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COMMUNICATION

One-pot mechanosynthesis of aromatic amides and dipeptides from carboxylic acids and amines†‡

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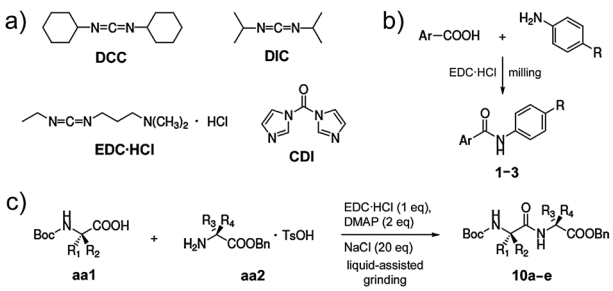
Environmentally friendly one-pot synthesis of amides, bis-amides and dipeptides by mechanochemical carbodiimide-mediated coupling of carboxylic acids and amines is described; high reaction yields and simple aqueous work-up allow for the clean, practical and fast preparation of a variety of compounds containing the amide bond from readily accessible reagents.

Amide functionality is one of the fundamental structural motifs in (bio)organic molecules such as peptides and proteins.[1] Many pharmaceutically active, naturally occurring (*e.g.* β-lactams)[2] and synthetic compounds (*e.g.* anaesthetic lidocaine)[3] possess the amide group as the basis of their biological effectiveness. Its geometric and electronic properties together with hydrogen-bonding ability render these compounds as useful materials, *e.g.* nylon polymers and Kevlar composites, whose bulk properties are greatly determined by the nature of the amide functionality.[4] The directionality of hydrogen bond donor and acceptor sites within the amide group allows for a rational design of materials by applying the principles of crystal engineering.[5] New chiral organocatalysts based on the amide group have been developed for direct asymmetric aldol condensations, Strecker and Morita–Baylis–Hillman reactions and allylic alkylations.[6]

While numerous reports for amide synthesis exist,[7] very few focus on solid-state grinding[8] as a means to access this class of compounds. Thakuria and Das have described the synthesis of quinoxalines by grinding the reactants using a mortar and pestle[9] whereas Vyle *et al.* have reported amide synthesis by mechanochemical milling of activated *N*-hydroxysuccinimidyl esters with amines.[10] Hernández and Juaristi[11] and Lamaty *et al.*[12] have used ball-milling of activated urethanes with amino acids to construct peptide derivatives in high yields.

In search of a procedure that would allow the amide mechanosynthesis without the need for pre-activated reagents, excess reagents or bulk solvents in the purification step,[10–12] we focused on further extension of the established benefits of milling mechanochemistry.[8] We now demonstrate that such a procedure, complementary to the existing mechanochemical methods, is accessible by ball-milling of commercially available amines and carboxylic acids or amino acids in one-pot mode. This enables the synthesis of aromatic achiral and chiral amides as well as dipeptides in excellent isolated yields in a simple and environmentally-friendly fashion. The key features of our approach are mechanochemical *in situ* activation of the carboxylic acid by *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and simple aqueous work-up of the reaction mixture which affords the amide products in high purity.

The mechanochemical screening of the typical coupling reagents[13] was performed by neat grinding (NG) using two 8 mm grinding balls (Scheme 1a). As a model reaction, we selected the condensation of benzoic acid (Ar = Ph) with *p*-anisidine (R = OCH_3) which yields *N*-(4-methoxyphenyl)-benzamide (**1a**) (Scheme 1b and Table S1, ESI‡). ^{1}H NMR analysis showed that *N*,*N*′-dicyclohexyl- (DCC) and *N*,*N*′-diisopropylcarbodiimide (DIC) gave similar results with the conversion of 87–88% after 30 minutes. EDC·HCl-mediated coupling resulted in slightly lower conversion (83%), whereas carbonyl diimidazole (CDI) failed to produce amide **1a** in an isolable quantity. As the beneficial effect of changing the size



Scheme 1 (a) Structures of the coupling reagents tested; (b) synthesis of *N*-aryl amides **1–3** under mechanochemical conditions in a ball mill; (c) one-pot mechanosynthesis of dipeptides **10a–e** in a ball-mill.

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‡ Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds and crystallographic data for **1e**, **2d**, **2e**, **4** and **6a**. CCDC 900474–900476. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36613d

and number of balls on the chemical reactivity has been previously established,[14] the same set of experiments was repeated with a single grinding ball of 12 mm diameter. A substantial increase in the conversion was achieved with EDC·HCl as the coupling reagent, which almost quantitatively (>97%) transformed reactants into the desired amide **1a** in only 10 minutes (Fig. S1, ESI‡). We found EDC·HCl especially suitable as a green chemistry reagent, as it allows the isolation procedure to be carried out in the absence of harmful organic solvents.

