

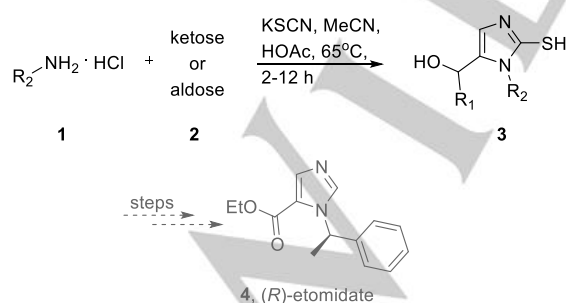
A Continuous Flow Method for the Desulfurization of Substituted Thioimidazoles Applied to the Synthesis of New Etomidate Derivatives

Marcus Baumann,^{*,[a]} and Ian R. Baxendale^[a]

Abstract: A simple yet robust flow set-up for the efficient desulfurization of a series of thioimidazoles is presented generating the corresponding imidazole derivatives in high yields. The strategic choice of peristaltic over piston pumps allowed reliable delivery of the heterogeneous stream of thioimidazole substrate into a T-piece where it reacted with NaNO₂ in the presence of acetic acid. This approach enabled the controlled and safe formation of the reactive nitrosonium species without uncontrolled exposure to hazardous nitrous oxide by-products as observed in related batch protocols. The value of the resulting imidazole products was further demonstrated by their conversion into various esters representing new derivatives of the known analgesic etomidate via an efficient one pot Corey-Gilman-Ganem oxidation procedure.

Introduction

Imidazoles are amongst the most prevalent bioactive heterocyclic entities and hence can be found not only in many natural products but also in numerous pharmaceutical and agrochemical agents.¹ Consequently, a considerable number of synthetic routes have been developed for their construction.² Paramount to accessing structurally diverse imidazoles remains the availability of suitable building blocks that quickly furnish the desired target structures in high yield and selectivity. Addressing this requirement, we recently reported on an extension of the classical Marckwald multicomponent reaction which produces highly substituted thioimidazoles in a single step and makes use of diverse amine and carbohydrate building blocks (dihydroxyacetone, ketoses and aldoses) that are incorporated without erosion of stereochemical information (Scheme 1).³



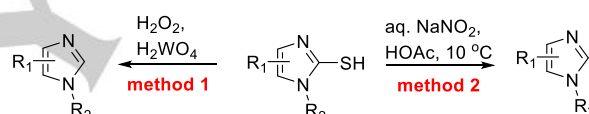
Scheme 1: Marckwald thioimidazole synthesis and structure of (R)-etomidate.

Building on this work we wish to now report on a subsequent study that focuses on using these thioimidazoles as precursors for various imidazole products that hold promise as bioactive structures for example (R)-etomidate⁴ (Scheme 1). Essential to this endeavor is the development of an efficient process allowing

desulfurization and hence expansion of the thioimidazole scaffolds. To render such a process more amenable to safe and efficient scale up we opted to harness the benefits of continuous flow chemistry as a valuable and well documented enabling technology.

Results and Discussion

With reliable access to diverse thioimidazole structures through the Marckwald reaction we initially surveyed the available literature for suitable methods to accomplish the desulfurization step. Amongst the methods reported two main options appeared attractive: (1) using a combination of hydrogen peroxide and a tungstic acid catalyst⁵ or (2) treating the thioimidazole substrates with aqueous sodium nitrite in glacial acetic acid⁶ (Scheme 2).



Scheme 2: Selected methods for desulfurizing thioimidazoles.

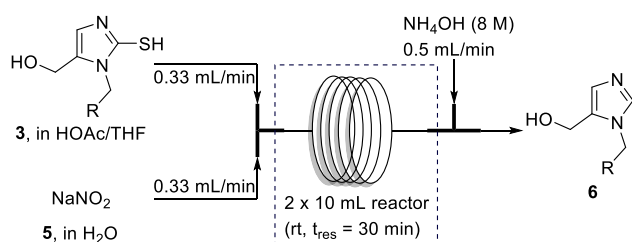
While the first method is interesting due to its green credentials, it was found that prolonged reaction times were needed to obtain full conversion of the substrate (8-14 h). Typically, this also required addition of further aliquots of both catalyst and hydrogen peroxide over time making this option less desirable. On the other hand, the second method is much faster (<1 h), yet requires cooling of the reaction mixture due to the reaction's exothermic nature and additionally generates toxic nitrous oxide gases. Based on this pre-evaluation we decided to develop a flow process for the second method (NaNO₂, glacial acetic acid) where we wished to harness the short reaction times and at the same time exploit the benefits of flow processing to mitigate risks associated with the exothermic nature of the reaction and the generation of toxic gases. Additionally, we wished to develop an efficient in-line quench process which would neutralize the acidic reaction mixture and gaseous by-products in a controlled manner.

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For this purpose, we opted to use a Vapourtec E-series flow system⁷ which utilizes peristaltic rather than more traditional piston pumps to feed streams of substrates and reagents into the reactor modules. This decision was furthermore supported by the limited solubility of the Marckwald thioimidazoles, which although convenient for their isolation represents a challenge when utilizing them in further flow-based transformations. We thus suspended the desired thioimidazole substrates in a mixture of acetic acid and THF (0.5 M, 50:50 by volume, stream A) and using the peristaltic pumps mixed this with a second stream containing NaNO₂ (2 M water, stream B) in a wide bore T-piece (Kinesis, 1.5 mm i.d.)⁸ as depicted in Scheme 3.



Scheme 3: Flow reactor set-up.

To ensure consistent delivery of the thioimidazole suspension it was found that a short 5 cm length of tubing leading into the peristaltic pump was beneficial. This small adjustment together with vigorously stirring of the thioimidazole suspension allowed a smooth feed of the thioimidazole substrate showcasing how slurries can be processed in flow, a challenge that has seen considerable interest within the community.⁹ Upon mixing at the T-piece the combined reaction mixture became homogeneous indicating rapid formation of the key nitrosonium species and its reaction with the thioimidazole substrates. Passing the reaction mixture through a tubular flow coil (2 x 10 mL, 30 min residence time) at ambient temperature ensured quantitative conversion of all substrates into the desired imidazole products (Figure 1).

