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Scale-Up of Organic Reactions in a Pharmaceutical Kilo-Lab Using a Commercial Microwave Reactor

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Abstract:

A range of pharmaceutically relevant reactions were investigated for scale-up in a kilo-lab environment using a commercial batch microwave reactor. Typical scale-up issues are discussed, taking into account the specific limitations of microwave heating in large-scale experiments. Examples of scale-up from 15 mL to 1 L are presented and demonstrate that the synthesis of compounds on greater than 100 g scale is feasible in one batch. Aided by this new technology reaction times have been significantly reduced and the productivity of our scale-up laboratory has been enhanced. Production rates of several hundred grams per day were achieved using microwave technology. The article concludes with a brief discussion of advantages and disadvantages of this type of batch microwave reactor.

Introduction

In the past few years, microwave heating has become a widely accepted technique for organic synthesis, used both in academic and industrial laboratories.[1] The major driving force for the widespread application of this innovative enabling technology, is that many microwave reactions experience a remarkable rate acceleration when compared to those with conventional heating. Such reactions are frequently coupled with increased yields and improved purity profiles.[2] For the last 10 years, dedicated microwave reactors for small-scale synthesis in research laboratories have been commercially available (typically in the range of few hundred milligrams to some grams) and offer a number of advantages.[3] Reaction mixtures can be rapidly heated under pressure in sealed vessels to temperatures above 200 °C, thus shifting reaction times from hours to minutes. Modern microwave reactors additionally allow controlled parallel or automated sequential processing of a large number of experiments and lead to significantly higher productivity. The use of automated microwave reactors also enables the rapid optimization of reaction conditions, and more recently, such devices have found their way into the pharmaceutical industry where they are used for the high throughput synthesis of chemical libraries.[4,5]

Today, the most common application of microwave irradiation is in the synthesis of new molecules on small scale for medicinal chemistry purposes. However, microwave technology is increasingly required in early scale-up phases, specifically for the synthesis of intermediates and active compounds in larger quantities. The question whether microwave technology could be used for the scale-up of organic reactions from gram to kilogram scale has become one of the major topics currently discussed among industrial process development chemists.[6−8] At present time the big challenge in this area is to establish a reliable and safe process setup, where typical scale-up issues, for example the limited penetration depth, a reliable temperature control and a suitable reactor design, are carefully considered.[8,9]

Small-scale organic synthesis is traditionally conducted in batches, and the majority of commercial microwave reactors also operate in this way, utilizing vessels generally below a 100 mL volume. The most restricting factor for scale-up is the limited penetration depth of the microwave field, which is dependent on the dielectric properties of the microwave absorbent reaction mixture, and is usually in a range of a few centimetres. The maximum size of a batch reactor, that can be simultaneously heated by standard magnetrons, is therefore approximately 2−3 L. Despite the fact that some commercial microwave batch reactors provide a relatively large power output of more than 1000 W, chemists have not yet been able to achieve the same steep heating and cooling profiles for litre volumes as those observed for small-scale experiments. In order to overcome these problems, stop-flow[3c] and continuous-flow reactors[3d] have been developed by a number of providers. Although being of advantage in terms of safety and productivity, the major drawback of a continuous-flow reactor is the well-reported fact that they are, in most cases, incompatible with heterogeneous mixtures.[8–10]

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A further, more general, obstacle that discourages chemists from using these instruments for chemical synthesis is that, to date, reactions in medicinal chemistry are normally performed in a batch mode, and transferring them into a continuous process requires additional time and optimization effort. It is therefore not surprising that the number of publications which describe the use of continuous flow reactors for synthesis on a 100 g scale or more is still very small. Wilson et al. used a noncommercial glass coiled flow cell which was introduced into the microwave cavity of a Emrys Optimizer to investigate nucleophilic aromatic substitution reactions, a Suzuki coupling, and an esterification on a 10 g scale.[10] They also reported that crystallization of the product and the formation of solid particles clogged the lines and frits, thus significantly reducing the utility of such a tool. Leadbeater et al. had a similar experience when they scaled up a range of organic reactions to hundreds of grams using a commercially available continuous flow microwave reactor.[11] They concluded that scale-up from small sealed tubes to continuous processing is feasible, as long as reaction mixtures are homogeneous and do not contain solid particles.

