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Mechanochemistry

Synthesis of 3-Iodobenzofurans by Electrophilic Cyclization under Solventless Conditions in a Ball Mill

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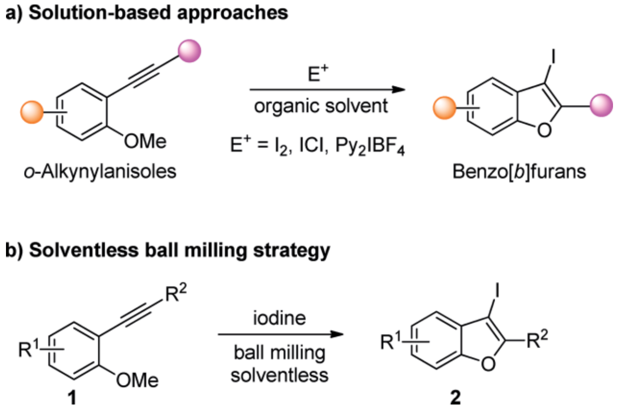
Abstract: Under mechanochemical conditions, electrophilic cyclizations of 2-alkynylanisoles provide 3-iodobenzofurans in the absence of a solvent. Equimolar amounts of iodine are sufficient for achieving good yields. The eco-friendly reaction conditions are mild, and various functional groups are tolerated.

Introduction

Among the most important methods for constructing hetero- and carbocycles are electrophilic cyclization reactions forming both carbon–carbon and carbon–heteroatom bonds.[1] Commonly, they are initiated by coordination of an electrophile to the π-electrons of an alkyne, alkene, allene, conjugated diene, or carbon–carbon multiple bond of another suitable substance. Two electrophilic cyclization routes towards heterocycles can be distinguished: The activated C–C multiple bond is either attacked by an *ortho* substituent[1] or it reacts with an aromatic ring at its *ipso* position.[2]

Benzofurans are important heterocyclic compounds being present as core units in various products exhibiting high biological activities.[3] A representative example is machicendiol, which is used in the treatment of asthma, ulcers, and rheumatism.[4] Common synthetic routes towards benzofurans involve electrophilic cyclizations of *o*-alkynylanisoles with molecular iodine, iodine monochloride, or bis(pyridine)iodonium tetrafluoroborate, among others (Scheme 1a).[5] Typically, such iodocyclizations are carried out in organic solvents such as DCM, 1,2-dichloroethane or toluene.[5] Choosing the right medium is important because it not only affects the iodocyclization/addition ratio,[4b] but also helps to minimize solubility constrains resulting from the onium salt intermediate.[5b,6] In recent years, ball milling techniques have facilitated the design of mechanochemical reactions in diverse areas of chemistry like organic,[7] organometallic,[8] inorganic,[9] biocatalysis,[10] and polymer chemistry.[11,12] Having the possibility to carry out solventless reactions and to overcome solubility restrictions are among the uppermost notable advantages of ball milling techniques. Due to these aspects, mechanochemistry has gained a reputation as a sustainable alternative for chemical synthesis and for enabling the discovery of new chemical reactivity.[13]



Scheme 1. Synthesis of benzo[*b*]furans by electrophilic cyclization.

In the field of mechanochemical cyclization reactions, Stolle and co-workers reported a $ZnBr_2$-mediated ring-closure of 2-alkynylanilines into indoles in a mixer mill.[14] Using stoichiometric amounts of the Lewis acid the mechanochemical intramolecular reaction afforded a variety of indole derivatives in good yields. With this precedent in mind, and curious to examine if a solventless iodocyclization of *o*-alkynylanisoles **1** could provide access to benzo[*b*]furans **2** mechanochemically, we decided to study the iodine-mediated 5-*endo-dig* cyclization of **1** by ball milling (Scheme 1b). The results are summarized here.

Results and Discussion

To commence the study, 1-methoxy-2-(phenylethynyl)benzene (**1a**) was chosen as model substrate for the electrophilic cyclization in the ball mill. In our first attempt a mixture of **1a** (0.25 mmol) and iodine (0.50 mmol) was milled for 2 h at a frequency of 25 Hz. Pleasingly, after purification by column chromatography benzofuran **2a** was obtained in 30 % yield (Table 1, entry 1). In order to improve the yield, milling parameters such as frequency and milling time were varied. Additionally, various iodine loadings and the use of milling auxiliaries were examined. When the milling was carried out at a higher speed, the reaction led mostly to decomposition of **1a** (Table 1,

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entry 2). Reducing the amount of iodine from 2 equiv. to 1 equiv. and shortening the milling time proved beneficial, doubling the yield of **2a** after only 60 min of milling (65 %; Table 1, entry 4). Next, varying the milling frequency revealed that milder milling conditions favored the iodocyclization of **1a**. In particular, milling **1a** with iodine (1 equiv.) at 15 Hz for 1 h gave benzofuran **2a** in 78 % yield (Table 1, entry 7). Further screening of the milling conditions did not improve the yield of **2a** (Table 1, entries 8–12). Therefore, milling an equimolar mixture of **1a** and iodine at 15 Hz for 1 h were selected as the optimal milling conditions (Table 1, entry 7). This selection balanced the need for achieving appropriate mixing of the reactants at low energy consumption (Table 1, entries 6–8).

