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Metal-Free Catalysis

A One-Pot Synthesis of *N*-Aryl-2-Oxazolidinones and Cyclic Urethanes by the Lewis Base Catalyzed Fixation of Carbon Dioxide into Anilines and Bromoalkanes

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Abstract: The multicomponent assembly of pharmaceutically relevant *N*-aryl-oxazolidinones through the direct insertion of carbon dioxide into readily available anilines and dibromoalkanes is described. The addition of catalytic amounts of an organosuperbase such as Barton's base enables this transformation to proceed with high yields and exquisite substrate functional-group tolerance under ambient CO_2 pressure and mild temperature. This report also provides the first proof-of-principle for the single-operation synthesis of elusive seven-membered ring cyclic urethanes.

The development of efficient methods to valorize CO_2 as an abundant and nontoxic chemical feedstock[1] entails a promising carbon-neutral approach while society shifts from fossil fuels towards sustainable energy sources.[2] Albeit this task is not trivial due to the stability and inertness of hyperoxidized CO_2 molecules,[3] the intrinsic value of the potential products is key to stimulate further research.[4] In this sense, the urethane motif features scintillating properties. For instance, converting a primary amine into an urethane is a common strategy in pharmaceutical development to improve the bioactivity of drug candidates.[5]

Specifically, *N*-aryl-oxazolidinones (NAOs) excel amongst urethane-containing pharmaceuticals as a result of their unmatched efficiency against a broad spectrum of gram-positive strains that are resistant to other powerful antibiotics.[6] Nowadays, the significance of developing efficient processes using CO_2 as a C-1 synthon to assemble the urethane core of NAOs, and also withdraw traditional toxic phosgene derivatives, is magnified by their synthetic origin, the relatively high production costs of their multistep syntheses and a global emergence of antimicrobial resistance.[7–9]

A number of the existing methods to directly prepare NAOs from CO_2 use suitably prefunctionalized substrates such as propargyl amines[10] or strained *N*-aziridines (Scheme 1 a).[11] In this manner, NAOs are afforded as a narrow set of structurally predefined products, or as the result of a multistep sequence that includes a late-stage *N*-arylation reaction of an intermediate 2-oxazolidinone and the respective purification steps.[12] Alternatively, two reports this year have disclosed the construction of NAOs by fixating simultaneously CO_2 into anilines and epoxides.[13] A contribution by Kleij and co-workers describes the partnership of a Al-based Lewis acid with a source of bromide to effectively catalyze the conversion of epoxy amines into NAOs at room temperature, yet using 10 bar of CO_2.[13c] However, the selectivity of this method relies on a precise tuning of the reaction conditions and a careful predesign of substrates.

In parallel, a report by Gao and co-workers illustrates the challenge to avoid prefunctionalizing the substrate by conducting intermolecularly this reaction with poorly nucleophilic anilines.[13a,b] In this case, high conversion rates are only achieved by resorting to a large excess of the epoxide, as well as high reaction temperatures and CO_2 pressures that are inimical to desirable levels of selectivity and substrate functional-group tolerance. As part of our research in CO_2 utilization,[14] herein we disclose the unprecedented construction of NAOs by the one-pot organocatalytic fixation of CO_2 into dibromoalkanes and anilines upon ambient pressure and mild temperature (Scheme 1 b).

Selecting aniline (**1 a**) and 1,2-dibromoethane (**2**) as the simplest possible model system, we began our investigation by evaluating the conditions from our previous work[14a] to convert 1,2-haloamines into the corresponding 2-oxazolidinones (Cs_2CO_3, EtOH, 35 bar CO_2, 50 °C, 16 h). While the desired *N*-phenyl-oxazolidinone (**3 a**) was obtained in just 9% yield (Table 1, entry 1), decreasing the pressure to 1 bar led the yield up to 15% (entry 2). This suggests that the main carbamate species at high pressures are barely able to cyclize and yield **3 a**. Inspection of different reaction solvents (entries 3–6) revealed the superiority of polar aprotic solvents that markedly enhanced the reaction conversions (entries 5, 6).

