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Quantification of the Efficiency of Prostaglandin dl-$PGF_{2\alpha}$ Synthesis

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Abstract

Selection of the optimum synthetic path to the active ingredient for any drug is a complex task. The lack of computational methods for performance assessment of chemical transformations does not allow quantitatively assessing the proposed synthesis options and efficiently using computational methods in their development. The method of quantification of syntheses efficiency considering changes in structural complexity of organic compounds, reaction conditions and results is developed.

Keywords: drug, organic synthesis, synthesis efficiency quantification

INTRODUCTION

Active ingredients (AI) of drugs represent a large group of biologically active compounds that are legally permitted for the prevention and treatment of human and animal diseases. One of the relevant issues of modern organic chemistry is the development of the optimum schemes of their synthesis. Almost all AI may be produced in several ways, however, the literature does not have satisfactory examples of quantification of organic synthesis schemes and their comparative analysis. Whereas the suggested approaches supporters of green chemistry of Sheldon [3] and Trust [1, 2] are oriented toward technology processes assessment.

The method of complex quantification of the effectiveness of organic synthesis schemes as a function of changes in the structural complexity of organic compounds, conditions, and results of the reaction is proposed [4]. Quantification allows ranking organic synthesis schemes and using computer technologies to increase their efficiency.

QUANTITATIVE ASSESSMENT METHODOLOGY OF THE EFFICIENCY OF SYNTHESIS SCHEMES

Obviously, assessing streamlined organic synthesis of biologically active compounds should be of a complex nature, and the proposed method should take into account all the main criteria that determine the efficiency of the synthesis scheme. One option of this assessment would be the cost of 1 g of a substance produced according to the scheme. However, the economic indicator is a biased factor influenced by supply and demand. In this regard, a formula for calculating the efficiency, which is based on the characteristics of

chemical processes and does not depend on the subjective factor, is proposed. Herewith, the structural complexity of the compound partially reflects the economic indicator, and the total yield and optical purity of the reaction product – the qualification indicator. In particular, there is proposed to consider the quantification of E efficiency as a function of changing the main parameters of the reaction:

$$E = f(\mathrm{Str} \cdot t \cdot \tau \cdot P \cdot Y \cdot \mathrm{OP}) \quad (1)$$

where Str is structural complexity; t is temperature; τ is reaction time; P is pressure, Y and OP are product total yield and optical purity, respectively.

When making a formula, a multiplicative scheme is accepted for the basis and all indicators are normalized from 0 to 1:

$$E = f(\mathrm{Str}) \cdot f(\tau) \cdot f(t) \cdot f(P) \cdot f(Y) \cdot f(\mathrm{OP}) \quad (2)$$

A particular attention is paid to the structural complexity of compounds as a crucial indicator of synthesis efficiency, and also the total yield of the end product and its optical purity. These parameters make the maximum contribution to the efficiency of the synthesis of the final product (E), when their values are equal to 1. The contribution of temperature and pressure are maximum during all stages of synthesis at atmospheric pressure and a temperature of 25 °C.

Structural complexity change indicator $f(\mathrm{Str})$ is computed according to the formula:

$$f(\mathrm{Str}) = e^{-(\mathrm{Str_r}/\mathrm{Str_p})} \quad (3)$$

where $\mathrm{Str_r}$ and $\mathrm{Str_p}$ are structural complexities of the initial compound of the Bertz transformation scheme [5] and the final product, respectively.

The greater the difference between the structural complexity of the source compound and the final product is, the greater the contribution of this parameter to the value of E efficiency is.

Reaction time indicator is computed according to the formula:

$$f(\tau) = e^{-0.01|\tau' N - \tau|/\tau} \quad (4)$$

where τ is total time of all steps of synthesis, h; τ' is the standard time of one step multistep synthesis (by default is 1 h); N is a number of synthesis steps.

The temperature parameter is taken into account as a function of deviation from 25 °C of the maximum and minimum temperatures of the reactions in the whole reaction network according to the formula:

$$f(t) = e^{-0.01(\Delta t/25)} \quad (5)$$

where $\Delta t = |25 - t_{\min}| + |25 - t_{\max}|$, °C; $t_{\min}, t_{\max}$ are minimum and maximum temperatures used in reaction network, °C.

