

Solvent-free reactions of alkynes in ball mills: It is definitely more than mixing*

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Abstract: This contribution presents two solvent-free reactions of terminal alkynes in ball mills: Pd-catalyzed Sonogashira cross-coupling and Cu-catalyzed homo-coupling (Glaser reaction). The results are compared to other solvent-free reaction protocols, which have been published up to date for those types of reactions. Reactions are assessed on the basis of reaction variables like type of catalyst and base or reaction time. Furthermore, performance-based parameters (yield, selectivity, turnover number, TON, and turnover frequency, TOF) are considered and evaluated. Findings from ball-milling experiments indicate that those processes are comparable to the energy entry by microwave irradiation with respect to reaction time and TOF.

Keywords: alternative energy entry; copper; Glaser reaction; metal catalysis; palladium; Sonogashira reaction.

INTRODUCTION

The omission of solvents or the reduction of solvent intensity in chemical reactions is one of myriad possibilities to decrease the *E*- or *Sheldon*-factor for chemical syntheses and thus improve the “greenness” of a chemical process [1]. It is generally understood that reactions performed in the absence of a classical, volatile, or hazardous organic solvent(s) are classified as *solvent-free* or *-less* reactions. This categorization seems to be arbitrary, because it often includes reactions conducted either in neoteric solvents or in the reactant(s) itself [2–5]. Following the definition of Tanaka and Toda [4], solvent-free reactions are solely those transformations carried out between solid reactants and thus are also called *solid-state* chemical transformations [4,6–8]. From the general viewpoint of organic synthesis, solvent-free reactions indicate those reaction protocols which are carried out in the absence of solvents, either in neat or in the solid state [8].

Despite this classification, solvent-free reactions can be initiated by different methods of energy entry. Starting with classical heating devices in combination with mechanical mixing to the application of microwave apparatus or the employment of cavitation phenomena (acoustic or hydrodynamic), the range of possibilities for the case of liquid-phase reactions is very wide. Using reacting reagents in the (quasi) solid state, another method has become popular within the last decade: comminuting in laboratory ball mills [7,9]. This technique is practically the advancement of grindstone chemistry, allowing for reproducible reaction conditions and for the definite control of reaction variables (energy entry, degree of mixing, reaction time).

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The present investigation describes the performance of metal-catalyzed reactions of alkynes in ball mills. Using the Sonogashira cross-coupling [10] and the homo-coupling of terminal alkynes (Glaser reaction) as the reaction models, the performance of ball-milling technique is compared with other methods of energy entry. The prerequisite for the reactions selected is their solvent-free accomplishment, without the limitations that through work-up solvents are required for isolation and analysis. Besides yield and selectivity, performance-based parameters are considered assessing the different solvent-free reaction protocols.

EXPERIMENTAL

Sonogashira reaction

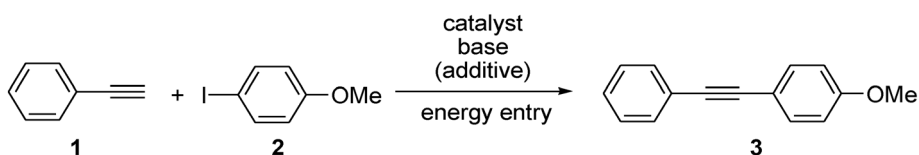
The grinding beakers (45 ml; agate or ZrO_2) were equipped with 6 milling balls of the same material ($d = 15$ mm). Afterwards, fused quartz sand (5 g), phenylacetylene (**1**; 2.5 mmol, 255 mg), 1,4-diazabicyclo[2.2.2]octane (= DABCO; 2.5 mmol, 280 mg), *p*-iodoanisole (**2**; 2 mmol, 468 mg), and $Pd(OAc)_2$ (5 mol %, 25 mg) were added in the given order. Milling was carried out at a rotation frequency v_{rot} of 13.3 Hz for 20 min using the planetary ball mill Fritsch Pulverisette 7 classic line. After cooling of the grinding beakers to room temperature, the crude products were extracted on a frit with a thin silica layer using chloroform (3×10 ml). The solvent was evaporated in vacuo, the crude product was dried, re-dissolved in 1.5 ml of chloroform, and analyzed by gas chromatography-flame ionization detection (GC-FID) and GC-MS. Analytical samples for NMR investigations were isolated by column chromatography using *n*-hexane/toluene mixtures. The reaction afforded the product in 65 and 57 % GC and isolated yield, respectively. Spectroscopic analyses (1H , ^{13}C) are in agreement with those reported in literature.

