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Miniaturization Improvement and Application Research of Organic Synthesis Experiments

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Abstract: The miniaturization of organic synthesis experiment is very beneficial for education and research laboratory. The effect on 4 main reactions has been studied here, those are esterification, aldol condensation, nucleophilic substitution, and oxidation. With the reduction of reagents from 10 - 50 mL(conventional)to 0.1 - 2.0mL(miniaturized),four comparison experiment were done on 120 students in 2 semester by miniaturized method. I gathered quantitative info on reaction yields, time efficient, reagents and students: The smaller protocol was 78.4%, the normal sized protocol was at an average of 74.6%. And it consumed 91.3% less solvent, and the cost per sample is down 68.5%. Students were more engaged and had better operations. From the results we can see that Organic synthesis miniaturization is green chemistry and undergrad lab improvement.

Keywords: Miniaturization, organic synthesis, green chemistry, undergraduate laboratory, reaction yield, chemical education.

1. Introduction

Laboratory methodological progress on the part of organic chemistry is quite different: it has changed a lot over recent twenty years because green chemistry was pushed for and also educational places made this happen. Traditional organic synthesis lab experiments have long comprised the foundation of undergraduate chemistry classes but use lots of organic solvents and reactants as well as making a lot of hazardous chemical trash that can endanger people working in labs [1]. Environmental laws grow stricter every day and the price of purchasing reagents and disposing waste keeps climbing as well, so both teachers and people doing experiments in schools are looking for good enough substitutes that still keep lab work true to science. Miniaturization-the systematic reduction of reaction volumes down to hundreds of microliters or less-may well prove to be boththe most compellingand the most pedagogical answer. Mayo and Pike's textbook contribution from the mid80s and Butcher (early 80's) showed us that we could run most of the simple synthetic rxns at a ~10x lower scale than what is used in macroscale protocols [2, 5]. Since then there's been quite a bit more work written up about how mini-lab techniques have worked and fallen short in different kinds of reactions as well[3].Although this is starting to build up as a body of evidence, there are still not many systematic comparisons which look at all four dimensions (yields/costs/environmental learning) together in one go for laboratories, especially those found in Chinese universities where classrooms come equipped with different lab resources and student populations [11-13]. To this goal, we do a whole data-driven investigation with respect to minisatized organic synthesis protocols of four different reactions types that are evaluated by way of group of 120 undergraduate students along many indicators.

2. Principles and Advantages of Miniaturized Organic Synthesis

Miniaturized organic synthesis relies on the principle that ultimately it is concentration, temperature, contact area and thermodynamic equilibrium which governs a chemical reaction, not the absolute amount of reactants. If reactions scale is reduced in proportion-keeping molar ratio's, concentration gradients, temperature profile constant, kentic & thermodynamic behaviour of the system does not change much. Invariance is what gives small scale protocols their legitimacy, it guarantees that what we find here is actually meaningful and translatable. In reality, small makes sense for many reasons. Heat transference becomes better when smaller scale is used because it has more surface area to volume so the reactions get started quicker and are evenly heated. Mixing is getting better: with some spreading, can be done more easily by short trips and it was alright when mixed gently. And also it'll usually be actually translated into some improvement, and then the selectivity, because we're talking about those types of reaction local overheat, concentrated heat across a larger area. By means of certain small glassware such as Hickman stills and conicals, the condensers must be tiny to accomplish this [4]. Environmentally speaking, the benefits of having smaller experiments is huge--each experiment makes a tenth less toxic organic waste. So less for me to throw away AND fewer tiny little bits and pieces of those awful fume volatiles going off into our lovely air. If there are less reagent then lesser the chance of a quick like spill, fire or breathing poison. When we take all these things together, it will have some relationship to the tenth Green Chem priciple formulated by Anastas and Warner of less hazarduous chemical intermediates.

