One-step Synthesis of 3,4-Disubstituted 2-Oxazolidinones via Base-catalyzed CO_2-Fixation and Aza-Michael Addition

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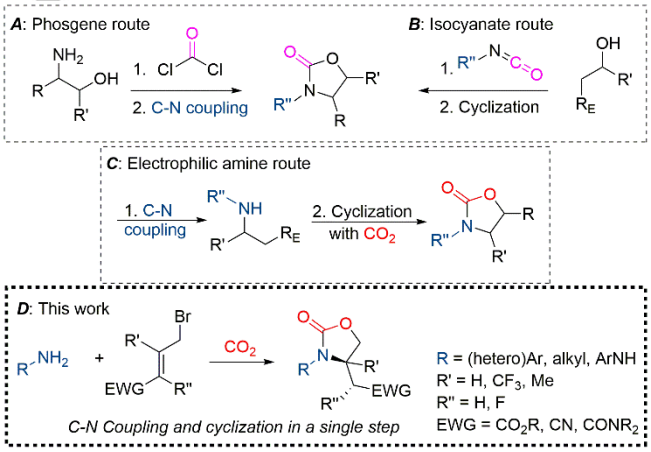
Abstract: 2-Oxazolidinones are saturated heterocyclic compounds, which are highly attractive targets in modern drug design. Here we describe a novel, single step approach to 3,4-disubstituted 2-oxazolidinones via aza-Michael addition using CO_2 as a carbonyl source and 1,1,3,3-tetramethylguanidine (TMG) as a catalyst. The modular reaction, which occurs between a γ-brominated Michael acceptor, CO_2 and an arylamine, aliphatic amine or phenylhydrazine, is performed under mild conditions. The regiospecific reaction displays good yields (avg. 75 %) and excellent functional group compatibility. In addition, late-stage functionalization of drug and drug-like molecules is demonstrated. The experimental results suggest a mechanism consisting of several elementary steps: TMG-assisted carbonylation of aniline; generation of an *O*-alkyl carbamate; and the final ring-forming step via an intramolecular aza-Michael addition.

Development of new and improved pharmaceutically active molecules is a complex process with many considerations, and interesting trends have emerged. For example, nitrogen containing heterocycles are important, as they are found in 59 % of FDA approved small-molecule drugs.[1] It is also shown that a higher fraction of sp^3 hybridized carbons (Fsp^3) and the presence of chiral centers correlates with the clinical success of drug candidates.[2] One group of compounds, that meets both of these criteria, is the 2-oxazolidinones, a type of five-membered cyclic carbamates. They are particularly attractive synthetic targets due to their wide-ranging biological activity and central role in several state-of the-art drugs[3–6] including antibiotics[7–10] and anti-cancer drugs.[11,12] Consequently, the 2-oxazolidinone core can be seen as a promising "isostere", a replacement of conventionally used (flat aromatic) structures in biological environments; it is a saturated, nitrogen-containing heterocycle with a tunable structure. As current methods of introducing such saturated heteroatom ring systems are fairly limited[13], new and straightforward synthetic methods are desired to introduce isosteres, such as 2-oxazolidinones, into core scaffolds.[14–17]

The most conventional 2-oxazolidinones synthesis is carried out by cyclizing amino alcohols with phosgene, followed by C-N coupling (Scheme 1A).[18–22] These steps may also be executed in reverse order.[7,23–25] A less common approach involves reacting the corresponding isocyanate with an electrophilic alcohol, which is then cyclized (Scheme 1B).[26–30] Despite being widely used for 2-oxazolidinone synthesis, these methods are constrained by the toxicity of the reagents.

There is an increasing interest in the use of carbon dioxide as an alternative, safer and more cost-efficient carbonyl source as compared to phosgene and isocyanates.[31] Indeed, several strategies for CO_2-based preparation of cyclic carbamates have been reported. In the most studied approach, primary amines are first coupled to an electrophilic group such as an alkyne[32–36], a strained ring[37–40], or an activated alcohol[41] followed by the CO_2-driven cyclization (Scheme 1C). All the above syntheses (Scheme 1A-C) are two-step processes, and consequently, relatively laborious routes.