A comparison of various commercially available microwave reactors with focus on scale-up issues was recently published by Moseley et al.[6] In their study, all three concepts (batch-mode, stop-flow, and continuous-flow) were tested by thorough comparison of a rearrangement reaction. They showed that the devices tested can be used for converting litres of reaction mixtures to yield products in a range from 50 to 200 g. However, a further investigation of a stop-flow microwave reactor revealed that the same limitation of clogging also exists for a stop-flow concept and that such a system works best when only homogeneous solutions are converted in multiple batches.[12]

Results and Discussion

Specific Requirements of a Scale-Up Laboratory. Synthesis work in a scale-up laboratory is traditionally performed in a batch-wise manner using conventional thermal heating techniques under atmospheric pressure. The limiting factor for the reaction temperature under such conditions is the boiling point of the solvent. In contrast to this, microwave heating in a pressurized vessel allows access to reaction temperatures far above the boiling point of the solvent. The superheating, thus occurring, leads to remarkably shortened reaction times as well as higher yields and reduced byproduct formation.[13] When choosing a reaction solvent, one can consider not only boiling point but also more favorable workup and purification properties, thus avoiding time-consuming workup procedures. Solvent choice is particularly important in scale-up and can lead to shorter processing times for a chemical synthesis and, therefore, to a higher productivity.

For chemists working in a scale-up laboratory, the use of microwave technology offers particular advantages in three main classes of chemical reactions. The first class consists of reactions which require moderately high temperatures (e.g. >80 °C) and long reaction times (e.g. >8 h). In such a case, decreasing the reaction time from hours to minutes often leads to an improved work-flow and to higher productivity.

The second class of reactions is composed of those requiring temperatures above 150 °C which normally have to be performed in high-boiling solvents such as DMSO, DMF, or NMP. In some cases, it is very laborious and time-consuming to remove these high-boiling solvents during the workup in order to isolate the product. Replacing these "work-up unfavorable" solvents by solvents which are "work-up friendly" can help to avoid these kinds of problems as demonstrated by an earlier work.[13]

Reactions which require more extreme conditions in terms of temperature, or which do not result in high enough yield or purity under conventional conditions, can be categorized in a third class. As a consequence, chemists are not able to utilize these reactions when using standard lab equipment. The application of microwave technology expands the chemical space which can be explored in the search for new interesting compounds. The conversion of phenols into aromatic thiols by the Newman-Kwart rearrangement,[14] which in some cases requires temperatures above 250 °C, is an interesting example which falls into this category. A second example is the valuable ortho-Claisen rearrangement, which normally requires temperatures above 200 °C.[15] In many cases, the use of microwave equipment instead of an oil bath for ortho-Claisen rearrangement is more convenient and offers significant advantages.[16−18]

A more recently explored example of chemical scope expansion are microwave-assisted organic reactions which are performed in water, under the so-called "near-critical" conditions reached in temperatures between 270 and 300 °C. Several useful transformations, such as the hydrolysis of esters and amides, Diels−Alder cycloadditions, pinacol rearrangements and the Fischer indole synthesis were successfully performed under these special near-critical conditions.[19]

Microwave Heating and Scale-Up of Batch Reactions. One of the first applications of a multimode parallel batch reactor for scale-up of microwave reactions from 1 to 100 mmol scale was published by Kappe et al. some years ago.[20] They found that for a range of reactions it was possible to achieve similar yields both 5 and 500 mL scale. However, for the experiments they reported, a prototype reactor with 8 reaction vessels was used, thus limiting the reaction volume to 500 mL. At that time, they did not have access to of the commercially available machines with a total volume >1 L which would be available for use today.