3. Experimental Design and Miniaturization Strategies

The experiment was set up in a way that we could have been able to compare the macroscale and miniaturized microscale conventional protocols on 4 different representative organic synthesis reaction such as acid catalyzed esterification (ethyl acetate), base-catalyzed aldol condensation (dibenzalacetone), nucleophilic substitution (SN2, 1-bromobutane), Chromic Acid Oxidation (cyclohexanocle from cyclohexanol) [5]. Of the 4, these were chosen as they would usually be learned in undergraduate organic chemistry, contain representatives of several distinct classes mechanistically and also had sufficient macroscale reference material available for comparison with miniscaled versions [9]. A paired experimental design was followed for every reaction, one group of student performs the traditional protocol described in the regular departmental lab manual and another group does the miniaturized version which is developed by us. In the traditional process we used glassware that is normal size for an undergrad with 15 - 30mLs of reagent and 20-35mLs of solvent. The Miniaturization used was with the use of vial capacity at 1-3ml's. Microcondenser's, Pasteur Pipette for Separation and Semi-microscale Distillation apparatus were utilized [10]. Reaction tempers were kept via controlled heating blocks instead of open oil baths; this improvmed therl uniormity as well as furtther reducd firh rick, whch wass solnb level hting. There were a total of 120 undergraduates in the Department of Chemistry that was split up between two equal cohorts during two consecutive semesters: Student performance was evaluated by trained laboratory instructor based on the operational proficiency, data recording correctness, safety compliance, and post laboratory report quality of each student. The reagent amounts were weighed and noted for every trial; the discarded material was then collected and counted after each one. Depending on the kind of reaction it was done through gravimetric method for yield or with GC analysis, purity is done with mp, bp or spec as needed [8]. And we have the data for some comparison on those two experiments.

4. Results and Discussion

4.1. Reagent and Solvent Consumption

The most immediate effect of the miniaturization study was the huge cutback on chemical materials in each of the 4 reaction sorts. As shown in Table 1, the average reagent volume decreased from 22.5 mL under conventional conditions to 0.73 mL under miniaturized conditions. The ratio is about 96.8%: From the average 27.5 ml per batch down to just 2.25ml was an amazing drop of 91.9%. And those same numbers, every single one, and a majority of cases go beyond or equal the cuts as per prior smaller labs by organisations over on both shores In the Oxidation, most notable of all is how much solvent I've reduced (92.5%). That's because instead of using a lot of bulk aqueous workup typical for traditional chromic acid oxidation transforms, it was replaced by a miniaturization and just 1.5mL dichloromethane necessary in my microextractions. The esterification reaction wasn't nearly as bad about decreasing like the aldol condensation did, both of those normally use way too much solvent to be convenient for easy isolation but we simply do not have this luxury on our tiny glass pieces and small distillations. It's worth noting that although there is a significant decrease in the amount, the molar stoichiometry of both reactions were kept in the miniaturization process. This way students can have same concept about reagents ratio and limiting reagent as before. The data in Table 1 show then, that not only are there environmental benefits to miniaturization, but it is consistent pedagogically with the goals of an "organic synthesis" course.

Table 1. Comparison of Reagent Volumes and Solvent Consumption Between Conventional and Miniaturized Methods

Reaction Type	Conv. Reagent Vol. (mL)	Mini. Reagent Vol. (mL)	Conv. Solvent (mL)	Mini. Solvent (mL)	Reduction (%)
Esterification	25.0	0.8	30.0	2.5	91.7
Aldol Condensation	20.0	0.6	25.0	2.0	92.0
Nucleophilic Substitution	30.0	1.0	35.0	3.0	91.4
Oxidation Reaction	15.0	0.5	20.0	1.5	92.5
Average	22.5	0.73	27.5	2.25	91.9

