The Seven Component Coupling

A New World Record by Ivar Ugi and Co-workers

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What is the maximum number of components which can be mixed together to form a product? Four, five, six... or more? The current world record is:seven!

In general, a chemical reaction proceeds only through unimolecular or bimolecular *elementary* steps. This is because the probability of three or more molecules coming together to interact at the same time is negligible. So, chemists generally use no more than two components in any given reaction step. (Of course, a catalyst may be added to accelerate the reaction). Complex molecules are made by sequencing many reaction steps, each involving a small number of components. After each step, the tedious and sometimes difficult task of isolating the product for further processing is carried out. The operation would be more efficient if at least some of the successive steps could be carried out without having to do the 'work-up'. One-pot synthesis is therefore quite popular with chemists (as with amateur cooks). It would be better if all the ingredients needed to make a molecule in a long sequence of reactions can be mixed at one go. But this involves the risk that some of the components may interact with each other or with one or more of the intermediates formed in the sequence in a manner which was not anticipated. This would lead to the formation of unwanted side products. Therefore, to be on the safe side, chemists avoid putting together too many components at any given time. This brings us to the following question: what is the maximum number of components which can be mixed together to form a product? Four, five, six... or more? The current world record is:seven!

A seven component coupling reaction was reported by Ivar Ugi and coworkers in *Angew.Chem.Int.Ed. Engl* (**1993**,*32*,563). The overall reaction stoichiometry is shown in *Figure 1*. Is it not incredible that you mix seven reactants in a vessel, and ultimately get a product in 43% yield (as a 2.5/1 mixture of diastereomers)? Such a multi-component reaction cannot obviously go through a single step for entropic reasons. A sketch of the reaction mechanism is given in *Figure 2*, which makes use of simple principles of organic chemical transformations. Using these steps, it is quite easy to see that the individual reaction steps are not unusual at all. It is only the clever combination of the reagents that has produced this remarkable seven-component reaction. Every component seems to wait for its turn to react with an intermediate product that is formed, without interfering with the logical sequence of Figure 2.

The first step shown is a simple nucleophilic displacement reaction. The second step is for-

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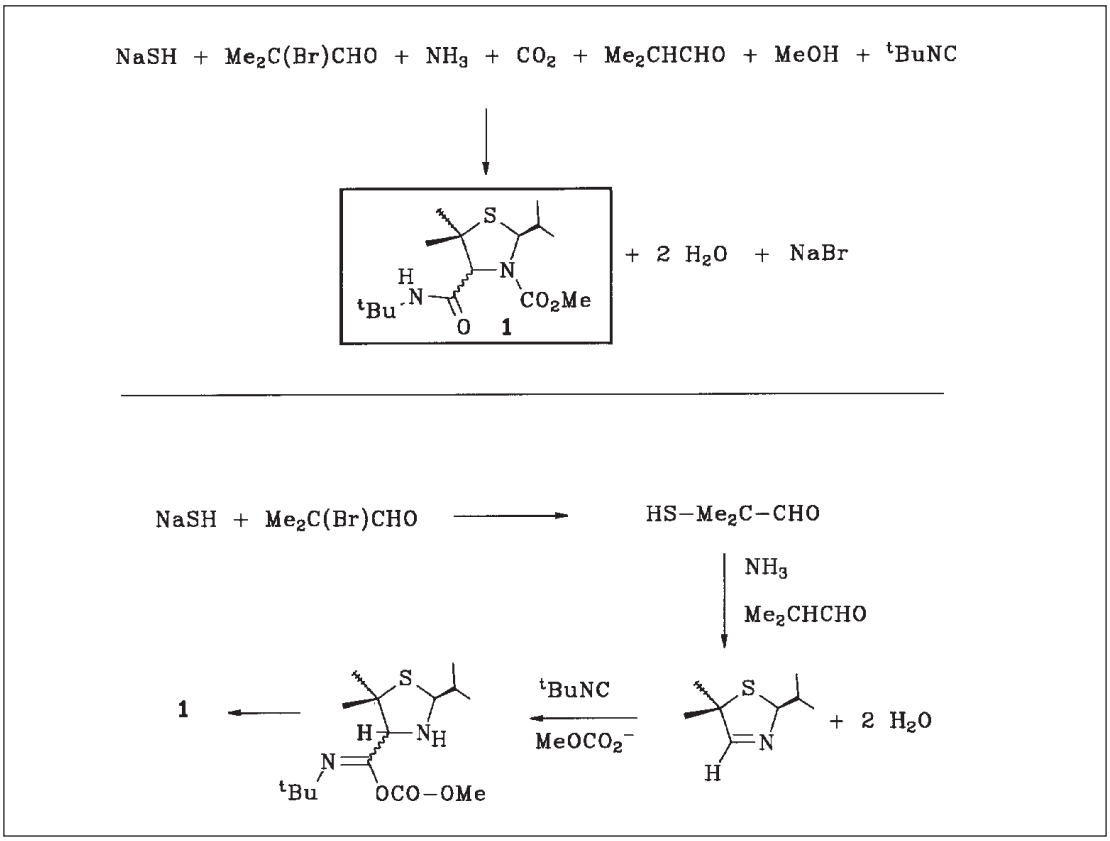

Figure 1, 2 Overall stoichiometry of Ugi's seven component coupling reaction (top). and a rational mechanism of Ugi's reaction (below).

mally a condensation reaction, in which a Schiff base formed from isobutyraldehyde and ammonia undergoes coupling (in the protonated form) with the thiol-substituted aldehyde. The protonated form of this intermediate then undergoes a nucleophilic attack by *t*-butylisocyanide, and the resulting $-N=C^{+}-$ unit is trapped by $MeOCO_2^-$ anion. Finally, the CO_2Me group undergoes a 'transfer' from the oxygen to the nitrogen in the same molecule to produce **1**.

Is it possible to have multicomponent coupling reactions with more than seven reagents? In principle yes, and perhaps some chemists are working towards this goal! We look forward to seeing an example which will break Ugi's record!

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