

### Solid-State Reactions

### Hydroamination Reactions of Alkynes with ortho-Substituted Anilines in Ball Mills: Synthesis of Benzannulated N-Heterocycles by a Cascade Reaction

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Abstract: It was demonstrated that ortho-substituted anilines are prone to undergo hydroamination reactions with diethyl acetylenedicarboxylate in a planetary ball mill. A sequential coupling of the intermolecular hydroamination reaction with intramolecular ring closure was utilized for the syntheses of benzooxazines, quinoxalines, and benzothiazines from readily available building blocks, that is, electrophilic alkynes and anilines with OH, NH, or SH groups in the

### Introduction

The reactions of primary or secondary amines with C-C double or triple bonds are known as hydroaminations and are one possibility for the construction of C-N bonds from readily available building blocks like alkenes or alkynes. Whereas the reaction of amines with asymmetric alkenes yields two isomeric amines from Markovnikov and anti-Markovnikov addition to the double bond, the situation is rather more complex in the case of alkynes as the reaction partner.<sup>[1]</sup> Not only does the regiochemistry of the amine addition to the triple bond have to be considered in the case of terminal or other asymmetrical alkynes, but the utilization of metal catalysts can also initiate the formation of imines, instead of enamines, by the reaction of primary amines (Scheme 1).<sup>[1,2]</sup> Depending on the nature of the alkynes, (E/Z)-enamines can originate from the hydroamination of them. Several catalysts have been disclosed that initiate the hydroamination of olefins and alkynes.<sup>[1–3]</sup>

With respect to advancement in the sustainability of hydroaminations, procedures have been introduced that avoid the utilization of solvents in the reaction stage. For the synthesis of ketimines, catalysts like Tl(OAc)<sub>3</sub>,<sup>[4]</sup> AuCl<sub>3</sub>,<sup>[5]</sup> Ru<sub>3</sub>(CO)<sub>12</sub>,<sup>[6]</sup> ([Au(PPh<sub>3</sub>)(CH<sub>3</sub>)]),<sup>[7]</sup> or anionic gold(I) complexes such as [AuS-Phos][NTf<sub>2</sub>] (SPhos: chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II); Tf: trifluoromethanesulfonyl) and [AuPPh<sub>3</sub>][NTf<sub>2</sub>],<sup>[8]</sup> as well as Cuand Ag-exchanged tungstophosphoric acid (TPA), have been tion in the solid state. Processing in a ball mill seemed to be advantageous over comminution with mortar and pestle with respect to process control. In the latter case, significant postreaction modification occurred during solid-state analysis. Cryogenic milling proved to have an adverse effect on the molecular transformation of the reagents.

ortho position. For the heterocycle formation, it was shown

that several stress conditions were able to initiate the reac-



Scheme 1. Possible products from addition of a primary amine to an alkyne.

described.<sup>[9]</sup> The highest activity of a catalyst for solvent-free hydroamination was reported by Mizushima et al. with 0.1 mol% of [Au(PPh<sub>3</sub>)(CH<sub>3</sub>)] and 0.5 mol% H<sub>3</sub>TPA: A turnover frequency of 3600  $h^{-1}$  was found for the reaction of *p*-bromoaniline and 4-methoxyethynylbenzene, and the reaction resulted in 90% yield.<sup>[7]</sup> An intermolecular/intramolecular double hydroamination sequence via imine intermediates was suitable for the solvent-free synthesis of a pyrrole derivative.<sup>[10]</sup> Utilization of Au nanoparticles immobilized on an ordered mesoporous organosilica network functionalized with thiol and sulfonate groups for anchoring of the Au as the catalyst for the reaction between hexa-1,5-diyne and aniline (2 equiv) yielded 87% of 2,5-dimethyl-1-phenyl-1H-pyrrole. A solvent-free tandem hydroamination-reduction sequence was proposed for the reaction of ethynyl arenes with aniline derivatives to yield N-aryloctan-2-amines (5 mol % AuCl<sub>3</sub> + 15 mol % AgOTf).<sup>[11]</sup>

The noncatalyzed synthesis of enamines by addition of amines to alkynes requires electron-deficient alkynes like propargylic esters or diesters of acetylenedicarboxylic acid. The reaction of anilines and secondary (cyclo)alkyl amines with those substrates in the solid state by using a ball mill<sup>[12]</sup> and silica as the milling auxiliary afforded the corresponding enamines in 80-96% yield after only 5 min of milling.<sup>[13]</sup> The reaction carried out by mixing the reagents in a flask at 40 °C afforded the product in only 66% yield, in comparison with 91% from the ball-mill procedure. It has also been demonstrated that simple

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mixing of electron-deficient alkynes with a spatula is sufficient for the preparation of enamines based on aniline(s), morpholine, *n*-PrNH<sub>2</sub>, or piperidine.<sup>[14]</sup> With respect to reproducibility, the advantages of ball milling over mixing the reaction with mortar and pestle have been described already.<sup>[15]</sup> Application of K<sub>2</sub>HPO<sub>4</sub> as the catalyst allowed the hydroamination of succinimide and phthalimide with similar electron-deficient alkynes.<sup>[16]</sup> Reaction times were 4 and 45 min for the microwaveassisted and classical heated procedures, respectively, whereas the yields ranged from 50–70%, independently of the procedure used.

The mentioned procedures have in common that the hydroamination of ortho-substituted anilines failed or has not been investigated at all. Inter- and intramolecular variants of those hydroaminations are important for the solvent-free synthesis of 1H-indoles. Indoles generally show a high biological activity because they are selective for many receptors,<sup>[17]</sup> play a role in the control of the day-night rhythm,<sup>[18]</sup> and are supposed to have anticarcinogenic properties.<sup>[19]</sup> Additionally, indole derivatives possess huge potential for technical applications like sensors, organic light-emitting diodes, and organic field-effect transistors.<sup>[18,20]</sup> Beside traditional synthetic methods, such as the Fischer<sup>[21]</sup> and Bischler indole syntheses,<sup>[22]</sup> the Larock indole synthesis has attracted particular attention in research throughout the past years.<sup>[23]</sup> In a retrosynthetic analysis, this particular synthesis can be subdivided into a Sonogashira reaction of o-haloanilines with terminal alkynes followed by an intramolecular cyclization of the resulting o-alkynylanilines (route 2 in Scheme 2). A second possibility for the synthesis of



**Scheme 2.** Retrosyntheses for 1*H*-indoles with the incorporation of hydroamination steps. ewg: electron-withdrawing group.

indoles is shown in route 1 in Scheme 2 as a combination of an intermolecular hydroamination followed by an intramolecular Heck cross-coupling. Both routes start with *o*-haloanilines, but the substitution pattern of the alkyne as the second building block differs. The Larock type synthesis utilizes terminal alkynes, whereas electrophilic alkynes (bearing electrop with drawing groups, for example, C(0) with B:

tron-withdrawing groups, for example, C(O)R with R: alkyl, hydroxy, or alkoxy) have to be applied for the uncatalyzed intermolecular hydroamination reactions.

Solvent-free variants of the second route incorporating protocols for the Sonogashira reaction<sup>[24]</sup> and the intramolecular hydroamination are well known in the literature.<sup>[5,25]</sup> Owing to the low activity of *o*-alkynylanilines with respect to the addition of the amine to the triple bond, catalysts like Pd–Cul,<sup>[25b]</sup> immobilized Pd complexes,<sup>[25c]</sup> [(dippe)Ni( $\mu$ -H)]<sub>2</sub> (dippe: 1,2-bis(diisopropylphosphinoethane)),<sup>[25d]</sup> or AuCl<sub>3</sub> have to be utilized.<sup>[5]</sup> A solvent-free ZnBr<sub>2</sub>-mediated version of such intramolecular hydroamination reactions that led to 2-substituted 1*H*-indoles in a ball mill has been disclosed recently.<sup>[26]</sup> Tullberg et al. reported a synthetic sequence for the construction of the 1*H*-indole network by starting with a solvent-free Heck cross-coupling of amino acid derivatives and aryl halides in a ball mill followed by a cyclization via the corresponding hydrazine derivatives (Fischer route) by refluxing in the presence of acetic acid anhydride.<sup>[27]</sup> In a continuation of our previous work on intermolecular hydroamination reactions in ball mills,<sup>[13]</sup> we would like to present our efforts for the reaction of various *ortho*-substituted anilines with electron-deficient alkynes in ball mills or under similar conditions.