Yield Data from table 2 give very good reason to believe that minimization is doing at least as well as macroscale for a number of cases, sometimes better [7]. For all 4 reactions, the smaller scale up did better, the biggest was +5.7 percentage points for the aldol condensation reaction and +4.5 percentage points for esterification Aldol condensation yield has also been improved: at a macro scale level the rate of chalcone precipitation relative to continued enolate production is important, so if there isn't good mixing or you over-basify your reaction mixture then it can give side-products. In micro-scale it's a little smaller reactor with more pH distributions, quicker equilibrium in temp which is good to pick up a product. Nucleophilic substitution and oxidation reaction had small yet steady improvements of 2.4%, and 2.3% percentage points respectively due probably because there was more heat being transferred, hence the loss due to solvent evaporation is lesser. Apart from the increases in yield, miniaturized process takes shorter amount of time for each individual reaction and on average they reduced about 17% which went down from 67.5min to only taking up 55.8mins The first thing that is efficient this time around scheduling labs in the curriculum when the length of sessions remain fixed, so inefficiently using it remains a recurring problem in education. In table 2, we can see a picture that is consistent; there seems to be an improvement in terms of chemical reaction as well as laboratory session efficiency with smaller apparatus size.

Table 2. Reaction Yields Under Conventional and Miniaturized Experimental Conditions

Reaction Type	Conv. Yield (%)	Mini. Yield (%)	Yield Change (pp)	Reaction Time Conv. (min)	Reaction Time Mini. (min)
Esterification	72.3	76.8	+4.5	90	75
Aldol Condensation	68.5	74.2	+5.7	60	50
Nucleophilic Substitution	78.9	81.3	+2.4	75	60
Oxidation Reaction	79.0	81.3	+2.3	45	38
Average	74.6	78.4	+3.7	67.5	55.8

4.2. Cost Efficiency Analysis

To find how much money was impacted from an economic standpoint; counting cost of reagent& solvent+expenses incurred for disposal of wastes + depreciation (glasswars) per STUDENT & SESSION on lab station [6]. As can be seen from the results of the analysis, shown in Table 3, there is a total cost decrease from 82.20 CNY per student per session under standard conditions to 23.10 CNY under miniaturized protocol. Reagent cost was the biggest single category of saving, it dropped by 70.5% from CNY 38.60 to CNY 11.40 The fact that drops mean lower reagents being thrown away as well when having a less handling amount - in case spills happen to the sides and vessel walls, you'll always end up with much more left behind than everything was made out of: Solvent cost dropped 67.7%. This was in line with the solvent consumption mentioned previously: In the waste disposal category, there was a massive 84.8% decrease in proportion; this is because the waste volume is less and also the large volume halogenated solvent has been shifted towards other chemicals which are less costly when it comes to disposing them. Depreciation of glassware is also a minor part that depreciated because there was little pressure from mechanical force on small equipment compared to large ones. Now scaling it up by how many savings we'd get per session up until the total number of academics year labs classes with 30 students (lets say approx. 8 - 10), so annual savings from just miniaturization could be over CNY140,000 which is a substantial amount that's part of most labs' budgets, maybe used for purchasing more equipment/instruments, maintaining existing ones, or other experiments/research endeavors! So these results add more gasoline to the economics of making mini as a practical change to how labs work.

Table 3. Cost Analysis of Conventional vs. Miniaturized Synthesis Experiments (Per Student, Per Session)

Cost Category	Conventional (CNY)	Miniaturized (CNY)	Savings (CNY)	Cost Reduction (%)
Reagent Costs	38.60	11.40	27.20	70.5
Solvent Costs	22.30	7.20	15.10	67.7
Waste Disposal	15.80	2.40	13.40	84.8
Glassware Depreciation	5.50	2.10	3.40	61.8
Total per Session	82.20	23.10	59.10	71.9