Similarly, the pressure parameter is taken into account as a function of deviation from atmospheric pressure (101 325 Pa):

$$f(P) = e^{-0.01(\Delta P/101\,325)} \quad (6)$$

where $\Delta P = |101\,325 - P_{\min}| + |101\,325 - P_{\max}|$; $P_{\min}$, $P_{\max}$ – minimum and maximum pressures used in reaction network, Pa.

The final product yield parameter $f(Y)$ is considered as the product of individual steps, in fractions of one, Y:

$$f(Y) = e^{0.1(Y-1)} \quad (7)$$

The optical purity factor is taken into account according to the formula:

$$f(\mathrm{OP}) = e^{(\mathrm{OP}-1)} \quad (8)$$

Upon synthesis of the optically pure product (OP = 1), its contribution to the E efficiency is maximum ($f(\mathrm{OP}) = 1$).

Thus, the following formula to compute the efficiency of the transformation scheme is produced:

$$\ln E = (\mathrm{OP} - 1) + 0.1(Y - 1) - \mathrm{Str_r}/\mathrm{Str_p} - 0.01(\Delta t/25 + \Delta P/101\,325 + |\tau' N - \tau|/\tau) \quad (9)$$

RESULTS ANF DISCUSSION

Formula (9) testing was carried out on an example of five schemes of prostaglandin dl-$PGF_{2\alpha}$ synthesis (1 [6], 2 [7], 3 [8], 4 [9], 5 [10]). As an example, Table 1 gives parameter values for each step of prostaglandin dl-$PGF_{2\alpha}$ synthesis from (R)-glycidol according to Scheme 5 [10] (Fig. 1).

Figure 2 and in Table 2 give data on the dependence of synthesis efficiency on changes in structural complexity of organic compounds, reaction conditions and results for synthesis according to Scheme 1. Structural complexity change parameter was selected in such a way that its contribution to synthesis efficiency would be maximum. This is indicated by an increase in the synthesis efficiency E with a rise in structural complexity. For two other indicators (changes of reaction conditions and results), inverse dependence is observed. A similar situation takes place for synthesis Schemes 2–5.

Figure 3 and Table 3 give data regarding synthesis efficiency on the number of steps for

TABLE 1

Parameter values for each step of prostaglandin dl-$PGF_{2\alpha}$ synthesis according to Scheme 5 [10]

Step	*Y*, UF	*T*, °C	τ, h	P, Pa	OP, UF
1	0.74	−30, 25	11	101 325	1
2	0.88	−78, −50, 25	8	101 325	1
3	0.84	40	12	101 325	1
4	0.70	−78	9	101 325	1

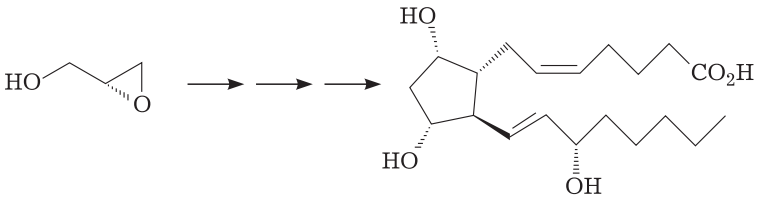

Fig. 1. Structural formulas of (R)-glycidol and prostaglandin dl-$PGF_{2\alpha}$.

all five synthesis schemes, in other words, on a change in reagent structural complexity. The greater the differences between the structural complexity of the reagent and the end product are, the greater the contribution of this parameter into synthesis efficiency value is. This is indicated by the slope of direct lines in Fig 3. For each of schemes, *E* values from the last intermediate compound are given, then, from the second to last one to prostaglandin and finally from the initial substance for this scheme to prostaglandin (the greatest difference of structural complexity value). It can be seen that synthesis schemes with the maximum difference of structural complexities of the initial compound and the final transformation product are most efficient. Some deviations from this dependence are related to the use of protective groups with a greater own index of structural complexity. Generally, a significant change of the Str parameter in the transformation chain attests to a low index of complexity of the initial compound, and therefore, about its availability, therefore consideration of this factor in the formula appears to be very important.

