

Route Redesign to Eliminate Use of PhOCN



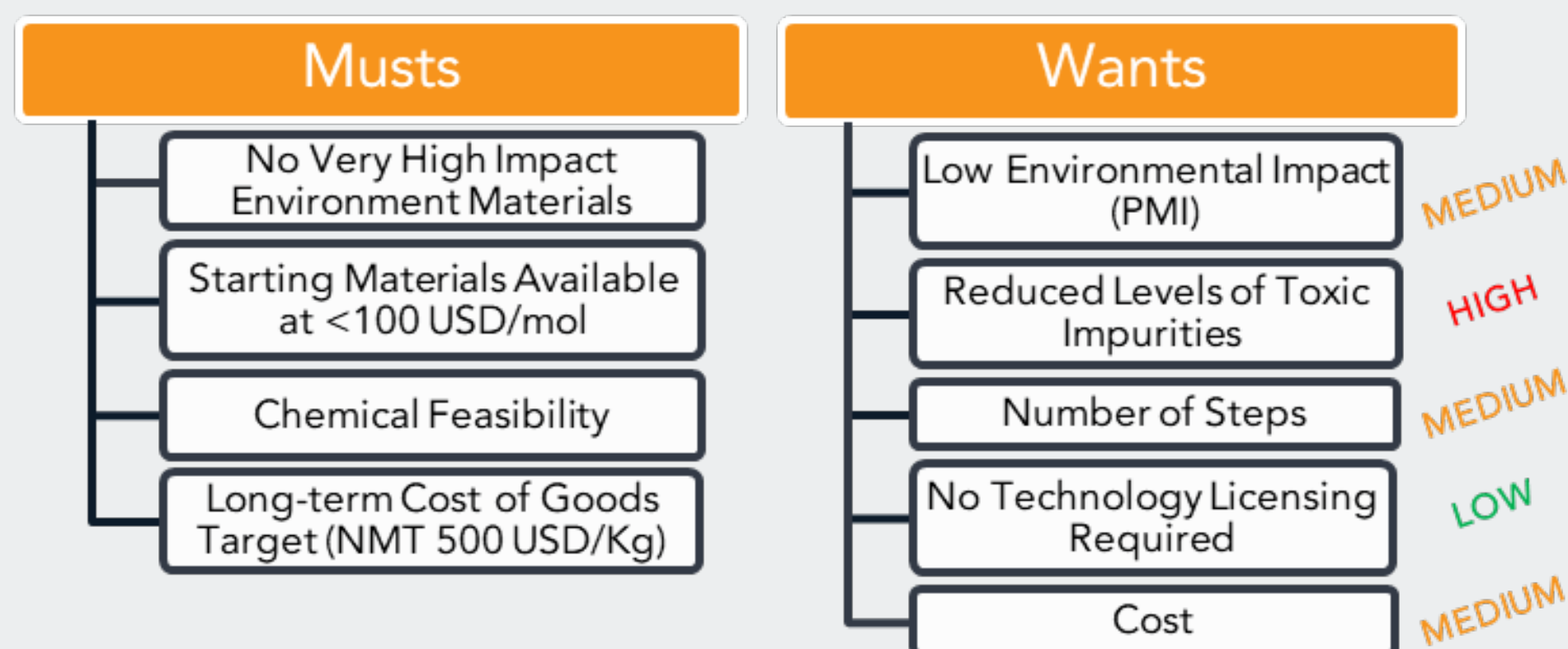
The challenge

The route supplied by the client involved the use of phenyl cyanate for functionalising a heterocyclic intermediate with a nitrile group. Its ongoing use would require cyanide monitoring, a dedicated waste stream treatment step, and there were concerns over the sourcing of material of appropriate quality over the long term.



How?

We used the Kepner-Tregoe Decision Analysis (1) (KTDA) to find a suitable alternative process. Criteria for the route selection were identified and divided into Musts and weighted Wants:



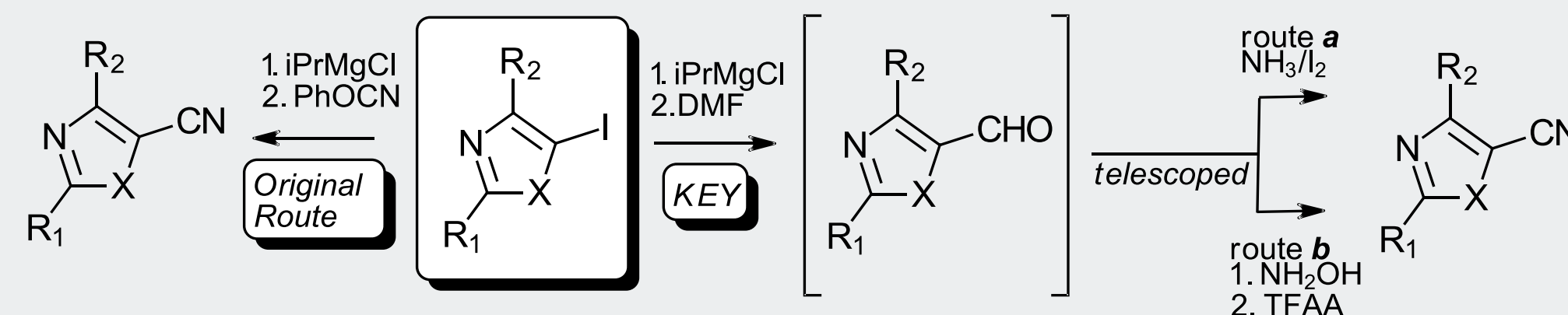
After brainstorming, a total of 7 potential approaches were identified. The routes which did not meet the 'Must' criteria were discarded while the remaining ones were scored on the basis of the weighting given to each one of the 'Wants' categories. (Scores: High (7-10), Medium (4-6) and Low (0-3))



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Route Selection:

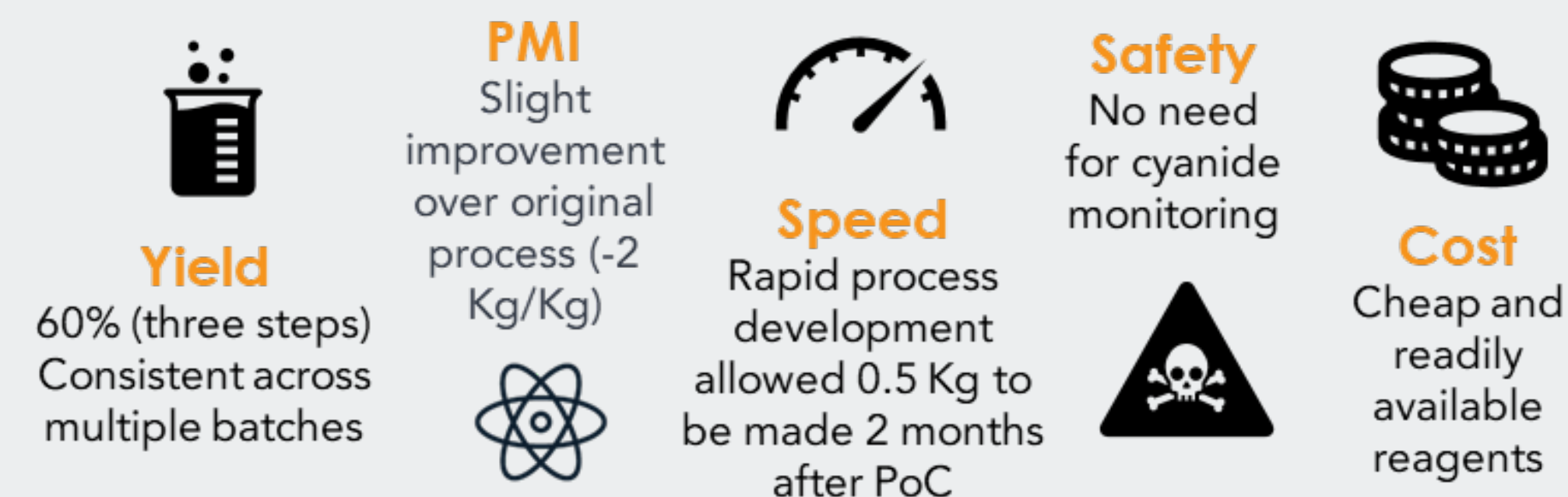
The two highest scoring routes from the KTDA process were prioritised and tested in the lab. Both routes relied on a key formylation step but Route a was initially prioritised due to the shorter sequence. This route however failed proof of concept as it generated a substantial amount of an impurity which was not initially accounted for.



Although Route b ranked lower in the initial KTDA due to the increased number of steps and predicted PMI, it was successfully carried out in the lab on a few grams scale. The chosen route risked contamination of target with a potentially mutagenic aldehyde impurity, however a paper-based purge factor risk assessment indicated this would be purged >>1010 ahead of API isolation.



The achievement



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