To resolve the above-discussed challenges, we turned our attention to the aza-Michael addition. Herein we report our results on direct unprecedented single-step synthesis of 3,4-disubstituted 2-oxazolidinones by a base-catalyzed aza-Michael addition, using organic carbamates generated *in situ* from (aryl)amines and CO_2 (Scheme 1D). The reaction is performed under mild conditions and displays good yields (avg. 75 %) and excellent functional group compatibility, and the method allows for late-stage functionalization of complex molecules. Additionally, quantitative ^{13}C nuclear magnetic resonance (NMR) studies, control experiments and isolation of a mechanistically relevant acylic carbamate shed light on a possible mechanism.



Scheme 1. Synthetic pathways to substituted 2-oxazolidinones. ***A-C***: Two-step syntheses. ***D***: Single step synthesis. R_E = electrophilic group. EWG = electron withdrawing group.

We initiated our study by using commercial methyl 4-bromocrotonate **1** as a Michael acceptor and aniline **2a** under a CO_2 atmosphere with various solvents and organic bases. Under optimized conditions 2-oxazolidinone **3a** formed regioselectively in 99 % yield, using 1,1,3,3-tetramethylguanidine (TMG, 20 mol%) in combination with Cs_2CO_3 (4 equiv) in dimethylformamide

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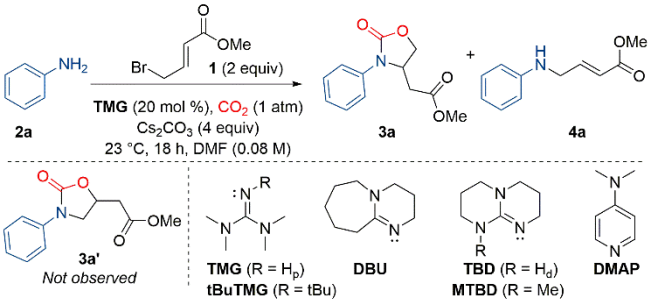
(DMF) (Table 1, entry 1). The formation of *N*-alkylated byproduct **4a** was eliminated by a slow addition (over 4 h) of Michael acceptor **1**. Regioisomer **3a'** was not observed at any point. For a detailed discussion of our optimization studies, see the Supporting Information (SI).

The catalytic effects of various organic bases were compared to TMG (pK_a 23.4 in acetonitrile[42]). It was found that 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (tBuTMG, pK_a 26.5[43]), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU, pK_a 24.3[42]), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, pK_a 26.0[42]) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD pK_a 25.44[42]) gave slightly lower yields of **3a**, despite a similar high Brønsted basicity compared to TMG (Table 1, entries 2-5, 89-91 % yields). Weaker bases such as triethylamine (pK_a 18.8[42]) and 4-(dimethylamino)pyridine (DMAP pK_a 18.0[42]) gave significantly lower yields (entries 6-7, 43-44 % yields). In light of these results, the catalytic base must have a sufficiently high basicity (pK_a > 23 in acetonitrile) to effectively facilitate the reaction. However, basicity alone is not the only factor influencing the catalysts' activity; tBuTMG, DBU, TBD and MTBD have basicities similar to TMG and might be expected to give a similar yield; but instead, slightly lower yields were obtained. In the neutral state, tBuTMG, DBU and MTBD are aprotic bases, whereas TMG and TBD are protic. The latter two differ structurally from each other. In TMG the proton is proximal (H_p) to the basic lone pair, while in TBD the proton is distal (H_d). Considering the above, it is likely that TMG stands out due to a secondary catalytic effect. The proximal proton (H_p) of TMG stabilizes the forming enolate of the conjugate addition, in contrast to the distal proton (H_d) of TBD (see mechanistic discussion below).

