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ARTICLE

Ball-Milling Synthesis of α -Bromoacrylates from Solvent-free *In-Situ* Prepared Ethyl DiethylbromophosphonateMarie Caldiero,^a Jean-Philippe Bouillon*^a and Thomas Castanheiro*^aReceived 00th January 20xx,
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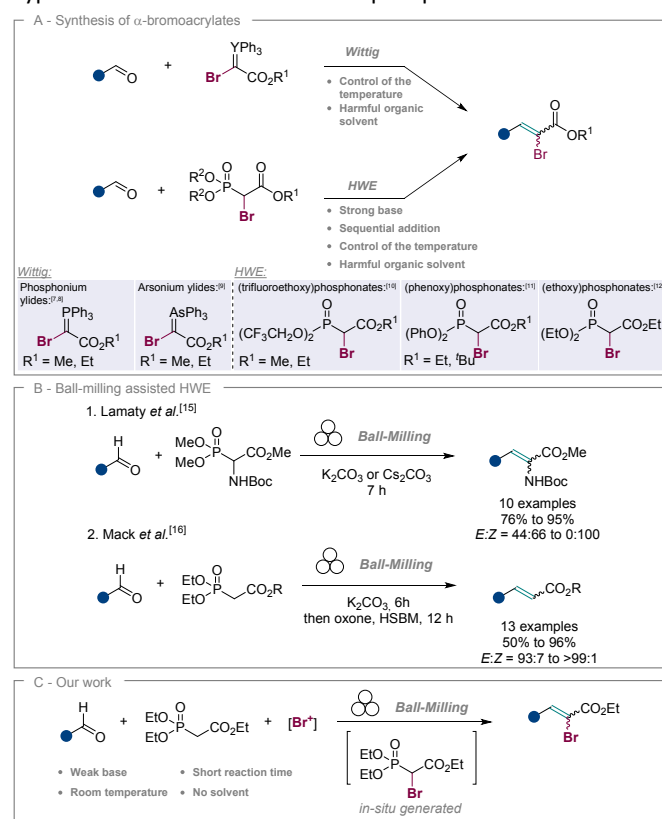
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A mechanosynthesis of α -bromoacrylates was described from commercially available triethyl phosphonoacetate by using a ball-milling-assisted bromination/HWE one-pot process. Initially, the bromination and the HWE protocols were independently optimized under mechanochemical conditions using a weak base and short reaction time. The solvent-free one-pot procedure required neither sequential addition nor an excess of reagents, thereby minimizing synthetic waste. α -Bromoacrylates were obtained with a general high efficiency, either through the solvent-free HWE (36 examples, from 26 to 98% yields) or *via* the one-pot procedure (9 examples, from 27 to 91% yields), with moderate *Z*-selectivity. This practical synthetic methodology was further extended to the synthesis of α -iodo- and α -chloroacrylates using NIS and NCS as iodinating and chlorinating agents, broadening the scope of halogenated alkenes formation through our one-pot approach. The α -bromoacrylates were then reacted in a ball-milling-assisted Ullman coupling, demonstrating the synthetic utility of the solvent-free synthesized products.

Introduction

Organohalide derivatives are highly important chemicals due to their widespread occurrence in natural products and biologically active compounds,¹ as well as their versatility as synthetic intermediates and building blocks in a plethora of organic transformations.² With the advent of transition-metal-catalysed cross-coupling reactions, the importance of vinyl halides has significantly increased over the years.^{2f-g} As an example, the synthesis of trisubstituted alkene, a motif widely represented in bioactive compounds³ and synthetically challenging, has been facilitated by the use of α , β -unsaturated esters. Indeed, they have been introduced in many transition-metal catalysed C–C bond formation, such as copper-catalysed trifluoromethylation and Suzuki, Stille, or Sonogashira-type cross-couplings.⁴ In addition, they have been introduced in other types of transformations, including radical cyclization, Diels-Alder, or Michael-type reactions.⁵ Consequently, the synthesis of α -bromoacrylates has become an area of significant importance in synthetic chemistry. Wittig and Horner-Wadsworth-Emmons (HWE) reactions are powerful and appealing strategies for the direct construction of polysubstituted alkenes from readily accessible carbonyl substrates.⁶ α -Bromoacrylates synthesis benefited from these powerful methods. Initially, brominated stabilized ylides have been used to synthesize α -bromoacrylates through the powerful Wittig strategy (Scheme 1A).⁷ More recently, Karama *et al.* developed a one-pot procedure for the formation of the