We typically begin our scale-up process with a trial on small scale (5−20 mL) in a Biotage Initiator microwave reactor,

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Table 1. **Comparison between ethanol heated to 150 °C in two different-scale microwave machines**

	Biotage Initiator	Synthos 3000
reaction volume	20 mL	16 × 60 mL = 960 mL
max. power	300 W	1400 W
ratio power/volume	15 W/mL	1.46 W/mL
time to heat to 150 °C	3 min	10 min
time to cool to 50 °C	5 min	30 min

which provides a so-called focused monomode microwave field and a power of 300 W. For synthesis on a larger scale, a Synthos 3000 Multiwave reactor is used. The Synthos machine is a multimode reactor capable of providing a maximum irradiation power of 1400 W and a maximum reaction volume of approximately 1.2 L, distributed between 16 vials. When we look at the heating process in more detail, it is obvious that rapid heating and, even more importantly, rapid cooling strongly depend on the ratio of volume to surface area of the reaction mixture. Of course, this ratio changes significantly when a reaction is scaled from a 20-mL scale to a 1000-mL scale. As a consequence, one should expect a longer heating period for the bigger batch reaction compared to a reaction performed on smaller scale. Although the volume of 1 L is distributed between 16 100-mL vials in a Synthos 3000 reactor, the same step heating rates as on small scale are rarely observed. A comparison of relevant parameters for a typical scale-up experiment is shown in Table 1.

The Biotage Initiator provides a maximum power of 300 W, and when a 20-mL vial is used to perform a reaction, the ratio of available power per volume of reaction mixture is 15 W/mL. Heating a 20-mL sample of ethanol to 150 °C in the Biotage Initiator required 3 min. The reactor required about 5 min to cool the sample back down to 50 °C.

In a second experiment using the Synthos 3000 Multiwave microwave, 960 mL (16 vials each filled with 60 mL) of ethanol were heated to 150 °C. The two magnetrons of the Synthos 3000 provide a maximum power of 1400 W. Correlated with the volume of 960 mL, a much lower ratio of power per volume of 1.46 W/mL is obtained. Nevertheless, only 10 min were required to heat the 48-fold amount of ethanol to 150 °C, which corresponds to an increase in the heating period by a factor of 3.3. To cool this volume down again to 50 °C, 30 min were required, which is 6 times longer compared to that for the Biotage Initiator.

When we look in more depth into the heating process (Figure 1) it becomes obvious that microwave heating, especially for batches of 1 L volume, has its own limitations. A simple test, where we heated 1.12 L of acetone in 16 vials to 180 °C using a constant power irradiation of 1400 W, revealed that the temperature rise is not a linear function of the irradiation time. Above 100 °C, acetone and other solvents such as ethanol and methanol become more transparent to microwave irradiation, and less energy is converted into heat.[21] In total, 18.5 min were required to heat this volume to 180 °C. Even more time is required to remove the energy after the heating process is stopped. As shown in Figure 1, about 37 min were required to cool a volume of 1.12 L of acetone to 50 °C. In summary, the time which is required to perform a reaction on a 1 L scale is mainly defined by the heating and cooling processes which are, especially for short reaction times, the dominating parts of the reaction process, an observation which is significantly different from the result of Kappe et al. who reported that it was possible to reach reaction temperatures of 180 °C in 2−3 min on a close to 500-mL scale.[20]

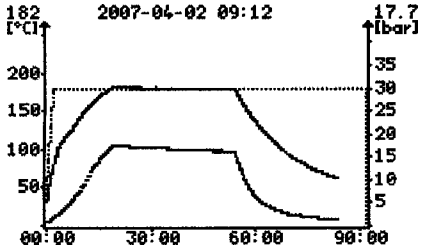
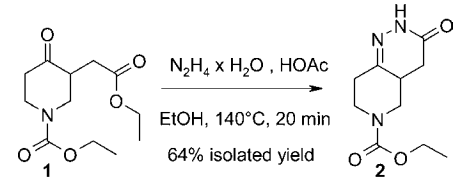


Figure 1. **Temperature profile when 1.12 L (16 × 70 mL) of acetone is heated to 180 °C.**

Examples for Optimization and Scale-Up. In the course of our daily business in the kilo-lab, we are frequently faced with the preparation of a number of intermediates or drug candidates on a larger scale in which at least one step of the original synthesis was performed in a microwave reactor. In order to increase the productivity in this early phase, it is of great importance to reduce the time which is required to produce these compounds on a larger scale. As previously mentioned, reactions requiring many hours or even days at elevated temperature are particularly interesting targets for improvement of the work-flow by the use of microwave technology.

