Development of an Efficient and Sustainable
Synthesis of 2-(3-Methyl-1H-1,2,4-triazol-1-yl)
Acetic Acid under Continuous-Flow Conditions

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ABSTRACT

A novel, metal-free process for the challenging synthesis of 2-(3-methyl-1H-1,2,4-triazol-1-yl)acetic acid (I) is reported, which features an efficient condensation for the triazole build-up under flow conditions. This continuous, two-step method is atom economical, highly selective and environmentally benign, due to the avoidance of chromatography and isolation steps. Compared to the earlier batch synthetic routes, higher yields were achieved in a flow reactor. In addition, a highly energetic intermediate could be controlled and handled in a safe manner. To generalize the established route, several triazoles were finally prepared under the described conditions, confirming that the methodology could find useful applications for the rapid and sustainable construction of differentially functionalized 1,2,4-triazoles.
Introduction

Small nitrogen-containing heterocycles are broadly present in molecular frameworks displaying functional properties of key relevance for the pharmaceutical, agrochemical and material science fields.\(^1\) In this context, 1,2,3- and 1,2,4-triazoles occupy a prominent role in modern synthetic chemistry\(^2\) and, thanks to their modularity, they can either be ‘bought-in’ within larger molecules by \(N\)-alkylation strategies, or alternatively ‘built-in’ directly via cyclization reactions. While the first approach is more suited for commercially available unsubstituted triazoles, the latter is addressing at best the need of adjustable mono-, bis- and tris- substituents on the triazole ring.\(^3\)

We became interested in developing a method to rapidly supply kilogram amounts of 2-(3-methyl-1\(H\)-1,2,4-triazol-1-yl)acetic acid (1). An obvious approach able to furnish initial multi-grams amount of material relied on the ‘buy-in’ strategy from commercial 3-methyl-1\(H\)-1,2,4-triazole (3) through alkylation with bromoacetate 2 (Scheme 1). Since moderate selectivity on the \(N\)-alkylation was anticipated, a chromatography to purify the desired \(N\)-1 isomer was deemed necessary.

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While on the short term this approach was a good fit, on the longer run we aimed to have a more efficient route achieving higher yields and devoid of chromatographic purifications, which are particularly problematic for large scale applications, due to the economic and environmental impacts associated with the use and disposal of large amounts of organic solvents.

Looking at alternative synthetic strategies for a more sustainable and efficient process, we rapidly realized that the selectivity problem associated with the $N$-alkylation of 2 could be overcome only with a ‘built-in’ approach, i.e. via the formation of 3-methyl triazole moiety by cyclization. To be competitive, the new strategy would require simple, commercially available starting materials and mild reaction conditions. A possible alternative, where the triazole could be assembled through condensation between simple ethyl hydrazinoacetate 4 as hydrazine synthon and acetimidamide 5 as electrophilic partner, was proposed from a different retrosynthetic disconnection (Scheme 2). The latter could be derived from commodity chemicals such as formamide and dimethylacetamide dimethylacetal 6.

Scheme 1. Initial synthetic ‘buy-in’ approach to acid 1.

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4 Screening of bases, solvents, temperatures and type of nucleophiles for the alkylation of 2 was performed (but not detailed here for the sake of conciseness), showing only a very limited effect on the selectivity. For a similar result, see: Fox, R. J.; Tripp, J. C.; Schultz, M. J.; Payack, J. F.; Fanfair, D. D.; Mudryk, B. M.; Murugesan, S.; Chen, C. P. H.; La Cruz, T. E.; Ivy, S. E.; Broxer, S.; Cullen, R.; Erdemir, D.; Xu, P. G. Z.; Fritz, A.; Doubleday, W. W.; Conlon, D. A. Org. Process Res. Dev. 2017, 21, 1095-1109.
Scheme 2. New retrosynthetic ‘built-in’ plan to acid 1.

A similar approach was previously reported for the preparation of 5-methyl-1,2,4-triazole derivatives.\(^5\) In those cases, acetamide was employed to generate reactive amide derivative 8 which underwent cyclization to 5-methyltriazoles 10 (Scheme 3).

\[ \text{Scheme 3. Literature precedent for the synthesis of 5-methyltriazole derivative through cyclization with amide derivative 8.}^{5} \]

Although the analogous acetimidamide 5 has never been described before and the preparation of 3-methyl-1,2,4-triazole derivatives has not been reported with such synthetic strategy,⁶ the existing precedents gave us good confidence about the alternative route. In addition, we aimed to develop a process under continuous flow conditions due to the well-recognized advantages of improving efficiency, selectivity, safety and reproducibility as compared to traditional batch chemistry.⁷ Making use of this principle, we describe herein the successful development of a new, scalable and concise synthesis of triazole acetic acid 1 and how the application of continuous-flow conditions allowed increased waste and yield efficiencies along with improved process safety.

