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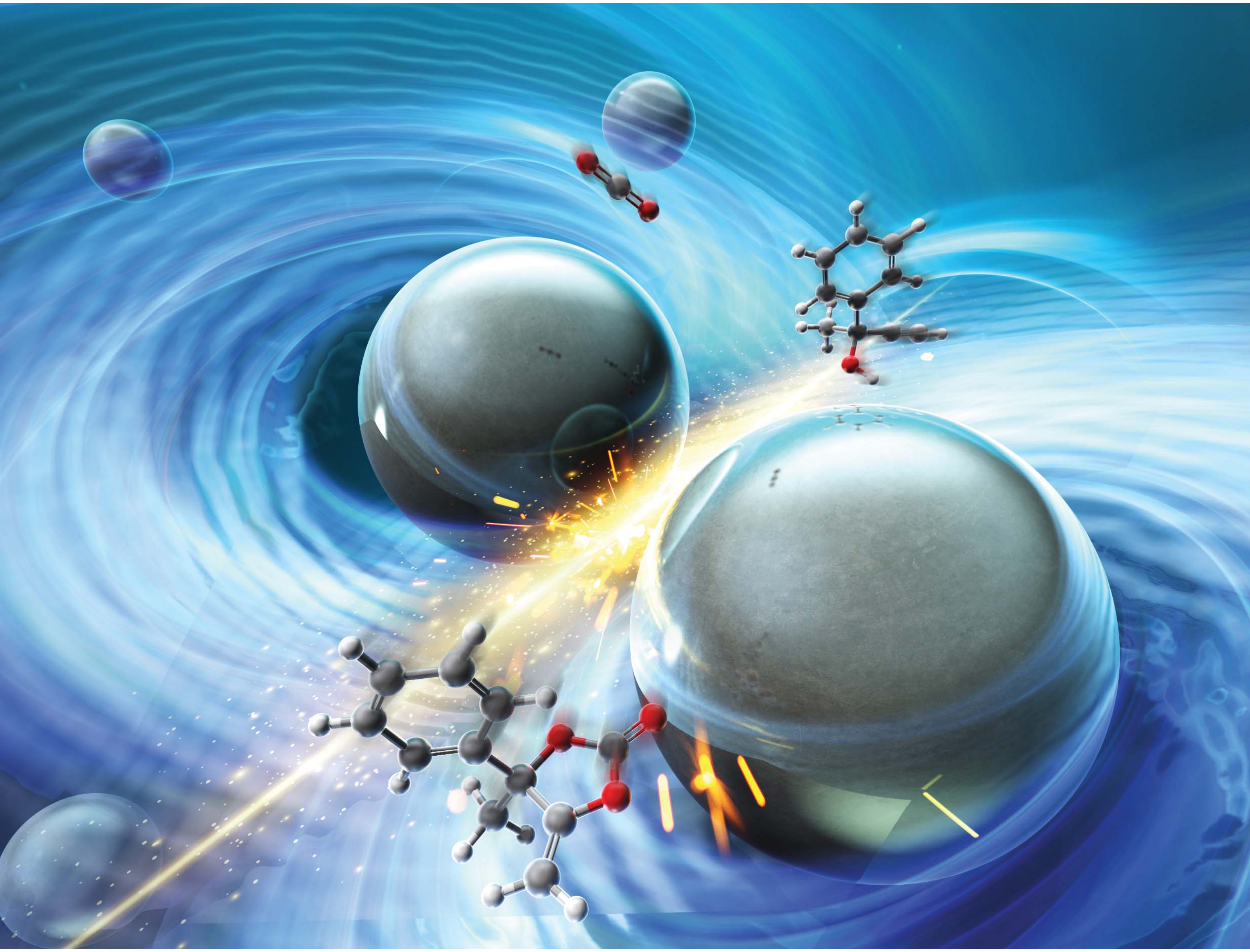

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Synthesis of cyclic carbonates *via* silver-catalysed fixation of CO_2 to propargyl alcohols under mechanochemical conditions

