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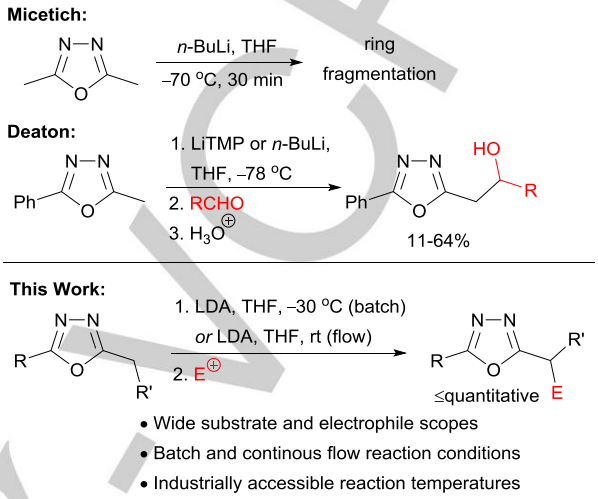
FULL PAPER

Batch *Versus* Flow Lithiation-Substitution of 1,3,4-Oxadiazoles: Exploitation of Unstable Intermediates Using Flow Chemistry

Jeff Y. F. Wong, John M. Tobin, Filipe Vilela and Graeme Barker*

Abstract: 1,3,4-Oxadiazoles are a common motif in pharmaceutical chemistry, but few convenient methods for their modification exist. A fast, convenient, high yielding and general α-substitution of 1,3,4-oxadiazoles has been developed using a metalation-electrophilic trapping protocol both in batch and under continuous flow conditions in contradiction to previous reports which suggest that α-metalation of this ring system results in ring fragmentation. In batch, lithiation is accomplished at an industrially convenient temperature, –30 °C, with subsequent trapping giving isolated yields of up to 91%. Under continuous flow conditions, metalation is carried out at room temperature, and subsequent in flow electrophilic trapping gave up to quantitative isolated yields. Notably, lithiation in batch at room temperature results only in ring fragmentation and we propose that the superior mixing in flow allows interception and exploitation of an unstable intermediate before decomposition can occur.



Scheme 1. Previous oxadiazole lithiations *vs.* this work

Introduction

Oxadiazoles occupy an important role in modern medicinal chemistry,[1] often acting as bioisosteres of carboxylate derivatives including amides,[2] esters,[2] carbamates[3] and hydroxamic esters[4] as well as attracting attention for their optoelectronic properties.[5] In almost all cases the 1,3,4-isomer exhibits pharmacologically favorable activity with respect to lipophilicity (log D), hERG inhibition and metabolic stability.[1] Examples of bioactive 1,3,4-oxadiazoles include raltegravir with an antiretroviral activity[6] and zibotentan as an endothelin receptor antagonist[7] (figure **1**). Often thought of as a comparatively delicate motif, oxadiazoles are typically installed late in target synthesis, and subsequent substitutions in adjacent positions analogous to isosteric α-amino acid-derived peptide stereocentres are correspondingly rare.

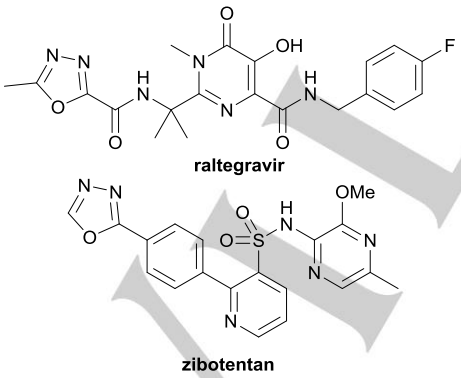


Figure 1. Bioactive 1,3,4-oxadiazoles

This paucity of oxadiazole modifications becomes problematic in light of the harsh conditions used to form the heterocycle, typically from a precursor hydrazide in DMSO or DMF at high temperature.[8] Therefore, there is a clear need to develop oxadiazole modifications in the heterobenzylic position. In this context, we herein disclose a convenient protocol for the α-lithiation substitution of alkyl-1,3,4-oxadiazoles under both batch and continuous flow conditions using industrially accessible temperatures (–30 °C in batch and room temperature in flow),[9] short reaction times (1.3 s – 1 min) and a readily available non-nucleophilic base, LDA.