The 3-dimethylaminopropyl urea by-product is water-soluble[13] and, assuming poor water-solubility of *N*-aryl amides,[15] a simple aqueous work-up and filtration should suffice to provide the pure amide products in a clean and environmentally benign way. With the optimized conditions in hand, the syntheses of a series of *N*-aryl benzamides **1a–e** were conducted. The liquid-assisted grinding (LAG)[16] approach worked well with all substrates. After 10 minutes, the crude mixture was suspended in water and upon stirring for 15 minutes the precipitated product was simply filtered off and dried in air to afford pure amide (Table 1).

By applying the same reaction conditions, analogous sets of *N*-aryl-1-naphthamides **2a–e** and *N*-aryl-2-naphthamides **3a–e** were prepared. While the isolated yields in 1-naphthamide series **2a–e** were lower even after 30 minutes of LAG (although still better than in NG experiments, Fig. S3, ESI‡), 2-naphthamide derivatives **3a–e** were isolated in an excellent >94% yield in just 10 minutes. This observation could be explained by steric effects imposed by a fused benzene ring of the 1-naphthyl framework. Considering the complexity and the number of different reaction pathways in amide bond-forming reactions,[13] we note a remarkable chemoselectivity and straightforward reactivity in this mechanochemical multicomponent one-pot reaction.

The scope of the reaction was investigated with aliphatic and aromatic acids and amines (Table 2). Succinic and fumaric acids were used for the synthesis of the corresponding bis-amides **4** and **5**. Aliphatic secondary amines morpholine and thiomorpholine provided tertiary *N*-benzoylated amides **6a** and **6b** in high yields after 10 minutes of grinding. Besides achiral reagents, we also studied EDC·HCl-coupling using chiral (1*R*,2*R*)-cyclohexyl- and (1*R*,2*R*)-1,2-diphenylethylenediamines. The chiral bis-amides **(1*R*,2*R*)-7** and **(1*R*,2*R*)-8** were obtained in excellent yields, suggesting that the milling methodology is applicable for the preparation of amide-based chiral ligands.[6]

When commercially available *N*-Boc-protected L-alanine was coupled with *p*-anisidine or 4-chloroaniline, the targeted anilides **9a** and **9b** were isolated in high yield. This result prompted us to explore one-pot milling for the synthesis of simple *N*- and *C*-termini protected dipeptides based on glycine and alanine (Scheme 1c). Having optimised the reaction conditions for Boc-L-Ala-Gly-OBn dipeptide **10c**,[17] we conducted the EDC·HCl-mediated mechanosynthesis of other homo- and heterodipeptides **10a–e** starting from *N*-Boc-protected glycine or alanine, benzyl esters of glycine and alanine in the form of tosylate salts and DMAP as the base (Table 3).

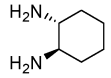
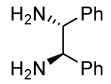
Whereas glycine-derived homodipeptide **10a** was obtained in moderate 70% yield, L-alanine homodipeptide **10b** was isolated in better yield of 80%. Its diastereomer Boc-D-Ala-L-Ala-OBn **10e**, as well as Boc-D-Ala-Gly-OBn **10d** which is the enantiomer of **10c**, were also successfully prepared. We did not notice racemisation under applied conditions,[12] which is the usual drawback of conventional solution-based procedures.[18] The established catalytic activity of dipeptides under grinding conditions[19] could therefore be coupled with

Table 1 Reaction conditions and yields for the mechanosynthesis of *N*-aryl amides **1–3** *via* EDC·HCl-mediated coupling

Product	Ar	R	Conditions[a]	Yield[b]/%
1a	Ph	OCH_3	LAG, 10 min	95
1b	Ph	CH_3	LAG, 10 min	97
1c	Ph	H	LAG, 10 min	92
1d	Ph	F	LAG, 10 min	95
1e	Ph	Cl	LAG, 10 min	99
2a	1-Naphthyl	OCH_3	LAG, 30 min	88
2b	1-Naphthyl	CH_3	LAG, 30 min	87
2c	1-Naphthyl	H	LAG, 30 min	85
2d	1-Naphthyl	F	LAG, 30 min	80/85[c]
2e	1-Naphthyl	Cl	LAG, 30 min	80/79[c]
3a	2-Naphthyl	OCH_3	LAG, 10 min	96
3b	2-Naphthyl	CH_3	LAG, 10 min	96
3c	2-Naphthyl	H	LAG, 10 min	96
3d	2-Naphthyl	F	LAG, 10 min	94
3e	2-Naphthyl	Cl	LAG, 10 min	95

[a] A single 12 mm diameter stainless steel ball, frequency of 30 Hz, anhydrous nitromethane as the grinding liquid (η = 0.25 μL mg^{-1}); [b] Isolated yield after aqueous work-up; [c] Yield after purification of the crude mixture by column chromatography.