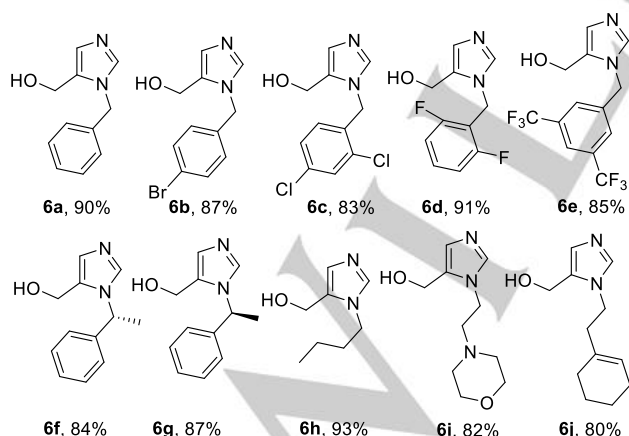
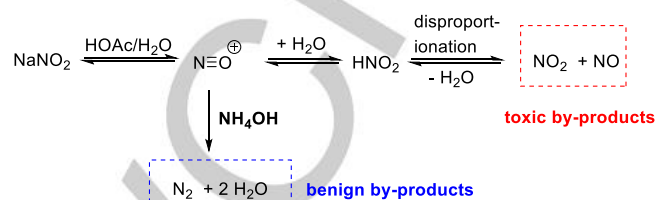


Figure 1. Imidazoles **6a-j** prepared via desulfurization in flow.

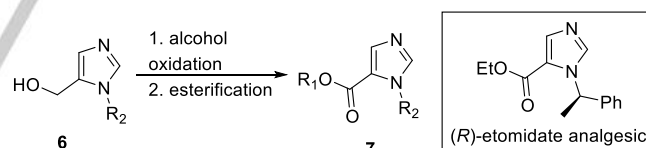
Having established a quick and safe method for desulfurizing thioimidazoles in flow we decided to also incorporate an in-line quench to neutralize the acetic acid as well as gaseous products. This was accomplished by mixing a stream of aqueous ammonia (8 M) with the reaction stream using a standard T-piece. The

reaction products were subsequently collected without passing a back-pressure regulator¹⁰ and isolated after aqueous extraction of the crude product stream yielding a series of imidazole products in high yield and purity. Crucially, it was found that this in-line quenching method not only neutralized the acetic acid, but more importantly eliminated any nitrous oxide by-products that are otherwise generated during this process. In light of this we propose a mechanism in which unreacted nitrosonium species will react with ammonia in a diazotization reaction that will generate benign nitrogen gas as the by-product (Scheme 4).¹¹



Scheme 4: Simplified mechanism for decomposing nitrous oxide by-products.

Pleasingly, it was found that the functional groups on the imidazole core such as the hydroxymethyl moiety as well as several substituted aryl and alkyl appendages are tolerated under the reaction conditions. In addition, this simple flow set-up was found to allow for successful scale-up generating multigram quantities of several substrates such as **6a**, **6c** and **6f** in equivalent yields with a typical productivity of ~10 mmol/h. Having accomplished the safe and efficient desulfurization of an array of thioimidazoles we next opted to evaluate their oxidative transformation into different ester products. To this end we exploited imidazoles **6** that upon oxidation of the hydroxymethyl group to an acid and subsequent ester formation render etomidate and various derivatives⁴ (Scheme 5).



Scheme 5: Oxidation-esterification strategy to access etomidate derivatives.

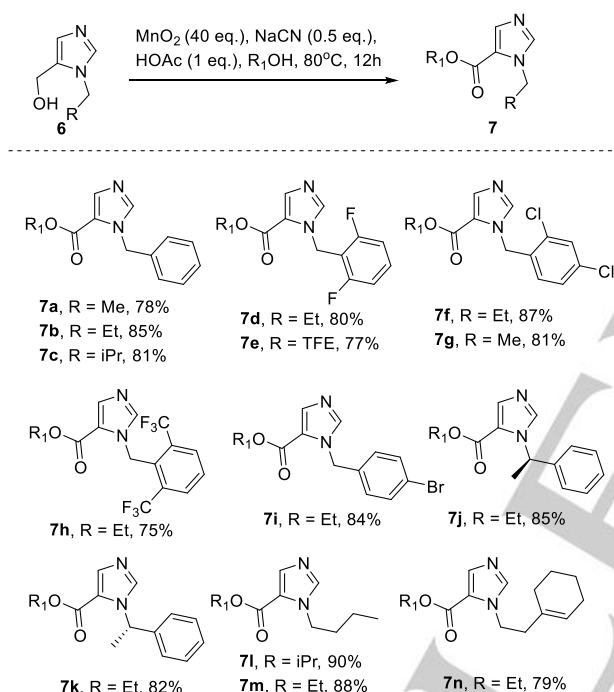
Although this oxidation and esterification sequence appears a straightforward process we anticipated the need for carefully selection of the reaction conditions as several standard oxidation procedures could affect the imidazole core or the reactive benzylic moiety. Furthermore, we were aware that the generation and isolation of the intermediate imidazole carboxylic acid might be cumbersome due to its polarity that would prohibit simple aqueous work-ups.

It was quickly established that several oxidation methods including Swern-type, TEMPO and MnO₂ do indeed generate the desired aldehyde derivative of our substrates, which under appropriate conditions can be further oxidized to the carboxylic acid species in a one-pot procedure (e.g. via TEMPO/BAIB)¹². However, the latter process turned out to be less desirable as it required prolonged reaction times (10–18 h) and extra care when isolating the carboxylic acid due to its polarity. Instead of

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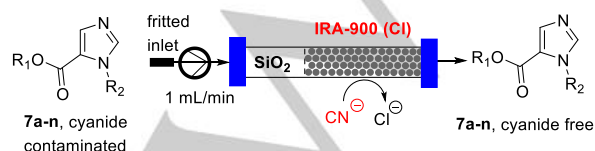
optimizing this procedure we therefore opted to employ a less frequently exploited strategy for converting an alcohol substrate directly to an ester product based on the Corey-Gilman-Ganem¹³ oxidation reaction. In this transformation, an activated alcohol is first oxidized with excess MnO_2 to the corresponding aldehyde that then reacts *in situ* with cyanide allowing for subsequent oxidation of the resulting cyanohydrin to a cyano ketone that is finally trapped as an ester upon reaction with an alcohol nucleophile (Scheme 6).

This approach not only mitigates isolation of any intermediate, but more importantly yields various ester products in a simple one-pot process. The desired structures (**7a-n**, Scheme 6) were isolated in good to excellent yields after conventional work-up and purification and include not only (*R*)- and (*S*)-etomidate but also various analogues possessing unprecedented substitution patterns on the aryl ring which we hope to evaluate for their analgesic properties in due course.