The cyclization of a γ-ketoester with hydrazine hydrate in Scheme 1 was part of a reaction sequence submitted to our kilo-lab for scale-up to 100 g. In the literature this reaction is described with a yield of approximately 60%.[22] Under conventional conditions (refluxing in ethanol for 4 h) we obtained product **2** in 53% yield. By performing the reaction in a Synthos 3000 microwave reactor at 140 °C for 20 min, we were able to improve the yield to 64% on a 20 g scale. Further scale-up to a batch size of 900 mL (130 g in 16 vials filled each with ∼60 mL) under the same conditions (140 °C/20 min) requiring no additional optimization, gave 73 g of product in a yield of 63%. With regard to productivity, this procedure allows the production of 500−600 g per 8 h working day.

Scheme 1. **Microwave-promoted cyclization of a γ-ketoester with hydrazine hydrate**



A well-known standard procedure in organic chemistry to form pyrazoles is the reaction of β-ketonitriles with hydrazines. The reaction shown in Scheme 2 is part of the synthesis of a p38 MAP kinase Inhibitor, which is described in literature with

(21) The ability of a solvent to absorb microwave energy is related to three main dielectric parameters: tangent delta, dielectric constant, and dielectric loss. Since these parameters are dependent on the temperature, the ability to absorb microwave energy changes with the temperature, and a lot of common solvents show a decrease in microwave susceptibility with temperature rise.

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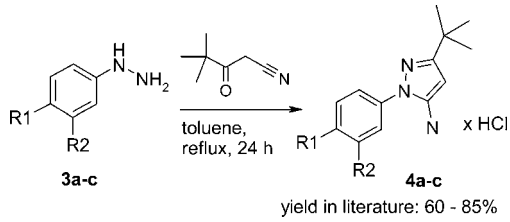
Scheme 2. **Microwave-promoted aminopyrazole synthesis**



a yield of 60−85% after refluxing in toluene for 24 h.[23] In the course of our investigations we replaced toluene with methanol and obtained a yield of 86% after 16 h at reflux. Under microwave conditions (130 °C, 20 min) the reaction of *p*-tolylhydrazine and pivaloylacetonitrile was scaled up by a factor of 4 (entry 1, Table 2) to give pyrazole **4a** in 85% yield (entry 2, Table 2). Furthermore, the required processing time (from the start of the reaction until the end of the cooling down period) was reduced significantly from 16 h to 55 min, allowing the production of multihundred grams per day. Similar results were obtained for the cyclization of 3,4-dimethyl phenylhydrazine with pivaloylacetonitrile to give pyrazole **4b** (entries 3 and 4, Table 2). Yields for this reaction were almost the same for both microwave and conventional heating, but due to the much shorter processing time under microwave irradiation, we were able to obtain nearly 200 g of product in less than one hour. By preparing 4 batches during an 8 h working day, it is possible to produce 800 g of this compound in high quality. When we tried to convert the deactivated 4-cyanophenylhydrazine into pyrazole **4c** under conventional conditions, we found that the reaction was still not complete after 16 h of reflux in methanol. However by using our microwave equipment, we were able to push the reaction to completion. Scaled-up to a 100 g scale, we isolated the pyrazole **4c** in a yield of 77% after 25 min reaction time at 140 °C (entry 6, Table 2, and Scheme 2).

These examples clearly show that a shift of the reaction temperature from 16 h to 15 min by application microwave conditions under pressure allows significant enhancement of the productivity. To produce some hundred grams of a product under conventional heating requires at least 16 h, independent of the scale. However, the use of a batch microwave with 1 L reaction volume enables a skilled person to run several batches sequentially per day and to produce several hundred gram within an 8 h working day.

Substitution of halogens on heteroaromatic rings is a common way to introduce new functionalities. Diamino pyrimidine **6** in Scheme 3 was required on a 100 g scale as an intermediate for the synthesis of purines and pteridines. In the literature, this exchange was performed on a 5 g scale using ammonia in ethanol in a sealed tube under pressure for 6 h at 125−130 °C with a yield of 76%.[24] After a couple of trials on small scale using our Synthos 3000 equipment, we found suitable microwave conditions of 170 °C for 180 min and obtained the desired product on a 120 g scale in 83% yield and high purity.

