15 and 8.16 (2 × s, 2 × 1H, H-8 and H-2)  |

[Table 1: 1-propargyl-adenine (6); 7-propargyladenine (7)] and the following stability order was obtained for the nitrogen substitution: N-1 (6) < N-3 (2) < N-7 (7) < N-9 (3). This reflects, in part, the heteroaromatic stabilization exerted by the imidazole and pyrimidine rings, which can be observed in their most stable forms in compounds 3 and 7. The energy difference between 2

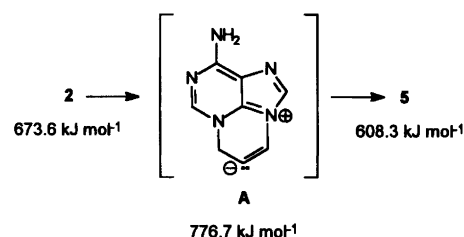
Table 3. Actual constraints of the reaction generator in RAIN.

|   |   |   |     |
|---|---|---|-----|
| Max. no. of reacting atoms                | 6 | Max. net charge/molecule                    | 1   |
| Max. no. of adjacency changing atoms      | 4 | Max. no. of rings                           | 3   |
| Max. no. of atoms changing free electrons | 2 | Max. no. of 3-/4-membered rings             | 0   |
| Max. change of free electrons             | 2 | Max. no. of 5-/6-membered rings             | 2   |
| Max. no. of reacting bonds                | 6 | Max. no. of 7-membered rings                | 1   |
| Max. no. of changing bonds/atom           | 2 | Max. no. of 8-/9-membered rings             | 0   |
| Max. no. of changing adjacencies          | 3 | Min. ringsize for triple/allenic bonds      | ∞   |
| Max. no. of changing adjacencies/atom     | 2 | Max. no. of molecules                       | 2   |
| Max. change of bond order                 | 1 | Max. heuristic reactivity index             | ∞   |
| Max. no. of charged atoms                 | 2 | Allow charge separation/recombination?      | No  |
| Max. no. of charged atoms/molecule        | 2 | Max. complexity of formal transition states | 1   |
| Max. net charge                           | 1 | Resonance/tautomers module                  | Off |

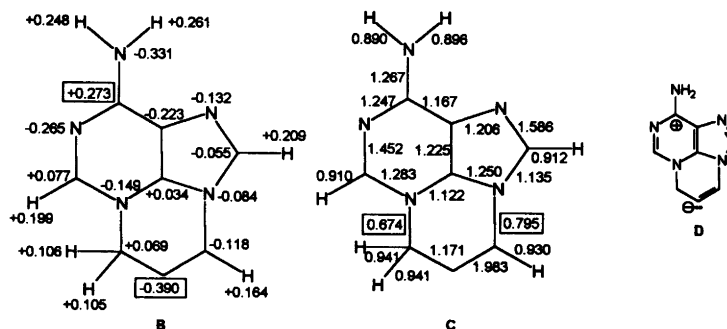
and 6, and 3 and 7, respectively, can probably be ascribed to the absence/presence of steric hindrance between the exocyclic amino and the propargyl groups.

Experimental proof for distinguishing between the two terminal atoms of the rearranging side-chain has also been sought after. Deuterium-labelled propargyl bromide<sup>16</sup> was used in the alkylation experiment, but most of the initial deuterium content was lost, making this substrate unsuitable for labeling studies. Next, 1-chloro-2-butyne-4-ol<sup>17</sup> was tried for the alkylation of adenine and *N*<sup>3</sup>-(4-hydroxy-2-butyne-1-yl)adenine (8, 34% from adenine) was subjected to rearrangement to give *N*<sup>9</sup>-(1-hydroxy-2,3-butadiene-2-yl)adenine (9) along with unreacted starting material. Selected physical and spectral data of compounds have been listed in Table 2. Satisfactory elemental analyses have been obtained for all new compounds.

There are several hypotheses on the mechanism of [3,3] sigmatropic rearrangement reactions, including concerted bond-breaking and bond-forming processes, biradicals, radical pairs, dipoles etc.<sup>3</sup> When investigating the 2→5 transformation, using AM1 calculations, it turned out that a concerted process is unlikely because small changes in internal coordinates are causing a large change in the distance between chemically bound atoms and the geometry optimization process would produce incorrect results. In turn, we have supposed an ionic transition state (e.g. A; many more may exist owing to resonance structures; Scheme 3). The net atomic charge and bond order calculations indicate that in this transition state (a) the most positive charge resides at C-6, with the most negative one at the central carbon of the former propargyl chain (B) and (b) the weakest bonds are those between the nitrogen atom (N-3) and the terminal



Scheme 3



Scheme 4

carbon, and the N-9 and other terminal carbon of the former side-chain, respectively, alluding to bond-breaking and bond-forming between the mentioned atoms (C; Scheme 4).

Interestingly, essentially the same transition state (D) was deduced to be the most likely when the above transformation was subjected to intermediate analysis using the computer program RAIN.<sup>18</sup> The boundary conditions of the calculations have been listed in Table 3.

The experimental and computational evidence presented seems to support the view that the [3,3] sigmatropic rearrangement of the 3-alkynyladenines mentioned above most probably follow a uni- and intramolecular pathway.

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