A sustainable approach to the Sonogashira reaction under solvent-free mechanochemical conditions

Leon Wickert, Lars Borchardt, lars.borchardt@rub.de, In-depth-Practical, Inorganic Chemistry I, Ruhr-Universität Bochum

Abstract *Mechanochemistry has gained remarkable attention as a green and sustainable alternative to conventional, solvent based synthesis. This new pathway comes with fewer reaction steps and a greatly reduced amount of waste. In this article, we report a solvent-free Sonogashira coupling of phenylacetlyene and iodobenzene via high-speed ball milling under various conditions. The milling balls simultaneously acted as the reaction catalyst resulting in an easy work-up and catalyst separation. Different milling conditions and bases were used to find optimal conditions for coupling. Various catalysts were tested to investigate the necessity of the co-catalyst. A solvent-free reaction was possible even without a co-catalyst, but the formation of undesireable side products could not be prevented yet.*

A mechanochemical reaction is a chemical reaction that is induced by the direct absorption of mechanical energy.[1]
Recently, mechanochemistry has gained a lot of attention due to its environmental and financial benefits. With this method, the energy required for a chemical reaction is provided by mechanical force. Thus, no solvent is needed in the synthetical pathway, which greatly reduces the amount of waste that would build up by the use of a solvent.[2] Also the work-up steps after the reaction are usually much more simple and energy efficient. Therefore, mechanochemistry can be used as a green alternative to solvent based synthesis of organic compounds. Numerous industrial relevant reactions have been carried out under mechanocatalytical conditions. Polymerizations for porous materials[3] or Suzuki-like polyphenylenes[4] as well as coupling reactions like the Sonogashira coupling[5] are possible.
In this study we investigate such a mechanochemical Sonogashira coupling in a high-speed ball mill. The Sonogashira coupling reaction is a useful tool for the incorporation of alkynyl functionality. It can be applied to complex molecules to synthesize pharmaceuticals[6,7], natural products[8], organic materials and biomolecules[9]. During the standard Sonogashira coupling, a carbon-carbon bond is formed between a terminal alkyne and an aryl or vinyl halide. The palladium catalyst and a copper-based co-catalyst are active under basic conditions. Frequently, an amine base is used as base and solvent simultaneously.[10] A homogeneous, zerovalent palladium complex as well as a copper(I) salt are needed in the standard method. In our mechanochemical approach that is based on the research of Mack et. al.[5] we want to make this reaction more sustainable and also cheaper. To do this, the reaction is carried out with a variety of vials and balls to find the optimal reaction conditions. The milling balls will simultaneously serve as catalysts to provide an easy separation and recovery after the reaction. Recently, it has been shown that nickel could be an alternative to palladium.[11] The rareness of palladium and a lack of novel resources lead to a continuous increase in price. Thus, a successful replacement of palladium with nickel would greatly reduce the costs of the catalyst. However, a copper source is still needed as a co-catalyst. Studies have shown that copper(0) can also be used as a co-catalyst.[5] This could make the use of copper salts obsolete. The omittance of cooper salts would be another step towards more sustainable reaction conditions in this reaction. The liquid bases will be replaced with solid ones that also act as bulk materials to provide effective grinding of all components. In our study, we started to investigate the mechanochemical Sonogashira coupling between phenylacetylene and iodobenzene under palladium and nickel catalysis with different reaction conditions. Furthermore, we focused our research on excluding the copper salts from the reaction to make the synthesis more sustainable.
As previously mentioned, Mack et. al. already performed Sonogashira reactions under ball mill conditions with different substrates and the use of $Pd(PPh_3)_4$ and 1 mol% of CuI.[5] We varied this reaction by using nickel balls that simultaneously act as a much cheaper catalyst compared to palladium. Specifically, the reaction was conducted by adding 2.5 mmol of phenylacetylene and 2.5 mmol of iodobenzene as well as 26 nickel milling balls (diameter <10 mm), 500 mg copper powder, 2 mol% copper iodide and 4 g potassium carbonate to a zirconium dioxide milling bowl. The bowl was placed in a planetary mill (PBM, P7) and milled for 1 h at 800 rpm (figure 1).