Previous reports of alkyl-1,3,4-oxadiazole metalations are sparse, stemming from Micetich's observation that attempted lithiation-trapping of 2,5-dimethyl-1,3,4-oxadiazole results solely in ring fragmentation (scheme **1**).[10] While neither substrate nor trapped oxadiazoles were recovered, details of the ring fragmentation products were not given. Deaton has reported the α-lithiation of 2-methyl-5-aryl-1,3,4-oxadiazoles followed by trapping with aldehydes during the synthesis of cathepsin K inhibitors, however yields were modest, presumably due to competing ring fragmentation (scheme **1**).[11] Katritzky has also reported the metalation of oxadiazolylmethyl-1*H*-benzotriazoles in the doubly benzylic position.[12] *Ortho*-metalation of aryl-1,3,4-oxadiazoles to manganese[13] and iridium[14] metallacycles has been demonstrated, though subsequent C-C bond forming processes have not been reported.

We have also optimised our new synthetic protocol for use under continuous flow conditions. Flow chemistry has enjoyed

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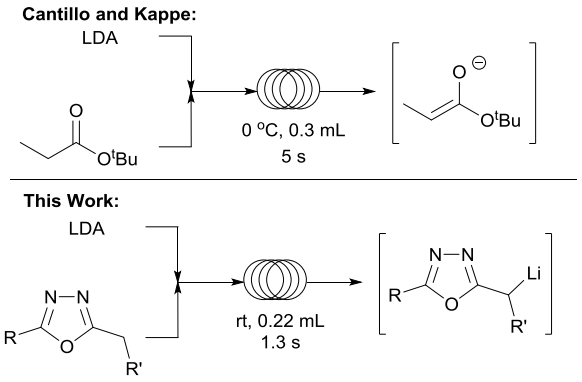


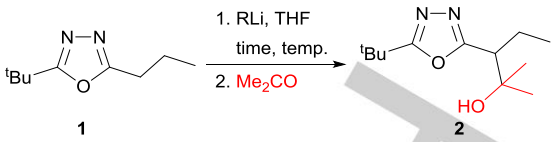
Scheme 2. Previous in-flow deprotonations *vs.* this work

considerable attention from synthetic chemists in recent years,[15] with multiple examples of group 1 and 2 organometallic reactions reported,[16] most notably by the groups of Knochel[17] and Ley.[18] However, formation of new organolithium species in flow has largely been restricted to halogen-lithium exchange or deprotonation at sp^2 centres. Alezra[19] as well as Cantillo and Kappe[20] have separately reported LDA-mediated enolate formation under continuous flow conditions, and Ley reports the LiHMDS-facilitated heterobenzylic lithiation of methylpyridines.[21] While these examples detail the formation of chemically stable organolithiums usable under batch conditions, we herein report sp^3 deprotonation to form an organolithium species which is unstable under comparable batch conditions. Subsequent in-flow interception by electrophilic trapping allows synthetic use of this intermediate and high yields of products could be obtained (scheme **2**).

1,3,4-Oxadiazoles have previously been employed as amide and ester bioisosteres.[2] Commonly derived from amino acids, naturally occurring amide and ester protein ligands feature branching points at the α-position. We therefore proposed to investigate the possibility of substituting alkyl-1,3,4-oxadiazoles at the analogous carbon *via* a metalation-substitution approach.

Results and Discussion

We began our investigations by screening a number of different organolithium bases at –78 °C and the industrially accessible –30 °C[9] for lithiation of oxadiazole **1** prior to electrophilic trapping with acetone (table **1**). When deprotonating with ^{n}BuLi (entries 1 and 2), modest conversions to **2** were observed with no remaining starting material due to competitive nucleophilic attack by ^{n}BuLi.[1] Switching to the more sterically hindered base ^{s}BuLi led to an increase in yields, providing 96% and 80% yields after 20 min at –78 °C and 1 min at –30 °C respectively (entries 3 and 4). We then investigated the milder and less