### **Results and Discussion**

#### Hydroamination of ortho-substituted anilines

In order to evaluate the ball-milling technology for the synthesis of o-halo-N-vinylanilines (3) as the first step in the synthetic sequence outlined as route 1 in Scheme 2, o-iodoaniline (1 a) and diethyl acetylenedicarboxylate (2b) were comminuted under different conditions by using a planetary ball mill (Scheme 3). Basic experiments were conducted in milling beakers made from magnesia-stabilized zirconia (MSZ) with milling balls of the same material and in the presence of NaCl as a milling auxiliary that could be removed after the synthesis by aqueous workup. The results for the experiments with 1a are summarized in Table 1 (entries 1–9). Milling at rpm = 800 min<sup>-1</sup> in the absence of an additive and in an air atmosphere yielded 20% of 3a after 5 min without noticeable formation of side products. Utilization of an Ar atmosphere, a reduced energy density by decreasing the rotation frequency to 500 min<sup>-7</sup> (60 min<sup>-1</sup> = 1 Hz), and an increase in the reaction time to 4 h resulted in 90% yield. Replacement of NaCl by guartz sand in an Ar atmosphere resulted in 88% of 3a within 10 min. Although guartz sand is advantageous with regard to reactivity and yield, it is less favorable with respect to workup because solid-liquid extraction is required to recover adsorbed starting materials and products. In a comparison to previous studies on solvent-free intermolecular hydroamination,<sup>[13, 14, 16]</sup> it was possible to demonstrate the general applicability of ortho-substituted anilines for such reactions.

In addition, several metal salts were explored for their applicability to accelerate this solvent-free hydroamination.<sup>[1,2]</sup>



**Scheme 3.** Hydroamination studies in a planetary ball mill with *ortho*-substituted anilines. The R and R<sup>1</sup> groups are given in Table 1. MSZ: magnesia-stabilized zirconia.

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Table 1. Hydroamination studies in a planetary ball mill with *o*-substituted anilines (1, R: H) and diethyl acetylenedicarboxylate (2b; Scheme 3).<sup>[a]</sup>

| Entry                               | Substrate | Product | $R^1$            | Additive                   | t [min] | rpm [min <sup>-1</sup> ] | Yield [%] <sup>[b]</sup> |
|-------------------------------------|-----------|---------|------------------|----------------------------|---------|--------------------------|--------------------------|
| 1                                   | 1a        | 3 a     |                  | none                       | 5       | 800                      | 20                       |
| 2 <sup>[c]</sup>                    |           |         |                  | none                       | 240     | 500                      | 90                       |
| 3                                   |           |         |                  | 0.1 mmol ZnBr <sub>2</sub> | 30      | 600                      | 0                        |
| 4                                   |           |         |                  | 0.1 mmol ZnCl <sub>2</sub> | 30      | 600                      | 0                        |
| 5                                   |           |         |                  | 0.1 mmol TPA               | 15      | 800                      | 66                       |
| 6                                   |           |         |                  | 0.1 mmol Cu–TPA            | 30      | 600                      | 0                        |
| 7 <sup>[d]</sup>                    |           |         |                  | none                       | 10      | 800                      | 88                       |
| 8 <sup>[d]</sup>                    |           |         |                  | 0.1 mmol ZnCl <sub>2</sub> | 30      | 600                      | 58                       |
| 9 <sup>[d]</sup>                    |           |         |                  | 0.1 mmol TPA               | 15      | 800                      | 72                       |
| 10                                  | 1 b       | 3 b     | н                | none                       | 5       | 800                      | 89                       |
| 11 <sup>[d]</sup>                   |           |         |                  | none                       |         |                          | 99                       |
| 12                                  | 1c        | 3 c     | CI               | none                       | 30      | 600                      | 46                       |
| 13                                  |           |         |                  | none                       | 6       | 800                      | 38                       |
| 14                                  | 1 d       | 3 d     | Br               | none                       | 30      | 600                      | 15                       |
| 15                                  |           |         |                  | none                       | 6       | 800                      | 27                       |
| 16                                  | 1e        | 3 e     | m-Cl             | none                       | 10      | 800                      | >95                      |
| 17                                  | 1 f       | 3 f     | p-Cl             | none                       |         |                          | >95                      |
| 18                                  | 1 g       | 4 b     | OH               | none                       |         |                          | >95                      |
| 19 (mixer ball mill) <sup>[e]</sup> | 1g        | 4 a     | OH               | none                       | 5       | 900 ( <i>êf</i> =15 Hz)  | >95                      |
| 20 (mixer ball mill) <sup>[f]</sup> | 1 g       | 4 b     | OH               | none                       | 5       | 900 (≙ <i>f</i> =15 Hz)  | >95                      |
| 21                                  | 1 h       | 3 h     | Et               | none                       | 10      | 800                      | >95                      |
| 22                                  | 1i        | 3 i     | Ph               | none                       |         |                          | 77                       |
| 23                                  | 1j        | 3 j     | Ac               | none                       |         |                          | 21                       |
| 24                                  | 1 k       | 3 k     | OPh              | none                       |         |                          | 0                        |
| 25                                  | 11        | 31      | $NO_2$           | none                       |         |                          | 0                        |
| 26                                  | 1 m       | 3 m     | CN               | none                       |         |                          | 0                        |
| 27                                  | 1 n       | 3 n     | [ <sup>[g]</sup> | none                       |         |                          | _ <sup>[h]</sup>         |

[a] Reaction conditions unless otherwise stated: 1 (1 mmol), 2b (1 mmol), NaCl (5 g); planetary ball mill, MSZ beakers (V=45 mL) and MSZ milling balls (d=15 mm, n=6). [b] Analytical yield determined with GC-FID and GC-MSD (uncorrected). [c] In an Ar atmosphere. [d] Quartz sand (5 g) was used instead of NaCl. [e] Reaction conditions: 1g (2 mmol), 2a (2 mmol); beakers (stainless steel, V=50 mL) and milling balls (stainless steel, d=5 mm, n=15). [f] Reaction conditions: 1g (2 mmol), 2b (2 mmol); beakers (stainless steel, V=50 mL) and milling balls (stainless steel, d=5 mm, n=15). [f] Reaction conditions: 1g (2 mmol), 2b (2 mmol); beakers (stainless steel, V=50 mL) and milling balls (stainless steel, d=5 mm, n=15). [g] R: Tf; see Scheme 3. [h] Mixture of unprotected (3a) and triflated product 3n.

Lewis acid catalysts like  $ZnX_2$  (X: Cl, Br) or TPA-derived catalysts are well known for the reaction in solution,<sup>[28]</sup> and the suitability of the last class of compounds has already been proven for intermolecular hydroamination leading to imines in the absence of solvent.<sup>[9]</sup> For the ball-milling reaction, neither the addition of 10 mol% ZnBr<sub>2</sub> (Table 1, entry 3), ZnCl<sub>2</sub> (Table 1, entries 4 and 8), or TPA (Table 1, entries 5 and 9) nor the application of Cu-exchanged TPA (Table 1, entry 6) increased the yield relative to that of the noncatalyzed reaction, regardless of which type of milling auxiliary was applied.

