Solvent-Free Synthesis of Enamines from Alkyl Esters of Propiolic or But-2-yne Dicarboxylic Acid in a Ball Mill

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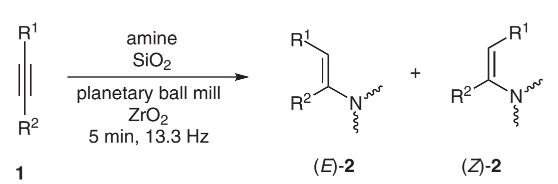
Abstract: A solvent-free method for the addition of amines to dialkylacetylendicarboxylates or alkylpropiolates using a planetary ball mill was developed. Conversion of educts was quantitative within five minutes without use of any catalyst or base. Beside the *E*-/*Z*-isomers, no side products were formed.

Key words: addition, amines, alkynes, enamines, green chemistry

Enamines based on dialkylacetylendicarboxylates or alkylpropiolates are important intermediates in the synthesis of heterocycles and multicomponent reactions,[1] also with potential medicinal application.[2] The synthesis and stereochemistry of enamines is well investigated.[3] A common method for their synthesis is the reaction between dialkylacetylendicarboxylates and alkylpropiolates with amines in MeOH.[1a] Recently Zhu et al. discovered that the solvent has a strong influence on the *E*/*Z* ratio of the product.[4] Also, kinetic studies for those amine–alkyne additions revealed that reactions follow a first-order kinetics, whereby the initial addition of the reactants is the rate-determining step.[5] However, noncatalyzed procedures in the absence of solvents have not been reported so far.

In this work a solvent-free reaction protocol for the addition of amines to dialkyl acetylenedicarboxylates or alkylpropiolates using a planetary ball mill is presented (Scheme 1). Synthetic chemistry carried out in ball mills is an emerging field of research, as indicated by the rising number of publications. It was found that ball milling is an excellent method for some organic reactions,[6,7] e.g. aldol-type reactions, oxidations, reductions, and metal-catalyzed bond-forming reactions. Ball mill protocols are often as capable as their solvent-based counterparts in solution or outperform the reactions regarding time and yield.



1a: $R^1 = R^2 = CO_2Me$
1b: $R^1 = R^2 = CO_2Et$
1c: $R^1 = CO_2Me$, $R^2 = H$
1d: $R^1 = CO_2Et$, $R^2 = H$

Scheme 1 Reaction of dialkyl acetylenedicarboxylates or alkylpropiolates with amines

Reactions were carried out in a planetary ball mill. Additionally, fused quartz sand (SiO_2) was used as inert grinding auxiliary to enable work with small batch sizes and facilitate the energy entry in the presence of liquid substrates by adsorbing them on the surface.[7m,n] No further additives or catalysts were needed for the azide–alkyne reaction of dimethyl (**1a**) or diethylacetylendicarboxylate (**1b**) as well as for amine addition to propargylic acid methyl (**1c**) or ethyl ester (**1d**). Reactions with several anilines and secondary alkyl amines were completed within five minutes reaction time only (Scheme 1 and Table 1). Structural analyses of the product mixtures indicate in the case of primary anilines the formation of the *E*- and *Z*-enamine exclusively (see Supporting Information and Figure 1). Neither the imine has been detected, nor an isomerization of the stereoisomers in solution during analysis took place.

For all examples, the conversion of the educts was quantitative and, aside from the stereoisomeric enamines, no side products were found in NMR and GC–MS analysis of the crude and isolated products. Isolated yields were about 90%; losses are a result of the workup procedure for removal of the milling auxiliary. In the case of dialkyl acetylenedicarboxylates, mainly the *E*-isomers have been identified as the major products by comparison of the chemical shift of the vinylic proton in ^1H NMR data with the literature data.[3b,c] In contrast, reactions with propiolates and anilines yielded favorably the *Z*-isomer (Table 1). Secondary alkyl amines furnished the *E*-isomer preferably, proven by comparing the coupling constants of the vinylic protons in ^1H NMR data which are approximately 8 Hz and 13 Hz for *Z*- and *E*-isomer, respectively (see Supporting Information). This is shown for enamine **2j** obtained from the reaction of methyl propargylate (**1c**) and aniline (Figure 1).[3a,b]