Glaser reaction

The grinding beakers (35 ml; ZrO_2) were equipped with 12 milling balls of the same material ($d = 10$ mm). $KF \cdot Al_2O_3$ (32 wt % KF; 4 g), phenylacetylene (**1**; 2 mmol, 204 mg), DABCO (2.5 mmol, 280 mg), and CuI (5 mol %, 18 mg) were added in the given order. Milling was accomplished with an oscillation frequency v_{osc} of 30 Hz for 10 min using the mixer mill *Retsch MM301*. After cooling to room temperature, the crude product was extracted on a frit with a thin silica layer using chloroform (3×10 ml). The solvent was evaporated in vacuo, the crude product was dried and analyzed by GC-FID and GC-MS. Analytical samples for NMR investigations were isolated by column chromatography using *n*-hexane/toluene mixtures. Reaction afforded the product in 96 % GC and 93 % isolated yield. Spectroscopic analyses (1H , ^{13}C) are in agreement with those reported in the literature.

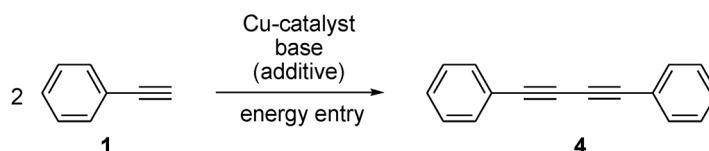
RESULTS AND DISCUSSION

Two types of metal-catalyzed reactions of alkynes have been chosen to assess different reaction protocols omitting the solvent during the reaction step. In all cases, solvent is applied for isolation and analysis of the reaction products. However, these amounts will not be considered in the present assessment, but they should be considered if the reactions are scaled up or evaluated in a kind of life-cycle assessment. On the one side, a $C(sp)-C(aryl)$ cross-coupling (Sonogashira reaction) between phenylacetylene (**1**) and *p*-iodoanisole (**2**) affording *p*-(phenylethynyl)anisole (**3**; Scheme 1) was investigated. Solvent-free protocols incorporating either Pd [10–14], Cu [15,16,] or Ni catalysts [17] have been reported, whereby the Pd-mediated reactions employ in some cases Cu compounds as co-catalyst [13,17].



Scheme 1 Sonogashira reaction of phenylacetylene (**1**) and *p*-iodoanisole (**3**).

On the other side, the Cu-catalyzed homo-coupling of **1** affording 1,4-diphenylbuta-1,3-diyne (**4**; Glaser reaction) has been chosen as a model reaction to assess the different methods of energy entry (Scheme 2). Solvent-free reaction protocols published so far for this type of reaction are catalyzed by both Cu(I) and Cu(II) compounds [18–21]. Furthermore, Bandini et al. proposed a solvent-free Glaser-type reaction catalyzed by an immobilized Pd complex in the presence of *p*-iodophenol for re-oxidation of the Pd in the reaction cycle [14].



Scheme 2 Glaser reaction of phenylacetylene (**1**) to 1,4-diphenylbuta-1,3-diyne (**4**).

Reactions in ball mills

Metal-catalyzed reactions in ball mills are so far restricted to Suzuki–Miyaura and Mizoroki–Heck cross-coupling reactions [9,22–24]. Recently, Fulmer et al. and Thorwirth et al. reported the successful performance of the air-sensitive Sonogashira reaction in a vibration ball mill and a planetary ball mill, respectively [10,13]. The difference between these two proposals are the reaction conditions applied. In the former case, Pd(PPh₃)₄, Cu(I), and potassium carbonate have been used as catalyst, co-catalyst, and base, respectively. Ball milling of the reactants for 17 h afforded **3** in 86 % isolated yield. Authors have demonstrated by employing phenylacetylene as the alkyne that the co-catalyst may be replaced by milling balls and beakers custom-made from Cu [13]. As described in the experimental section and in [10] the application of a planetary ball mill significantly reduces the reaction time to 20 min, affording **3** in 57 % isolated yield. The reaction was performed in the presence of DABCO, Pd(OAc)₂, and quartz sand as base, catalyst, and milling auxiliary*, respectively. The addition of Cu leads to a significantly reduced product selectivity compared to 98 % for the Cu-free procedure. Furthermore, the authors have demonstrated that the Pd-salt can be exchanged by PdCl₂ or Pd(PPh₃)₄ without a negative effect on yield or selectivity [10]. Both procedures proved their versatility in terms of alkyne and aryl halide.