Results and Discussion

1ˢᵗ generation batch process. The triazole N-alkylation synthesis used at the beginning of our investigation to satisfy the need of the first multi-gram amount of carboxylic acid 1 is outlined in

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Scheme 4. The choice of benzyl bromoacetate 2a was dictated by the high polarity and hydrophilic nature of acid 1. Extraction of the free acid from aqueous phases was, in fact, not possible with conventional organic washes. The benzyl group decreased the polarity of the corresponding ester 11a while improving its UV detection by conventional LC/MS and allowed the ester cleavage in the last step to be performed in the absence of water. N-alkylation of the triazole 3, performed under acetone/K$_2$CO$_3$ conditions, afforded in quantitative yields an isomeric mixture with no selectivity towards the N-1 isomer 11a which was present in a poor 46% a/a purity.

Scheme 4. 1$^{st}$ generation batch synthesis of 2-(3-methyl-1H-1,2,4-triazol-1-yl)acetic acid (1).

Since the crude mixture appeared as an oily residue and attempts of purification by direct precipitation were unsuccessful, a silica gel plug was required to remove the N-4 isomer, while the N-2 isomer could not be separated at this stage from 11a due to the very similar retention factor. The plug was highly efficient and required only 1.8 wt. silica and 23 vol. solvent relative to the crude isomeric mixture. From the purified ca. 1:1 mixture obtained after the plug, a selective crystallization from TBME gave ester 11a as a white solid. The price to pay for this tedious
purification sequence was reflected by a total yield of only 20%. Hydrogenation occurred with no issue and the acid product 1 was obtained in high purity with excellent yield for this step. Even if the limitations of this ‘built-in’ approach are undeniable, the process was robust enough to be used several times and fulfill material needs, with a maximum scale of 1.6 kg of triazole 3 as input and 498 g of acid 1 as output (see experimental part for details).

2nd generation batch process. According to the alternative synthetic strategy outlined in Scheme 2, acetimidamide 5 was obtained in good yields by simply heating a mixture of formamide and N,N’-dimethylacetamide dimethylacetal (6) in dioxane at 50 °C and removal of the generated methanol under reduced pressure (Scheme 5).8

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\[
\begin{align*}
6 \quad \text{dioxane, 50 °C} & \quad 180-140 \text{ mbar} \\
\quad \text{(MeOH)} & \quad 75-85\% \\
\quad \text{formamide} & \quad 5 \\
\quad \text{dioxane, rt} & \quad \text{open form}
\end{align*}
\]
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Scheme 5. 2nd generation synthesis of 1: formation of the triazole ethyl ester 11b in batch mode.

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Subsequently, by dosing isolated intermediate 5 into a suspension of ethyl hydrazinoacetate hydrochloride (4a) in dioxane at room temperature, to our delight the formation of triazole ethyl ester 11b occurred rapidly under mild conditions, with the observation of the open intermediate as well. The resulting suspension was filtered to remove insoluble salts formed, followed by ordinary aqueous work-up to afford the product in ca. 80% yield as crude but only 70% purity. After crystallization, triazole 11b was obtained in a poor 35% yield albeit in pure form (>99% a/a, >98% w/w). Attempts to optimize purity and recovery on this condensation step by looking at solvents, additives such as acids and bases, order of addition and temperature gave scarce results. The low recovery of the isolated crude could be attributed to the presence of several polar impurities, with the major one being hydrazine adduct 12 which precipitated from the reaction mixture and was subsequently filtered off.

While the hydrazine content in the acetate 4a can in principle be controlled by the purity of the starting material itself, the finding demonstrates no kinetic advantage of the desired reaction pathway towards possible side-reactions. Impurities either coming from the starting materials (hydrazine) or from the synthesis could have a detrimental effect on the reaction performance due to the highly reactive nature of acetimidamide 5.

Not surprisingly, intermediate 5 is also an energetic compound, as shown by the differential scan calorimetry (DSC) where a ΔH of 328 J/g and a left limit temperature of 50 °C were found (Figure 1), indicating thermal decomposition and potential hazard for this compound already at room temperature. Ideally, intermediate 5 should be produced and reacted in situ avoiding any isolation.

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9 The open form intermediate was not isolated but only detected by LC-MS and its structure confirmed by m/z data.

10 Different batches and suppliers of ethyl hydrazinoacetate hydrochloride 4a were not tested and at this stage there is no information about hydrazine content on commercial supplies of 4a.
This could be practically realized under flow conditions through the design of a *one-pot*, two-step continuous process where every new molecule of acetimidamide 5 formed in a first reactor is directly pumped into a second reactor with hydrazine 4a for the condensation step, limiting its accumulation and handling. In this way, we also sought to improve the yield and purity as a direct consequence of the minimization of thermal stress and concentration effects which might favor decomposition pathways of intermediate 5.