The effect of different reaction components was evaluated by a series of control experiments. Only trace amounts of 2-oxazolidinone **3a** were formed without a CO_2 atmosphere and the major product was *N*-alkylated **4a** (entry 8). In the absence of Cs_2CO_3, 2-oxazolidinone **3a** was obtained in 85 % yield, providing strong evidence that the carbonyl in **3a** originates from CO_2, and not from the carbonate anion (entry 9). In the absence of TMG, the yield of **3a** was significantly decreased (46 %, entry 10), which was comparable to entries 6 and 7, suggesting triethylamine and DMAP had no catalytic effect. Other inorganic bases gave inferior yields, even with tetrabutylammonium iodide (TBAI) or CsBr as phase transfer-catalysts (entries 11-14). These results indicate that Cs_2CO_3 is superior, as it has a better solubility than other inorganic bases.[44]

Further experimental studies show that the reaction has a broad scope (Scheme 2). The electronic and steric properties of the parent aniline affected the optimal addition rate of Michael acceptor **1**. For example, with the standard rate of addition (4 h), electron-rich *ortho*-substituted **3b** was obtained in a ca 50 % yield, which was improved to 88 % by a slower addition of **1** (over 6 h). This indicates that *ortho*-substitution retards the reaction rate due to steric hindrance. Strongly electron withdrawing substituents (**3f** and **3g**) necessitated a very slow addition of **1** (over 12 h), regardless of substitution at the *ortho* or *para*-position, suggesting a lower concentration of the forming carbamate ion due to electronic destabilization. Medicinally relevant heterocylic aminopyridine **2l** and -thiazole **2m** gave high yields (**3l** 78 %, **3m** 63 %). The methodology was successfully extended to aliphatic amines (**3n**-**3p**, 71-73 %) and phenylhydrazine (**3q**, 58 %). A slow addition of the Michael acceptor **1** (over 12 h) was necessary to avoid formation of corresponding *N*-alkylated by-products (**4n**-**4p**). This can be ascribed to the higher nucleophilicity of aliphatic amines in comparison to anilines. Finally, we conducted a mechanistic investigation with *N*-methylaniline **2r**, which we assumed should be able to capture CO_2, but not undergo the subsequent aza-Michael addition. As predicted, an acylic *O*-alkyl carbamate was obtained (**3r**, 57 %).

Table 1. Evaluation of reaction components.



Entry	Deviation from above	Yield of **3a** (%)[a]
1	None	99
2	tBuTMG, instead of TMG	89
3	DBU, instead of TMG	90
4	TBD, instead of TMG	90
5	MTBD, instead of TMG	91
6	Et_3N, instead of TMG	43
7	DMAP, instead of TMG	44
8[b]	Ar, instead of CO_2	<5
9[b]	No Cs_2CO_3, excess TMG (4.2 eq)	85
10[b]	No TMG	46
11[b]	K_2CO_3, instead of Cs_2CO_3	29
12[b]	K_3PO_4, instead of Cs_2CO_3	64
13[b]	K_2CO_3 and TBAI (4 eq), instead of Cs_2CO_3	18
14[b]	K_3PO_4 and CsBr (4 eq), instead of Cs_2CO_3	55