Extended analysis of the side products in the case of the Sonogashira reaction (Scheme 1) in the presence of Cu and Pd [10] led to the identification of noticeable amounts of homo-coupling product **4**. Modification of the reaction conditions and total replacement of Pd(OAc)₂ by Cu(I) allowed for the synthesis of **4** from **1** in 93 % isolated yield (Scheme 2). The proposed experimental protocol is the first reaction protocol for a Cu-catalyzed reaction in a ball mill**. This solvent-free Glaser reaction furnishes **4** with >99 % selectivity. Although the type of planetary ball mill has been exchanged, the reac-

*The milling auxiliary helps solidify liquid reactants by surface absorption, making them accessible to energy transfer by the milling process.

Meanwhile, Cu-catalyzed azide-alkyne cycloaddition in a ball mill has been published: R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild, U. S. Schubert. *Chem. Commun.* **47, 4370 (2011).

tion time is still 10 min only. Cu(I), DABCO, and KF-Al₂O₃ with a KF-content of $w = 32$ wt % have been applied as catalyst, base, and milling auxiliary. Both the cross- and homo-coupling reactions are performed under aerobic conditions without the need for additional ligands or solvents during the reaction.

Reaction parameters

Tables 1 and 2 summarize the reaction conditions and reaction parameters for solvent-free Sonogashira cross- and Glaser homo-coupling reactions, respectively. The data reveal that for the cross-coupling reaction PdCl₂(PPh₃)₂ and high-performance Pd EnCatTM 40 outperform the other catalysts with respect to turnover frequency (TOF; Table 1). The latter especially needs low catalyst loading and furnishes the product in 90 % yield within reasonable time [12]. Apart from the TOF, all reactions afford the cross-coupling product in 58 to 92 % yield, independently from the metal and the method for energy entry. Comparison of the application of different metals as catalyst reveals a clear decrease in reactivity: Pd >> Cu > Ni. For the less active metals, the addition of *N*-mono- (**5**) or bi-dentate ligands (**6**; Scheme 3) [15,16] or PPh₃ [17] is necessary to yield reasonable amounts of the product.

Table 1 Comparison of reaction conditions for solvent-free Sonogashira reaction between phenylacetylene (**1**) and *p*-iodoanisole (**2**; Scheme 1).^a

Reference	Condition	Catalyst	Base	Additive	Time (h)	Yield 3 (%)	TON	TOF (h ⁻¹)
[10] – this work	Ball milling	Pd(OAc) ₂	DABCO	Quartz sand ^b	0.33	58	12	35
[11]	Stirring (N ₂)	PdCl ₂ (PPh ₃) ₂	TBAF	–	0.50	92	30	61
[12]	Stirring	Pd EnCat TM 40	Pyrrolidone	–	3	90	900	300
[13]	Ball milling	Pd(PPh ₃) ₄	K ₂ CO ₃	Cu(I)	17	86	34	2.0
[15]	Stirring	Cu(OAc) ₂	TBAF	5	20	83	8	0.42
[16]	Stirring	Cu(OAc) ₂	TBAF	6	14	86	9	0.61
[17]	Microwave	Ni-powder	KF-Al ₂ O ₃	Cu(I) + PPh ₃	0.15	73	3	19

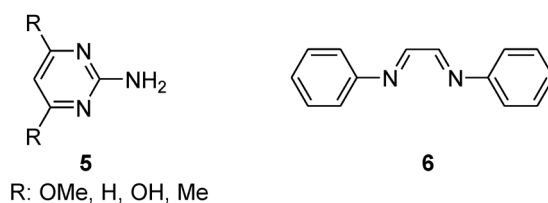
^aDABCO = 1,4-diazabicyclo[2.2.2]octane, TBAF = tetrabutylammonium fluoride, **5** = 4,6-dimethoxypyrimidin-2-amine, **6** = 1,4-diphenyl-1,4-diazabuta-1,3-diene.