![Figure 1. DSC of acetimidamide 5 (heat ramp: 4 °C/min).](image)

**2nd generation continuous-flow process.** To develop a combined, two-step process, we used a continuous-flow system consisting of coil tubes of 10 mL internal volume coupled with peristaltic pumps. Each of the two reaction steps was first optimized individually.

For the synthesis of the acetimidamide 5, Figure 2 shows the influence of residence time, solvent and temperature on the conversion of formamide and purity of 5.
Figure 2. Effect of residence time, temperature and solvent on the conversion of formamide (white squares) and acetimidamide 5 purity (black circles) under continuous-flow conditions.

The conversion of formamide increased with the residence time (left graph, Figure 2), from 33% a/a at a residence time of 2 min to 98% a/a at 20 min, remaining constant afterwards. The purity of intermediate 5, on the other hand, first increased with the residence time, reaching a maximum of 60-65% a/a at a residence time of 10-13.3 min, before starting to drop with prolonged times. Compared to the batch protocols where the reactions took several hours to complete, it is well known that the use of a continuous reactor improves the throughput and shorten reaction times thanks to the better transport phenomena (mixing, diffusion) in the small cross-section of the reactor. The temperature had a less marked impact on the conversion, since only minor changes could be detected in the product feed between 80 and 120 °C (central graph, Figure 2). The product purity, in contrast, increases with the temperature, from 60% a/a at 80 °C to 85% a/a at 120 °C, suggesting that higher temperatures accelerate the main reaction while limiting potential secondary ones. The role of the solvent (dioxane, DMF, and DMSO; right graph, Figure 2) was also studied.
showing little influence on the conversion but an effect on the purity, with better results in DMSO and DMF (85.4 and 91% a/a purity, respectively).

Based on these results, our optimal conditions for the acetimidamide 5 formation step were a temperature of 120 °C, pressure of 1 bar and a residence time of 13.3 min. DMSO was chosen as solvent over DMF due to easier removal in the aqueous phase during the work-up (see experimental part for details).

For the subsequent condensation step to form triazole 11b, we also explored the influence of residence time and temperature on the isolated yield as well as purity of the final product. The results are reported on Table 1. In this case, the pressure was kept at 1 bar to allow the two steps to be run consecutively without any intermediate work-up or manipulation.

**Table 1. Influence of residence time and temperature on the synthesis of 11b under continuous-flow conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>( \tau ) [min]</th>
<th>Yield(^a)</th>
<th>Purity(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>25</td>
<td>5.0</td>
<td>57%</td>
<td>84% (89%)</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>25</td>
<td>6.7</td>
<td>64%</td>
<td>89% (95%)</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>50</td>
<td>5.0</td>
<td>46%</td>
<td>85% (89%)</td>
</tr>
<tr>
<td>4</td>
<td>DMSO</td>
<td>70</td>
<td>5.0</td>
<td>45%</td>
<td>89% (91%)</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>25</td>
<td>5.0</td>
<td>39%</td>
<td>81% (82%)</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>−30</td>
<td>5.0</td>
<td>32%</td>
<td>82% (84%)</td>
</tr>
</tbody>
</table>

\(^a\) Upon isolation. \(^b\) Determined by LC-MS (% a/a). \(^c\) Determined by \(^1\)H-NMR with internal standard.
The isolated yield of 11b increased with the residence time from 57% at a residence time of 5 min, to 64% at 6.7 min (entries 1 and 2, respectively). The purity of 11b also improved, passing from 85-90% at 5 min to 90-95% at 6.7 min. Longer residence times were also explored (up to 20 min; not shown in the table for the sake of conciseness) but did not improve the reaction further. The temperature, also in this case, seemed to have a less pronounced effect on the reaction, as the yield decreased only slightly going from 25 °C to 70 °C (from 57% to 46%, entries 1, 3 and 4), confirming the findings on the instability of intermediate 5 and suggesting low temperatures to minimize side reactions. Analysis of the aqueous aliquots of the reactions at 50 and 70 °C (entries 3 and 4) after work-up showed a higher fraction of the polar side-products, such as 12, as observed during the development of the batch process. We then explored the possibility to perform the reaction below 0 °C using a cryostat to cool the coil. For this purpose, DMF was used to avoid freezing of the solvent and, as comparison, the reaction at 25 °C was performed achieving lower isolated yield (39%) and product purity (80-82%, entry 5). At -30 °C, the result is even worse, with 32% isolated yield and 80-85% purity (entry 6). As a result, optimal reaction conditions for the second step were therefore T = 25 °C and τ = 6.7 min.