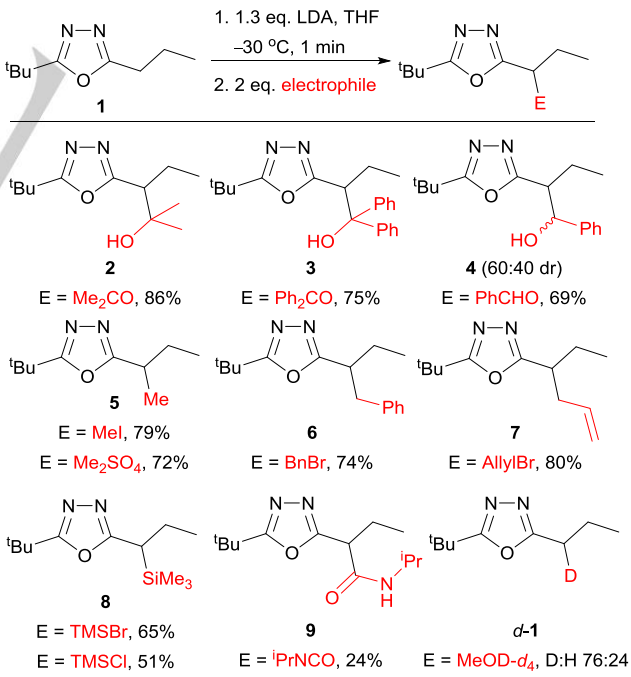


Entry	Base (1.3 eq.)	Temp./°C	Time	Yield[a]
1	^{n}BuLi	–78	1 h	44%
2	^{n}BuLi	–30	15 min	48%
3	^{s}BuLi	–78	20 min	96%
4	^{s}BuLi	–30	1 min	80%
5	LDA	–78	20 min	92%
6	LDA	–30	1 min	95%
7	LDA	rt	10 s	0%
8	LDA	rt	1.3 s	40%

[a] as determined by ^{1}H NMR in the presence of dimethylsulfone

Table 1. Optimisation of oxadiazole modification

nucleophilic base LDA: yields of 92% after 20 min at –78 °C and 95% after 1 min at –30 °C were obtained. Raising the temperature to rt resulted in decomposition of the lithiated intermediate after 10 s (entry 7) – inspection of the ^{1}H NMR spectrum of the crude reaction mixture revealed a complex



Scheme 3. Electrophile scope

mixture of products (not including **1** or **2**) which we were unable to separate, but which we propose arise from the ring fragmentation observed by Micetich.[10] Reducing the metalation

[1] For further details, see ESI.

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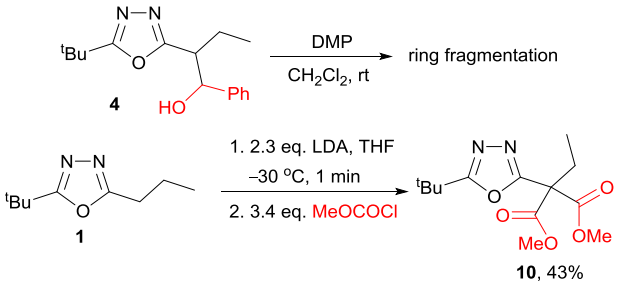
time to 1.3 s at rt gave a 40% yield of **2** with no remaining **1** (entry 8), indicating that decomposition happens quickly after lithiation at room temperature.

Having determined optimal metalation conditions, the wide electrophile scope was demonstrated. Good isolated yields were obtained after trapping with acetone, benzophenone, benzaldehyde, MeI, BnBr, Me_2SO_4, allyl bromide, and TMSBr (scheme **3**). Attempted trapping with TMSCl gave only 51% of silylated product **8**. Trapping with MeOD-d_4 gave deuterated



Scheme 4. β-Carbonyl derivative instability

oxadiazole *d*-**1** with 76% D incorporation. Attempts to trap with electrophiles to give β-carbonyloxadiazoles were less successful, with only a 24% isolated yield of amide **9** obtained after trapping with ^{i}PrNCO, and we were unable to isolate the expected products after trapping with BzCl, MeOCOCl or DMF. We propose that rather than inefficient trapping with these electrophiles, the products are unstable. Indeed, oxidation of a diastereopure sample of alcohol **4** (obtained from electrophilic trapping using PhCHO) with Dess-Martin periodinane led to initial formation of the expected ketone product (as observed by ^{1}H NMR of the crude reaction mixture), which then decomposed to an unidentifiable complex mixture of products before purification could be carried out (scheme **4**). Lithiation using 2.3 eq. LDA followed by 3.4 eq. MeOCOCl gave disubstituted product **10** in 43% yield *via* interception of the unstable monosubstituted product by a second deprotonation-trapping event (scheme **4**).