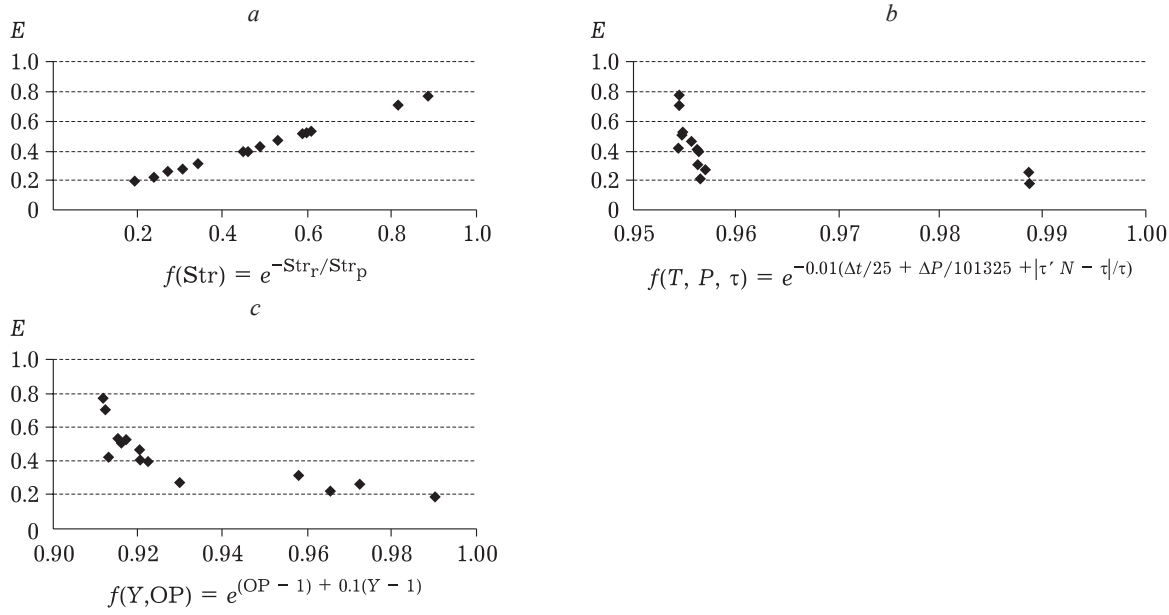

Fig. 2. Stepwise dependence of prostaglandin dl-$PGF_{2\alpha}$ synthesis efficiency (*E*) on changes in structural complexity of organic compounds (*a*), reaction conditions (*b*) and results of (*c*) for Scheme 1.

TABLE 2

Stepwise dependence of prostaglandin dl-PGF$_{2\alpha}$ synthesis efficiency (E) according to scheme 1 on structural complexity function, conditions and reaction results

Step	$f(\mathrm{Str}) = e^{-\mathrm{Str_r}/\mathrm{Str_p}}$	$f(t, P, \tau) = e^{-0.01(\Delta t/25 + \Delta P/101\ 325 + \lvert\tau' N - \tau\rvert/\tau)}$	$f(Y, \mathrm{OP}) = e^{(\mathrm{OP}-1) + 0.1(Y-1)}$	E
14	0.19	0.99	0.99	0.19
13→14	0.27	0.99	0.97	0.26
12→14	0.24	0.96	0.97	0.22
11→14	0.34	0.96	0.96	0.31
10→14	0.31	0.96	0.93	0.27
9→14	0.45	0.96	0.92	0.39
8→14	0.46	0.96	0.92	0.40
7→14	0.53	0.96	0.92	0.47
6→14	0.60	0.95	0.92	0.53
5→14	0.59	0.95	0.91	0.51
4→14	0.61	0.95	0.91	0.53
3→14	0.49	0.95	0.91	0.43
2→14	0.81	0.95	0.91	0.71
1→14	0.89	0.95	0.91	0.77

Furthermore, we used the method of expert assessment. Table 4 gives efficiency assessment results for prostaglandin dl-PGF$_{2\alpha}$ synthesis schemes performed by six invited experts. Five synthesis schemes according to efficiency are arranged in the following order: $5 > 1 > 2 > 4 \geq 3$.

Calculations by our formula gave the following result (Table 5): $5 > 1 > 3 > 2 > 4$.