With the two reactions separately optimized, we assembled the system to allow the direct pumping of the product stream from the acetimidamide formation into the second step using the conditions outlined above (Figure 3). The excellent heat transfer in the flow reactor allows the acetimidamide stream to be heated and mixed with the hydrazine stream without any concern due to heat accumulation. Besides, this system required no additional solvent because the same solvent (DMSO) was used in both reactors. To achieve efficient mixing of the stream from the first step with the stream of hydrazine derivative 4a for the second step, a T-junction was used. This mixer was kept at 25 °C and proved to mix the two streams effectively. Sampling the stream at the outlet
of the second reactor showed only the presence of product 11b. In a 1 g test experiment, 11b was obtained in 60% isolated yield with 95% NMR assay purity. The reaction was further intensified in a large-scale run, yielding 117.1 g of pure product (95% NMR assay purity) over approximately 48 h of continuous operation, with an isolated yield of 57% and a productivity of 2.4 g h\(^{-1}\). This demonstrated that the method could be efficiently intensified from small (1 gram) to large (100 grams) scale.

**Figure 3.** Continuous-flow system set-up used for scale-up experiment.
Having developed an efficient and practical 2nd generation route through a one-pot continuous flow process to access triazole 11b, we needed the development of a non-conventional hydrolysis able to convert ethyl ester 11b into target acid 1 with the avoidance of any aqueous work-up due to the reported high hydrophilic nature of 1 (see above). After some experimentation, it was found that ester hydrolysis could be performed in toluene with only stoichiometric amounts of concentrated aqueous NaOH while residual water and EtOH were removed by azeotropic distillation upon full conversion. Trituration with TBME afforded an off-white solid corresponding to the sodium salt 13 in high yield (Scheme 6).

Scheme 6. 2nd generation synthesis of 1: ester 11b hydrolysis in batch mode.

When the salt was treated with trifluoroacetic acid (TFA) in acetonitrile, free acid 1 was smoothly formed and precipitated as white suspension easily filtered off and recovered in quantitative yield and high purity. In this way, triazole ethyl ester 11b obtained from the continuous flow process, could be converted in two simple steps into triazole acid 1 in high overall yields.

The development of more sustainable and lower environmental impact manufacturing processes for API and intermediates is of high priority in the pharmaceutical industry. Green chemistry metrics are at best used to mirror ecological aspects as well as process efficiency. Given the short synthesis and the restricted amount of data available at this early stage of development, a meaningful green score card calculation was not possible and only some representative parameters
such as process mass intensity (PMI), relative process greenness (RPG), relative process improvement (RPI) besides yield were taken into consideration to benchmark the 2nd generation flow process with the batch approaches (Table 1).11

In terms of yield, the winning position of the flow process over the two others by a factor of 2-3 was anticipated thanks to the minimized handling of unstable intermediate 5 and to the high selectivity of the new process versus the 1st route, respectively. The impact of the chromatography for the 1st generation is reflected in the significantly higher PMI compared to the more efficient 2nd generation route. The inferior PMI of the flow process compared to the batch one is explained by the unoptimized work-up which was still performed in batch mode and accounted for increased volumes and solvent waste. As consequence of the PMI values, the RPG is for the 1st generation below average with 12%, while with 58 and 44% the 2nd generation batch and flow rank respectively good to average as manufacturing processes in early development stage.11

Table 2. Green metrics comparison for the different routes to 11.

<table>
<thead>
<tr>
<th>Route</th>
<th>Yield</th>
<th>PMI</th>
<th>Complexity</th>
<th>RPG</th>
<th>RPI</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st generation batch</td>
<td>12%</td>
<td>212</td>
<td>1</td>
<td>12%</td>
<td>-</td>
<td>1-3 kg</td>
</tr>
<tr>
<td>2nd generation batch</td>
<td>29%</td>
<td>91</td>
<td>2</td>
<td>58%</td>
<td>46%</td>
<td>0.1 kg</td>
</tr>
<tr>
<td>2nd generation flow</td>
<td>57%</td>
<td>120</td>
<td>2</td>
<td>44%</td>
<td>32%</td>
<td>0.1 kg</td>
</tr>
</tbody>
</table>

Finally, the benefit of the 2nd generation is illustrated with the RPI values, respectively of 46% and 32% for the batch and the flow processes which reflect the overall easiness and efficiency of

the new route compared to the 1\textsuperscript{st} generation. Even if the flow approach suffers from a less competitive PMI (and as consequence lower RPG and RPI) compared to the batch process, based on the available data, it should be pointed out that this is due to the unoptimized work-up at such early phase of development. Significant improvements in waste reduction could be achieved by implementing, for example, continuous strategies for work-up and product isolation, such as continuous membrane-assisted liquid-liquid extraction or continuous crystallization.\textsuperscript{12}

Finally, to demonstrate the generality of the described methodology, the flow conditions were applied in a small screening of other substrates, as depicted in Table 3. As an example of the chemical diversification that can be achieved, triazole derivative 14 was obtained in a straightforward manner and in good yields by using 3-bromo-5-carboxyamide pyridine as amide source. When different hydrazines were used to couple with acetimidamide 5, methyl-triazole derivatives 15-18 were obtained. Remarkably, the same conditions optimized for our target substrate 11b could be applied as well to the new products. The results collected hint to the diversity of substrates that can be obtained using our novel route and open paths for extended, follow-up synthetic investigations.