In the course of our work as a support function for medicinal chemistry, we were asked to produce a larger quantity of

Scheme 3. **Microwave-promoted nucleophilic substitution of a chloropyrimidine**

6-bromoquinazin-4-one **7** (Scheme 4) as an intermediate in the synthesis of biologically active compounds.[25−27] A common method for the formation of the 3H-quinazolin-4-one ring is based on the Niementowski reaction which involves the condensation and cyclization of anthranilic acid derivatives with formamide.[28] Such a procedure usually requires high temperatures (150−180 °C) and is coupled with lengthy and tedious workup conditions.[29] On bench scale, microwave-assisted reactions gave yields varying from 55% to 75%. Similar procedures using microwave technology are described in literature, however, with examples on a milligram scale.[26,29] We tested these conditions (150 °C, 20 min) on a 5 g scale using our microwave equipment but found that the reaction did not go to completion. Analysis of the reaction mixture by HPLC revealed about 55% conversion to product with about 45% of remaining starting material. On performing a scale-up experiment we found that the reaction proceeded in a fast and very clean manner at 180 °C with a reaction time of 30 min. Although it is reported that formamide may decompose above 170 °C to form ammonia, the highest pressure measured inside the vials was 2.3 bar. Since the boiling point of formamide is 210 °C, this pressure reflects the formation of water during the reaction or a slow decomposition of formamide and the formation of ammonia.[30] After executing a simple workup procedure (the reaction mixture was poured into water, the precipitated product was filtered and dried), we isolated compound **7** in 89% yield and a purity of >99% on a 200 g scale in one single batch.

Compared to other published procedures in which the synthesis of compound **7** is performed in two steps using various reagents (*e.g.*, ammonia, EDC·HCl, HOBt), solvents (*e.g.*, DMF), and a relatively complicated multistep workup,[25] our scale-up approach fulfills several principles of green chemistry and can be regarded as environmentally benign.[31] Our reaction protocol is performed under solvent-free conditions; for workup, only water is used, and the amount of chemical waste is minimized. The reaction is efficient with regard to atom economy; the only byproduct of the reaction is water. The use

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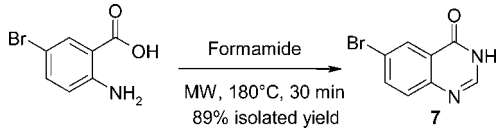
Table 2. **Comparison of aminopyrazole 4a−c formation in methanol**

entry	product	scale	reaction temp., time	yield[a] (%)	isol. product (g)
1	**4a**: $R^1 = Me$, $R^2 = H$	20 g, 200 mL	reflux, 16 h	86	28.8
2	**4a**: $R^1 = Me$, $R^2 = H$	82 g, 800 mL	MW, 130 °C, 20 min	85	117
3	**4b**: $R^1 = R^2 = Me$	8.6 g, 100 mL	reflux, 16 h	91.5	12.8
4	**4b**: $R^1 = R^2 = Me$	128 g, 900 mL	MW, 130 °C, 15 min	92	192
5	**4c**: $R^1 = CN$, $R^2 = H$	2 g, 15 mL	reflux, 16 h	n.d.[b]	n.d.
6	**4c**: $R^1 = CN$, $R^2 = H$	102 g, 800 mL	MW, 40 °C, 25 min	77	128.5

[a] Isolated yield. [b] Only 70% conversion to product detected by HPLC.

Scheme 4. **Microwave-assisted synthesis of 6-bromoquinazin-4-one 7**



of microwave heating and the shortened reaction time lead to a better energy efficiency. Due to the cleanliness of such a reaction and to the high yield, no additional purification is required, thus avoiding the formation of additional waste.