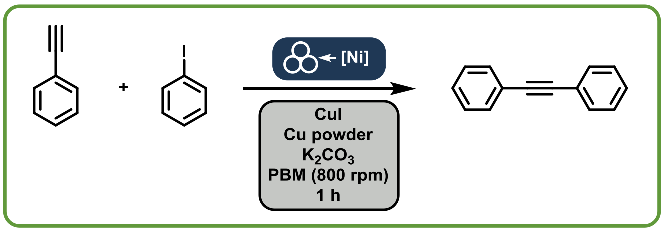

Figure 1. First attempt of the nickel catalysed mechanochemical Sonogashira coupling in a planetary ball mill (PBM). Nickel was used as catalytically active milling balls, as the symbol for mechanochemical reactions, introduced by Hanusa, indicates. CuI was still neccessary as a co catalyst, but should be interchangeable by a copper milling vessel, according to the findings of Mack et al.[5]

Valid information from NMR-analysis could not be obtained. Hence, GC-MS measurements were done. For this, 1 ml of 10 % HCl solution was added to a small sample of the reaction mixture. The resulting suspension was extracted with 2 ml of *n*-pentane. The organic layer was filtered with a cotton filter and transferred into a GC-MS vial.

The components of the sample were quantified by their percentage area in the respective gas chromatogram. This resulted in peaks for 178 m/z, 204 m/z and 202 m/z. The peak for 178 m/z can be assigned to the desired Sonogashira product diphenylacetylene. The second observable product could belong to a Glaser-like homo-coupling product. Unlike the Sonogashira reaction, the Glaser reaction does not need another catalyst besides a copper(I) or copper(II) salt.[12] The Glaser coupling is therefore an unpleasant competing reaction to the Sonogashira coupling. There has also been abrasion of the nickel with an amount of 1.5 g that occurred in every run with 26 nickel balls.

To prove the catalytic activity of nickel the reaction was repeated, but instead of nickel balls, zirconium dioxide balls were used. As expected, no Sonogashira product was observed in this run. However, the Glaser product could still be observed. Subsequently, an attempt with 4 eq. of iodoebenzene has been made to enhance the probability of the desired conversion. Interestingly, only traces of the Sonogashira product could be found. The reaction (figure 1) was repeated with 4 g KOtBu instead of potassium carbonate resulting in a higher yield of the desired Sonogashira product with an area percentage of 17.3 % and 6.7 % for the Glaser product. The reaction was also carried out in a copper vial and two palladium/copper alloy balls as well lead to the formation of Sonogashira product. The results are summarized in table 1. The remaining necessity of copper(I) salts in the reaction is not desirable for our purposes because it is a harmful substance that would also lead to more work-up steps and contamination in the final product. Therefore, our next goal was the removal of copper(I)iodide from the reaction. The first attempt was the reaction shown in scheme 1 but without the use of CuI. The area percentages of both products in the respective gas chromatogram dropped to around 10 %. However, the ratio of Sonogashira to Glaser product was higher. We also considered changing the pKa value of the base to increase the amount of Sonogashira product. By using KOH, the product ratio increased again, but the overall yield was lower. The use of KOtBu with CuI was the most successful run, but without the co-catalyst, the yield dropped close to zero. Other attempts like liquid assisted grinding, varying the amount of grinding balls or the use of another mill (table 3) did not improve the reaction. The results of the reactions were summed up in table 2 and 3. In the work of Mack et. al. copper vials, copper balls and a palladium complex have been used for the Sonogashira reaction. Therefore, we considered using a copper vial and palladium or palladium/copper alloy milling balls. For this reaction, different mixer mills (MM) have been used. The use of palladium/copper alloy as a ball material did only lead to a formation of the Glaser product. With the use of palladium balls the area percentage of the Sonogashira product was 5.7 %, but twice as much of the Glaser product has been formed.

The experiments have shown that a mechanochemical Sonogashira coupling of phenylacetylene and iodobenzene with nickel as catalyst and milling material and CuI as co-catalyst is possible in a short amount of time. The base and the milling material play a crucial role in this reaction. The highest amount of diphenylacetylene could be achieved with KOtBu as base, nickel balls as milling material and catalyst and CuI as co-catalyst. Conducting this reaction without the undesirable CuI appeared to be much harder. The best results were obtained with potassium carbonate and nickel balls. However, the Glaser product appeared in both reactions and could not be prevented yet. The milling speed and milling time must be optimized as well as the equivalents of iodobenzene. Also, the abrasion of the nickel balls could be prevented by using nickel alloy balls. Another promising variation is the use of copper coated milling bowls to enhance the probability of a catalytic reaction similar to the approach of Mack et. al. The mechanisms of mechanochemical reactions are still unknown, which hinders finding the best reaction conditions. Therefore, further research in this reaction is necessary.

Experimental Section

All reagents and solvents were purchased from commercial suppliers and used without further purification. The reactions were carried out in a Fritsch Planetary Micro Mill Pulverisette 7 (P7) with 80 ml zirconium oxide grinding vessels and a Retsch MM 500 with copper grinding vials. The crude products were analysed via gas chromatography-mass spectrometry in *n*-pentane with a Finnigan Mat GCQ. The area percentage of the product peaks were calculated with OpenChrom Lablicate Edition.