Scheme 6: Batch synthesis of etomidate derivatives.

In order to more efficiently isolate these ester products (**7a-n**) and at the same time decrease the risk of exposure to cyanide we opted to develop a final flow-based procedure trapping the used cyanide on an ion-exchange resin (Scheme 7).



Scheme 7: Improved continuous isolation of ester products **7a-n**.

To this end triethylamine (1 equiv.) and chloroform (10 mL) were added to the crude reaction mixture at ambient temperature. Mixing was stopped and the MnO_2 suspension allowed to settle. The supernatant was then pumped from the flask (1 mL/min) and directed into a glass column containing a small plug of silica (~2 g) and Amberlite IRA-900 resin (chloride form, 10 equiv., ambient temperature). To minimise aspirating MnO_2 particles the inlet tubing was covered with a microporous fritted filter. Upon passing through this column residual cyanide was exchanged for benign chloride that was subsequently removed by silica column chromatography allowing isolation of the desired products in very good yield and purity as before. Although not exploited in this instance, through this amendment the MnO_2 slurry could also be recovered for re-use which would be especially worthwhile at larger scale as it allows to redefine this batch set-up as a continuously stirred tank reactor (CSTR), which could be utilized in sequential batch operations.

Conclusions

In summary, we have developed a simple flow process for the efficient desulfurization of a number of thioimidazoles furnishing the corresponding imidazole derivatives in high yield and purity. By utilizing peristaltic pumps our approach demonstrates the reliable and accurate delivery of the substrate as a suspension that reacts with sodium nitrite in the presence of acetic acid as co-solvent prior to an in-line quench. Crucially, this flow strategy mitigates the need to perform this transformation at low temperature and at the same time does not liberate excessive amounts of toxic nitrous oxide by-products as observed in batch. Finally, we demonstrated the value of the generated imidazole products by their conversion into various analogues of the etomidate analgesic for which we exploited an efficient one-step Corey-Gilman-Ganem oxidation process in batch mode.

Experimental Section

All solvents, substrates and reagents were used as purchased without further purification. ^1H -NMR spectra were recorded on 400 MHz instruments and are reported relative to residual solvent: CHCl_3 (δ 7.26 ppm) or d_6 -DMSO (2.50 ppm). ^{13}C -NMR spectra were recorded on the same instruments and are reported relative to CHCl_3 (δ 77.16 ppm) or d_6 -DMSO (39.52 ppm). Data for ^1H -NMR are reported as follows: chemical shift (δ / ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br. s = broad singlet, app = apparent. Data for ^{13}C -NMR are reported in terms of chemical shift (δ / ppm) and multiplicity (C, CH, CH_2 or CH_3). Data for ^{19}F -NMR were recorded on the above instruments at a frequency of 376 MHz using CFCl_3 as external standard. DEPT-135, COSY, HSQC, HMBC and NOESY experiments were used in the structural assignment. IR spectra were recorded neat (ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21-70% of tallest signal) or strong (s, >71% of tallest signal). Low and high resolution mass spectrometry was performed using the indicated techniques on instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. For accurate mass measurements the deviation from the calculated formula is reported in ppm. Melting points were recorded on an automated melting point system with a heating rate of 1 $^\circ\text{C}/\text{min}$ and are uncorrected.

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General procedure for flow desulfurisation:

Using a Vapourtec E-series flow system a vigorously stirred suspension of thioimidazole substrate **3** (0.5 M in HOAc/THF 50:50 by volume; 0.33 mL/min) was directed into a wide bore T-piece (Kinesis, 1.5 mm i.d.) where it was combined with a solution of sodium nitrite (2 M, water; 0.33 mL/min). Upon uniting both streams the heterogeneous mixture quickly became homogeneous and generated gaseous by-products. This mixture was then directed into two flow coils (10 mL each, room temperature) giving a residence time of about 30 min. Using a further T-piece a solution of ammonium hydroxide (8 M, water; 0.5 mL/min) was added to the crude reaction mixture. Upon passing a further segment of tubing (~15 cm) the crude mixture was collected in a flask. After partitioning between EtOAc and water the desired product was obtained after drying (Na₂SO₄) and evaporating the organic layer.

(1-Benzyl-1*H*-imidazol-5-yl)methanol 6a

Off-white solid. Yield: 90%. ¹H-NMR (400 MHz, d₆-DMSO) δ/ppm: 7.69 (d, *J* = 0.9 Hz, 1H), 7.32-7.38 (m, 2H), 7.26-7.32 (m, 1H), 7.17 (d, *J* = 6.9 Hz, 2H), 6.83 (s, 1H), 5.24 (s, 2H), 5.14 (t, *J* = 4.5 Hz, 1H), 4.32 (d, *J* = 4.5 Hz, 2H). ¹³C-NMR (101 MHz, d₆-DMSO) δ/ppm: 138.9 (CH), 138.1 (C), 132.1 (C), 129.1 (2CH), 128.0 (CH), 127.9 (CH), 127.5 (2CH), 53.3 (CH₂), 48.0 (CH₂). IR (neat, ν/cm⁻¹): 3182 (br m), 2947 (m), 2868 (m), 1457 (m), 1439 (m), 1356 (m), 1248 (m), 1209 (m), 1103 (s), 1017 (s), 968 (m), 926 (m), 835 (s), 715 (s), 656 (m). HR-MS (TQF+) calculated for C₁₁H₁₃N₂O 189.1028, found 189.1028.

(1-(4-Bromobenzyl)-1*H*-imidazol-5-yl)methanol 6b

Off-white solid. Melting range: 136.0-138.1 °C. Yield: 87%. ¹H-NMR (400 MHz, d₆-DMSO) δ/ppm: 7.71 (s, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 5.22 (s, 2H), 5.19 (br s, 1H), 4.33 (s, 2H). ¹³C-NMR (101 MHz, d₆-DMSO) δ/ppm: 139.0 (CH), 137.5 (C), 132.1 (C), 132.0 (2CH), 129.7 (2CH), 128.0 (CH), 121.1 (C), 53.2 (CH₂), 47.4 (CH₂). IR (neat, ν/cm⁻¹): 3238 (m), 3111 (m), 2946 (m), 1488 (s), 1435 (m), 1247 (m), 1101 (m), 1073 (m), 1011 (s), 966 (m), 920 (m), 837 (s), 804 (s), 763 (m), 733 (s), 669 (m). HR-MS (TQF+) calculated for C₁₁H₁₂N₂OBr 267.0133, found 267.0122.