desired (*Z*)- α -bromoacrylates starting from commercially available (carboethoxymethylene)triphenylphosphorane. The *in-situ* formation of the brominated stabilized ylides was enabled by reacting *N*-bromosuccinimide as a bromine source.⁸ Huang and co-workers reported a strategy employing α -hypervalent iodine-functionalized phosphonium or arsonium



Scheme 1 State of the art and present work.

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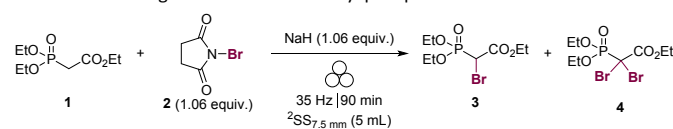
ylides (Scheme 1A).⁹ In the presence of *n*Bu₄NBr as nucleophile, the phosphonium or arsonium ylides acted as umpolung ylides, generating the corresponding brominated *in situ*, which subsequently underwent a Wittig-type olefination. This approach predominantly afforded α -bromo- α,β -unsaturated esters with high *Z*-selectivity. Over the years, HWE strategies employing different brominated phosphonates have also been developed to access α -bromoacrylates with high yields and excellent stereoselectivities. In 2000, Kogen *and coll.* designed and prepared a phosphonate, bis(2,2,2-trifluoroethoxy)-bromophosphonate (Scheme 1A), which reacted efficiently with aldehydes to afford the desired products with a high *E*-selectivity.¹⁰ In 2004, Brückner and co-workers adopted an Ando's variant of the HWE for the selective synthesis of (*E*)- α -bromoacrylates.^{11a} A 64:36 mixture of mono- and dibrominated (phenoxy)-phosphonates was synthesized and subsequently reacted with aldehydes in the presence of NaH at 0 °C, affording the desired α -bromoacrylates with a high *E*-selectivity (Scheme 1A). This strategy was also extended to the synthesis of α -chloroacrylates with a 94:6 *E:Z* selectivity. However, the corresponding chlorinated (phenoxy)phosphonate was obtained in low yield. Very recently, Ando *et al.* reported the preparation of *t*-butyl(diphenylphosphono)-bromoacetate using 1.1 equivalents of NaH and 1.0 equivalent of Br(CCl₂)₂Br at 0 °C in a two-step, one-pot sequence.^{11b} The corresponding mono-brominated phosphonate was obtained with good selectivity. The α -bromoacrylates were subsequently synthesized in good yields and with high *E*-selectivity through a two-step sequence conducted at low temperature. In addition, (*E*)-iodoacrylates were synthesized by reacting *t*-butyl(diphenylphosphono)bromoacetate with NaI and NaH at 0 °C in a first step, followed by reaction with the corresponding aldehyde at -78 °C in the second step. Ethyl(diethylphosphono)bromoacetate was also employed to produce α -bromoacrylates (Scheme 1A); however, this approach resulted in lower selectivity, favoring the *Z*-isomer.¹² Although these strategies efficiently afford highly desirable α -bromoacrylates either with *Z*- or *E*-selectivity, they require the use of strong bases, strict temperature control (both high or low temperatures), sequential addition of reagents, and harmful organic solvents to achieve satisfactory outcomes. Therefore, the development of more practical and efficient methods for α -bromoacrylates synthesis, with particular attention paid to sustainability, is somewhat needed.