Summary

The scale-up of a range of organic reactions using a commercially available microwave reactor was investigated, with special focus on handling, workflow, and typical scale-up issues. The Synthos 3000 batch mode reactor provides a relatively large reaction volume (maximum 16 vials which can be filled with up to 70 mL each), allows high temperature and pressure (240 °C/40 bar), and proved to be very robust. The magnetic stirring system allows the handling of suspensions; however, there is way of controlling whether stirring is efficient in each vial. In some cases we experienced variability in conversion in parallel vials because the magnetic stirrer bar was blocked during the reaction or stirring did not work efficiently enough. Most of the time the reaction conditions applied on a 15-mL scale in a Biotage Initiator unit were easily transferred to our Synthos 3000 microwave reactor and led to comparable results. Only in a few cases was additional optimization required, and this was mostly limited to moderate adjustments in reaction temperature or reaction time.

In general, the results from small-scale trials were reproduced on a larger scale without any significant optimization effort. Nevertheless, filling and removal of all 16 of the vials is laborious, and the cooling period even for large reaction volumes is comparatively long. A further disadvantage with regard to the production of larger quantities is the fact that it is not possible to run several batches sequentially in an automated manner.

In many scale-up experiments, we experienced the use of microwave technology leading to a significant decrease in the reaction time and in some cases to less byproduct formation and higher yield. Microwave technology allows us to optimize a reaction with special focus on workup and purification, independent of the required reaction temperature and the boiling point of the solvent. Furthermore, the possibility to reach temperatures greater than 200 °C significantly expands the chemical scope of organic chemistry and allows us to run reactions which are otherwise difficult to perform under conventional conditions. Especially when considering the synthesis of compounds on a 100-g scale, the use of a microwave reactor supports the development of environmentally benign processes and green chemistry.

At the present time, none of the three strategies that have evolved for scale-up (batch, stop-flow, and continuous flow) offers solutions to all the scale-up-related problems that chemists face.[6,9] For a microwave batch reactor, the penetration depth is still a limiting factor, and the reaction volume of commercially available microwave reactors does not exceed the 1−2 L range. With regard to a stop-flow or continuous flow regime, the handling of suspensions and precipitating products which may block the lines and valves, is still a severe limitation that hinders the broad use of these tools for the scale-up of organic reactions. Nevertheless, we have demonstrated that a microwave batch reactor, for example the Synthos 3000, is a useful tool for the scale-up of organic reactions and suitable for the delivery of several hundred grams per day to meet medicinal chemistry needs. We were also able to show that our productivity and output can be significantly increased by using microwave technology. With regard to true process development and scale-up towards multikilogram scale we conclude, along with others in this field, that there is presently no commercially available microwave solution that fulfils all the requirements without any drawbacks.[6]

Experimental Section

General Experimental. All reagents were obtained commercially and used as received unless otherwise noted. TLC was performed on Merck silica gel plates 60 F-254, Art. Nr. 5729 with detection by UV (254 nm).

Reverse phase HPLC analyses were performed on an Agilent-1100 machine using a Macherey-Nagel CC 70/4 Nucleosil 100-13 C18 HD column, acetonitrile and water (both containing 0.05% TFA), a column temperature of 35 °C, with a flow rate of 1.0 mL/min, and measuring at 216 nm. The standard gradient used was 20−100% MeCN over 6 min, 100% MeCN for 3 min followed by 100−20% MeCN over 0.5 min.

NMR spectroscopy was performed using a 400 MHz Varian instrument, AS 400 Oxford; ^{1}H shifts were referenced to DMSO-d_6 at 2.49 ppm and $CDCl_3$ at 7.25 ppm with tetramethylsilane as internal standard for ^{1}H NMR. Melting points were measured using a Büchi, B-545 instrument.

Equipment Used. Reactions on small scale were performed in the commercial Biotage Initiator Sixty monomode microwave unit with IR temperature monitoring and noninvasive pressure transducers, using 20-mL quartz vials.

Scale-up experiments were performed in a commercial Synthos 3000 Multiwave microwave unit. We used the configuration with 16 100-mL PTFE lined tubes in ceramic cases, allowing a maximum load of ~70 mL per tube. Temperature and pressure were monitored continuously in a reference tube by an internal gas balloon thermometer; 240 °C and 40 bar are reachable. In addition, all vials were monitored by an external IR sensor.

