Carbon dioxide utilization

LEVERAGING CO_2 FOR THE CONTINUOUS SYNTHESIS OF CARBAMATES AND OXAZOLIDINONES

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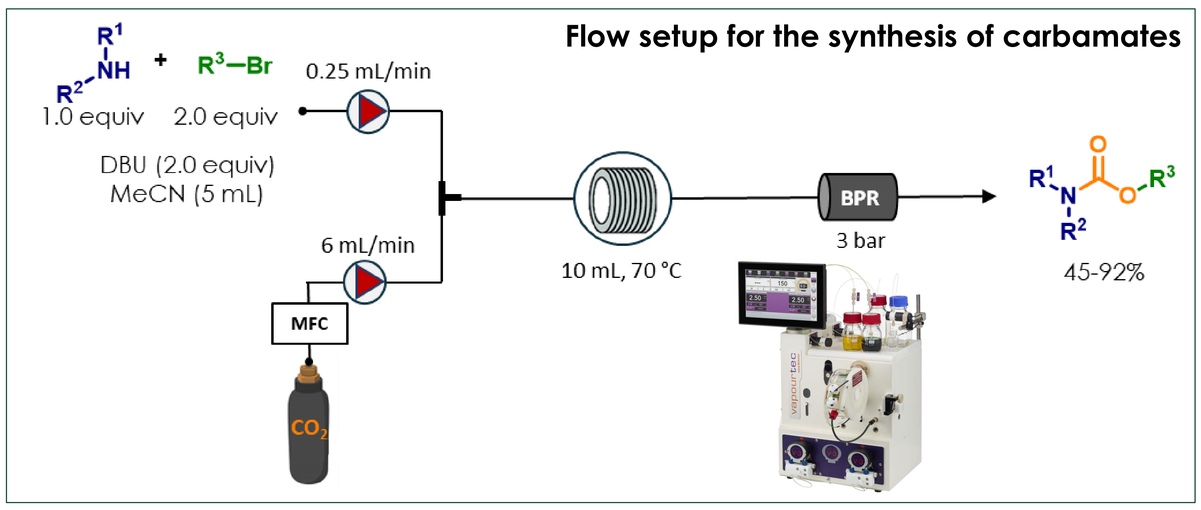
ABSTRACT

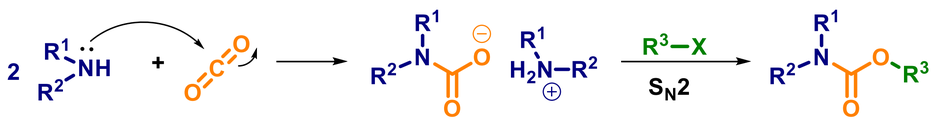
The utilization of carbon dioxide has become one of the most critical challenges for the chemical community in the 21st century. Chemists have developed various strategies to use CO_2 as a C1 building block for the synthesis of valuable chemical compounds.[1] Carbamates are widely used in pharmaceuticals, agrochemicals, and polymer industries.[2] Traditional methods for carbamate synthesis often involve toxic isocyanates or costly catalysts, posing environmental and safety concerns.[3] As alternative, the continuous synthesis of carbamates directly from carbon dioxide and amines, employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the sole additive, is presented.[4] This method provides a more sustainable alternative, avoiding hazardous reagents while maintaining high efficiency.

1 SYNTHESIS OF CARBAMATES

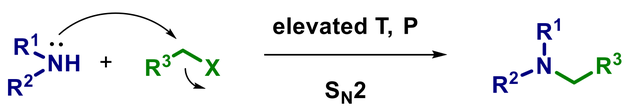
FLOW SETUP AND MECHANISM OF THE REACTION



In the first step of the reaction, **CO_2 is attacked by the amine** nucleophile, leading to the formation of a **carbamate anion**, which attacks the **alkyl halide** to form the **alkyl carbamate**. At harsher conditions, the *N*-alkylated by-product formation is faster than the formation of the carbamate anion. Acetonitrile's polar and aprotic nature might also favor the S_N2 substitution of the halide, forming the *N*-alkyl derivatives.