(1-(2,4-Dichlorobenzyl)-1*H*-imidazol-5-yl)methanol 6c

Off-white solid. Melting range: 144.2-146.8 °C. Yield: 83%. ¹H-NMR (400 MHz, d₆-DMSO) δ/ppm: 7.49 (s, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.87 (s, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.29 (s, 2H), 5.11 (br s, 1H), 4.37 (s, 2H). ¹³C-NMR (101 MHz, d₆-DMSO) δ/ppm: 138.8 (CH), 133.9 (C), 133.8 (C), 133.2 (C), 132.0 (C), 129.6 (CH), 129.2 (CH), 128.1 (CH), 127.7 (CH), 53.4 (CH₂), 45.7 (CH₂). IR (neat, ν/cm⁻¹): 3070 (br m), 1589 (w), 1563 (w), 1504 (m), 1477 (m), 1401 (m), 1318 (m), 1241 (m), 1103 (s), 1027 (s), 925 (s), 887 (m), 925 (s), 857 (m), 827 (s), 778 (s), 732 (m), 653 (s). HR-MS (TQF+) calculated for C₁₁H₁₁N₂OCl₂ 257.0248, found 257.0242.

(1-(2,6-Difluorobenzyl)-1*H*-imidazol-5-yl)methanol 6d

Off-white solid. Yield: 91%. ¹H-NMR (400 MHz, d₆-DMSO) δ/ppm: 7.52 (s, 1H), 7.45-7.50 (m, 1H), 7.16 (app t, *J* = 8.2 Hz, 2H), 6.79 (s, 1H), 5.30 (s, 2H), 5.14 (s, 1H), 4.44 (s, 2H). ¹³C-NMR (101 MHz, d₆-DMSO) δ/ppm: 161.2 (2CF, dd, *J* = 249, 8 Hz), 138.5 (CH), 132.1 (C), 131.7 (CH, t, *J* = 11 Hz), 127.6 (CH), 112.8 (C, t, *J* = 19 Hz), 112.4 (2CH, m), 53.1 (CH₂), 36.3 (CH₂, t, *J* = 4 Hz). ¹⁹F-NMR (367 MHz, d₆-DMSO) δ/ppm: -114.5. IR (neat, ν/cm⁻¹): 3094 (br m), 2828 (m), 1624 (m), 1591 (m), 1505 (m), 1468 (s), 1451 (m), 1360 (m), 1273 (m), 1255 (m), 1235 (m), 1212 (m), 1112 (m), 1029 (s), 1017 (s), 933 (m), 833 (s), 793 (s), 767 (s), 677 (s), 660 (s), 533 (m). HR-MS (TQF+) calculated for C₁₁H₁₁N₂OF₂ 225.0839, found 225.0841.

(1-(3,5-bis-(Trifluoromethyl)benzyl)-1*H*-imidazol-5-yl)methanol 6e

Off-white solid. Melting range: 102.3-105.0 °C. Yield: 85%. ¹H-NMR (400 MHz, CDCl₃) δ/ppm: 7.82 (s, 1H), 7.59 (s, 2H), 7.46 (s, 1H), 6.88 (s, 1H), 5.38 (2H), 4.50 (s, 2H), 3.77 (br s, 1H). ¹³C-NMR (101 MHz, CDCl₃) δ/ppm: 139.1 (C), 138.5 (CH), 132.4 (2C, q, *J* = 34 Hz), 131.4 (C), 128.6 (CH), 127.2 (2CH, m), 122.9 (2CF₃, q, *J* = 274 Hz), 120.2 (CH, m), 54.0 (CH₂), 47.9 (CH₂). ¹⁹F-NMR (367 MHz, CDCl₃) δ/ppm: -63.0. IR (neat, ν/cm⁻¹): 3150 (br m), 1500 (w), 1379 (w), 1350 (w), 1275 (s), 1169 (s), 1124 (s), 1021 (m), 910 (m), 844 (m), 704 (m), 682 (s), 661 (m). HR-MS (TQF+) calculated for C₁₃H₁₁N₂OF₆ 325.0776, found 325.0775.

1-[(1*S*)-1-Phenylethyl]-5-hydroxymethylimidazole 6f

Beige solid. Melting range: 110.6-112.3 °C. Yield: 87%. ¹H-NMR (400 MHz, CDCl₃) δ/ppm: 7.63 (d, *J* = 1.0 Hz, 1H), 7.24-7.36 (m, 3H), 7.08-7.13 (m, 2H), 6.93 (s, 1H), 5.61 (q, *J* = 7.1 Hz, 1H), 4.51 (d, *J* = 13.5 Hz, 1H), 4.34 (d, *J* = 13.5 Hz, 1H), 2.79 (br s, 1H), 1.86 (d, *J* = 7.1 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ/ppm: 141.7 (C), 136.2 (CH), 131.2 (C), 129.0 (2CH), 128.7 (CH), 127.9 (CH), 125.8 (2CH), 54.8 (CH), 54.4 (CH₂), 22.5 (CH₃). IR (neat, ν/cm⁻¹): 3090 (m), 2990 (m), 2843 (m), 1497 (m), 1450 (m), 1323 (m), 1236 (m), 1212 (m), 1110 (m), 1020 (s), 931 (s), 867 (m), 821 (m), 706 (s), 667 (s). HR-MS (TQF+) calculated for C₁₂H₁₅N₂O 203.1184, found 203.1184.

1-[(1*R*)-1-Phenylethyl]-5-hydroxymethylimidazole 6g

Beige solid. Melting range: 111.0-112.8 °C. Yield: 84%. ¹H-NMR (400 MHz, CDCl₃) δ/ppm: 7.69 (d, *J* = 1.0 Hz, 1H), 7.27-7.37 (m, 3H), 7.08-7.12 (m, 2H), 7.00 (s, 1H), 5.60 (q, *J* = 7.1 Hz, 1H), 4.53 (d, *J* = 13.4 Hz, 1H), 4.35 (d, *J* = 13.4 Hz, 1H), 1.88 (d, *J* = 7.1 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ/ppm: 141.8 (C), 136.4 (CH), 130.9 (C), 129.1 (CH), 129.0 (2CH), 128.0 (CH), 125.7 (2CH), 54.8 (CH), 54.6 (CH₂), 22.5 (CH₃). IR (neat, ν/cm⁻¹): 3090 (m), 2989 (m), 2841 (m), 1497 (m), 1450 (m), 1323 (m), 1236 (m), 1212 (m), 1110 (m), 1020 (s), 931 (s), 867 (m), 821 (m), 788 (m), 743 (m), 705 (s), 667 (s). HR-MS (TQF+) calculated for C₁₂H₁₅N₂O 203.1184, found 203.1186.