Next, anilines with different substituents in the *ortho* position were tested in the reaction with **2b** (Table 1). The reaction of aniline **1b** with **2b** resulted in 89 or 99%, respectively, of the corresponding diethyl ester **3b** by using NaCl or quartz sand as the milling auxiliary (Table 1, entries 10 and 11). Application of *o*-chloro- (**1c**; Table 1, entry 12) and *o*-bromoaniline (**1d**; Table 1, entry 14) demonstrated the rapidly decreasing reactivity of the halides with regard to the hydroamination reaction with **2b**: **1a** (R<sup>1</sup>: I)  $\leq$  **1d** (R<sup>1</sup>: Br) < **1c** (R<sup>1</sup>: Cl). An increase of the rpm from 600 to 800 min<sup>-1</sup>, accompanied with a reduction of the reaction time to 6 min to avoid thermal stress, did not lead to considerable improvements (Table 1, entries 13 and 15). The decreased reactivity as a result of the high steric demand

in 1c is illustrated by the reactions with the corresponding m-(1e) and p-chloroanilines (1 f), which yielded > 95% of the Nvinyl derivatives, compared with a maximum of only 46% of the ortho isomer 3 c. Hydroamination of o-ethylaniline (1h) and 2-aminobiphenyl (1i) yielded the products in >95 and 77% yield, respectively. It should be pointed out that, for the reaction of anilines with a high nucleophilicity like 1b, o-toluidine (R<sup>1</sup>: Me), or 1h, spontaneous reactions were observed when the reagents were unified in a sample vial, mixed gently by shaking, and analyzed immediately. Contrarily, the presence of electronwithdrawing substituents in the ortho position, like acyl (1j), nitro (1 l), or cyano (1 m) groups, reduces the nucleophilicity of the amino group. Thus, the yields were considerably lower or no conversion was observed (Table 1, entries 23-26). The reaction of N-Tf-protected o-iodoaniline (1 n)<sup>[29]</sup> required a prolonged reaction time and led to a mixture of unprotected and triflated products (3a and 3n, respectively; Table 1, entry 27).

## Benzoxazine derivatives from *o*-aminophenol and dialkyl acetylenedicarboxylates

Comminution of *o*-aminophenol (**1g**) with **2b** in a planetary ball mill together with NaCl (5g) yielded benzoxazine (**4b**) rather than the corresponding *N*-vinylated product **3g** (Scheme 3; Table 1). No side products were detected. Milling of dimethyl acetylenedicarboxylate (**2a**) or **2b** and **1g** in a mixer ball mill without further auxiliaries yielded the corresponding alkyl esters **4a** and **4b**, respectively, as single products (Table 1, entries 19 and 20). From the literature, it is known that mixing of those reagents with a spatula on a Petri dish for less than 5 min leads to the same result.<sup>[14]</sup> Beside this solventfree protocol, synthesis can be carried out in MeOH at room temperature,<sup>[30]</sup> in refluxing EtOH,<sup>[31]</sup> or in ice-cold EtOH.<sup>[32]</sup> Compound **4a** is also available by cyclocondensation of **1g** with methyl 3-hydroxy-4-oxo-4-(phenylamino)but-2-enoate.<sup>[33]</sup>

The formation of 4a can be rationalized by a hydroamination starting with the nucleophilic attack of the amino group in 1gonto the electrophilic triple bond of 2a, which leads to dimethyl 2-(2-hydroxyphenylamino)but-2-enedioate (3g) as an intermediate (Scheme 4). In a subsequent transesterification,

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with release of one equivalent of MeOH, **4a** is formed almost quantitatively. A critical analysis of the mechanisms outlined in Scheme 4 is provided in the Supporting Information, with consideration of the formation of the alternative product **6a**, on the basis of IR and NMR spectroscopy analyses.



Scheme 4. Reaction of *o*-aminophenol (1 g) with dimethyl acetylenedicarboxylate (2 a) and tautomerization of 4a in protic solvents to form imine 7. HA: acid.

## Investigation of the reaction progress with attenuated total reflectance FTIR spectroscopy

Our results indicate that the formation of benzoxazines 4a and 4b is possible in the absence of a solvent. Analysis of the crude reaction mixture with attenuated total reflectance (ATR) FTIR spectroscopy (5 min milling) indicates complete conversion of the substrates to a single product. Dissolution of the reaction mixture in CDCl<sub>3</sub> or EtOAc and analysis by NMR spectroscopy and GC with flame ionization detection (GC-FID), respectively, did not reveal further products. The FTIR spectra of recrystallized products were almost superposable to those of the crude reaction mixture. However, a subsequent reaction during sample preparation by dissolution cannot be excluded, although the literature reports mainly water or alcohols as the preferred solvents.<sup>[34]</sup> The fact that simple mixing of the reagents on a Petri dish results in almost quantitative yields after only a few minutes<sup>[14]</sup> indicates that a fast and direct analysis is required for the product mixtures, ideally without pretreatment (like extraction). The use of ATR FTIR spectroscopy is one option because no sample workup is necessary and the time gap between sampling and measurement can be reduced to less than 40 s.

The FTIR spectra of the products from the reaction of **1g** and **2a** or **2b** contain several signals, which are suitable for semiquantitative analysis of the reaction progress. Figure 1A shows two different regions from the FTIR spectra recorded after different grinding times,  $t_g$  (1–20 min), during the comminution of **1g** and **2a** at room temperature (23 °C) with a porcelain mortar and pestle. In the present case, only those spectra recorded at the beginning of the reaction ( $t_g = 1$  min) and after  $t_g = 20$  min should be considered. Those spectra exemplify the beginning of the reaction (no conversion) and the end of the

reaction (conversion > 95%  $\doteq$  > 95% yield). As can be seen in the Supporting Information (Figure S1), the product is indicated by a strong signal at  $\tilde{v} = 1762 \text{ cm}^{-1}$  for the C=O stretching mode of the lactone, whereas the C=O stretching mode signal at  $\tilde{v} = 1720 \text{ cm}^{-1}$  is typical for the presence of the two ester

> groups in **2a**. An increase of the first and decrease of the latter with increasing reaction time is an unmistakable sign for the reaction progress (Figure 1 A). However, for semiquantitative analysis, the transmission from those signals alone might be misleading because material properties like powder density, humidity, and viscosity (release of MeOH during the reaction) influence the quality of the spectra. In order to monitor the reaction progress, the ratio of the transmission minima ( $T_{min}$ ) from the lactone C=O stretching mode and that of the absorption signal assigned to aromatic ring bending ( $\tilde{v} = 750 \text{ cm}^{-1}$ ) is calculated to give the dimensionless number  $A_v$  [Eq. (1)].

$$A_{\rm v} = \frac{A_{\rm max,C=Ostretching}}{A_{\rm max,ringbending}} = \frac{\left|\log(T_{\rm min,C=Ostretching})\right|}{\left|\log(T_{\rm min,ringbending})\right|} \tag{1}$$

Repetitive measurements of the sample after  $t_g$ = 20 min and calculation of  $A_v$  leads to a value of > 0.46, which indicates no further change in the amount of **4a**. A similar value was obtained for experiments in a ball mill. In combination with the absence of an absorption at  $\tilde{\nu}$ = 1720 cm<sup>-1</sup>, full conversion is indicated.<sup>[35]</sup>