By-product formation



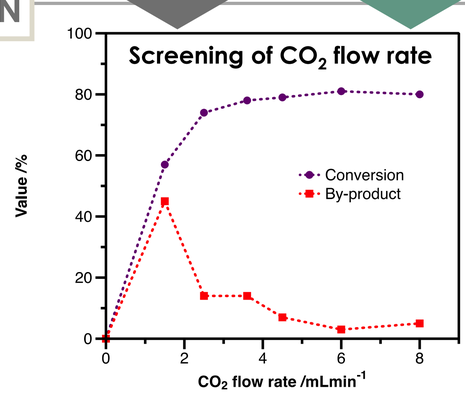
2 SYNTHESIS OF CARBAMATES

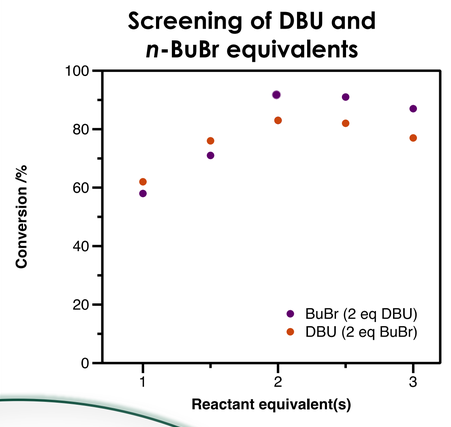
OPTIMIZATION OF THE REACTION

Screening of temperature and pressure

Entry[a]	Temperature (°C)	Pressure/bar	Carbamate (%)[b]	By-product (%)[b]
1	60	3	67	3
2	70	3	81	2
3	80	3	79	9
4	70	1	51	5
5	70	5	91	7
6	70	7	83	13

[a]Performed with 4.3 mmol (1.0 eq.) aniline, 8.6 mmol (2.0 eq.) DBU and 8.6 mmol (2.0 eq.) butyl bromide in 5 mL MeCN in a 10-mL coil reactor. Reaction mixture flow rate: 250 µL/min, CO_2 flow rate: 6 mL/min. The product was collected for 50 minutes. [b]Determined by GC-MS analysis.

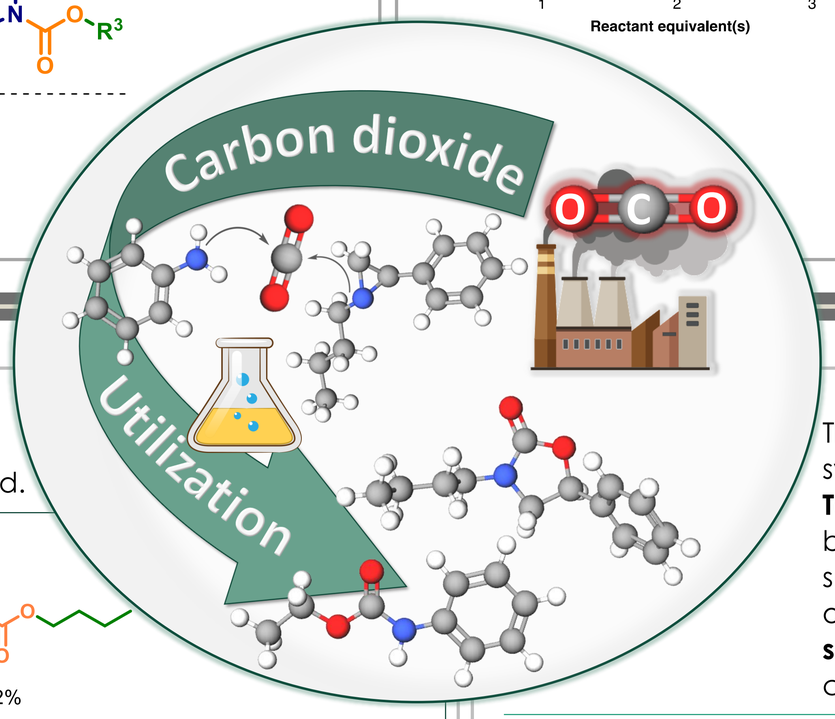




Screening of alkylating agents

Entry[a]	Reagent	Carbamate (%) [b]	By-product (%) [b]
1	1-Bromobutane	82 (79)[c]	4
2	1-Chlorobutane	0	0
3	1-Iodobutane	36	8
4	1-(Trimethylsilyloxy)butane	48	44
5	*Iso*-butyl bromide	57	0
6	*Sec*-butyl bromide	41	0
7	*Tert*-butyl bromide	0	0
8	Benzyl bromide	0	0
9	2-Bromoethane	68 (59)[c]	6
10	1-Bromododecane	83 (76)[c]	10

[a]Performed with 4.3 mmol (1.0 eq.) aniline, 8.6 mmol (2.0 eq.) alkylating agent, and 8.6 mmol (2.0 eq.) DBU in 5 mL MeCN in a 10-mL coil reactor. Reaction mixture flow rate: 250 µL/min, CO_2 flow rate: 6 mL/min. The product was collected for 50 minutes. [b]Determined by GC-MS analysis. [c]Isolated yields.