Table 2 Scope of the EDC·HCl-mediated mechanochemical coupling of (amino)acids with aliphatic and aromatic amines

Product	Acid	Amine	Conditions[a]	Yield[b]/%
4	Succinic	Aniline[c]	NG, 10 min	77
5	Fumaric	*p*-Anisidine[c]	LAG, 30 min	79
6a	Benzoic	Morpholine	LAG, 10 min	93[d]
6b	Benzoic	Thiomorpholine	LAG, 10 min	92[d]
(1*R*,2*R*)-7	Benzoic[e]		LAG, 30 min	98
(1*R*,2*R*)-8	Benzoic[e]		LAG, 30 min	88
9a	Boc-Ala-OH	*p*-Anisidine	LAG, 30 min	87
9b	Boc-Ala-OH	4-Chloroaniline	LAG, 30 min	88

[a] 12 mm diameter stainless steel grinding ball, 30 Hz frequency, LAG with nitromethane, η = 0.25 μL mg^{-1}. [b] Isolated yield. [c] 2 equivalents of amine. [d] Purified by column chromatography. [e] 2 equivalents of benzoic acid.

Table 3 EDC·HCl-mediated mechanosynthesis of dipeptides **10a–e**[a]

Product	**aa1**/**aa2**	R_1	R_2	R_3	R_4	Yield[b]/%
10a	Boc-Gly-OH/Gly-OBn[c]	H	H	H	H	70
10b	Boc-L-Ala-OH/L-Ala-OBn[c]	CH_3	H	H	CH_3	80
10c	Boc-L-Ala-OH/Gly-OBn[c]	CH_3	H	H	H	78
10d	Boc-D-Ala-OH/Gly-OBn[c]	H	CH_3	H	H	79
10e	Boc-D-Ala-OH/L-Ala-OBn[c]	H	CH_3	H	CH_3	81

[a] A single 12 mm diameter stainless steel ball, 180 minutes, 30 Hz frequency, LAG with nitromethane, η = 0.25 μL mg^{-1}, 2 equivalents of DMAP as the base to deprotonate the unprotected amino acid and as the activator of EDC·HCl and 20 equivalents of NaCl as the grinding auxiliary. [b] Isolated yield after aqueous work-up. [c] **aa2** were used in the form of tosylate salts.

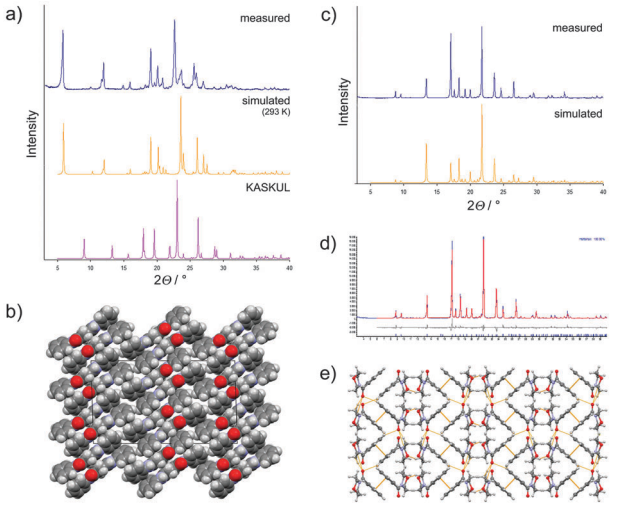


Fig. 1 (a) Measured and simulated PXRD patterns of diamide **4**; (b) crystal packing of succinamide **4** β-form (view down the *b*-axis); (c) measured and simulated PXRD patterns of amide **6a**; (d) Rietveld plot for **6a** (blue – measured, red – calculated, grey – difference); (e) arrangement of **6a** molecules in the crystal structure (view down the *c*-axis).

our approach to provide a fully mechanochemical synthesis–catalysis sequence.

The crystal and molecular structures of **2d**, **2e** and **4** were determined by single-crystal X-ray analysis. In crystals of **2d** and **2e** amide molecules are connected by intermolecular hydrogen bonds of the N–H···O=C type forming a linear tape along the crystallographic *a*-axis (Fig. S47–S51, ESI‡). Although the crystal structure of **4** was known (CCDC code KASKUL),[20] we now report a second monoclinic β-polymorph whose simulated pattern matches the one for the milling product (Fig. 1a). Differences in molecular structures are small and mostly in the spatial arrangement of terminal phenyl rings (Fig. S55, ESI‡). The primary structural motif in both forms are molecular arrays assembled by N–H···O=C hydrogen bonds in a symmetrical $R_2^2(14)$ supramolecular synthon. In β-form, parallel chains are stacked by C–H···π interactions into a 2-D network (Fig. 1b, S53 and S54, ESI‡).

The purity of synthesised amides (see ESI‡) enabled structure determination from PXRD data[21] collected on a laboratory diffractometer, in line with the requirements of a solvent-free research laboratory.[14,16] In the crystal, **1e** molecules are connected by linear hydrogen bonds into 1-D tapes (Fig. S44, ESI‡). Molecules of **6a** are held together by weak C–H···O and C^{Ar}–H···H–C^{Ar} interactions (Fig. 1c–e).

In summary, we demonstrated a mechanochemical methodology for the efficient synthesis of amides and dipeptides from commercially available acids and amines. *In situ* EDC·HCl-mediated coupling obviates the need to pre-activate reactants and allows the amide product isolation using only water. This reactivity demonstrates how the course and design of mechanosynthesis can be augmented by stoichiometric or catalytic auxiliaries.[22]

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