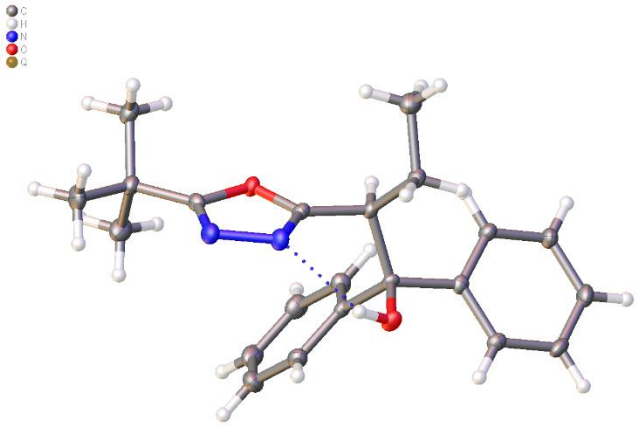
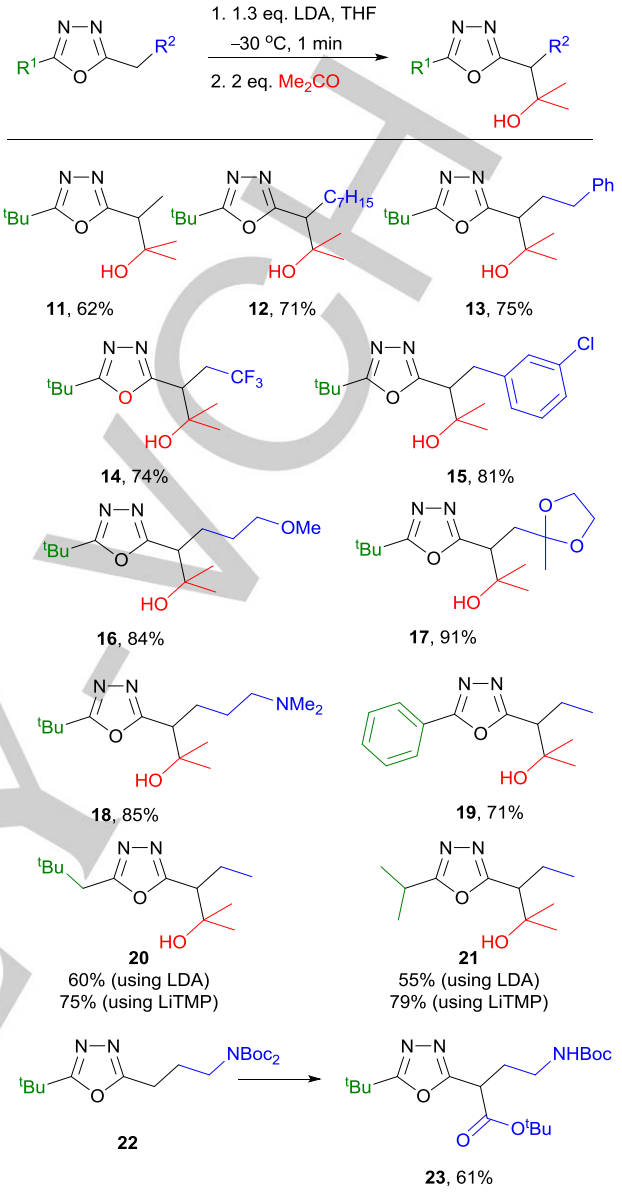


Figure 2. X-ray structure of product **3**.

An X-ray crystal structure of benzophenone trapped product **3** indicated favorable hydrogen bonding between a β-hydroxyl substituent and the oxadiazole N3 position (figure **2**). This observation led us to hypothesize that a decomposition pathway of β-carbonyloxadiazoles exists *via* formation of the enol tautomer. Indeed, when enol formation is disfavored (e.g. in product **9**) or impossible (**10**), β-carbonyl bearing products can be obtained.



Scheme 5. Substrate scope.