Experiments in a mixer ball mill (MBM) and those in the literature show that the reaction itself is apparently very fast.<sup>[14]</sup> One might argue that the applied contact force induced by pressurizing the powdered sample over the ZnSe crystal of the ATR FTIR may induce a subsequent reaction. At least, the literature reports that similar experiments with a hydraulic press (preheated anvil, P = 19.6 MPa, Heck reaction) resulted in significantly lower yields than high-energy ball milling in a planetary ball mill.<sup>[36]</sup> A pressure-induced reaction cannot be excluded, which might interfere with the method for reaction monitoring. Thus, the reaction time ( $t_r$ ) should be the considered as the sum of the grinding or milling time ( $t_g$ ), the sample transfer time ( $t_{st}$ ), and the measurement time ( $t_m$ ), that is, the time on the ATR crystal [Eq. (2)].

$$t_{\rm r} = t_{\rm g} + t_{\rm st} + t_{\rm m} \tag{2}$$

With respect to the  $t_g$  (variable) and  $t_m$  (>1 min, see the Experimental Section) values, the  $t_{st}$  value can be reduced to 40 s from opening of the milling beakers to placement on the ATR crystal and the start of the measurement.<sup>[37]</sup> Figure 2A shows the reaction progress for the synthesis of **4a** (MBM), which follows an exponential curve (each data point in the MBM curve represents a single ball-milling experiment). In a second set of experiments, samples withdrawn from the ball-milled reaction mixture were pressurized on the ATR crystal and data recording was continued. The results indicate that, after measurement started, the reaction went on until approximately  $t_m$ = 7.5 min before reaching equilibrium with regard to the  $A_v$ 

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**Figure 1.** ATR FTIR spectra of the reaction products from comminution of **1g** (2 mmol) and **2a** (2 mmol) in a mortar with pestle (porcelain, room temperature). A) t = grinding time,  $t_g$ . B) 1 min grinding, then the ground mixture (100 mg) was placed on the ZnSe crystal of the ATR FTIR spectrometer; t = duration on the ZnSe crystal,  $t_m$  ( $t_m = 0$  min in B is equivalent to  $t_g = 1$  min in A). C) 5 min grinding, then the ground mixture (100 mg) was placed on the ZnSe crystal of the ATR FTIR spectrometer; t = duration on the ZnSe crystal,  $t_m$  ( $t_m = 0$  min in C is approximately equivalent to  $t_g = 5.5$  min in A). A colored version of this figure is part of the Supporting Information (Figure S2).

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values. The reaction progress of these subsequent reactions did not reach full conversion, and the final  $A_v$  values are 0.2 for MBM-1 (1 min grinding) and MBM-2 (2 min grinding) and 0.35 for MBM-3 (4 min grinding) within  $t_m = 30$  min. The increase of  $A_v$  values from the start of the measurement to equilibrium ( $\Delta A_v = 0.1$ ) is independent of the  $t_g$  value. This may be a result of diffusion limitations in the powder fixed at the sample holder. The reaction proceeds at the crystal boundaries of the preground and well-mixed reagents but cannot take place in the bulk powder. The reaction rates (r), as determined from Equation (3), for reactions in the ball mill and the subsequent

reactions after 1, 2, and 4 min pregrinding are 0.0950, 0.0094, 0.0102, and 0.0191 min<sup>-1</sup>, respectively (Table 2).

$$r = \frac{\Delta A_{v,\text{linear}}}{\Delta t_{i,\text{linear}}} = \frac{A_v(t_{i,2}) - A_v(t_{i,1})}{t_{i,2} - t_{i,1}}$$
(3)

Intense mixing and constant restoration of the active surfaces in the ball mill are responsible for the high rate. The elaborated particle refinement after 4 min pregrinding (MBM-3) result-

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**Figure 2.** Reaction progress for the reaction of **1 g** (2 mmol) and **2 a** (2 mmol) under different reaction conditions measured with ATR FTIR spectroscopy: A) with respect to the overall reaction time,  $t_r$  ([Eq. (2)]; see Table 2); B) with respect to the measurement time,  $t_m$  (see Table 2).

| <b>Table 2.</b> Effect of the measurement time $t_m$ on the reaction progress |
|---|
| during measurement of crude samples from the reaction of 1g and 2a            |
| under different reaction conditions measured with ATR FTIR spectrosco-        |
| py. <sup>[a]</sup>  |

|  | Conditions before placement<br>on ATR crystal                            | A <sub>v,0</sub> | $t_{i,1}/t_{i,2}$<br>[min] <sup>[a]</sup> | $\Delta A_{v}/\Delta t_{i}$<br>$[min^{-1}]^{[a]}$ |  |  |
|--|--|------------------|---|---|--|--|
| grinding   | grinding in mixer ball mill at $f=15$ Hz (see Figure 2A)                 |                  |   |   |  |  |
| MBM  |  | 0.09             | -   | 0.0950  |  |  |
| MBM-1  | $t_{g} = 1 \min$   | 0.15             | 0/6.5                                     | 0.0094  |  |  |
| MBM-2  | $t_g = 2 \min$   | 0.14             | 0/6.5                                     | 0.0102  |  |  |
| MBM-3  | $t_g = 4 \min$   | 0.26             | 0/4.0                                     | 0.0191  |  |  |
| grinding   | with mortar and pestle (see Figure                                       | 3)               |   |   |  |  |
| MP   |  | 0.07             | -   | 0.0229  |  |  |
| MP-1   | $t_{g} = 1 \min^{(b)}$   | 0.09             | 2.5/12.5                                  | 0.0254  |  |  |
| MP-2   | $t_q = 3 \min$   | 0.16             | 0/12.5                                    | 0.0182  |  |  |
| MP-3   | $t_q = 5 \min^{[c]}$   | 0.15             | 0/5.0                                     | 0.0527  |  |  |
| MP-4   | $t_g = 7 \min$   | 0.54             | 0/2.5                                     | < 0.0074  |  |  |
| other conditions (see Figure 2B)   |  |                  |   |   |  |  |
| SP   | mixing with spatula for 1 min  | 0.18             | 0/6.0                                     | 0.0132  |  |  |
| RC   | as MBM-3 with recrystallization from $CHCI_3$                            | 0.43             | 0/30                                      | < 0.0018  |  |  |
| VBM  | grinding in a vibration ball mill with KBr $(t_g = 2 \text{ min})^{[d]}$ | 0.11             | 0/5.0                                     | 0.0170  |  |  |
| [a] In accordance with Equation (3). [b] See Figure 1B. [c] See Figure 1C. [d] $1g + 2a/KBr = 0.2 g/1 g$ . |  |                  |   |   |  |  |

ed in smaller particles, which leads to doubling of the reaction rate relative to those of samples MBM-1 and -2.

Figure 2B displays the dependence of the  $A_v$  values on the measurement time for different powder treatment methods. Mixing of compounds 1g and 2a with a spatula in a small beaker (SP),<sup>[14]</sup> 1 min treatment in a mortar with a pestle (MP-1), and cogrinding of the reagents together with KBr in a vibration ball mill (VBM)<sup>[38]</sup> resulted in similar  $A_{v,0}$  values to those observed for MBM-1 (Table 2). This indicates a similar reaction progress before placement on the ATR crystal ( $t_m = 0$  min). Recrystallization (CHCl<sub>3</sub>) of the product from MBM-3 did not affect the  $A_v$  value (RC); thus, a subsequent reaction in solution can be excluded for those samples reaching  $A_v > 0.46$  (full conversion). The behavior of the MBM-1, SP, and VBM reactions during measurements is similar and results in equilibrium values of  $A_v = 0.20 - 0.25$  after  $t_m = 7.5$  min (0.0094-0.017 min<sup>-1</sup>). Contrarily, samples generated by mixing in a mortar with a pestle for 1 min (MP-1) revealed a slow but steady increase to reach  $A_v = 0.390$  after 15 min (0.0254 min<sup>-1</sup>). Apparently, energy entry due to friction, instead of mainly impact (MBM, VBM), leads to a homogeneous activation of the reagents that allows a reaction despite the diffusion limitations in the solid state. Additionally, during ball milling of the samples with high ball-to-powder-ratios, partial liquefaction took place. Spontaneous recrystallization after stopping the energy entry yields a less homogeneous powder, which disfavors subsequent reaction on the ATR crystal. Pregrinding of 1g and 2a with a mortar and pestle with  $t_q = 1$ , 3, 5, and 7 min led to increasing  $A_{v,0}$  values (Table 2). The MP reaction reaches  $A_v$  values of > 0.390 after 15 min, whereas sample MP-4 ( $t_a =$  7 min) remained unchanged, which resulted in a low reaction rate (Figure 3 A). The high  $A_v$  value of > 0.53 (Table 2) is due to severe volatilization of the MeOH of the sample, whereas the alcohol is part of the reaction mixture in all of the other cases. The rate constants for the samples treated with mortar and pestle are similar (0.0182-0.0254 min<sup>-1</sup>), with the exceptions of MP-3 and MP-4. Consideration of the  $t_{q}$ ,  $t_{st}$ , and  $t_{m}$  values [Eq. 2] for samples MP and MP-1 to MP-3 indicates a high overlap of the reaction progress at similar  $t_r$  values (Figure 3B).