^bQuartz sand was employed as milling auxiliary and is not incorporated in the reaction.

Table 2 Comparison of reaction conditions for solvent free homo-coupling reactions of phenylacetylene (**1**; Scheme 2).

Reference	Condition	Catalyst	Base	Additive	Time (h)	Yield 4 (%)	TON	TOF (h ⁻¹)
[14]	Stirring	[Pd] ^a	Et ₃ N	^a	12	84	84	7.0
[18]	Microwave	CuCl ₂	KF-Al ₂ O ₃	–	0.13	75	0.20	1.6
[19]	Microwave	CuI	Morpholine	Al ₂ O ₃	0.17	82	16	96
[20]	Stirring	Cu(OAc) ₂	Morpholine	KF-Al ₂ O ₃	3	96	5	1.6
[21]	Stirring	CuCl ₂	Et ₃ N	–	6	96	32	5.3
This work	Ball milling	CuI	DABCO	KF-Al ₂ O ₃	0.17	96	19	113

^aAn immobilized Pd complex was used as catalyst. Reaction was only successful in presence of 2 equiv *p*-iodophenol.



Scheme 3 Ligands applied in Cu-catalyzed Sonogashira reactions [15,16].

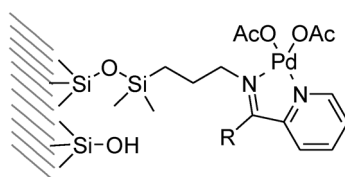
The procedures for the solvent-free Sonogashira reaction can be operated in most cases without a co-catalyst [10–12,15,16]. Only in case of the Ni-catalyzed reaction [17] and for the ball-milling procedure employing an inorganic base [13] the addition of CuI is necessary, whereas in the last case co-catalyst (CuI) could be substituted by milling balls and beakers made from Cu. Due to high energy impact during grinding, Cu is released from the surfaces and is made available for reaction. The ball-milling procedures are especially interesting to compare: on the one side, the active Pd-0 catalyst $\text{Pd}(\text{PPh}_3)_4$ is combined with a less active base (potassium carbonate) [13] and on the other side the reactivity is exchanged by applying plain $\text{Pd}(\text{OAc})_2$ in combination with an amine-base (DABCO) [10]. The capability of this bicyclic diamine is demonstrated also by a metal-free reaction procedure employing DABCO as base [25]. Interestingly, the optimal ratios between base and substrate are similar to those reported for the ball-milling procedure [10,25]. Consideration of the reaction time and thus the TOF for the model reaction favors the later ball-milling arrangement. The method of energy entry (stirring, microwave, ball milling) shows no significant effect on the TOF. However, the reaction time can be reduced significantly by applying microwave irradiation or ball milling in a planetary ball mill. With respect to this, another important fact has to be considered: the state of aggregation of the reaction mixtures. For both types of ball mills, a strongly heterogeneous mixture is present [10,13], whereas in the case of liquid-base pyrrolidone a solution probably exists [12]. This could also account for the high TOF due to low catalyst loading. At least in this case the definition of solvent-free reaction conditions is questionable [2,8,26], since the reactants are homogeneously dispersed in the solvent pyrrolidone.

Beside those solvent-free Sonogashira cross-couplings of aryl halides with terminal alkynes discussed above (Scheme 1), the Pd-catalyzed solvent-free reaction of acyl chlorides with terminal alkynes has been described in the literature also [27,28]. Equimolar amount of NEt_3 and 0.2 mol % $\text{Pd}(\text{OAc})_2$ are employed as base and catalyst, respectively, and the reaction yielded ynones in 40–98 % yield within 10 min. In the presence of secondary amines a sequential Michael addition furnished β -enammones in reasonable yields. Reactions are carried out in neat substances by stirring the reactants at room temperature.