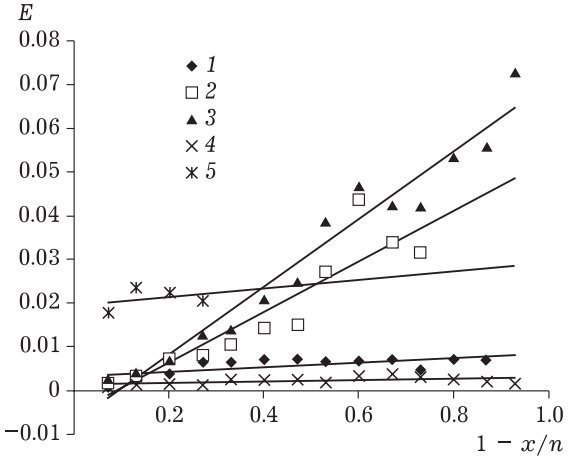

Fig. 3. Stepwise dependence of efficiency of synthesis of prostaglandin dl-PGF$_{2\alpha}$. *1–5* – schemes 1–5, respectively.

CONCLUSION

There has been proposed quantification of schemes of organic synthesis efficiency (E) as a function of changes in structural complexity from the reagent to the product, reaction conditions (temperature, reaction time, and pressure) and results (yield and optical density).

It is particularly worth noting that only preparation schemes of the same compound may be correctly compared between themselves. The test version of the program [11] that allows performing calculations according to this formula is available on the website of the Bashkir State University (URL: http://chemrcc.xyz/). Our proposed approach is open to further development, and the software product suggests an opportunity to include therein other formulas different from those offered by us.

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TABLE 3

Stepwise dependence of prostaglandin dl-PGF$_{2\alpha}$ synthesis efficiency for synthesis schemes 1–5

1		2		3		4		5	
$1 - x/n$	E	$1 - x/n$	E	$1 - x/n$	E	$1 - x/n$	E	$1 - x/n$	E
0.93	0.19	0.88	0.46	0.93	0.48	0.93	0.27	0.75	0.16
0.86	0.26	0.75	0.50	0.87	0.46	0.86	0.19	0.50	0.51
0.79	0.22	0.63	0.45	0.80	0.37	0.79	0.16	0.25	0.11
0.71	0.31	0.50	0.59	0.73	0.53	0.71	0.25	0.00	0.81
0.64	0.27	0.38	0.59	0.67	0.51	0.64	0.08		
0.57	0.40	0.25	0.53	0.60	0.52	0.57	0.26		
0.50	0.40	0.13	0.58	0.53	0.53	0.50	0.32		
0.43	0.47	0.00	0.59	0.47	0.57	0.43	0.31		
0.36	0.53			0.40	0.35	0.36	0.20		
0.29	0.51			0.33	0.55	0.29	0.32		
0.21	0.53			0.27	0.36	0.21	0.25		
0.14	0.43			0.20	0.24	0.14	0.34		
0.07	0.71			0.13	0.59	0.07	0.44		
0.00	0.77			0.07	0.49	0.00	0.47		
				0.00	0.70				

Note. n is total number of synthesis step, $x = 1, 2...n$; E is efficiency.

TABLE 4

Results of expert assessment of the efficiency of syntheses schemes 1–5

Expert	Scheme				
	1	2	3	4	5
	Efficiency assessment				
G. Yu. Ishmuratov	3	2	1	4	5
M. S. Miftakhov	5	1	4	2	3
O. S. Kukovinets	2	5	1	4	3
Kenji Mori	4	3	2	1	5
F. A. Valeev	4	3	2	1	5
V. N. Odinokov	4	3	2	1	5
Total	22	17	12	13	26

Note. 1. Expert evaluation was performed on a five-point system, where 5 – maximum evaluation, 1 – minimum. 2. Expert staff: M. S. Miftakhov, F. A. Valeev – Prof. UFICh RAS (Ufa, Russia), Kenji Mori – Emeritus Professor, University of Tokyo (Japan), V. N. Odinokov – Prof. INC RAS (Ufa, Russia), O. S. Kukovinets – Prof. Bashkir state University (Ufa, Russia).

TABLE 5

Results of calculations of synthesis schemes 1–5

Parameter	Scheme				
	1	2	3	4	5
Str_r	41.06	134.1	69.28	204.37	33.87
Str_p	342.1	342.1	342.1	342.1	342.1
Δt	97	128	120	165	118
ΔP	0	0	0	0	0
OP	1	1	1	1	1
Y	0.08	0.30	0.06	0.08	0.38
τ'	1	1	1	1	1
τ	68	38	59	79	40
N	14	8	15	14	4
E	0.77	0.59	0.70	0.47	0.81

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