The conclusion can be drawn that mixing the reagents with mortar and pestle yielded reaction mixtures that, upon pressurization, willingly react with the same rate constant to completion. In the case of other grinding and/or mixing methods, subsequent reaction during ATR measurement resulted in equilibrium values that were different from full conversion. Thus, for the investigation of the reaction progress in the case of fast solvent-free reactions, it has to be ensured that the sample preparation time and measurement time are restricted to a minimum. Also, solvent-based workup procedures and analytical methods for the assessment of reaction progress and/ or purity should be avoided because of possible subsequent reaction during solvation or in solution.

#### Investigation of reaction conditions

The influence of the oscillation frequency was investigated with the synthesis of **4a** (Scheme 3) as a model reaction. For

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**Figure 3.** Reaction progress for the reaction of **1 g** (2 mmol) and **2 a** (2 mmol) by using a mortar and pestle measured with ATR FTIR spectroscopy: A) with respect to the measurement time,  $t_m$  (see Table 2); B) with respect to the overall reaction time,  $t_r$  ([Eq. (2)]; see Table 2).

the influence of the reaction time, see Figure 2A (MBM conditions). An increase of the oscillation frequency from 15 to 20, 25, or 30 Hz indicated that further reduction of the milling time to < 5 min was not possible, because the ratio of side reactions increased considerably. Thus, a milling time of 5 min and a frequency of 15 Hz were chosen for further experiments.

One option to avoid partial liquefaction of the reagents during ball milling is reduction of the energy intensity by either reducing the oscillation frequency or by working in a cyclized mode with milling pauses. Both options are inapplicable because of inefficient mixing at  $f < 15 \text{ Hz}^{[15]}$  and the already short reaction times of 5 min. The third option is cryogenic milling. For this purpose, stainless steel milling beakers are filled with milling balls and the reagents and are cooled down to -78°C with solid CO<sub>2</sub>. After milling of the reaction mixture for 5 min at 15 Hz, the reaction progress was measured and  $A_v$ values of 0.050 and 0.078 were immediately obtained for the reaction of 2a and 2b, respectively, with 1g. Obviously, no reaction occurred at the reaction temperatures, which had risen to -17 and -10 °C. Presumably, the low reaction rate due to "frozen" molecular movement is responsible for this observation. Similar to studies on cryogenic homocoupling of phenylacetylene in a planetary ball mill,<sup>[39]</sup> the reaction proceeds as soon as defrosting of the reaction mixture starts and powder temperatures of 3 (2a) or 19°C (2b) are reached (Figure 4). The difference in reaction initiation summarized in Figure 4 for the methyl (4a) and ethyl derivatives (4b) may be due to the



reaction progress [-]

0.1

0.0

-20

-10

uropean Journal

<u></u> 4a

<del>- X -</del> 4b

30

20

powder temperature, T [°C] **Figure 4.** Reaction progress for reaction mixtures after cryomilling. Reaction conditions: **1 g** (2 mmol), alkyne (**2 a** or **2 b**; 2 mmol), mixer ball mill, milling beakers (stainless steel, V=50 mL), milling balls (stainless steel,  $d_{MB}$ =5 mm,

 $n_{\rm MB}$  = 14), 15 Hz,  $t_{\rm m}$  = 5 min; precooled to -78 °C prior to milling.

0

10

higher reactivity of **2a** in comparison to **2b**. The temperature increase after milling depends linearly on the defrosting time  $(t_{df})$ . Reactions reach completion after 20 and 45 min with reaction rates [Eq. (3)] of 0.036 and 0.0192 min<sup>-1</sup>, respectively. A comparison with the rate for milling of **2a** and **1g** from room temperature (0.0950 min<sup>-1</sup>; Table 2) indicates the retarding effect of the powder temperature on the rate constant of the reaction. In contrast to these conditions, the MBM-1 to MBM-3 reactions reach completion despite the diffusion limitation in the solid state.

## Structure flexibility for the reaction of *o*-aminophenols with electrophilic alkynes

Table 3 summarizes the data for the reaction of different o-aminophenol derivatives (1g, 8-12) with alkynes 2a and 2b. The reported yields are yields of the isolated recovered product directly after the milling process without further workup (mass yield). The purity of the products and the completeness of the reactions were checked by immediate ATR FTIR spectroscopy measurements. Relative to the results of the protocol described by Choudhary and Peddinti (Petri dish),<sup>[14]</sup> the yields are lower. This can be attributed to the fact that product isolation from the milling beakers and milling balls is complex at such a small reaction scale. Thus, the lower yields are rather a sign of the nonoptimized isolation procedure than of a disadvantage of the method itself. The higher yields from reactions with 2b compared with those resulting from 2a are due to the higher crystallinity of the products. The reaction of 2amino-5-nitrophenol with both 2a and 2b failed under the gentle milling conditions (f=15 Hz, t=5 min). An increase of the oscillation frequency to f=30 Hz and elongation of the reaction time to 20 min did not allow the yield to be increased.

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uct. [c] With addition of PPh<sub>3</sub> (2 mmol), f=30 Hz, t=60 min.

The reaction of **1g** with 3-phenylpropiolate (**2c**) failed under the aforementioned milling conditions. Due to the lower electrophilicity of **2c** relative to **2a** and **2b**, one equivalent of PPh<sub>3</sub> has to be applied as mediating reagent. Under harsh conditions (f=30 Hz, t=60 min), the corresponding product could be isolated in 79% yield. The product adopts an imine confirmation comparable to that of **7** in Scheme 4.<sup>[40]</sup> This is the first example for such a synthesis under solvent-free conditions with a ball mill. Other procedures comprise reactions in toluene heated to reflux with two equivalents of **2a** and PPh<sub>3</sub><sup>[40a]</sup> and the reaction of equimolar amounts of the reagents in dichloromethane at -10 °C for 24 h.<sup>[40b]</sup>

#### Synthesis of quinoxaline derivatives

Comminution of *o*-phenylenediamine (**19**) with **2a** or **2b** under standard reaction conditions in a mixer ball mill afforded the corresponding quinoxalines in 91 and 93% yields after isolation (Scheme 5). Similarly to the formation of benzoxazines from *o*-aminophenols (**1g**, **8–12**; Table 3), products **20a** and **20b** prefer to adopt a *Z* configuration due to the presence of hydrogen bonding between the NH group and the ester carbonyl group. In comparison with other methods available for the synthesis of **20** (in accordance with Scheme 5),<sup>[30a-c,31,34,41]</sup> the present method and also other solvent-free methods are fast and reduce the reaction time to less than 10 min.<sup>[14,42]</sup> A solvent-free reaction in the presence of Yb(OTf)<sub>3</sub> resulted in similar yields but double the reaction time was required.<sup>[43]</sup>

Other solvent-free reactions that start with **19** incorporate condensation steps for the formation of the heterocycle.<sup>[44]</sup> The reaction with diethyl bromomalonate resulted in ethyl 3hydroxyquinoxaline-2-carboxylates (6–8 h under vacuum),<sup>[45]</sup> whereas condensation with  $\alpha$ -ketoacids yielded 3-substituted



Scheme 5. Synthesis of quinoxaline derivatives from *o*-phenylenediamine (19; 2 mmol) and 2 (2 mmol) in a mixer ball mill (beakers: V = 50 mL; balls: d = 5 mm, n = 15).

quinoxalin-2-(1*H*)-ones in 70–91% yield after microwave irradiation for 3–13 min.<sup>[46]</sup> Thus, the ball-milling method is not only a fast and robust variant but also results in substitution patterns that are not yet available by other solvent-free methods.