Next, we turned our attention to the substrate scope (scheme **5**) and began by investigating the effect of altering the alkyl chain undergoing metalation. Exchanging *n*-propyl for either ethyl (**11**) or *n*-octyl (**12**) chains maintained the efficiency of the reaction, with yields of 62% and 71% obtained respectively. We then probed functional group tolerance, and found that aryl (**13**, 75% yield of trapped product), haloaryl (**15**, 81%), ether (**16**, 84%), trifluoromethyl (**14**, 74%), acetal (**17**, 91%) and dimethylamino (**18**, 85%) motifs were pleasingly all compatible with the methodology. Di-*N*-Boc aminoalkyloxadiazole **22** also underwent efficient metalation, although in this case migration of a Boc group to give **23** in 61% yield outcompeted trapping with an external electrophile. We then investigated the compatibility of a second oxadiazole substituent which could conceivably undergo metalation: phenylpropyloxadiazole underwent efficient substitution to give **19** in 71% yield with no evidence of aryl metalation observed. To our delight, when a second deprotonatable alkyl substituent is present, metalation trapping

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occurs with complete selectivity at the less sterically hindered position, thought in these cases slightly higher yields were obtained using LiTMP rather than LDA (75% *vs.* 60% for **20** and 79% *vs.* 55% for **21**). No trace of product arising from metalation

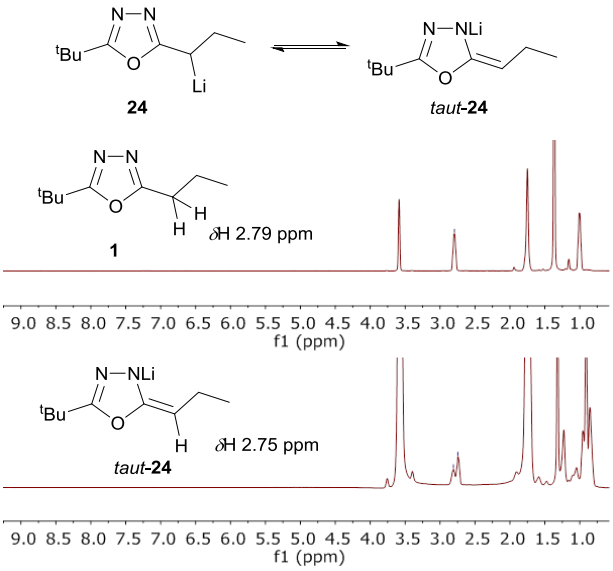


Figure 3. Lithiation of **1** followed by *in situ* ^{1}H NMR

at the other alkyl position was observed.

Next, we investigated attempting to optimize an enantioselective lithiation-substitution procedure. Unfortunately, after assaying a range of chiral lithium amide bases and a range of chiral diamine ligands in the presence of ^{s}BuLi, we were only able to obtain high yields of near racemic (best er = 55:45) products, and a "poor man's Hoffman test" suggested that the lithiated intermediate might be configurationally unstable (see ESI).[22] Instead, we hypothesized that the lithiated intermediate **24** may preferentially adopt its azaenolate form *taut*-**24** in solution, precluding stereoselective substitution. To probe this, a sample of

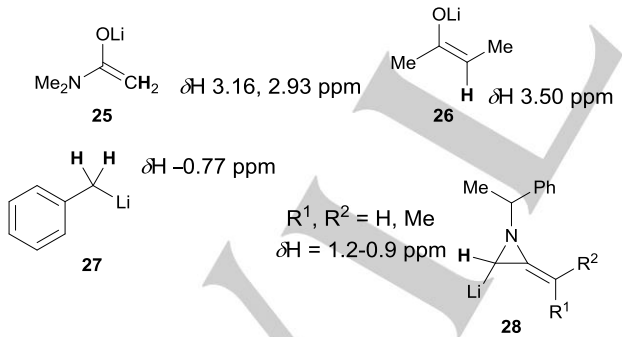
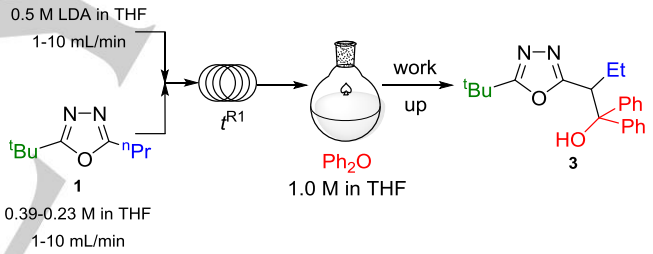