Hitherto existing solvent-free reaction procedures for Glaser homo-coupling of **1** furnishing **4** (Scheme 2) are summarized in Table 2. Furthermore, solid-state homo-coupling of propargylic alcohols in the presence of a $\text{CuCl}_2 \times \text{pyridine}$ complex has been described gaining access to several symmetrical hexa-2,4-diyne-1,6-diols [29]. Except for [14], all reactions employ Cu as catalysts either in its cupric or cuprous compounds [18–21], whereas the last ones are distinctly more reactive manifested in the lower catalyst loading and the higher TOF of 96 and 113 h^{-1} . The bases applied for the deprotonation of **1** are another difference. Cyclic amines like morpholine and DABCO are distinctly more prone to abstract the hydrogen than NEt_3 or $\text{KF-Al}_2\text{O}_3$ [10,25]. In the case of the ball-milling procedure presented, KF-loaded Al_2O_3 was employed as milling auxiliary. Blind tests without the amine base following the above-mentioned protocol yielded **4** in 42 % isolated yield, approving the activity proposed by Kabalka et al. [18]. Thus, a cooperative effect of DABCO and $\text{KF-Al}_2\text{O}_3$ account for the high TOF in the heterogeneous ball-milling reaction. Interestingly, comminuting the reactants and heating of the reactants in the microwave field for an adequate period of time result in a similar yield and TOF [19]. This is also demonstrated for solvent-free cross-coupling procedures summarized in Table 1. At least for these reaction types and for Suzuki–Miyaura cross-coupling [30], grinding processes seem to be an

interesting tool as powerful as the irradiation of reaction mixtures with microwaves. Furthermore, from the viewpoint of energy efficiency ball milling seems to be superior compared to dielectric heating, proved for Suzuki–Miyaura reaction [30], Knoevenagel condensation [31], and the oxidative homo-coupling of anilines to azo dyes [32].

Two of the six procedures summarized in Table 2 employ the liquid-base NEt_3 for deprotonation and trapping of the proton [14,21]. In the case of the Pd-catalyzed reaction [14], it has to be mentioned that a supported Pd complex is employed as the catalyst (Scheme 4). The Glaser-type homo-coupling of **1** could only be realized in the presence of electron-rich aryl halides such as *p*-iodophenol. In their absence, no reaction occurred at all or the selectivities between cross- and homo-coupling product were equal. A twofold excess of *p*-iodophenol furnishes 1,4-diphenylbuta-1,3-diyne in 84 % yield and the product selectivity was 50:1 disfavoring the Sonogashira reaction. Authors propose that the iodophenol reoxidizes the Pd to the reactive Pd(II) complex during the reaction. However, reduction products of the haloarenes have not been identified [14]. In contrast, the Cu-catalyzed reactions are performed under aerobic conditions [18–21]. Thus, air oxygen is responsible for reoxidation of the catalyst in the reaction cycle [33].



Scheme 4 Pd catalyst for solvent-free Glaser reaction (R = H, Me) [14].

CONCLUSION

Two solvent-free reactions of alkynes in ball mills are presented. Results are compared with other methods of energy entry, which have been published until today for solvent-free accomplishment of the respective reactions. Whereas in the case of Sonogashira cross-coupling reaction, comminuting in a planetary ball mill results in medium yield after 20 min, phenylacetylene is almost completely converted to the homo-coupling product (Glaser reaction) within 10 min. Both reactions made use of DABCO as base and are catalyzed by plain $\text{Pd}(\text{OAc})_2$ or $\text{Cu}(\text{I})$, respectively. For both model reactions the product selectivity was very high. Comparison to other methods of energy entry revealed that ball milling is as powerful as irradiation by microwave if the reaction conditions (catalyst, base) are comparable. Reactions carried out in ball mills are characterized by a high mixing efficiency. Thus, the dispersion of the reactants of the heterogeneous starting mixture is high and the possibility for reactive contacts is significantly increased compared to mechanical mixing by a stirring bar.

However, assessment of the different solvent-free reaction protocols is difficult, since in some cases most of the reactants are liquid. Those reaction protocols are rather more comparable to solvent-based experiments than to heterogeneous reactions in the solid state. From this point of view, a harmonized definition of solvent-free or -less processes is needed for an assessment and categorization of reactions performed in the absence of solvents.

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