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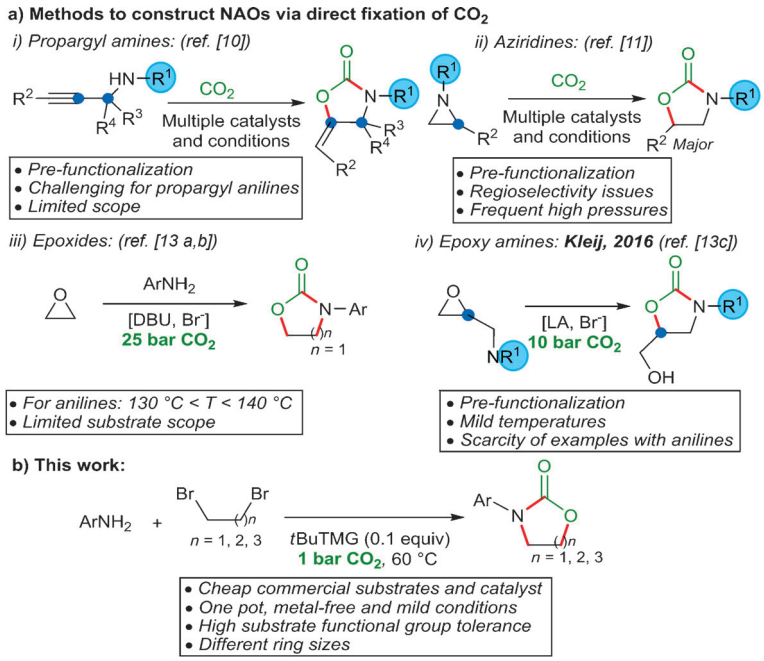
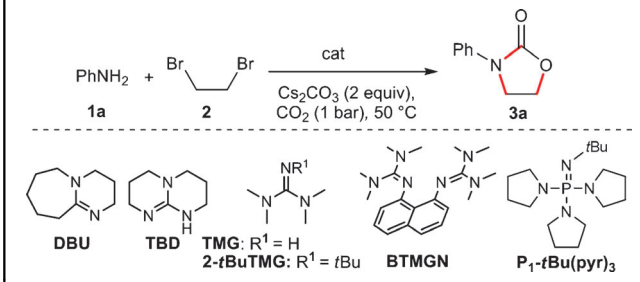


Scheme 1. Different synthetic methodologies to construct NAOs by CO_2 fixation.

Table 1. Screening of reaction conditions for the direct insertion of CO_2 into aniline and 1,2-dibromoethane.[a]



Entry	Solvent	Cat. [mol%]	t [h]	Yield [%][b]
1[c]	EtOH	–	16	9
2	EtOH	–	16	15
3	THF	–	16	3
4	PhMe	–	16	0
5	DMF	–	16	48
6	MeCN	–	16	49
7[d]	MeCN	–	16	4
8	MeCN	DBU (10)	16	70
9	MeCN	TMG (10)	16	41
10	MeCN	2-*t*BuTMG (10)	16	72
11	MeCN	P_1-*t*Bu(pyr)$_3$ (10)	16	36
12	MeCN	BTMGN (10)	16	44
13[e]	MeCN	TBD (10)	20	75
14[e]	MeCN	2-*t*BuTMG (10)	20	99

[a] **1a** (1.0 equiv), **2** (2.0 equiv), Cs_2CO_3 (2.0 equiv), 50 °C, CO_2 (1 bar), solvent (0.2 M), 16 h. [b] Yields determined by GCMS analysis using hexadecane as a standard. [c] Reaction with 35 bar of CO_2. [d] Reaction without CO_2. [e] Reaction at 60 °C. For full details, see the Supporting Information.

Additionally, a control experiment demonstrated that only traces of **3a** are formed in MeCN without CO_2 pressure (Table 1, entry 7).

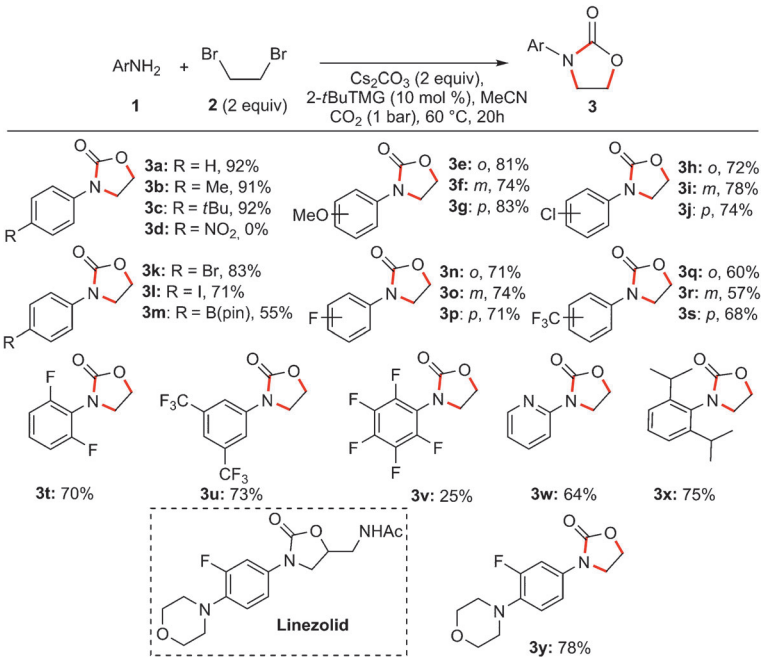
At this point, our interest concerning Lewis bases in the catalytic activation of small molecules,[15] and their rising prevalence in recent research to utilize CO_2,[16,17] led us to explore their potential catalytic role in the reaction (Table 1, entries 8–12). Originally, strong nitrogen bases such as TMG (entry 9), a hindered phosphazene (entry 11), or the proton sponge BTMGN (entry 12), failed to effect any negligible change. Gratifyingly, a nearly two-fold increase of yield ensued the addition of 10 mol% of a guanidine base such as 2-*t*BuTMG (entry 10, 72%). However, limited catalytic amplification was found by using larger amounts of this base. Additionally, the amidine base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided a slightly inferior result (entry 8, 70%).