Figure 4. ^{1}H NMR shifts of lithium enolates and lithium carbanions

1 was metalated at –67 °C in THF-d_8 and the reaction followed by ^{1}H NMR spectroscopy (figure **3**).[23] Before addition of base, the heterobenzylic protons of **1** appear at δH 2.79 ppm. After addition of LDA, two signals are clearly visible at δH 2.79 and δH 2.75 ppm, corresponding to residual **1** and the alkenyl proton of azaenolate *taut*-**24**. While this may at first glance appear unusually upfield for an sp^2 center proton, this does correspond to the spectrum for the analogous enolate of dimethylacetamide **25** as reported by Rathke (δH 3.16 and 2.93 ppm) and enolate **26** reported by Still (δH 3.50 ppm).[24] In contrast, the protons of *C*-lithated carbanions display considerably upfield shifts, with the benzylic protons of benzyllithium **27** at δH –0.77 ppm in THF-d_8 and 2-lithioaziridines such as **28** in the range δH 1.20-0.90 ppm.[23a, 25]

Next, we turned our attention to optimizing lithiation-substitutions under continuous flow conditions. While we have shown that the reaction did not proceed in high yields at room temperature in batch due to decomposition of the lithiated intermediate (table **1**, entries 7 and 8), we proposed that the superior mixing, heat transfer and control of reaction timing under continuous flow conditions would allow fast metalation then interception of the unstable intermediate with an electrophile before decomposition could take place. This is similar to the "flash chemistry" approach developed by Nagaki and Yoshida to intercept unstable reaction products or intermediates.[26] For example, ketone products may be obtained after treatment of acylchlorides with organolithiums without further reaction to the tertiary alcohol, and esters may be isolated after trapping organolithiums with Boc_2O.[27] However, in–flow generation of unstable organolithium species has largely been limited to carbolithiation[28] and halogen-lithium exchange[29] processes; deprotonations are limited to a single example at an sp^2 center,[30] or benzylic lithiations at low temperatures (≥–98 °C).[31] In this context, we have developed the first room temperature organolithium-mediated deprotonation to form an unstable



Entry	[**1**]/M	t^{R1}/s	Yield[a]	RSM[a]
1	0.39	5.6	39%	24%
2	0.39	14.0	41%	22%
3	0.39	28	34%	16%
4	0.23	28	45%	0%
5	0.23	2.8	86%	0%

[a] as determined by ^{1}H NMR in the presence of dimethylsulfone

Table 2. Optimisation of continuous flow metalation.

intermediate followed by fast in-flow trapping before decomposition can take place as it would under batch conditions.