(1-Butyl-1*H*-imidazol-5-yl)methanol 6h

Off-white solid. Yield: 93%. ¹H-NMR (400 MHz, CDCl₃) δ/ppm: 7.19 (s, 1H), 6.61 (s, 1H), 6.38 (br s, 1H), 4.44 (s, 2H), 3.84 (t, *J* = 7.4 Hz, 2H), 1.56-1.66 (m, 2H), 1.18 (app hex, *J* = 7.4 Hz, 2H), 0.78 (t, *J* = 7.4 Hz, 3H). ¹³C-NMR (101 MHz, CDCl₃) δ/ppm: 137.3 (CH), 131.7 (C), 127.0 (CH), 53.2 (CH₂), 44.8 (CH₂), 32.8 (CH₂), 19.8 (CH₂), 13.5 (CH₃). IR (neat, ν/cm⁻¹): 3171 (br s), 2958 (s), 2873 (s), 1503 (s), 1460 (m), 1368 (m), 1251 (m), 1211 (m), 1111 (s), 1021 (s), 926 (m), 822 (s), 758 (m), 663 (s). HR-MS (TQF+) calculated for C₈H₁₅N₂O 155.1184, found 155.1193.

(1-(2-Morpholinoethyl)-1*H*-imidazol-5-yl)methanol 6i

Yellow oil. Yield: 82%. ¹H-NMR (400 MHz, d₄-MeOH) δ/ppm: 7.87 (d, *J* = 1.0 Hz, 1H), 6.99 (s, 1H), 4.63 (s, 2H), 4.24 (app t, *J* = 6.1 Hz, 2H), 3.65-3.73 (m, 4H), 2.78 (app t, *J* = 6.1 Hz, 2H), 2.50-2.57 (m, 4H). ¹³C-NMR (101 MHz, d₄-MeOH) δ/ppm: 138.3 (CH), 131.8 (C), 125.6 (CH), 66.3 (2CH₂), 58.6 (CH₂), 53.5 (2CH₂), 52.5 (CH₂), 42.0 (CH₂). IR (neat, ν/cm⁻¹): 2900-3200 (broad), 2854 (w), 1707 (m), 1564 (m), 1453 (m), 1363 (m), 1262 (s), 1112 (s), 1010 (s), 854 (m), 660 (m), 608 (m). HR-MS (TQF+) calculated for C₁₀H₁₈N₃O₂ 212.1399, found 212.1392.

(1-(2-(Cyclohex-1-en-1-yl)ethyl)-1*H*-imidazol-5-yl)methanol 6j

Colourless oil. Yield: 80%. ¹H-NMR (400 MHz, CDCl₃) δ/ppm: 7.33 (s, 1H), 6.73 (s, 1H), 5.35 (br s, 1H), 4.56 (s, 2H), 4.26 (br s, 1H), 4.04 (app t, *J* = 7.2 Hz, 2H), 2.36 (app t, *J* = 7.2 Hz, 2H), 1.85-1.97 (m, 4 H), 1.54-1.65 (m,

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2 H), 1.43–1.52 (m, 2H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 137.9 (CH), 133.5 (C), 131.3 (C), 127.6 (CH), 124.5 (CH), 53.8 (CH₂), 43.9 (CH₂), 39.2 (CH₂), 28.3 (CH₂), 25.2 (CH₂), 22.8 (CH₂), 22.2 (CH₂). IR (neat, v/cm^{-1}): 3110 (broad, 2925 (m), 2835 (m), 1501 (m), 1437 (m), 1361 (m), 1110 (m), 1019 (s), 919 (m), 820 (m), 728 (s), 661 (s). HR-MS (TQF+) calculated for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}$ 207.1497, found 207.1474.

General procedure for batch oxidation:

To a solution of alcohol **6** in the desired alcohol solvent (0.3 M) was added MnO_2 (40 equiv.), NaCN (0.5 equiv.) and acetic acid (2 drops). This mixture was heated at 80 °C until t.l.c. and ^1H -NMR indicated complete conversion of the substrate into the desired ester species (typically 12 h). The reaction mixture was cooled to 25 °C and filtered over a pad of celite yielding the crude product after evaporation of the solvents. Final purification was accomplished by silica column chromatography using EtOAc/hexanes (10–30% EtOAc) as eluent.

Methyl 1-benzyl-1H-imidazole-5-carboxylate 7a

Off-white solid. Yield: 78%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.76 (d, J = 1.0 Hz, 1H), 7.61 (s, 1H), 7.28–7.35 (m, 3H), 7.13–7.18 (m, 2H), 5.50 (s, 2H), 3.80 (s, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.6 (C), 142.2 (CH), 138.0 (CH), 136.2 (C), 128.9 (2CH), 128.1 (CH), 127.3 (2CH), 122.5 (C), 51.5 (CH₃), 50.0 (CH₂). IR (neat, v/cm^{-1}): 1709 (s), 1541 (m), 1436 (m), 1363 (s), 1295 (m), 1222 (s), 1200 (m), 1107 (s), 918 (w), 809 (m), 765 (m), 711 (s), 657 (s). HR-MS (TQF+) calculated for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2$ 217.0977, found 217.0980.

Ethyl 1-benzyl-1H-imidazole-5-carboxylate 7b

Off-white solid. Melting range: 53.0–54.9 °C. Yield: 85%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.76 (d, J = 1.0 Hz, 1H), 7.60 (s, 1H), 7.25–7.33 (m, 3H), 7.13–7.16 (m, 2H), 5.49 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.2 (C), 142.2 (CH), 137.9 (CH), 136.3 (C), 128.9 (2CH), 128.1 (CH), 127.2 (2CH), 122.8 (C), 60.5 (CH₂), 50.0 (CH₂), 14.2 (CH₃). IR (neat, v/cm^{-1}): 2983 (w), 1708 (s), 1539 (w), 1373 (m), 1293 (m), 1221 (s), 1124 (s), 1103 (s), 1019 (w), 921 (w), 840 (w), 765 (m), 713 (s), 658 (m). HR-MS (TQF+) calculated for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ 231.1134, found 231.1132.