Table 1. Screening of milling conditions for the formation of **2a**.[a]

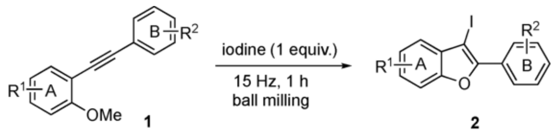
1a **2a**

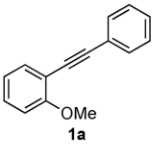
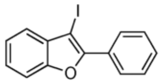
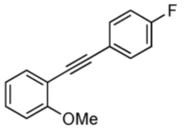
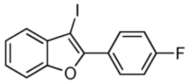
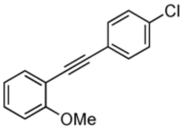
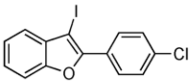
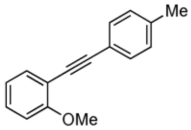
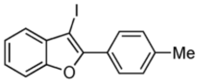
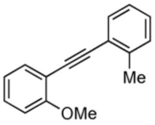
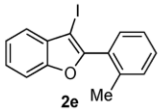
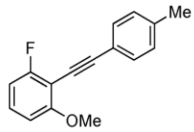
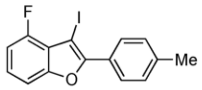
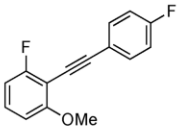
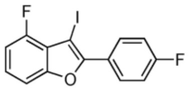
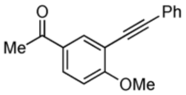
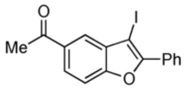
Entry	Iodine [equiv.]	Milling frequency [Hz]	Milling time [h]	Yield [%][b]
1	2	25	2	30
2	2	30	2	–
3	1	25	2	27
4	1	25	1	65
5	1	25	0.5	59
6	1	20	1	76
7	**1**	**15**	**1**	**78**
8	1	10	1	72
9	1	15	2	73
10	1.5	15	1	58
11	2	15	1	54
12[c]	1	15	1	72

[a] Reaction conditions: **1a** (0.25 mmol) and molecular iodine were milled in a 10 mL in volume stainless steel milling jar with one ball made of the same material (10 mm in diameter). [b] Yields after column chromatography. [c] NaCl was added as a milling auxiliary (1.0 g).

After the reaction conditions were established, substrates **1** with substituted arenes were applied in the mechanochemical iodocyclizations (Table 2). Uncovering potential substitution effects on the yield of benzofurans **2** was of interest because in solution, electronic effects were reported to play an important role in favoring 5-*endo-dig* cyclizations over potential additions of iodine across the triple bond, leading to di-iodinated olefins.[5a,5d] Here, the use of anisole derivative **1b** bearing an electron-withdrawing *para*-fluoro substituent on arene B facilitated the electrophilic cyclization leading to benzo[*b*]furan **2b** in 83 % after purification by column chromatography (Table 2, entry 2). Similarly, *para*-chloro-substituted **1c** gave the corresponding cyclization product in 66 % yield (Table 2, entry 3). In contrast, substituting arene B with electron-donating methyl groups disfavored 5-*endo-dig* cyclizations, especially in the case of substrate **1d** bearing a methyl group in *para*-position (Table 2, entries 4 and 5). The presence of an electron-withdrawing fluoro substituent on arene A was beneficial as revealed by comparing the yields of cyclized products **2d** and **2f**, which were formed in 58 % and 74 %, respectively (Table 2, entry 6 vs. entry 4). On the other hand, when both arenes were substituted with fluoro groups as in **1g**, the product yield was only 32 % yield (Table 2, entry 7). Finally, 4′-methoxyacetophenone derivative **1h** reacted poorly affording benzo[*b*]furan **2h** in 30 % yield (Table 2, entry 8).