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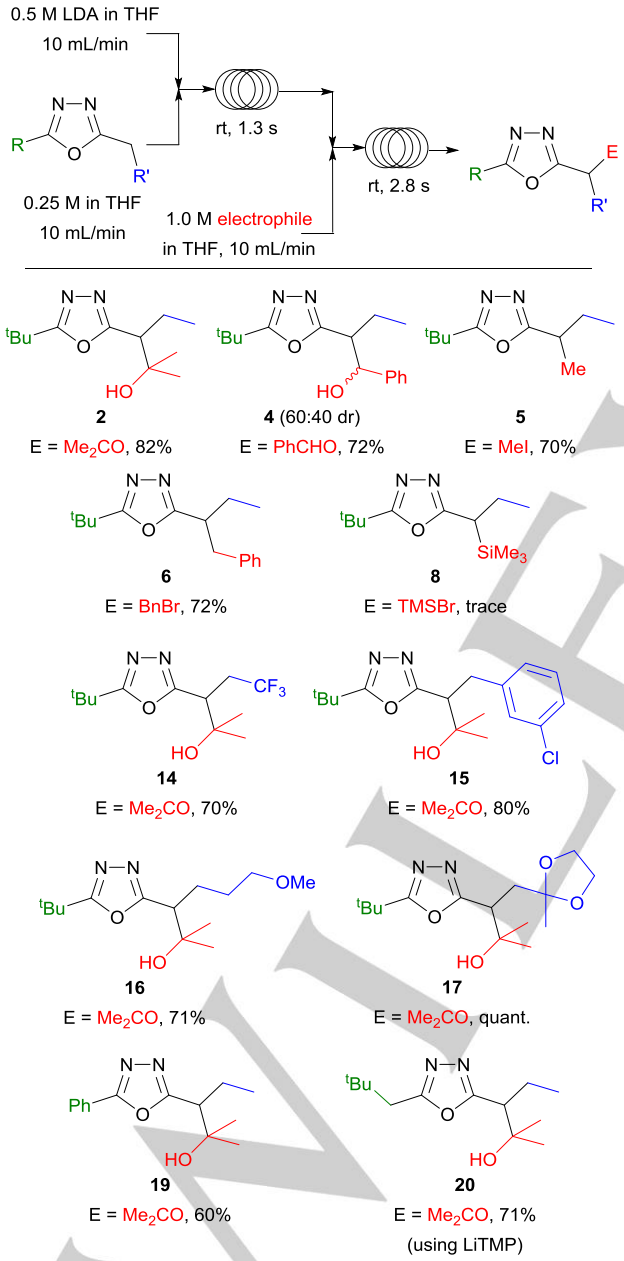
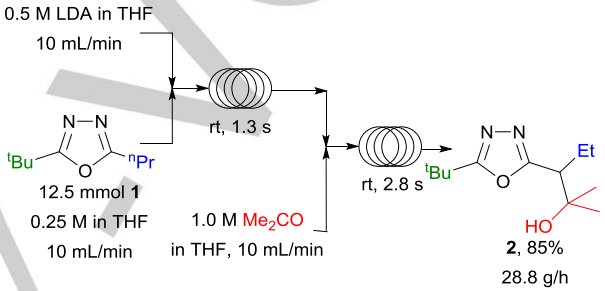
We began by investigating the effect of metalating oxadiazole **1** with LDA under continuous flow conditions at rt and pumping the resulting solution into a flask containing a rapidly stirring solution of benzophenone in THF at rt (table **2**). Reactor residence time (t^{R1}) for the metalation step was varied by changing the flow rate. When utilizing a 0.39 M solution of oxadiazole **1** in THF (analogous stoichiometry to our optimized batch conditions), a significant amount of starting material was recovered, even after extended reactor residence times (entries 1-3). For example, after t^{R1} = 28 s, only a 34% yield of **3** was obtained, with 16% **1** remaining. Inspection of the ^{1}H NMR spectrum of the crude product revealed that the significant mass loss was due to competitive ring fragmentation. Reduction of the



Scheme 6. Oxadiazole lithiation-substitution in flow

concentration of the **1** feedstock solution was able to remedy this problem, with a 45% yield of **3** obtained with no remaining **1** after t^{R1} = 28 s (entry 4). Reducing the residency time to 2.8 s greatly reduced ring fragmentation, and an 86% yield of **3** was obtained with no remaining **1** (entry 5).

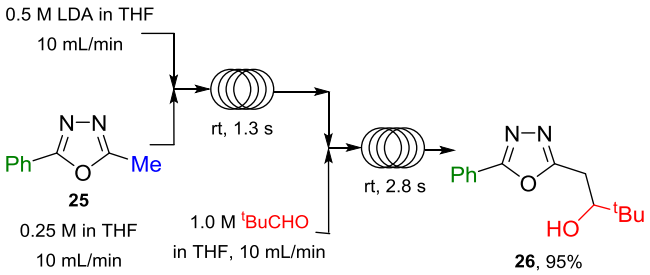
With high-yielding continuous flow metalation conditions in hand, we decided to investigate subsequent in-flow electrophilic trapping. To our delight, metalation of oxadiazole **1** with LDA in THF at rt with a reactor residence time (t^{R1}) of 1.3 s followed by trapping with acetone (t^{R2} = 2.8 s) afforded product **2** in 82% yield, comparable with the batch yield of 86% (scheme **6**). A selection of oxadiazoles and electrophiles was then chosen to demonstrate the scope of the reaction under continuous flow conditions (scheme **6**) and in each case yields were comparable to the equivalent batch synthesis at –30 °C. Notably, acetal-containing oxadiazole **18** was obtained in quantitative yields. As an exception to this rule, we found that when flow metalation-trapping was attempted with a slowly reacting electrophile, TMSBr, only a trace amount of product **8** was obtained.