Mechanochemistry, which is known for centuries,¹³ is re-emerging as a powerful synthetic tool for developing more practical and sustainable synthetic methodologies by minimizing the use of harmful solvents. Removing solvent from the reaction mixture by using ball-milling in synthesis not only enhances sustainability metrics of reactions but also often improves their overall performance. Indeed, ball-milling frequently leads to enhanced or unprecedented reactivities and selectivities, eliminates the need for external heating, reduces reaction times, and enables efficient one-pot procedures, all key advantages of this solvent-free approach.¹⁴ In this context, Lamaty and co-workers developed in 2010 a HWE procedure for the synthesis of Boc-protected unsaturated amino esters under ball-milling conditions (Scheme 1B).¹⁵ This methodology enabled a one-pot process, avoiding the need for a preliminary generation of the deprotonated phosphonate. Furthermore, in

contrast to the strong base commonly used in such transformations (NaH, ^tBuLi), K₂CO₃ or Cs₂CO₃ were successfully employed as a milder alternative. However, the reaction still required seven hours to reach completion and was limited to aldehydes. Later, Mack and coll. reported a ball-milling-assisted synthesis of α,β -unsaturated esters starting from commercially available triethyl phosphonoacetate *via* a HWE process (Scheme 1B).¹⁶ Although K₂CO₃ was used as a base, an additional 12-hours ball-milling oxidation step was necessary to consume the excess aldehyde that remained unreacted after the initial 6-hours solvent-free HWE step. In both cases, the reactions proceeded with good to excellent stereoselectivity. This mechanochemical-assisted HWE process was then applied for the synthesis of α,β -unsaturated amides,¹⁷ phosphonocinamic esters,¹⁸ and valuable monofluoroalkenes.¹⁹ However, none of this strategy was applied for the formation of α -bromoacrylates.

Inspired by the pioneering work of Lamaty's group¹⁵ and subsequent ball-milling-assisted HWE strategies that have been developed,¹⁶⁻¹⁹ we sought to develop an innovative solvent-free synthesis of valuable α -bromoacrylates starting from commercially available triethyl phosphonoacetate. To establish a practical protocol, we designed a one-pot procedure involving the ball-milling-assisted bromination of triethyl phosphonoacetate, followed by a ball-milling-assisted HWE reaction carried out in the same milling vessel (Scheme 1C). However, since no solvent-free synthesis of triethyl bromophosphonoacetate **3** had been reported to date, at the outset of our investigation, we investigated the preparation of **3** under ball-milling conditions (Table 1). Fortunately, when **1** was subjected to ball-milling in the presence of 1.06 equivalent of *N*-bromosuccinimide and NaH, the common base used for the solution-phase bromination of **1**, the desired brominated phosphonoacetate **3** was obtained in a good yield (Table 1, entry 1). A minor amount of the dibrominated product **4** was also detected, with 6 % ³¹P NMR yield.