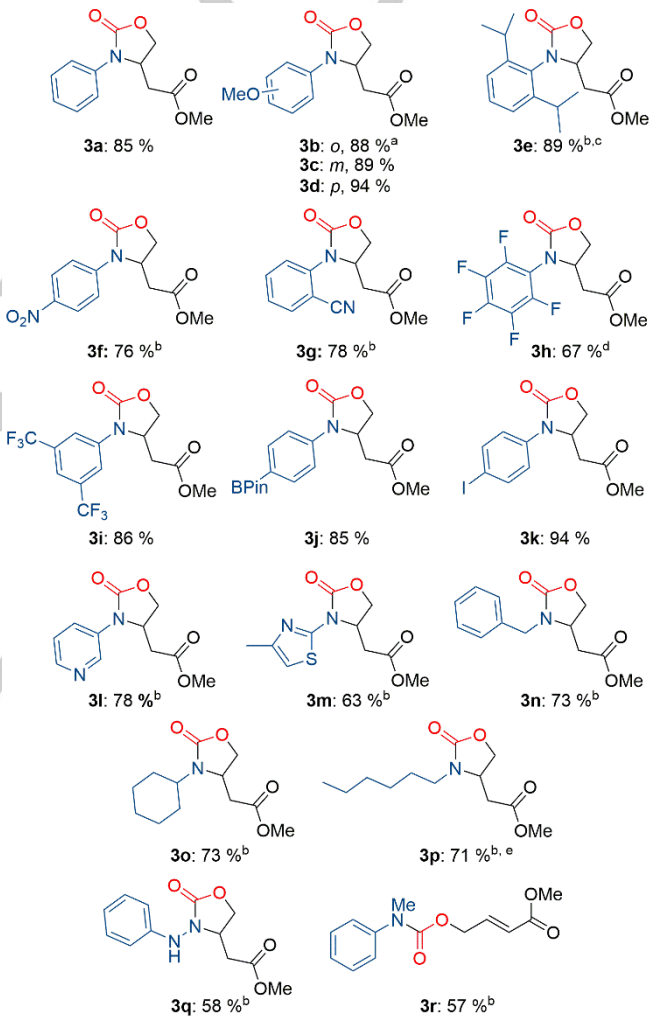
[a] Yield determined by GC-FID with mesitylene as an internal standard. [b] Control experiment.

A major fraction of previous research within medicinal chemistry has focused on the C-C and C-N coupling of flat aromatic moieties.[14–16] Thus, there is an increasing interest in novel syntheses of three-dimensional structures consisting of sp^3 hybridized carbons,[2] and the introduction of fluoroalkyl groups.[45]

In accordance to the above, we report nitrile **5a**, amide **5b** and fluorinated esters **5c** and **5d** as viable Michael acceptors (Scheme 3A). The desired 2-oxazolidinones **6a**-**d** formed in good yields (51-86 %). Intriguingly, a diastereoselective cyclization reaction was observed for **5d**, leading preferentially to the *syn*-2-oxazolidinone **6d-2**.[46] The observed diastereoselectivity (19:60) originated from the fluorine gauche effect, and was comparable to the selectivities in a previously reported intramolecular aza-Michael addition.[47] Consequently, our method is a rare example of diastereoselective fixation of CO_2 into a cyclic structure.[48] Furthermore, our approach is well-suited for late stage organic synthesis (Scheme 3B). Deacetyl linezolid **2s**, an antibiotic aliphatic amine,[10] yielded **3s** smoothly (74 %) with full retention of the original chiral configuration. Arylamine **2t** reacted to form **3t** in a moderate yield (40 %), which was likely due to the strongly electron-deficient character of the aromatic ring. Further modification of **3t** by Suzuki-coupling provided **7**, a novel derivative of anti-cancer drug buparlisb,[49] in good yield (60 %).