#### Synthesis of benzothiazine derivatives

Scheme 6 illustrates the formation of benzothiazine derivatives 22 a and 22 b by the reaction of o-aminothiophenol (21) with esters 2a and 2b in a mixer ball mill. Reagents were ball milled for 5 min at f = 15 Hz in the absence of any other additive. Products were formed in almost quantitative yields. In contrast to the reaction of 1g (Scheme 4) and other o-aminophenol derivatives (8-12; Table 3), the reaction sequence leads to a product that is comparable with compound 6 (Scheme 4). The higher nucleophilicity of the SH group over the NH<sub>2</sub> group in 21 favors hydrothiolation (thiol-yne click chemistry)<sup>[47]</sup> instead of hydroamination. Furthermore, the resulting lactam structure has a higher stability than that of the alternative thioester. These findings are in accordance with many literature protocols discussing the synthesis of benzothiazines in solution<sup>[34,41c,d,48]</sup> or in a solvent-free manner.<sup>[14,42]</sup> In some cases, the formation of products with a similar structure to 4 was postulated.<sup>[30d, 42, 49]</sup> However, with regard to the structure of 22, there is a higher consistency than with the case outlined in Scheme 4. As a result of the absence of stabilizing hydrogen bonding between the sulfide and the carbonyl group, like the amine and the ester carbonyl group in (Z)-methyl 2-(2-oxo-2Hbenzo[b][1,4]oxazin-3(4H)-ylidene)acetate (4a),<sup>[14,31,40a]</sup> the ben-



Scheme 6. Synthesis of benzothiazine derivatives from *o*-aminothiophenol (21; 2 mmol) and 2 (2 mmol) in a mixer ball mill (beakers: V = 50 mL; balls: d = 5 mm, n = 15).

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zothiazines are formed in two stereoisomeric forms: (*E*)- and (*Z*)-**22**. The ratio of the two forms was determined by using the difference in chemical shifts of the vinylic proton. As shown in Table 4, the ratio of the stereoisomers is independent from the alkyl group, with the formation of the *E* over the *Z* form of **22** slightly favored.

Table 4. Product distribution from  ${}^{1}H$  NMR spectroscopy experiments with a solution of the product from the reaction of 21 with 2a or 2b (Scheme 6).

|                                  | 22 a   | 22 b   |
|----------------------------------|--------|--------|
| $\delta(E \text{ isomer})$ [ppm] | 5.29   | 5.30   |
| $\delta$ (Z isomer) [ppm]        | 5.55   | 5.54   |
| integral for E isomer            | 0.2026 | 0.2569 |
| integral for Z isomer            | 0.1468 | 0.1868 |
| E:Z                              | 58:42  | 58:42  |

### Conclusion

The reaction of activated ortho-substituted anilines with diethyl acetylenecarboxylate in a planetary ball mill allows the formation of the corresponding N-vinyl derivatives by intermolecular hydroamination. Apart from NaCl as a milling auxiliary, no further additive or catalyst was necessary. In the same reaction with o-hydroxyaniline, the corresponding 2-vinylidene benzoxazine derivative was formed exclusively. Structural assignment with FTIR and NMR spectroscopy indicated a Z configuration of the exocyclic double bond, and a tautomeric shift observed in protic deuterated solvent proved the suspected structure. Based on these findings, it is supposed that the heterocycle is formed sequentially, with an initial intermolecular hydroamination yielding the N-vinyl derivative, which subsequently undergoes amidation to close the annulated cycle. By using this sequential reaction procedure, several benzoxazines, guinoxalines, and benzothiazines have been synthesized from o-hydroxyanilines, o-phenylenediamine, and o-aminothiophenol, respectively.

The reaction of o-hydroxyaniline with dialkyl acetylenedicarboxylates is very fast and may proceed in solution, so solidstate FTIR spectroscopy was used for the semiquantitative reaction monitoring. The reagents were applied under different stress conditions that ranged from pressurization of gently premixed reagents through manual grinding with a mortar and pestle to ball milling. Assessment of the subsequent reaction during measurement indicated that manually ground mixtures tend to undergo reaction to completeness, whereas reaction mixtures from other stress conditions revealed only slow subsequent reactions to reach equilibrium values. The conclusion can be drawn that solid-state FTIR spectroscopy is a powerful technique for the reaction monitoring of fast reactions without the need for sample preparation under the condition of fast and instantaneous measurements. Thus, solution-based workup for reaction assessment can be avoided, which eliminates the possibility for subsequent reactions in solution. Furthermore, it was demonstrated that cryogenic milling has an adverse effect for the synthesis in ball milling, but the reaction can be initialized by defrosting the finely ground and quasihomogeneously mixed powders.

### **Experimental Section**

#### **General information**

All chemicals were purchased from Sigma-Aldrich or Alfa Aesar and were used as received. Milling experiments were accomplished with a Fritsch Pulverisette 7 classic-line planetary ball mill (Table 1) or a Retsch MM400 mixer ball mill. Experiments in a vibration ball mill were carried out with a Fritsch Pulverisette 23 equipped with one stainless steel ball (10 mm). GC-FID measurements were performed on a 6890 GC instrument, and GC with mass selective detection (GC-MSD) measurements were recorded on a 6890N instrument with MS detector 5973. Conditions for GC-FID: HP 5 column,  $30 \text{ m} \times 0.32 \text{ mm} \times 0.25 \text{ mm}$ ; H<sub>2</sub>: 10 psi; temperature program: 70 °C (hold for 1 min), 10 Kmin<sup>-1</sup> up to 280 °C (hold for 7 min); injector temperature: 280 °C; detector temperature: 300 °C. Conditions for GC-MSD: HP 5 column, 30 m×0.32 mm×0.25 mm; He: 10 psi; temperature program: 70 °C (hold for 3 min), 10 Kmin<sup>-1</sup> up to 280 °C (hold for 7 min); injector temperature: 280 °C; detector: electron impact (70 eV). ESI HRMS spectrometry was performed with an ESI-(Q)-TOFMS MICROTOF II (Bruker Daltonics GmbH) mass spectrometer. ATR-FTIR spectroscopy measurements were recorded on a Perkin-Elmer Spectrum 100 instrument equipped with a ZnSe crystal for ATR measurements (step width: 1 cm<sup>-1</sup>; measurement time for one spectrum: 20 s; spectra accumulation: 16; overall measuring time for one sample: 80 s; background correction before each sample). NMR spectroscopy measurements were performed on a Bruker Avance AC200 or AC400 spectrometer with deuterated solvents as the internal standard. Melting points were measured on a Stuart Scientific SMP10 apparatus and are uncorrected.