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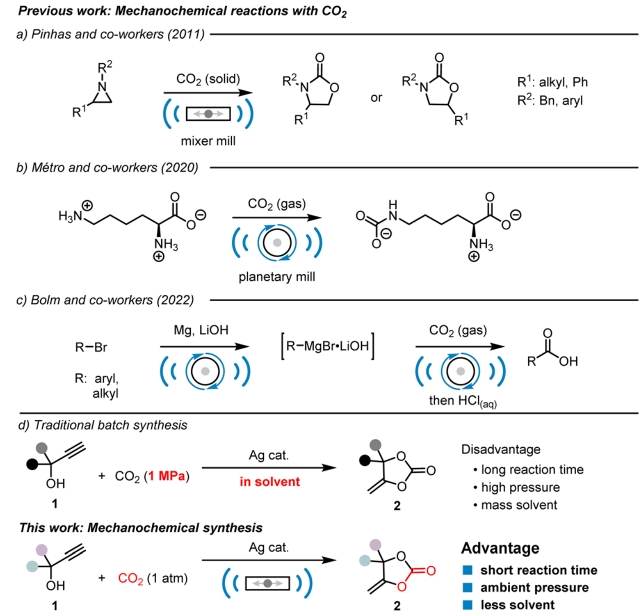
This paper describes the development of a mechanochemical method for the synthesis of cyclic carbonate esters *via* CO_2 fixation on propargyl alcohols. This solvent-free process is rapid and occurs under ambient conditions, thus offering a sustainable and efficient alternative to conventional solvent-based protocols. The mechanochemistry, which utilises the energy generated from milling, has the advantage of minimising waste, reducing reaction times, and simplifying work-up. The developed protocol demonstrates broad functional group tolerance, high yields, and the elimination of complex setups, thus highlighting its potential for application in organic and pharmaceutical synthesis.

Introduction

The introduction of CO_2 as a valuable C1 building block within the domain of organic synthesis has led to the emergence of a rapidly growing field of research. Significant research has been conducted with the aim of developing synthetic strategies for the incorporation of CO_2 into high-value fine chemicals.[1–4] One of the most promising reactions is the carboxylation of propargyl alcohol, which facilitates the synthesis of α-alkylidene cyclic carbonates. This process has become a crucial step in the pharmaceutical industry and is a fundamental step in the synthesis of polycarbonates and polyurethanes.[5–7] A variety of catalytic systems have been developed for the synthesis of cyclic carbonates,[8] although most of them require high CO_2 pressure and elevated temperatures. It would be highly beneficial to explore the possibility of developing processes that operate without solvents and at ambient temperature.[9] However, it should be noted that all of the aforementioned systems still required a relatively long reaction time and large amounts of CO_2. Consequently, there is a necessity for further research to develop processes that operate without solvents and at ambient temperature.

Mechanochemistry denotes chemical transformations, typically conducted on solid-phase substrates, that are activated through the application of mechanical energy, most notably *via* grinding in ball mills.[10a] Well established in the fields of crystal engineering and polymorphism, mechanochemistry has recently attracted renewed attention as a method for organic synthesis.[10h] To further clarify, mechanochemistry, defined as the utilisation of grinding jars or balls to induce chemical reactions, is gaining increasing attention as a promising solvent-free synthesis technique.[10] It is anticipated that this method could provide practical solutions to a number of issues associated with conventional solvent-based protocols. Recent examples of mechanochemically induced Suzuki-coupling,[11] Birch reductions[12] and Grignard reactions[13] have demonstrated key advantages of mechanochemistry, such as the reduction or



Scheme 1 Previously reported mechanochemical reactions with CO_2 and silver-catalyzed synthesis of cyclic carbonate derivatives.

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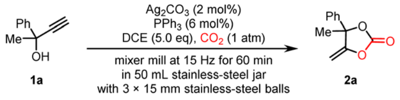
elimination of solvents, shorter reaction times, cleaner reaction mixtures, and simpler work-up procedures. These approaches have been shown to significantly reduce the generation of waste, particularly from solvents used in reactions or during the purification of intermediates. The integration of organic reactions with mechanochemical methods thus represents a major step forward in developing environmentally friendly synthetic strategies. To date, only three studies have reported mechanochemical CO_2 insertions: (i) the transformation of aziridine into oxazolidinone using dry ice, (ii) the addition of gaseous CO_2 to L-lysine, resulting in the formation of its ε-carbamate, and (iii) the Grignard reaction with CO_2 (Scheme 1a–c).[13a,14,15] Utilization of solid CO_2 surrogates, such as $NaHCO_3$, was also explored.[16]

This communication delineates the development of a mechanochemical method for synthesising cyclic carbonate esters *via* CO_2 fixation on various propargyl alcohols. Compared to conventional methods that typically require solvents, long reaction times, and high CO_2 pressure (Scheme 1d),[8c] our solvent-free process proceeds rapidly under ambient conditions with minimal CO_2 input. Furthermore, this study was extended to bioactive substances, thereby demonstrating the efficacy of a simple mechanochemical protocol.