Table 1 Ball-milling bromination of triethyl phosphonoacetate



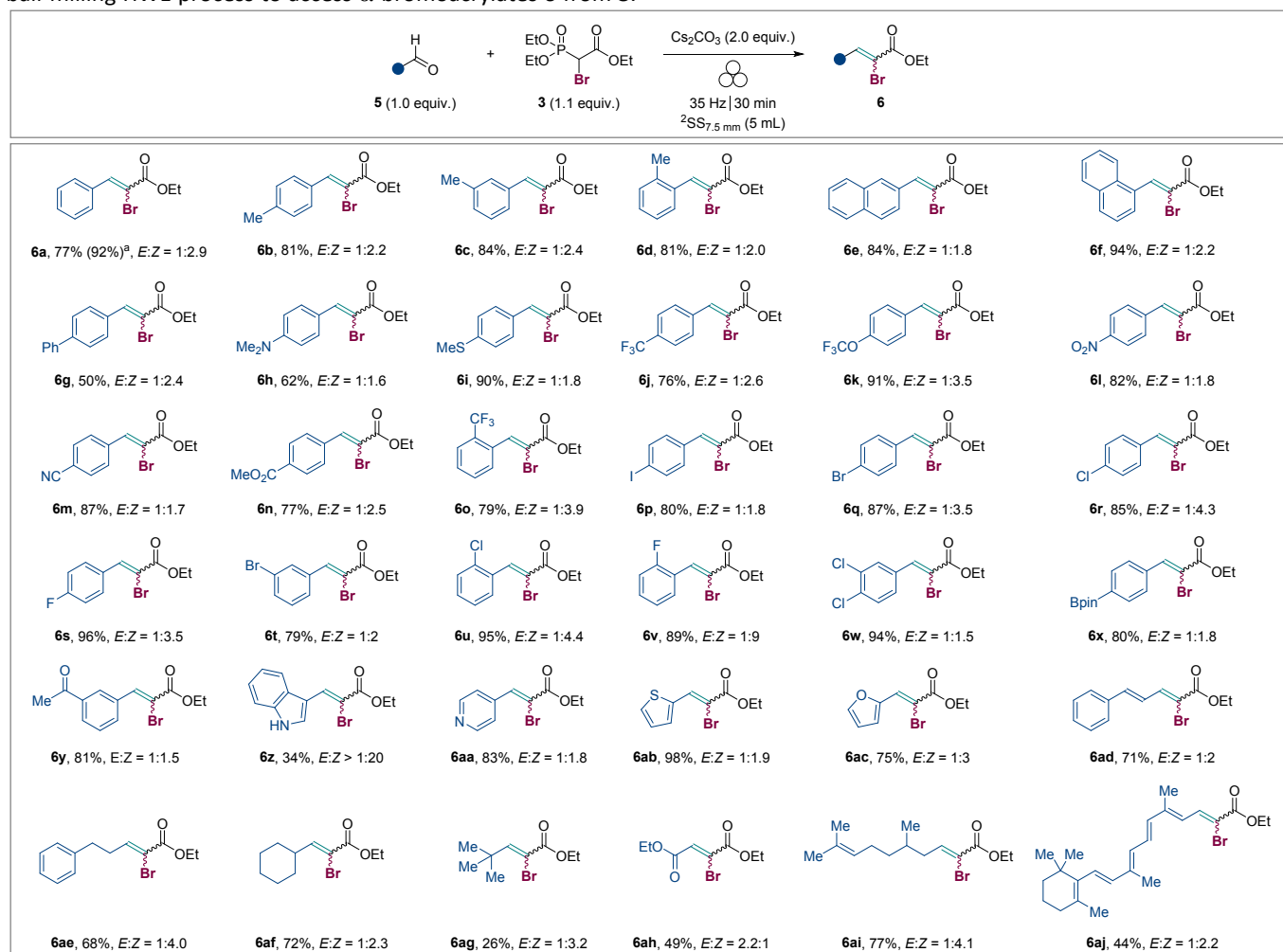
Entry	Variation from standard conditions	Yield 3 (%) ^a	Yield 4 (%) ^a
1	none	61	6
2	1.06 equiv. of ^t BuOK	68	9
3	1.06 equiv. of KOH	80	10
4	1.06 equiv. of K ₂ CO ₃	85	11
5	1.06 equiv. of Cs ₂ CO ₃	82 (63) ^b	8
6	1.06 equiv. of NEt ₃	0	0
7	1.06 equiv. of Cs ₂ CO ₃ , 15 min	84	14
8	1.06 equiv. of Cs ₂ CO ₃ , 10 min	88 (56) ^b	11
9	1.06 equiv. of Cs ₂ CO ₃ , 10 min, no ball-milling	6	13

^a ³¹P NMR yield calculated with diethyl methylphosphonate as internal standard. ^b Isolated yield