We were pleased to find quantitative conversion after raising the reaction time from 16 to 20 h and the temperature up to 60 °C (Table 1, entry 14). Interestingly, the protic guanidine base TBD, that often is deemed as the base of choice in many studies to facilitate the insertion of CO_2 into O–H and N–H bonds,[17a–d] showed inferior catalytic activity upon these optimized conditions (entry 13, 75%).

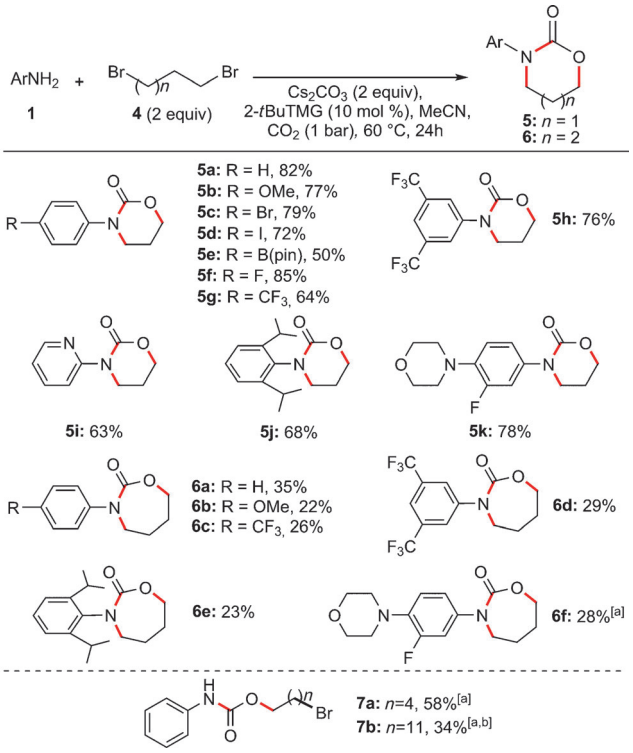
We then turned our attention to the substrate scope of the reaction, initially focusing on the aniline component since its nucleophilicity was a key factor in previous precedents (Scheme 2).[13] To our delight, the high yield obtained of **3a** (92% yield) was the general trend observed for several anilines with either electron-donating (Me, *t*Bu, OMe) or -withdrawing (Cl) substituents (**3b–j**, 72–92%), with the notable exception of NO_2 that diminished enough the nucleophilicity to prevent any conversion (**3d**). Notably, we also found that the reaction tolerates rather well the presence of a coordinating heteroatom (**3w**, 64%), or severe steric hindrance near the reaction site (**3x**, 75%). We then sought to investigate the conversion of anilines bearing pharmaceutically important groups that are barely compatible with the drastic conditions used in many of the previous reports.[13]

In practice, the reaction accommodated well the presence of groups (Br, I, B(pin)) that may provide a versatile synthetic handle for further transformations on the aniline ring (**3k–m**, 55-83%). Furthermore, the presence of one or two, F or CF_3 groups, in different locations of the aniline ring did not compromise the reaction yields (**3n–u**, 57–74%). We also successfully extended our protocol to 3-fluoro-4-morpholinoaniline (**3y**, 78%), a motif present in the last generation antibiotic Linezolid. On the other hand, a perfluorinated aniline proved to be remarkably less reactive under the optimized conditions (**3v**, 25%).