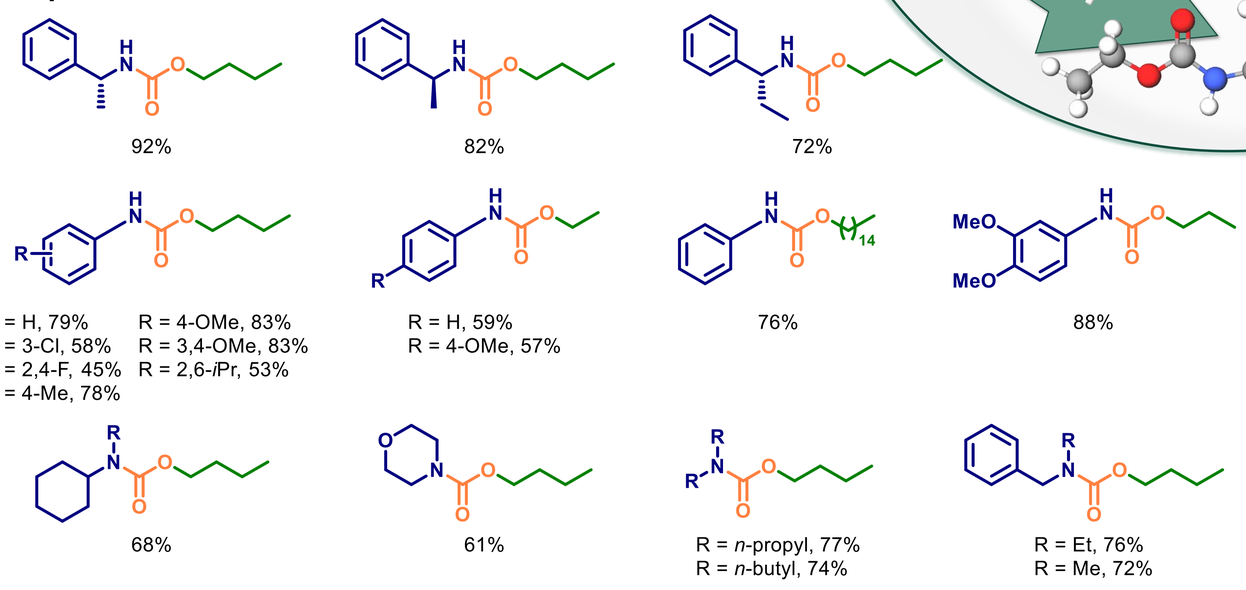


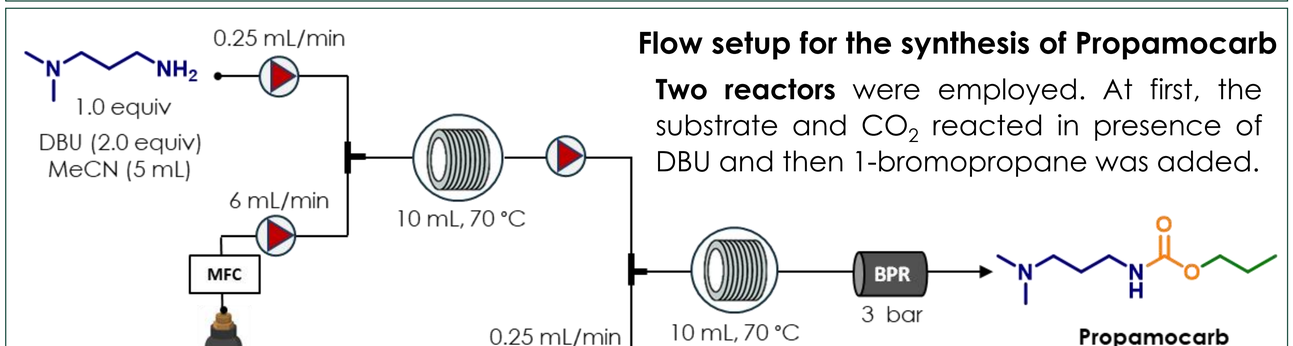
3 SYNTHESIS OF CARBAMATES

SCOPE OF THE REACTION AND APPLICATIONS

After testing a series of **alkylating agents**, we investigated **various amines** to extend the scope of our developed method.