We then explored the use of milder inorganic bases (entries 2 to 5). The reaction proceeded efficiently with either K_2CO_3 or Cs_2CO_3 , both of which have been identified as optimal bases in previously reported ball-milling-assisted HWE process.¹⁵⁻¹⁹ However, due to purification difficulties arising from the simultaneous formation of **4**, the desired triethyl bromophosphonoacetate **3** was isolated in a 63% yield (entry 5). The use of an organic base such as triethylamine failed to promote the bromination of **1** (entry 6). With the goal of developing a one-pot ball-milling bromination/HWE protocol, the bromination step was evaluated at shorter milling times (15 and 10 minutes, entries 7 and 8). Remarkably, formation of triethyl bromophosphonoacetate **3** was observed with 88% ^{31}P NMR yield after only 10 minutes of milling at 35 Hz (entry 8). Due to the close polarity between **3** and **4**, the desired monobrominated product has been isolated with only 56% yield. It is noteworthy that in the absence of ball-milling, the desired product **3** was formed in only a 6% ^{31}P NMR yield (entry 9). Finally, the addition of liquid additives (LAG), and variation of the equivalence of base and number of stainless-steel balls were also tested without any significant impact on the reaction outcome. With the optimized ball-milling-assisted bromination in hand (Table 1, entry 8), we next focused on developing the ball-milling HWE process to access α -bromoacrylates **6** from **3**.

Building on the pioneering work of Lamaty's group¹⁵ and previous reports,^{16, 19} 1.1 equiv. of **3** was reacted with benzaldehyde under 35 Hz of milling for 30 min using stainless-steel milling materials (jar and balls). Cs_2CO_3 was employed as a base to aim for the one-pot bromination/HWE procedure. Pleasingly, the desired product **6a** was obtained in a good 77% yield and 1:2.9 *E:Z* ratio (Scheme 2). The reaction proved to be efficient for the synthesis of α -bromoacrylate on a 3.0 mmol scale with an increased isolated yield (92%). A broad range of substituted aromatic aldehydes were compatible under our solvent-free conditions without any impact of the physical state of the starting aldehyde (Scheme 2), including aliphatic, electron-donating, and electron-withdrawing substituents at the *para*-, *meta*- or *ortho*-position. Notably, steric hindrance had no significant effect on the reaction outcome. The presence of a Me substituent, regardless of its position on the aromatic ring, had little influence on the yield or stereoselectivity (**6b** to **6d**). Polyaromatic aldehydes also reacted efficiently, delivering the desired products **6e** and **6f** in high yields. Both electron-donating (Ph **6g**, NMe₂ **6h** or SMe **6i**) and electron-withdrawing (CF₃ **6j**, OCF₃ **6k**, NO₂ **6l**, CN **6m** and CO₂Me **6n**) groups at the *para*-position enabled the formation of the expected products

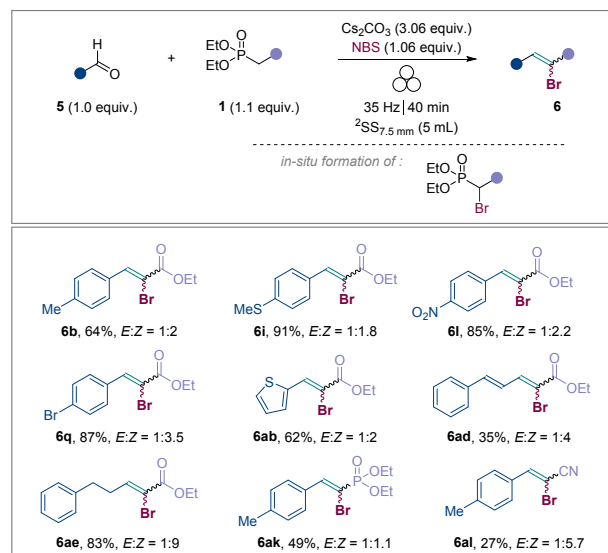


Scheme 2 Ball-milling synthesis of α -bromoacrylates through solvent-free HWE. ^a Reaction performed on 3 mmol scale.