Using CO_2 as synthon is not only underdeveloped for the construction of six-membered cyclic urethanes, but to the best of our knowledge, also unprecedented for seven-membered ones, despite their interesting biological profiles.[18] Thus, we set out to investigate the synthetic utility of our method toward the construction of these cyclic products (Scheme 3). In practice, we were pleased to find a similar pattern of reactivity for the formation of several six-membered rings with diverse



Scheme 2. 2-*t*BuTMG-catalyzed syntheses of NAOs by the multicomponent fixation of CO_2. Yields refer to the isolated product (for full details, see the Supporting Information).



Scheme 3. 2-*t*BuTMG-catalyzed syntheses of six- and seven-membered cyclic urethanes by the multicomponent fixation of CO_2. Yields refer to the isolated product (for full details, see the Supporting Information). [a] Reaction carried out with 20 mol% of 2-*t*BuTMG. [b] Reaction conducted for 36 h.

electronic properties in moderate to good yield (**5a–e**, 50–82%), using 1,3-dibromopropane as an electrophile upon our optimized conditions. Analogously to the formation of five-membered rings, our protocol also was fit-for-purpose to convert aniline substrates with troublesome features such as the presence of a coordinating heteroatom (**5i**, 63%), or severe steric hindrance near the newly formed urethane functionality (**5j**, 75%). Furthermore, the reaction also proceeded rather well with fluorine-based groups of pharmaceutical interest (**5f–h**, 64–85% and **5k**, 78%).

We suggest that this CO_2 fixation method also holds promise for the generation of scarce seven-membered urethanes. To that end, we gathered a valuable proof-of-principle by isolating in a relatively respectable yield the products of the reaction between 1,4-dibromobutane and several anilines (**6a–f**, 22–35%). Conversely, our conditions were not effective enough to render the corresponding cyclized products using larger chain dibromoalkyl electrophiles such as 1,5-dibromopentane or 1,12-dibromododecane. Instead, the large ring strain (eight-membered ring formation) or entropic contribution (15-membered ring formation) prevents the final cyclization from occurring, as was corroborated by the isolation of the corresponding acyclic linear urethanes with a distal bromide substituent in moderate yields (**7a–b**, 34–58%).

DFT calculations at the PCM(MeCN)-M06-2X/6-311+G(d)//M06-2X/6-31+G(d) level[19] were carried out to gain more insight into the reaction mechanism of the above described NAOs formation. To this end, the formation of the parent NAO **3a** from aniline and 1,2-dibromoethane (**2**) in the presence of CO_2 and catalytic amounts of 2-*t*BuTMG was explored. As seen in Figure 1, which shows the computed reaction profile gathering the corresponding relative free energies (ΔG, at 298 K), the process begins with the slightly exergonic formation of intermediate **INT2** ($\Delta G_R = -0.8$ kcal mol^{-1}).