4.3. Student Learning Outcomes and Engagement

In addition to looking at the chemical and monetary impacts of miniaturization, we also focused on how it affects what students learn as well as their interest in school. The standardized evaluation result shown in table 4, every dimension of the five evaluations shows that the miniaturization is more than experiment. The most striking change was seen with safety compliance score, which went up from 78.3 on average in the conventional group to 88.1 in the miniaturized one ($t = 8.92$, $p < .001$). And this is what we would expect: students who have to work with less dangerous chemicals tend to be more careful about procedure, if only because mistakes stand out in a more relative way when you're dealing with such tiny volumes - one drop can make up half the batch! Scores on Operations proficiency also greatly rose from 74.2 -> 82.6 possibly because there was a need for more precise dispensing & transferring of very small amounts so it required/invoked more meticulous lab work techniques. The data recording was also correct and the quality of the lab reports greatly improved, it is clear that small things matter. Overall student satisfaction of the lab (out of 5) went up from 3.52 to 4.37, which is also the largest single point improvement across all of our measured assessments End of semester survey qualitative feedback shows that miniaturized group felt the experiments were more mentally stimulating, they mentioned the personal responsibility for smaller amount motivated them and they have more faith in doing independent synthesis type work themselves. The above is consistent with the larger body of research on educational interventions in which the act of placing more operations into the hands of the students results in higher engagement and better conceptualization. So the numbers in table 4 give clear evidence that miniaturization is something more than just a trick to fit on an undergrad's syllabus, it really makes the teaching better.

Table 4. Student Performance and Engagement Assessment Outcomes (n = 120, Two Semesters)

Assessment Dimension	Conv. Group Score (Mean ± SD)	Mini. Group Score (Mean ± SD)	t-value	p-value
Operational Proficiency	74.2 ± 8.3	82.6 ± 7.1	6.83	< 0.001
Data Recording Accuracy	71.8 ± 9.1	80.4 ± 7.8	5.97	< 0.001
Safety Compliance	78.3 ± 7.6	88.1 ± 5.9	8.92	< 0.001
Post-lab Report Quality	72.5 ± 8.9	79.3 ± 8.2	4.71	< 0.001
Overall Satisfaction (1–5)	3.52 ± 0.61	4.37 ± 0.48	9.14	< 0.001

5. Applications in Educational Settings

Implications for this study go way past just these particular 4 reactions that were looked at, it’s something useful for all the different types of undergraduate synthesis lessons out there. But some considerations do need for institution when take those little procedures: First off you'll need some good little glassware: conical vials, little condensers, Hickman stills, tiny spatulas. The first capital outlay seems to be high but according to table 3 we can see that it will be recovered by way of saving on reagent & disposal costs for one academic year only. Second, training of teachers is important. Miniature procedures needs a different set of hands from macro-synthesis does, so maybe a structued workshop + Instructional video can help with the instructor's comfort on doing microorganic techniques. Lastly, students need to know what is special about the work being done at this scale- precise dispensing technique, understanding how do a micro separation and interpreting data form such minute amounts of materials. The standard rubric created in this paper can be seen as a supplement. And looking forward from there, combining those little synthesizers with prediction tools and real-time spectroscopy is going to be where we take organic chem on the instruction front. It should also lower waste of materials and acquaint pupils with the digital technologies shaping the world of professional synthetic chemistry; which would make undergrad lab training more like today's actual research work.

6. Conclusion

It contains the whole set of experimentally verified facts proving that having anorganic synthesis lab is valid in terms of being scientific, economical and educational over teaching undergraduate students. To see what the big difference our representative synthesis reactions make compared to conventional miniaturized protocol: Here you can notice that it has around %91.9 in lesser solvent consumption meaning more than 71.9% less money per student lab cost. This represents an average improvement over yield of each pp and all around quicker too (%): Analyze the students' performances of the 120 undergraduates, all aspects have improved significantly. The performance is statistically significant in terms of operations, safety compliance, general satisfaction, etc. All these findings together show that miniaturized organic synthesis is an answer in miniature to some key problems with chemistry teaching today – making less mess, cheaper labs, safer work, better handling of the “labour” part. In this research, we have created some protocols and assessment tools which can be used in various different institutional settings, and the authors encourage its usage amongst the wider chemistry education community. Futur works need more miniaturization towards multi-step synthesis sequences and try to incorporate insitu spectroscopic monitoring if its posible so we have better evidance on the change of the curriculim on organic chemistry lab practices.

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