

One-Pot Synthesis: On the Order of Introducing Reagents

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The effect of altering the order of introduction of reactants into the reaction vessel in organic synthetic reactions is discussed. A method is presented by which it is possible to select a small subset of introduction orders to determine whether or not the order of mixing plays any role in the course of the reaction. The possibility of detecting important interactions between reaction constituents is discussed. The proposed strategy is exemplified with a study of titanium tetrachloride/triethylamine induced self-condensation of 3,3-dimethyl-2-butanone (pinacolone).

The current trend in organic synthesis is to develop one-pot procedures to carry out synthetic transformations. This means that various reagents are introduced in sequence into the reaction vessel. Sometimes it is evident how this should be done, e.g. a deprotonation by base to yield an enolate must precede an alkylation step. With some reactions the order of events is not evident. Many established synthetic procedures can be described as 'witchcraft chemistry' whereby an innovator presents a procedure which is then followed by practitioners in the field, e.g. preparation of catalysts for hydrogenation.¹

Most organic reactions involve several chemical species which must be introduced sequentially into the reaction vessel. The experimental result is sometimes highly dependent on the order of introduction of the constituents in the final mixture. In our own field we have observed several cases when this is important, e.g. in the synthesis of enamines in the presence of titanium tetrachloride where reversal of the order of mixing improved the yield and shortened the reaction time, from 70 % overnight to 95 % after 5 min.² Other examples are provided by the synthesis of carboxamides³ and silyloxy dienes.⁴ These experiences suggest that this problem has often been met by synthetic chemists. However, publications on synthetic procedures almost never mention that the effect of the order of introduction has been investigated. This probably reflects that the effect of varying the mixing order has never been investigated. It cannot, therefore, be excluded that promising ideas may have been abandoned when initial experiments have failed owing to an inappropriate order of introduction. We suggest that ideas for new synthetic procedures should not be abandoned before the consequences of altering the order of introduction of reagents to a reaction mixture have been considered.

Scope of the problem

The only way to be absolutely sure of obtaining the best result is to check all possible combinations. Even with a limited number of constituents the number of possible combinations will be prohibitively high. If experimental conditions, such as the rate of addition, temperature, delay before addition of the next constituent etc., are also taken into account the situation becomes absurd; with five constituents, $5! = 120$ different orders are possible and if the rate of addition, the temperature and the delay before the next addition in a minimum fractional factorial design are included, the number of combinations increases to 480 possible different experimental procedures. To allow a systematic search using a manageable number of test experiments a selection principle must be applied. In this paper we propose a simple method for selecting such experiments.

An alternative way of analyzing the problem would be to use graph theory to determine all possible connections of starting material and reagents to the product(s). Such considerations might give another optimum subset for testing, provided that certain assumption can be fulfilled. However, such an analysis would not be simple.

Selection of test items

We suggest that selection along the following principles stands a good chance of detecting important differences between altered orders of mixing reaction constituents. With n constituents (A,B,C...M,N), run n experiments in such a way that the order of introduction is a cyclic permutation of the sequence ABC...MN, i.e. ABC...MN, NABC...M,, BC...MNA.

In this subset of n items out of $n!$ possible combinations, the items represent orders in which each of the components is added as the last component. If the order of addition really matters, it is an indication that at least two constitu-

ents in the reaction mixture must interact to produce a necessary intermediate. In addition, one of the constituents may react with another constituent to form an undesired complex or secondary product prior to the introduction of a critical component.

In the suggested subset of n different orders there will be at least one for which a necessary intermediate *cannot* be formed until the last step. A likely consequence is that the yield will be lowered in this case. For at least one of the introduction sequences in the subset, the necessary intermediate *can* be formed before the component with the possibility of reacting in an undesirable way is introduced to the reaction mixture. The next step in the investigation will depend on the results obtained in the n experiments.

(a) If there is no significant difference in the results, it is likely that the order of introducing the reagents does not really matter. Further investigations of the introduction order will probably not improve the result.

(b) A significant difference is observed and one combination gives a *satisfactory* result. Then the next step will be to elaborate optimum experimental conditions for this order by a suitable experimental design.

(c) Significant differences between the n runs are observed and one gives a promising result. Then the next step will be to keep the last added reagent unchanged and vary the mixing order of the remaining reagents in a series of $(n-1)$ cyclic permutations of which one experiment was already present in the first series of experiments etc.

(d) If there are several promising results, the situation is more complicated. To draw a safe conclusion it is necessary to investigate each of these combinations according to (c). From a practical point of view, it would be easiest to begin with the most promising, or in some other way most practical, combination according to (c) and stop when a satisfactory result is obtained.

In order to elucidate the presence of one or several critical intermediates in a reaction it is necessary to analyze further the combination which gives the poorest result. In this case, several possibilities exist, e.g. (1) a necessary intermediate involving the last added reagent not being formed rapidly enough, which has a negative influence on the result; (2) an intermediate giving rise to side reactions being formed and reagents being consumed to yield other products; (3) a higher-order complex between three or more constituents being necessary, the formation of which is dependent on the detailed order of introduction.