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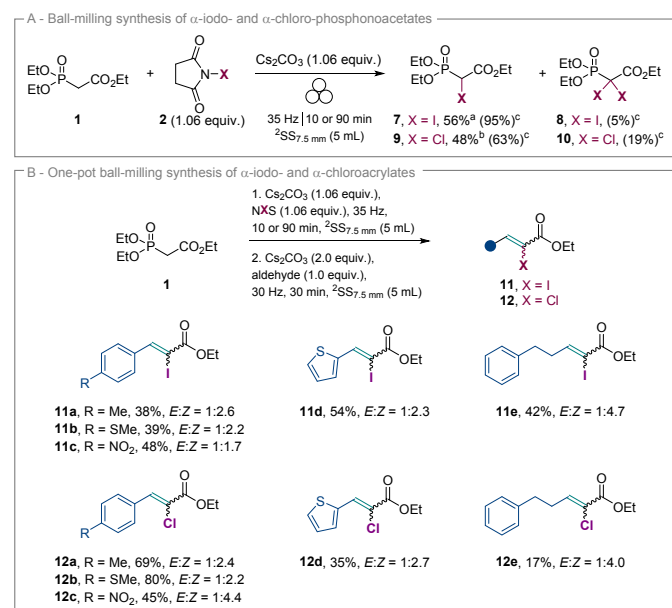
in high efficiency and moderate *E:Z* ratios. In addition, shifting the electron-withdrawing substituents enabled the formation of the desired product with similar results, with even better *Z*-selectivity (**6o**). It is worth mentioning that valuable post-functionalizable moieties were well tolerated, including an amine (**6h**), a thioether (**6i**), a nitro (**6l**), a cyano (**6m**), and an ester motif (**6n**). Halogen atoms, such as iodine (**5p**), bromine (**5q** and **5t**), chlorine (**5r**, **5u** and **5w**), and fluorine (**5s** and **5v**), were also suitable substrates with our solvent-free reaction conditions, affording the desired products with high efficiency. These products open significant opportunities for further transformations. Once again, the presence of a halogen atom at the *ortho*-position enabled an increase in stereoselectivity in favor of the *Z*-isomer (**6u** and **6v**). Additionally, a boronic ester-substituted aldehyde (**5x**) efficiently produced the corresponding product, highlighting potential for subsequent Suzuki-Miyaura-type cross-coupling reactions. Complete regioselectivity towards the aldehyde moiety was observed when using 3-acetylbenzaldehyde (**5y**). Heteroaryl aldehydes were also suitable substrates. While indole derivative aldehyde (**5z**) led to lower yields, pyridine-, thiophene- and furan-derived aldehydes (**5aa**, **5ab**, and **5ac**) afforded the bromoalkene product in good to excellent yields. Interestingly, improved *Z*-selectivity was observed when using furan (*E:Z* = 1:3) and indole derivatives (*E:Z* > 1:20). Furthermore, a synthetically valuable brominated diene (**6ad**) was synthesized in 71% yield with moderated *Z*-selectivity. Aliphatic aldehydes also proved to be competent substrates, giving moderate to good yields and moderate to good stereoselectivities. Phenylpropane- and cyclohexane-derived aldehydes (**5ae** and **5af**) showcased a high efficiency, whereas *t*Bu-derived aldehyde (**5ag**) provided a lower yield, albeit with improved *E:Z* ratio. Ethyl oxoacetate afforded product **6ah** with a decent yield and reversed stereoselectivity. To further demonstrate the robustness of our solvent-free strategy, more complex aldehydes were evaluated. Citronellal (**5ai**), responsible for the characteristic lemon fragrance of citronella oil, and retinal (**5aj**), a polyene chromophore considered as one of the forms of vitamin A, were successfully transformed in moderate to good yields and stereoselectivities. In contrast, ketones failed to react under our optimal solvent-free conditions. Having established the optimal conditions for the ball-milling-assisted formation of triethyl bromophosphonoacetate and delineated the scope and limitations of our solvent-free HWE process for the synthesis of α -bromoacrylates, we then investigated the targeted bromination/HWE *one-pot* sequence (Scheme 3). Initially, 4-methylbenzaldehyde was reacted with 1.1 equivalent of triethyl phosphonoacetate in the presence of 3.06 equivalents of Cs_2CO_3 and 1.06 equivalent of NBS. Pleasingly, after 40 minutes of grinding, the combination of both previously optimized reaction conditions enabled the successful formation of the corresponding α -bromoacrylate **6b** with a good 64% and moderate stereoselectivity.