Results and discussion

In order to optimise CO_2 fixation under ball-milling conditions, reaction parameters were extensively investigated using 2-phenyl-3-butyn-2-ol (**1a**) as a model substrate (see: Tables 1 and S1 in SI). Following the optimisation process, a maximum isolated yield of 96% (99% GC yield) was achieved for the targeted carbonate **2a** under a 1 atm of CO_2 atmosphere. The reaction was carried out utilising Ag_2CO_3 (2 mol%) as the catalyst for alkyne activation, PPh_3 (6 mol%) as the ligand for the silver catalyst,[9a] and dichloroethane (DCE, 5.0 equiv.) as a liquid-assisted grinding (LAG) agent to enhance mixing and reaction efficiency under mechanochemical conditions.[10t] The reaction was carried out in a 50 mL stainless-steel jar equipped with three 15 mm milling balls, operating at a frequency of 15 Hz for 60 min using a mixer mill (Entry 1). Transpositioning to a planetary mill operating at 800 rpm, as was employed in our previous ball-milling investigations,[17] resulted in a marked reduction in the mass balance, yielding only 48% of **2a** despite an almost complete conversion of **1a** (96%) within 30 min (Entry 2). This result is attributed to decomposition of the product caused by the excessive mechanical energy.[18] The size of the milling balls significantly impacted both the mass balance and substrate conversion. The utilisation of 15 mm balls resulted in a close correlation between the conversion of **1a** (98% with five balls; 78% with three balls) and the yields of **2a** (95% with five balls; 77% with three balls). However, notable discrepancies were observed when employing 10 mm balls (seven balls) or a single 25 mm ball (Entries 3–6). Furthermore, increasing the milling frequency from 15 Hz to 20 or 25 Hz resulted in diminished recovery yields, indicating that high-energy inputs promoted decompositions of the product (Entries 7 and 8). Attempts to replace Ag_2CO_3 and PPh_3 with alternative silver catalysts and phosphine ligands did not improve the yields (Entries 9 and 10). Control experiments, excluding Ag_2CO_3, PPh_3, or DCE, demonstrated the indispensability of all three components, as no product formation was observed in their absence (Entries 11–13). Conventional stirring conditions in a recovery flask yielded a mere 7% of the desired product **2a** (Entry 14).

Table 1 Optimisation of reaction conditions for the synthesis of **2a**[a]

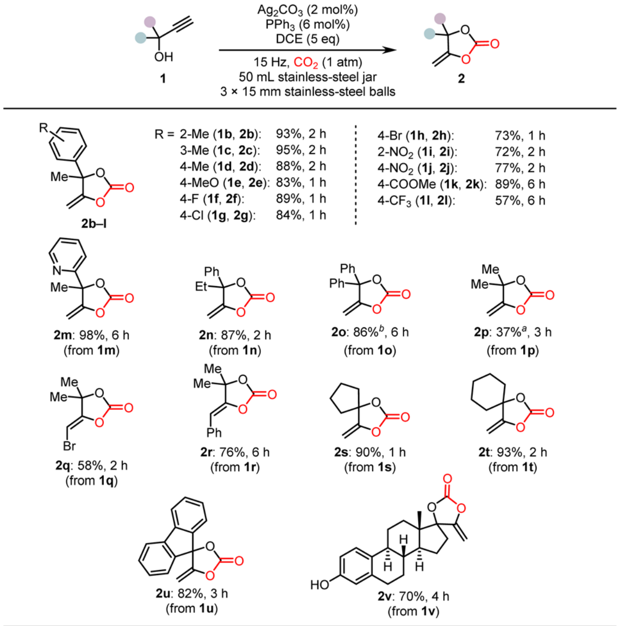


Entry	Difference from standard conditions	Conv.[b] (%)	Yield of **2a**[b] (%)
1	None	100	99 (96)
2[c]	Planetary mill instead of mixer 3 × 15 mm mill for 30 min	96	48
3	7 × 10 mm instead of 3 × 15 mm balls for 30 min	97	89
4	5 × 15 mm instead of 3 × 15 mm balls for 30 min	98	95
5	30 min instead of 60 min	78	77
6	1 × 25 mm instead of 3 × 15 mm balls for 30 min	71	58
7	20 Hz instead of 15 Hz milling frequency for 30 min	93	80
8	25 Hz instead of 15 Hz milling frequency for 30 min	84	43
9	AgOAc instead of Ag_2CO_3 for 30 min	9	1
10	(*p*-tol)$_3$P instead of PPh_3 for 30 min	82	31
11	Without Ag_2CO_3 for 30 min	31	0
12	Without PPh_3 for 30 min	10	0
13	Without DCE for 30 min	1	0
14	Stir bar mixing in recovery flask for 30 min	18	7

[a] Unless otherwise specified, all reactions were performed with **1a** (0.5 mmol), Ag_2CO_3 (0.02 mmol), PPh_3 (0.06 mmol), DCE (2.5 mmol) and CO_2 (1 atm) at ambient conditions. [b] Determined by GC analysis with decane as the internal standard. Yields of isolated products are given in parentheses. [c] Reaction carried out in a 20 mL ZrO_2 bowl with 50 × 5 mm ZrO_2 balls mixing at 800 rpm.