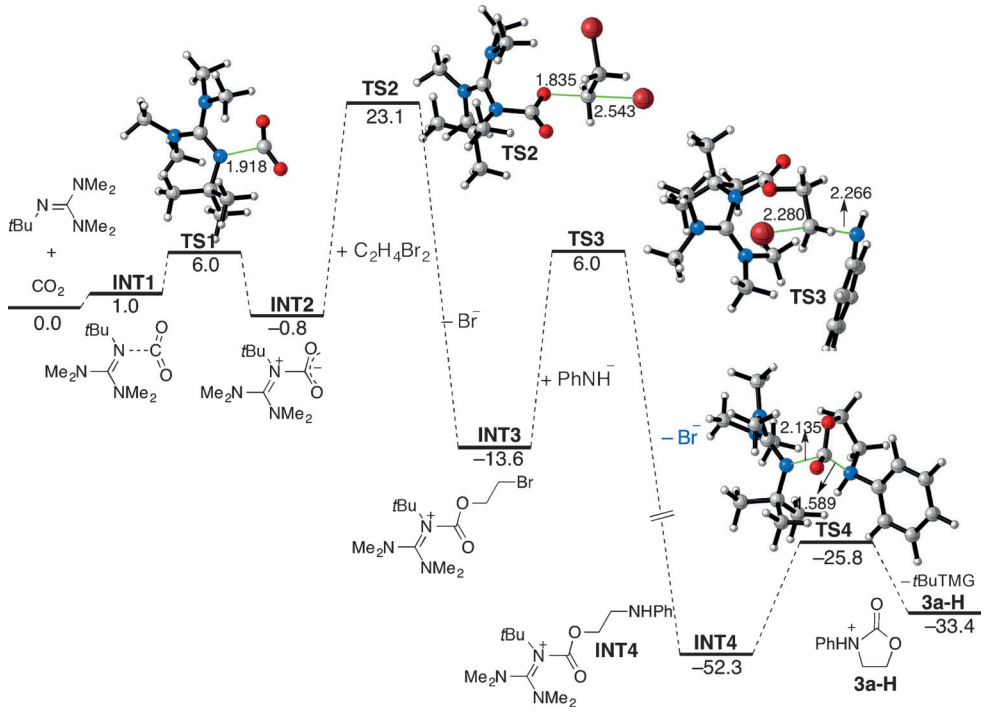


Figure 1. Computed reaction profile for the reaction of aniline and 1,2-dibromoethane (**2**) in the presence of CO_2 and catalytic amounts of 2-*t*BuTMG. Relative free energies and bond distances are given in kcal mol^{-1} and Å, respectively. All data have been computed at the PCM(MeCN)-M06-2X/6-311 + G(d)//M06-2X/6-31 + G(d) level.

This zwitterionic species, which strongly resembles that isolated in the reaction of CO_2 with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD),[20] derives from the easy nucleophilic attack of 2-*t*BuTMG to CO_2 via **TS1** (activation barrier of only 6.0 kcal mol^{-1} from the separate reactants). **INT2** is then transformed into **INT3** by reaction with 1,2-dibromoethane through **TS2** in a strongly exergonic transformation ($\Delta G_R = -12.8$ kcal mol^{-1}). This saddle point is associated with the formation of the new C–O bond and release of bromide following a typical S_N2 reaction ($\Delta G^{\neq} = 23.9$ kcal mol^{-1}). From **INT3**, a new S_N2 reaction involving deprotonated aniline as a nucleophile (readily formed in the presence of Cs_2CO_3) leads to the formation of the new C–N bond of **INT4** with concomitant release of the second bromide again in a highly exergonic process ($\Delta G_R = -38.7$ kcal mol^{-1}) with an activation barrier of 19.6 kcal mol^{-1} via **TS3**.[21] A final intramolecular cyclization reaction affords the protonated NAO **3a** (which would produce the observed **3a** by reaction with base) regenerating the catalyst 2-*t*BuTMG. This last step proceeds with an activation barrier of 26.5 kcal mol^{-1}, which indicates that the final cyclization reaction constitutes the rate-limiting step of the entire transformation. Indeed, the computed activation barrier for the analogous cyclization reaction involving the corresponding **INT4** derived from 1,5-dibromopentane was 49.1 kcal mol^{-1}, which suggests that the formation of the eight-membered ring derivative is unfeasible, as experimentally observed (see above).[22]

In summary, we have described an unprecedented construction of NAOs by the one-pot fixation of CO_2 into dibromoalkanes and anilines. This constitutes a significant advance in the area because 1) it is a robust multicomponent reaction providing access to a wide range of NAOs in a single step from highly cost-effective commercial substrates; 2) it takes place upon ambient pressure and mild temperature, yet only requires a relatively low loading of an Lewis base as organocatalyst;[16] 3) it presents high substrate functional-group tolerance amenable for drug-development programs; 4) it is also a proof-of-principle for the single-step syntheses of six-membered, and elusive seven-membered cyclic urethanes. In addition, with the help of DFT calculations it is suggested that the process involves the formation of an initial zwitterion by reaction of CO_2 and the organocatalyst followed by successive S_N2 reactions and final cyclization reaction. Work is ongoing in our laboratories to further expand the substrate scope of this multicomponent process to more challenging electrophiles partners such as secondary and tertiary bromides or alkenes, which would reinforce even more the pharmaceutical applicability of our methodology.

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Keywords: 2-oxazolidinones · antibiotics · carbon dioxide · density functional calculations · guanidine superbases

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[21] Alternatively, it can be also suggested that deprotonated aniline may react first with 1,2-dibromoethane and the resulting bromo-derivative would then generate **INT4** by reaction with zwitterion **INT2**.

[22] At variance, the activation barrier for the formation of the corresponding six-membered ring is much lower ($\Delta G^{\neq} = 31.9$ kcal mol^{-1}).

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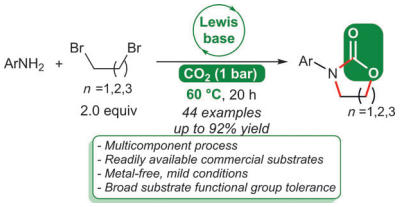
■■ – ■■

A One-Pot Synthesis of *N*-Aryl-2-Oxazolidinones and Cyclic Urethanes by the Lewis Base Catalyzed Fixation of Carbon Dioxide into Anilines and Bromoalkanes



Come together: Carbon dioxide can be simultaneously fixated into anilines and primary dibromoalkanes under metal-free ambient mild conditions to afford a broad range of *N*-aryl-oxazolidinones or six and seven-membered cyclic urethanes in good yields.