Experimental Procedures for the Reactions Performed in this Study. *Preparation of 3-Oxo-3,4,4a,5,7,8-hexahydro-2H-pyrido[4,3-c]pyridazine-6-carboxylic Acid Ethyl Ester (2) under Conventional Conditions.* To a solution of 3-ethoxycarbonylmethyl-4-oxo-piperidine-1-carboxylic acid ethyl ester **1** (20 g, 78 mmol) in ethanol (60 mL) were added hydrazine hydrate (3.9 g, 78 mmol) and acetic acid (7.8 mL, 136 mmol) at ambient temperature. The mixture then was heated to reflux for 4 h. After cooling to ambient temperature, the reaction mixture was concentrated *in vacuo*, and the remaining solid was triturated in ethanol (40 mL). The product was filtered and dried in a vacuum oven at 60 °C to yield the title compound **2** as an off-white crystalline solid (9.4 g, 54%). HPLC (t_R 4.33 min, 99%); mp 166−167 °C (lit.[22] 167−169 °C).

Preparation of 3-Oxo-3,4,4a,5,7,8-hexahydro-2H-pyrido[4,3-c]pyridazine-6-carboxylic Acid Ethyl Ester (2) in Anton Paar Synthos 3000. 3-Ethoxycarbonylmethyl-4-oxo-piperidine-1-carboxylic acid ethyl ester, **1** (130 g, 505 mmol), hydrazine hydrate (24.6 mL, 505 mmol), and acetic acid (50.6 mL, 884 mmol) were dissolved in ethanol (800 mL). This stock solution (~900 mL) was charged to 16 PTFE tubes, each containing a magnetic stirring bar, sealed in ceramic cases, and placed inside a 16-position rotor. One tube was fitted with a gas balloon thermometer; the temperature of the other vials was monitored by an IR-sensor. The reaction mixtures were heated with magnetic stirring to 140 °C over 12 min with 1400 W available power, held for 20 min at 140 °C, and then cooled by air ventilation to 60 °C over 30 min. The contents of all tubes were combined, and solvent was evaporated *in vacuo*. The remaining solid was recrystallized from ethanol (300 mL). After filtration and drying, product **2** was isolated as a white crystalline solid (73 g, 64%). HPLC (t_R 4.32 min, 99%); mp 167−168 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.27 (t, J = 7 Hz, 3H), 2.50 (dt, J = 17, 6 Hz, 4H), 2.83 (m, 1H), 3.57 (t, J = 6 Hz, 2H), 3.65 (t, J = 6 Hz, 2H), 4.14 (q, J = 7 Hz, 2H).

Preparation of 5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-ylamine, 4a, and 5-tert-Butyl-2-(3,4-dimethyl-phenyl)-2H-pyrazol-3-ylamine (4b) on Small Scale under Conventional Conditions. In a typical procedure, *p*-tolylhydrazine hydrochloride (20 g, 126 mmol) and pivaloylacetonitrile (17.3 g, 139 mmol) were mixed in methanol (200 mL) and heated to reflux. Conversion to product was monitored by HPLC and found to be complete after 16 h. Methanol was evaporated, and the remaining solid was triturated in refluxing DCM (100 mL). After cooling to 0 °C, the precipitated product was filtered and dried to give 3-aminopyrazole, **4a**, as colorless crystals (28.8 g, 86% as HCl salt). HPLC (t_R 3.74 min, 100%); mp 195 °C dec.

Compound **4b** was obtained by a similar procedure and isolated as an off-white solid (12.8 g, 91.5% yield). HPLC (t_R 3.87 min, 100%); mp 219−220 °C.