Scheme 3 Ball-milling-assisted bromination/HWE *one-pot* process.

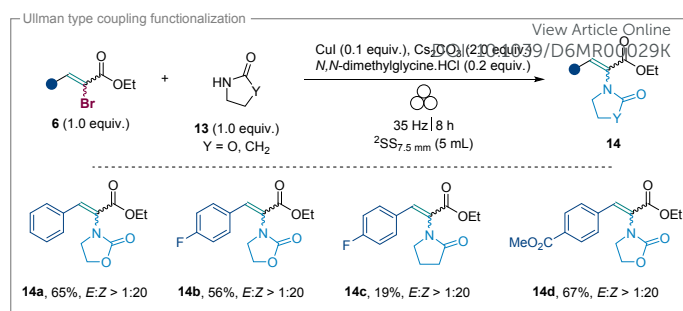
These milling conditions were then applied to a variety of aldehydes and proved to be tolerant to a broad range of functional groups. Aldehydes containing either an electron-donating (**5i**) or an electron-withdrawing substituent (**5l**) on the aromatic ring were efficiently converted with results comparable to those obtained when performing both reactions separately. When a thiophene-derived aldehyde (**5ab**) was subjected to the *one-pot* reaction, the desired product was obtained in decreased, though still with decent efficiency. The reaction with cinnamaldehyde afforded the corresponding product **6ad** in a modest 35% yield; however, the good *E:Z* ratio of 1:4 (previously observed in the stepwise process) was maintained. An aliphatic aldehyde also proved to be a suitable substrate, producing the targeted product in even higher yield (**6ae**, 83%). Interestingly, the *E:Z* ratio improved significantly under *one-pot* conditions, reaching up to 1:9 compared to a 1:4 ratio when performing both steps separately. To further expand the scope of accessible brominated alkenes, tetraethyl methylenebis(phosphonate) and diethyl (cyanomethyl)-phosphonate were also tested under our ball-milling-assisted *one-pot* bromination/HWE protocol. Gratifyingly, **6ak** was obtained in a decent yield, while α -bromoacrylonitrile **6al** was isolated in a lower yield, albeit with a good *Z*-stereoselectivity compared to **6ak**. These results underscore the efficiency and versatility of our mechanochemical synthetic strategy for accessing synthetically valuable α -bromoalkene derivatives, and open new avenues for the synthesis of alkenes from functionalized bromo-phosphonoacetate derivatives.





Scheme 4 Application of ball-milling-assisted one-pot halogenation/HWE to α -iodo- and α -chloroacrylates. ^a The iodination step was performed for 10 min of reaction. ^b The chlorination step was performed for 90 min of reaction. ^c ³¹P NMR yield with diethyl methylphosphonate as internal standard.

We then wondered whether the corresponding iodinated and chlorinated analogues could be synthesized under our ball-milling procedure by replacing NBS with either NIS and NCS. We initially focused on the formation of triethyl iodophosphonoacetate (**7**) and triethyl chlorophosphonoacetate (**9**) under our mechanochemical conditions (Scheme 4A). **7** was formed with a high 95% ³¹P NMR yield after only 10 minutes of milling, with a minimal formation of the diiodinated byproduct (**8**). In contrast, the mechanochemical synthesis of the chlorinated analogue required extended milling time (up to 90 minutes) to afford a satisfactory ³¹P NMR yield, with the dichlorinated byproduct **10** also detected in 19% ³¹P NMR yield. Unfortunately, due to the inherent instability of both desired products **7** and **9**, they were isolated in moderate 56% and 48% yields, respectively. Nevertheless, having demonstrated that triethyl iodophosphonoacetate **7** and triethyl chlorophosphonoacetate **9** could be generated under mechanochemical conditions, we next sought to develop *one-pot* iodination/HWE and chlorination/HWE procedures, which could circumvent the need for isolating **7** and **9** (Scheme 4B). When all reagents were introduced simultaneously at the start of the milling process, the desired α -iodo- and α -chloroacrylates (**11a–11d**) and α -chloroacrylates (**12a–12d**) in moderate to good yields. The iodination/HWE sequence afforded the desired products in generally moderate yields (**11a–c**), regardless of the electronic nature of the substituents on the aromatic ring.