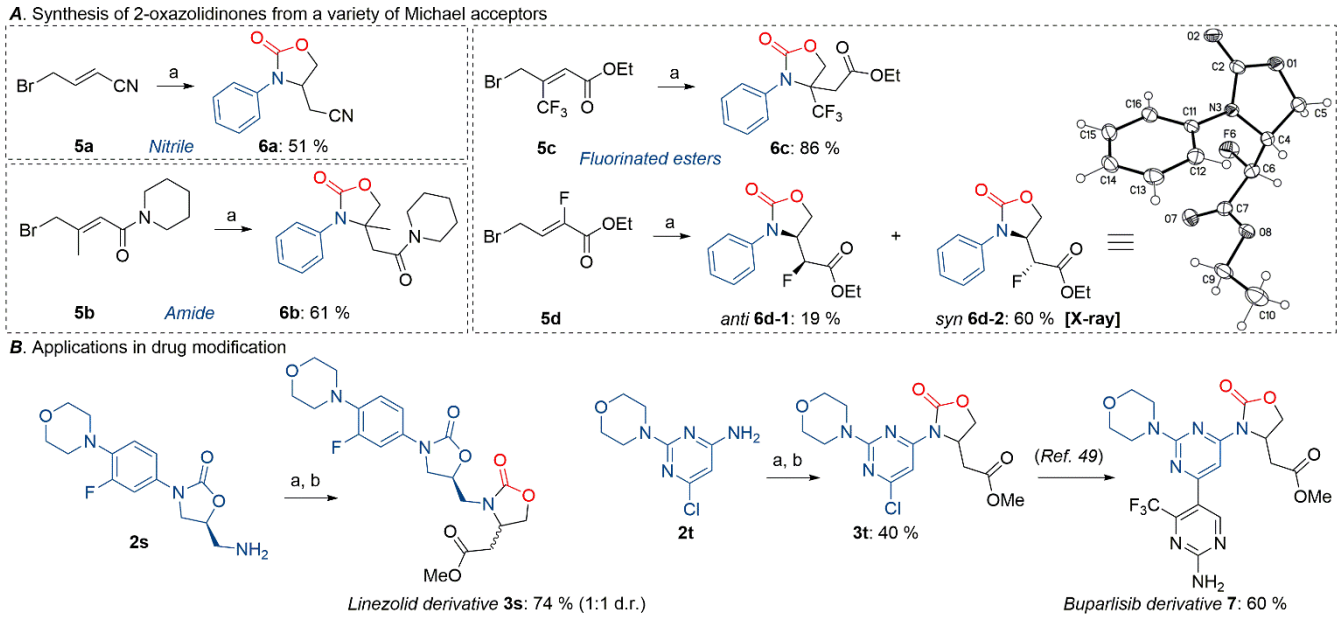
We propose a mechanism based on quantitative ^{13}C NMR experiments, an isolated acyclic carbamate, control experiments and previous literature (Scheme 4). Initially, TMG reacts reversibly with CO_2 to form a zwitterionic intermediate **A**, as has been previously established.[50–52] Then, **A** undergoes CO_2 exchange with aniline **2a** to provide the mixed carbamate **B**,[52–54] as observed by quantitative ^{13}C NMR studies (see SI).[55] In the following step, the mixed carbamate **B** reacts with Michael acceptor **1** by nucleophilic substitution of bromine to form the acyclic *O*-alkyl carbamate **C** and TMG·HBr. Intermediate **C** was identified by using *N*-methylaniline as a substrate, leading to the isolation of acyclic carbamate **3r**. Next, highly-soluble Cs_2CO_3 regenerates TMG by deprotonation. The equilibrium is driven by precipitation of Cs salts, as was observed in control experiments presented in Table 1 (entries 11-14). In transition state **D**, it is shown how TMG catalyzes the cyclization by proton transfer[56] and enolate stabilization.[57,58] Therefore, it is likely that the carbamate N-H bond is broken by TMG, which also donates its proximal proton (H_p) to the enolate. This simultaneously affords the desired 2-oxazolidinone **3a** and regenerates TMG. Other strong bases such as tBuTMG, DBU and MTBD lack a proximal proton, and are thus unable to stabilize the enolate, which results in lower yields of **3a**, as presented in Table 1 (entries 2-5). It is unlikely that the distal proton of TBD can stabilize the enolate, as this would create a larger ring, compared to TMG, which is energetically unfavorable.

In conclusion, we describe here a novel base-catalyzed method for the synthesis of 3,4-disubstituted 2-oxazolidinones. The catalytic pathway consists of three steps: carbonylation of the aniline; generation of a corresponding *O*-alkyl carbamate; and cyclization via an intramolecular aza-Michael addition. TMG as a catalyst has two distinct roles in the synthesis. Firstly, TMG reacts with (aryl)amines to form a mixed carbamate (R-NHCOO$^-$ + TMGH$^+$), which reacts further to form an *O*-alkyl carbamate. Secondly, free TMG catalyzes cyclization of the *O*-alkyl carbamate by acting as a base, while simultaneously stabilizing the forming enolate through hydrogen bonding. As shown here, the method readily tolerates various substrates including heteroaromatics, anilines with different functional groups, aliphatic amines, and phenylhydrazine as a substrate. γ-Brominated α,β-unsaturated esters, amides and nitriles are viable Michael acceptors. A slow addition of the Michael acceptor prevents formation of *N*-alkylated by-products, resulting in good yields. The reactions are conducted using simple reaction setups at room temperature. The presented modular synthesis yields a wide range of 3,4-disubstituted 2-oxazolidinones using CO_2 as a benign carbonyl source. Accordingly, this facilitates a direct introduction of a saturated heteroatom ring-structure to a molecular scaffold.