Comparative experiments with **1a** and aniline using a normal flask were done under solvent-free conditions by simple stirring of the reactants (Scheme 2). A mixture was obtained with only 80% conversion and a *E*/*Z* ratio of 87:13. Furthermore, side products were formed limiting the overall selectivity of the enamine isomers to 83%. Us-

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Table 1 Reaction of Dialkylacetylendicarboxylates or (**1a**,**b**) Alkylpropiolates (**1c**,**d**) with Amines[a]

Entry	Alkyne	Amine	Yield (%)[b]	Ratio *E*/*Z*[c]
2a	**1a**	aniline	91	97:3
2b		*p*-toluidine	87	98:2
2c		*o*-toluidine	88	96:4
2d		*m*-anisidine	89	97:3
2e		piperidine	82	>99:<1
2f		morpholine	84	>99:<1
2g		diisopropylamine	94	>99:<1
2h	**1b**	aniline	92	97:3
2i		*p*-toluidine	93	97:3
2j	**1c**	aniline	89	7:93
2k		*p*-toluidine	85	8:92
2l		piperidine	81	>99:<1
2m		morpholine	83	>99:<1
2n		diisopropylamine	96	>99:<1
2o	**1d**	aniline	92	7:93
2p		*p*-toluidine	87	7:93

[a] Reactions conditions: alkyne (1 mmol), amine (1 mmol), SiO_2 (5 g), 13.3 Hz, 5 min, 45-mL ZrO_2 milling beaker, 6 × 15 mm ZrO_2 milling balls.

[b] Isolated yields.

[c] ^1H NMR spectroscopy.

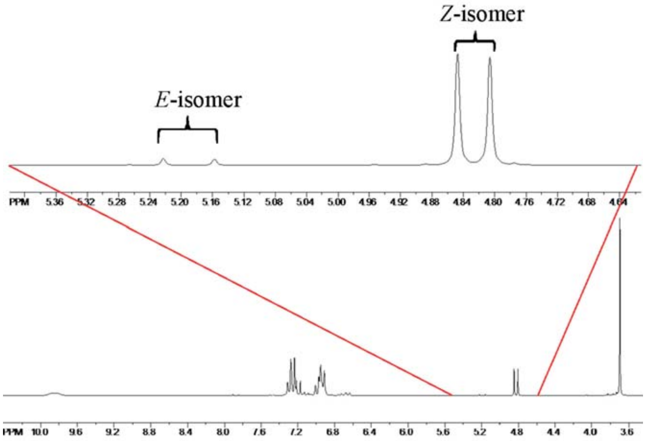
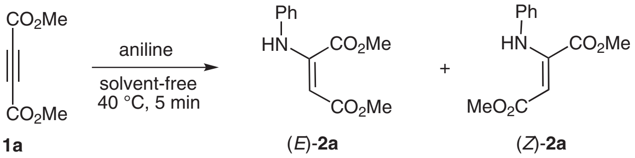


Figure 1 ^1H NMR spectrum of extracted crude product of **2j** (bottom); zoom-in of vinylic proton region (top)

ing a ball mill the reaction was chemoselective and resulted in a *E*/*Z* ratio of 97:3 (Table 1).

In conclusion, a new solvent-free protocol for the addition of amines to dialkylacetylendicarboxylates or alkylpropiolates using a planetary ball mill has been developed. Yields were nearly quantitative within five minutes reaction time without noticeable formation of side products, and in case of secondary alkyl amines the resulting enamines were stereoisomerically pure as well.



Scheme 2 Reaction of **1a** (5 mmol) and aniline (5 mmol) in a flask under solvent-free conditions (40 °C, 5 min)

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental details and NMR characterization data.

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