Table 3. Substrate scope for the continuous-flow acetamide formation and triazole cyclisation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Chemical Structure 1" /></td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Chemical Structure 2" /></td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Chemical Structure 3" /></td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Chemical Structure 4" /></td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Chemical Structure 5" /></td>
<td>72</td>
</tr>
</tbody>
</table>

Conclusions

In conclusion, an alternative and novel route for the synthesis of substituted 1,2,4-triazole acetic acid 1 has been developed and presented herein. The approach constitutes a significant improvement compared to the more traditional 1st generation ‘buy-in’ approach due to the simple starting materials employed, mild reaction conditions, and chromatography-free isolations. The implementation of the two reactions into an integrated and continuous process allowed a modular
and efficient scale up and rapidly provided with multi gram amounts of target triazole 1, avoiding extensive purification and work-up procedures, and reducing the manual handling of dangerous intermediates. Flow chemistry confirmed to be a successful and useful technology for the process/organic chemist’s toolbox to shorten the time for development and scale-up, enabling rapid reaction optimization and precise control of the reaction conditions within the small flow pipes. In this case, remarkable benefits are the almost doubled yield as compared to the batch process, the safe handling of an unstable and energetic intermediate, with effects in terms of cost efficiency, sustainability, and process safety.

In our view, the new continuous-flow route constitutes a viable and appealing alternative to traditional ‘buy-in’ approaches used in the synthesis of 1,2,4-triazole derivative 1. We believe that the method, which was further demonstrated in the preparation of other similar 1,2,4-triazoles, will find further useful application in the rapid, modular, and automated construction of differentially functionalized triazoles.

**Experimental Section**

1. General

All commercially available chemicals employed were used as such with no further purification. LC/MS analyses were performed using Aqutiy Waters system equipped with an Agilent G4220A binary pump coupled with Thermo Finnigan MSQ Plus MS (Ionisation: ESI+), Agilent DAD-G4212A and column oven Dionex TCC-3200. GC/MS analyses were performed on a Zebron ZB-5 MS column (15 m×0.25 mm ID, 0.25 µm film), using a column volumetric flow of 1.2 mL min⁻¹, and helium as carrier gas. Further LC/MS and GC/MS conditions are detailed in the Supporting Information. Novel compounds were characterized with ¹H, ¹³C NMR, IR and, when applicable, HRMS and melting point. ¹H and ¹³C (proton decoupled) spectra were recorded on a Bruker NMR
500MHz spectrometer Avance HD equipped with DCH-Cryoprobe and with a Bruker NMR 500MHz Spectrometer Avance 2. Chemical shifts (δ) values are reported in parts per million using residual solvent signal as reference and the coupling constants (J) are reported in Hz. Infrared spectra were recorded on a Perkin Elmer SPECTRUM ONE-Spectrophotometer and are reported as cm⁻¹ (w = weak, m = medium, s = strong). High resolution mass spectrometric measurements were performed with SYNAPT G2 MS (Waters) Q-Tof instrument that can provide up to 40’000 FWHM resolution, data-acquisition rate of 20 spectra/second, exact mass (1ppm RMS) information and a dynamic range of up to five orders of magnitude (conditions for analysis in the Supporting Information). Melting points were measured with DSC analyses on a Mettler Toledo STARe System (DSC822e module: measuring cell with ceramic sensor).

2. 1st generation batch process

Benzyl 2-(3-methyl-1H-1,2,4-triazol-1-yl) acetate (11a)

3-Methyl-1H-1,2,4-triazole 3 (1.6 kg, 19.3 mol, 1.0 equiv) and potassium carbonate (325 mesh size, 5.3 kg, 38.5 mol, 2.0 equiv) were suspended in acetone (8 L, 5 vol). Benzyl 2-bromoacetate (3.1 L, 19.3 mol, 1.0 equiv) was slowly added over 1 h at 25 °C. At reaction completion (ca. 4 h), isopropyl acetate (6.4 L, 4 vol) was added, followed by H₂O (16 L, 10 vol). The layers were separated, and the organic layer was evaporated to dryness, affording 5.12 kg of a brown oil as crude material. This product was purified by silica gel plug (9 kg), eluting with ethyl acetate/n-heptane from 75/25 to 90/10 (120 L total) to give 3.87 kg of intermediate product (87% overall yield, isomeric ratio 53:47) as an orange oil. This was taken up in TBME (18.5 L, 5 vol) and the resulting solution heated to 40 °C. After cooling to 20 °C for 2 h and 5 °C for 1 h, precipitation occurred. By filtration of the formed suspension followed by drying, pure 11a product was obtained as a white solid. 832 g, 19% overall yield, 100% a/a (LC/MS). Mp: 73 °C (DSC). ¹H
NMR (400 MHz, CDCl$_3$) $\delta$: 8.07 (s, 1 H), 7.34-7.42 (m, 5 H), 5.24 (s, 2 H), 4.94 (s, 2 H), 2.43 (s, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 166.59, 161.67, 144.67, 134.64, 128.81, 128.74, 128.56, 67.92, 50.25, 13.90. HRMS (ESI, m/z): m/z calcd for C$_5$H$_7$N$_3$O$_2$ ([M+H]$^+$): 142.0617; found: 142.0000. IR (ATR) $\nu$: 3126-3001 (w), 2028 (w), 1728 (s), 1589 (w), 1501 (w), 1474 (w), 1456 (w), 1391 (m), 1360 (m), 1310 (m), 1221 (s), 1202 (s), 1173 (s), 1033 (m), 964 (m), 941 (m), 909 (w), 884 (w), 830 (w), 801 (m), 747 (s), 722 (m), 659 (w), 638 (w) cm$^{-1}$.

