PROBLEM 39

[SUPPL Problem 39 # 1]

Arabic compound numbers in TAPSOC,
Roman numerals in Supplementary material

In Perspective

MCRs, which as you may surmise this particular reaction refers to, not only have become a tremendously powerful entry into molecular complexity, but complexity itself may be furthered by various approaches: the Single Reactant Replacement (SRR) strategy which expands considerably fundamental MCR reactions [1]. Tapsoc Scheme 39.1 is a noteworthy example.

What is SRR?

Without doubt, MCRs are an excellent method to improve synthesis methodology by reducing the number of bench-steps (reaction → isolation → characterization → reaction → isolation…) while enhancing overall yields. Considerable complexity can be built in a few hours.

This powerful technique can be improved further by a detailed knowledge of the mechanism of involved reactions and by introducing a systematic exploration of different components in the MCR mix. This is the idea of SRR. Let's see how this works in more detail.

Imagine that you work in a combinatorial synthesis environment aiming to enhance a set of biological activities of a given compound. MCR with, say, four components A – D is your MCR setting (Figure SP39.1.1, next page).

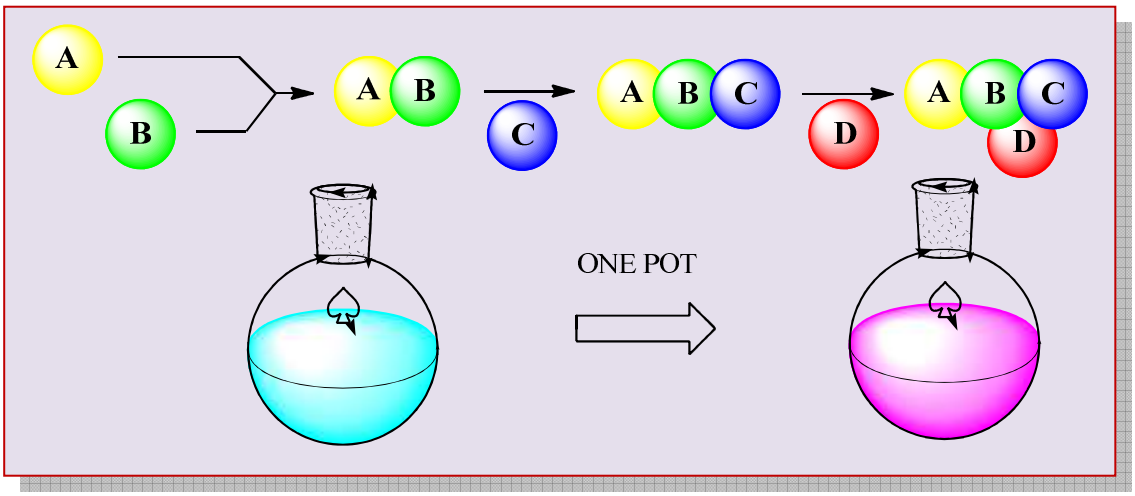

FIGURE SP39.1.1

You can two at least two basic things to reengineer and expand your setting:

1) Replace systematically one single component to widen the spectrum of end products, e.g. the isocyanide in an Ugi-type reaction, while maintaining the functional group. Substituents, chain length, structural and stereoisomers, and so forth are modified. Bring the process to its limits when no further complexity can be built in the final product or reactions fail to go. Repeat with each component (Figure SP39.1.2).