Isopropyl 1-benzyl-1H-imidazole-5-carboxylate 7c

Off-white solid. Yield: 81%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.76 (d, J = 1.0 Hz, 1H), 7.59 (s, 1H), 7.27–7.39 (m, 3H), 7.14–7.18 (m, 2H), 5.51 (s, 2H), 5.14 (sept, J = 6.3 Hz, 1H), 1.28 (d, J = 6.3 Hz, 6H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 159.8 (C), 142.0 (CH), 137.8 (CH), 136.3 (C), 128.9 (2CH), 128.1 (CH), 127.2 (2CH), 123.2 (C), 68.2 (CH), 50.1 (CH₂), 21.9 (2CH₃). IR (neat, v/cm^{-1}): 2983 (w), 1708 (s), 1543 (w), 1459 (w), 1374 (s), 1294 (w), 1225 (s), 1124 (m), 1100 (s), 715 (m), 657 (w). HR-MS (TQF+) calculated for $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_2$ 245.1290, found 245.1262.

Ethyl 1-(2,6-difluorobenzyl)-1H-imidazole-5-carboxylate 7d

Off-white solid. Yield: 80%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.72 (d, J = 1.0 Hz, 1H), 7.50 (s, 1H), 7.32 (app tt, J = 8.4, 6.5 Hz, 1H), 6.93 (dd, 8.4, J = 7.6 Hz, 2H), 5.63 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 161.4 (2CF, dd, J = 252, 7 Hz), 160.3 (C), 141.7 (CH), 137.5 (CH), 131.1 (CH, t, J = 10 Hz), 122.9 (C), 111.7 (2CH, m), 111.5 (C, m), 60.6 (CH₂), 38.0 (CH₂), 14.3 (CH₃). ^{19}F -NMR (376 MHz, CDCl_3) δ /ppm: -114.0. IR (neat, v/cm^{-1}): 2984 (w), 1710 (s), 1627 (m), 1471 (s), 1374 (m), 1351 (m), 1220 (s), 1101 (s), 1025 (s), 902 (w), 834 (m), 792 (s), 763 (m), 655 (s). HR-MS (TQF+) calculated for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2\text{F}_2$ 267.0945, found 267.0949.

2,2,2-Trifluoroethyl 1-(2,6-difluorobenzyl)-1H-imidazole-5-carboxylate 7e

Off-white solid. Yield: 77%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.83 (d, J = 1.0 Hz, 1 H), 7.58 (s, 1H), 7.35 (app tt, J = 8.5, 6.5 Hz, 1H), 6.95 (dd, J = 8.5, 6.5 Hz, 2H), 5.61 (s, 2H), 4.65 (q, J = 8.3 Hz, 2H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 161.4 (2CF, dd, J = 252, 7 Hz), 158.3 (C), 142.8 (CH), 139.2 (CH), 131.2 (CH, t, J = 10 Hz), 122.9 (CF₃, q, J = 277 Hz), 121.1 (C), 111.7 (2CH, m), 111.3 (C, t, J = 19 Hz), 60.0 (CH₂, q, J = 37 Hz), 38.1 (CH₂, t, J = 4 Hz). ^{19}F -NMR (376 MHz, CDCl_3) δ /ppm: -73.7, -114.0. IR (neat, v/cm^{-1}): 1728 (s), 1628 (m), 1537 (m), 1472 (m), 1365 (m), 1273 (m), 1219 (m), 1164 (s), 1102 (s), 1028 (m), 971 (m), 840 (m), 791 (m), 757 (m), 651 (s). HR-MS (TQF+) calculated for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2\text{F}_5$ 321.0662, found 321.0665.

Ethyl 1-(2,4-dichlorobenzyl)-1H-imidazole-5-carboxylate 7f

Off-white solid. Melting range: 90.5–91.6 °C. Yield: 87%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.76 (d, J = 1.0 Hz, 1H), 7.61 (d, J = 1.0 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.12 (dd, J = 8.4, 2.1 Hz, 1H), 6.70 (dd, J = 8.4, 0.8 Hz, 1H), 5.53 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.0 (C), 142.4 (CH), 138.0 (CH), 134.9 (C), 133.3 (C), 133.0 (C), 129.5 (CH), 129.0 (CH), 127.6 (CH), 122.7 (C), 60.7 (CH₂), 47.2 (CH₂), 14.2 (CH₃). IR (neat, v/cm^{-1}): 3097 (w), 2993 (w), 1698 (s), 1541 (m), 1470 (m), 1373 (s), 1347 (m), 1295 (m), 1264 (m), 1234 (s), 1194 (m), 1121 (s), 1101 (s), 1047 (m), 1022 (m), 864 (m), 834 (m), 817 (m), 766 (s), 658 (m). HR-MS (TQF+) calculated for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}_2$ 299.0354, found 299.0352.

Methyl 1-(2,4-dichlorobenzyl)-1H-imidazole-5-carboxylate 7g

Off-white solid. Melting range: 102.4–105.0 °C. Yield: 81%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.72 (d, J = 1.1 Hz, 1H), 7.60 (d, J = 1.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 8.3, 2.1 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H), 5.51 (s, 2H), 3.73 (s, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.4 (C), 142.5 (CH), 138.1 (CH), 134.5 (C), 133.3 (C), 132.9 (C), 129.5 (CH), 129.0 (CH), 127.6 (CH), 122.4 (C), 51.6 (CH₃), 47.1 (CH₂). IR (neat, v/cm^{-1}): 3024 (w), 2963 (w), 1698 (s), 1532 (m), 1473 (m), 1426 (m), 1365 (s), 1298 (m), 1262 (m), 1225 (s), 1196 (s), 1115 (s), 1047 (m), 953 (m), 831 (s), 771 (s), 655 (s). HR-MS (TQF+) calculated for $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_2\text{Cl}_2$ 285.0198, found 285.0189.