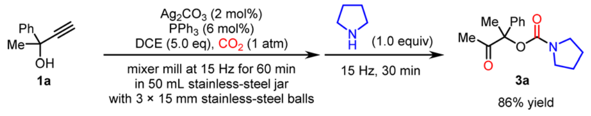
Propargyl alcohols **1b–v** were subjected to the reaction under the optimised conditions (Scheme 2). The reaction yielded cyclic carbonates **2b–l** in isolated yields ranging from 57% to 95%, irrespective of the position or nature of the substituents (methyl, methoxy, fluorine, chlorine, bromine, nitro, methoxycarbonyl, and trifluoromethyl groups) on the benzene rings. These functional groups did not adversely impact the reaction outcome. The presence of a pyridyl group at the propargyl position in **1m** had no detrimental effect, and resulted in an excellent 98% isolated yield of **2m**. Sterically more hindered propargylic alcohols such as **1n**, were also efficiently converted into their corresponding cyclic carbonates (**2n**) in yields of 87%. The reaction of *gem*-diphenyl propargyl alcohol **1o** yielded the desired product **2o** in an 86% yield, while *gem*-dimethyl propargylic alcohol **1p** produced **2p** in an isolated yield of 37%, which was comparatively lower. Conversely, internal propargyl alcohols (**1q** and **1r**) were effectively transformed into *Z*-vinylidene cyclic carbonates, yielding **2q** and **2r** in 58% and 76% isolated yields, respectively. Spirocyclic compounds **2s–v** were obtained in moderate to good yields (70–93%) when cyclic propargylic alcohols **1s–v** were employed. Importantly, this methodology was effective when applied to the estrogenic active pharmaceutical ingredient, ethinylestradiol (**1v**), bearing both a phenolic hydroxyl group and a steroid skeleton. The reaction proceeded efficiently, furnishing the corresponding cyclic carbonate **2v** in a commendable 70% isolated yield.

In this study, a novel one-pot process combining the synthesis of cyclic carbonates and subsequent transformation utilising a ball-milling apparatus was explored (Scheme 3). Following the fixation of CO_2 to propargyl alcohol **1a** under optimised ball-milling conditions, pyrrolidine was introduced directly into the reaction mixture within the milling jar, and additional milling at 15 Hz was conducted for 30 min. This integrated procedure efficiently yielded β-oxopropylcarbamates **3a**[19] in 86%, without requiring any intermediate operation steps.



Reaction conditions: propargyl alcohol (0.5 mmol), DCE (5 eq.), Ag_2CO_3 (2 mol%) and PPh_3 (6 mol%) were in a stainless-steel jar (50 mL) with a stainless-steel ball (15 mm, 3 pieces). [a] Using Ag_2CO_3 (1 mol%) and PPh_3 (3 mol%). [b] Using Ag_2CO_3 (4 mol%) and PPh_3 (12 mol%).

Scheme 2 Substrate scope.



Scheme 3 One-pot transformation to carbamates.

Conclusions

A novel mechanochemical strategy for the synthesis of cyclic carbonate esters *via* the fixation of CO_2 onto propargylic alcohols has been developed. This protocol facilitates the rapid production of cyclic carbonates without the need for complex reaction setups or sophisticated synthetic techniques, thus offering a more streamlined and efficient alternative to conventional methods. The process is highly effective in producing a wide range of cyclic carbonate derivatives, demonstrating excellent functional group tolerance, short reaction times, and high yields. This streamlined approach is expected to hold significant relevance in the domains of organic synthesis and pharmaceutical development. We further anticipate that the mechanochemical processes could be adapted for large-scale chemical production in the near future.

Author contributions

N. T., H. S., and T. I. contributed to the preparation of the manuscript and SI. H. S. and T. I. contributed to research design. All authors have approved the version of the manuscript for publication.

Conflicts of interest

There are no conflicts to declare.

Data availability

All data of this study are documented within the manuscript and its SI. Supplementary information: experimental details, ^1H and ^{13}C NMR spectra, and other spectra data. See DOI: **https://doi.org/10.1039/d5mr00072f**.

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18 We conducted an experiment to evaluate the stability of the product **2a** under the conditions: **2a** (0.5 mmol) was subjected to planetary ball milling with 50 × 5 mm zirconia balls in a 20 mL zirconia bowl at 800 rpm for 15 minutes. The recovery yield of **2a** was 83%, suggesting partial decomposition of the product under such conditions.

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