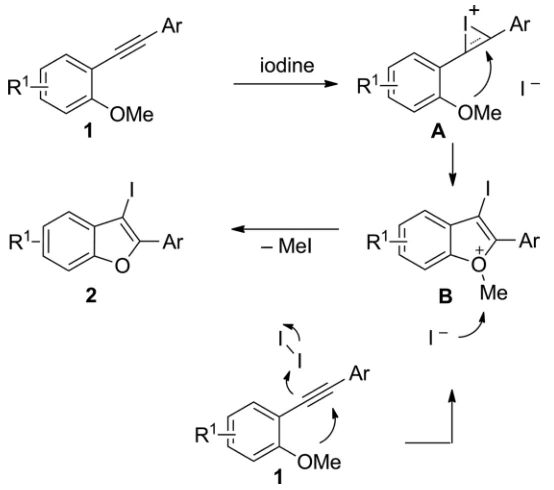
Table 2. Mechanochemical electrophilic cyclization of 2-alkynylanisoles **1**.



Entry	Substrate	Product	Yield [%]
1	 **1a**	 **2a**	78
2	 **1b**	 **2b**	83
3	 **1c**	 **2c**	66
4	 **1d**	 **2d**	58
5	 **1e**	 **2e**	78
6	 **1f**	 **2f**	74
7	 **1g**	 **2g**	32
8	 **1h**	 **2h**	30

Under the aforementioned conditions, the moderate yields resulted from incomplete conversions of starting materials, which could be recovered. Increasing the milling frequency, extending the reaction time or using an excess of iodine led to diiodinated *E*-alkenes. The same product type was observed in attempts to use substrates with alkyl groups instead of arene B.

With respect to the mechanism, various aspects have to be taken into account, which could eventually lead to altered reaction pathways when moving from solution-based to solventless ring-closing systems.[13,15] This is particularly true, when charged species are involved. As suggested for cyclization reactions of 2-alkynylanisoles **1** in solution, interactions of molecular iodine with the triple bonds of **1** could lead to iodonium cations **A** and iodide (Scheme 2, top). Subsequent cyclizations of **A** would generate intermediates **B**, which upon expulsion of methyl iodide could provide 3-iodobenzo[*b*]furans **2**. In solution, charge-separated species such as cations **A** and **B** as well as iodide would experience significant interactions by solvent molecules. Under solventless mechanochemical conditions, however, those (potentially) stabilizing effects are lacking. Consequently, other cyclization pathways could dominate. For example, product **2** could be formed by simultaneous iodine–alkyne interactions/demethylations involving essentially only neutral species (Scheme 2, bottom). In addition, radical species might be relevant. At this stage, we cannot distinguish such routes, but surely, those issues have to be addressed in future studies, because the findings might eventually also prove relevant for other solventless reaction systems.



Scheme 2. Potential reaction mechanisms.

Conclusions

In summary, we studied mechanochemical cyclization reactions of 1-methoxy-2-(phenylethynyl)benzenes to give benzofurans in the presence of iodine. In a ball mill the iodocyclizations proceeded in the absence of organic solvent and required only equimolar amounts of iodine. Several substrates with various substituents reacted well, providing the corresponding products in satisfying to good yields.

Experimental Section

General Procedure for Electrophilic Cyclizations in a Ball Mill: A mixture of 2-alkynylanisole **1** (0.25 mmol) and iodine (0.25 mmol) was transferred to a stainless steel milling jar (10 mL in volume) with one stainless steel ball (10 mm in diameter). Then, the content of the milling jar was milled at 15 Hz. After 1 h of milling, the reaction was stopped and the benzo[*b*]furan **2** was recovered by washing the vessel a minimal amount of EtOAc (3 × 10 mL). The mixture was then concentrated in vacuo, and the product was purified by flash chromatography (*n*-pentane).

Acknowledgments

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Keywords: Ball milling · Heterocycles · Cyclization · Mechanochemistry · Synthesis design

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[15] A very detailed mechanistic analysis is presented in ref.[5a] There, the solvent was dichloromethane.

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Mechanochemistry

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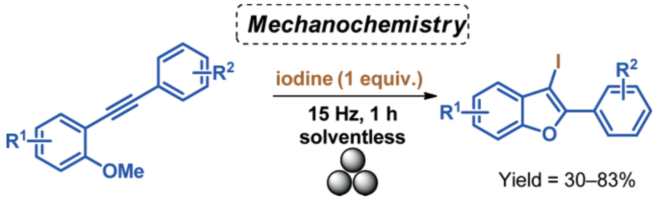

In the present study mechanochemistry was applied to synthesize 3-iodobenzofurans. Solventless milling of 2-(arylethynyl)anisoles with iodine favored the electrophilic cyclization affording iodobenzofurans in yields ranging from 30 % to 83 %. In general, the mechanochemical iodocyclization took place after short reaction times and under mild milling conditions.

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