Scheme 5 Further functionalization of α -bromoacrylates under mechanochemical conditions

In contrast, the chlorination/HWE sequence provided higher yields for the corresponding products (**12a–c**). However, the introduction of an electron-withdrawing motif on the starting aldehyde resulted in a decreased yield (see **12c**). Heteroaryl and aliphatic aldehydes reacted with similar reaction efficiency within the iodination/HWE sequence (**11d–e**), whereas lower yields were obtained for the corresponding chlorinated products (**12d–e**). Overall, moderate $E:Z$ ratios were obtained, except in the case of aliphatic aldehydes.

To demonstrate the synthetic utility of our synthesized products, we sought to exploit the $\text{C}(\text{sp}^2)\text{--Br}$ bond to develop a C--N bond formation under mechanochemical conditions. Initially, we developed a solvent-free Ullman-type coupling (Scheme 5). Under ball-milling at 35 Hz in stainless-steel milling equipment, **6a** reacted with oxazolidinone-2-one **13** in the presence of CuI as catalyst, affording the expected coupling product **14a** in a good 65% yield and with high Z -selectivity. These milling conditions were subsequently applied to **6s**, leading to the formation of **14b** in a decent 56% yield with excellent stereoselectivity ($E:Z > 1:20$). In contrast, the use of 2-pyrrolidinone as a coupling partner resulted in lower reaction efficiency, although a high $E:Z$ ratio was still observed. An electron-withdrawing group-substituted α -bromoacrylate also proved to be a competent substrate in this solid-state Ullmann-type reaction, delivering the desired product **14d** in a good 67% yield, with same high Z -selectivity.

Conclusions

As a conclusion, we report herein a practical and more sustainable solvent-free synthesis of synthetically valuable α -bromoacrylates under ball-milling conditions at room temperature, using a weak base (Cs_2CO_3) in a short reaction time. Intending to access these compounds from commercially available triethyl phosphonoacetate through a *one-pot* bromination/HWE sequence, we first developed the ball-milling bromination of triethyl phosphonoacetate. Once the solvent-free formation of triethyl bromophosphonate was established, we developed a ball-milling assisted HWE transformation to obtain the desired α -bromoacrylates. This mild process proved to be highly efficient and broadly tolerant to various functional groups (36 examples, from 26 to 98% yields), including aldehydes bearing electron-donating, and electron-withdrawing motifs, and halogen atoms, with no notable impact of steric hindrance. Heteroaryl, aliphatic aldehydes, and natural



products derived aldehydes were also suitable substrates. The reaction afforded the desired products with moderate to good *E:Z* ratios (from 1:1 to > 1:20). With both reactions developed independently under similar reaction conditions, in hand, we demonstrated that the α -bromoacrylates could be obtained directly from the commercially available triethyl phosphonoacetate through a *one-pot* bromination/HWE process under ball-milling conditions with broad functional group tolerance in a short reaction time, mild and sustainable conditions (9 examples, from 27 to 91% yields). We further showed that our ball-milling bromination could be extended to iodination and chlorination using NIS and NCS, enabling solvent-free formation of triethyl iodophosphonoacetate and triethyl chlorophosphonoacetate after 10 and 90 minutes of milling, respectively. Therefore, our conditions were then used for the ball-milling assisted synthesis of α -iodo- and α -chloroacrylates from commercially available triethyl phosphonoacetate. However, the protocol was performed in a *one-pot* two-step sequence. Finally, we proved the synthetic value of our α -bromoacrylates by engaging them in a solvent-free Ullman-type coupling reaction using ball-milling.

Author contributions

M. C. J.-P. B., and T. C. conceived and designed the experiments. M. C. performed the experiments. M. C., J.-P. B. and T. C. analyzed the data. T. C. wrote the manuscript with the input from all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article can be found in the Supporting Information.

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