Phenylacetylene (275 µl , 2.5 mmol, 1 eq.), iodobenzene (280 µl, 2.5 mmol, 1 eq.), potassium carbonate (4 g, xs), copper powder (500 mg, 7.86 mmol, 3.1 eq.) and an excess amount of base were put into the milling bowls. The amount of base was adjusted to fill the bowl to a third of the maximum volume. For the reactions in table 1, CuI (9.5 mg, 0.05 mmol, 0.02 eq.) was also added to the bowls. The milling bowl was placed into the mills and was milled with the respective parameters. Afterwards, the reaction mixture was removed from the bowl. To small amounts of the reaction mixture 3 drops of 10 % HCl solution were added and the resulting aqueous solution was extracted with *n*-pentane. After filtration the solvent was removed to obtain the crude product.

Table 1. Results of Sonogashira reactions with addition of 2 mol% CuI in P7 (ZrO_2 bowl) and IST (copper vial) within 1 h

Balls (no.)	**Equivalents of iodobenzene**	**Base (mass)**	**% Area Sonogashira product**	**% Area Glaser product**
Nickel (26)	1	K_2CO_3 (4 g)	16.4	26.9
ZrO_2 (26)	1	K_2CO_3 (4 g)	0	8.9
Nickel (26)	4	K_2CO_3 (4 g)	1.5	2.0
Nickel (26)	1	KOtBu (4 g)	17.3	6.7
PdCu40 (2)	1	K_2CO_3 (0.5 g)	0	3.9
Nickel (2)	1	K_2CO_3 (0.5 g)	0	0

Table 2. Results of Sonogashira reactions in P7 with copper powder and 26 nickel balls in the absence of CuI at 800 rpm in 1 h

LAG Additive (volume)	Equivalents of iodobenzene	Base (mass)	% Area Sonogashira product	% Area Glaser product
/	1	K_2CO_3 (4 g)	9.1	10.9
/	1	KOH (224 mg)	4.1	1.8
/	2	K_2CO_3 (4 g)	1.1	2.1
/	4	K_2CO_3 (4 g)	0	0
water (115 µl)	1	K_2CO_3 (4 g)	1.2	3.4
Ethanol (115 µl)	1	K_2CO_3 (4 g)	4.1	1.9
/	1	KOtBu (1 g)	1.6	3
/	1	K_2CO_3 (5 g)	3.6	6.6

Table 3. Results of the Sonogashira reaction in the MM500 at 35 Hz with different milling balls in 1:1 ration of the educts

Vial	Reaction time	Educt	Balls (no.)	Base (mass)	% area Sonogashira product	% area Glaser product
Copper	1.5 h	Phenylacetylene	Pd(0) (1)	K_2CO_3 (1.5 g)	5.7	12.4
Copper	1.5 h	Phenylacetylene	Pd/Cu alloy (1)	K_2CO_3 (1.5 g)	0	2.3

References

[1] K. Horie, M. Barón, R. B. Fox, J. He, M. Hess, J. Kahovec, T. Kitayama, P. Kubisa, E. Maréchal, W. Mormann, et al., *Pure Appl. Chem.* **2004**, *76*, 889–906.
[2] R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13*, 854.
[3] S. Grätz, D. Beyer, V. Tkachova, S. Hellmann, R. Berger, X. Feng, L. Borchardt, *Chem. Commun.* **2018**, *54*, 5307–5310.
[4] C. G. Vogt, S. Grätz, S. Lukin, I. Halasz, M. Etter, J. D. Evans, L. Borchardt, *Angew. Chem. Int. Ed.* **2019**, DOI 10.1002/anie.201911356.
[5] D. A. Fulmer, W. C. Shearouse, S. T. Medonza, J. Mack, *Green Chem.* **2009**, *11*, 1821.
[6] M. Bakherad, H. Nasr-Isfahani, A. Keivanloo, N. Doostmohammadi, *Tetrahedron Lett.* **2008**, *49*, 3819–3822.
[7] S. Frigoli, C. Fuganti, L. Malpezzi, S. Serra, *Org. Process Res. Dev.* **2005**, *9*, 646–650.
[8] B.-C. Hong, R. Nimje, *Curr. Org. Chem.* **2006**, *10*, 2191–2225.
[9] N. D. P. Cosford, L. Tehrani, J. Roppe, E. Schweiger, N. D. Smith, J. Anderson, L. Bristow, J. Brodkin, X. Jiang, I. McDonald, et al., *J. Med. Chem.* **2003**, *46*, 204–206.
[10] K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49.
[11] O. Vechorkin, D. Barmaz, V. Proust, X. Hu, *J. Am. Chem. Soc.* **2009**, *131*, 12078–12079.
[12] F. Bohlmann, H. Schönowsky, E. Inhoffen, G. Grau, *Chem. Ber.* **1964**, *97*, 794–800.