Ethyl 1-(3,5-bis(trifluoromethyl)benzyl)-1H-imidazole-5-carboxylate 7h

Off-white solid. Melting range: 63.8–65.0 °C. Yield: 75%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.78 (m, 2H), 7.73 (s, 1H), 7.59 (s, 2H), 5.62 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.1 (C), 142.1 (CH), 139.1 (C), 138.3 (CH), 132.2 (2C, q, J = 34 Hz), 127.3 (2CH, m), 123.0 (2CF₃, q, J = 274 Hz), 122.6 (C), 122.1 (CH, dt, J = 8, 4 Hz), 60.8 (CH₂), 49.0 (CH₂), 14.1 (CH₃). ^{19}F -NMR (376 MHz, CDCl_3) δ /ppm: -63.0. IR (neat, v/cm^{-1}): 1711 (m), 1543 (w), 1477 (w), 1376 (m), 1353 (m), 1276 (s), 1170 (s), 1123 (s), 905 (m), 843 (m), 704 (m), 682 (m), 659 (m). HR-MS (TQF+) calculated for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_2\text{F}_6$ 367.0881, found 367.0876.

Ethyl 1-(4-bromobenzyl)-1H-imidazole-5-carboxylate 7i

Off-white solid. Melting range: 66.5–68.9 °C. Yield: 84%. ^1H -NMR (400 MHz, CDCl_3) δ /ppm: 7.74 (d, J = 1.0 Hz, 1H), 7.61 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 5.43 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, CDCl_3) δ /ppm: 160.1 (C), 142.1 (CH), 138.0 (CH), 135.4 (C), 132.0 (2CH), 128.8 (2CH), 122.6 (C), 122.0 (C), 60.6 (CH₂), 49.4 (CH₂), 14.2 (CH₃). IR (neat, v/cm^{-1}): 3096 (w), 2983 (w), 1700 (s), 1540 (m), 1487 (m), 1368 (m), 1343 (s), 1260 (m), 1227

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(s), 1184 (m), 1105 (s), 1010 (m), 917 (m), 766 (m), 752 (m), 659 (m). HR-MS (TQF+) calculated for $C_{13}H_{14}N_2O_2Br$ 309.0239, found 309.0246.

(R)-Ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate 7j

Colourless Oil. Yield: 85%. 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 7.78 (d, J = 1.1 Hz, 1H), 7.73 (s, 1H), 7.31–7.39 (m, 2H), 7.26–7.31 (m, 1H), 7.15–7.22 (m, 2H), 6.37 (q, J = 7.1 Hz, 1H), 4.19–4.34 (m, 2H), 1.87 (d, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$) δ /ppm: 160.3 (C), 141.1 (C), 139.7 (CH), 138.0 (CH), 128.8 (2CH), 128.0 (CH), 126.2 (2CH), 122.7 (C), 60.4 (CH₂), 55.3 (CH), 22.2 (CH₃), 14.3 (CH₃). IR (neat, ν/cm^{-1}): 2982 (w), 1709 (s), 1537 (w), 1451 (m), 1373 (m), 1347 (m), 1210 (s), 1130 (s), 1107 (s), 1054 (m), 1028 (m), 921 (m), 764 (s), 699 (s), 658 (s). HR-MS (TQF+) calculated for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1281.

(S)-Ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate 7k

Colourless Oil. Yield: 82%. 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 7.78 (d, J = 1.1 Hz, 1H), 7.73 (s, 1H), 7.31–7.37 (m, 2H), 7.25–7.31 (m, 1H), 7.16–7.21 (m, 2H), 6.37 (q, J = 7.1 Hz, 1H), 4.16–4.35 (m, 2H), 1.86 (d, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$) δ /ppm: 160.3 (C), 141.2 (C), 139.7 (CH), 138.1 (CH), 128.8 (2CH), 128.0 (CH), 126.3 (2CH), 122.6 (C), 60.4 (CH₂), 55.3 (CH), 22.2 (CH₃), 14.3 (CH₃). IR (neat, ν/cm^{-1}): 2983 (w), 1709 (s), 1537 (w), 1451 (m), 1373 (s), 1347 (s), 1209 (s), 1130 (s), 1106 (s), 1054 (m), 1028 (m), 921 (m), 764 (s), 699 (s), 659 (s). HR-MS (TQF+) calculated for $C_{14}H_{17}N_2O_2$ 245.1290, found 245.1283.

Isopropyl 1-butyl-1H-imidazole-5-carboxylate 7l

Colourless oil. Yield: 90%. 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 7.67 (d, J = 1.0 Hz, 1H), 7.52 (s, 1H), 5.15 (sept, J = 6.3 Hz, 1H), 4.24 (t, J = 7.3 Hz, 2H), 1.72 (tt, J = 8.3, 6.7 Hz, 2H), 1.30 (d, J = 6.3 Hz, 6H), 1.24–1.29 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$) δ /ppm: 159.8 (C), 141.7 (CH), 137.7 (CH), 122.8 (C), 68.0 (CH), 46.7 (CH₂), 33.1 (CH₂), 21.9 (2CH₃), 19.7 (CH₂), 13.6 (CH₃). IR (neat, ν/cm^{-1}): 2961 (w), 1706 (s), 1540 (m), 1468 (m), 1372 (s), 1300 (m), 1251 (m), 1220 (s), 1133 (s), 1094 (s), 923 (m), 839 (m), 767 (m), 658 (m). HR-MS (TQF+) calculated for $C_{11}H_{19}N_2O_2$ 211.1447, found 211.1444.

Ethyl 1-butyl-1H-imidazole-5-carboxylate 7m

Colourless oil. Yield: 88%. 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 7.68 (d, J = 1.0 Hz, 1H), 7.53 (s, 1H), 4.20–4.31 (m, 4H), 1.72 (tt, J = 8.3, 6.8 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.16–1.30 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$) δ /ppm: 160.2 (C), 141.8 (CH), 137.9 (CH), 122.4 (C), 60.4 (CH₂), 46.7 (CH₂), 33.1 (CH₂), 19.7 (CH₂), 14.3 (CH₃), 13.5 (CH₃). IR (neat, ν/cm^{-1}): 2961 (m), 1711 (s), 1539 (m), 1478 (m), 1373 (s), 1349 (s), 1250 (m), 1219 (s), 1131 (s), 1097 (s), 1019 (w), 921 (w), 766 (m), 658 (s). HR-MS (TQF+) calculated for $C_{10}H_{17}N_2O_2$ 197.1290, found 197.1287.