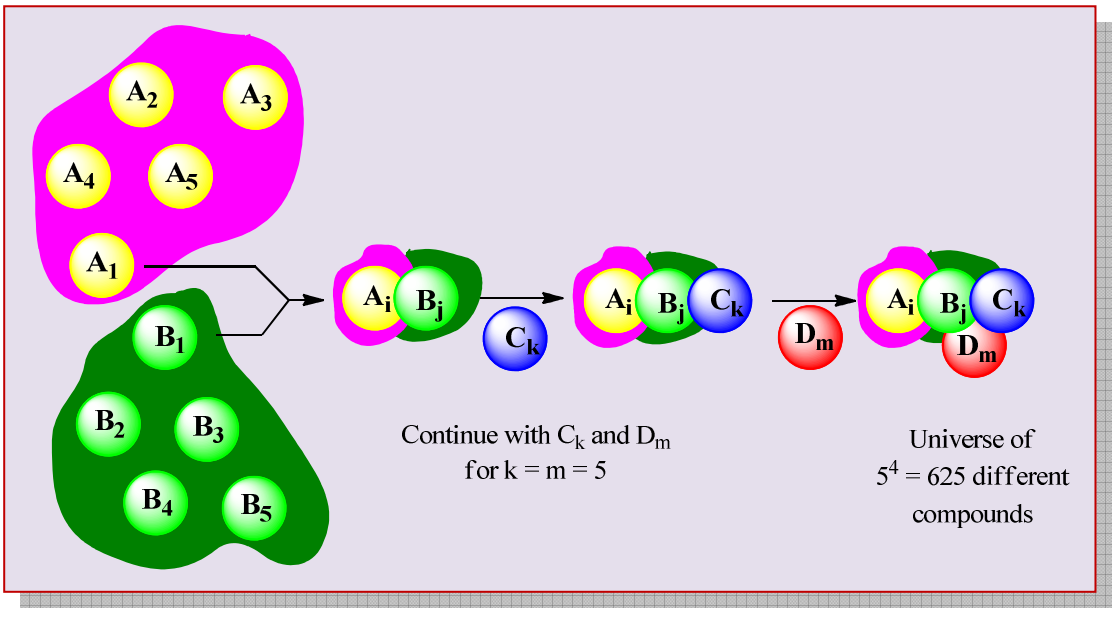

FIGURE SP39.1.2

In your *four* component combination A,B,C,D, with a spectrum of *five* different structural variations per component A_i,B_j,C_k,D_m (i = j = k = m = 5), potentially a total of 5^4 = 625 new compounds can be created using the same reaction protocol. Automated (robotic) MCRs with a precisely defined experimental design can procure this many compounds for biotesting in a relatively short period of time and low cost. Surprises may be found along the way as changes in substitution pattern are likely to modify products in each combination, leading to discovery by serendipity.

This is quite standard in combinatorial chemistry, after all. But there is another more inviting strategy.

2) If the reaction mechanism for each reaction pair of the A,B,C,D compounds is known in detail, one might replace the functional group involved in the concerned condensation reaction with a mimic, a CH=NR for a CH=O for example.

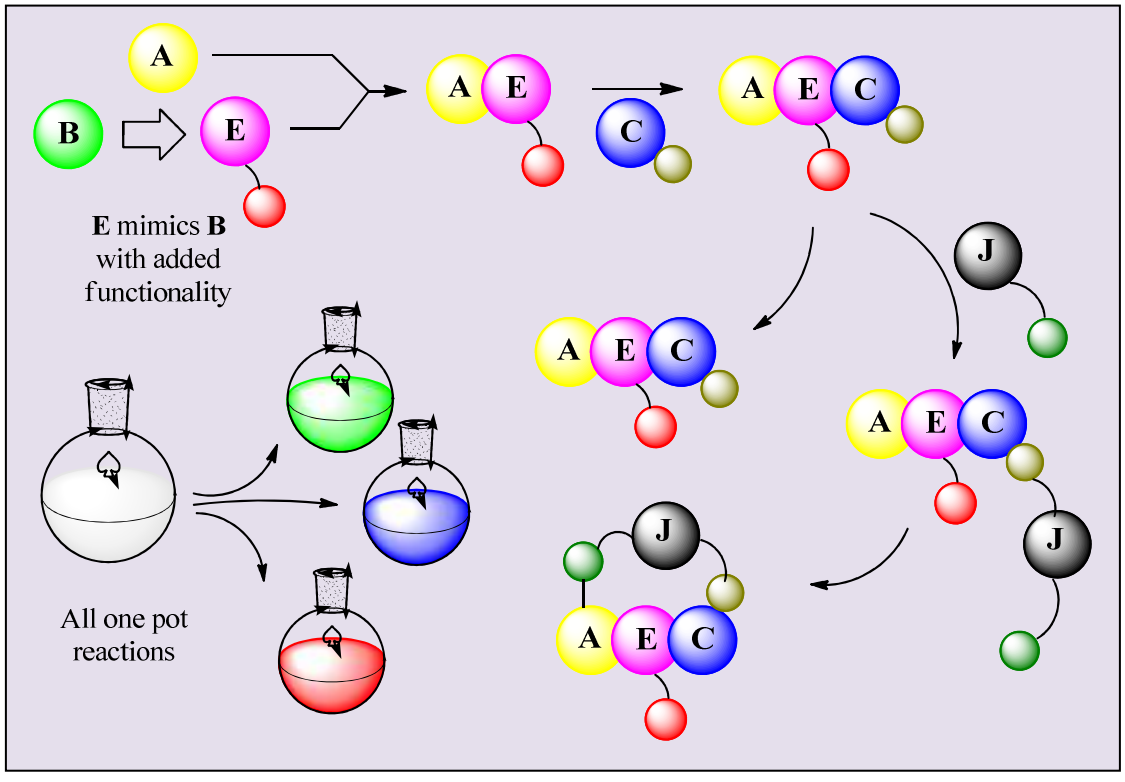

FIGURE SP39.1.3

As Figure SP39.1.3 also portrays, by inserting additional functionality in either component (the smaller tethered spheres there), the reactivity universe of the ensuing condensations and of the end product can not only be expanded substantially but novel reactivity patterns stemming from cascade reactions may turn up. Controlled innovation replaces serendipity although expanding the functionality universe may hold surprises too.

For several examples of this latter strategy to expand the repertoire of available MCRs, please study Prof. Bruce Ganem review [2].

REFERENCES

[1] See, for example: Houpis LN, Loannis N, Van Hoeck J-P, Tilstam U. Synth. Lett. 2007;(14):2179-2184.

[2] For a review, see: Ganem B. Acc. Chem. Res. 2009;42:463-472.