Scope of the reaction





Results:

- Up to 92% yield
- No purification needed
- 50 minutes reaction time
- Continuous methodology
- No catalysts or additives needed
- Synthesis of pesticide Propamocarb

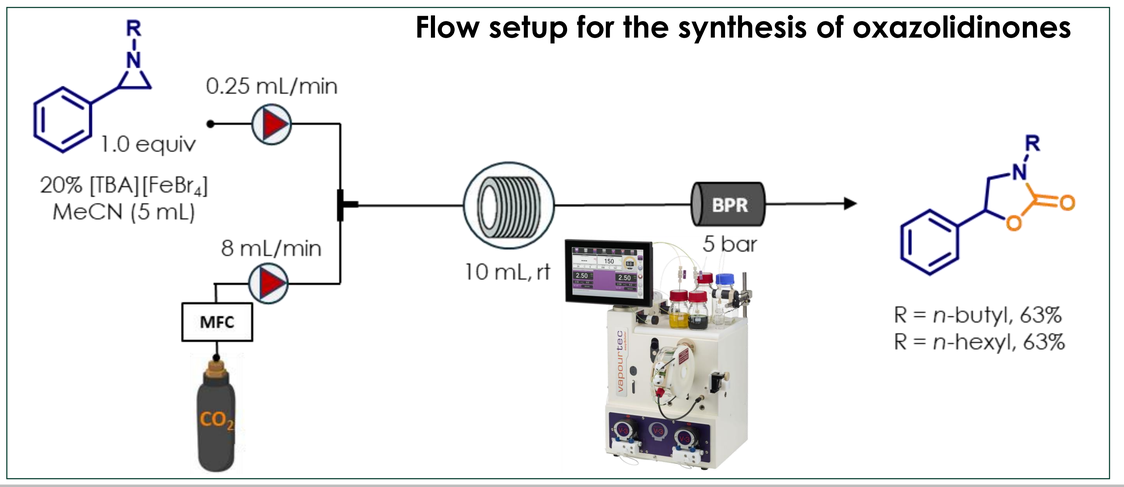
4 SYNTHESIS OF OXAZOLIDINONES

OPTIMIZATION OF THE REACTION

The developed methodology was adapted to the synthesis of **oxazolidinones** [5] from aziridines. **Tetrabromoferrate salts**, formed from tetrabutylammonium bromide (TBAB) and $FeBr_3$, were found to be the most suitable **catalyst** for the continuous-flow formation of oxazolidinone derivatives. This method demonstrated **high selectivity**, as we only observed marginal amounts of the corresponding piperazine dimer by-products.

Entry	Catalyst/conditions	CO_2 flow rate/mL min^{-1}	Conversion (%)[a]	Oxazolidinone (%)[a]	By-product (%)[a]
1	10% L-Threonine, 110 °C, 0.86 M	6	n.d	n.d	n.d
2	10% $TPPH_2Cl_2$, 70 °C, 0.86 M	6	n.d	n.d	n.d
3	10% TBAB, 70 °C, 0.86 M	6	98	3	95
4	10% [TBA][$FeBr_4$], 70 °C, 0.86 M	6	1	1	n.d
5	10% [TBA][$FeBr_4$], 50 °C, 0.43 M	8	78	36	42
6	10% [TBA][$FeBr_4$], 30 °C, 0.15 M	8	96	63	33
7	10% [TBA][$FeBr_4$], 25 °C, 0.15 M	8	88	62	26
8	20% [TBA][$FeBr_4$], 25 °C, 0.15 M	8	>99	95	5

[a]Determined by GC–MS analysis.



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References:
[1] Saravanan, A.; Senthil kumar, P.; Vo, D.-V. N.; Jeevanantham, S.; Bhuvaneswari, V. et al. Chem. Eng. Sci. 236 (2021) 116515.
[2] Ghosh, A. K.; Brindisi, M. J. Med. Chem. 58 (2015) 2895.
[3] Chaturvedi, D.; Mishra, N.; Mishra, V. Curr. Org. Synth. 4 (2007) 308.
[4] Stagel, K.; Ielo, L.; Bica-Schröder, K. ACS Omega 8 (2023) 48444.
[5] Fernandes, G. F. S.; Scarim, C. B; Kim, S.-H.; Wu, J.; Castagnolo, D. RSC Med. Chem. 14 (2023) 823.