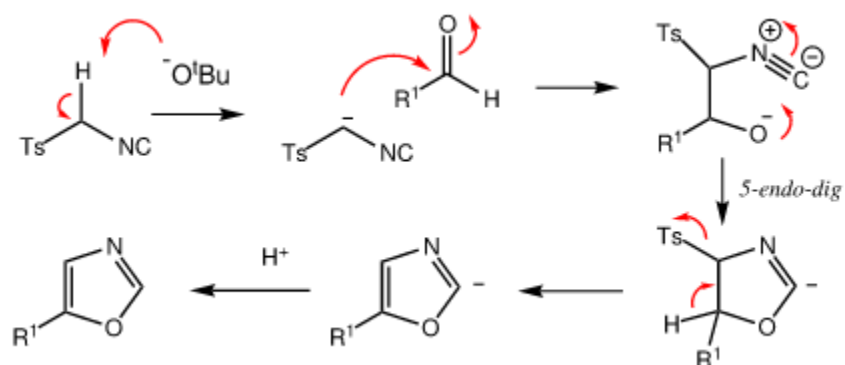
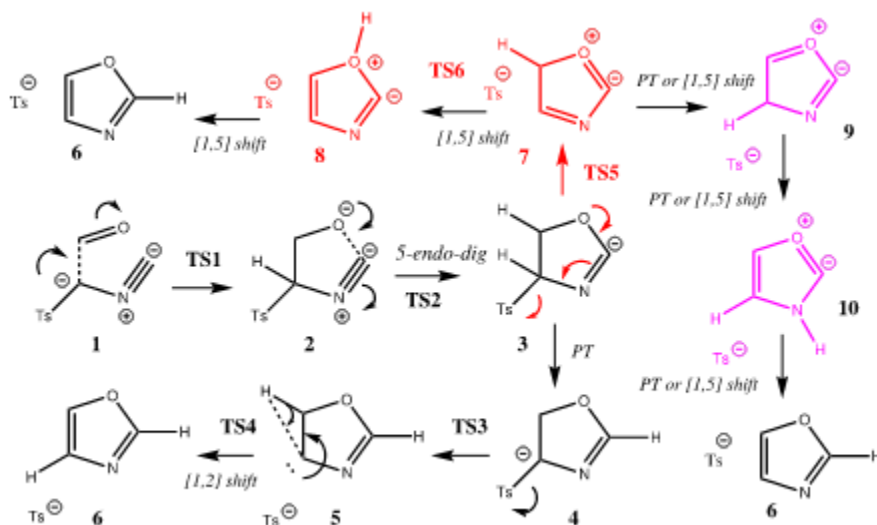


Mechanism of the Van Leusen reaction

This is a [follow-up](#) to comment posted by Ryan, who asked about isocyanide's role (in the form of the anion of tosyl isocyanide, or TosMIC): "In Van Leusen, it (the isocyanide) acts as an electrophile". The [Wikipedia article](#) (recently updated by myself) shows nucleophilic attack by an oxy-anion on the carbon of the C≡N group, with the isocyanide group acting as the acceptor of these electrons (in other words, the electrophile). In the form shown below, one negatively charged atom appears to be attacking another also carrying a negative charge. Surely this breaks the rules that like charges repel? So we shall investigate to see if this really happens.



I have extended the basic mechanistic scheme below to investigate other possibilities (with the aim of probing using the ω B97XD/6-311G(d,p)/scrf=methanol theory to see how realistic any of these routes might be). Starting from **1**, the product **6** can now be formed by three routes from the common intermediate **3** (there may be other routes of course not considered here). The relative computed free energies of these various species, and some of the transition states leading to them are listed in the table below.



The path leading to **3** is very low energy which may in part also be due to my using formaldehyde for expediency rather than a substituted aldehyde (I have to confess to having taken another short-cut, which is to miss out any counter-ion to the TosMIC anion). The first step is defined by **TS1**, which forms a C-C bond, and results in the intermediate **2**. **TS2** corresponds to O...C bond formation to yield **3**. Getting to **3** is thus a two-stage process, or a stepwise cycloaddition. The alternative would have been to regard TosMIC anion as a 1,3-dipole (isoelectronic with e.g. diazomethane) in which these two steps are conflated into a concerted cycloaddition across the carbonyl group.

TS2 is the interesting step from the point of view of the question raised above. It has a very low free-energy barrier from either **1** or **2**, and therefore appears very facile. The angle of approach by the oxyanion to the triple bond (we established it as being triple in the [previous post](#)) is 87°. This angle explains why a carbon bearing (a formal) negative charge easily accepts attack on itself by a nucleophile (*i.e.* acting as an electrophile). The formal negative charge originates from an electron lone pair located in an sp-hybrid orbital lying along the axis of the C≡N bond. But the nucleophilic attack is occurring at 87° to this axis, putting electrons into the empty π^* orbital of the C≡N bond. So in effect the two apparent "negative charges" in the mechanistic schemes above are orthogonal to each-other, which in a simplistic way explains why the diagram is not actually contradictory. The reaction itself is an example of [Baldwin's rules in action](#); one of these is that a 5-*endo-dig* cyclisation is allowed. This angle of attack and Baldwin's rules may of course be related.

| System | Relative free energy |
|--------|----------------------|
| 1 | 0.0 |
| TS1 | 1.2 |
| 2 | -3.1 |
| TS2 | 1.7 |
| 3 | -14.4 |
| 4 | -16.7 |
| TS3 | 5.9 |
| 5 | 4.0 |
| TS4 | 17.7 |
| 6 | -51.1 |
| TS5 | -2.3 |
| 7 | -3.1 |
| TS6 | 57.0 |
| "8" | -37.4 |
| "9" | -36.2 |
| 10 | -25.3 |

After **3**, the mechanism can channel several ways. For example, a proton transfer can precede the departure of **Ts** to give **4** and thence **5**. The final [1,2] shift to form the product **6** has a relatively high barrier however. More likely is the Ts group heterolysing off **3** via **TS5** to form **7**. All that is now needed is to shift a proton from **7** to form **6**, and this also can take several routes. One would involve base/acid catalysed deprotonation/reprotonation. Alternatively, the hydrogen could migrate by a series of uncatalysed [1,5]sigmatropic hydrogen shifts via e.g. **8**, **9** or **10**. In fact, the calculated

geometries of both **8** and **9** show that the C...O bond is broken, thus forming entirely different products. Thus the most probable route is indeed a simple catalysed proton transfer from **7**.

This computational exploration of the mechanism has reinforced the accepted one, and hopefully cast some light on why an isocyanide can appear to act as an electrophile.

Source: <http://www.ch.imperial.ac.uk/rzepa/blog/?p=10656>