2-(3-Methyl-1H-1,2,4-triazol-1-yl) acetic acid (1)

An autoclave was charged with 5% Pd/C (41 g) and a solution of pure 11a (414 g, 1.79 mol, 1.00 equiv) in MeOH (2.1 L, 5 vol). The resulting mixture was hydrogenated at 1-1.5 bar of H$_2$ and at a jacket temperature of 20-25 °C, until the H$_2$ update ceased and the IPC showed full conversion. This required approximately 3.5 h. The mixture was filtered over Celite (207 g, 0.5 wt.) and the filtrate was rinsed with MeOH (3 L, 7.2 vol). The filtrate was then evaporated to dryness to yield acid 1 as a white to off-white solid. 251 g, 99% yield from 11a, 98% a/a (LC/MS). **Mp:** 165 °C. 1H NMR (500 MHz, DMSO) $\delta$: 13.17-13.38 (m, 1 H), 8.33 (s, 1 H), 4.97 (s, 2 H), 2.24 (s, 3 H). 13C NMR (125 MHz, DMSO) $\delta$: 169.52, 160.09, 145.97, 50.23, 13.99. HRMS (ESI, m/z): m/z calcd for C$_5$H$_7$N$_3$O$_2$ ([M+H]$^+$): 142.0617; found: 142.0000. IR (ATR) $\nu$: 3296 (w), 3125 (m), 3000 (w), 2958 (w), 2728 (w), 2498 (w), 1976 (w), 1733 (s), 1536 (s), 1484 (m), 1407 (m), 1364 (m), 1315 (s), 1184 (s), 1054 (m), 1018 (s), 965 (m), 892 (s), 812 (s), 795 (m), 697 (s), 648 (s) cm$^{-1}$.

3. 2nd generation batch process

N'-Formyl-N,N-dimethylacetimidamide (5)
A yellow solution of formamide (35 g, 0.769 mol, 1 equiv) and N,N-dimethylacetamide dimethyl acetal (6) (102 g, 0.769 mol, 1 equiv) in dioxane (525 mL, 15 vol) was heated up to 50 °C under reduced pressure (150-180 mbar) and the formation of 5 monitored by NMR. After 2 h, the solution was cooled down to room temperature and yield and purity determined by drying and analyzing a small aliquot which solidified upon standing. 83 g, 95% yield, 77% w/w (1H-NMR assay) and 86% a/a (GC/MS). Mp: 131 °C. 1H NMR (500 MHz, CDCl3) δ: 8.90-8.93 (m, 1 H), 2.99 (s, 6 H), 2.13 (s, 3 H). 13C NMR (125 MHz, CDCl3) δ: 172.3, 169.1, 77.4, 77.1, 16.5. MS [M+H]+: 114.15. IR (ATR) v 2937 (m), 2835 (m), 2739 (m), 2161 (w), 2030 (m), 1700 (m), 1655 (s), 1620 (m), 1421 (w), 1389 (s), 1288 (s), 1200 (s), 1158 (s), 1016 (s), 917 (m), 873 (w), 792 (s), 714 (s) cm⁻¹.