Preparation of 3-Aminopyrazoles 4a−c on Large Scale in Anton Paar Synthos 3000. In a typical procedure, *p*-tolylhydrazine hydrochloride (82 g, 517 mmol) and pivaloylacetonitrile (71.2 g, 569 mmol) were dissolved in methanol (650 mL). Sixteen vials were filled with 50 mL each of this solution and placed in the rotor. The reaction mixtures were heated with magnetic stirring to 130 °C over 5 min with 1400 W available power, held for 20 min at 130 °C, and then cooled by air ventilation to 50 °C over 30 min. The contents of all tubes were combined, and solvent was evaporated *in vacuo*. The remaining solid was partly dissolved in hot DCM (100 mL) and precipitated again by addition of diisopropyl ether (100 mL). The suspension was cooled to 0 °C, stirred for 20 min, and filtered. After filtration and drying 5-*tert*-butyl-2-*p*-tolyl-2*H*-pyrazol-3-ylamine **4a** was isolated as an off-white solid (117 g, 85%). HPLC (t_R 3.74 min, 100%); mp 196 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 9H), 2.38 (s, 3H), 5.67 (s, 1H), 7.36−7.50 (m, 4H).

Preparation of 5-tert-Butyl-2-(3,4-dimethyl-phenyl)-2H-pyrazol-3-ylamine (4b). 3,4-Dimethyl-phenylhydrazine hydrochloride (128 g) was dissolved in methanol (700 mL), and 16 tubes were filled with 60 mL each. The reaction mixtures were heated to 130 °C over 5 min and held for 15 min at 130 °C. After cooling to 50 °C, the solvent was evaporated, and the residual oil was precipitated by addition of diethyl ether (500 mL). The crystalline solid was filtered and dried. Compound **4b** was isolated as a white solid (178 g, 86%); HPLC (t_R 3.87 min, 100%); mp 220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (s, 9H), 2.29 (s, 6H), 5.66 (s, 1H), 7.26−7.29 (m, 1H), 7.32−7.39 (m, 2H).

Preparation of 5-tert-Butyl-2-(4-cyanophenyl)-2H-pyrazol-3-ylamine (4c). 4-Cyanophenylhydrazine hydrochloride (102 g) was dissolved in methanol (700 mL), and 16 tubes were filled with 50 mL each. The reaction mixtures were heated to 140 °C over 5 min and held for 25 min at 140 °C. After cooling to 50 °C, the solvent was evaporated and the residual oil solidified upon standing. The crude material was suspended in DCM (400 mL), cooled to 0 °C, and filtered. The crystalline product was dried, compound **4c** was obtained as a white solid (128.5 g, 77%). HPLC (t_R 3.97 min, 100%); mp 199−200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (s, 9H), 5.62 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H).

Preparation of 4,5-Diamino-6-chloropyrimidine (6). Portions of 5-amino-4,6-dichloropyrimidine (7.5 g each, 732 mmol) were charged to 16 PTFE tubes, and a solution of 10% ammonia in ethanol (60 mL for each tube) was added. The tubes were carefully sealed in ceramic cases, placed in the rotor, and heated to 170 °C in the microwave cavity over 5 min and held for 180 min at 170 °C. After cooling to 50 °C, the content of all tubes was combined, and the precipitated solid was filtered and suspended again in water (750 mL) and stirred at ambient temperature for 30 min. The precipitate was filtered, washed with water, and dried in vacuo to give compound **6** as a yellow solid (87.8 g, 83%); mp 248−250 °C dec (lit.[24] 249−250 °C).^{1}H NMR (400 MHz, DMSO-d_6) δ 4.95 (s, 2H), 6.76 (s, 2H), 7.65 (s, 1H).

Preparation of 6-Bromoquinazin-4(3H)-one (7). Portions of 2-amino-5-bromobenzoic acid (15 g each, 1.11 mol) were charged to 16 PTFE tubes and suspended in formamide (35 mL for each tube). The tubes were carefully sealed in ceramic cases, placed in the rotor and heated to 180 °C in the microwave cavity over 5 min and held at 170 °C for 30 min. After cooling to 70 °C, the content of all tubes was poured into water (2.4 L) and stirred at ambient temperature for 30 min. The precipitated solid was filtered and washed with water (500 mL) and dried in vacuo to give compound **7** as an off-white solid (222.5 g, 89%); mp 273−274 °C (lit.[26] 262 °C). HPLC (t_R 3.83 min, 100%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 8.6 Hz, 1H), 7.92 (dd, J = 8.6 Hz, 2.35 Hz, 1H), 8.11 (s, 1H), 8.16 (d, J = 2.35 Hz, 1H), 12.4 (br s, 1H).

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