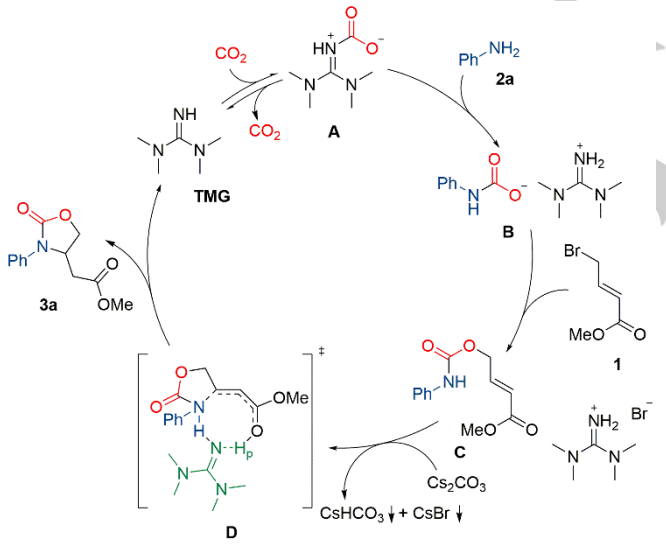
Yields refer to the isolated product (for full details, see SI). Reaction conditions: (aryl)amine 2.0 mmol, CO_2 (1 atm), Michael acceptor **1** (2 equiv) added over 4 h by a syringe pump, TMG (0.2 equiv), Cs_2CO_3 (4 equiv), DMF (0.08 M), 18 h, RT. [a] Michael acceptor **1** added over 6 h. [b] Michael acceptor **1** added over 12 h. [c] 40 °C [d] Michael acceptor **1** (3 equiv) added over 21 h. [e] 2 h at 40 °C

Scheme 2. Scope of the TMG-catalyzed synthesis of 3,4-disubstituted 2-oxazolidinones.



Yields refer to the isolated product (for full details, see SI). [a] Reaction conditions: (aryl)amine 2.0 mmol, CO_2 (1 atm), Michael acceptor **5** (2 equiv) added over 4 h by a syringe pump, TMG (0.2 equiv), Cs_2CO_3 (4 equiv), DMF (0.08 M), 18 h, RT. [b] Michael acceptor **1** added over 12 h.

Scheme 3. Applicability of the TMG-catalyzed synthesis of 3,4-disubstituted 2-oxazolidinones.



Scheme 4. Proposed mechanism of the TMG-catalyzed synthesis of 3,4-disubstituted 2-oxazolidinones.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: carbon dioxide fixation • cyclization • heterocycles • Michael addition • organocatalysis

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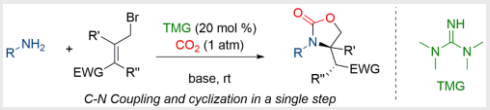

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One-step Synthesis of 3,4-Disubstituted 2-Oxazolidinones via Base-catalyzed CO_2-Fixation and Aza-Michael Addition

Base makes CO_2 stick: 1,1,3,3-Tetramethylguanidine (TMG) catalyzes the one-step synthesis of 3,4-disubstituted 2-oxazolidinones via an aza-Michael addition using CO_2 as a carbonyl source. The modular reaction occurs between a γ-brominated Michael acceptor, CO_2 and an arylamine, aliphatic amine or phenylhydrazine. The method displays high yields (avg. 75 %) and enables late-stage functionalization of complex drug-like molecules.