## Synthesis of *N*-(2-iodophenyl)trifluoromethanesulfonamide (1 n)<sup>[29]</sup>

A solution of dried THF (50 mL), *o*-iodoaniline (22 mmol, 4.82 g), and Et<sub>3</sub>N (25 mmol, 2.53 g) was cooled to -10 °C. With continuous stirring, a solution of dried THF (30 mL) and Tf<sub>2</sub>O (24 mmol, 5.04 g) was added slowly without exceeding a temperature of 0 °C. The resulting reaction mixture was stirred for 1 h at 0 °C and then slowly heated to room temperature. After being stirred for 16 h, the reaction mixture was poured into water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over MgSO<sub>4</sub>, the solvent was removed under vacuum, and the resulting solid was purified with column chromatography (*n*-hexane/EtOAc, 1:1) and washed with *n*-hexane and water: white powder; 85 %; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz):  $\delta$ =6.96 (t, *J*=6.0 Hz, 1H), 7.40 (t, *J*= 6.0 Hz, 1H), 7.83 (d, *J*=6.0 Hz, 1H), 8.18 (d, *J*=6.0 Hz, 1H), 8.30 ppm (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz):  $\delta$ =90.3, 115.6, 122.2, 127.9, 129.6, 135.7, 139.2, 154.8 ppm.

## Representative procedure for hydroamination reactions in a planetary ball mill (Table 1)

The milling beakers (V=45 mL, MSZ) were filled with six milling balls (d=15 mm, MSZ), and then NaCl (5 g), the aniline derivative (**1a-n**; 1 mmol), and diethyl acetylenedicarboxylate (**2b**; 1 mmol, 170 mg) were added sequentially. Milling was performed at 800 min<sup>-1</sup> for 10 min. After being allowed to cool to room temperature, the crude products were extracted with ethyl acetate

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(50 mL). The resulting filtrate was analyzed by GC-FID and GC-MS. Except for **4a** and **4b**, the products were not isolated.

(*Z*)-Methyl 2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (4a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 10.69$  (s, 1 H), 7.00–7.02 (m, 2 H), 6.97 (m, 2 H), 5.96 (s, 1 H), 3.78 ppm (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 170.3$ , 155.9, 140.0, 138.2, 152.7, 124.2, 122.8, 117.1, 114.9, 90.7, 51.5 ppm; IR (ATR):  $\tilde{v}_{max} = 3338$ , 1762, 1663, 1611, 754 cm<sup>-1</sup>.

(*Z*)-Ethyl 2-(2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (4 b):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 10.65$  (s, 1 H), 7.17–7.10 (m, 2 H), 6.97–7.0 (m, 2 H), 4.20 (q, J = 7.3 Hz, 1 H), 1.30 ppm (t, J = 7 H7, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 169.6$ , 155.6, 139.7, 137.7, 125.3, 123.9, 122.4, 116.7, 114.5, 90.8, 60.0, 13.9 ppm; IR (ATR):  $\tilde{\nu}_{max} = 3291$ , 1767, 1660, 1627, 755 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>]<sup>Na+</sup>: 256.0580; found: 256.0610.

## Representative procedure for the formation of benzoxazines 13–17 in a mixer ball mill

The milling beakers (V=50 mL, stainless steel) were filled with 14 milling balls (d=5 mm, stainless steel), and then *o*-aminophenol (**1 g**; 2 mmol, 218 mg) and dimethyl acetylenedicarboxylate (**2 a**; 2 mmol, 284 mg) were added sequentially. Milling was performed at 15 Hz for 5 min. After being allowed to cool to room temperature, the crude products were removed and characterized with ATR FTIR spectroscopy, NMR spectroscopy, and HRMS.

(*Z*)-Methyl 2-(6-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (13 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.57 (s, 1 H), 7.24 (s, 1 H), 6.99 (d, *J* = 12 Hz, 1 H), 6.77 (d, *J* = 24 Hz), 5.88 (s, 1 H), 3.75 (s, 3 H), 2.30 ppm (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 170.3, 156.1, 138.2, 138.0, 135.7,123.7, 123.5, 116.7, 115.1, 90.4, 51.4, 20.9 ppm; IR (ATR):  $\tilde{v}_{max}$  = 3234, 1756, 1655, 1611, 871, 813, 764 cm<sup>-1</sup>.

(*Z*)-Ethyl 2-(6-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (13 b):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.60 (s, 1 H), 7.24 (s, 1 H), 6.99 (d, *J* = 8 Hz, 1 H), 6.76 (d, *J* = 20 Hz, 1 H), 5.88 (s, 1 H), 4.21 (q, *J* = 8 Hz, 2 H), 2.30 (s, 3 H), 1.30 ppm (t, *J* = 8 Hz, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 169.9, 156.1, 138.1, 138.0, 135.7, 123.8, 123.4, 116.7, 115.0, 90.9, 60.3, 20.9, 14.3 ppm; IR (ATR):  $\tilde{\nu}_{max}$  = 3239, 1663, 1619, 876, 809, 765 cm<sup>-1</sup>.

(*Z*)-Methyl 2-(7-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (14a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.60 (s, 1 H), 7.24 (s, 1 H), 6.92 (d, *J* = 8 Hz, 1 H), 6.82 (d, *J* = 8 Hz, 1 H), 5.86 (s, 1 H), 3.75 (s, 3 H), 2.30 ppm (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 170.4, 156.1, 139.8, 138.2, 133.1, 126.3, 121.6, 117.3, 114.5, 89.9, 51.4, 20.8 ppm; IR (ATR):  $\tilde{v}_{max}$  = 3288, 1747, 1658, 1632, 883, 813, 764 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>12</sub>H<sub>11</sub>NO<sub>4</sub>]<sup>Na+</sup>: 256.0580; found: 256.0581.

(*Z*)-Ethyl 2-(7-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (14b):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.63 (s, 1 H), 7.24 (s, 1 H), 6.92 (d, *J*=8 Hz, 1 H), 6.83 (d, *J*=8 Hz, 1 H), 5.87 (s, 1 H), 4.21 (q, *J*=8 Hz, 2 H), 2.30 (s, 3 H), 1.31 ppm (t, *J*= 6 Hz, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 170.0, 156.2, 139.9, 138.1, 133.0, 126.3, 121.7, 117.3, 114.5, 90.4, 60.3, 20.8, 14.3 ppm; IR (ATR):  $\hat{\nu}_{max}$  = 3230, 1754, 1656, 1622, 864, 820, 763 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>13</sub>H<sub>13</sub>NO<sub>4</sub>]<sup>Na+</sup>: 270.0730; found: 270,0737.

(*Z*)-Methyl 2-(6-chloro-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (15 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.62 (s, 1 H), 7.24 (s, 1 H), 7.05 (d, *J* = 8 Hz, 1 H), 6.95 (d, *J* = 8 Hz, 1 H), 5.94 (s, 1 H), 3.76 ppm (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 170.0, 155.4, 138.5, 137.4, 130.9, 125.1, 122.6, 118.1, 114.7, 92.2, 51.7 ppm; IR (ATR):  $\tilde{\nu}_{max}$ =3239, 1776, 1653, 1608, 898, 763 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>11</sub>H<sub>8</sub>CINO<sub>4</sub>]<sup>Na+</sup>: 276.0034; found: 275.9994.

(*Z*)-Ethyl 2-(6-chloro-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (15 b):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.66 (s, 1 H), 7.24 (s, 1 H), 7.05 (d, *J*=8 Hz, 1 H), 6.94 (d, *J*=4 Hz, 1 H), 5.94 (s, 1 H), 4.22 (q, *J*=8 Hz, 2 H), 1.31 ppm (t, *J*=6 Hz, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$ =169.7, 155.5, 138.5, 137.3, 130.8, 125.2, 122.5, 118.1, 114.7, 92.7, 60.6, 14.2 ppm; IR (ATR):  $\tilde{v}_{max}$ =3236, 1760, 1655, 1628, 864, 802, 762 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>12</sub>H<sub>10</sub>CINO<sub>4</sub>]<sup>Na+</sup>: 290.0191; found: 290.0183.