Scheme 7. Large scale flow lithiation-substitution

We also wished to demonstrate the utility of our flow protocol on a larger scale and determine the productivity rate (scheme **7**). Thus, under our standard continuous flow conditions, 12.5 mmol of oxadiazole **1** was metalated and trapped over 5 min to give an 85% yield of **2**. This corresponds to a productivity rate of 28.8 g/h, or alternatively 7.9 h would be required to produce a mole of product.

Finally, we wished to demonstrate the utility of the in-flow lithiation-substitution with a formal synthesis of a sub-nanomolar cathepsin K inhibitor developed to combat osteoporosis.[11] Thus, oxadiazole **25** was subjected to our standard in-flow metalation conditions before in-flow trapping with pivaldehyde to give key inhibitor synthetic intermediate **26** in 95% yield (scheme **8**).



Scheme 8. Formal synthesis of a cathepsin K inhibitor

Conclusions

In conclusion, we have developed a fast and convenient lithiation-substitution protocol for alkyl-1,3,4-oxadiazoles and demonstrated its utility with a wide range of substrates and electrophiles both in batch and under continuous flow conditions. Our approach addresses key limitations of previous attempts to

effect oxadiazole metalation, namely competitive decomposition of the metalated intermediate and extremely limited substrate and electrophile scope. In batch, our conditions (–30 °C for 1 min then electrophilic trapping) are amenable for use on a process scale and gave up to 91% isolated yields, while under flow conditions room temperature may be used, giving up to quantitative yields. The success of our approach rested on the use of a non-nucleophilic lithium amide base (LDA or LiTMP) and either cooling to –30 °C in batch or the use of a fast deprotonation-trapping strategy in flow to avoid decomposition of reaction intermediates.

Experimental Section

Typical procedures for batch and flow lithiation-substitutions of an alkyl-1,3,4-oxadiazole are given below. For full details and all data, see SI.

General Lithiation-Substitution Procedure in Batch:

LDA (1.3 eq.) was added dropwise to a stirred solution of oxadiazole (1.0 eq.) in THF at –30 °C. The resulting solution was stirred at –30 °C for 1 min then electrophile (2.0 eq.) was added. The resulting solution was stirred at –30 °C for 10 min then allowed to warm to rt over 16 h. Saturated $NH_4Cl_{(aq)}$ solution was added and the layers separated, extracting the aqueous with Et_2O (×3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General Lithiation-Substitution Procedure in Continuous Flow:

All continuous flow reactions were carried out using the easy-Photochem flow reactor from Vapourtec Ltd. A 0.25 M solution of oxadiazole in THF and a 0.5 M solution of LDA in THF were driven through two separate peristaltic pumps at 10 mLmin^{-1} at rt. The solutions were pumped through 1 mm I.D. PTFE tubing and mixed at a T-junction. The resulting solution was passed through a length of tubing (10 mLmin^{-1}, 0.28 mL, t^{R1} = 1.3 s) before mixing at a second T-junction with a 1.0 M solution of electrophile pumped at 10 mLmin^{-1} through a third peristaltic pump. The resulting solution was passed through a second length of tubing (10 mLmin^{-1}, 0.47 mL, t^{R2} = 2.8 s) and collected as the product solution. After the flow had reached a steady state, the product solution was collected for 15 s. A saturated solution of $NH_4Cl_{(aq)}$ was added to the collected product solution and the layers were separated, extracting the aqueous with Et_2O (×3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

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Keywords: heterocycles • lithiation • synthetic methods • alkylation

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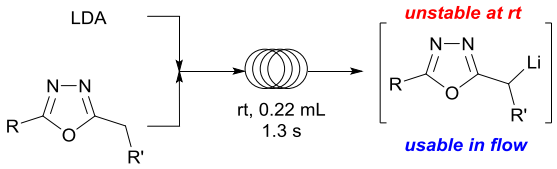

A convenient new substitution of alkyl-1,3,4-oxadiazoles, a key pharmaceutical motif, is described. The reaction tolerates a wide scope of substrates and can be carried out in either batch or continuous flow conditions. In batch cooling to –30 °C is required to avoid decomposition of an unstable intermediate while in flow this may be quickly intercepted and synthesis carried out at room temperature.

*Jeff Y. F. Wong, John M. Tobin, Filipe Vilela and Graeme Barker**

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Batch *Versus* Flow Lithiation-Substitution of 1,3,4-Oxadiazoles: Exploitation of Unstable Intermediates Using Flow Chemistry