**Ethyl 2-(3-methyl-1H-1,2,4-triazol-1-yl) acetate (11b)**

To a suspension of ethyl hydrazinoacetate hydrochloride 4a (89.1 g, 0.553 mol, 1 equiv) in dioxane (400 mL, 4.4 vol), a solution of 5 (82 g, 0.553 mol, 1 equiv) in dioxane (ca 400 mL, 4.4 vol) was added at room temperature within 35 min (exothermic). After 4 h, LC/MS analysis showed full conversion. Therefore, the mixture was partially concentrated, and the residue taken up in DCM (900 mL, 10 vol) and water (540 mL, 6 vol). The two layers were separated, and the aqueous phase extracted with DCM (450 ml, 5 vol). The combined organic layers were concentrated to afford an orange oil as crude material (82.26 g). This material was crystallized in TBME (166 mL, 2 vol) by dissolving at 50 °C, seeding at 20 °C, and cooling at 0-5 °C for 1.5 h. After filtration and drying, a white solid corresponding to 11b was obtained. 37.5 g, 50% yield for the crystallization, 35% total yield, 98.7% w/w (1H-NMR assay) and 100% a/a (LC/MS). Mp: 64 °C. 1H NMR (500 MHz, CDCl3) δ: 8.10 (s, 1 H), 4.89 (s, 2 H), 4.26 (q, J = 7.2 Hz, 2 H), 2.42 (m, 3 H), 1.30 (t, J = 7.1 Hz, 3 H). 13C NMR (125 MHz, CDCl3) δ: 166.7, 161.4, 144.6, 62.3, 50.3, 14.1, 13.9. HRMS (ESI,
m/z): m/z calcd for C\textsubscript{7}H\textsubscript{12}N\textsubscript{3}O\textsubscript{2} ([M+H]	extsuperscript{+}): 170.0930; found: 170.0924. IR (ATR) ν 3128 (m), 2989 (m), 2952 (m), 2187 (w), 2147 (w), 2023 (w), 1983 (w), 1729 (s), 1674 (m), 1525 (s), 1474 (m), 1445 (w), 1402 (w), 1379 (s), 1309 (s), 1182 (s), 1113 (w), 1018 (s), 937 (w), 875 (m), 790 (s), 725 (s), 699 (s), 658 (w) cm\textsuperscript{-1}.

4. 2\textsuperscript{nd} generation continuous-flow process

Reaction optimization for the synthesis of \textit{5} in flow. A solution of formamide (0.885 mL, 22.2 mmol, 1 equiv) in DMSO, DMF, or dioxane (40 mL) and a solution of \textit{6} (3.61 mL, 22.2 mmol, 1 equiv) in DMSO, DMF, or dioxane (40 mL) were pumped through a T-mixer, mixed together, and entered a 10 mL Hastelloy coil reactor. The reaction was conducted at different temperatures (80-120°C) and residence times (2-40 min), and at a total pressure of 1 bar. At the end of each run, the reaction mixture was evaporated and extracted with water and DCM. The combined organic layers were washed with water and brine, dried over MgSO\textsubscript{4}, filtered and concentrated to dryness to afford the intermediate \textit{5}.

Reaction optimization for the synthesis of \textit{11b} in flow. A solution of \textit{5} (1 equiv) in DMSO (40 mL) was mixed with a solution of \textit{4a} (4.112 g, 25.5 mmol, 1.15 equiv) in DMSO (92 mL), and pumped into a 10 mL PFA coil reactor at 1 bar. The reaction was conducted at different temperatures (25-70 °C) and residence times (5-7 min). At the end of each run, the reaction mixture was evaporated and extracted with water and DCM. The combined organic layers were washed with water and brine, dried over MgSO\textsubscript{4}, filtered and concentrated to dryness to afford the final triazole product \textit{11b} as an off-white solid.

One-pot flow synthesis of \textit{11b} (100 g scale). A solution of formamide (48.7 mL, 1.22 mol, 1 equiv) in DMSO (1.1 L) and a solution of \textit{6} (198 mL, 1.22 mol, 1 equiv) in DMSO (990 mL) were pumped
each with a flow of 0.375 mL min\(^{-1}\) through a 10 mL Hast-C coil (residence time 13.3 min) at 120 °C and 1 bar. The intermediate solution was cooled to room temperature and directly pumped further, mixed with a solution of 4a (197 g, 1.22 mol, 1 equiv) in DMSO (2200 mL), both with a flow of 0.75 mL min\(^{-1}\) in a 10 mL PFA coil (residence time of 6.7 min) at room temperature and 1 bar. The collecting flask was filled with 4 L brine under stirring. The work up was done in 3 portions of ca. 2 L. Each portion was extracted with DCM (1×1 L, 2×0.5 L) and the combined organic layer was washed with 300 mL brine and 300 mL water + 100 mL brine. After evaporation to dryness 11b was obtained as an off-white solid. 117.11 g, 57% overall yield from formamide, 95% w/w (\(^1\)H-NMR assay).