Ethyl 1-(2-cyclohex-1-en-1-yl)ethyl)-1H-imidazole-5-carboxylate 7n

Colourless Oil. Yield: 79%. 1H -NMR (400 MHz, $CDCl_3$) δ /ppm: 7.69 (d, J = 1.1 Hz, 1H), 7.48 (s, 1H), 5.28 (br s, 1H), 4.32 (t, J = 7.0 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.33 (t, J = 7.0 Hz, 2H), 1.83–1.95 (m, 4 H), 1.55–1.64 (m, 2 H), 1.45–1.52 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C -NMR (101 MHz, $CDCl_3$) δ /ppm: 160.3 (C), 142.0 (CH), 137.8 (CH), 133.2 (C), 124.6 (CH), 122.3 (C), 60.4 (CH₂), 45.6 (CH₂), 39.5 (CH₂), 28.2 (CH₂), 25.2 (CH₂), 22.8 (CH₂), 22.2 (CH₂), 14.3 (CH₃). IR (neat, ν/cm^{-1}): 2927 (m), 2857 (w), 1711 (s), 1539 (m), 1478 (m), 1373 (m), 1350 (m), 1220 (s), 1124 (s), 1104 (s), 1022 (m), 922 (m), 835 (w), 766 (m), 659 (m). HR-MS (TQF+) calculated for $C_{14}H_{21}N_2O_2$ 249.1603, found 249.1613.

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Keywords: imidazole • thioimidazole • flow chemistry • desulfurization • etomidate analgesic

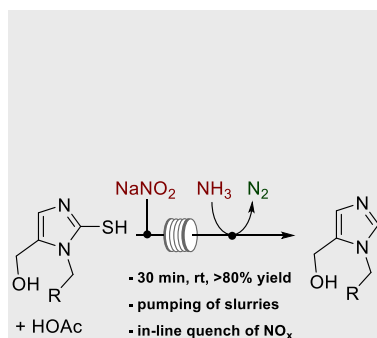
- [1] a) S.M. Weinreb, *Nat. Prod. Rep.* **2007**, *24*, 931–948; b) L. Zhang, X.-M. Peng, G.L.V. Damu, R.-X. Geng, C.-H. Zhou, *Med. Res. Rev.* **2014**, *34*, 340–437.
- [2] a) M. Baumann, I.R. Baxendale, S.V. Ley, N. Nikbin, *Beilstein J. Org. Chem.* **2011**, *7*, 442–495. Also, see reference 1a.
- [3] a) M. Baumann, I.R. Baxendale, *Org. Lett.* **2014**, *16*, 6076–6079.
- [4] a) J.M. Bergen, D.C. Smith, *J. Emerg. Med.* **1997**, *15*, 221–230; b) D.C. Smith, J.M. Bergen, H. Smithline, R. Kirschner, *J. Emerg. Med.* **2000**, *18*, 13–16; c) J.F. Cotton, S.S. Husain, S.A. Forman, K.W. Miller, E.W. Kelly, H.H. Nguyen, D.E. Raines, *Anesthesiology* **2009**, *111*, 240–249; d) E. Pejo, P. Santer, S. Jeffrey, H. Gallin, S.S. Husein, D.E. Raines, *Anesthesiology* **2014**, *121*, 290–301.
- [5] a) K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 12386–12387; b) J.H. Chang, K.W. Lee, D.H. Nam, W.S. Kim, H. Shin, *Org. Process Res. Dev.* **2002**, *6*, 674–676.
- [6] a) P.E. Maligres, M.S. Waters, S.A. Weissman, J.C. McWilliams, S. Lewis, J. Cowen, R.A. Reamer, R.P. Volante, P.J. Reider, D. Askin, *J. Heterocycl. Chem.* **2003**, *40*, 229–240; b) D. Przybyla, U. Nubbemeyer, *Eur. J. Org. Chem.* **2017**, 695–703; c) J.P. Collman, M. Zhong, S. Costanzo, C. Zhang, *J. Org. Chem.* **2001**, *66*, 8252–8256.
- [7] Further details on the Vapourtec E-series flow system can be obtained from their website: <https://www.vapourtec.com/products/e-series-flow-chemistry-system-overview/>.
- [8] 3-Way connectors (T-pieces) were purchased from Kinesis: <http://kinesis.co.uk/knowledgebase/low-volume-flow-paths>.
- [9] a) R.L. Hartman, *Org. Process Res. Dev.* **2012**, *16*, 870–887; b) T. Horie, M. Sumino, T. Tanaka, Y. Matsushita, T. Ichimura, J. Yoshida, *Org. Process Res. Dev.* **2010**, *14*, 405–410; c) J. Sedelmeier, S.V. Ley, I.R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618–3821; d) C.S. Polster, K.P. Cole, C.L. Burcham, B.M. Campbell, A.L. Frederick, M.M. Hansen, M. Harding, M.R. Heller, M.T. Miller, J.L. Phillips, P.M. Pollock, N. Zaborenko, *Org. Process Res. Dev.* **2014**, *18*, 1295–1309; e) P. Koos, D.L. Browne, S.V. Ley, *Green Process. Synth.* **2012**, *1*, 11–18; f) P. Filippini, A. Gioiello, I.R. Baxendale, *Org. Process Res. Dev.* **2016**, *20*, 371–375.
- [10] It was noted that using a back-pressure regulator can in some cases increase the likelihood of solids depositing in the peristaltic pump of stream A, which can lead to inaccurate flow rates and even blocking of the pump. Despite forming gaseous by-products, it was found that an open reactor exit mitigates this risk and still allows for the reaction to reach completion within the flow coils.
- [11] Alternative mechanisms can be postulated where nitrous acid (HONO) or nitrite anion reacts with ammonium hydroxide, either of which exist in equilibria with the nitrosonium species we propose. Please see: a) N. Takenaka, I. Takahashi, H. Suekane, K. Yamamoto, Y. Sadanga, H. Bandow, *J. Phys. Chem. A* **2011**, *115*, 14446–14451; b) J.H. Dusenbury, R.E. Powell, *J. Am. Chem. Soc.* **1951**, *73*, 3266–3268.
- [12] a) J.B. Epp, T.S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293–295.
- [13] a) E.J. Corey, N.W. Gilman, B.E. Ganem, *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617; b) N.W. Gilman, *Chem. Commun.* **1971**, 733–734; c) J.S. Foot, H. Kanno, G.M.P. Giblin, R.J.K. Taylor, *Synthesis* **2003**, *7*, 1055–1064; d) Corey-Gilman-Ganem Oxidation. *Comprehensive Organic Name Reactions and Reagents* **2010**, *158*, 722–725.

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Flow Desulfurisation

M. Baumann, I.R. Baxendale***Page No. – Page No.****A Continuous Flow Method for the Desulfurization of Substituted Thioimidazoles Applied to the Synthesis of New Etomidate Derivatives**

*one or two words that highlight the emphasis of the paper or the field of the study