An example

The synthesis of enamines from pinacolone using titanium tetrachloride as a catalyst was accompanied by considerable self-condensation.⁵ By using a tertiary amine, e.g. triethylamine (TEA), the self-condensation can be forced to be the dominant reaction (Scheme 1). Initial experiments showed that pinacolone and titanium tetrachloride or pinacolone and TEA alone did not afford any condensation products and that the presence of all three constituents



Scheme 1.

is necessary. A similar self-condensation of tetralones has been published.⁶

With three constituents to mix, a total of $3! = 6$ different orders of mixing reagents are possible. Three of them represent a cyclic permutation subset. The results of these experiments are shown in Table 1.

Discussion

In this reaction given as an example above, there are at least three plausible mechanisms.

(a) The critical step is that titanium tetrachloride and pinacolone form a complex which polarizes the carbonyl group. Addition of triethylamine gives, by proton abstraction, a titanium enolate which attacks titanium-tetrachloride-polarized pinacolone, followed by a base-induced elimination of the elements of titanium oxide.

(b) Titanium tetrachloride and amine give a Lewis acid–base complex.⁷ At least one of these mixed complexes has increased reactivity towards the carbonyl oxygen and forms a carbonyl–TiCl_x–amine complex² which, in the presence of an excess of amine, gives a titanium-coordinated enolate. The reaction then proceeds as for (a).

(c) Pinacolone in the presence of an amine gives an enolate which, owing to steric congestion has a low reactivity towards unenolized pinacolone. Addition of titanium tetrachloride gives a pinacolone–TiCl₄ complex which polarizes the carbonyl group, and traps the enolized ketone as titanium enolate. Coupling then occurs between the polarized ketone and the enolate.

Any of these proposed mechanisms can be appended to 'explain' the results of the procedure if only one of the procedures is examined experimentally. In view of the results in Table 1, (a) and (c) are least likely to apply.

The principles given above are not foolproof, but they allow the importance of altering the order of mixing reagents in one-pot procedures to be detected in a limited number of experimental runs.

In many published experimental procedures it is common practice to give *ad hoc* explanations involving hypo-

Table 1. Yields obtained using different orders of mixing of the reactants.

Order of introduction ^a	Yield (%)
ABC	43.5
CAB	1.5
BCA	66.4

^aA (3,3-dimethyl-2-butanone), B (triethylamine), C (TiCl₄).

thetical reaction mechanisms. Sometimes these proposals can give valuable ideas for a thorough study of the reaction mechanism, but sometimes they can be totally misleading, especially when it not is realized that they are just hypotheses. Although the screening procedure proposed in this paper can not furnish detailed mechanistic information, at least some 'ad hoc' speculations can be ruled out.

Experimental

The reactions were run in a magnetically stirred Erlenmeyer flask (100 ml). The reactants were dissolved in hexane and 10 ml of each solution were mixed in the order given in Table 1. The solutions had the following concentrations: solution A [6.0 mmol of 3,3-dimethyl-2-butanone (10 ml)]; solution B [24.0 mmol triethylamine (10 ml)]; solution C (9.0 mmol titanium tetrachloride (10 ml)). The mixing was performed by dropwise addition of the solutions to the flask at room temperature. When the last constituent had been added, the flask was placed in an oil bath (79–80 °C) and the stirring was continued. Samples (0.400 ml) were withdrawn at regular intervals and monitored by GLC. The samples withdrawn were shaken with water and diluted with pentane and an accurately known amount of dodecane (internal standard) was added. The yield was determined from the integrated peak areas in the gas chromatogram. A Milton Roy CI-10 integrator was used. The yields obtained after 4 h are given in Table 1, after which period the increase in yield was insignificant.

When the reaction was complete, 100 ml of water were added to quench the titanium chloride. The aqueous layers was extracted three times with hexane (50 ml) and the combined organic extracts were analyzed by GLC. The yield of the worked-up mixture agreed to within 1.5 % of that determined from the aliquot taken after 4 h.

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References

1. For an example, see Mozingo, R. *Org. Synth. Coll. Vol. 3* (1955) 181.
2. Carlson, R., Nilsson, Å. and Strömquist, M. *Acta Chem. Scand., Ser. B* 37 (1983) 7.
3. Nordahl, Å. and Carlson, R. *Acta Chem. Scand., Ser. B* 42 (1988) 28.
4. Hansson, L. and Carlson, R. *Acta Chem. Scand.* 43 (1989) 1888.
5. Carlson, R., Hansson, L. and Lundstedt, T. *Acta Chem. Scand., Ser. B* 40 (1986) 444.
6. Holba, A. G., Premasager, V., Barot, R. C. and Eisenbraun, E. J. *Tetrahedron Lett.* 26 (1985) 571.
7. (a) Trost, W. R. *Can. J. Chem.* 30 (1952) 835; (b) Fowles, G. W. A. and Hoodless, R. A. *J. Chem. Soc.* (1963) 33.

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