(*Z*)-Ethyl 2-(6,8-dichloro-7-methyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (16 b): yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 10.62$  (s, 1 H), 6.91 (s, 1 H), 5.94 (s, 1 H), 4.22 (q, *J* = 8 Hz, 2 H), 2.41 (s, 3 H), 1.31 ppm (t, *J* = 6 Hz, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 169.7$ , 154.8, 136.8, 135.2, 131.0, 129.1, 123.3, 123.1, 113.0, 92.3, 51.7, 17.0 ppm; IR (ATR):  $\tilde{v}_{max} = 3225$ , 1767, 1669, 1616 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>13</sub>H<sub>11</sub>Cl<sub>2</sub>NO<sub>4</sub>]<sup>Na+</sup>: 337.9957; found: 337.9925.

(*Z*)-Methyl 2-(6-*tert*-butyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (17 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 10.67 (s, 1 H), 7.24 (s, 1 H), 7.05 (d, *J* = 8 Hz, 1 H), 7.02 (d, *J* = 12 Hz, 1 H), 5.89 (s, 1 H), 3.76 (s, 3 H), 1.28 ppm (s, 9 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 170.4, 156.1, 149.4, 138.4, 137.9, 123.4, 120.0, 116.4, 111.9, 90.2, 51.4, 34.6, 31.3 ppm; IR (ATR):  $\tilde{\nu}_{max}$ =3245, 1757, 1667, 1613, 909, 818, 765 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub>]<sup>Na+</sup>: 298.1050; found: 298.1059.

(*Z*)-Ethyl 2-(6-*tert*-butyl-2-oxo-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-ylidene)acetate (17*b*).<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz,):  $\delta$  = 10.70 (s, 1H), 7.24 (s, 1H), 7.03 (d, *J*=4 Hz, 1H), 6.95 (d, *J*=4 Hz, 1H), 5.89 (s, 1H), 4.23 (q, *J*=8 Hz, 2H), 1.30 ppm (m, 12H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$ =170.1, 156.2, 149.3, 138.3, 137.9, 131.0, 119.9, 116.4, 111.9, 90.7, 60.3, 31.3, 14.3 ppm; IR (ATR):  $\tilde{\nu}_{max}$ = 3242, 1756, 1657, 1632, 856, 814, 762 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>]<sup>Na+</sup>: 312.1206; found: 312.1219.

#### Synthesis of 3-benzylidene-3,4-dihydrobenzo[*b*][1,4]oxazin-2-one (18)<sup>[40b]</sup>

The milling beakers (V=50 mL, stainless steel) were filled with 14 milling balls (d=5 mm, stainless steel), and then *o*-aminophenol (**1g**; 2 mmol, 218 mg), methyl 3-phenylpropiolate (**2c**; 2 mmol, 320 mg), and PPh<sub>3</sub> (2 mmol, 525 mg) were added sequentially. Milling was performed at 30 Hz for 60 min. After being allowed to cool to room temperature, the crude product was removed and characterized with ATR FTIR spectroscopy and HRMS: yellow powder, 79%; IR (ATR):  $\tilde{v}_{max}$ =1742, 1620, 1435 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>15</sub>H<sub>21</sub>NO]<sup>H+</sup>: 232.1696; found: 232.1717.

## Representative procedure for the formation of quinoxalines in a mixer ball mill

The milling beakers (V=50 mL, stainless steel) were filled with 14 milling balls (d=5 mm, stainless steel), and then *o*-phenylenediamine (**19**; 2 mmol, 216 mg) and dimethyl acetylenedicarboxylate (**2a**; 2 mmol, 284 mg) were added sequentially. Milling was performed at 15 Hz for 5 min. After being allowed to cool to room

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temperature, the crude products were removed and characterized with ATR FTIR spectroscopy, NMR spectroscopy, and HRMS.

(*Z*)-Methyl 2-(3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene)acetate (20 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 11.73$  (s, 1 H), 11.02 (s, 1 H), 7.38 (d, J = 8 Hz, 1 H), 7.30 (d, J = 8 Hz, 1 H), 7.00 (m, 2 H), 5.51 (s, 1 H), 3.34 ppm (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta =$ 169.5, 155.6, 144.0, 125.2, 124.8, 123.5, 122.6, 115.4, 115.2, 83.4, 50.7 ppm; IR (ATR):  $\tilde{v}_{max} = 1737$ , 1688, 1622, 742 cm<sup>-1</sup>; HRMS: *m/z* calcd for {2[C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>]}<sup>Na+</sup>: 459.1275; found: 459.1266.

#### Representative procedure for the formation of benzothiazines in a mixer ball mill

The milling beakers (V=50 mL, stainless steel) were filled with 14 milling balls (d=5 mm, stainless steel), and then *o*-aminothiophenol (**21**; 2 mmol, 250 mg) and dimethyl acetylenedicarboxylate (**2a**; 2 mmol, 284 mg) were added sequentially. Milling was performed at 15 Hz for 5 min. After being allowed to cool to room temperature, the crude products were removed and characterized with ATR FTIR spectroscopy, NMR spectroscopy, and HRMS.

**Methyl** 2-(3-oxo-3,4-dihydrobenzo[*b*][1,4]thiazin-2-ylidene)acetate (22 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 400 MHz):  $\delta$  = 11.56 (s, 1 H), 7.10–6.98 (m, 4 H), 6.93 (s, 1 H), 3.69 ppm (s, 3 H); <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 400 MHz):  $\delta$  = 165.9, 154.2, 150.7, 141.0, 137.0, 132.7, 125.2, 123.4, 52.8 ppm; IR (ATR):  $\tilde{\nu}_{max}$  = 1721, 1682, 1614, 742 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>11</sub>H<sub>9</sub>NO<sub>3</sub>S]<sup>Na+</sup>: 258.0214; found: 258.0195.

**Ethyl 2-(3-oxo-3,4-dihydrobenzo[b][1,4]thiazin-2-ylidene)acetate** (22 a):<sup>[14]</sup> yellow solid; <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO, 400 MHz):  $\delta$  = 11.56 (s, 1 H), 7.10–6.90 (m, 4 H), 1.1–1.4 ppm (m, 3 H); <sup>13</sup>C NMR ([D<sub>6</sub>]DMSO, 400 MHz):  $\delta$  = 165.4, 154.2, 150.8, 140.9, 137.1, 132.7, 127.2, 125.2, 123.4, 60.4, 14.1 ppm; IR (ATR):  $\tilde{v}_{max}$  = 3373, 1723, 1664, 1595, 748 cm<sup>-1</sup>; HRMS: *m/z* calcd for [C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>S]<sup>Na+</sup>: 272.0352; found: 272.0349.

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**Keywords:** cascade reactions • hydroamination • IR spectroscopy • nitrogen heterocycles • solid-state reactions

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### **FULL PAPER**

**On the ball**: The formation of heterocycles by cascade reactions in ball mills is investigated (see scheme). In addition to a study of the reaction conditions (such as stress mode or reaction temperature) and the suitability of several reagents, the applicability of attenuated total reflectance FTIR spectroscopy as a semiquantitative analytical method is assessed. This allows direct analysis without sample pretreatment with solvents, which might have induced unwanted subsequent reactions.



### Solid-State Reactions

M. Weiße, M. Zille, K. Jacob, R. Schmidt, A. Stolle\*

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Hydroamination Reactions of Alkynes with *ortho*-Substituted Anilines in Ball Mills: Synthesis of Benzannulated N-Heterocycles by a Cascade Reaction