2-(3-Methyl-1\(H\)-1,2,4-triazol-1-yl) acetate sodium(I) salt (13)

To a solution of 11b (30 g, 0.174 mol, 1.0 equiv) in toluene (150 mL, 5 vol), 32% NaOH (16.1 mL, 0.174 mol, 1.0 equiv) was added dropwise and stirred for 1 h followed by distillation to dryness. The light-yellow foam obtained was suspended in TBME and stirred at room temperature for 20 min before filtration. An off-white solid corresponding to 13 was obtained. 26 g, 92% yield, 85% w/w (\(^1\)H NMR assay). **Mp:** 217 °C. \(^1\)H NMR (500 MHz, DMSO) \(\delta\): 8.18 (s, 1 H), 4.39 (m, 2 H), 2.46-2.53 (m, 3 H). \(^{13}\)C NMR (125 MHz, DMSO) \(\delta\): 169.62, 158.54, 145.03, 53.70, 14.09. IR (ATR) \(\nu\) 3481 (m), 3241 (m), 3126 (m), 2180 (w), 2032 (w), 1979 (w), 1659 (w), 1532 (m), 1476 (s), 1445 (m), 1390 (s), 1316 (m), 1293 (s), 1206 (m), 1180 (s), 1038 (s), 989 (m), 916 (w), 881 (m), 812 (s), 700 (s) cm\(^{-1}\).

2-(3-Methyl-1\(H\)-1,2,4-triazol-1-yl) acetic acid (1)

To a suspension of 13 (5 g, 0.0261 mol, 1 equiv) in acetonitrile (15 mL, 3 vol), trifluoroacetic acid (2.02 mL, 0.0261 mol, 1 equiv) was added dropwise at room temperature. The white suspension
formed was stirred for 30 min at room temperature and then filtered to get acid 1 (3.6 g, 98% yield).

**Ethyl 2-(5-(5-bromopyridin-3-yl)-3-methyl-1H-1,2,4-triazol-1-yl)acetate (14)**

The synthesis was conducted following the experimental conditions described above (2nd generation continuous-flow process), starting from 5-bromonicotinamide (22.2 mmol, 1 equiv) and a solution of 6 (3.61 mL, 22.2 mmol, 1 equiv) in DMSO at step 1; and adding a solution of 4a (4.112 g, 25.5 mmol, 1.15 equiv) at step 2. The reaction gave 14 with a yield of 52%. The compound is not novel and was already characterized. **LC**: r.t. 0.71 min. **MS** [M+H]+: 327.01.

**1-(4-fluorophenyl)-3-Methyl-1H-1,2,4-triazole (15)**

The synthesis was conducted following the experimental conditions described above (2nd generation continuous-flow process), starting from formamide (0.885 mL, 22.2 mmol, 1 equiv) and a solution of 6 (3.61 mL, 22.2 mmol, 1 equiv) in DMSO at step 1; and adding a solution of (4-fluorophenyl)hydrazine (25.5 mmol, 1.15 equiv) at step 2. The reaction gave 15 with a yield of 63%. The compound is not novel and was already characterized. **LC**: r.t. 0.70 min. **MS** [M+H]+: 178.24.

**1-Benzyl-3-methyl-1H-1,2,4-triazole (16)**

The synthesis was conducted following the experimental conditions described above (2nd generation continuous-flow process), starting from formamide (0.885 mL, 22.2 mmol, 1 equiv) and a solution of 6 (3.61 mL, 22.2 mmol, 1 equiv) in DMSO at step 1; and adding a solution of benzylhydrazine (25.5 mmol, 1.15 equiv) at step 2. The reaction gave 16 with a yield of 73%. The compound is not novel and was already characterized. **LC**: r.t. 0.60 min. **MS** [M+H]+: 174.20.
1-(4-methoxybenzyl)-3-Methyl-1H-1,2,4-triazole (17)

The synthesis was conducted following the experimental conditions described above (2nd generation continuous-flow process), starting from formamide (0.885 mL, 22.2 mmol, 1 equiv) and a solution of 6 (3.61 mL, 22.2 mmol, 1 equiv) in DMSO at step 1; and adding a solution of (4-methoxybenzyl)hydrazine (25.5 mmol, 1.15 equiv) at step 2. The reaction gave 17 with a yield of 66%. The compound is not novel and was already characterized. LC: r.t. 0.58 min. MS [M+H]^+: 204.21.

1-cyclohexyl-3-methyl-1H-1,2,4-triazole (18)

The synthesis was conducted following the experimental conditions described above (2nd generation continuous-flow process), starting from formamide (0.885 mL, 22.2 mmol, 1 equiv) and a solution of 6 (3.61 mL, 22.2 mmol, 1 equiv) in DMSO at step 1; and adding a solution of cyclohexylhydrazine (25.5 mmol, 1.15 equiv) at step 2. The reaction gave 18 with a yield of 72%. The compound is not novel and was already characterized. LC: r.t. 0.58 min. MS [M+H]^+: 166.13.

ASSOCIATED CONTENT

Supporting Information. Experimental conditions and analysis of products. This information is available free of charge via the Internet.

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**ABBREVIATIONS**

DSC, differential scan calorimetry; T, temperature; τ, residence time; rt, room temperature; IPC, in-process control; PMI, process mass intensity; RPG, relative process greenness; RPI, relative process improvement.